CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 090589

Name: Epinephrine Injection USP, 0.15mg and 0.3 mg (Auto Injector)

Sponsor: Teva Pharmaceuticals

Approval Date: August 16, 2018

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA090589Orig1s000

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 090589

APPROVAL LETTER

ANDA 090589

ANDA APPROVAL

Teva Pharmaceuticals USA, Inc.
425 Privet Road
Horsham, PA 19044
Attention: Cory Wohlbach
Senior Director, US Generics Regulatory Affairs

Dear Sir:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on November 21, 2008, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Epinephrine Injection USP, 0.15 mg (Auto-Injector), and Epinephrine Injection USP, 0.3 mg (Auto-Injector).

Reference is also made to the complete response letter issued by this office on February 23, 2016, and to any amendments thereafter.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the ANDA is **approved**, effective on the date of this letter. The Office of Bioequivalence has determined your Epinephrine Injection USP, 0.15 mg (Auto-Injector), and Epinephrine Injection USP, 0.3 mg (Auto-Injector), to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug (RLD), EpiPen Jr. Auto-Injector, 0.15 mg and EpiPen Auto-Injector, 0.3 mg, of Mylan Specialty L.P. (Mylan).

The RLD upon which you have based your ANDA, Mylan's EpiPen Jr. Auto-Injector, 0.15 mg and EpiPen Auto-Injector, 0.3 mg, is subject to periods of patent protection. The following patents and expiration dates are currently listed in the Agency's publication titled *Approved Drug Products with Therapeutic Equivalence Evaluations* (the "Orange Book"):

U.S. Patent Number	Expiration Date
7,449,012 (the '012 patent)	September 11, 2025
7,794,432 (the '432 patent)	September 11, 2025
8,048,035 (the '035 patent)	September 11, 2025
8,870,827 (the '827 patent)	September 11, 2025
9,586,010 (the '010 patent)	September 11, 2025

Your ANDA contains paragraph IV certifications to each of the patents[1] under section 505(j)(2)(A)(vii)(IV) of the FD&C Act stating that the patents are invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Epinephrine Injection USP, 0.15 mg (Auto-Injector), and Epinephrine Injection USP, 0.3 mg (Auto-Injector), under this ANDA. You have notified the Agency that Teva Pharmaceuticals USA, Inc. (Teva) complied with the requirements of section 505(j)(2)(B) of the FD&C Act and that litigation was initiated within the statutory 45-day period against Teva for infringement of the '012 and '432 patents in the United States District Court for the District of Delaware [King Pharmaceuticals, Inc. and Meridian Medical

Technologies, Inc. v. Teva Parenteral Medicines, Inc. and Teva Pharmaceuticals USA, Inc., Civil Action No. 09-00652]. You have also notified the Agency that this case was dismissed on May 1, 2012. You further notified the Agency that no action for infringement was brought against Teva after recertifying to the '012, '432, and '035 patents in connection with an amendment dated December 30, 2014.

With respect to 180-day generic drug exclusivity, we note that Teva was the first ANDA applicant for Epinephrine Injection USP, 0.15 mg (Auto-Injector), and Epinephrine Injection USP, 0.3 mg (Auto-Injector), to submit a substantially complete ANDA with a paragraph IV certification. Therefore, with this approval, Teva may be eligible for 180 days of generic drug exclusivity for Epinephrine Injection USP, 0.15 mg (Auto-Injector), and Epinephrine Injection USP, 0.3 mg (Auto-Injector). This exclusivity, which is provided for under 505(j)(5)(B)(iv) of the FD&C Act, would begin to run from the date of the commercial marketing identified in section 505(j)(5)(B)(iv). The Agency notes that Teva failed to obtain tentative approval of this ANDA within 30 months after the date of which the ANDA was filed. See section 505(j)(5)(D)(i)(IV) of the FD&C Act (forfeiture of exclusivity for failure to obtain tentative approval). The Agency is not, however, making a formal determination at this time of Teva's eligibility for 180-day generic drug exclusivity. It will do so only if a subsequent paragraph IV applicant becomes eligible for full approval (a) within 180 days after Teva begins commercial marketing of Epinephrine Injection USP, 0.15 mg (Auto-Injector), and Epinephrine Injection USP, 0.3 mg (Auto-Injector), or (b) at any time prior to the expiration of the '012 patent if Teva has not begun commercial marketing. Please submit correspondence to this ANDA notifying the Agency within 30 days of the date of the first commercial marketing of this drug product or the RLD. If you do not notify the Agency within 30 days, the date of first commercial marketing will be deemed to be the date of the drug product's approval. See 21 CFR 314.107(c)(2).

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

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

REPORTING REQUIREMENTS

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98 and at section 506I of the FD&C Act. The Agency should be advised of any change in the marketing status of this drug or if this drug will not be available for sale after approval. In particular, under section 506I(b) of the FD&C Act, you are required to notify the Agency in writing within 180 days from the date of this letter if this drug will not be available for sale within 180 days from the date of approval. As part of such written notification, you must include (1) the identity of the drug by established name and proprietary name (if any); (2) the ANDA number; (3) the strength of the drug; (4) the date on which the drug will be available for sale, if known; and (5) the reason for not marketing the drug after approval.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling materials prior to publication or dissemination. Please note that these submissions are voluntary. To do so, submit, in triplicate, a cover letter requesting advisory comments, the

proposed materials in draft or mock-up form with annotated references, and the package insert (PI), Medication Guide, and patient PI (as applicable) to:

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

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

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

ANNUAL FACILITY FEES

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

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

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical in content to the approved labeling (including the package insert, and any patient package insert and/or Medication Guide that may be required). Information on submitting SPL

files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf. The SPL will be accessible via publicly available labeling repositories.

Sincerely yours,

{See appended electronic signature page}

For Vincent Sansone, Pharm.D.
Deputy Director
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research

[1] The Agency notes that the '012, '432, '035, '827, and '010 patents were submitted to the Agency after submission of your ANDA. Litigation, if any, with respect to these patents would not create a statutory stay of approval.
[2] Some of these provisions were amended by the Generic Drug User Fee Amendments of 2017 (GDUFA II) (Public Law 115-52, Title III).

Sarah Kurtz

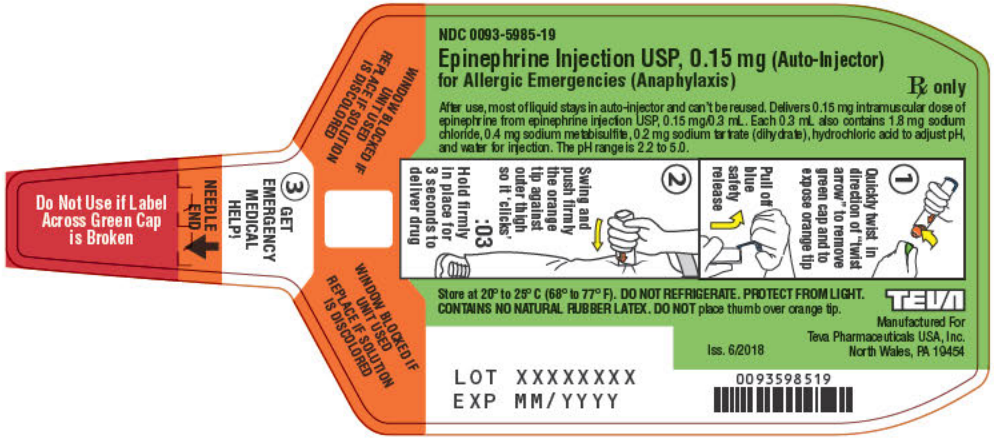
Digitally signed by Sarah Kurtz
Date: 8/16/2018 11:59:06AM
GUID: 54078879000a1b9e15dd31ed6f0343ca

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 090589

LABELING


Do Not Use if Label Across Green Cap is Broken
NEEDLE END
3 GET EMERGENCY MEDICAL HELP!
WINDOW BLOCKED IF UNIT USED OR IF SOLUTION IS DISCOLORED
WINDOW BLOCKED IF UNIT USED REPLACE IF SOLUTION IS DISCOLORED
NDC 0093-5985-19
Epinephrine Injection USP, 0.15 mg (Auto-Injector)
for Allergic Emergencies (Anaphylaxis)
℞ only
After use, most of liquid stays in auto-injector and can't be reused. Delivers 0.15 mg intramuscular dose of epinephrine from epinephrine injection USP, 0.15 mg/0.3 mL. Each 0.3 mL also contains 1.8 mg sodium chloride, 0.4 mg sodium metabisulfite, 0.2 mg sodium tartrate (dihydrate), hydrochloric acid to adjust pH, and water for injection. The pH range is 2.2 to 5.0.
1 Quickly twist in direction of "twist arrow" to remove green cap and to expose orange tip
2 Pull off blue safety release
Swing and push firmly the orange tip against outer thigh so it 'clicks'
Hold firmly in place for 3 seconds to deliver drug
:03
Store at 20° to 25° C (68° to 77° F). DO NOT REFRIGERATE. PROTECT FROM LIGHT.
CONTAINS NO NATURAL RUBBER LATEX. DO NOT place thumb over orange tip.
TEVA
Manufactured For
Teva Pharmaceuticals USA, Inc.
North Wales, PA 19454
Iss. 6/2018
LOT XXXXXXXX
EXP MM/YYYY
0093598519

NDC 0093-5986-19
Epinephrine Injection USP, 0.3 mg (Auto-Injector)
for Allergic Emergencies (Anaphylaxis)
℞ only
After use, most of liquid stays in auto-injector and can't be reused. Delivers 0.3 mg intramuscular dose of epinephrine from epinephrine injection USP, 0.3 mg/0.3 mL. Each 0.3 mL also contains 1.8 mg sodium chloride, 0.4 mg sodium metabisulfite, 0.4 mg sodium tartrate (dihydrate), hydrochloric acid to adjust pH, and water for injection. The pH range is 2.2 to 5.0.
1
Quickly twist in direction of "twist arrow" to remove yellow cap and to expose orange tip
Pull off blue safety release
2
Swing and push firmly the orange tip against outer thigh so it 'clicks'
:03
Hold firmly in place for 3 seconds to deliver drug
Store at 20° to 25° C (68° to 77° F). DO NOT REFRIGERATE. PROTECT FROM LIGHT.
CONTAINS NO NATURAL RUBBER LATEX. DO NOT place thumb over orange tip.
TEVA
Manufactured For
Teva Pharmaceuticals USA, Inc.
North Wales, PA 19454
Iss. 6/2018
0093598619
LOT XXXXXXXX
EXP MM/YYYY
WINDOW BLOCKED IF UNIT USED
REPLACE IF SOLUTION IS DISCOLORED
WINDOW BLOCKED IF UNIT USED
REPLACE IF SOLUTION IS DISCOLORED
3 GET EMERGENCY MEDICAL HELP!
NEEDLE END
Do Not Use if Label Across Yellow Cap is Broken

Lot.
Exp.

88.9mm x 30mm
Non Varnish/Coding Area

Open This End

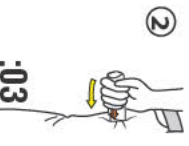
NDC 0093-5985-27

℞ only

Epinephrine Injection USP, 0.15 mg (Auto-Injectors)

2 Auto-Injectors and 1 Trainer

See enclosed Patient Information Leaflet for complete instructions for use.

① 

Quickly twist in direction of "twist arrow" to remove green cap and to expose orange tip.

Pull off blue safety release

②

Swing and push firmly the orange tip against outer thigh so it "clicks"

:03

Hold firmly in place for 3 seconds to deliver drug

③ **GET EMERGENCY MEDICAL HELP!**

Note: The Needle comes out of the orange tip.
Never put your thumb, fingers or hand over the orange tip.

Replace if the epinephrine solution appears discolored (pinkish or darker than slightly yellow) or if it contains a precipitate. Discard unit after use.
Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature].
DO NOT REFRIGERATE. PROTECT FROM LIGHT.
The Trainer contains no medicine and no needle.

TEVA

Iss. 6/2018

THIS COPY PRINTS INSIDE TOP FLAP

For more information about allergic emergencies (anaphylaxis) and Epinephrine Injection USP, please see the enclosed insert and visit www.TevaEpinephrine.com

NDC 0093-5985-27

℞ only
2-Pack

Epinephrine Injection USP, 0.15 mg (Auto-Injectors)

Never put thumb, fingers or hand over orange tip. Do not remove the blue safety release until ready to use.

Contains no natural rubber latex.

Each 2-Pack Carton Contains 2 Epinephrine Injection USP, 0.15 mg (Auto-Injectors) and 1 Trainer. Each Epinephrine Injection USP, 0.15 mg (Auto-Injector) delivers one 0.15 mg intramuscular dose of epinephrine from epinephrine injection USP 0.15 mg/0.3mL.

Register your Epinephrine Auto-Injectors at **www.TevaEpinephrine.com** to receive free refill reminders

Read enclosed patient package insert carefully before using. For more information please visit www.TevaEpinephrine.com.

TEVA

NDC 0093-5985-27

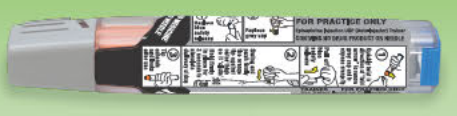
2-Pack

Epinephrine Injection USP, 0.15 mg (Auto-Injectors)
For Allergic Emergencies (Anaphylaxis)

Each carton contains:

Two green Epinephrine Injection USP, 0.15 mg (Auto-Injectors)

One grey Trainer



℞ only

2 Auto-Injectors and 1 Trainer

TEVA

Scan for more information on Teva products or go to www.TevaGenerics.com

For more information about allergic emergencies (anaphylaxis) and Epinephrine Injection USP, please see the enclosed insert and visit www.TevaEpinephrine.com

Manufactured For:
Teva Pharmaceuticals USA, Inc.
North Wales, PA 19454

GTIN 00300935985275

N 3 0093-5985-27 5

NDC 0093-5985-27

Epinephrine Injection USP, 0.15 mg (Auto-Injectors)

2 Auto-Injectors and 1 Trainer

℞ only
2-Pack

TEVA

UNVARNISHED GLUE AREA

UNVARNISHED GLUE AREA

Lot.
Exp.

88.9mm x 30mm
Non Varnish/Coding Area

Open This End

NDC 0093-5986-27

℞ only

Epinephrine Injection USP, 0.3 mg (Auto-Injectors)

2 Auto-Injectors and 1 Trainer

See enclosed Patient Information Leaflet for complete instructions for use.

① **Quickly twist in direction of "twist arrow" to remove yellow cap and to expose orange tip.**

Pull off blue safety release

② **Swing and push firmly the orange tip against outer thigh so it "clicks"**

Hold firmly in place for 3 seconds to deliver drug

:03

③ **GET EMERGENCY MEDICAL HELP!**

Note: The Needle comes out of the orange tip.
Never put your thumb, fingers or hand over the orange tip.

Replace if the epinephrine solution appears discolored (pinkish or darker than slightly yellow) or if it contains a precipitate. Discard unit after use.
Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature].
DO NOT REFRIGERATE. PROTECT FROM LIGHT.
The Trainer contains no medicine and no needle.

TEVA

Iss. 6/2018

THIS COPY PRINTS INSIDE TOP FLAP

For more information about allergic emergencies (anaphylaxis) and Epinephrine Injection USP, please see the enclosed insert and visit www.TevaEpinephrine.com

NDC 0093-5986-27

℞ only
2-Pack

Epinephrine Injection USP, 0.3 mg (Auto-Injectors)
Never put thumb, fingers or hand over orange tip. Do not remove the blue safety release until ready to use.
Contains no natural rubber latex.
Each 2-Pack Carton Contains 2 Epinephrine Injection USP, 0.3 mg (Auto-Injectors) and 1 Trainer. Each Epinephrine Injection USP, 0.3 mg (Auto-Injector) delivers one 0.3 mg intramuscular dose of epinephrine from epinephrine injection USP, 0.3 mg/0.3 mL.
Register your Epinephrine Auto-Injectors at **www.TevaEpinephrine.com** to receive free refill reminders
Read enclosed patient package insert carefully before using. For more information please visit www.TevaEpinephrine.com.
TEVA

NDC 0093-5986-27

2-Pack

Epinephrine Injection USP, 0.3 mg (Auto-Injectors)
For Allergic Emergencies (Anaphylaxis)

Each carton contains:

Two yellow Epinephrine Injection USP, 0.3 mg (Auto-Injectors)

One grey Trainer

℞ only

2 Auto-Injectors and 1 Trainer

TEVA

Scan for more information on Teva products or go to www.TevaGenerics.com

For more information about allergic emergencies (anaphylaxis) and Epinephrine Injection USP, please see the enclosed insert and visit www.TevaEpinephrine.com

Manufactured For:
Teva Pharmaceuticals USA, Inc.
North Wales, PA 19454

GTIN 00300935986272

N 3 0093-5986-27 2

UNVARNISHED GLUE AREA

UNVARNISHED GLUE AREA

NO MEDICINE
NO NEEDLE

To Reset Trainer

① Replace blue safety release

② Replace grey cap

TRAINER

FOR PRACTICE ONLY

Epinephrine Injection USP (Auto-Injector) Trainer

CONTAINS NO DRUG PRODUCT OR NEEDLE

① Quickly twist in direction of "Twist arrow" to remove grey cap and to expose orange tip

Pull off blue safety release

② Swing and push firmly the orange tip against outer thigh so it 'clicks'

Hold firmly in place for 3 seconds to simulate delivery of drug

:03

③ Tip extends and locks after use

TRAINER FOR PRACTICE ONLY

See Trainer Insert for Full Instructions

NO MEDICINE
NO NEEDLE

LOT XXXXXXX
EXP MM/YYYY

TEVA

Iss. 6/2018

Manufactured For
Teva Pharmaceuticals USA, Inc.
North Wales, PA 19454

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use EPINEPHRINE INJECTION, 0.3 mg and EPINEPHRINE INJECTION, 0.15 mg safely and effectively. See full prescribing information for EPINEPHRINE INJECTION, 0.3 mg and EPINEPHRINE INJECTION, 0.15 mg.

EPINEPHRINE injection, 0.3 mg (Auto-Injector),
EPINEPHRINE injection, 0.15 mg (Auto-Injector),
for intramuscular or subcutaneous use
Initial U.S. Approval: 1939

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

Epinephrine Injection, 0.3 mg and Epinephrine Injection, 0.15 mg contain epinephrine, a non-selective alpha and beta-adrenergic receptor agonist, indicated in the emergency treatment of allergic reactions (Type I) including anaphylaxis. (1)

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

- Patients greater than or equal to 30 kg (66 lbs): Epinephrine injection, 0.3 mg (2)
- Patients 15 to 30 kg (33 lbs to 66 lbs): Epinephrine injection, 0.15 mg (2)

Inject Epinephrine Injection, 0.3 mg and Epinephrine Injection, 0.15 mg intramuscularly or subcutaneously into the anterolateral aspect of the thigh, through clothing if necessary. Each device is a single-use injection. (2)

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

- Epinephrine: Injection, 0.3 mg: 0.3 mg/0.3 mL epinephrine, USP, pre-filled auto-injector (3)
- Epinephrine: Injection, 0.15 mg: 0.15 mg/0.3 mL epinephrine, USP, pre-filled auto-injector (3)

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

None (4)

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

- In conjunction with use, seek immediate medical or hospital care. (5.1)
- Do not inject intravenously, into buttock, or into digits, hands, or feet. (5.2)
- To minimize the risk of injection related injury, instruct caregivers to hold the child's leg firmly in place and limit movement prior to and during injection when administering to young children. (5.2)
- Rare cases of serious skin and soft tissue infections have been reported following epinephrine injection. Advise patients to seek medical care if they develop signs or symptoms of infection. (5.3)
- The presence of a sulfite in this product should not deter use. (5.4)
- Administer with caution in patients with heart disease; may aggravate angina pectoris or produce ventricular arrhythmias. (5.5)

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

Adverse reactions to epinephrine include anxiety, apprehensiveness, restlessness, tremor, weakness, dizziness, sweating, palpitations, pallor, nausea and vomiting, headache, and/or respiratory difficulties. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Teva Pharmaceuticals USA, Inc. at 1-888-838-2872 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

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

- Cardiac glycosides or diuretics: observe for development of cardiac arrhythmias. (7)
- Tricyclic antidepressants, monoamine oxidase inhibitors, levothyroxine sodium, and certain antihistamines: potentiate effects of epinephrine. (7)
- Beta-adrenergic blocking drugs: antagonize cardiostimulating and bronchodilating effects of epinephrine. (7)
- Alpha-adrenergic blocking drugs: antagonize vasoconstricting and hypertensive effects of epinephrine. (7)
- Ergot alkaloids: may reverse the pressor effects of epinephrine. (7)

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

- Elderly patients may be at greater risk of developing adverse reactions. (5.5, 8.5)

See 17 for PATIENT COUNSELING INFORMATION and FDA approved patient labeling.

Revised: 06/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Epinephrine Injection, 0.3 mg and Epinephrine Injection, 0.15 mg are indicated in the emergency treatment of allergic reactions (Type I) including anaphylaxis to stinging insects (e.g., order Hymenoptera, which include bees, wasps, hornets, yellow jackets and fire ants) and biting insects (e.g., triatoma, mosquitoes), allergen immunotherapy, foods, drugs, diagnostic testing substances (e.g., radiocontrast media) and other allergens, as well as idiopathic anaphylaxis or exercise-induced anaphylaxis.

Epinephrine Injection, 0.3 mg and Epinephrine Injection, 0.15 mg are intended for immediate administration in patients who are determined to be at increased risk for anaphylaxis, including individuals with a history of anaphylactic reactions.

Anaphylactic reactions may occur within minutes after exposure and consist of flushing, apprehension, syncope, tachycardia, thready or unobtainable pulse associated with a fall in blood pressure, convulsions, vomiting, diarrhea and abdominal cramps, involuntary voiding, wheezing, dyspnea due to laryngeal spasm, pruritus, rashes, urticaria or angioedema.

Epinephrine Injection, 0.3 mg and Epinephrine Injection, 0.15 mg are intended for immediate administration as emergency supportive therapy only and are not a substitute for immediate medical care.

2 DOSAGE AND ADMINISTRATION

Selection of the appropriate dosage strength (epinephrine injection, 0.3 mg or epinephrine injection, 0.15 mg) is determined according to patient body weight.

- Patients greater than or equal to 30 kg (approximately 66 pounds or more): Epinephrine injection, 0.3 mg
- Patients 15 to 30 kg (33 pounds to 66 pounds): Epinephrine injection, 0.15 mg

Inject epinephrine injection, 0.3 mg or epinephrine injection, 0.15 mg intramuscularly or subcutaneously into the anterolateral aspect of the thigh, through clothing if necessary. Instruct caregivers of young children who are prescribed an epinephrine injection, 0.3 mg or epinephrine injection, 0.15 mg and who may be uncooperative and kick or move during an injection to hold the leg firmly in place and limit movement prior to and during an injection [*see Warnings and Precautions (5.2)*].

Each epinephrine injection, 0.3 mg or epinephrine injection, 0.15 mg contains a single dose of epinephrine for single-use injection. Since the doses of epinephrine delivered from epinephrine injection, 0.3 mg or epinephrine injection, 0.15 mg are fixed, consider using other forms of injectable epinephrine if doses lower than 0.15 mg are deemed necessary.

The prescriber should carefully assess each patient to determine the most appropriate dose of epinephrine, recognizing the life-threatening nature of the reactions for which this drug is indicated. With severe persistent anaphylaxis, repeat injections with an additional epinephrine injection, 0.3 mg or epinephrine injection, 0.15 mg may be necessary. More than two sequential doses of epinephrine should only be administered under direct medical supervision [*see Warnings and Precautions (5.1)*].

The epinephrine solution in the clear window of the epinephrine (auto-injector) should be inspected visually for particulate matter and discoloration. Epinephrine is light sensitive and the (auto-injector) is manufactured from transparent UV stabilized polycarbonate [*see How Supplied/Storage and Handling (16.2)*].

3 DOSAGE FORMS AND STRENGTHS

Epinephrine: Injection, 0.3 mg/0.3 mL epinephrine injection USP, pre-filled auto-injector

Epinephrine: Injection, 0.15 mg/0.3 mL epinephrine injection USP, pre-filled auto-injector

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Emergency Treatment

Epinephrine injection, 0.3 mg and epinephrine injection, 0.15 mg are intended for immediate administration as emergency supportive therapy and are not intended as a substitute for immediate medical care. **In conjunction with the administration of epinephrine, the patient should seek immediate medical or hospital care.** More than two sequential doses of epinephrine should only be administered under direct medical supervision [*see Indications and Usage (1), Dosage and Administration (2) and Patient Counseling Information (17)*].

5.2 Injection-Related Complications

Epinephrine injection, 0.3 mg and epinephrine injection, 0.15 mg should **only** be injected into the anterolateral aspect of the thigh [*see Dosage and Administration (2) and Patient Counseling Information (17)*].

- **Do not inject intravenously.** Large doses or accidental intravenous injection of epinephrine may result in cerebral hemorrhage due to sharp rise in blood pressure. Rapidly acting vasodilators can counteract the marked pressor effects of epinephrine if there is such inadvertent administration.
- **Do not inject into buttock.** Injection into the buttock may not provide effective treatment of anaphylaxis. Advise the patient to go immediately to the nearest emergency room for further treatment of anaphylaxis. Additionally, injection into the buttock has been associated with Clostridial infections (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.** Since epinephrine is a strong vasoconstrictor, accidental injection into the digits, hands or feet may result in loss of blood flow to the affected area. Advise the patient to go immediately to the nearest emergency room and to inform the healthcare provider in the emergency room of the location of the accidental injection. Treatment of such inadvertent administration should consist of vasodilation, in addition to further appropriate treatment of anaphylaxis [*see Adverse Reactions (6)*].
- **Hold leg firmly during injection.** Lacerations, bent needles, and embedded needles have been reported when epinephrine injection, 0.3 mg and epinephrine injection, 0.15 mg have been injected into the thigh of young children who are uncooperative and kick or move during an injection. To minimize the risk of injection related injury when administering epinephrine injection to young children, instruct caregivers to hold the child's leg firmly in place and limit movement prior to and during injection.

5.3 Serious Infections at the Injection Site

Rare cases of serious skin and soft tissue infections, including necrotizing fasciitis and myonecrosis caused by Clostridia (gas gangrene), have been reported at the injection site following epinephrine injection for anaphylaxis. *Clostridium* spores can be present on the skin and introduced into the deep tissue with subcutaneous or intramuscular injection. While cleansing with alcohol may reduce presence of bacteria on the skin, alcohol cleansing does not kill *Clostridium* spores. To decrease the risk of *Clostridium* infection, do not inject epinephrine injection into the buttock [*see Warnings and Precautions (5.2)*]. Advise patients to seek medical care if they develop signs or symptoms of infection, such as persistent redness, warmth, swelling, or tenderness, at the epinephrine injection site.

5.4 Allergic Reactions Associated with Sulfite

The presence of a sulfite in this product should not deter administration of the drug for treatment of serious allergic or other emergency situations even if the patient is sulfite-sensitive.

Epinephrine is the preferred treatment for serious allergic reactions or other emergency situations even though this product contains sodium metabisulfite, a sulfite that may, in other products, cause allergic-type reactions including anaphylactic symptoms or life-threatening or less severe asthmatic episodes in certain susceptible persons.

The alternatives to using epinephrine in a life-threatening situation may not be satisfactory.

5.5 Disease Interactions

Some patients may be at greater risk for developing adverse reactions after epinephrine administration. Despite these concerns, it should be recognized that the presence of these conditions is not a contraindication to epinephrine administration in an acute, life-threatening situation. Therefore, patients with these conditions, and/or any other person who might be in a position to administer epinephrine injection, 0.3 mg or epinephrine injection, 0.15 mg to a patient experiencing anaphylaxis should be carefully instructed in regard to the circumstances under which epinephrine should be used.

- Patients with Heart Disease

Epinephrine should be administered with caution to patients who have heart disease, including patients with cardiac arrhythmias, coronary artery or organic heart 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)*].

- Other Patients and Diseases

Epinephrine should be administered with caution to patients with hyperthyroidism, diabetes, elderly individuals, and pregnant women. Patients with Parkinson's disease may notice a temporary worsening of symptoms.

6 ADVERSE REACTIONS

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.

Common adverse reactions to systemically administered epinephrine include anxiety; apprehensiveness; restlessness; tremor; weakness; dizziness; sweating; palpitations; pallor; nausea and vomiting; headache; and/or respiratory difficulties. These symptoms occur in some persons receiving therapeutic doses of epinephrine, but are more likely to occur in patients with hypertension or hyperthyroidism [*see Warnings and Precautions (5.5)*].

Arrhythmias, including fatal ventricular fibrillation, have been reported, particularly in patients with underlying cardiac disease or those receiving certain drugs [*see Warnings and Precautions (5.5)* and *Drug Interactions (7)*].

Rapid rises in blood pressure have produced cerebral hemorrhage, particularly in elderly patients with cardiovascular disease [*see Warnings and Precautions (5.5)*].

Angina may occur in patients with coronary artery disease [*see Warnings and Precautions (5.5)*].

Rare cases of stress cardiomyopathy have been reported in patients treated with epinephrine.

Accidental injection into the digits, hands or feet may result in loss of blood flow to the affected area [*see Warnings and Precautions (5.2)*].

Adverse events experienced as a result of accidental injections may include increased heart rate, local reactions including injection site pallor, coldness and hypoesthesia or injury at the injection site resulting in bruising, bleeding, discoloration, erythema or skeletal injury.

Lacerations, bent needles, and embedded needles have been reported when epinephrine injection has been injected into the thigh of young children who are uncooperative and kick or move during the injection [*see Warnings and Precautions (5.2)*].

Injection into the buttock has resulted in cases of gas gangrene [*see Warnings and Precautions (5.2)*].

Rare cases of serious skin and soft tissue infections, including necrotizing fasciitis and myonecrosis caused by Clostridia (gas gangrene), have been reported following epinephrine injection, including epinephrine injection 0.3 mg, in the thigh [*see Warnings and Precautions (5.3)*].

7 DRUG INTERACTIONS

Patients who receive epinephrine while concomitantly taking cardiac glycosides, diuretics, or anti-arrhythmics should be observed carefully for the development of cardiac arrhythmias [*see Warnings and Precautions (5.5)*].

The effects of epinephrine may be potentiated by tricyclic antidepressants, monoamine oxidase inhibitors, levothyroxine sodium, and certain antihistamines, notably chlorpheniramine, tripelennamine, and diphenhydramine.

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 also reverse the pressor effects of epinephrine.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects

Pregnancy Category C.

There are no adequate and well controlled studies of the acute effect of epinephrine in pregnant women.

Epinephrine was teratogenic in rabbits, mice and hamsters. 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 has been shown to have teratogenic effects when administered subcutaneously in rabbits at approximately 30 times the maximum recommended daily subcutaneous or intramuscular dose (on a mg/m^2 basis at a maternal dose of 1.2 mg/kg/day for two to three days), in mice at approximately 7 times the maximum daily subcutaneous or intramuscular dose (on a mg/m^2 basis at a maternal subcutaneous dose of 1 mg/kg/day for 10 days), and in hamsters at approximately 5 times the maximum recommended daily subcutaneous or intramuscular dose (on a mg/m^2 basis at a maternal subcutaneous dose of 0.5 mg/kg/day for 4 days).

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

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 injection, 0.3 mg is administered to a nursing woman.

8.4 Pediatric Use

Epinephrine injection, 0.3 mg or epinephrine injection, 0.15 mg may be administered to pediatric patients at a dosage appropriate to body weight [*see Dosage and Administration (2)*]. 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. Since the doses of epinephrine delivered from epinephrine injection, 0.3 mg and epinephrine injection, 0.15 mg are fixed, consider using other forms of injectable epinephrine if doses lower than 0.15 mg are deemed necessary.

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, epinephrine injection, 0.3 mg should be administered with caution in elderly individuals, who may be at greater risk for developing adverse reactions after epinephrine administration [*see Warnings and Precautions (5.5), Overdosage (10)*].

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 rapidly acting vasodilators or alpha-adrenergic blocking drugs and/or respiratory support.

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, and kidney failure. Suitable corrective measures must be taken in such situations.

11 DESCRIPTION

Epinephrine Injection USP, 0.3 mg and Epinephrine Injection USP, 0.15 mg are auto-injectors and combination products containing drug and device components.

Each Epinephrine Injection USP, 0.3 mg (Auto-Injector) delivers a single dose of 0.3 mg epinephrine, USP from epinephrine injection USP 0.3 mg/0.3 mL in a sterile solution.

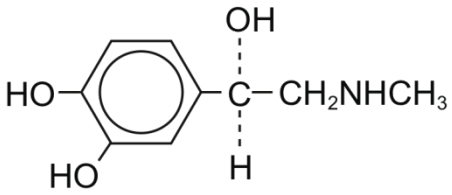
Each Epinephrine Injection USP, 0.15 mg (Auto-Injector) delivers a single dose of 0.15 mg epinephrine, USP from epinephrine injection USP 0.15 mg/0.3 mL in a sterile solution.

The Epinephrine Injection USP, 0.3 mg and Epinephrine Injection USP, 0.15 mg (Auto-Injectors) each contain 1 mL epinephrine, USP solution. Approximately 0.7 mL remains in the auto-injector after activation, but is not available for future use, and should be discarded.

Each 0.3 mL in the Epinephrine Injection USP, 0.3 mg (Auto-Injector) contains 0.3 mg epinephrine, USP, 1.8 mg sodium chloride, 0.4 mg sodium metabisulfite, 0.4 mg sodium tartrate (dihydrate), hydrochloric acid to adjust pH, and water for injection. The pH range is 2.2 to 5.0.

Each 0.3 mL in the Epinephrine Injection USP, 0.15 mg (Auto-Injector) contains 0.15 mg epinephrine, USP, 1.8 mg sodium chloride, 0.4 mg sodium metabisulfite, 0.2 mg sodium tartrate (dihydrate), hydrochloric acid to adjust pH, and water for injection. The pH range is 2.2 to 5.0.

Epinephrine, USP is a sympathomimetic catecholamine. Chemically, epinephrine, USP is (-)-3,4-Dihydroxy-α-[(methylamino)methyl]benzyl alcohol with the following structure:



Epinephrine, USP solution deteriorates rapidly on exposure to air or light, turning pink from oxidation to adrenochrome and brown from the formation of melanin. Replace Epinephrine Injection USP, 0.3 mg and Epinephrine Injection USP, 0.15 mg if the epinephrine, USP solution appears discolored (pinkish or darker than slightly yellow) or if it contains a precipitate.

Thoroughly review the patient instructions and operation of Epinephrine Injection USP, 0.3 mg or Epinephrine Injection USP, 0.15 mg with patients and caregivers prior to use [*see Patient Counseling Information (17)*].

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.

When given subcutaneously or intramuscularly, epinephrine has a rapid onset and short duration of action.

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* and to be an oxidative mutagen in a *WP2* bacterial reverse mutation assay.

Epinephrine was positive in the DNA Repair test with *B. subtilis* (REC) assay, but was not mutagenic in the *Salmonella* bacterial reverse mutation assay.

The potential for epinephrine to impair fertility has not been evaluated.

This should not prevent the use of epinephrine under the conditions noted under *Indications and Usage (1)*.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Epinephrine Injection USP, 0.3 mg (Auto-Injectors) (epinephrine injections USP, 0.3 mg/0.3 mL) are available as Epinephrine Injection USP, 0.3 mg 2-Pack, NDC 0093-5986-27, a pack that contains two Epinephrine Injection USP, 0.3 mg (Auto-Injectors) (epinephrine injections USP, 0.3 mg/0.3 mL) and one Epinephrine Injection (Auto-Injector) trainer device.

Epinephrine Injection USP, 0.15 mg (Auto-Injectors) (epinephrine injections USP, 0.15 mg/0.3 mL) are available as Epinephrine Injection USP, 0.15 mg 2-Pack, NDC 0093-5985-27, a pack that contains two Epinephrine Injection USP, 0.15 mg (Auto-Injectors) (epinephrine injections USP, 0.15 mg/0.3 mL) and one Epinephrine Injection (Auto-Injector) trainer device.

Epinephrine Injection USP, 0.3 mg 2-Pack and Epinephrine Injection USP, 0.15 mg 2-Pack also include a W-clip to clip two auto-injectors together.

Rx only

16.2 Storage and Handling

Epinephrine, USP is light sensitive and the auto-injector is manufactured from transparent UV stabilized polycarbonate to protect it from light. Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature].

PROTECT FROM LIGHT.

DO NOT REFRIGERATE.

Before using, check to make sure the solution in the auto-injector is clear and colorless. Replace the auto-injector if the solution is discolored (pinkish or darker than slightly yellow) or if it contains a precipitate.

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

17 PATIENT COUNSELING INFORMATION

[*See FDA-Approved Patient Labeling (Patient Information and Instructions for Use).*]

A healthcare provider should review the patient instructions and operation of epinephrine injection, 0.3 mg and epinephrine injection, 0.15 mg in detail, with the patient or caregiver.

Epinephrine is essential for the treatment of anaphylaxis. Patients who are at risk of or with a history of severe allergic reactions (anaphylaxis) to insect stings or bites, foods, drugs, and other allergens, as well as idiopathic and exercise-induced anaphylaxis, should be carefully instructed about the circumstances under which epinephrine should be used.

Administration and Training

Instruct patients and/or caregivers in the appropriate use of epinephrine injection, 0.3 mg and epinephrine injection, 0.15 mg. Epinephrine injection, 0.3 mg and epinephrine injection, 0.15 mg should be injected into the middle of the outer thigh (through clothing, if necessary). Each device is a single-use injection. Advise patients to seek immediate medical care in conjunction with administration of epinephrine injection, 0.3 mg and epinephrine injection, 0.15 mg.

Instruct caregivers to hold the leg of young children firmly in place and limit movement prior to and during injection. Lacerations, bent needles, and embedded needles have been reported when epinephrine injection, 0.3 mg and epinephrine injection, 0.15 mg have been injected into the thigh of young children who are uncooperative and kick or move during an injection [*see Warnings and Precautions (5.2)*].

Complete patient information, including dosage, directions for proper administration and precautions can be found inside each epinephrine injection, 0.3 mg or epinephrine injection, 0.15 mg carton. A printed label on the surface of epinephrine injection, 0.3 mg and epinephrine injection, 0.15 mg shows instructions for use and a diagram depicting the injection process.

Instruct patients and/or caregivers to use and practice with the Trainer to familiarize themselves with the use of epinephrine injection, 0.3 mg and epinephrine injection, 0.15 mg in an allergic emergency. The Trainer may be used multiple times. A Trainer device is provided in 2-Pack cartons.

Adverse Reactions

Epinephrine may produce symptoms and signs that include 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 signs and symptoms usually subside rapidly, especially with rest, quiet and recumbency. Patients with hypertension or hyperthyroidism may develop more severe or persistent effects, and patients with coronary artery disease could experience angina. Patients with diabetes may develop increased blood glucose levels following epinephrine administration. Patients with Parkinson’s disease may notice a temporary worsening of symptoms [*see Warnings and Precautions (5.5)*].

Accidental Injection

Advise patients to seek immediate medical care in the case of accidental injection. Since epinephrine is a strong vasoconstrictor when injected into the digits, hands, or feet, treatment should be directed at vasodilatation if there is such an accidental injection to these areas [*see Warnings and Precautions (5.2)*].

Serious Infections at the Injection Site

Rare cases of serious skin and soft tissue infections, including necrotizing fasciitis and myonecrosis caused by Clostridia (gas gangrene), have been reported at the injection site following epinephrine injection for anaphylaxis. Advise patients to

seek medical care if they develop signs or symptoms of infection, such as persistent redness, warmth, swelling, or tenderness, at the epinephrine injection site [*see Warnings and Precautions (5.3)*].

Storage and Handling

Instruct patients to inspect the epinephrine solution visually through the clear window of the auto-injector periodically. Replace epinephrine injection, 0.3 mg and epinephrine injection, 0.15 mg if the epinephrine solution appears discolored (pinkish or darker than slightly yellow) or if it contains a precipitate. Epinephrine is light sensitive and should be protected from light. The auto-injector is not waterproof. Instruct patients that epinephrine injection, 0.3 mg and epinephrine injection, 0.15 mg must be used or properly disposed once the blue safety release is removed or after use [*see Storage and Handling (16.2)*].

Complete patient information, including dosage, directions for proper administration and precautions can be found inside each epinephrine injection, 0.3 mg (Auto-Injector) and epinephrine injection, 0.15 mg (Auto-Injector) carton.

Manufactured For:
Teva Pharmaceuticals USA, Inc.
North Wales, PA 19454

Iss. 6/2018

PATIENT INFORMATION and INSTRUCTIONS FOR USE

Epinephrine Injection USP, 0.3 mg (Auto-Injector)
Epinephrine Injection USP, 0.3 mg = one dose of 0.3 mg epinephrine USP, 0.3 mg/0.3 mL

Epinephrine Injection USP, 0.15 mg (Auto-Injector)
Epinephrine Injection USP, 0.15 mg = one dose of 0.15 mg epinephrine USP, 0.15 mg/0.3 mL

For allergic emergencies (anaphylaxis)

Patient Information

Read this Patient Information Leaflet carefully before using the epinephrine injection, 0.3 mg (auto-injector) or epinephrine injection, 0.15 mg (auto-injector) and each time you get a refill. There may be new information. You, your parent, caregiver, or others who may be in a position to administer epinephrine injection, 0.3 mg (auto-injector) or epinephrine injection, 0.15 mg (auto-injector), should know how to use it before you have an allergic emergency.

This information does not take the place of talking with your healthcare provider about your medical condition or your treatment.

What is the most important information I should know about epinephrine injection, 0.3 mg and epinephrine injection, 0.15 mg?

1. Epinephrine injection, 0.3 mg and epinephrine injection, 0.15 mg contain a medicine used to treat allergic emergencies (anaphylaxis). Anaphylaxis can be life threatening, can happen within minutes, and can be caused by stinging and biting insects, allergy injections, foods, medicines, exercise, or unknown causes.

Symptoms of anaphylaxis may include:

- trouble breathing
- wheezing
- hoarseness (changes in the way your voice sounds)
- hives (raised reddened rash that may itch)
- severe itching
- swelling of your face, lips, mouth, or tongue
- skin rash, redness, or swelling
- fast heartbeat
- weak pulse
- feeling very anxious
- confusion
- stomach pain
- losing control of urine or bowel movements (incontinence)
- diarrhea or stomach cramps
- dizziness, fainting, or “passing out” (unconsciousness)

2. **Always carry your epinephrine injection, 0.3 mg or epinephrine injection, 0.15 mg with you because you may not know when anaphylaxis may happen.**

   Talk to your healthcare provider if you need additional units to keep at work, school, or other locations. Tell your family members, caregivers, and others where you keep your epinephrine injection, 0.3 mg or epinephrine injection, 0.15 mg and how to use it before you need it. You may be unable to speak in an allergic emergency.

3. **When you have an allergic emergency (anaphylaxis)**

   - **Use epinephrine injection, 0.3 mg or epinephrine injection, 0.15 mg right away.**
   - **Get emergency medical help right away.** You may need further medical attention. You may need to use a second epinephrine injection, 0.3 mg or epinephrine injection, 0.15 mg if symptoms continue or recur. Only a healthcare provider should give additional doses of epinephrine if you need more than 2 injections for a single anaphylaxis episode.

What are epinephrine injection, 0.3 mg and epinephrine injection, 0.15 mg?

- Epinephrine injection, 0.3 mg and epinephrine injection, 0.15 mg are disposable, prefilled automatic injection devices (auto-injectors) used to treat life-threatening, allergic emergencies including anaphylaxis in people who are at risk for or have a history of serious allergic emergencies. Each device contains a single dose of epinephrine.
- Epinephrine injection, 0.3 mg and epinephrine injection, 0.15 mg are for immediate self (or caregiver) administration and do not take the place of emergency medical care. You should get emergency help right away after using epinephrine injection, 0.3 mg and epinephrine injection, 0.15 mg.
- Epinephrine injection, 0.3 mg and epinephrine injection, 0.15 mg are for people who have been prescribed this medicine by their healthcare provider.
- The Epinephrine Injection, 0.3 mg (Auto-Injector) is for patients who weigh 66 pounds or more (30 kilograms or more).
- The Epinephrine Injection, 0.15 mg (Auto-Injector) is for patients who weigh about 33 to 66 pounds (15 to 30 kilograms).
- It is not known if epinephrine injection, 0.3 mg and epinephrine injection, 0.15 mg are safe and effective in children who weigh less than 33 pounds (15 kilograms).

What should I tell my healthcare provider before using the epinephrine injection, 0.3 mg or epinephrine injection, 0.15 mg?

Before you use epinephrine injection, 0.3 mg or epinephrine injection, 0.15 mg, tell your healthcare provider about all your medical conditions, but especially if you:

- have heart problems or high blood pressure
- have diabetes
- have thyroid problems
- have asthma
- have a history of depression
- have Parkinson’s disease
- have any other medical conditions
- are pregnant or plan to become pregnant. It is not known if epinephrine will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if epinephrine passes into your breast milk.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Tell your healthcare provider of all known allergies.

Especially tell your healthcare provider if you take certain asthma medicines.

Epinephrine injection, 0.3 mg or epinephrine injection, 0.15 mg and other medicines may affect each other, causing side effects. Epinephrine injection, 0.3 mg or epinephrine injection, 0.15 mg may affect the way other medicines work, and other medicines may affect how epinephrine injection, 0.3 mg or epinephrine injection, 0.15 mg work.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

Use your epinephrine injection, 0.3 mg or epinephrine injection, 0.15 mg for treatment of anaphylaxis as prescribed by your healthcare provider, regardless of your medical conditions or the medicines you take.

How should I use epinephrine injection, 0.3 mg and epinephrine injection, 0.15 mg?

- Each epinephrine injection, 0.3 mg (auto-injector) or epinephrine injection, 0.15 mg (auto-injector) contains only 1 dose of medicine.
- Epinephrine injection, 0.3 mg or epinephrine injection, 0.15 mg should be injected into the middle of your outer thigh (upper leg). It can be injected through your clothing if needed.
- Read the Instructions for Use at the end of this Patient Information Leaflet about the right way to use epinephrine injection, 0.3 mg and epinephrine injection, 0.15 mg.

- Your healthcare provider will show you how to safely use the epinephrine injection, 0.3 mg (auto-injector) or epinephrine injection, 0.15 mg (auto-injector).
- Use your epinephrine injection, 0.3 mg or epinephrine injection, 0.15 mg exactly as your healthcare provider tells you to use it. You may need to use a second epinephrine injection, 0.3 mg or epinephrine injection, 0.15 mg if symptoms continue or recur. Only a healthcare provider should give additional doses of epinephrine if you need more than 2 injections for a single anaphylaxis episode.
- **Caution: Never put your thumb, fingers, or hand over the orange tip. Never press or push the orange tip with your thumb, fingers, or hand.** The needle comes out of the orange tip. Accidental injection into finger, hands or feet may cause a loss of blood flow to these areas. **If this happens, go immediately to the nearest emergency room.** Tell the healthcare provider where on your body you received the accidental injection.
- Your epinephrine injection, 0.3 mg (auto-injector) and epinephrine injection, 0.15 mg (auto-injector) may come packaged with an Epinephrine Injection Trainer and separate Epinephrine Injection Trainer Instructions for Use. **The Epinephrine Injection Trainer has a grey color. The grey Epinephrine Injection Trainer contains no medicine and no needle.** Periodically practice with your Epinephrine Injection Trainer before an allergic emergency happens to make sure you are able to safely use the real epinephrine injection, 0.3 mg (auto-injector) and epinephrine injection, 0.15 mg (auto-injector) in an emergency. Always carry your real epinephrine injection, 0.3 mg (auto-injector) or epinephrine injection 0.15 mg (auto-injector) with you in case of an allergic emergency. Additional training resources are available at *www.TevaEpinephrine.com*.
- Do not drop the auto-injector. If the auto-injector is dropped, check for damage and leakage. Dispose of the auto-injector and replace if damage or leakage is noticed or suspected.

What are the possible side effects of epinephrine injection, 0.3 mg and epinephrine injection, 0.15 mg?

Epinephrine injection, 0.3 mg and epinephrine injection, 0.15 mg may cause serious side effects.

- **The epinephrine injection, 0.3 mg or epinephrine injection, 0.15 mg should only be injected into the middle of your outer thigh (upper leg). Do not** inject the epinephrine injection, 0.3 mg or epinephrine injection, 0.15 mg into your:
  - veins
  - buttocks
  - fingers, toes, hands, or feet

  If you accidentally inject epinephrine injection, 0.3 mg or epinephrine injection, 0.15 mg into any other part of your body, go to the nearest emergency room right away. Tell the healthcare provider where on your body you received the accidental injection.
- Rarely, patients who have used epinephrine injection, 0.3 mg or epinephrine injection, 0.15 mg may develop infections at the injection site within a few days of an injection. Some of these infections can be serious. Call your healthcare provider right away if you have any of the following at an injection site:
  - redness that does not go away
  - swelling
  - tenderness
  - the area feels warm to the touch
- Cuts on the skin, bent needles, and needles that remain in the skin after the injection, have happened in young children who do not cooperate and kick or move during an injection. If you inject a young child with epinephrine injection, 0.3 mg or epinephrine injection, 0.15 mg, hold their leg firmly in place before and during the injection to prevent injuries. Ask your healthcare provider to show you how to properly hold the leg of a young child during injection.
- **If you have certain medical conditions, or take certain medicines, your condition may get worse or you may have longer lasting side effects when you use your epinephrine injection, 0.3 mg or epinephrine injection, 0.15 mg.** Talk to your healthcare provider about all your medical conditions.

Common side effects of epinephrine injection, 0.3 mg and epinephrine injection, 0.15 mg include:

- fast, irregular or “pounding” heartbeat
- sweating
- headache
- weakness
- shakiness
- paleness
- feelings of over excitement, nervousness or anxiety
- dizziness
- nausea or vomiting
- breathing problems

These side effects may go away with rest. **Tell your healthcare provider if you have any side effect that bothers you or that does not go away.**

These are not all the possible side effects of the epinephrine injection, 0.3 mg or epinephrine injection, 0.15 mg. For more information, ask your healthcare provider or pharmacist.

Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store epinephrine injection, 0.3 mg and epinephrine injection, 0.15 mg?

- Store epinephrine injection, 0.3 mg and epinephrine injection, 0.15 mg at room temperature between 68° to 77°F (20° to 25°C).
- Protect from light.
- **Do not** expose to extreme cold or heat. For example, **do not** store in your vehicle’s glove box and **do not** store in the refrigerator or freezer.
- Examine the contents in the clear window of your auto-injector periodically. The solution should be clear. If the solution is discolored (pinkish or darker than slightly yellow) or if it contains a precipitate, replace the unit.
- Always protect your epinephrine injection, 0.3 mg (auto-injector) and epinephrine injection, 0.15 mg (auto-injector) from damage and water.
- The blue safety release helps to prevent accidental injection. Keep the blue safety release on until you need to use epinephrine injection, 0.3 mg or epinephrine injection, 0.15 mg.
- Your epinephrine injection, 0.3 mg or epinephrine injection, 0.15 mg has an expiration date. Replace it before the expiration date.

Keep epinephrine injection, 0.3 mg and epinephrine injection, 0.15 mg and all medicines out of the reach of children.

General information about the safe and effective use of epinephrine injection, 0.3 mg and epinephrine injection, 0.15 mg

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information Leaflet. Do not use the epinephrine injection, 0.3 mg or epinephrine injection, 0.15 mg for a condition for which it was not prescribed. Do not give your epinephrine injection, 0.3 mg or epinephrine injection, 0.15 mg to other people.

This Patient Information Leaflet summarizes the most important information about epinephrine injection, 0.3 mg and epinephrine injection, 0.15 mg. If you would like more information, talk to your healthcare provider. You can ask your pharmacist or healthcare provider for information about epinephrine injection, 0.3 mg and epinephrine injection, 0.15 mg that is written for health professionals.

For more information and video instructions on the use of epinephrine injection, 0.3 mg and epinephrine injection, 0.15 mg go to *www.TevaEpinephrine.com* or call 1-888-838-2872.

What are the ingredients in epinephrine injection, 0.3 mg and epinephrine injection, 0.15 mg?

Active Ingredients: Epinephrine

Inactive Ingredients: sodium chloride, sodium metabisulfite, sodium tartrate (dihydrate), hydrochloric acid, and water.

Important Information

- **The Epinephrine Injection, 0.3 mg (Auto-Injector) has a yellow colored label.**
- **The Epinephrine Injection, 0.15 mg (Auto-Injector) has a green colored label.**
- **The Epinephrine Injection Trainer has a grey color and contains no medicine and no needle.**
- **Your auto-injector is designed to work through clothing.**
- **The blue safety release on the Epinephrine Injection, 0.3 mg (Auto-Injector) and Epinephrine Injection, 0.15 mg (Auto-Injector) helps to prevent accidental injection of the device. Do not remove the blue safety release until you are ready to use it.**
- **Only inject into the middle of the outer thigh (upper leg). Never inject into any other part of the body.**
- **Never put your thumb, fingers, or your hand over the orange tip. The needle comes out of the orange tip.**
- **If an accidental injection happens, get medical help right away.**

Instructions for Use

Epinephrine Injection USP, 0.3 mg (Auto-Injector)
Epinephrine Injection USP, 0.3 mg = one dose of 0.3 mg epinephrine USP, 0.3 mg/0.3 mL

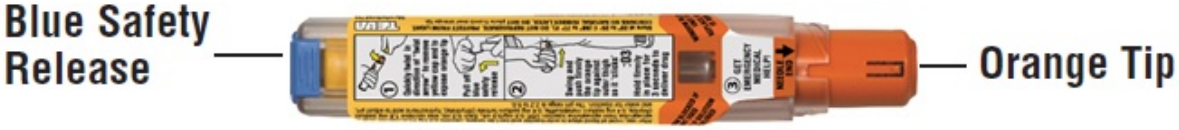
Epinephrine Injection USP, 0.15 mg (Auto-Injector)
Epinephrine Injection USP, 0.15 mg = one dose of 0.15 mg epinephrine USP, 0.15 mg/0.3 mL

For allergic emergencies (anaphylaxis)

Read these Instructions for Use carefully before you use epinephrine injection, 0.3 mg or epinephrine injection, 0.15 mg. Before you need to use your epinephrine injection, 0.3 mg or epinephrine injection, 0.15 mg, make sure your healthcare provider shows you the right way to use it. Parents, caregivers, and others who may be in a position to administer epinephrine injection, 0.3 mg (auto-injector) or epinephrine injection, 0.15 mg (auto-injector) should also understand how to use it as well. If you have any questions, ask your healthcare provider.

Your Epinephrine Injection, 0.3 mg (Auto-Injector) and Epinephrine Injection, 0.15 mg (Auto-Injector)

- A CARRYING TUBE IS NOT PROVIDED AS SEEN WITH OTHER PRODUCTS.
- **Epinephrine Injection, 0.3 mg Auto-Injector (yellow label) with Yellow Cap**



- **Epinephrine Injection, 0.3 mg Auto-Injector (yellow label) with Yellow Cap Removed**
- **Epinephrine Injection, 0.15 mg Auto-Injector (green label) with Green Cap**

- **Epinephrine Injection, 0.15 mg Auto-Injector (green label) with Green Cap Removed**

A dose of epinephrine injection, 0.3 mg or epinephrine injection, 0.15 mg requires 3 simple steps: Prepare, Administer and Get emergency medical help

Step 1. Prepare epinephrine injection, 0.3 mg or epinephrine injection, 0.15 mg for injection

Quickly twist the yellow cap off the epinephrine injection, 0.3 mg auto-injector or the green cap off the epinephrine injection, 0.15 mg auto-injector in the direction of the "twist arrow" to remove it.

Grasp the auto-injector in your fist with the orange tip (needle end) pointing downward. With your other hand, **pull off the blue safety release.**

Note:

- The needle comes out of the orange tip.
- To avoid an accidental injection, never put your thumb, fingers or hand over the orange tip. If an accidental injection happens, get medical help right away.

Step 2. Administer epinephrine injection, 0.3 mg or epinephrine injection, 0.15 mg

If you are administering epinephrine injection, 0.3 mg or epinephrine injection, 0.15 mg to a young child, hold the leg firmly in place while administering an injection.

Place the orange tip against the middle of the outer thigh (upper leg) at a right angle (perpendicular) to the thigh.
Swing and push the auto-injector firmly until it 'clicks'.
The click signals that the injection has started.

Hold firmly in place for 3 seconds (count slowly 1,2,3).
The injection is now complete.

Remove the auto-injector from the thigh. The orange tip will extend to cover the needle. If the needle is still visible, do not attempt to reuse it.

Massage the injection area for 10 seconds.

Step 3. Get emergency medical help now.

You may need further medical attention. **You may need to use a second epinephrine injection, 0.3 mg auto-injector or epinephrine injection, 0.15 mg auto-injector if symptoms continue or recur.**

- Take your used auto-injector with you when you go to see a healthcare provider.
- Tell the healthcare provider that you have received an injection of epinephrine. Show the healthcare provider where you received the injection.
- Give your used epinephrine injection, 0.3 mg auto-injector or epinephrine injection, 0.15 mg auto-injector to the healthcare provider for inspection and proper disposal.
- Ask for a refill, if needed.

Note:

- A carrying tube is not provided as seen with other products.
- Epinephrine injection, 0.3 mg and epinephrine injection, 0.15 mg are single-use injectable devices that deliver a fixed dose of epinephrine. The auto-injector cannot be reused. Do not attempt to reuse epinephrine injection after the device has been activated. It is normal for most of the medicine to remain in the auto-injector after the dose is injected. The correct dose has been administered if the orange needle tip is extended and the window is blocked.
- Your epinephrine injection, 0.3 mg auto-injector and epinephrine injection, 0.15 mg auto-injector may come packaged with an Epinephrine Injection Trainer and separate Epinephrine Injection Trainer Instructions for Use. The Epinephrine Injection Trainer has a grey color. The grey Epinephrine Injection Trainer contains no medicine and no

needle. Practice with your Epinephrine Injection Trainer, but always carry your real epinephrine injection, 0.3 mg auto-injector or epinephrine injection, 0.15 mg auto-injector in case of an allergic emergency.

- If you are administering epinephrine injection, 0.3 mg or epinephrine injection, 0.15 mg to a young child, ask your healthcare provider to show you how to properly hold the leg in place while administering a dose.
- Do not try to take the epinephrine injection, 0.3 mg auto-injector or epinephrine injection, 0.15 mg auto-injector apart.

This Patient Information and Instructions for Use has been approved by the U.S. Food and Drug Administration.

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

Manufactured For:
Teva Pharmaceuticals USA, Inc.
North Wales, PA 19454

Iss. 6/2018

Epinephrine Injection USP, 0.3 mg (Auto-Injector)

Epinephrine Injection USP, 0.3 mg = one dose of 0.3 mg epinephrine USP, 0.3 mg/0.3 mL

Epinephrine Injection USP, 0.15 mg (Auto-Injector)

Epinephrine Injection USP, 0.15 mg = one dose of 0.15 mg epinephrine USP, 0.15 mg/0.3 mL

TevaEpinephrine.com

Register your Epinephrine Injection 0.3 mg Auto-Injector or Epinephrine Injection 0.15 mg Auto-Injector at **www.TevaEpinephrine.com** and find out more about:

- Free Epinephrine Injection Auto-Injector **Refill Reminder Program**. It is important to keep your auto-injector up-to-date.

Register up to 6 Epinephrine Injection 0.3 mg Auto-Injectors or Epinephrine Injection 0.15 mg Auto-Injectors and receive automatic **Refill Reminder Alerts.**

- Receive periodic information related to allergies and allergens.
- Instructional Video

For more information about Epinephrine Injection 0.3 mg Auto-Injector or Epinephrine Injection 0.15 mg Auto-Injector and proper use of the products, call Teva at 1-888-838-2872 or visit *www.TevaEpinephrine.com*.

Epinephrine Injection Trainer Instructions for Use

In an emergency: Do not use the grey Trainer. Use your real yellow Epinephrine Injection 0.3 mg Auto-Injector or green Epinephrine Injection 0.15 mg Auto-Injector.

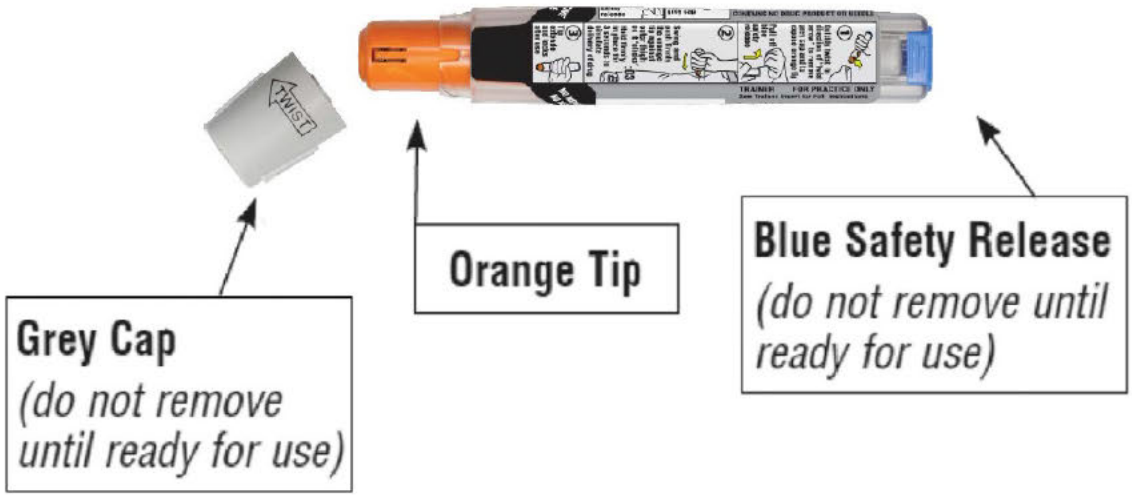
Important Information

- **The Trainer label has a grey color.**
- **The Trainer contains no medicine and no needle.**
- Periodically practice with the grey colored Trainer before an allergic emergency (anaphylaxis) happens to make sure you are able to safely use the real yellow epinephrine injection 0.3 mg auto-injector or green epinephrine injection 0.15 mg auto-injector in case of an emergency.
- Always carry your real yellow epinephrine injection 0.3 mg auto-injector or green epinephrine injection 0.15 mg auto-injector in case of an allergic emergency.

The Epinephrine Injection Trainer

Familiarize yourself with this grey Trainer. Practice until you are comfortable using it.

Your grey colored Trainer:



- Never put your thumb, other fingers, or hand over the Orange Tip (below grey safety cap).
- The Orange Tip is where the needle comes out of your epinephrine injection 0.3 mg auto-injector or epinephrine injection 0.15 mg auto-injector.

Practice Instructions

1 **Prepare** the Trainer for Simulated Injection

- **Grasp the grey Trainer in your fist with the orange tip pointing downward** and twist off Grey Cap in the direction of "twist arrow".
- With your other hand, **pull off blue safety release**.
- Removing the blue safety release unlocks the Trainer.

2 **Administer** the Trainer Simulation

- **If practicing with a young child, hold the leg firmly in place while using the Epinephrine Trainer.**

Ask your healthcare provider to show you how to properly hold the leg to practice so that you will be prepared before an allergic emergency happens.

- Place the orange tip against the middle of the outer thigh (upper leg) at a right angle (perpendicular) to the thigh.
- **Swing and push the trainer firmly** until it 'clicks'. The click signals that the injection has started.
- **Hold firmly in place for 3 seconds (count slowly 1,2,3).**
- **Remove the Trainer from the thigh** and massage the injection area for 10 seconds. The orange tip automatically extends out after use.

Note:

- In an actual emergency, you would need to seek medical help right away
- The actual auto-injector is made to work through clothing
- Do not inject into any other part of the body

3 **To reset** the Trainer

- Put the blue safety release back on the Trainer
- Replace Grey Cap

NOTE: With the real yellow Epinephrine Injection 0.3 mg Auto-Injector or green Epinephrine Injection 0.15 mg Auto-Injector, the orange tip covers the needle after self-injection to help protect you from accidentally sticking yourself or others.

Practice Session Information

In case of an allergic emergency, use the real yellow Epinephrine Injection 0.3 mg Auto-Injector or green Epinephrine Injection 0.15 mg Auto-Injector and not the grey Trainer.

Follow instructions above. Repeat as often as needed until you are able to self-inject quickly and correctly.

Reread:

- These Trainer Instructions for Use
- The "Patient Information" that comes with your Epinephrine Injection 0.3 mg Auto-Injector or Epinephrine Injection 0.15 mg Auto-Injector

Train others who could help you in an emergency:

- Your parents, caregivers, and others who may be in a position to administer epinephrine injection 0.3 mg or epinephrine injection 0.15 mg should know how to help you during an allergic emergency (anaphylaxis). Before an emergency occurs, have them:
  - Practice activating the Trainer
  - Read these Trainer Instructions and the "Patient Information"

For more information about the Epinephrine Injection 0.3 mg Auto-Injector and Epinephrine Injection 0.15 mg Auto-Injector and the proper use of the products, go to *www.TevaEpinephrine.com*.

Caution:

Important differences between the Trainer and your real yellow Epinephrine Injection 0.3 mg (Auto-Injector) or green Epinephrine Injection 0.15 mg (Auto-Injector)

			
	TRAINER (Grey)	**Epinephrine Injection 0.3 mg (Yellow)**	**Epinephrine Injection 0.15 mg (Green)**
Contains medication?	**NO**	**YES**	**YES**
Has needle?	**NO**	**YES**	**YES**
Comes in Carrier Tube?	**NO**	**NO**	**NO**
Color of label	**Grey**	**Yellow**	**Green**
Has expiration date?	**YES**	**YES**	**YES**
Can be reused?	**YES**	**NO (use only once)**	**NO (use only once)**
Okay to remove and replace cap and/or safety release?	**YES**	**NO (remove just once before use)**	**NO (remove just once before use)**
Pressure needed to hold against thigh?	**Moderate**	**Strong**	**Strong**

This Trainer Instructions for Use has been approved by the U.S. Food and Drug Administration.

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

Manufactured For:
Teva Pharmaceuticals USA, Inc.
North Wales, PA 19454

Iss. 6/2018

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 090589

LABELING REVIEW(S)

LABELING REVIEW

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

Date of This Review	6/25/2018
ANDA Number(s)	090589
Review Number	8
Applicant Name	Teva Pharmaceuticals USA, Inc.
Established Name & Strength(s)	Epinephrine Injection USP, 0.3 mg (Auto-Injector) and Epinephrine Injection USP, 0.15 mg (Auto-Injector)
Proposed Proprietary Name	NA
Submission Received Date	6/22/2018
Primary Labeling Reviewer	Eunjung Esther Chuh
Secondary Labeling Reviewer	Marshall Florence

Review Conclusion

☒ ACCEPTABLE – No Comments.

☐ ACCEPTABLE – Include Post Approval Comments

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

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

†Theme - Choose an item.

Justification for Major Deficiency - Choose an item.

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

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

1. LABELING COMMENTS

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT

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

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE

The Division of Labeling has no further questions/comments at this time based on your labeling submission dated June 22, 2018.

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

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

1.3 POST APPROVAL REVISIONS

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

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

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

REVIEW HISTORY pertinent to this Labeling Review

12/21/2007	Original ANDA 090589 submitted to FDA
11/21/2008	Original ANDA 090589 received to FDA for filing
6/4/2009	**Labeling Review #1** completed by A.Payne – Inadequate
10/12/2010	Labeling Amendment submitted by the applicant
2/2/2011	**Labeling Review #2** completed by A. Payne – Inadequate
8/1/2014	Labeling Amendment submitted by the applicant.
9/26/2014	**Labeling Review #3** by K. Rains – Inadequate *(comments sent under Review #4)*
12/30/2014	Quality Minor Amendment and *Unsolicited* Amendment to provide for change in the manufacturing and testing site, formulation and device. Includes labeling.
5/4/2015	**Labeling Review #4** completed by E.Chuh – Inadequate *(Deficiency comments include comments from Review #3)*
11/18/2015	Labeling Easily Correctable Deficiency (ECD) Amendment submitted by applicant.
12/10/2015	**Labeling Review #5** completed by E.Chuh - Inadequate
9/26/2016	**Addendum to Review #5** (inadequate) completed to address updated RLD labeling approved on 5/18/2016 on the container, carton, and insert labeling. *(comments were not yet sent to the applicant upon completion of the review as consult to DMEPA was pending))*
10/13/2016	**DMEPA Consult requested** through DARRTS (based on labeling review #5 and its addendum review.
10/28/2016	Complete Response Amendment (includes labeling).
12/9/2016	**Labeling Review #6** completed by E-Chuh - Inadequate *(comments were not yet sent the applicant upon completion of the review, however incorporated to the consult request to DMEPA for evaluation)*
3/8/2017	Applicant submitted Request for Proprietary Name Review [redacted] (b) (4)
3/24/2017	Proprietary Name Review found unacceptable per DMEPA (review and letter in DARRTS)
6/2/2017	Labeling Amendment (RLD labeling update approved on 4/18/17)
6/11/2018	DMEPA Consult Review Memo in DARRTS (in response to consult requested on 10/13/2016, with additional inquiry requested 11/15/2016)
6/14/2018	**Labeling Review #7** completed– Inadequate [comment sent out to applicant on 6/21/18; includes comments from review #5 (addendum) and #6]
6/22/2018	Labeling Amendment submitted by the applicant - ***subject of this review***

PREVIOUS DEFICIENCY AND FIRM'S RESPONSE

The below is applicant's response based on our comments from the labeling review C7 based on the submissions dated 10/28/2016, 03/8/2017, and 6/2/2017:

Teva Pharmaceuticals USA Inc., submits herewith responses to the above-referenced pending Abbreviated New Drug Application corresponding to a June 21, 2018 Discipline Review letter. The original FDA comments are presented below in bold, followed by Teva's responses.

1. GENERAL COMMENTS

a. Please ensure that your final container label, carton labeling and SPL (STRUCTURED PRODUCT LABELING) appropriately reflect your proposed product without the proprietary name. We note that these label/labeling with proprietary name are currently found in your ANDA as final label/labeling.

Teva Response:
Teva acknowledges the Agency's comment and ensures that the final container labels, carton labeling and SPL appropriately reflect only the proposed product name without a proprietary name.

b. On the container label and carton labeling, the illustration for step 2 does not clearly depict the injection site (e.g., the entire leg, including the foot). Revise the illustration to further clarify the proper injection site.

Teva Response:
Teva acknowledges the Agency's comment and has revised the illustration for Step 2 accordingly.

2. CONTAINER LABEL

a. For the 0.15 mg strength:
In the section that starts with the statement "After use most of liquid stays in auto-injector and can't be reused...", second sentence, remove the ratio expression (1:2000) and revise the strength statement so that it reads "Delivers 0.15 mg intramuscular dose of epinephrine from epinephrine injection USP, 0.15 mg/0.3 mL.".

Teva Response:
Teva acknowledges the Agency's comment and has revised the noted statement to read: "Delivers 0.15 mg intramuscular dose of epinephrine from epinephrine injection USP, 0.15 mg/0.3 mL.".

b. For the 0.3 mg strength:
In the section that starts with the statement "After use most of liquid stays in auto-injector and can't be reused.", second sentence, remove the ratio expression (1:1000) and revise the strength statement so that it reads "Delivers 0.3 mg intramuscular dose of epinephrine from epinephrine injection USP, 0.3 mg/ 0.3 mL.".

Teva Response:
Teva acknowledges the Agency's comment and has revised the noted statement to read: "Delivers 0.3 mg intramuscular dose of epinephrine from epinephrine injection USP, 0.3 mg/0.3 mL.".

3. CARTON LABELING
a. On the principal display panel (PDP), remove "xx mg each" following "For Allergic Emergencies (Anaphylaxis)". Refer to RLD labeling.

Teva Response:
Teva acknowledges the Agency's comment and has removed the statement "xx mg each" from both, the 0.3 mg and 0.15 mg, principal display panels.

b. On the PDP, remove "For intramuscular use" and "For one time use." statements to be same as the RLD labeling.

Teva Response:
Teva acknowledges the Agency's comment and has removed the statements "For intramuscular use" and "For one time use." from both, the 0.3 mg and 0.15 mg, principal display panels.

c. On the side panel, remove the ratio expression of strength (1:2000 and 1:1000) and revise the strength statement to "xx mg/xx mL" format. Refer to Container Label comments.

Teva Response:
Teva acknowledges the Agency's comment and has removed the ratio expression of strength from both, the 0.3 mg and 0.15 mg, container labels and revised the strength statement to the "xx mg/xx mL format.

4. PATIENT INFORMATION and INSTRUCTIONS FOR USE
In the title section under PATIENT INFORMATION and under INSTRUCTIONS FOR USE, remove the parenthesis to read "one dose of 0.3 mg epinephrine USP, 0.3 mg/0.3 mL" for the 0.3 mg auto-injector and "one dose of 0.15 mg epinephrine USP, 0.15 mg /0.3 mL" for the 0.15 mg auto-injector. Make the same revision in the applicable section at the end of the INSTRUCTIONS FOR USE.

Teva Response:
Teva acknowledges the Agency's comment and has removed the parenthesis from the noted sections of the Patient Information and Instructions for Use labeling text. In addition, please note the PPI/IFU and the trainer IFU were also revised to include the updated images of the devices due to the FDA requested changes to the device labels. The revised trainer IFU labeling is also being included in this submission.

Reviewer Comments:

Applicant's response to the comments is acceptable.

2.1 CONTAINER AND CARTON LABELS

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

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

Reviewer Comments:

2.2 ADDITIONAL BACKGROUND INFORMATION PERTINENT TO THE REVIEW

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

Reviewer Comments:

There are three entries filed in SharePoint regarding Epinephrine.

- Epinephrine Ratio Strength Expression and USP Chapter 7

Title	Epinephrine Ratio Strength Expression and USP Monograph General Chapter 7
Date:	8/24/2016
Brief Description	Presentation given at the Division meeting regarding a Working Group formed to implement compliance to USP General Chapter 7 Labeling requirement that no single-entity injectable products may contain ratio expressions in the labeling. Epiniphrine is the primary focus but includes Neostigmine and Isoproterenol Injections too.

- Memo allowing removal of ration expression of strength

Title	Memo to file allowing removal of ratio expression of strength from single entity ...
Date:	8/24/2017
Is this a Review?	☐
What Type of File?	E-mails
Attachments	How to handle labeling for inj. products removing ratio expression of strength.msg
Hyperlink to Review	No hyperlink inserted
Active Ingredient	Epinephrine
Dosage Forms:	Injection
Manufacturer:	
Brief Description	Memo to file allowing ANDAs to differ from RLD with the removal of ratio expression of strength from epinephrine, neostigmine, and isoproterenol inj.

-

3. LABELING REVIEW INFORMATION AND REVIEWER ASSESSMENT

3.1 REGULATORY INFORMATION

Are there any pending issues in DLR's SharePoint Drug Facts? NO – there are entries in Sharepoint, however the issues are resolved for this product. SP entries are added in section 2.2 for reference. If Yes, please explain in section 2.2 Additional Background Information Pertinent to the Review
Is the drug product listed in the Policy Alert Tracker on OGD's SharePoint? YES If Yes, please explain. Following is in the Policy Alert Tracker:

Policy Alert Basis	Docket #	Brand Name (or Drug Class)	Generic Name / Dosage Form / Strengths	Action Requested or Issue Description
CP	FDA-2017-P-3352	Multiple: epinephrine injection products	Multiple: epinephrine auto-injectors containing sulfites	Requests FDA amend the sulfite warning requirement in 21 C.F.R. 201.22 for sulfite-containing epinephrine for injection for use in emergency situations, in order to remove misleading information and acknowledge the current availability of approved epinephrine products that do not contain sulfite.

RLD# (or reference standard)	Approval Actions (TA/AP)	Communications (CRL, CC/IR/DRL)	Notes	Date Filed (~)	OGD Policy Lead
Multiple	No Approval Actions (AP/TA) can be taken prior to contacting Policy Lead	No CRL can be issued prior to contacting Policy Lead; No CC/IR/DRL for Filing or Labeling		5/26/2017	Geeta Daniel

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

3.2 MODEL PRESCRIBING INFORMATION

Table 1: Review Model Labeling for Prescribing Information and Patient Labeling (Check the box used as the Model Labeling)

☒ **MOST RECENTLY APPROVED NDA MODEL LABELING**

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

NDA#/Supplement# (S-000 if original): NDA 019430/S-067

Supplement Approval Date: 4/28/2017

Proprietary Name: EpiPen and EpiPen Jr

Established Name: epinephrine injection USP

Description of Supplement:

This Changes Being Effected supplemental new drug application proposes to update the prescribing information to remove the ratio expressions (e.g. 1:1000) and replace them with an appropriate "strength/mL" statement and to add stress cardiomyopathy to the Adverse Reactions section of the labeling.

**** Note that only Prescribing Information is approved under this S-067. Updates to container labels, cartons, patient information and instructions for use and trainer instructions for use reflecting the change in the expression of product strength was submitted in subsequent Annual Report (Y-031, submitted 2/20/18) per the NDA applicant's commiment to the Agency stated on the cover page of S-067 submitted 4/13/17.**

☐ **MOST RECENTLY APPROVED ANDA MODEL LABELING**

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

Supplement Approval Date: Click here to enter text.

Proprietary Name: Click here to enter text.

Established Name: Click here to enter text.

Description of Supplement:

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

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

Reviewer Assessment:

Is the Prescribing Information same as the model labeling, except for differences allowed under 21 CFR 314.94(a)(8)? **YES**

Are the specific requirements for format met under 21 CFR 201.57(new) or 201.80(old)? **YES**

Does the Model Labeling have combined insert labeling for multiple dosage forms? **NO**

Reviewer Comments:

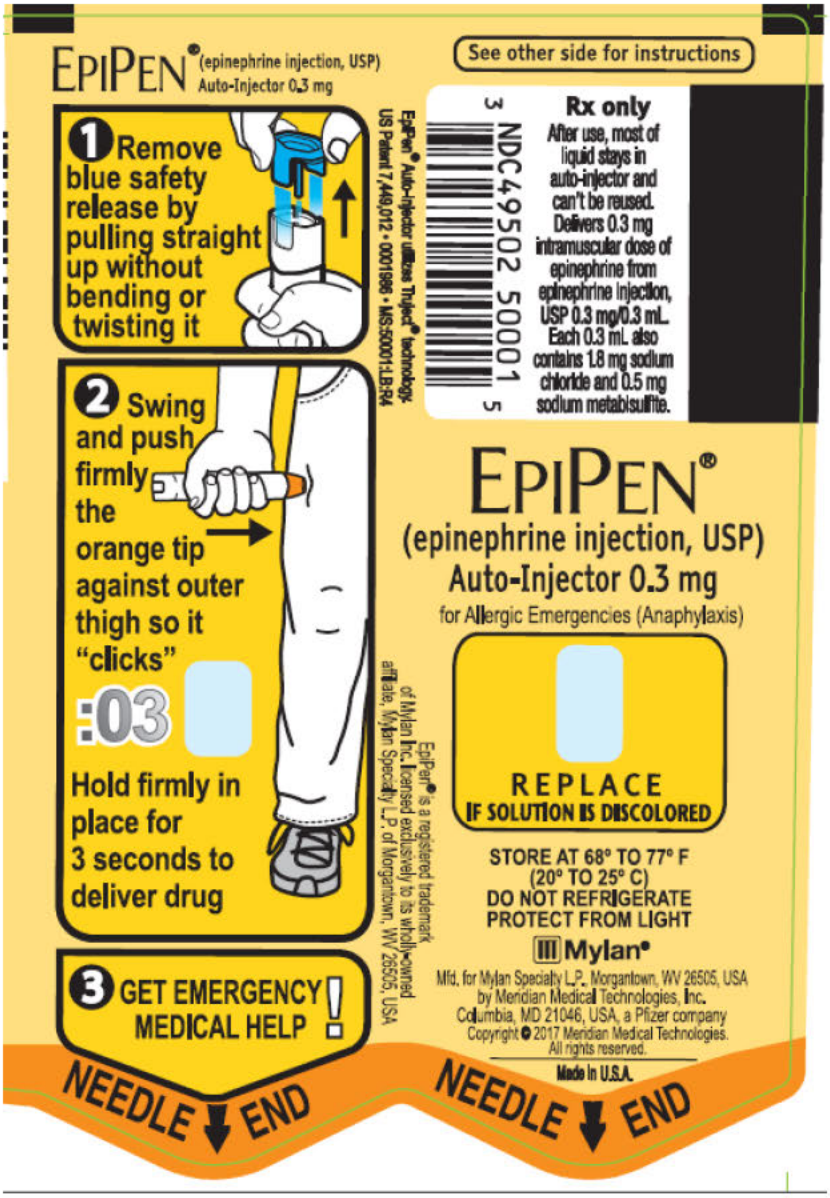
-PRESCRIBING INFORMATION – acceptable

-TRAINER INSTRUCTION FOR USE – acceptable.

-PATIENT INFORMATION and INSTRUCTIONS FOR USE – acceptable

3.3 MODEL CONTAINER LABELS

Model container/carton/blister labels [Source: NDA 19430/Y-031, submitted 2/20/2018]



EPIPEN 2-PAK®
(epinephrine injection, USP)
Auto-Injectors 0.3 mg

Never put thumb, fingers or hand over orange tip.
Do **not** remove blue safety release until ready to use.

EpiPen 2-Pak® contains 2 **EpiPen®** Auto-Injectors and 1 Trainer.
Each **EpiPen®** Auto-Injector delivers one 0.3 mg intramuscular dose of epinephrine from epinephrine injection, USP 0.3 mg/0.3 mL.
Discard unit after use. The Trainer contains no medicine and no needle.
Read enclosed patient package insert carefully before using.

NDC 49502-500-02

For Allergic Emergencies (Anaphylaxis)

Rx only

EPIPEN 2-PAK®
(epinephrine injection, USP)
Auto-Injectors 0.3 mg

Each carton contains: **Two yellow EpiPen®** Auto-Injectors **One grey Trainer**

Register your EpiPen® Auto-Injectors at **www.epipen.com** to receive free refill reminders

Mylan®

EPIPEN 2-PAK®
(epinephrine injection, USP)
Auto-Injectors 0.3 mg

Replace if discolored. Store at 68° to 77°F (20° to 25°C). Do not refrigerate. Protect from light.

Manufactured for Mylan Specialty L.P., Morgantown, WV 26505, USA by Meridian Medical Technologies, Inc., Columbia, MD 21046, USA, a Pfizer company
EpiPen® and EpiPen Jr® are registered trademarks of Mylan Inc. licensed exclusively to its wholly-owned affiliate, Mylan Specialty L.P. of Morgantown, WV 26505, USA

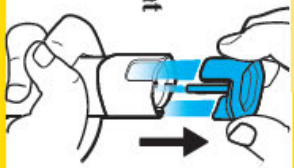
3 49502 50002 2

GTIN: 00349502500022

Open This End

See enclosed Patient Information Leaflet for complete instructions for use.

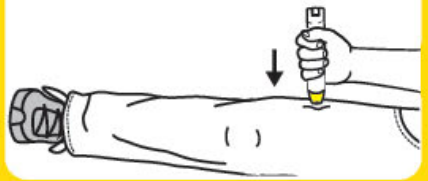
1 Remove the blue safety release by pulling straight up without bending or twisting it



2 Swing and push firmly the orange tip against outer thigh so it "clicks"

:03

Hold firmly in place for 3 seconds to deliver drug



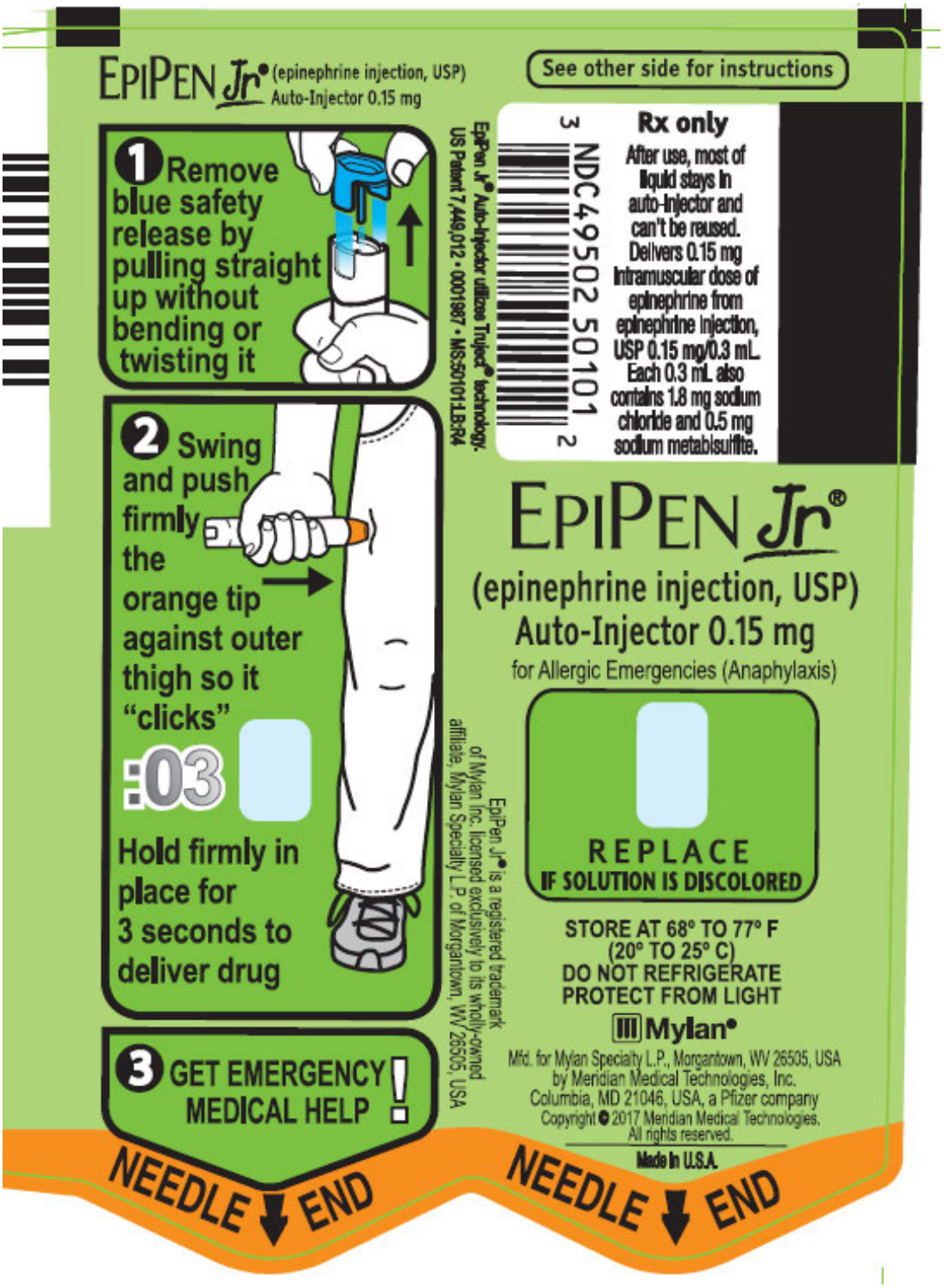
3 GET EMERGENCY MEDICAL HELP

Note: The needle comes out of the orange tip. Never put your thumb, fingers or hand over the orange tip.

EPIPEN 2-PAK®
(epinephrine injection, USP)
Auto-Injectors 0.3 mg

Mylan®

Scan here to learn more


EPIPEN Jr® (epinephrine injection, USP)
Auto-Injector 0.15 mg
See other side for instructions
1 Remove blue safety release by pulling straight up without bending or twisting it
2 Swing and push firmly the orange tip against outer thigh so it "clicks"
:03
Hold firmly in place for 3 seconds to deliver drug
3 GET EMERGENCY MEDICAL HELP
NEEDLE END
NEEDLE END
EpiPen Jr® Auto-Injector utilizes Trujec® technology.
US Patent 7,449,012 • 0001987 • MS:50101-LB-R4
3 NDC 49502 50101 2
Rx only
After use, most of liquid stays in auto-injector and can't be reused.
Delivers 0.15 mg intramuscular dose of epinephrine from epinephrine injection, USP 0.15 mg/0.3 mL.
Each 0.3 mL also contains 1.8 mg sodium chloride and 0.5 mg sodium metabisulfite.
EPIPEN Jr®
(epinephrine injection, USP)
Auto-Injector 0.15 mg
for Allergic Emergencies (Anaphylaxis)
REPLACE
IF SOLUTION IS DISCOLORED
STORE AT 68° TO 77° F
(20° TO 25° C)
DO NOT REFRIGERATE
PROTECT FROM LIGHT
Mylan®
Mfd. for Mylan Specialty L.P., Morgantown, WV 26505, USA
by Meridian Medical Technologies, Inc.
Columbia, MD 21046, USA, a Pfizer company
Copyright © 2017 Meridian Medical Technologies.
All rights reserved.
Made in U.S.A.
EpiPen Jr® is a registered trademark of Mylan Inc. licensed exclusively to its wholly-owned affiliate, Mylan Specialty L.P. of Morgantown, WV 26505, USA

EpiPen Jr 2-Pak®
(epinephrine injection, USP)
Auto-Injectors 0.15 mg

Never put thumb, fingers or hand over orange tip.
Do **not** remove blue safety release until ready to use.

EpiPen Jr 2-Pak® contains 2 **EpiPen Jr®** Auto-Injectors and 1 Trainer.
Each **EpiPen Jr®** Auto-Injector delivers one 0.15 mg intramuscular dose of epinephrine from epinephrine injection, USP 0.15 mg/0.3 mL.
Discard unit after use. The Trainer contains no medicine and no needle.
Read enclosed patient package insert carefully before using.

NDC 49502-501-02

Rx only

For Allergic Emergencies (Anaphylaxis)

EpiPen Jr 2-Pak®
(epinephrine injection, USP)
Auto-Injectors 0.15 mg

Each carton contains: **Two green EpiPen Jr®** Auto-Injectors **One grey Trainer**

Register your EpiPen Jr® Auto-Injectors at **www.epipen.com** to receive free refill reminders

Mylan®

EpiPen Jr 2-Pak®
(epinephrine injection, USP)
Auto-Injectors 0.15 mg

Mylan®

Replace if discolored. Store at 68° to 77°F (20° to 25°C). Do not refrigerate. Protect from light.

Manufactured for Mylan Specialty LP, Morgantown, WV 26505, USA by Meridian Medical Technologies, Inc., Columbia, MD 21046, USA, a Pfizer company

3 49502 50102 9

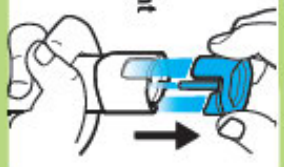
EpiPen Jr 2-Pak®
(epinephrine injection, USP)
Auto-Injectors 0.15 mg

GTIN: 00349502501029

Open This End

See enclosed Patient Information Leaflet for complete instructions for use.

1 Remove the blue safety release by pulling straight up without bending or twisting it



2 Swing and push firmly the orange tip against outer thigh so it "clicks"

Hold firmly in place for 3 seconds to deliver drug

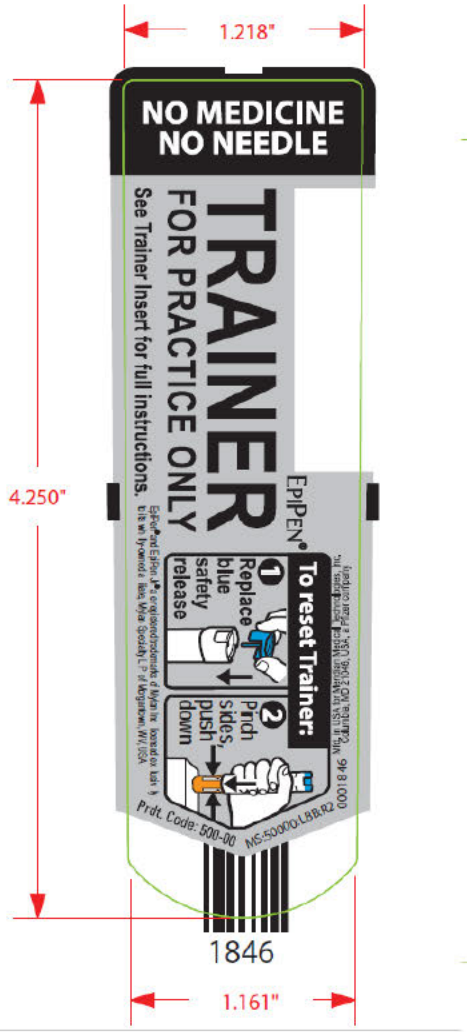
3 GET EMERGENCY MEDICAL HELP

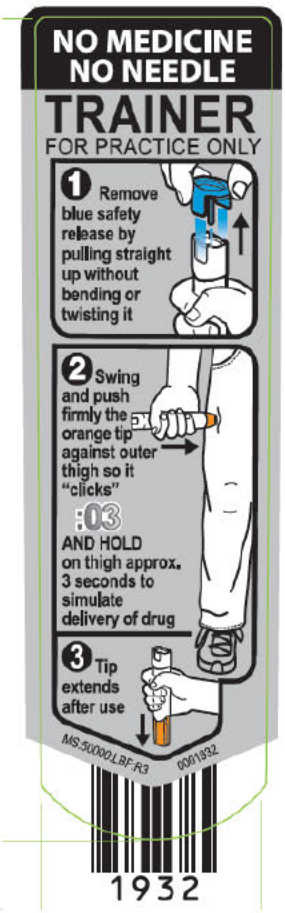
Note: The needle comes out of the orange tip. Never put your thumb, fingers or hand over the orange tip.

EpiPen Jr 2-Pak®
(epinephrine injection, USP)
Auto-Injectors 0.15 mg

Mylan®

Scan here to learn more





(Front remains the same)

Source: NDA 019430/S-058

(Back modified – step 2)

Source NDA 19430/S-061

3.4 UNITED STATES PHARMACOPEIA (USP)

The USP was searched on 6/25/2018.

	YES or NO	Date	Monograph Title (NA if no monograph)	Packaging and Storage/Labeling Statements (NA if no monograph)
Official Monograph	YES		**USP Monographs: Epinephrine Injection**	**Packaging and storage**—Preserve in single-dose or multiple-dose, light-resistant containers, preferably of Type I glass. **Labeling**—The label indicates that the Injection is not to be used if its color is pinkish or darker than slightly yellow or if it contains a precipitate.
Pending Monograph Proposed	YES	8/1/2018	Same as above	Same as above

Reviewer Assessment:

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

Reviewer Comments:

3.5 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 6/25/2018.

Table 3 provides Orange Book patents for the Model Labeling NDA 19430 and ANDA patent certifications. (For applications that have no patents, N/A is entered in the patent number column)

Table 3: Impact of Model Labeling Patents on ANDA Labeling

Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact (enter Carve-out or None)
7449012	9/11/2025			IV	12/30/2014	None
7794432	9/11/2025			IV	12/30/2014	None
8048035	9/11/2025			IV	12/30/2014	None
8870827	9/11/2025			IV	12/30/2014	None
9586010	09/11/2025			IV	6/23/2017	None

Reviewer Assessment:

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

Reviewer Comments:

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

Table 4: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling

Exclusivity Code	Exclusivity Expiration	Exclusivity Code Definition	Exclusivity Statement	Date of Exclusivity Submission	Labeling Impact (enter Carve-out or None)
NA					

Reviewer Assessment:

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

Reviewer Comments:

4. DESCRIPTION, HOW SUPPLIED AND MANUFACTURED BY STATEMENT

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

Reviewer Assessment:

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

Table 5: Comparison of DESCRIPTION Section or Inactive Ingredients Subsection (OTC)		
Previous Labeling Review	**Currently Proposed**	**Assessment**
Each 0.3 mL in the Epinephrine Injection USP, 0.3 mg (Auto-Injector) contains 0.3 mg epinephrine, USP, 1.8 mg sodium chloride, 0.4 mg sodium metabisulfite, 0.4 mg sodium tartrate (dihydrate), hydrochloric acid to adjust pH, and water for injection. The pH range is 2.2 to 5.0. Each 0.3 mL in the Epinephrine Injection USP, 0.15 mg (Auto-Injector) contains 0.15 mg epinephrine, USP, 1.8 mg sodium chloride, 0.4 mg sodium metabisulfite, 0.2 mg sodium tartrate (dihydrate), hydrochloric acid to adjust pH, and water for injection. The pH range is 2.2 to 5.0.	Each 0.3 mL in the Epinephrine Injection USP, 0.3 mg (Auto-Injector) contains 0.3 mg epinephrine, USP, 1.8 mg sodium chloride, 0.4 mg sodium metabisulfite, 0.4 mg sodium tartrate (dihydrate), hydrochloric acid to adjust pH, and water for injection. The pH range is 2.2 to 5.0. Each 0.3 mL in the Epinephrine Injection USP, 0.15 mg (Auto-Injector) contains 0.15 mg epinephrine, USP, 1.8 mg sodium chloride, 0.4 mg sodium metabisulfite, 0.2 mg sodium tartrate (dihydrate), hydrochloric acid to adjust pH, and water for injection. The pH range is 2.2 to 5.0.	**same**

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

Table 6: Comparison of HOW SUPPLIED Section or Packaging Sizes for OTC Products		
16 HOW SUPPLIED/STORAGE AND HANDLING **16.1 How Supplied** Epinephrine Injection USP, 0.3 mg (Auto-njectors) (epinephrine injections USP, 0.3 mg/0.3 mL) are available as Epinephrine Injection USP, 0.3 mg 2-Pack, NDC 0093-5986-27, a pack that contains two Epinephrine Injection USP, 0.3 mg (Auto-njectors) (epinephrine injections USP, 0.3 mg/0.3 mL) and one Epinephrine Injection (Auto-njector) trainer device. Epinephrine Injection USP, 0.15 mg (Auto-njectors) (epinephrine injections USP, 0.15 mg/0.3 mL) are available as Epinephrine njection USP, 0.15 mg 2-Pack, NDC 0093-5985-27, a pack that contains two Epinephrine njection USP, 0.15 mg (Auto-Injectors) (epinephrine injections USP, 0.15 mg/0.3 mL) and one Epinephrine Injection (Auto-Injector) trainer device. Epinephrine Injection USP, 0.3 mg 2-Pack and Epinephrine Injection USP, 0.15 mg 2-Pack also nclude a W-clip to clip two auto-injectors together. Rx only **16.2 Storage and Handling** Epinephrine, USP is light sensitive and the auto-njector is manufactured from transparent UV stabilized polycarbonate to protect it from light. Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature]. PROTECT FROM LIGHT. DO NOT REFRIGERATE. Before using, check to make sure the solution in the auto-injector is clear and colorless. Replace the auto-injector if the solution is discolored (pinkish or darker than slightly yellow) or if it contains a precipitate. KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.	**16 HOW SUPPLIED/STORAGE AND HANDLING** **16.1 How Supplied** Epinephrine Injection USP, 0.3 mg (Auto-Injectors) (epinephrine injections USP, 0.3 mg/0.3 mL) are available as Epinephrine Injection USP, 0.3 mg 2-Pack, NDC 0093-5986-27, a pack that contains two Epinephrine Injection USP, 0.3 mg (Auto-Injectors) (epinephrine injections USP, 0.3 mg/0.3 mL) and one Epinephrine Injection (Auto-Injector) trainer device. Epinephrine Injection USP, 0.15 mg (Auto-Injectors) (epinephrine injections USP, 0.15 mg/0.3 mL) are available as Epinephrine Injection USP, 0.15 mg 2-Pack, NDC 0093-5985-27, a pack that contains two Epinephrine Injection USP, 0.15 mg (Auto-Injectors) (epinephrine injections USP, 0.15 mg/0.3 mL) and one Epinephrine Injection (Auto-Injector) trainer device. Epinephrine Injection USP, 0.3 mg 2-Pack and Epinephrine Injection USP, 0.15 mg 2-Pack also include a W-clip to clip two auto-injectors together. Rx only **16.2 Storage and Handling** Epinephrine, USP is light sensitive and the auto-injector is manufactured from transparent UV stabilized polycarbonate to protect it from light. Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature]. PROTECT FROM LIGHT. DO NOT REFRIGERATE. Before using, check to make sure the solution in the auto-injector is clear and colorless. Replace the auto-injector if the solution is discolored (pinkish or darker than slightly yellow) or if it contains a precipitate. KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.	**same**

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

Table 7: Manufacturer/Distributor/Packer Statements		
Manufactured For: **Teva Pharmaceuticals USA, Inc.** **North Wales, PA 19454**	**Manufactured For:** **Teva Pharmaceuticals USA, Inc.** **North Wales, PA 19454**	**same**

5. COMMENTS FOR OTHER REVIEW DISCIPLINES

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

Reminder: Refer to chemistry review to verify labeling section (per Chemistry-Labeling MOU) is complete. Refer to DCR review for combination product to verify if labeling comments were communicated to applicant.

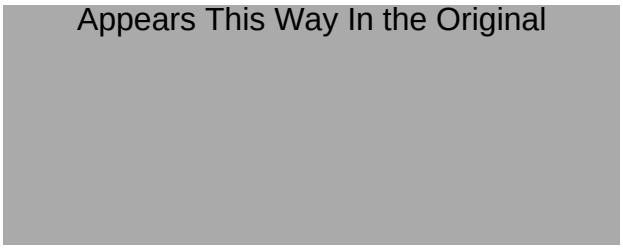
Reviewer Comments:

6. OVERALL ASSESSMENT OF MATERIALS REVIEWED

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

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

Table 8: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	**Packaging Sizes**	**Submission Received Date**	**Recommendation**
Container	Final	0.15 mg auto-injector 0.3 mg auto-injector One trainer device	6/22/2018	Satisfactory
Blister	NA			
Carton	Final	2 Pak (two auto-injectors and one trainer device)	6/22/2018	Satisfactory
Container	Final	0.15 mg auto-injector 0.3 mg auto-injector One trainer device	6/22/2018	Satisfactory
Table 9 Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	**Revision Date and/or Code**	**Submission Received Date**	**Recommendation**
Prescribing Information	Draft	**Iss. 6/2018**	6/22/2018	Satisfactory
Trainer Instruction for Use	Draft	**Iss. 6/2018**	6/22/2018	Satisfactory
Patient Information and Instruction for Use	Draft	**Iss. 6/2018**	6/22/2018	Satisfactory
SPL Data Elements		Revised: 6/2018	6/22/2018	Satisfactory


Appears This Way In the Original

Esther Chuh

Digitally signed by Esther Chuh
Date: 6/26/2018 10:02:04AM
GUID: 508da70700028b78f2f9ebd95bfb4a18

Marshall Florence

Digitally signed by Marshall Florence
Date: 6/26/2018 12:51:56PM
GUID: 55eefa420051b501ac3ced124279f785

LABELING REVIEW

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

Date of This Review	6/20/2018 (addendum)
ANDA Number(s)	090589
Review Number	7
Applicant Name	Teva Pharmaceuticals USA, Inc.
Established Name & Strength(s)	Epinephrine Injection USP, 0.3 mg (Auto-Injector) and Epinephrine Injection USP, 0.15 mg (Auto-Injector)
Proposed Proprietary Name	NA
Submission Received Date	10/28/2016, 03/08/2017, and 6/2/2017
Primary Labeling Reviewer	Marshall Florence, PharmD.
Secondary Labeling Reviewer	Malik Imam (Acting Secondary)

Review Conclusion

☐ ACCEPTABLE – No Comments.

☐ ACCEPTABLE – Include Post Approval Comments

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

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

†Theme - Choose an item.

Justification for Major Deficiency - Choose an item.

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

On Policy Alert List ☒ **YES** ☐ NO

1. LABELING COMMENTS

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT

Labeling Deficiencies determined on June 12, 2018, based on your submissions dated October 28, 2016, March 8, 2017 and June 2, 2017:

1. GENERAL COMMENTS
   a. Please ensure that your final container label, carton labeling and SPL (STRUCTURED PRODUCT LABELING) appropriately reflect your proposed product without the proprietary name. We note that these label/labeling with proprietary name are currently found in your ANDA as final label/labeling.

   b. On the container label and carton labeling, the illustration for step 2 does not clearly depict the injection site (b) (4)). Revise the illustration to further clarify the proper injection site.

2. CONTAINER LABEL
   a. For the 0.15 mg strength:
      In the section that starts with the statement "After use most of liquid stays in auto-injector and can't be reused...", second sentence, remove the ratio expression (1:2000) and revise the strength statement so that it reads "Delivers 0.15 mg intramuscular dose of epinephrine from epinephrine injection USP, 0.15 mg/0.3 mL.".

   b. For the 0.3 mg strength:
      In the section that starts with the statement "After use most of liquid stays in auto-injector and can't be reused.", second sentence, remove the ratio expression (1:1000) and revise the strength statement so that it reads "Delivers 0.3 mg intramuscular dose of epinephrine from epinephrine injection USP, 0.3 mg/ 0.3 mL.".

3. CARTON LABELING
   a. On the principal display panel (PDP), remove "xx mg each" following "For Allergic Emergencies (Anaphylaxis)". Refer to RLD labeling.
   b. On the PDP, remove "For intramuscular use" and "For one time use." statements to be same as the RLD labeling.
   c. On the side panel, remove the ratio expression of strength (1:2000 and 1:1000) and revise the strength statement to "xx mg/xx mL" format. Refer to Container Label comments.

4. PATIENT INFORMATION and INSTRUCTIONS FOR USE
   In the title section under PATIENT INFORMATION and under INSTRUCTIONS FOR USE, remove the parenthesis to read "one dose of 0.3 mg epinephrine USP, 0.3 mg/0.3 mL" for the 0.3 mg auto-injector and "one dose of 0.15 mg epinephrine USP, 0.15 mg /0.3 mL" for the 0.15 mg auto-injector. Make the same revision in the applicable section at the end of the INSTRUCTIONS FOR USE.

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

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

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

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

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE

The Division of Labeling has no further questions/comments at this time based on your labeling submission (s) dated (add date)

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

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

1.3 POST APPROVAL REVISIONS

These comments will be addressed post approval (in the first labeling supplement review).

None

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

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

REVIEW HISTORY pertinent to this Labeling Review

12/21/2007	Original ANDA 090589 submitted to FDA
11/21/2008	Original ANDA 090589 received to FDA for filing
6/4/2009	**Labeling Review #1** completed by A.Payne – Inadequate
10/12/2010	Labeling Amendment submitted by the applicant
2/2/2011	**Labeling Review #2** completed by A. Payne – Inadequate
8/1/2014	Labeling Amendment submitted by the applicant.
9/26/2014	**Labeling Review #3** by K. Rains – Inadequate *(comments sent under Review #4)*
12/30/2014	Quality Minor Amendment and *Unsolicited* Amendment to provide for change in the manufacturing and testing site, formulation and device. Includes labeling.
5/4/2015	**Labeling Review #4** completed by E.Chuh – Inadequate *(Deficiency comments include comments from Review #3)*
11/18/2015	Labeling Easily Correctable Deficiency (ECD) Amendment submitted by applicant.
12/10/2015	**Labeling Review #5** completed by E.Chuh - Inadequate
9/26/2016	Addendum to Review #5 (inadequate) completed to address updated RLD labeling approved on 5/18/2016 on the container, carton, and insert labeling. *(comments were not yet sent to the applicant upon completion of the review as consult to DMEPA was pending))*
10/13/2016	**DMEPA Consult requested** through DARRTS (based on labeling review #5 and its addendum review.
10/28/2016	Complete Response Amendment (includes labeling).
12/9/2016	**Labeling Review #6** completed by E-Chuh - Inadequate *(comments were not yet sent the applicant upon completion of the review, however incorporated to the consult request to DMEPA for evaluation)*
3/8/2017	Applicant submitted Request for Proprietary Name Review ((b) (4)
3/24/2017	Proprietary Name Review found unacceptable per DMEPA (review and letter in DARRTS)
6/2/2017	Labeling Amendment (RLD labeling update approved on 4/18/17) – ***subject of this review***
6/11/2018	DMEPA Consult Review Memo in DARRTS (in response to consult requested on 10/13/2016, with additional inquiry requested 11/15/2016) - ***subject of this review***

Reviewer Comments:

This review updates comments to the applicant identified in Labeling Review #6 completed on 12/9/2016 and in Addendum Review to #5 completed on 9/26/2016. The comments from these two reviews were not sent to the applicant as they were under further consultation with DMEPA.

This review also evaluates the DMEPA Consult Memo completed on 6/11/2018 in response to our consult requested on 10/13/2016 (based on Labeling Review #5 and addendum Review #5) with additional inquiry requested on 11/15/2016 (based on Labeling Review #6). This review also evaluates labeling amendment submitted on 6/2/2017 to be in accordance with the most recently approved RLD labeling NDA 19430/S-067, approved on 4/28/2017.

➢ DMEPA Consult Memo: [Refer to section 2.2 for full consult memo]

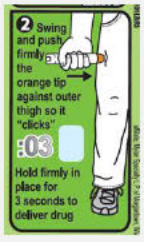
- Based on the consult memo completed by DMEPA on 6/11/2018, we find that the proposed product differentiation of the two strengths by use of the same coloring scheme on the container label and carton labeling that is same as the RLD product is adequate for the safe use of the product. Refer to below excerpt from the Memo.

> We note that the two strengths are differentiated by color in the proposed carton labeling for ANDA 090589 (i.e., green for 0.15 mg/0.3 mL strength product and yellow for the 0.3 mg/0.3 mL strength product), which aligns with the colors used by the RLD to differentiate the EpiPen and EpiPen Jr. strengths. However, we note that the proposed product will not include the term (b) (4) with respect to the 0.15 mg/0.3 mL strength, whereas the RLD uses the proprietary name "EpiPen Jr." for this strength. Although we agree that the inclusion of patient weight information on the carton labeling for each strength (e.g., "FOR ALLERGIC EMERGENCIES in patients weighing over 66 lbs" for the 0.3 mg/0.3 mL strength and "FOR ALLERGIC EMERGENCIES in patients weighing 33 lbs to 66 lbs" for the 0.15 mg/0.3 mL strength[1]) would further differentiate the two strengths, we note this information is not included in the RLD labeling. We do not think that this information is necessary for the safe use of the product, particularly because the Applicant proposes to differentiate the two strengths using the same carton and container coloring scheme as the RLD. As a result, we do not think that the proposed labels and labeling for ANDA 090589 require additional labeling statements to further differentiate the two strengths from a safety perspective.

- In addition, per the consult memo (see excerpt below), we will request for further clarification on the illustration of the foot in step 2. Refer to labeling comment section 1.

> **3 CONCLUSION**
>
> We note that the proposed labels and labeling should be clarified with respect to the depiction of the injection site. The illustration in Step 2 of the proposed product does not clearly indicate the outer thigh. We recommend that the illustration clearly depict the injection site (e.g. the entire leg, including the foot) to avoid confusion. Therefore, we agree with DLR that the applicant should revise the illustration to address this concern.

(b) (4)



Proposed product RLD

➢ Labeling update on insert labeling (amendment 6/2/2017):

- PI is acceptable. Ratio expression in the strength statement was appropriately removed to be same as the RLD.
- PIL/IFU need revision with the product name. Refer to Labeling Comments.

➢ Container and Carton labeling – Inadequate

There was no update to the container/carton labeling since last review. However applicant needs to remove the ration expression in the strength statement to be consistent with the statements in the updated Prescribing Information. See section 2.1 and labeling comments to applicant in section 1 for further comments.

2.1 CONTAINER AND CARTON LABELS

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

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

Reviewer Comments:

- Applicant did not submit further update to the container and carton labeling in the latest amendment which is subject of this review. However we note that the current final container/carton labeling in the ANDA are the ones with their proposed proprietary name which the request was found unacceptable by DMEPA/OSE. Proprietary Name Denied letter was sent to the applicant by DMEPA on 3/24/2017. We will ask the applicant to ensure that the final container and carton labeling submitted to the ANDA appropriately reflect the product without the proprietary name.

  Revising the comment to depict the injection site for the addendum:

- On the container label and carton labeling, the illustration for step 2 does not clearly depict the injection site (b) (4) Revise the illustration to further clarify the proper injection site.

- We will ask the applicant to remove the ratio expression in the strength statement to follow the USP Chapter 7 (refer to section 2.2) and the recent RLD labeling update.

- We will ask the applicant to remove following statements in the carton labeling to be same as the RLD labeling:
  - On the PDP, remove "xx mg each" following "For Allergic Emergencies (Anaphylaxis)"
  - Remove "For intramuscular use" and "For one time use." statements to be same as the RLD labeling.

2.2 ADDITIONAL BACKGROUND INFORMATION PERTINENT TO THE REVIEW

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

Reviewer Comments:

There are three entries filed in SharePoint regarding Epinephrine.

- Epinephrine Ratio Strength Expression and USP Chapter 7

Title	Epinephrine Ratio Strength Expression and USP Monograph General Chapter 7
Date:	8/24/2016
Brief Description	Presentation given at the Division meeting regarding a Working Group formed to implement compliance to USP General Chapter 7 Labeling requirement that no single-entity injectable products may contain ratio expressions in the labeling. Epiniphrine is the primary focus but includes Neostigmine and Isoproterenol Injections too.

- Memo allowing removal of ration expression of strength

Title	Memo to file allowing removal of ratio expression of strength from single entity ...
Date:	8/24/2017
Is this a Review?	☐
What Type of File?	E-mails
Attachments	How to handle labeling for inj. products removing ratio expression of strength.msg
Hyperlink to Review	No hyperlink inserted
Active Ingredient	Epinephrine
Dosage Forms:	Injection
Manufacturer:	
Brief Description	Memo to file allowing ANDAs to differ from RLD with the removal of ratio expression of strength from epinephrine, neostigmine, and isoproterenol inj.

-

- Following is DMEPA Consult Memo completed on 6/11/2018 in response to DLR Consult requested on 10/13/2016, with additional inquiry requested via email on 11/15/2016. The memo is also archived in DARRTS.

3. LABELING REVIEW INFORMATION AND REVIEWER ASSESSMENT

3.1 REGULATORY INFORMATION

Are there any pending issues in DLR's SharePoint Drug Facts? NO – there are entries in Sharepoint, however the issues are resolved for this product. SP entries are added in section 2.2 for reference. If Yes, please explain in section 2.2 Additional Background Information Pertinent to the Review
Is the drug product listed in the Policy Alert Tracker on OGD's SharePoint? YES If Yes, please explain. Following is in the Policy Alert Tracker:

Policy Alert Basis	Docket #	Brand Name (or Drug Class)	Generic Name / Dosage Form / Strengths	Action Requested or Issue Description
CP	FDA-2017-P-3352	Multiple: epinephrine injection products	Multiple: epinephrine auto-injectors containing sulfites	Requests FDA amend the sulfite warning requirement in 21 C.F.R. 201.22 for sulfite-containing epinephrine for injection for use in emergency situations, in order to remove misleading information and acknowledge the current availability of approved epinephrine products that do not contain sulfite.

RLD# (or reference standard)	Approval Actions (TA/AP)	Communications (CRL, CC/IR/DRL)	Notes	Date Filed (~)	OGD Policy Lead
Multiple	No Approval Actions (AP/TA) can be taken prior to contacting Policy Lead	No CRL can be issued prior to contacting Policy Lead; No CC/IR/DRL for Filing or Labeling		5/26/2017	Geeta Daniel

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

3.2 MODEL PRESCRIBING INFORMATION

Table 1: Review Model Labeling for Prescribing Information and Patient Labeling (Check the box used as the Model Labeling)

☒ **MOST RECENTLY APPROVED NDA MODEL LABELING**

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

NDA#/Supplement# (S-000 if original): NDA 019430/S-067

Supplement Approval Date: 4/28/2017

Proprietary Name: EpiPen and EpiPen Jr

Established Name: epinephrine injection USP

Description of Supplement:

This Changes Being Effected supplemental new drug application proposes to update the prescribing information to remove the ratio expressions (e.g. 1:1000) and replace them with an appropriate "strength/mL" statement and to add stress cardiomyopathy to the Adverse Reactions section of the labeling.

**** Note that only Prescribing Information is approved under this S-067. Updates to container labels, cartons, patient information and instructions for use and trainer instructions for use reflecting the change in the expression of product strength was submitted in subsequent Annual Report (Y-031, submitted 2/20/18) per the NDA applicant's commiment to the Agency stated on the cover page of S-067 submitted 4/13/17.**

MOST RECENTLY APPROVED ANDA MODEL LABELING

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

Supplement Approval Date: Click here to enter text.

Proprietary Name: Click here to enter text.

Established Name: Click here to enter text.

Description of Supplement:

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

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

Reviewer Assessment:

Is the Prescribing Information same as the model labeling, except for differences allowed under 21 CFR 314.94(a)(8)? **YES**

Are the specific requirements for format met under 21 CFR 201.57(new) or 201.80(old)? **YES**

Does the Model Labeling have combined insert labeling for multiple dosage forms? **NO**

Reviewer Comments:

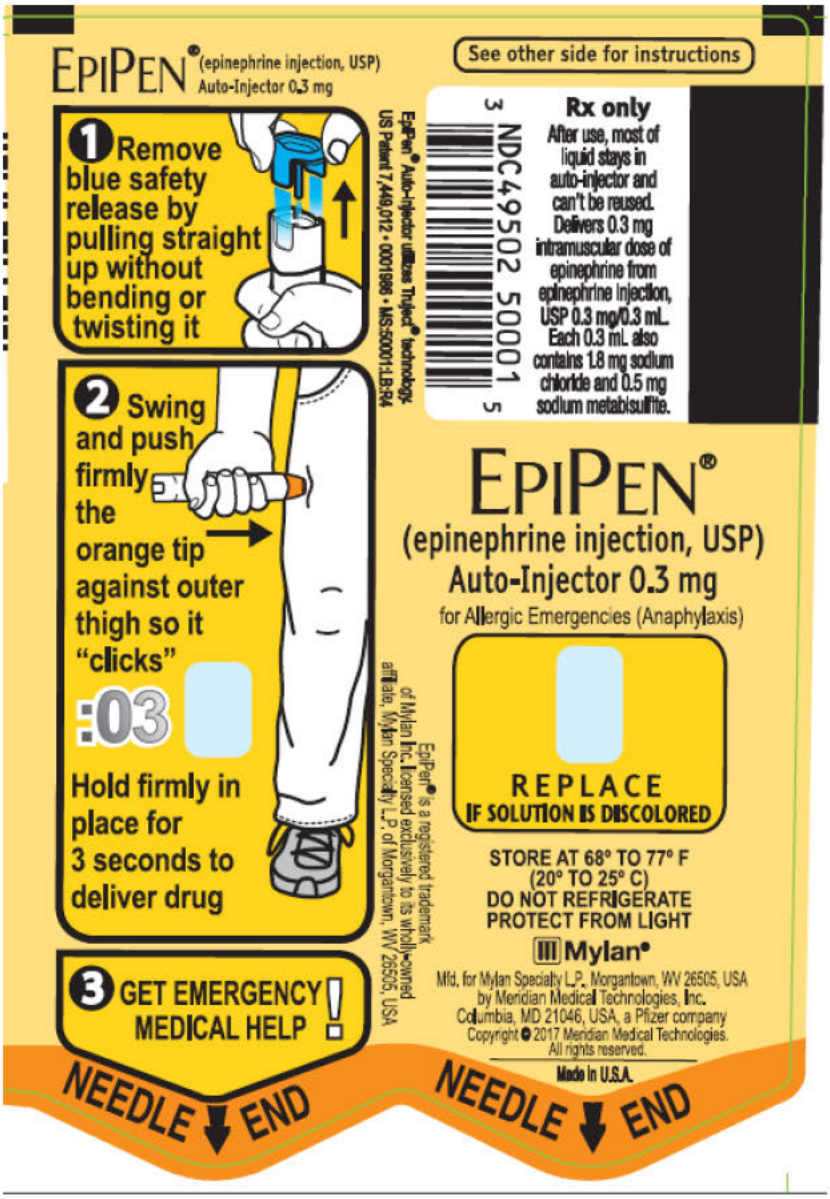
-PRESCRIBING INFORMATION – acceptable

-TRAINER INSTRUCTION FOR USE – acceptable.

-PATIENT INFORMATION and INSTRUCTIONS FOR USE: revision in the title section is needed. Refer to Labeling Comments section.

3.3 MODEL CONTAINER LABELS

Model container/carton/blister labels [Source: NDA 19430/Y-031, submitted 2/20/2018]



EPIPEN 2-PAK®
(epinephrine injection, USP)
Auto-Injectors 0.3 mg

Never put thumb, fingers or hand over orange tip.
Do **not** remove blue safety release until ready to use.

EpiPen 2-Pak® contains 2 **EpiPen®** Auto-Injectors and 1 Trainer.
Each **EpiPen®** Auto-Injector delivers one 0.3 mg intramuscular dose of epinephrine from epinephrine injection, USP 0.3 mg/0.3 mL.
Discard unit after use. The Trainer contains no medicine and no needle.
Read enclosed patient package insert carefully before using.

NDC 49502-500-02

For Allergic Emergencies (Anaphylaxis)

Rx only

EPIPEN 2-PAK®
(epinephrine injection, USP)
Auto-Injectors 0.3 mg

Each carton contains: **Two yellow EpiPen®** Auto-Injectors **One grey Trainer**

Register your EpiPen® Auto-Injectors at **www.epipen.com** to receive free refill reminders

Mylan®

EPIPEN 2-PAK®
(epinephrine injection, USP)
Auto-Injectors 0.3 mg

Replace if discolored. Store at 68° to 77°F (20° to 25°C). Do not refrigerate. Protect from light.

Manufactured for Mylan Specialty L.P., Morgantown, WV 26505, USA by Meridian Medical Technologies, Inc., Columbia, MD 21046, USA, a Pfizer company
EpiPen® and EpiPen Jr® are registered trademarks of Mylan Inc. licensed exclusively to its wholly-owned affiliate, Mylan Specialty L.P. of Morgantown, WV 26505, USA

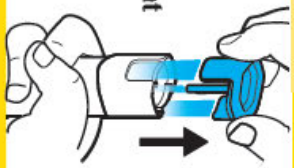
3 49502 50002 2

GTIN: 00349502500022

Open This End

See enclosed Patient Information Leaflet for complete instructions for use.

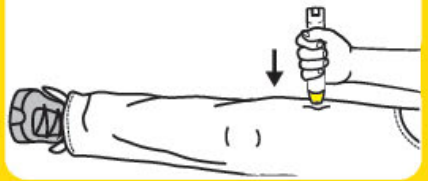
1 Remove the blue safety release by pulling straight up without bending or twisting it



2 Swing and push firmly the orange tip against outer thigh so it "clicks"

:03

Hold firmly in place for 3 seconds to deliver drug



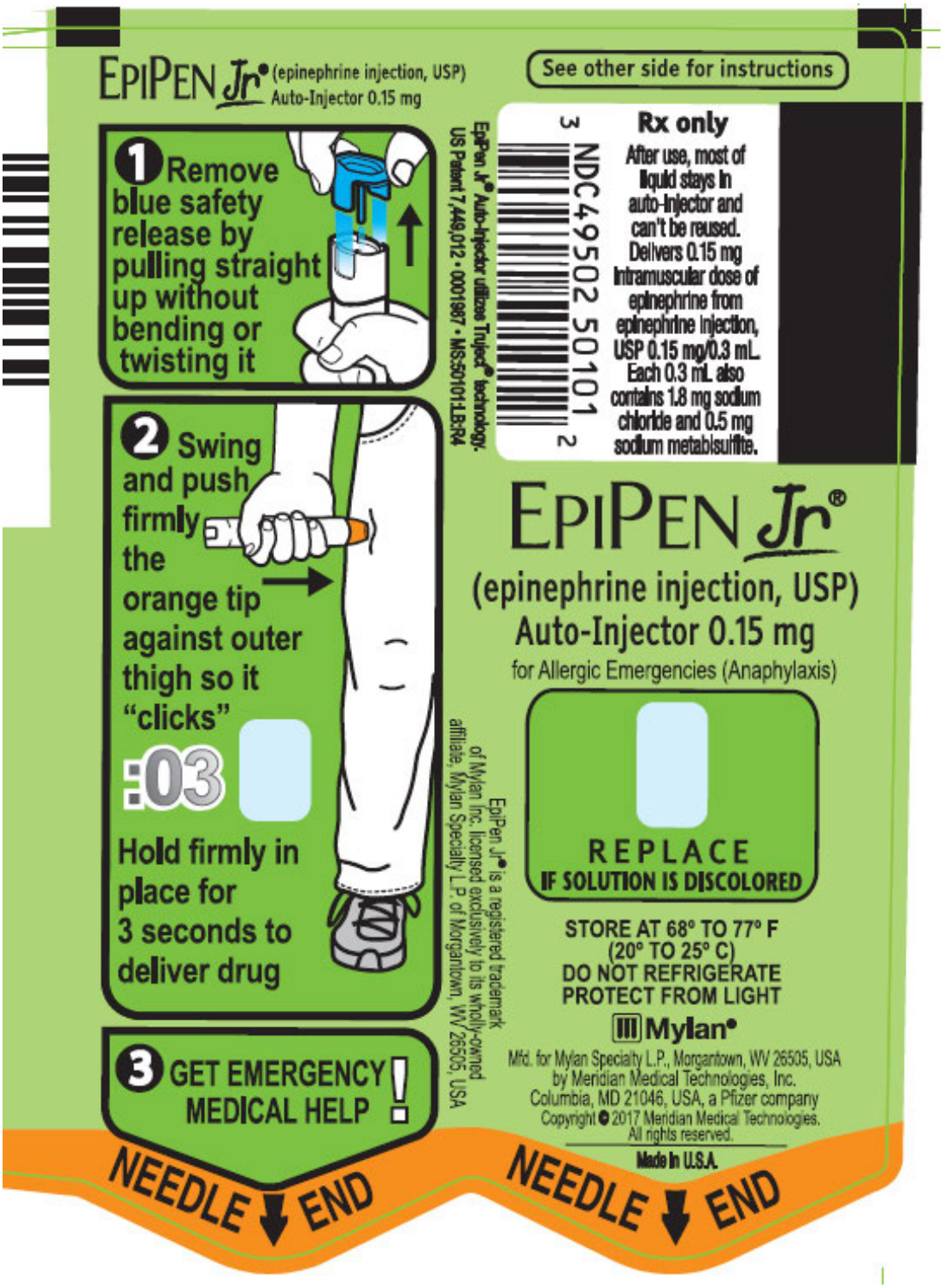
3 GET EMERGENCY MEDICAL HELP

Note: The needle comes out of the orange tip. Never put your thumb, fingers or hand over the orange tip.

EPIPEN 2-PAK®
(epinephrine injection, USP)
Auto-Injectors 0.3 mg

Mylan®

Scan here to learn more


EPIPEN Jr® (epinephrine injection, USP)
Auto-Injector 0.15 mg
See other side for instructions
1 Remove blue safety release by pulling straight up without bending or twisting it
2 Swing and push firmly the orange tip against outer thigh so it "clicks"
:03
Hold firmly in place for 3 seconds to deliver drug
3 GET EMERGENCY MEDICAL HELP
NEEDLE END
NEEDLE END
EpiPen Jr® Auto-Injector utilizes Trijoct® technology.
US Patent 7,449,012 • 0001987 • MS:50101-LB-R4
3 NDC 49502 50101 2
Rx only
After use, most of liquid stays in auto-injector and can't be reused.
Delivers 0.15 mg intramuscular dose of epinephrine from epinephrine injection, USP 0.15 mg/0.3 mL.
Each 0.3 mL also contains 1.8 mg sodium chloride and 0.5 mg sodium metabisulfite.
EPIPEN Jr®
(epinephrine injection, USP)
Auto-Injector 0.15 mg
for Allergic Emergencies (Anaphylaxis)
REPLACE
IF SOLUTION IS DISCOLORED
STORE AT 68° TO 77° F
(20° TO 25° C)
DO NOT REFRIGERATE
PROTECT FROM LIGHT
Mylan®
Mfd. for Mylan Specialty L.P., Morgantown, WV 26505, USA
by Meridian Medical Technologies, Inc.
Columbia, MD 21046, USA, a Pfizer company
Copyright © 2017 Meridian Medical Technologies.
All rights reserved.
Made in U.S.A.
EpiPen Jr® is a registered trademark of Mylan Inc. licensed exclusively to its wholly-owned affiliate, Mylan Specialty L.P. of Morgantown, WV 26505, USA

EPIPEN Jr 2-PAK®
(epinephrine injection, USP)
Auto-Injectors 0.15 mg

Never put thumb, fingers or hand over orange tip.
Do **not** remove blue safety release until ready to use.

EpiPen Jr 2-Pak® contains 2 **EpiPen Jr®** Auto-Injectors and 1 Trainer.
Each **EpiPen Jr®** Auto-Injector delivers one 0.15 mg intramuscular dose of epinephrine from epinephrine injection, USP 0.15 mg/0.3 mL.
Discard unit after use. The Trainer contains no medicine and no needle.
Read enclosed patient package insert carefully before using.

NDC 49502-501-02

Rx only

For Allergic Emergencies (Anaphylaxis)

EPIPEN Jr 2-PAK®
(epinephrine injection, USP)
Auto-Injectors 0.15 mg

Each carton contains: **Two green EpiPen Jr®** Auto-Injectors **One grey Trainer**

Register your EpiPen Jr® Auto-Injectors at **www.epipen.com** to receive free refill reminders

Mylan®

EPIPEN Jr 2-PAK®
(epinephrine injection, USP)
Auto-Injectors 0.15 mg

Mylan®

Replace if discolored. Store at 68° to 77°F (20° to 25°C). Do not refrigerate. Protect from light.

Manufactured for Mylan Specialty LP, Morgantown, WV 26505, USA by Meridian Medical Technologies, Inc., Columbia, MD 21046, USA, a Pfizer company

3 49502 50102 9

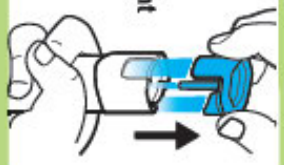
EPIPEN Jr 2-PAK®
(epinephrine injection, USP)
Auto-Injectors 0.15 mg

GTIN: 00349502501029

Open This End

See enclosed Patient Information Leaflet for complete instructions for use.

1 Remove the blue safety release by pulling straight up without bending or twisting it



2 Swing and push firmly the orange tip against outer thigh so it "clicks"

Hold firmly in place for 3 seconds to deliver drug

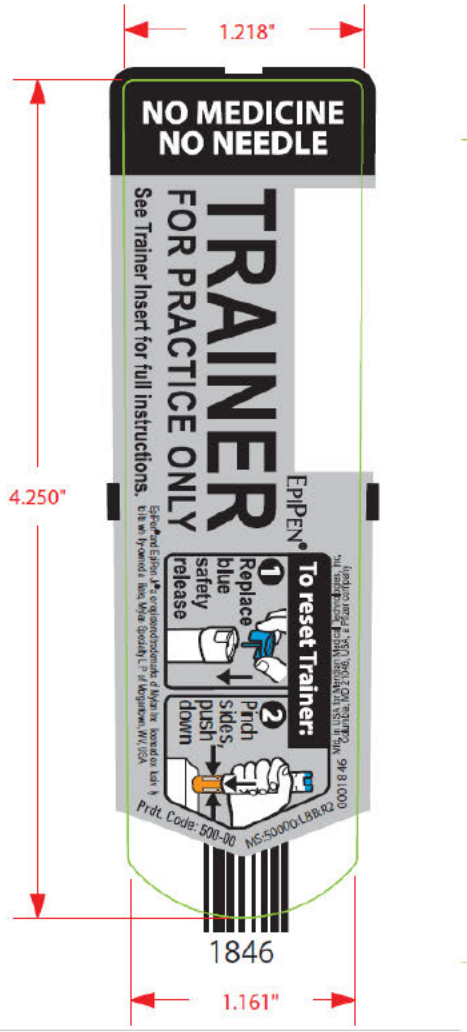
3 GET EMERGENCY MEDICAL HELP

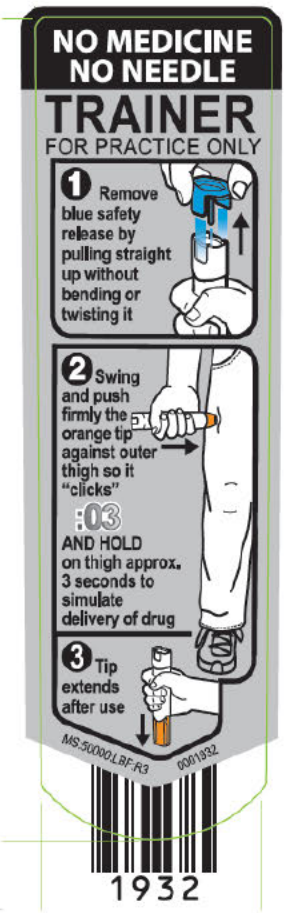
Note: The needle comes out of the orange tip. Never put your thumb, fingers or hand over the orange tip.

EPIPEN Jr 2-PAK®
(epinephrine injection, USP)
Auto-Injectors 0.15 mg

Mylan®

Scan here to learn more





(Front remains the same)

Source: NDA 019430/S-058

(Back modified – step 2)

Source NDA 19430/S-061

3.4 UNITED STATES PHARMACOPEIA (USP)

The USP was searched on 6/13/2018.

	YES or NO	Date	Monograph Title (NA if no monograph)	Packaging and Storage/Labeling Statements (NA if no monograph)
Official Monograph	YES		**USP Monographs: Epinephrine Injection**	**Packaging and storage**—Preserve in single-dose or multiple-dose, light-resistant containers, preferably of Type I glass. **Labeling**—The label indicates that the Injection is not to be used if its color is pinkish or darker than slightly yellow or if it contains a precipitate.
Pending Monograph Proposed	YES	8/1/2018	Same as above	Same as above

Reviewer Assessment:

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

Reviewer Comments:

3.5 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 6/13/2018.

Table 3 provides Orange Book patents for the Model Labeling NDA 19430 and ANDA patent certifications. (For applications that have no patents, N/A is entered in the patent number column)

Table 3: Impact of Model Labeling Patents on ANDA Labeling

Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact (enter Carve-out or None)
7449012	9/11/2025			IV	12/30/2014	None
7794432	9/11/2025			IV	12/30/2014	None
8048035	9/11/2025			IV	12/30/2014	None
8870827	9/11/2025			IV	12/30/2014	None
9586010	09/11/2025			IV	6/23/2017	None

Reviewer Assessment:

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

Reviewer Comments:

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

Table 4: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling

Exclusivity Code	Exclusivity Expiration	Exclusivity Code Definition	Exclusivity Statement	Date of Exclusivity Submission	Labeling Impact (enter Carve-out or None)
NA					

Reviewer Assessment:

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

Reviewer Comments:

4. DESCRIPTION, HOW SUPPLIED AND MANUFACTURED BY STATEMENT

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

Reviewer Assessment:

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

Table 5: Comparison of DESCRIPTION Section or Inactive Ingredients Subsection (OTC)

Previous Labeling Review	Currently Proposed	Assessment
Each 0.3 mL in the Epinephrine Injection USP, 0.3 mg (Auto-Injector) contains 0.3 mg epinephrine, USP, 1.8 mg sodium chloride, 0.4 mg sodium metabisulfite, 0.4 mg sodium tartrate (dihydrate), hydrochloric acid to adjust pH, and water for injection. The pH range is 2.2 to 5.0. Each 0.3 mL in the Epinephrine Injection USP, 0.15 mg (Auto-Injector) contains 0.15 mg epinephrine, USP, 1.8 mg sodium chloride, 0.4 mg sodium metabisulfite, 0.2 mg sodium tartrate (dihydrate), hydrochloric acid to adjust pH, and water for injection. The pH range is 2.2 to 5.0.	Each 0.3 mL in the Epinephrine Injection USP, 0.3 mg (Auto-Injector) contains 0.3 mg epinephrine, USP, 1.8 mg sodium chloride, 0.4 mg sodium metabisulfite, 0.4 mg sodium tartrate (dihydrate), hydrochloric acid to adjust pH, and water for injection. The pH range is 2.2 to 5.0. Each 0.3 mL in the Epinephrine Injection USP, 0.15 mg (Auto-Injector) contains 0.15 mg epinephrine, USP, 1.8 mg sodium chloride, 0.4 mg sodium metabisulfite, 0.2 mg sodium tartrate (dihydrate), hydrochloric acid to adjust pH, and water for injection. The pH range is 2.2 to 5.0.	**same**

Table 6: Comparison of HOW SUPPLIED Section or Packaging Sizes for OTC Products

Previous Labeling Review	Currently Proposed	Assessment

Table 6: Comparison of HOW SUPPLIED Section or Packaging Sizes for OTC Products		
16 HOW SUPPLIED/STORAGE AND HANDLING **16.1 How Supplied** Epinephrine Injection USP, 0.3 mg (Auto-Injectors) (epinephrine injections USP, 1:1000, 0.3 mL) are available as Epinephrine Injection USP, 0.3 mg 2-Pack, NDC 0093-5986-27, a pack that contains two Epinephrine Injection USP, 0.3 mg (Auto-njectors) (epinephrine injections USP, 1:1000, 0.3 mL) and one Epinephrine Injection (Auto-Injector) trainer device. Epinephrine Injection USP, 0.15 mg (Auto-njectors) (epinephrine injections USP, 1:2000, 0.3 mL) are available as Epinephrine Injection USP, 0.15 mg 2-Pack, NDC 0093-5985-27, a pack that contains two Epinephrine Injection USP, 0.15 mg (Auto-Injectors) (epinephrine injections USP, 1:2000, 0.3 mL) and one Epinephrine Injection (Auto-Injector) trainer device. Epinephrine Injection USP, 0.3 mg 2-Pack and Epinephrine Injection USP, 0.15 mg 2-Pack also nclude an W-clip to clip two auto-injectors together. Rx only **16.2 Storage and Handling** Epinephrine, USP is light sensitive and the autoinjector is manufactured from transparent UV stabilized polycarbonate to protect it from light. Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30° (59° to 86°F) [See USP Controlled Room Temperature]. PROTECT FROM LIGHT. DO NOT REFRIGERATE. Before using, check to make sure the solution in the auto-injector is clear and colorless. Replace the autoinjector if the solution is discolored (pinkish or darker than slightly yellow) or if it contains a precipitate. KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.	16 HOW SUPPLIED/STORAGE AND HANDLING **16.1 How Supplied** Epinephrine Injection USP, 0.3 mg (Auto-Injectors) (epinephrine injections USP, 0.3 mg/0.3 mL) are available as Epinephrine Injection USP, 0.3 mg 2-Pack, NDC 0093-5986-27, a pack that contains two Epinephrine Injection USP, 0.3 mg (Auto-njectors) (epinephrine injections USP, 0.3 mg/0.3 mL) and one Epinephrine Injection (Auto-Injector) trainer device. Epinephrine Injection USP, 0.15 mg (Auto-njectors) (epinephrine injections USP, 0.15 mg/0.3 mL) are available as Epinephrine Injection USP, 0.15 mg 2-Pack, NDC 0093-5985-27, a pack that contains two Epinephrine Injection USP, 0.15 mg (Auto-Injectors) (epinephrine injections USP, 0.15 mg/0.3 mL) and one Epinephrine Injection (Auto-Injector) trainer device. Epinephrine Injection USP, 0.3 mg 2-Pack and Epinephrine Injection USP, 0.15 mg 2-Pack also nclude a W-clip to clip two auto-injectors together. Rx only **16.2 Storage and Handling** Epinephrine, USP is light sensitive and the auto-njector is manufactured from transparent UV stabilized polycarbonate to protect it from light. Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature]. PROTECT FROM LIGHT. DO NOT REFRIGERATE. Before using, check to make sure the solution in the auto-injector is clear and colorless. Replace the auto-injector if the solution is discolored (pinkish or darker than slightly yellow) or if it contains a precipitate. KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.	**Acceptable.** Ratio expression is removed to be same as the RLD labeling.

Table 7: Manufacturer/Distributor/Packer Statements		
Previous Labeling Review	**Currently Proposed**	**Assessment**
Manufactured For: **Teva Pharmaceuticals USA, Inc.** North Wales, PA 19454 Iss. 7/2016	**Manufactured For:** **Teva Pharmaceuticals USA, Inc.** **North Wales, PA 19454**	**same**

5. COMMENTS FOR OTHER REVIEW DISCIPLINES

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

Reviewer Comments:

Following is taken from CMC review dated 6/1/18 in GDRP. There is no comment for the labeling reviewer.

II. Review of Common Technical Document-Quality (Ctd-Q) Module 1

A. Labeling & Package Insert

a) DESCRIPTION section

i) Is the information accurate? ☒ Yes ☐ No

If "No," explain.

ii) Is the drug product subject of a USP monograph? ☒ Yes ☐ No

If "Yes," state if labeling needs a special USP statement in the Description. (e.g., USP test pending. Meets USP assay test 2. Meets USP organic impurities test 3.) No.

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

b) HOW SUPPLIED section

i) Is the information accurate? ☒ Yes ☐ No
If "No," explain.

ii) Are the storage conditions acceptable? ☒ Yes ☐ No
If "No," explain.

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

Did the applicant provide quality data to support in-use conditions (e.g. diluent compatibility studies)? ☐ Yes ☐ No ☒ N/A
If "No," explain.

d) For OTC Drugs and Controlled Substances: N/A

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

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

ANDA Strength	Length (mm)	Imprint Code

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

6. OVERALL ASSESSMENT OF MATERIALS REVIEWED

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

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

Table 8: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	Packaging Sizes	Submission Received Date	Recommendation

Container	Final	0.15 mg auto-injector 0.3 mg auto-injector One trainer device	10/28/2016	Revise
Blister	NA			
Carton	Final	2 Pak (two auto-injectors and one trainer device)	10/28/2016	Revise
(Other – specify)	NA			

Table 9 Review Summary of Prescribing Information and Patient Labeling

	Final or Draft or NA	**Revision Date and/or Code**	**Submission Received Date**	**Recommendation**
Prescribing Information	Draft	**Iss. 5/2017**	6/2/2017	Satisfactory
Trainer Instruction for Use	Draft	**Iss. 5/2017**	6/2/2017	Satisfactory
Patient Information and Instruction for Use	Draft	**Iss. 5/2017**	6/2/2017	Revise
SPL Data Elements		Revised: 3/2017	3/8/2017	Revise (product name)

Marshall Florence

Digitally signed by Marshall Florence
Date: 6/20/2018 04:58:32PM
GUID: 55eefa420051b501ac3ced124279f785

Malik Imam

Digitally signed by Malik Imam
Date: 6/21/2018 09:01:37AM
GUID: 508da70800028c685bf6578d234e223f

LABELING REVIEW

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

Date of This Review	11/2/2016, revised 12/9/2016
ANDA Number(s)	90589
Review Number	6
Applicant Name	Teva Pharmaceuticals USA
Established Name & Strength(s)	Epinephrine Injection USP, 0.3 mg (Auto-Injector) and Epinephrine Injection USP, 0.15 mg (Auto-Injector)
Proposed Proprietary Name	N/A
Submission Received Date	10/28/2016
Labeling Reviewer	Eunjung Esther Chuh
Labeling Team Leader	Thuyanh (Ann) Vu

Review Conclusion

☐ ACCEPTABLE – No Comments.

☐ ACCEPTABLE – Include Post Approval Comments

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

*Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Easily Correctable Deficiency if all other OGD reviews are acceptable. Otherwise, the labeling minor deficiencies will be included in the Complete Response (CR) letter to the applicant.

☐ On Policy Alert List

1. LABELING COMMENTS

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT

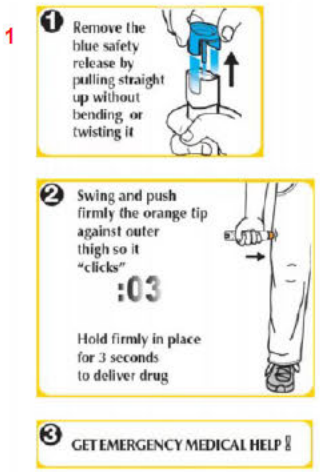
Labeling Deficiencies determined on December 9, 2016, based on your submission dated October 28, 2016:

1. GENERAL COMMENTS
   a. As stated previously, please be advised that if any additional labeling concerns are raised upon Agency's evaluation of your response to the comments related to the auto-injector device and its safe use, we may have further labeling comments.

   b. In ALL your labels and labeling, under step 2 (see below) we note that your illustration does not include the full leg as pictured under step 2 in the reference listed drug (RLD). This may cause confusion as the injection site is not clearly depicted in your illustration. Revise the illustration to maintain consistency with the RLD and to further clarify the proper injection site.

INNOVATOR'S LABEL

(Instruction section)



(b) (4)

2. CONTAINER LABEL

   To further differentiate the two strengths, revise "For Allergic Emergencies (Anaphylaxis)" to "For Allergic Emergencies (Anaphylaxis) in patients weighing 33lbs to 66lbs" on the 0.15 mg strength, and revise "For Allergic Emergencies (Anaphylaxis)" to "For Allergic Emergencies (Anaphylaxis) in patients weighing over 66lbs" on the 0.3 mg strength.

3. CARTON LABELING
   a. To further differentiate the two strengths, revise "For Allergic Emergencies (Anaphylaxis) 0.15 mg each" to "For Allergic Emergencies (Anaphylaxis) in patients weighing 33lbs to 66lbs" on the 0.15 mg strength, and revise "For Allergic Emergencies (Anaphylaxis) 0.3 mg each" to "For Allergic Emergencies (Anaphylaxis) in patients weighing over 66lbs" on the 0.3 mg strength.
   b. For the 0.15 mg strength: On the side panel, correct the typographical error in the statement " Each Epinephrine Injection… delivers… injection 1:2000 USP (0.15 mL)" by correcting "0.15 mL" to "0.3. mL"

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

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

However, prior to the submission of your amendment, please check labeling resources, including DRUGS@FDA, the electronic Orange Book and the NF-USP online, for recent updates and make any necessary revisions to your labels and labeling.

In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address –

http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE

The Division of Labeling has no further questions/comments at this time based on your labeling submission (s) dated (add date)

1.3 POST APPROVAL REVISIONS

These comments will NOT be sent to the applicants at this time.
These comments will be addressed post approval (in the first labeling supplement review).

None

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

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

REVIEW HISTORY

12/21/2007	Original ANDA 090589 submitted to FDA
11/21/2008	Original ANDA 090589 received to FDA for filing
6/4/2009	Labeling Review #1 completed
10/12/2010	Labeling Amendment, response to deficiencies issued on 6/4/2009
2/2/2011	Labeling Review #2 completed
8/1/2014	Labeling Amendment. Response to deficiencies issued on 2/2/2011. Also provides for update to be in accordance with the innovator labeling update approved on 4/30/2014.
9/26/2013	Labeling Review #3. *(Deficiencies to this review is not yet sent out as Complete Response Letter is pending Agency. The comments issued to the applicant from review #4 will supersede the comments that were prepared for the applicant on review #3.)*
12/30/2014	Quality Minor Amendment and Unsolicited Amendment to provide for change in the manufacturing and testing site, formulation and device. Specifically the application provides for following change: drug product manufacturing site and device assembly site change; formulation change (b) (4) sodium metabisulfite (b) (4) addition of sodium tartrate (b) (4) in accordance with CFR 314.94(a)(9)(iii); and change to the device to improve the design to ensure the user will not be presented with a device that has delivered the drug product but has not engaged the safety guard. This amendment also provides for a Human Factor Study.
11/18/2015	Easily Correctable Deficiency(ECD) Amendment, response to ECD sent to the applicant on 11/3/2015.
12/10/2015	Labeling Review #5 completed based on ECD amendment dated 11/18/2015.
9/26/2016	Addendum to Review #5 completed to address new RLD labeling update approved on 5/18/2016 on the container, carton, and insert labeling. Consult was also prepared and sent to DMEPA to consult if there will be any impact to the proposed product by updating the labeling to be in accordance with the revised RLD labeling. Consult also includes our proposed deficiency comments to the applicant.
10/28/2016	Complete Response Amendment (includes labeling). This amendment is subject of this review.

PREVIOUS DEFICIENCY AND FIRM'S RESPONSE

Below comments/response are from the labeling review #5 based on review of submission dated 11/18/2015. Please note that the applicant received the deficiency comments from Review #5 only. In the addendum to review #5 completed on 9/26/2016, deficiency comments from Rev #5 were revised to address the RLD update on 5/18/2016; however the comments are not yet communicated to the applicant. Although the applicant did not receive the revised comment, the applicant addressed them in the CR amendment which is subject of this review.

1. GENERAL COMMENTS

Please be advised that if any additional labeling concerns are raised upon Agency's evaluation of your response to the comments related to the auto-injector device and its safe use, we may have further labeling comments.

Response:
We acknowledge that Agency may have further labeling comments.

2. CONTAINER LABEL (0.30 mg and 0.15 mg)

We recommend further increasing the prominence of the established name and the strength.

Response:
We have increased the prominence of the established name and the strength on the 0.3 mg and 0.15 mg container labels submitted herewith in Module 1.14.2.

3. CARTON LABELING (0.30 mg and 0.15 mg)

a. Please ensure that the established name and the strength are the most prominent information on the label. We refer you to the draft guidance, "Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors" http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm349009.pdf.

Response:
The established name and strength are the most prominent information on the 0.3 mg and 0.15 mg carton labeling submitted herewith in Module 1.14.2.

b. We recommend further differentiation between the two strengths. We recommend using colors that provide sufficient contrast for the strength statements or using other means to differentiate the two strengths (e.g., boxing, highlighting, etc.).

1.11.4 Response to FDA Complete Response (Bioequivalence, Clinical Bioequivalnce, Labeling)
ANDA #090589 / Sequence # 0033
Epinephrine Injection, USP, 0.3 mg/0.3mL (Auto-Injectors) and 0.15/0.3 mL (Auto-Injectors)

Response:
We have added color to the cartons (0.3 mg and 0.15 mg) to differentiate between the two strengths [redacted] (b) (4) submitted herewith in Module 1.14.2.

c. To decrease clutter on the principal display panel (PDP), you may consider relocating "Register your… to receive free refill reminders..." statement to the side panel.

Response:
We have relocated "Register your… to receive free refill reminders..." statement to the side panel (0.3 mg and 0.15 mg) of the cartons; this labeling is submitted herewith in Module 1.14.2.

d. Delete the duplicate statement ("Each Carton Contains….") on the side panel, immediately below "(Auto-Injectors) 2 Pack.

Response:
We have deleted the duplicate statement ("Each Carton Contains….") on the side panel, immediately below "(Auto-Injectors) 2 Pack (0.3 mg and 0.15 mg) of the cartons; this labeling is submitted herewith in Module 1.14.2.

4. PRESCRIBING INFORMATION (Insert Labeling, Patient Information and Instruction for Use)

Throughout your labeling, delete "(auto-injector)" where you state "epinephrine injection, 0.3 mg and epinephrine injection, 0.15 mg (auto-injector)". You may choose to add "(auto-injector)" after the "0.3 mg" instead.

Response:
Throughout our labeling we have added "(auto- injector)" after the "0.3 mg".

REVIEWER COMMENTS

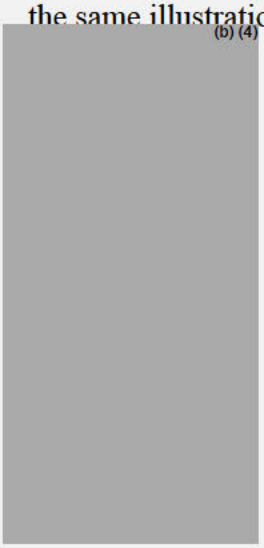
- **Product Differentiation on the Container and Carton Labeling.**
  - We consulted DMEPA for recommendation on the product differentiation, possibly to add "adult" or "pediatric" or weight requirement on the container/carton labeling. Below was recommended by DMEPA to further differentiate the two strengths.

> **B. Carton Label**
> 1. Add the statement, "FOR ALLERGIC EMERGENCIES in patients weighing 33lbs to 66lbs" on the 0.15 mg strength and "FOR ALLERGIC EMERGENCIES in patients weighing over 66lbs" on the 0.3 mg strength to further differentiate the strengths.

Based on DMEPA's recommendation we will issue the following comment to the applicant on the container and carton labeling:

> To further differentiate the two strengths, revise "For Allergic Emergencies (Anaphylaxis) 0.15 mg each" to "For Allergic Emergencies (Anaphylaxis) in patients weighing 33lbs to 66lbs" on the 0.15 mg strength, and revise "For Allergic Emergencies (Anaphylaxis) 0.3 mg each" to "For Allergic Emergencies (Anaphylaxis) in patients weighing over 66lbs" on the 0.3 mg strength.

- **All Labels and Labeling (Container Labels, Carton labeling, Instruction for Use)**
  - It is noted in this review cycle (h/v this is not a change from previously submitted label) that the proposed product does not present a clear picture of the leg versus the RLD. Illustration provided in the RLD includes a picture of a leg with a foot so that it is very clear that the injector is being pushed into the thigh. For the proposed product, it is questionable if the picture would be interpreted the same as the RLD. This reviewer recommends adding a foot/shoe to the leg to depict the same illustration as the RLD.



Proposed product RLD

DMEPA was consulted and they agreed with our comment. Refer to section 6 on their review. Per DMEPA's recommendation, following general comment will be issued to the applicant:

> In ALL your labels and labeling, under step 2 (see below) we note that your illustration does not include (b) (4) as pictured under step 2 in the reference listed drug (RLD). This may cause confusion as the injection site is not clearly depicted in your illustration. Revise the illustration to maintain consistency with the RLD and to further clarify the proper injection site.

- **Container Label**
  - Revisions to the container label submitted to the 10/28/2016 amendment is acceptable.
  - As requested, applicant increased prominence of established name and strength (increase font size)
  - Applicant also revised the labels to be in accordance with the recently revised RLD label
    - Direction #2: reworded to "push firmly" and revise to" HOLD.. 3 seconds" from "10 seconds". Revision is same as the RLD.
    - Changed picture of clock to " :03" . This is same as the RLD.
  - Other change : Reworded "Window black" to "window blocked

- **Carton Labeling**
  - Revisions to the carton labeling submitted to the 10/28/2016 amendment is acceptable.
  - Applicant adequately responded to the deficiencies:
    - Increased prominence of the established name and strength
    - Differentiation: background color changed from (b) (4) to green (0.15 mg) and yellow (0.3 mg). The color scheme is same as the RLD carton labeling. This color differentiation helps to further differentiate between the two strengths to prevent potential medication selection error.
    - Other minor revisions were made as requested
  - Applicant also revised the labels to be in accordance with the recently revised RLD label
    - Same change as the container label (Direction #2)
  - Side panel for the 0.15 mg strength: Correct the typographical error in the statement " Each Epinephrine Injection… delivers… injection 1:2000 USP (0.15 mL)" by correcting "0.15 mL" to "0.3. mL" . [Container label and How Supplied of the PI states "0.3 mL" which is consistent with the RLD.]

- **Insert Labeling (PI, Patient Information, Instruction for Use)**
    - Revisions were made to be in accordance with the revised RLD labeling:
        - As mentioned in the previous reviews, it is noted that the proposed product does not have a carrying tube. Therefore the labeling was revised in sections where the RLD references the carrying tube. Currently, stated, this difference is acceptable. However this decision may change with any additional labeling concerns that may be raised upon Agency's evaluation of the auto-injector device and its safe use.
    - It is noted that proposed product states "precipitate" when the RLD states" particle" in the statement "Replace the auto-injector if the solution…. contains particles". This difference is acceptable as the USP uses the term "precipitate" also. Refer to section 3.4.

2.1 CONTAINER AND CARTON LABELS

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

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

Reviewer Comments:

2.2 ADDITIONAL BACKGROUND INFORMATION PERTINENT TO THE REVIEW

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

Reviewer Comments:

Following is "for the record" taken from previous review cycle #4 and #5:

Notes for the record

1)The labels and labeling provided on this unsolicited amendment was reviewed and comments are under section 1.Labeling Comments. However complete analysis of the labeling on the drug product is deferred until the evaluation of the device and the human factor study provided on this amendment is complete. The human factor study was requested by CDRH for the applicant to demonstrate that the device can be used by the representative users under simulated use conditions without producing patterns of failures that could result in negative clinical impact to patients or injury to the device users.

2)There is a Citizen's Petition submitted to the Agency on 1/16/2015 by Mylan which requests Agency to refrain from approving this ANDA "unless, after conducting an appropriately rigorous review under the established standards for proposed generic emergency use auto-injectors, the agency concludes that the proposed product is the "same as" the EpiPen® auto-injector". Much of their concern is related to the proper use of the auto-injector in an emergency situation. This reviewer also notes the difference in the device, such as the "twist off" function of the cap for the proposed product versus the "pull out" of the cap from a carrier tube on the RLD. At this time, the evaluation on the functionality and safe use of the device as a generic equivalent to RLD is pending with the subject experts in the Agency

3) Teva refers the lower dose epinephrine injection as (b) (4) Auto-Injector". As RLD name is trademarked as following: Epipen®, Epipen JR®, Epipen JR2-Pak®, this reviewer finds that the generic of Epipen Jr should not be referred as the (b) (4) Auto- Injector". Even if the (b) (4) is not trademarked, the terminology of (b) (4) Auto- Injector" is not a conventional way of referring to a lower strength auto-injector. This reviewer finds that (b) (4) may be proposed as a part of a proprietary name or the applicant may indicate the lower strength without the designation of (b) (4)

NOTE ON PREVIOUS CONSULTS ON THE ANDA:

11/13/2008 OGD consulted OND (Division of Pulmonary and Allergy Products) for a comparative review between the MOA of the Innovator's Auto-Injector versus TEVA's proposed Auto Injector. Per the consult response, it was concluded that the mechanism of action (mechanism of release) is the same between the TEVA's and the innovator's product and that Teva's product should be filed under the 505(j) pathway.

5/29/2009 Consult to CDRH on the device master file. CDRH requested that the applicant submit a Human Factors Study as part of the demonstration that generic device use is the same as the RLD device use. *Human Factor Study submitted on 12/30/2014 is pending review.*

4/29/2013 Consult to Division of Clinical Review on the difference on the length of the needle. Per the consult, slightly longer needle length of Teva's product compared to the RLD is not clinically significant, and should not be a factor in the approval of ANDA 90589 as a generic to EpiPen.

Update on the consults:

Consults to CDRH(device), DCR (formulation) OSE(human factor study) are completed and deficiency comments are incorporated by appropriate review disciplines. Refer to the Complete Response Deficiency letter that will be issued for the comments.

It is noted that OSE/DMEPA concluded that the Human Factor Study did not show that the end users who are switching from the reference listed product (RLD) to the proposed product can safely and effectively use the proposed product in accordance with the product's Instructions for Use (IFU) without the prescribing health care provider's intervention or training prior to use, and that the difference in the steps between the two devices may lead to errors if the product is substituted for the EpiPen (RLD) without additional training. DMEPA's review also noted that the approval of the proposed product as a generic substitution for the EpiPen may result in detrimental error due to confirmation bias with current EpiPen users.

2015-1409
Epinephrine Human Fa

Review of Human Factor Study (DMEPA/OSE)] DRAFT review

Since my review #5 on 12/10/2015, DMEPA's "draft" review (above) was finalized on 2/11/2016 with conclusion that the data provided by the applicant is insufficient to show that it can be substituted with the RLD without additional training or physician intervention before use of the proposed product.

2015-1409
Epinephrine Human Fa

5 CONCLUSION

DMEPA concludes that the study data results show that some current users of EpiPen who may be dispensed the AJE product in place of EpiPen without additional training prior to use would not be able to use the proposed AJE product appropriately. Thus, there is continued residual uncertainty regarding whether the proposed AJE can be substituted for the RLD.

The study report data identifies a new type of use error for the AJE product in the first step of administration (i.e., not twisting off the yellow cap) that is attributable to a difference in a critical design attribute in design of the AJE product when compared to the EpiPen product. In addition, the Applicant has not provided sufficient comparative data to characterize whether the rate of error in removing the cap of the AJE product among current EpiPen users is less than, or not significantly greater than, the rate of error in removing the carrier tube if those current EpiPen users continued to use only EpiPen. Furthermore, the Applicant did not identify any measure to mitigate this error. Although the data do not allow us to characterize the expected rate of occurrence of this particular error with the proposed AJE product in actual use because of limitations in the study design employed, we can reasonably conclude from the data that if the proposed AJE is approved under 505(j) (and subsequently substituted for EpiPen), FDA would expect that some current users of EpiPen would be unable to use the Applicant's proposed product appropriately based on the pattern of observed errors and close calls observed in the human factors study. It may be possible that the rate of errors observed with this task for the AJE product is within an acceptable margin so as not to be significantly worse than the rate of errors observed with the RLD task of removing the carrier tube, but the data from this human factors study are insufficient to support this conclusion. On this basis we find that the data provided by the Applicant with respect to its proposed AJE product is insufficient to show that the proposed AJE product can be substituted for the RLD without additional training or physician intervention before use of the proposed AJE. We understand that this Applicant has outstanding deficiencies that will be communicated in a Complete Response (CR) letter, and recommend that OGD communicate this deficiency to the Applicant in such CR letter. We also would be happy to work with OGD further post-CR letter to assist the Applicant with respect to submitting data that might be appropriate to address this deficiency.

ANDA90589.TEVA.Epi
Pen.CDRH Engineering

[Review of the Device– CDRH] 10/23/2015

CP citizen petition (Docket No: FDA-2015-P-0181): Agency has denied the petition to refrain from approving the current application by Teva (ANDA 090589) unless a rigorous review under the established standards for proposed generic emergency use auto-injectors was performed and the Agency concludes that the proposed product is the same as the EpiPen auto-injectors. CP was denied on 6/15/2015.

CP.pdf

[CP Response] 6/15/2015

More on Consults:

9/11/2016: Division of Bio III sent consult to OPQ and DCR regarding the sodium tartrate dehydrate (STD) in the proposed product. Per DBE III review dated 9/12/2016 in GDRP, the responses received from OPQ and DCR supported the BE portion of the application to remain in adequate status.

9/1/2016: OPQ sent consult to CDRH for assessment of the cGMP compliance of the device manufacturing facility (b) (4) and for determination on whether an inspection is needed or if the facility is currently acceptable. *This consult is currently pending.*

Model RLD Labeling approved 5/18/2016:

RLD labeling (NDA S-061) approved 5/18/2016 provides for changes in the container label, carton labeling, Prescribing Information, and Patient Information and Instruction for Use. Accordingly, ANDA applicant revised all their label/labeling to be in in accordance with the updated RLD labeling.

Background on the approval of NDA S-061 [Taken from the Medical Officer's Review, Division of Pulmonary Allergy and Rheumatology Products, 5/2/2016]:

NDA S-061 was submitted in response to a February 5, 2016, FDAA, Safety Labeling Changes Notification Letter for two safety issues of lacerations and embedded needles caused by epinephrine auto-injector use in children, and Clostridial infections following injection of epinephrine for treatment of anaphylaxis. These safety issues were each the subject of a Tracked Safety Issue (TSI) involving each of the approved epinephrine products, TSI 1541for lacerations, etc., and TSI 1555 for Clostridial infections.

IV. Labeling

The agreed class labeling (Warnings and Precautions) for the above safety issues is summarized below. Note that the Division decided that only the auto-injectors need to have the safety issue of injection related injuries added as a Warning and Precaution. The epinephrine injection products that are administered in a hospital/clinic setting only have additional class language regarding the need to hold the leg during the injection in the Dosage and Administration section. In addition to changes to the Warnings and Precautions, related changes were incorporated in the Dosage and Administration, Adverse Reactions, Patient Information, and Instructions for Use (IFU) sections. Specifically, the new Instructions for Use include the class statement that "If you are administering [product name] to a young child, hold the leg firmly in place and limit movement prior to and while administering an injection." The agreed upon language is very similar to the original language in the February 9, 2016, FDAAA SLC Notification Letter.

New Warnings and Precautions

The following class labeling is being added to Section 5.2, Injection-Related Complications:

> **Hold the leg firmly during injection**. Lacerations, bent needles, and embedded needles have been reported when [product name] has been injected into the thigh of young children who are uncooperative and kick or move during an injection. To minimize the risk of injection related injury when administering [product name] to young children, instruct caregivers to hold the child's leg firmly in place and limit movement prior to and during injection.

The following class labeling is being added as a new section:

> **Serious Infections at the Injection Site**. Rare cases of serious skin and soft tissue infections, including necrotizing fasciitis and myonecrosis caused by Clostridia (gas gangrene), have been reported at the injection site following epinephrine injection for anaphylaxis. *Clostridium* spores can be present on the skin and introduced into the deep tissue with subcutaneous or intramuscular injection. While cleansing with alcohol may reduce presence of bacteria on the skin, alcohol cleansing does not kill *Clostridium* spores. To decrease the risk of *Clostridium* infection, do not inject [product name] into the buttock. Advise patients to seek medical care if they develop signs or symptoms of infection, such as persistent redness, warmth, swelling, or tenderness, at the epinephrine injection site.

Other Labeling Changes

As noted above, all factors that contribute to the safe use of these products were considered as part of these supplements. In that regard, each manufacturer was asked to respond to specific safety questions regarding their product as well as to provide safety suggestions as to how to address these issues. As part of their response, Mylan proposed to change the Instructions for Use to a 3-second hold time after triggering the injection, and they provided and/or referenced the data to support this request. After review, the Division found that Mylan's request is reasonable, in light of the fact that 1) this shortened time might reduce the likelihood of lacerations while parents or caregivers are trying to maintain the needle in the thigh of a child who is fighting an injection, and 2) the shortened hold time still factors in a large safety margin over the actual injection time. As a result, the instruction set in the EpiPen IFU (and in other locations of the EpiPen labeling) was changed from the current "Hold firmly against the thigh for approximately 10 seconds to deliver the drug" to an instruction to "Hold firmly in place for 3 seconds (count slowly 1, 2, 3)" before removing the auto-injector from the thigh.

Below are changes that were made on the RLD labeling (S-061):

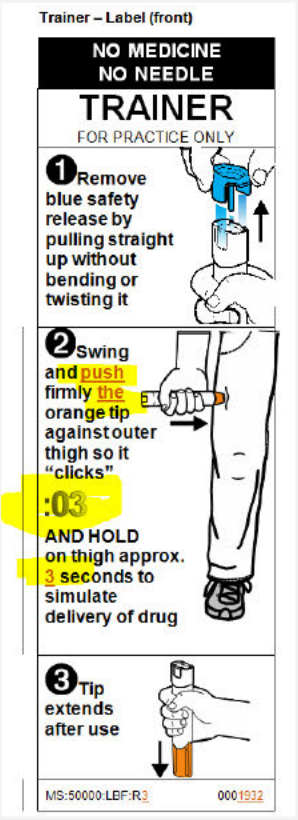
Container and carton for both strengths were revised on Step #2 of the injection instruction:

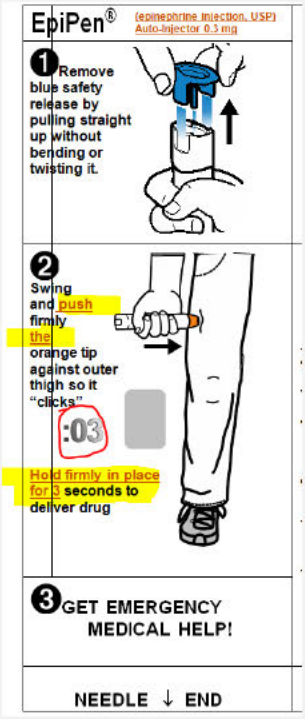
- **Revised "Swing and firmly push" to "Swing and push firmly the orange tip"**
- **Revised "10 seconds" to "3 seconds" both in words in graphic.**
- **Revised "AND HOLD on thigh approx.. 10 seconds.." to "Hold firmly in place for 3**

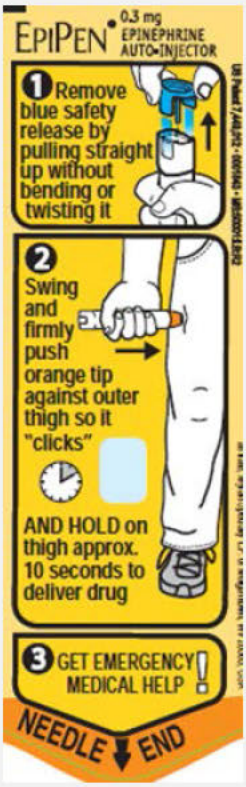
seconds.."

- Note that proposed ANDA product has the same direction as previously approved RLD labeling. In the 10/28/2016 amendment, applicant revised their labeling to be in accordance with the most currently approved RLD labeling (S-061). In terms of the change in the instruction for use and the hold time, DMEPA was consulted to ensure that the same type of change is appropriate for the proposed ANDA product as the proposed device is not same as the RLD. Refer to section 6 for their conclusion on the device.

(b) (4)







Trainer **Epipen**

Updated RLD(S-061) **Previous RLD (S-058)** **Proposed ANDA**

Prescribing Information:

Following statements were added to the NDA labeling to address the injection related complications and the infection at the injection site:

- **2 DOSAGE AND ADMINISTRATION**
  - **Following statements were added:**

> Inject EpiPen or EpiPen Jr intramuscularly or subcutaneously into the anterolateral aspect of the thigh, through clothing if necessary. Instruct caregivers of young children who are prescribed an EpiPen or EpiPen Jr and who may be uncooperative and kick or move during an injection to hold the leg firmly in place and limit movement prior to and during an injection [*see Warnings and Precautions (5.2)*].

- **5 WARNING AND PRECAUTIONS**
  - **Section 5.2 Injection-Related Complications [fourth bullet added with statements below**

    - **Hold leg firmly during injection.** Lacerations, bent needles, and embedded needles have been reported when EpiPen and EpiPen Jr have been injected into the thigh of young children who are uncooperative and kick or move during an injection. To minimize the risk of injection related injury when administering EpiPen to young children, instruct caregivers to hold the child's leg firmly in place and limit movement prior to and during injection.

  - **5.3 Serious Infection at the Injection Site [this new section was added]**

    5.3 Serious Infections at the Injection Site
    Rare cases of serious skin and soft tissue infections, including necrotizing fasciitis and myonecrosis caused by Clostridia (gas gangrene), have been reported at the injection site following epinephrine injection for anaphylaxis. *Clostridium* spores can be present on the skin and introduced into the deep tissue with subcutaneous or intramuscular injection. While cleansing with alcohol may reduce presence of bacteria on the skin, alcohol cleansing does not kill *Clostridium* spores. To decrease the risk of *Clostridium* infection, do not inject EpiPen into the buttock [see *Warnings and Precautions (5.2)*]. Advise patients to seek medical care if they develop signs or symptoms of infection, such as persistent redness, warmth, swelling, or tenderness, at the epinephrine injection site.

- **6 ADVERSE REACTIONS** [following highlighted paragraphs are added at the end of this section]

  Lacerations, bent needles, and embedded needles have been reported when EpiPen has been injected into the thigh of young children who are uncooperative and kick or move during the injection [*see Warning and Precautions (5.2)*].

  Injection into the buttock has resulted in cases of gas gangrene [*see Warnings and Precautions (5.2)*].

  Rare cases of serious skin and soft tissue infections, including necrotizing fasciitis and myonecrosis caused by Clostridia (gas gangrene), have been reported following epinephrine injection, including EpiPen, in the thigh [*see Warnings and Precautions (5.3)*].

- **17 PATIENT COUNSELING INFORMATION**
  - **Under Administration and Training following statements were added**

    Instruct caregivers to hold the leg of young children firmly in place and limit movement prior to and during injection. Lacerations, bent needles, and embedded needles have been reported when EpiPen and EpiPen Jr have been injected into the thigh of young children who are uncooperative and kick or move during an injection [*see Warnings and Precautions (5.2)*].

  - **Following sub-heading and section was added:**

    Serious Infections at the Injection Site
    Rare cases of serious skin and soft tissue infections, including necrotizing fasciitis and myonecrosis caused by Clostridia (gas gangrene), have been reported at the injection site following epinephrine injection for anaphylaxis. Advise patients to seek medical care if they develop signs or symptoms of infection, such as persistent redness, warmth, swelling, or tenderness, at the epinephrine injection site [*see Warnings and Precautions (5.3)*].

Patient Information and Instruction for Use

- Patient Information: Following highlighted sections were added

What are the possible side effects of the EpiPen and EpiPen Jr?

EpiPen and EpiPen Jr may cause serious side effects.

- **The EpiPen or EpiPen Jr should only be injected into the middle of your outer thigh (upper leg). Do not** inject the EpiPen or EpiPen Jr into your:
  - veins
  - buttocks
  - fingers, toes, hands, or feet

  If you accidentally inject EpiPen or EpiPen Jr into any other part of your body, go to the nearest emergency room right away. Tell the healthcare provider where on your body you received the accidental injection.

- Rarely, patients who have used EpiPen or EpiPen Jr may develop infections at the injection site within a few days of an injection. Some of these infections can be serious. Call your healthcare provider right away if you have any of the following at an injection site:
  - redness that does not go away
  - swelling
  - tenderness
  - the area feels warm to the touch

- Cuts on the skin, bent needles, and needles that remain in the skin after the injection, have happened in young children who do not cooperate and kick or move during an injection. If you inject a young child with EpiPen or EpiPen Jr, hold their leg firmly in place before and during the injection to prevent injuries. Ask your healthcare provider to show you how to properly hold the leg of a young child during injection.

- Instruction for use – following highlighted sections were revised in Step 2:
  - ➢ It is noted that the proposed ANDA's instruction for use is the same as previously approved RLD (S-058) for Step 2. ***DMEPA was consulted to ensure that the same type of change is appropriate for the proposed ANDA product as the proposed device is not same as the RLD. Refer to Section 6 on their conclusion on the device.***

Step 2. Administer EpiPen or EpiPen Jr

If you are administering EpiPen or EpiPen Jr to a young child, hold the leg firmly in place while administering an injection.

Place the orange tip against the middle of the outer thigh (upper leg) at a right angle (perpendicular) to the thigh.

Swing and push the auto-injector firmly until it 'clicks'. The

click signals that the injection has started.

Hold firmly in place for 3 seconds (count slowly 1,2,3). The injection is now complete.

Remove the auto-injector from the thigh. The orange tip will extend to cover the needle. If the needle is still visible, do not attempt to reuse it.

Massage the injection area for 10 seconds.

3. LABELING REVIEW INFORMATION AND REVIEWER ASSESSMENT

3.1 REGULATORY INFORMATION

Are there any pending issues in DLR's SharePoint Drug Facts? NO If Yes, please explain in section 2.2 Additional Background Information Pertinent to the Review
Is the drug product listed in the Policy Alert Tracker on OGD's SharePoint? NO If Yes, please explain.

3.2 MODEL PRESCRIBING INFORMATION

Table 1: Review Model Labeling for Prescribing Information and Patient Labeling (Check the box used as the Model Labeling)

☒ **MOST RECENTLY APPROVED NDA MODEL LABELING**

(If NDA is listed in the discontinued section of the Orange Book, also enter ANDA model labeling information.)

NDA# /Supplement# (S-000 if original): NDA 019430/S-061

Supplement Approval Date: 5/18/2016

Proprietary Name: EpiPen Auto-Injector and EpiPen Jr Auto-Injector

Established Name: epinephrine

Description of Supplement:

We also refer to our letter dated February 5, 2016, notifying you, under Section 505(o)(4) of the FDCA, of **new safety information** that we believe should be included in the labeling for EpiPen and EpiPen Jr (epinephrine injection). This information pertains to reports of lacerations and embedded needles after epinephrine injection and post-marketing adverse event reports of serious infection (e.g. *Clostridium perfringens*) at the injection site following epinephrine injection for anaphylaxis.

This supplemental new drug application provides for revisions to the labeling for EpiPen and EpiPen Jr. consistent with our February 5, 2016, letter and the changes agreed upon in our March 24, and 31, and April 15, 2016, correspondences, and changes to the carton and container labeling to incorporate USP information and revised instructions for use.

☐ **MOST RECENTLY APPROVED ANDA MODEL LABELING**

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

Supplement Approval Date: Click here to enter text.

Proprietary Name: Click here to enter text.

Established Name: Click here to enter text.

Description of Supplement:

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

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

Reviewer Assessment:

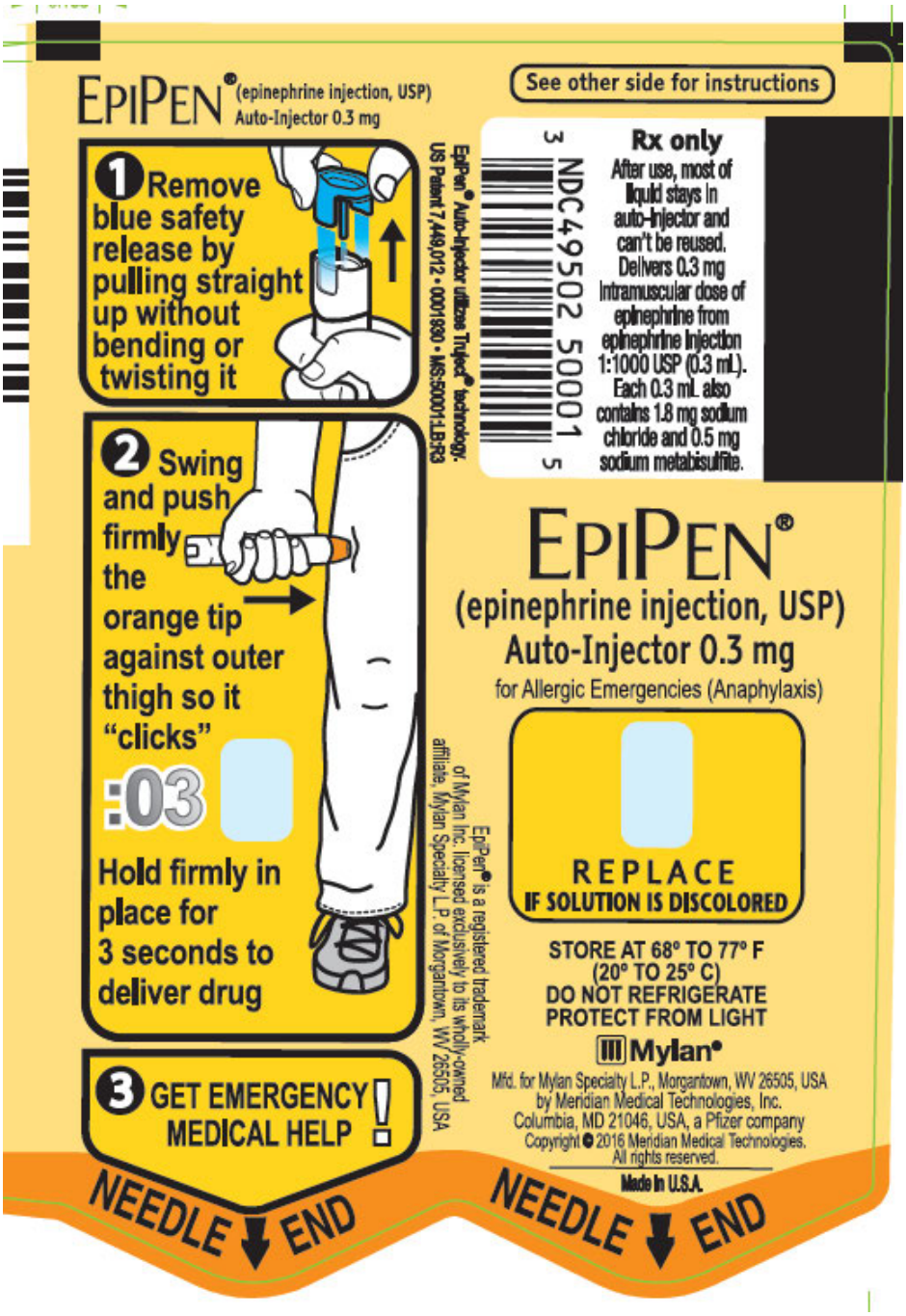
Is the Prescribing Information same as the model labeling, except for differences allowed under 21 CFR 314.94(a)(8)? **YES**
Are the specific requirements for format met under 21 CFR 201.57(new) or 201.80(old)? **YES**
Does the Model Labeling have combined insert labeling for multiple dosage forms? **NO**

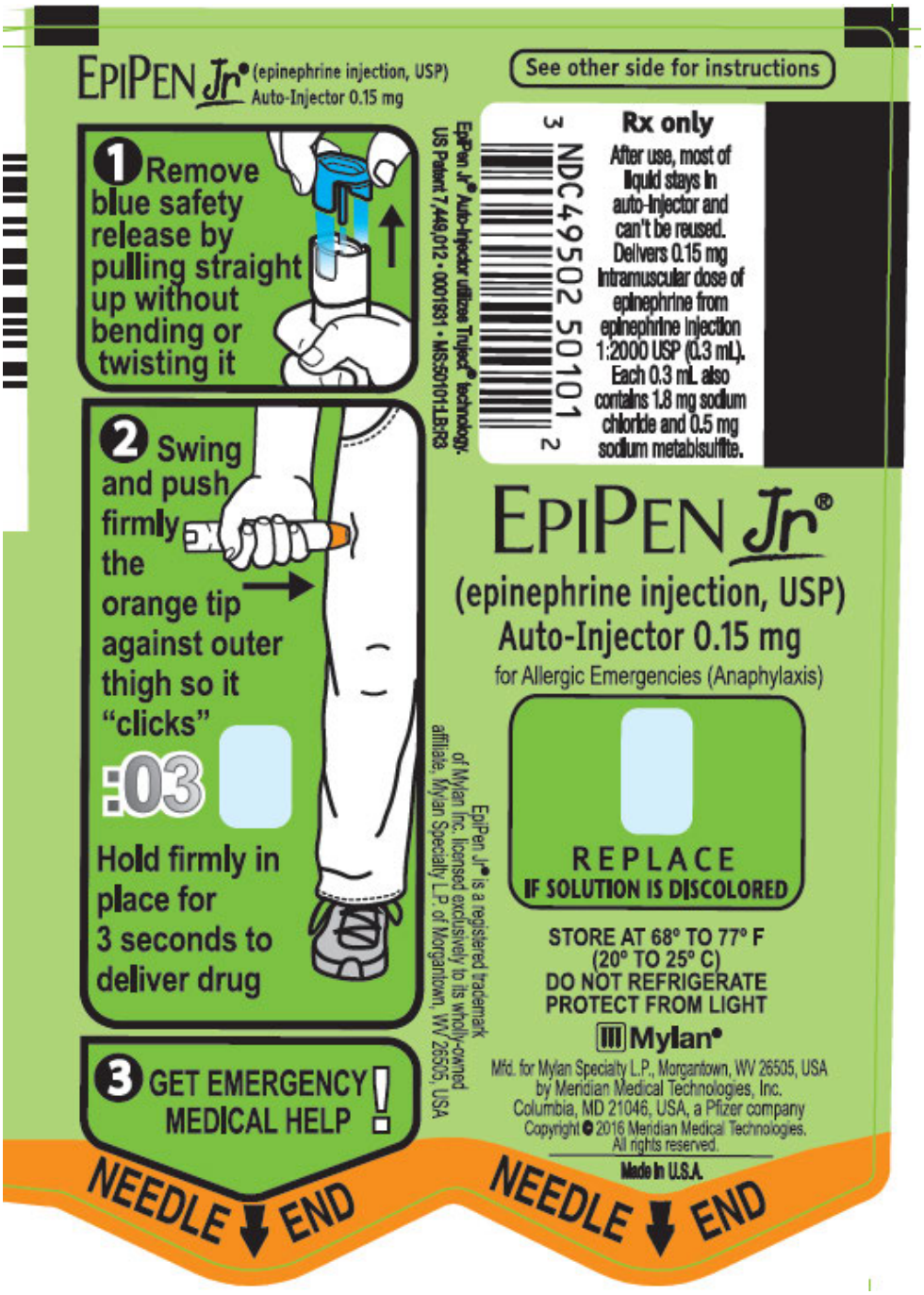
Reviewer Comments:

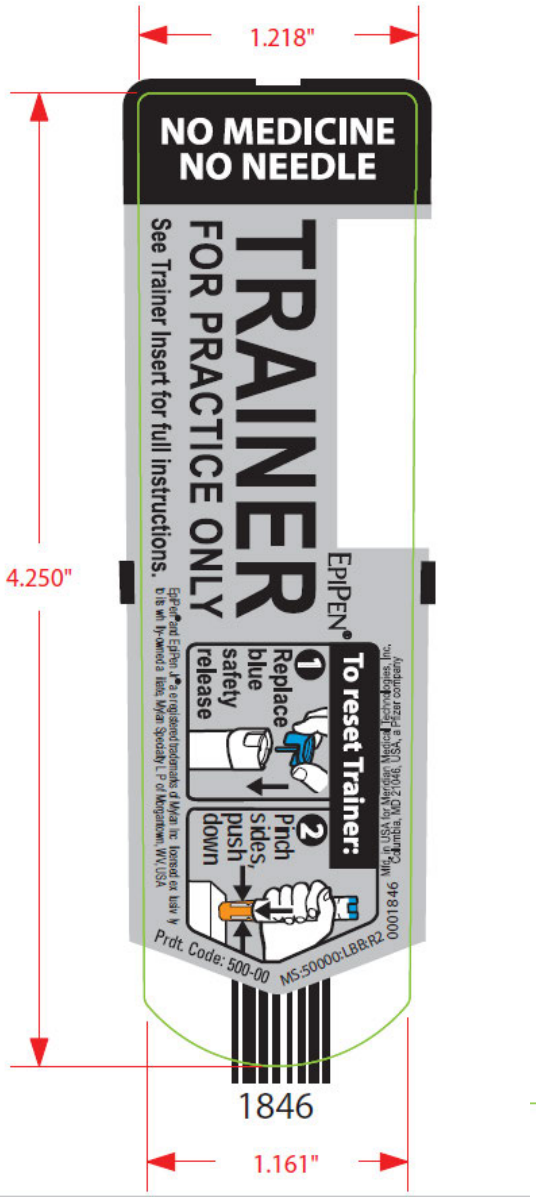
Review of the insert labeling [PI, Patient Information, Instruction for Use] was based on the RLD labeling NDA 19430/S-061 approved 5/18/2016. The PI is acceptable. As mentioned under section 2, revision is needed in the Instruction for Use on the illustration step #2 to maintain consistency with the RLD and to further clarify the proper injection site.

3.3 MODEL CONTAINER LABELS

Model container/carton/blister labels [Source: NDA 019430/S-061, submitted 6/1/2016]

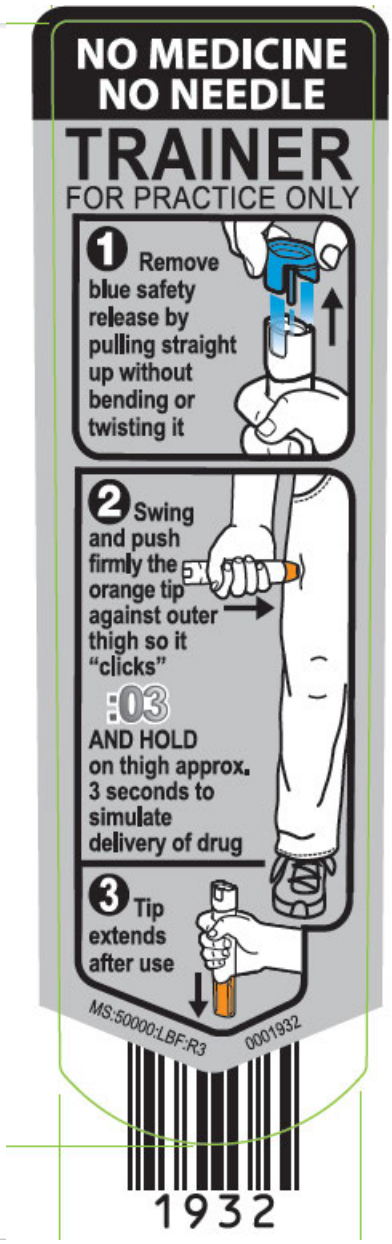

EPIPEN® (epinephrine injection, USP)
Auto-Injector 0.3 mg
See other side for instructions
1 Remove blue safety release by pulling straight up without bending or twisting it
2 Swing and push firmly the orange tip against outer thigh so it "clicks"
:03
Hold firmly in place for 3 seconds to deliver drug
3 GET EMERGENCY MEDICAL HELP
NEEDLE END
NEEDLE END
EpiPen® Auto-Injector utilizes Trufect® technology.
US Patent 7,449,012 • 0001930 • MS:50001:LB:R3
3 NDC 49502 50001 5
Rx only
After use, most of liquid stays in auto-injector and can't be reused.
Delivers 0.3 mg intramuscular dose of epinephrine from epinephrine injection 1:1000 USP (0.3 mL).
Each 0.3 mL also contains 1.8 mg sodium chloride and 0.5 mg sodium metabisulfite.
EPIPEN®
(epinephrine injection, USP)
Auto-Injector 0.3 mg
for Allergic Emergencies (Anaphylaxis)
REPLACE
IF SOLUTION IS DISCOLORED
STORE AT 68° TO 77° F
(20° TO 25° C)
DO NOT REFRIGERATE
PROTECT FROM LIGHT
Mylan
Mfd. for Mylan Specialty L.P., Morgantown, WV 26505, USA
by Meridian Medical Technologies, Inc.
Columbia, MD 21046, USA, a Pfizer company
Copyright © 2016 Meridian Medical Technologies.
All rights reserved.
Made in U.S.A.
EpiPen® is a registered trademark of Mylan Inc. licensed exclusively to its wholly-owned affiliate, Mylan Specialty L.P. of Morgantown, WV 26505, USA


EPIPEN Jr® (epinephrine injection, USP)
Auto-Injector 0.15 mg
See other side for instructions
1 Remove blue safety release by pulling straight up without bending or twisting it
2 Swing and push firmly the orange tip against outer thigh so it "clicks"
3 GET EMERGENCY MEDICAL HELP
Hold firmly in place for 3 seconds to deliver drug
NEEDLE END
NEEDLE END
EpiPen Jr® Auto-Injector utilizes Trujject® technology.
US Patent 7,449,012 • 0001931 • MS-50101-LBR3
3 NDC 49502 50101 2
Rx only
After use, most of liquid stays in auto-injector and can't be reused.
Delivers 0.15 mg intramuscular dose of epinephrine from epinephrine injection 1:2000 USP (0.3 mL).
Each 0.3 mL also contains 1.8 mg sodium chloride and 0.5 mg sodium metabisulfite.
EPIPEN Jr®
(epinephrine injection, USP)
Auto-Injector 0.15 mg
for Allergic Emergencies (Anaphylaxis)
REPLACE
IF SOLUTION IS DISCOLORED
STORE AT 68° TO 77° F
(20° TO 25° C)
DO NOT REFRIGERATE
PROTECT FROM LIGHT
Mylan®
Mfd. for Mylan Specialty L.P., Morgantown, WV 26505, USA
by Meridian Medical Technologies, Inc.
Columbia, MD 21046, USA, a Pfizer company
Copyright © 2016 Meridian Medical Technologies.
All rights reserved.
Made in U.S.A.
EpiPen Jr® is a registered trademark of Mylan Inc. licensed exclusively to its wholly-owned affiliate, Mylan Specialty L.P. of Morgantown, WV 26505, USA



(Front remains the same)

Source: NDA 019430/S-058



(Back modified – step 2)

Source NDA 19430/S-061

EPIPEN 2-PAK®
(epinephrine injection, USP)
Auto-Injectors 0.3 mg

Never put thumb, fingers or hand over orange tip.
Do **not** remove blue safety release until ready to use.

EpiPen 2-Pak® contains 2 **EpiPen®** Auto-Injectors and 1 Trainer.
Each **EpiPen®** Auto-Injector delivers one 0.3 mg intramuscular dose of epinephrine from epinephrine injection 1:1000 USP (0.3 mL).
Discard unit after use. The Trainer contains no medicine and no needle.
Read enclosed patient package insert carefully before using.

NDC 49502-500-02

For Allergic Emergencies (Anaphylaxis)

Rx only

EPIPEN 2-PAK®
(epinephrine injection, USP)
Auto-Injectors 0.3 mg

Each carton contains: **Two yellow EpiPen® Auto-Injectors** **One grey Trainer**

Register your EpiPen®Auto-Injectors at **www.epipen.com** to receive free refill reminders

Mylan®

EPIPEN 2-PAK®
(epinephrine injection, USP)
Auto-Injectors 0.3 mg

Mylan®

EPIPEN 2-PAK®
(epinephrine injection, USP)
Auto-Injectors 0.3 mg

Replace if discolored. Store at 68° to 77°F (20° to 25°C). Do not refrigerate. Protect from light.

3 49502 50002 2

Open This End

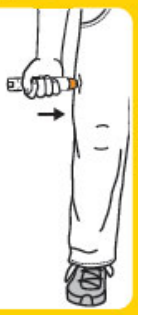
See enclosed Patient Information Leaflet for complete instructions for use.

1. Remove the blue safety release by pulling straight up without bending or twisting it

2. Swing and push firmly the orange tip against outer thigh so it "clicks"

:03

Hold firmly in place for 3 seconds to deliver drug



3. GET EMERGENCY MEDICAL HELP

Note: The needle comes out of the orange tip. Never put your thumb, fingers or hand over the orange tip.

Open This End

See enclosed Patient Information Leaflet for complete instructions for use.

1. Remove the blue safety release by pulling straight up without bending or twisting it

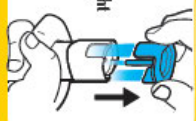
2. Swing and push firmly the orange tip against outer thigh so it "clicks"

:03

Hold firmly in place for 3 seconds to deliver drug

3. GET EMERGENCY MEDICAL HELP

Note: The needle comes out of the orange tip. Never put your thumb, fingers or hand over the orange tip.



EPIPEN 2-PAK®
(epinephrine injection, USP)
Auto-Injectors 0.3 mg

Mylan®

Scan here to learn more

EPIPEN Jr 2-PAK®
(epinephrine injection, USP)
Auto-Injectors 0.15 mg

Never put thumb, fingers or hand over orange tip.
Do **not** remove blue safety release until ready to use.

EpiPen Jr 2-Pak® contains 2 **EpiPen Jr**® Auto-Injectors and 1 Trainer.
Each **EpiPen Jr**® Auto-Injector delivers one 0.15 mg intramuscular dose of epinephrine from epinephrine injection 1:2000 USP (0.3 mL).
Discard unit after use. The Trainer contains no medicine and no needle.
Read enclosed patient package insert carefully before using.

NDC 49502-501-02

For Allergic Emergencies (Anaphylaxis)

Rx only

EPIPEN Jr 2-PAK®
(epinephrine injection, USP)
Auto-Injectors 0.15 mg

Each carton contains: **Two green EpiPen Jr®** Auto-Injectors **One grey Trainer**

Register your EpiPen Jr® Auto-Injectors at www.epipen.com to receive free refill reminders

Mylan®

EPIPEN Jr 2-PAK®
(epinephrine injection, USP)
Auto-Injectors 0.15 mg

Mylan®

Replace if discolored. Store at 68° to 77°F (20° to 25°C). Do not refrigerate. Protect from light.

Manufactured for Mylan Specialty LP, Morgantown, WV 26505, USA by Meridian Medical Technologies, Inc., Columbia, MD 21046, USA, a Pfizer company
EpiPen® and EpiPen Jr® are registered trademarks of Mylan Inc. licensed exclusively to its wholly-owned affiliate, Mylan Specialty L.P. of Morgantown, WV 26505, USA

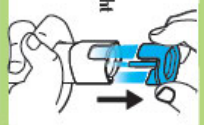
3 49502 50102 9

EPIPEN Jr 2-PAK®
(epinephrine injection, USP)
Auto-Injectors 0.15 mg

Open This End

See enclosed Patient Information Leaflet for complete instructions for use.

1. Remove the blue safety release by pulling straight up without bending or twisting it



2. Swing and push firmly the orange tip against outer thigh so it "clicks"
:03
Hold firmly in place for 3 seconds to deliver drug

3. GET EMERGENCY MEDICAL HELP!

Note: The needle comes out of the orange tip. Never put your thumb, fingers or hand over the orange tip.

Open This End

EPIPEN Jr 2-PAK®
(epinephrine injection, USP)
Auto-Injectors 0.15 mg

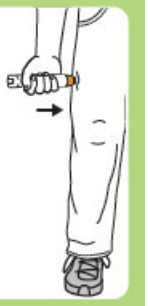
Mylan®

Open This End

See enclosed Patient Information Leaflet for complete instructions for use.

1. Remove the blue safety release by pulling straight up without bending or twisting it

2. Swing and push firmly the orange tip against outer thigh so it "clicks"
:03
Hold firmly in place for 3 seconds to deliver drug



3. GET EMERGENCY MEDICAL HELP!

Note: The needle comes out of the orange tip. Never put your thumb, fingers or hand over the orange tip.

EPIPEN Jr 2-PAK®
(epinephrine injection, USP)

Mylan®

Scan here to learn more

3.4 UNITED STATES PHARMACOPEIA (USP) & PHARMACOPEIA FORUM (PF)

We searched the USP and PF to determine if the drug product under review is the subject of a USP monograph or proposed USP monograph.

Table 2: USP and PF Search Results				
	Date Searched	Monograph? YES or NO	Monograph Title (NA if no monograph)	Packaging and Storage/Labeling Statements (NA if no monograph)
USP	11/2/2016	YES	**Epinephrine Injection**	**Packaging and storage—**Preserve in single-dose or multiple-dose, light-resistant containers, preferably of Type I glass. **Labeling—**The label indicates that the Injection is not to be used if its color is pinkish or darker than slightly yellow or if it contains a precipitate.
PF	11/2/2016	YES	**Epinephrine Injection**	Same as above

Reviewer Comments:

3.5 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 11/3/2016.

Table 3 provides Orange Book patents for the Model Labeling NDA 019430 and ANDA patent certifications.

(For applications that have no patents, N/A is entered in the patent number column)

Table 3: Impact of Model Labeling Patents on ANDA Labeling						
Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact (enter "Carve-out" or "None")
7449012	9/11/2025			IV	12/30/2014	None
7794432	9/11/2025			IV	12/30/2014	None
8048035	9/11/2025			IV	12/30/2014	None
8870827	9/11/2025			IV	12/30/2014	None

Reviewer Assessment:

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

Reviewer Comments:

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

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

Table 4: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling					
Click here to enter text.					

Reviewer Assessment:

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

Reviewer Comments:

Click here to enter text.

4. DESCRIPTION, HOW SUPPLIED AND MANUFACTURED BY STATEMENT

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

Reviewer Assessment:

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

Table 5: Comparison of DESCRIPTION Section or Inactive Ingredients Subsection (OTC)		
Previous Labeling Review	**Currently Proposed**	**Assessment**
Each 0.3 mL in the Epinephrine Injection USP, 0.3 mg (Auto-Injector) contains 0.3 mg epinephrine, USP, 1.8 mg sodium chloride, 0.4 mg sodium metabisulfite, 0.4 mg sodium tartrate (dihydrate), hydrochloric acid to adjust pH, and water for injection. The pH range is 2.2 to 5.0. Each 0.3 mL in the Epinephrine Injection USP, 0.15 mg (Auto-Injector) contains 0.15 mg epinephrine, USP, 1.8 mg sodium chloride, 0.4 mg sodium metabisulfite, 0.2 mg sodium tartrate (dihydrate), hydrochloric acid to adjust pH, and water for injection. The pH range is 2.2 to 5.0.	Each 0.3 mL in the Epinephrine Injection USP, 0.3 mg (Auto-Injector) contains 0.3 mg epinephrine, USP, 1.8 mg sodium chloride, 0.4 mg sodium metabisulfite, 0.4 mg sodium tartrate (dihydrate), hydrochloric acid to adjust pH, and water for injection. The pH range is 2.2 to 5.0. Each 0.3 mL in the Epinephrine Injection USP, 0.15 mg (Auto-Injector) contains 0.15 mg epinephrine, USP, 1.8 mg sodium chloride, 0.4 mg sodium metabisulfite, 0.2 mg sodium tartrate (dihydrate), hydrochloric acid to adjust pH, and water for injection. The pH range is 2.2 to 5.0.	**same**

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

Table 6: Comparison of HOW SUPPLIED Section or Packaging Sizes for OTC Products		
Epinephrine Injection USP, 0.3 mg (Auto-Injectors) (epinephrine injections USP, 1:1000, 0.3 mL) are available as Epinephrine Injection USP, 0.3 mg 2-Pack, NDC 0093-5986-27, a pack that contains two Epinephrine Injection USP, 0.3 mg (Auto-njectors) (epinephrine injections USP, 1:1000, 0.3 mL) and one Epinephrine njection (Auto-Injector) trainer device. **Epinephrine Injection USP, 0.15 mg (Auto-Injectors) (epinephrine injections USP, 1:2000, 0.3 mL) are available** as Epinephrine njection USP, 0.15 mg 2-Pack, NDC 0093-5985-27, a pack that contains two Epinephrine njection USP, 0.15 mg (Auto-Injectors) (epinephrine injections USP, 1:2000, 0.3 mL) and one Epinephrine Injection (Auto-Injector) trainer device. Epinephrine Injection USP, 0.3 mg 2-Pack and Epinephrine Injection USP, 0.15 mg 2-Pack also includes an Wclip to clip two auto-injectors together.	Epinephrine Injection USP, 0.3 mg (Auto-njectors) (epinephrine injections USP, 1:1000, 0.3 mL) are available as Epinephrine Injection USP, 0.3 mg 2-Pack, NDC 0093-5986-27, a pack that contains two Epinephrine Injection USP, 0.3 mg (Auto-Injectors) (epinephrine injections USP, 1:1000, 0.3 mL) and one Epinephrine Injection (Auto-Injector) trainer device. Epinephrine Injection USP, 0.15 mg (Auto-njectors) (epinephrine injections USP, 1:2000, 0.3 mL) are available as Epinephrine Injection USP, 0.15 mg 2-Pack, NDC 0093-5985-27, a pack that contains two Epinephrine Injection USP, 0.15 mg (Auto-Injectors) (epinephrine njections USP, 1:2000, 0.3 mL) and one Epinephrine Injection (Auto-Injector) trainer device. Epinephrine Injection USP, 0.3 mg 2-Pack and Epinephrine Injection USP, 0.15 mg 2-Pack also nclude an W-clip to clip two auto-injectors together. \	**Same**

Table 7: Manufacturer/Distributor/Packer Statements		
Previous Labeling Review	**Currently Proposed**	**Assessment**
Manufactured For: **TEVA PHARMACEUTICALS USA, INC.** North Wales, PA 19454 Iss. 11/2015	Manufactured For: **Teva Pharmaceuticals USA, Inc.** North Wales, PA 19454 Iss. 7/2016	**same**

5. COMMENTS FOR CHEMISTRY REVIEWER

Describe issue(s) sent to and/or received from the chemistry (also known as drug product quality) reviewer:

Reviewer Comments:

Click here to enter text.

6. COMMENTS FOR OTHER REVIEW DISCIPLINES

Describe questions/issue(s) sent to and/or received from other discipline reviewer(s):

Reviewer Comments:

DLR's CONSULT TO DMEPA

On 10/11/2016. DLR sent a consult to DMEPA for the review of the container labels, carton labeling, and the insert labeling with following specific request:

COMMENTS/SPECIAL INSTRUCTIONS: Please evaluate TEVA's labeling and labels as follows:

1. NDA 19430/S-61 (EpiPen and EpiPen Jr) approved on May 18, 2016, provides for new safety information that modifies the instruction for use of the drug product. Specifically, in order to address the reports of the laceration and embedded needles caused by the auto-injector used in the children, the container label, carton labeling, and the Instruction for Use leaflet are revised (step #2 in the instruction) and the "hold" time for the injection is decreased from 10 seconds to 3 seconds.

2. In addition, we would like to consult on the presentation of the established name between the adult and the pediatric strength for ANDA 90589 so that the two strengths are adequately differentiated for safe use by the two population groups. The established name is "Epinephrine Injection USP, 0.3 mg (Auto-Injector)" for the adult strength and "Epinephrine Injection USP, 0.15 mg (Auto-Injector)" for the pediatric strength. In addition to using different carton color, RLD further differentiates the adult dose from the pediatric dose by adding "Jr" after the product name for the lower dose. However we note that "Jr" cannot be used for the generic product as "Jr" is part of registered trademark for the RLD EpiPen Jr. We would like to consult on any alternative approach to differentiating the two strengths. Will it be acceptable to add statements such as "Adult dose" and " Pediatric dose"; "Adult Auto Injector" or "Pediatric Auto Injector" after the established name or would it be allowable/acceptable to include weight requirement on the carton labeling to provide differentiation between the two doses. For an example, please note that Auvi-Q (epinephrine injection USP, NDA

eference ID: 3998197

201739; TE code BX) uses same proprietary name on both strengths. The two strengths are differentiated by use of different carton color (blue for 0.3mg and orange for 0.15 mg strength) and further differentiated by adding the patient weight requirement on the PDP of the carton.

3. Lastly, please evaluate our labeling comments to the applicant and provide any comment related to the safe use of the product. Below are the comments to the applicant.

I. GENERAL COMMENTS

Please be advised that if any additional labeling concerns are raised upon Agency's evaluation of your response to the comments related to the auto-injector device and its safe use, we may have further labeling comments.

II. CONTAINER LABEL (0.30 mg and 0.15 mg)

a. Revise your label to be in accordance with the most recently approved label for the reference listed drug (RLD), EpiPen® and EpiPen Jr®, NDA019430/S-061, approved May 18, 2016.

b. We recommend further increasing the prominence of the established name and the strength.

III. CARTON LABELING (0.30 mg and 0.15 mg)

a. Revise your labeling to be in accordance with the most recently approved labeling for the RLD, EpiPen® and EpiPen Jr®, NDA019430/S-061, approved May 18, 2016.

b. Provide further differentiation between the 0.3 mg and 0.15 mg auto-injectors to ensure that the products are adequately differentiated to prevent possible product selection error. As currently presented, your proposed products are not adequately differentiated between the two strengths. We recommend using colors that provide sufficient contrast for the strength statements or using other means to differentiate the two strengths (e.g., boxing, highlighting, etc.).

c. To decrease clutter on the principal display panel (PDP), you may consider relocating "Register your… to receive free refill reminders.." statement to the side panel.

d. Delete the duplicate statement ("Each Carton Contains….") on the side panel, immediately below "(Auto-Injectors) 2 Pack.

IV. PRESCRIBING INFORMATION (Insert Labeling, Patient Information and Instruction for Use)

a. Revise your labeling to be in accordance with the most recently approved labeling for the RLD, EpiPen® and EpiPen Jr®, NDA019430/S-061, approved May 18, 2016.

b. Revise "Epinephrine Injection USP, 0.3 mg and Epinephrine Injection USP, 0.15 mg (Auto-Injectors)" to following. Please note as both strengths are auto-injectors the two products should be expressed consistently.
"Epinephrine Injection USP, 0.3 mg and Epinephrine Injection USP, 0.15 mg"
or
"Epinephrine Injection USP, 0.3 mg (Auto-Injector) and Epinephrine Injection USP, 0.15 mg (Auto-Injector)

Upon review of the 10/28/2016 amendment, DLR sent additional comments to DMEPA as following:

1. Please note that applicant provided labeling amendment on 10/28/2016. We would like to inform you that the applicant provided revised labeling to be in accordance with recently revised RLD labeling NDA 019430/s-061 approved May 18, 2016. We find that the revision is consistent with the RLD labeling update. Although the applicant did not yet receive the deficiency comments that were sent to you with the consult request on 10/11/2016, their labeling amendment addresses those comments also.

2. Please note that the applicant provided further product differentiation by revising the carton color from [redacted] (b) (4) to green (0.15mg strength) and to yellow (0.3 mg strength). However, as requested in our consult to you, further written differentiation may be needed in place of [redacted] (b) (4) designated for the lower strength in the RLD labeling.

3. We note that the picture of the [redacted] (b) (4). This is not a change from the previously proposed labeling, however upon further review of the illustration, we note that the proposed picture may not clearly depict the location of the injection site versus the illustration provided in the RLD labeling.

DMEPA's RESPONSE:

DMEPA_2016-2377
and 2016-2346 Epinep

Following is taken from DMEPA's review (attached above) OSE RCM # 2016-2377 and 2016-2346, pg 5 &6:

In addition, OGD requested that we review the container labels, carton labeling, the prescribing information, labeling comments provided by OGD, and the presentation of the established name between the adult and pediatric strengths.

We reviewed the labels and labeling and we agree with the recommendations provided by OGD (see Appendix F). The two strengths have been differentiated by color; however, the proposed product will not list the term [redacted] (b) (4) on the 0.15 mg/0.3 mL strength. Therefore, the established name presentation between the products, only differ by the strength. We note that this differentiation may not be sufficient alone to distinguish between the adult strength and the pediatric strength. In addition, upon review on the illustration demonstrating the location to inject, we note that the illustration does not contain [redacted] (b) (4) We agree with OGD, that the proposed picture may not clearly depict the location of the injection site versus the illustration provided in the RLD labeling. Therefore, we provide recommendations to further differentiate the two strengths and to clarify the injection site in Section 4.1.

5 CONCLUSION & RECOMMENDATIONS

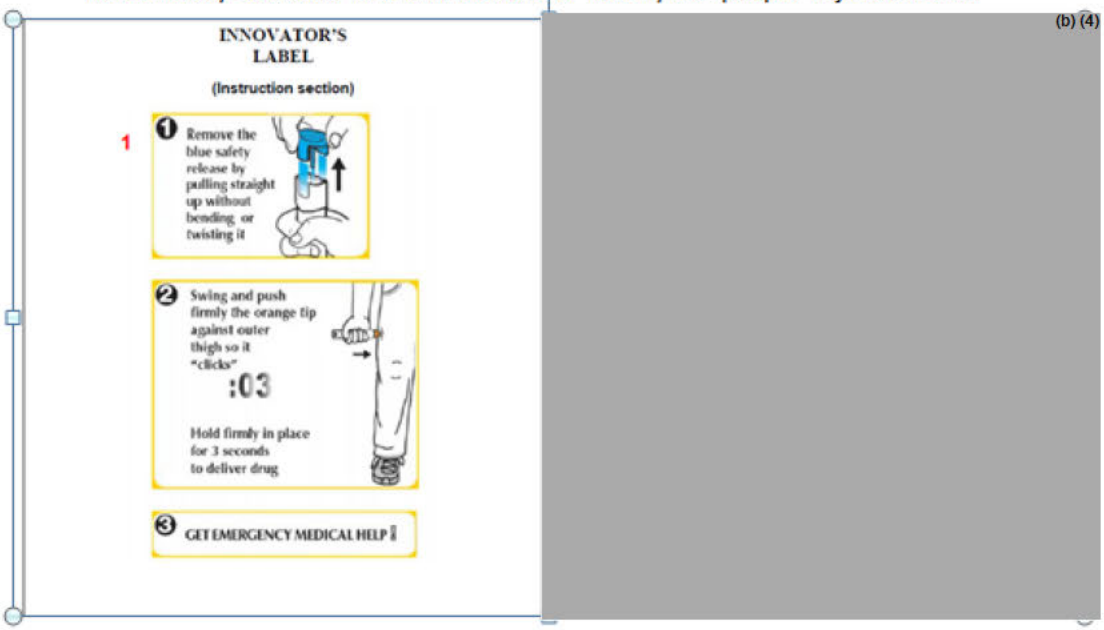
In regards to the human factors data submitted on September 26, 2016, we agree with the assessment of the Office of Biostatistics that there is no difference between AJE and RLD with regard to cumulative use error rates, and the design difference of the cap with AJE does not introduce a new risk of error compared to the tube with RLD. We note that the proposed label and labeling information can be improved to increase the prominence of important information to promote the safe use of the product.

5.1 RECOMMENDATIONS FOR THE OFFICE OF GENERIC DRUGS

We recommend the following be implemented prior to approval of this ANDA:

A. All Labels and Labeling

1. Under step 2 (see below) we note that your illustration does not include the full leg as pictured under step 2 in the RLD. This may cause confusion as the injection site is not clearly depicted in your illustration. Revise the illustration to maintain consistency with the RLD and to further clarify the proper injection site.



B. Carton Label

1. Add the statement, "FOR ALLERGIC EMERGENCIES in patients weighing 33lbs to 66lbs" on the 0.15 mg strength and "FOR ALLERGIC EMERGENCIES in patients weighing over 66lbs" on the 0.3 mg strength to further differentiate the strengths.

7. OVERALL ASSESSMENT OF MATERIALS REVIEWED

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

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

Table 8: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	Packaging Sizes	Submission Received Date	Recommendation

Container	Final	0.15 mg/ 0.3mL 0.3 mg/ 0.3 mL	10/28/2016	Revise
Blister	NA			
Carton	Final	2 Pak (two injections and one trainer device)	10/28/2016	Revise
(Other – specify)	NA			
Table 9 Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	**Revision Date and/or Code**	**Submission Received Date**	**Recommendation**
Prescribing Information	Final	Click here to enter text.	10/28/2016	Satisfactory
Trainer Instruction for Use	Final	Click here to enter text.	10/28/2016	Revise (Step 2 illustration)
Patient Information and Instruction for Use	Final	Click here to enter text.	10/28/2016	Revise (Step 2 illustration)
SPL Data Elements		Revised: 10/2016	10/28/2016	Satisfactory

LABELING REVIEW – Addendum to Rev #5

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

Date of This Review	12/10/2015 9/26/2016 Addendum ***[This addendum review supersedes previous review #5. Sections written in this blue color are the changes from the previous review dated 12/10/2015. This addendum was created to address the new RLD labeling update approved on 5/18/2016 on the container, carton, PI, and patient information/instruction for use leaflet.***
ANDA Number(s)	090589
Review Number	5- **Addendum**
Applicant Name	Teva Pharmaceuticals USA
Established Name & Strength(s)	Epinephrine Injection USP, 0.3 mg (Auto-Injector) and Epinephrine Injection USP, 0.15 mg (Auto-Injector)
Proposed Proprietary Name	N/A
Submission Received Date	11/18/2015
Labeling Reviewer	Eunjung Esther Chuh
Labeling Team Leader	Thuyanh (Ann) Vu

Review Conclusion

☐ ACCEPTABLE – No Comments.

☐ ACCEPTABLE – Include Post Approval Comments

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

*Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Easily Correctable Deficiency if all other OGD reviews are acceptable. Otherwise, the labeling minor deficiencies will be included in the Complete Response (CR) letter to the applicant.

☐ On Policy Alert List

1. LABELING COMMENTS

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT

Labeling Deficiencies determined on October 3, 2016, based on your submission dated November 18, 2015.

1. GENERAL COMMENTS

   Please be advised that if any additional labeling concerns are raised upon Agency's evaluation of your response to the comments related to the auto-injector device and its safe use, we may have further labeling comments.

2. CONTAINER LABEL (0.30 mg and 0.15 mg)
   a. Revise your label to be in accordance with the most recently approved label for the reference listed drug (RLD), EpiPen® and EpiPen Jr®, NDA019430/S-061, approved May 18, 2016.

   b. We recommend further increasing the prominence of the established name and the strength.

3. CARTON LABELING (0.30 mg and 0.15 mg)
   a. Revise your labeling to be in accordance with the most recently approved labeling for the RLD, EpiPen® and EpiPen Jr®, NDA019430/S-061, approved May 18, 2016.

   b. Provide further differentiation between the 0.3 mg and 0.15 mg auto-injectors to ensure that the products are adequately differentiated to prevent possible product selection error. As currently presented, your proposed products are not adequately differentiated between the two strengths. We recommend using colors that provide sufficient contrast for the strength statements or using other means to differentiate the two strengths (e.g., boxing, highlighting, etc.).

c. To decrease clutter on the principal display panel (PDP), you may consider relocating "Register your… to receive free refill reminders.." statement to the side panel.

d. Delete the duplicate statement ("Each Carton Contains….") on the side panel, immediately below "(Auto-Injectors) 2 Pack.

4. PRESCRIBING INFORMATION (Insert Labeling, Patient Information and Instruction for Use)
   a. Revise your labeling to be in accordance with the most recently approved labeling for the RLD, EpiPen® and EpiPen Jr®, NDA019430/S-061, approved May 18, 2016.

   b. Revise "Epinephrine Injection USP, 0.3 mg and Epinephrine Injection USP, 0.15 mg (Auto-Injectors)" to following. Please note as both strengths are auto-injectors the two products should be expressed consistently.

      "Epinephrine Injection USP, 0.3 mg and Epinephrine Injection USP, 0.15 mg"
      Or
      "Epinephrine Injection USP, 0.3 mg (Auto-Injector) and Epinephrine Injection USP, 0.15 mg (Auto-Injector)

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

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with your last submitted labeling with all differences annotated and explained.

Prior to the submission of your amendment, please check labeling resources, including DRUGS@FDA, the electronic Orange Book and the NF-USP online, for recent updates and make any necessary revisions to your labels and labeling.

In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address –

http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE

The Division of Labeling has no further questions/comments at this time based on your labeling submission (s) dated (add date)

1.3 POST APPROVAL REVISIONS

These comments will NOT be sent to the applicants at this time.
These comments will be addressed post approval (in the first labeling supplement review).

None

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

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

REVIEW HISTORY

12/21/2007	Original ANDA 090589 submitted to FDA
11/21/2008	Original ANDA 090589 received to FDA for filing
6/4/2009	Labeling Review #1 completed
10/12/2010	Labeling Amendment, response to deficiencies issued on 6/4/2009
2/2/2011	Labeling Review #2 completed
8/1/2014	Labeling Amendment. Response to deficiencies issued on 2/2/2011. Also provides for update to be in accordance with the innovator labeling update approved on 4/30/2014.
9/26/2013	Labeling Review #3. ***(Deficiencies to this review is not yet sent out as Complete Response Letter is pending Agency. The comments issued to the applicant from review #4 will supersede the comments that were prepared for the applicant on review #3.)***
12/30/2014	Quality Minor Amendment and Unsolicited Amendment to provide for change in the manufacturing and testing site, formulation and device. Specifically the application provides for following change: drug product manufacturing site and device assembly site change; formulation [redacted (b) (4)] sodium metabisulfite [redacted (b) (4)] and [redacted (b) (4)] sodium tartrate [redacted (b) (4)] in accordance with CFR 314.94(a)(9)(iii); and change to the device to improve the design to ensure the user will not be presented with a device that has delivered the drug product but has not engaged the safety guard. This amendment also provides for a Human Factor Study.
11/18/2015	Easily Correctable Deficiency(ECD) Amendment, response to ECD sent to the applicant on 11/3/2015. *This amendment is subject of this review.*

PREVIOUS DEFICIENCY AND FIRM'S RESPONSE

The below comments are from the labeling review C4 based on the submission dated 12/30/2014"

The Agency's original comment is presented below in bold, followed by Teva's response.

Labeling Comments:

1. GENERAL COMMENTS

a. The drug product name should be expressed consistently throughout the labeling. For an example you refer to your product as "Epinephrine 0.3 mg (auto-injector)", "Epinephrine Auto-Injector (0.3 mg)" and also as "epinephrine auto-injector". Please revise. We refer you to the established name of the drug product, "Epinephrine Injection USP, 0.3 mg" and "Epinephrine Injection USP, 0.15 mg".

Response:

For consistency, we have expressed our drug product name as Epinephrine Injection USP, 0.3 mg" and "Epinephrine Injection USP, 0.15 mg". Also, for consistency we called out the term "auto-injector" throughout the labeling to match the RLD.

b. We note that you refer to your lower strength auto-injector as "(b) (4) Auto-Injector". (b) (4) is not a conventional way of expressing lower dose strength of a drug product and (b) (4) found in the name from the Reference Listed Drug (RLD) is part of a registered trademark. Please comment.

Response:

We have removed all reference to (b) (4) from our labeling and we refer to the lower strength as "Epinephrine Injection USP, 0.15 mg".

2. CARTON LABEING

a. Revise, "I.M. use" to "Intramuscular use".

Response:

We have revised "I.M. use" to "Intramuscular use".

b. Revise, "Replace if discolored." to correspond to the USP 37-NF 32 (8/1/2014-11/30/2014) labeling statement below:
"The label indicates that the Injection is not to be used if its color is pinkish or darker than slightly yellow or if it contains a precipitate."

Response:

We have revised our discolored solution statement to comply with USP 37-NF 32 (8/2/2014-11/30/2014). The discolored solution statement now reads, "Replace if the epinephrine solution appears discolored) pinkish or darker than slightly yellow) or if it contains a precipitate."

c. The color bands with "TEVA" are more prominent than the color bands that distinguish the strengths of the two products. Revise the presentations so that the green color bands representing the auto-injector for the 0.15 mg and the yellow color bands representing the 0.3 mg strength are the most prominent color bands on each label respectively.

Response:

We have increased the color bands on the labeling as request. When we submit final printed labeling we will further distinguish the product strengths by using (b) (4) (b) (4) however,

3. PRESCRIBING INFORMATION

a. **HIGHLIGHTS OF PRESCRIBING INFORMATION Highlights Limitation Statement: Revise "Epinephrine Injection" to read "EPINEPHRINE INJECTION" (all in capital letters) to comply with the PLR format.**

Response:

We have revised the product name to all capital letters in the HIGHLIGHTS section to comply with the PLR format.

b. **The "Epinephrine" in the product title, immediately above the U. S. approval date, should be revised to all capital letters "EPINEPHRINE" to comply with the RLR format requirements.**

Response:

We have revised the product name in the product title to all capital letters to comply with the PLR format requirements.

c. **Revise the description of the discolored solution in applicable sections to correspond to the USP 37-NF 32 (8/1/2014-11/30/2014) labeling statement below:**
"The label indicates that the Injection is not to be used if its color is pinkish or darker than slightly yellow or if it contains a precipitate."

Response:

We have revised our discolored solution statement to comply with USP 37-NF 32 (8/2/2014-11/30/2014). The discolored solution statement now reads, "Replace if the epinephrine solution appears discolored) pinkish or darker than slightly yellow) or if it contains a precipitate."

4. PATIENT INFORMATON AND INSTRUCTION FOR USE

1.11.4 Response to FDA Request for Information - Multiple Module

a. **Under "How should I store.." after 4th bullet, we note that you have deleted the fourth bullet provided under the RLD. Please add this bullet which instructs the patients to protect the device from damage and water. Revise the statement to fit your drug product (no carrier tube).**

Response:

We have added the 4th bullet to our labeling to instruct the patients to protect the device from damage and water.

b. **Revise "Epinephrine Trainer" to Epinephrine Injection Trainer".**

Response:

We have revised the Epinephrine Trainer to read "Epinephrine Injection Trainer".

5. **TRAINING INSTRUCTION**

a. **We encourage you to align the three steps under the Practice Instruction as with RLD.**

Response:

We have revised Trainer Practice Instructions to align with the three steps of the RLD Trainer Practice Instructions. We believe that the Practice Instructions are now equivalent from a user perspective and that the steps included in the revised Practice Instructions fully simulate the auto-injector experience drug training.

b. **We encourage you to make the headings (i.e.: "Practice Instruction", "Practice Session Information") more prominent such as by highlighting them as seen with the RLD.**

Response:

We have made the heading "Practice Instruction" and "Practice Session Information" more prominent by revising them to match the RLD.

6. **STRUCTURED PRODUCT LABELING (SPL)**

Revise the total volume in the Strength Statement to read as "0.3 mg in 0.3 mL" (from "0.3 mg in 1 mL") and to read as "0.15 mg in 0.3 mL" (from 0.15 mg in 1 mL") for the lower strength auto-injector.

Response:

We have revised the total volume in the strength statement to read as 0.3 mg in 0.3 mL and 0.15 mg in 0.3 mL. Also, the dosage form was changed to "Injection".

Reviewer Comments to the applicant's response submitted on November 18, 2015:

Applicant's response to the deficiencies is acceptable. Product name is revised to remove (b) (4) for the lower strength (0.15 mg) and the established name is expressed consistently throughout the labeling as requested. Labeling statement regarding the discoloration/precipitation of the solution required by the USP is properly placed on all labeling.

Further comments need to be communicated to the applicant.

-Carton and Container - Applicant need to ensure that the product name and the strength are most prominently placed on the container and the carton. Also, recommend further differentiation between the two strengths by use of color, etc.

-Insert Labeling – Throughout the insert, the proposed products are sometimes expressed as "epinephrine injection, 0.3 mg and epinephrine injection, 0.15 mg (auto-injector)". As both strengths are auto-injectors, the two products should be expressed consistently. Recommend deleting the "(auto-injector)" after the 0.15 mg or adding the "(auto-injector)" after the 0.3 mg.

-All label/labeling need to be revised to be in accordance with the new RLD labeling NDA S-61 approved 5/18/16.

2.1 CONTAINER AND CARTON LABELS

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

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

Reviewer Comments:

2.2 ADDITIONAL BACKGROUND INFORMATION PERTINENT TO THE REVIEW

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

Reviewer Comments:

Following are from previous review cycle #4:

Notes for the record

1)The labels and labeling provided on this unsolicited amendment was reviewed and comments are under section 1.Labeling Comments. However complete analysis of the labeling on the drug product is deferred until the evaluation of the device and the human factor study provided on this amendment is complete. The human factor study was requested by CDRH for the applicant to demonstrate that the device can be used by the representative users under simulated use conditions without producing patterns of failures that could result in negative clinical impact to patients or injury to the device users.

2)There is a Citizen's Petition submitted to the Agency on 1/16/2015 by Mylan which requests Agency to refrain from approving this ANDA "unless, after conducting an appropriately rigorous review under the established standards for proposed generic emergency use auto-injectors, the agency concludes that the proposed product is the "same as" the EpiPen® auto-injector". Much of their concern is related to the proper use of the auto-injector in an emergency situation. This reviewer also notes the difference in the device, such as the "twist off" function of the cap for the proposed product versus the "pull out" of the cap from a carrier tube on the RLD. At this time, the evaluation on the functionality and safe use of the device as a generic equivalent to RLD is pending with the subject experts in the Agency

3) Teva refers the lower dose epinephrine injection as (b) (4) Auto-Injector". As RLD name is trademarked as following: Epipen®, Epipen JR®, Epipen JR2-Pak®, this reviewer finds that the generic of Epipen Jr should not be referred as the (b) (4) Auto- Injector". Even if the (b) (4) is not trademarked, the terminology of (b) (4) Auto- Injector" is not a conventional way of referring to a lower strength auto-injector. This reviewer finds that (b) may be proposed as a part of a proprietary name or the applicant may indicate the lower strength without the designation of (b) (4)

NOTE ON PREVIOUS CONSULTS ON THE ANDA:

11/13/2008 OGD consulted OND (Division of Pulmonary and Allergy Products) for a comparative review between the MOA of the Innovator's Auto-Injector versus TEVA's proposed Auto Injector. Per the consult response, it was concluded that the mechanism of action (mechanism of release) is the same between the TEVA's and the innovator's product and that Teva's product should be filed under the 505(j) pathway.

5/29/2009 Consult to CDRH on the device master file. CDRH requested that the applicant submit a Human Factors Study as part of the demonstration that generic device use is the same as the RLD device use. *Human Factor Study submitted on 12/30/2014 is pending review.*

4/29/2013 Consult to Division of Clinical Review on the difference on the length of the needle. Per the consult, slightly longer needle length of Teva's product compared to the RLD is not clinically significant, and should not be a factor in the approval of ANDA 90589 as a generic to EpiPen.

Update on the consults:

Consults to CDRH(device), DCR (formulation) OSE(human factor study) are completed and deficiency comments are incorporated by appropriate review disciplines. Refer to the Complete Response Deficiency letter that will be issued for the comments.

It is noted that OSE/DMEPA concluded that the Human Factor Study did not show that the end users who are switching from the reference listed product (RLD) to the proposed product can safely and effectively use the proposed product in accordance with the product's Instructions for Use (IFU) without the prescribing health care provider's intervention or training prior to use, and that the difference in the steps between the two devices may lead to errors if the product is substituted for the EpiPen (RLD) without additional training. DMEPA's review also noted that the approval of the proposed product as a generic substitution for the EpiPen may result in detrimental error due to confirmation bias with current EpiPen users.

2015-1409
Epinephrine Human Fa

Review of Human Factor Study (DMEPA/OSE)] DRAFT review

Since my review #5 on 12/10/2015, DMEPA's "draft" review (above) was finalized on 2/11/2016 with

conclusion that the data provided by the applicant is insufficient to show that it can be substituted with the RLD without additional training or physician intervention before use of the proposed product.

2015-1409
Epinephrine Human Fa

5 CONCLUSION

DMEPA concludes that the study data results show that some current users of EpiPen who may be dispensed the AJE product in place of EpiPen without additional training prior to use would not be able to use the proposed AJE product appropriately. Thus, there is continued residual uncertainty regarding whether the proposed AJE can be substituted for the RLD.

The study report data identifies a new type of use error for the AJE product in the first step of administration (i.e., not twisting off the yellow cap) that is attributable to a difference in a critical design attribute in design of the AJE product when compared to the EpiPen product. In addition, the Applicant has not provided sufficient comparative data to characterize whether the rate of error in removing the cap of the AJE product among current EpiPen users is less than, or not significantly greater than, the rate of error in removing the carrier tube if those current EpiPen users continued to use only EpiPen. Furthermore, the Applicant did not identify any measure to mitigate this error. Although the data do not allow us to characterize the expected rate of occurrence of this particular error with the proposed AJE product in actual use because of limitations in the study design employed, we can reasonably conclude from the data that if the proposed AJE is approved under 505(j) (and subsequently substituted for EpiPen), FDA would expect that some current users of EpiPen would be unable to use the Applicant's proposed product appropriately based on the pattern of observed errors and close calls observed in the human factors study. It may be possible that the rate of errors observed with this task for the AJE product is within an acceptable margin so as not to be significantly worse than the rate of errors observed with the RLD task of removing the carrier tube, but the data from this human factors study are insufficient to support this conclusion. On this basis we find that the data provided by the Applicant with respect to its proposed AJE product is insufficient to show that the proposed AJE product can be substituted for the RLD without additional training or physician intervention before use of the proposed AJE. We understand that this Applicant has outstanding deficiencies that will be communicated in a Complete Response (CR) letter, and recommend that OGD communicate this deficiency to the Applicant in such CR letter. We also would be happy to work with OGD further post-CR letter to assist the Applicant with respect to submitting data that might be appropriate to address this deficiency.

ANDA90589.TEVA.Epi
Pen.CDRH Engineering

[Review of the Device– CDRH] 10/23/2015

CP citizen petition (Docket No: FDA-2015-P-0181): Agency has denied the petition to refrain from approving the current application by Teva (ANDA 090589) unless a rigorous review under the established standards for proposed generic emergency use auto-injectors was performed and the Agency concludes that the proposed product is the same as the EpiPen auto-injectors. CP was denied on 6/15/2015.

CP.pdf

[CP Response] 6/15/2015

More on Consults:

9/11/2016: Division of Bio III sent consult to OPQ and DCR regarding the sodium tartrate dehydrate (STD) in the proposed product. Per DBE III review dated 9/12/2016 in GDRP, the responses received from OPQ and DCR supported the BE portion of the application to remain in adequate status.

9/1/2016: OPQ sent consult to CDRH for assessment of the cGMP compliance of the device manufacturing facility (b) (4) and for determination on whether an inspection is needed or if the facility is currently acceptable. *This consult is currently pending.*

Model RLD Labeling approved 5/18/2016:

RLD labeling (NDA S-061) approved 5/18/2016 provides for changes in the container label, carton labeling, Prescribing Information, and Patient Information and Instruction for Use. ANDA applicant will need to revise all their label/labeling to be in in accordance with the updated RLD labeling.

Background on the approval of NDA S-061 [Taken from the Medical Officer's Review, Division of Pulmonary Allergy and Rheumatology Products, 5/2/2016]:

NDA S-061 was submitted in response to a February 5, 2016, FDAA, Safety Labeling Changes Notification Letter for two safety issues of lacerations and embedded needles caused by epinephrine auto-injector use in children, and Clostridial infections following injection of epinephrine for treatment of anaphylaxis. These safety issues were each the subject of a Tracked Safety Issue (TSI) involving each of the approved epinephrine products, TSI 1541for lacerations, etc., and TSI 1555 for Clostridial infections.

IV. Labeling

The agreed class labeling (Warnings and Precautions) for the above safety issues is summarized below. Note that the Division decided that only the auto-injectors need to have the safety issue of injection related injuries added as a Warning and Precaution. The epinephrine injection products that are administered in a hospital/clinic setting only have additional class language regarding the need to hold the leg during the injection in the Dosage and Administration section. In addition to changes to the Warnings and Precautions, related changes were incorporated in the Dosage and Administration, Adverse Reactions, Patient Information, and Instructions for Use (IFU) sections. Specifically, the new Instructions for Use include the class statement that "If you are administering [product name] to a young child, hold the leg firmly in place and limit movement prior to and while administering an injection." The agreed upon language is very similar to the original language in the February 9, 2016, FDAAA SLC Notification Letter.

New Warnings and Precautions

The following class labeling is being added to Section 5.2, Injection-Related Complications:

> **Hold the leg firmly during injection**. Lacerations, bent needles, and embedded needles have been reported when [product name] has been injected into the thigh of young children who are uncooperative and kick or move during an injection. To minimize the risk of injection related injury when administering [product name] to young children, instruct caregivers to hold the child's leg firmly in place and limit movement prior to and during injection.

The following class labeling is being added as a new section:

> **Serious Infections at the Injection Site**. Rare cases of serious skin and soft tissue infections, including necrotizing fasciitis and myonecrosis caused by Clostridia (gas gangrene), have been reported at the injection site following epinephrine injection for anaphylaxis. *Clostridium* spores can be present on the skin and introduced into the deep tissue with subcutaneous or intramuscular injection. While cleansing with alcohol may reduce presence of bacteria on the skin, alcohol cleansing does not kill *Clostridium* spores. To decrease the risk of *Clostridium* infection, do not inject [product name] into the buttock. Advise patients

to seek medical care if they develop signs or symptoms of infection, such as persistent redness, warmth, swelling, or tenderness, at the epinephrine injection site.

Other Labeling Changes

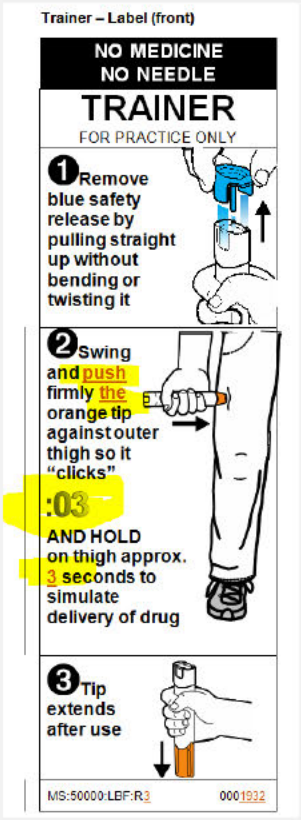
As noted above, all factors that contribute to the safe use of these products were considered as part of these supplements. In that regard, each manufacturer was asked to respond to specific safety questions regarding their product as well as to provide safety suggestions as to how to address these issues. As part of their response, Mylan proposed to change the Instructions for Use to a 3-second hold time after triggering the injection, and they provided and/or referenced the data to support this request. After review, the Division found that Mylan's request is reasonable, in light of the fact that 1) this shortened time might reduce the likelihood of lacerations while parents or caregivers are trying to maintain the needle in the thigh of a child who is fighting an injection, and 2) the shortened hold time still factors in a large safety margin over the actual injection time. As a result, the instruction set in the EpiPen IFU (and in other locations of the EpiPen labeling) was changed from the current "Hold firmly against the thigh for approximately 10 seconds to deliver the drug" to an instruction to "Hold firmly in place for 3 seconds (count slowly 1, 2, 3)" before removing the auto-injector from the thigh.

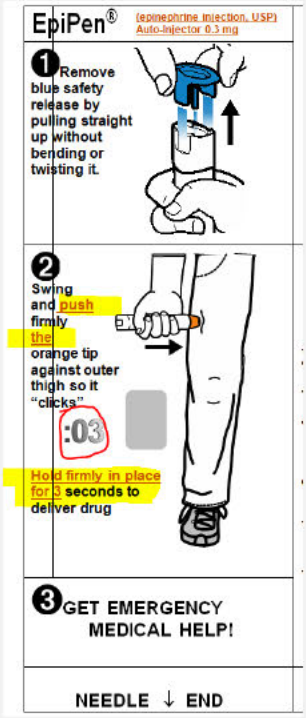
Below are changes that were made on the RLD labeling (S-061):

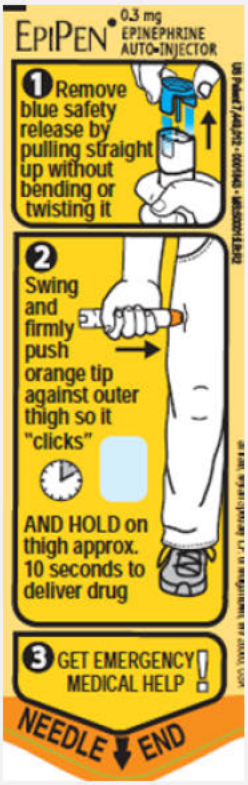
Container and carton for both strengths were revised on Step #2 of the injection instruction:

- **Revised "Swing and firmly push" to "Swing and push firmly the orange tip"**
- **Revised "10 seconds" to "3 seconds" both in words in graphic.**
- **Revised "AND HOLD on thigh approx.. 10 seconds.." to "Hold firmly in place for 3 seconds.."**
- ***Note that proposed ANDA product has the same direction as previous RLD labeling. Applicant will need to modify the labeling to be in accordance with the RLD labeling. In terms of the change in the instruction for use and the hold time, DMEPA will be consulted to ensure that the same type of change is appropriate for the proposed ANDA product as the proposed device is not same as the RLD.***

(b) (4)







Trainer **Epipen**

Updated RLD(S-061) **Previous RLD (S-058)** **Proposed ANDA**

Prescribing Information:

Following statements were added to the NDA labeling to address the injection related complications and the infection at the injection site:

- **2 DOSAGE AND ADMINISTRATION**
  - **Following statements were added:**

    Inject EpiPen or EpiPen Jr intramuscularly or subcutaneously into the anterolateral aspect of the thigh, through clothing if necessary. Instruct caregivers of young children who are prescribed an EpiPen or EpiPen Jr and who may be uncooperative and kick or move during an injection to hold the leg firmly in place and limit movement prior to and during an injection [*see Warnings and Precautions (5.2)*].

- **5 WARNING AND PRECAUTIONS**
  - **Section 5.2 Injection-Related Complications [fourth bullet added with statements below**

    - **Hold leg firmly during injection.** Lacerations, bent needles, and embedded needles have been reported when EpiPen and EpiPen Jr have been injected into the thigh of young children who are uncooperative and kick or move during an injection. To minimize the risk of injection related injury when administering EpiPen to young children, instruct caregivers to hold the child's leg firmly in place and limit movement prior to and during injection.

  - **5.3 Serious Infection at the Injection Site [this new section was added]**

5.3 Serious Infections at the Injection Site

Rare cases of serious skin and soft tissue infections, including necrotizing fasciitis and myonecrosis caused by Clostridia (gas gangrene), have been reported at the injection site following epinephrine injection for anaphylaxis. *Clostridium* spores can be present on the skin and introduced into the deep tissue with subcutaneous or intramuscular injection. While cleansing with alcohol may reduce presence of bacteria on the skin, alcohol cleansing does not kill *Clostridium* spores. To decrease the risk of *Clostridium* infection, do not inject EpiPen into the buttock [see *Warnings and Precautions (5.2)*]. Advise patients to seek medical care if they develop signs or symptoms of infection, such as persistent redness, warmth, swelling, or tenderness, at the epinephrine injection site.

- **6 ADVERSE REACTIONS** [following highlighted paragraphs are added at the end of this section]

Lacerations, bent needles, and embedded needles have been reported when EpiPen has been injected into the thigh of young children who are uncooperative and kick or move during the injection [*see Warning and Precautions (5.2)*].

Injection into the buttock has resulted in cases of gas gangrene [*see Warnings and Precautions (5.2)*].

Rare cases of serious skin and soft tissue infections, including necrotizing fasciitis and myonecrosis caused by Clostridia (gas gangrene), have been reported following epinephrine injection, including EpiPen, in the thigh [*see Warnings and Precautions (5.3)*].

- **17 PATIENT COUNSELING INFORMATION**
  - **Under Administration and Training following statements were added**

Instruct caregivers to hold the leg of young children firmly in place and limit movement prior to and during injection. Lacerations, bent needles, and embedded needles have been reported when EpiPen and EpiPen Jr have been injected into the thigh of young children who are uncooperative and kick or move during an injection [*see Warnings and Precautions (5.2)*].

  - **Following sub-heading and section was added:**

Serious Infections at the Injection Site

Rare cases of serious skin and soft tissue infections, including necrotizing fasciitis and myonecrosis caused by Clostridia (gas gangrene), have been reported at the injection site following epinephrine injection for anaphylaxis. Advise patients to seek medical care if they develop signs or symptoms of infection, such as persistent redness, warmth, swelling, or tenderness, at the epinephrine injection site [*see Warnings and Precautions (5.3)*].

Patient Information and Instruction for Use

- Patient Information: Following highlighted sections were added

What are the possible side effects of the EpiPen and EpiPen Jr?

EpiPen and EpiPen Jr may cause serious side effects.

- **The EpiPen or EpiPen Jr should only be injected into the middle of your outer thigh (upper leg). Do not** inject the EpiPen or EpiPen Jr into your:
  - veins
  - buttocks
  - fingers, toes, hands, or feet

  If you accidentally inject EpiPen or EpiPen Jr into any other part of your body, go to the nearest emergency room right away. Tell the healthcare provider where on your body you received the accidental injection.

- Rarely, patients who have used EpiPen or EpiPen Jr may develop infections at the injection site within a few days of an injection. Some of these infections can be serious. Call your healthcare provider right away if you have any of the following at an injection site:
  - redness that does not go away
  - swelling
  - tenderness
  - the area feels warm to the touch

- Cuts on the skin, bent needles, and needles that remain in the skin after the injection, have happened in young children who do not cooperate and kick or move during an injection. If you inject a young child with EpiPen or EpiPen Jr, hold their leg firmly in place before and during the injection to prevent injuries. Ask your healthcare provider to show you how to properly hold the leg of a young child during injection.

- Instruction for use – following highlighted sections were revised in Step 2:
  - It is noted that the proposed ANDA's instruction for use is the same as previously approved RLD (S-058) for Step 2. ***DMEPA will be consulted to ensure that the same type of change is appropriate for the proposed ANDA product as the proposed device is not same as the RLD.***

Step 2. Administer EpiPen or EpiPen Jr

If you are administering EpiPen or EpiPen Jr to a young child, hold the leg firmly in place while administering an injection.

Place the orange tip against the middle of the outer thigh (upper leg) at a right angle (perpendicular) to the thigh.

Swing and push the auto-injector firmly until it 'clicks'. The

click signals that the injection has started.

Hold firmly in place for 3 seconds (count slowly 1,2,3).
The injection is now complete.

Remove the auto-injector from the thigh. The orange tip will extend to cover the needle. If the needle is still visible, do not attempt to reuse it.

Massage the injection area for 10 seconds.

3. LABELING REVIEW INFORMATION AND REVIEWER ASSESSMENT

3.1 REGULATORY INFORMATION

Are there any pending issues in DLR's Repository files? NO If Yes, please explain in section 2.2 Additional Background Information Pertinent to the Review
Are there any pending issues in DLR's SharePoint Drug Facts? NO If Yes, please explain.
Is the drug product listed in the Policy Alert Tracker on OGD's SharePoint? NO If Yes, please explain.

3.2 MODEL PRESCRIBING INFORMATION

Table 1: Review Model Labeling for Prescribing Information and Patient Labeling (Check the box used as the Model Labeling)

☒ **MOST RECENTLY APPROVED NDA MODEL LABELING**

(If NDA is listed in the discontinued section of the Orange Book, also enter ANDA model labeling information.)

NDA# /Supplement# (S-000 if original): NDA 019430/S-061

Supplement Approval Date: 5/18/2016

Proprietary Name: EpiPen Auto-Injector and EpiPen Jr Auto-Injector

Established Name: epinephrine

Description of Supplement:

We also refer to our letter dated February 5, 2016, notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we believe should be included in the labeling for EpiPen and EpiPen Jr (epinephrine injection). This information pertains to reports of lacerations and embedded needles after epinephrine injection and post-marketing adverse event reports of serious infection (e.g. *Clostridium perfringens*) at the injection site following epinephrine injection for anaphylaxis.

This supplemental new drug application provides for revisions to the labeling for EpiPen and EpiPen Jr. consistent with our February 5, 2016, letter and the changes agreed upon in our March 24, and 31, and April 15, 2016, correspondences, and changes to the carton and container labeling to incorporate USP information and revised instructions for use.

NOTE: Review #5 was based on RLD labeling NDA 19430/ S-058 approved on 7/17/2014 which provided for update on the carton, container, and trainer label. [PAS was to update the carton labels to provide a visual summary of the three steps (Prepare, Administer, and Finalize) used to administer EpiPen, and to ensure that the administration summaries on the carton, container, and trainer labels match the three steps for administration of EpiPen in the approved instructions for use.]

☐ **MOST RECENTLY APPROVED ANDA MODEL LABELING**

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

Supplement Approval Date: Click here to enter text.

Proprietary Name: Click here to enter text.

Established Name: Click here to enter text.

Description of Supplement: Click here to enter text.

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

☐ OTHER (Describe):

Reviewer Assessment:

Is the Prescribing Information same as the model labeling, except for differences allowed under 21 CFR 314.94(a)(8)? **NO**

Are the specific requirements for format met under 21 CFR 201.57(new) or 201.80(old)? **YES**

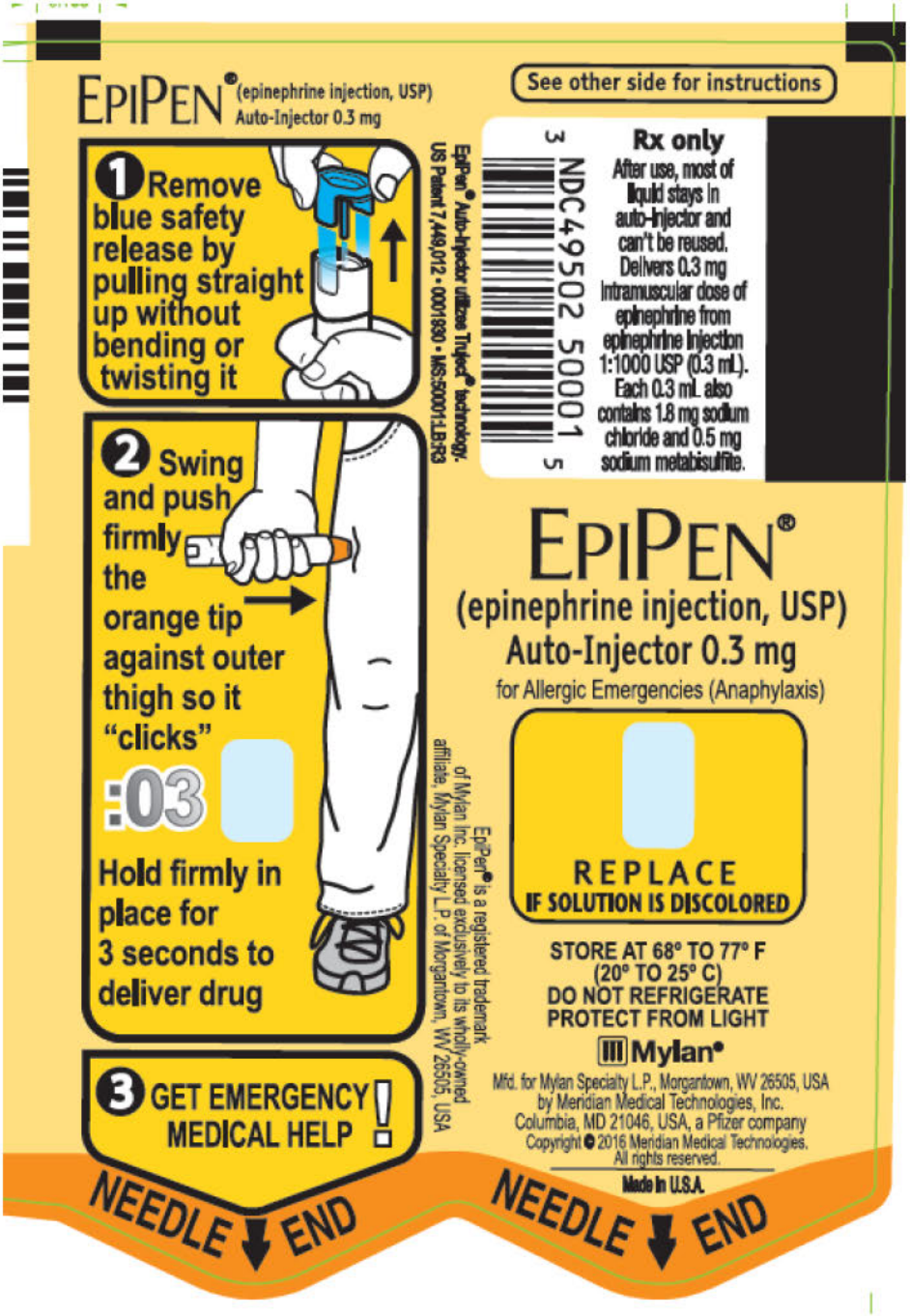
Does the Model Labeling have combined insert labeling for multiple dosage forms? **NO**

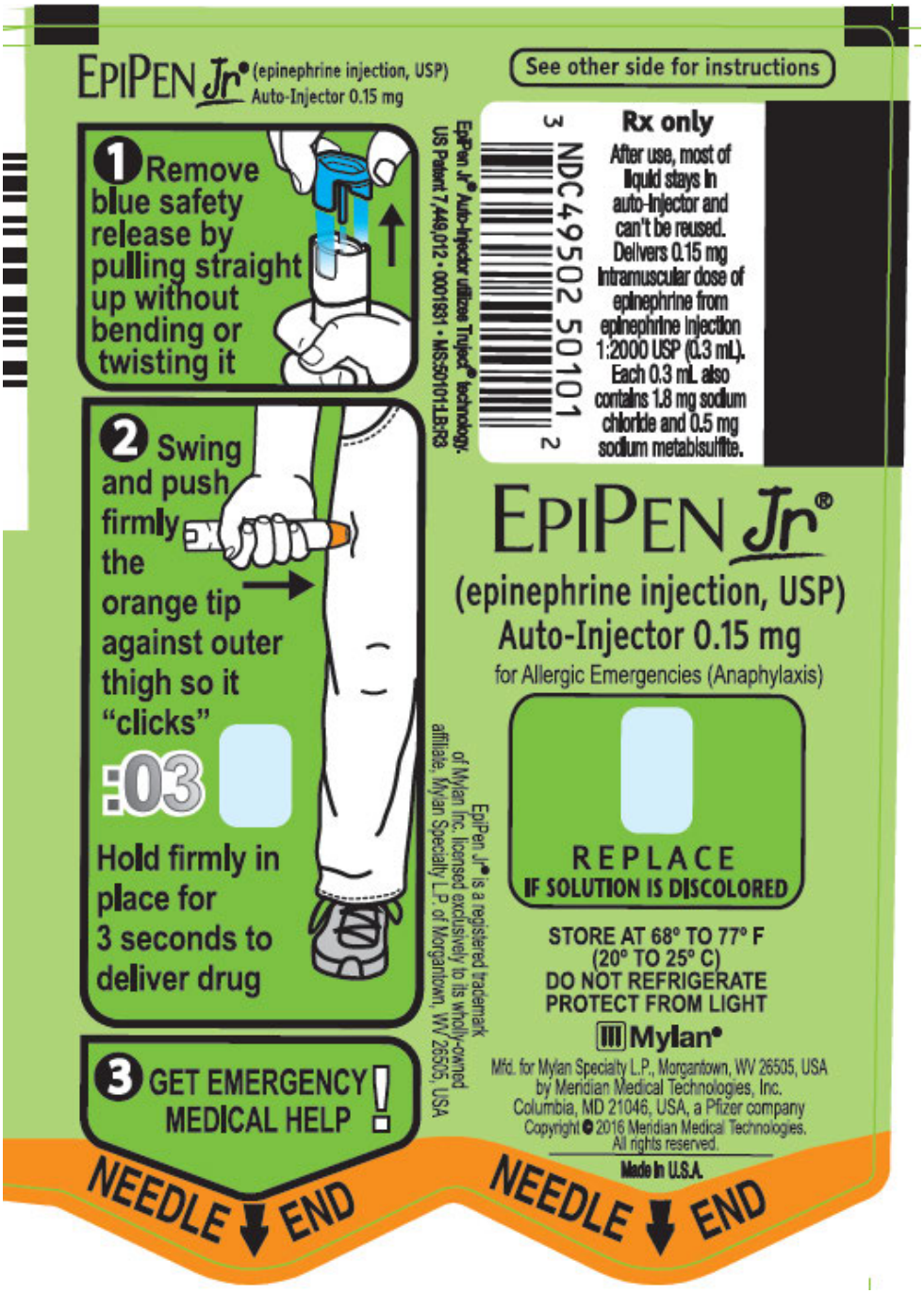
Reviewer Comments:

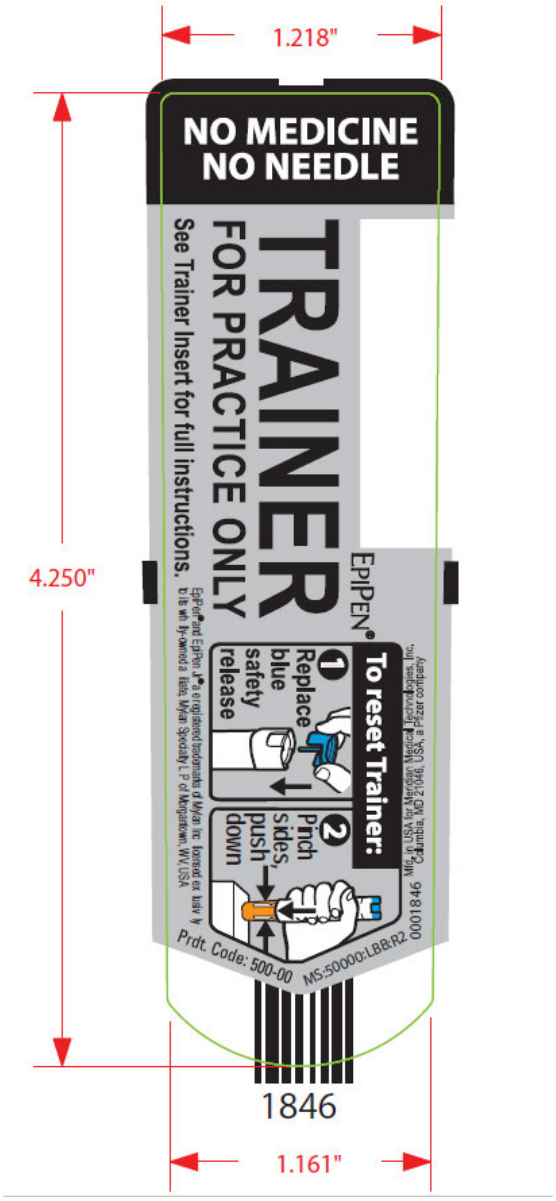
Applicant will need to revise the labeling (PI, Patient Information, Instruction for Use) to be in accordance with the RLD labeling NDA 19430/S-061 approved 5/18/2016. **HOWEVER**, please note that further evaluation of the inserts may be needed based on any change to the device made per the OSE's recommendation from the review of the Human Factor Study, Per the review by OSE (2015-1409), "DMEPA concludes that the validation study results do not show that end users who are switching from the reference listed product to the AJE can safely and effectively use the proposed product in accordance with the product's Instructions for Use (IFU) without the prescribing health care provider's intervention or training prior to use.". Refer to Additional Background section 2.2 for further information on the consult review.

3.3 MODEL CONTAINER LABELS

Model container/carton/blister labels [Source: NDA 019430/S-061, submitted 6/1/2016]

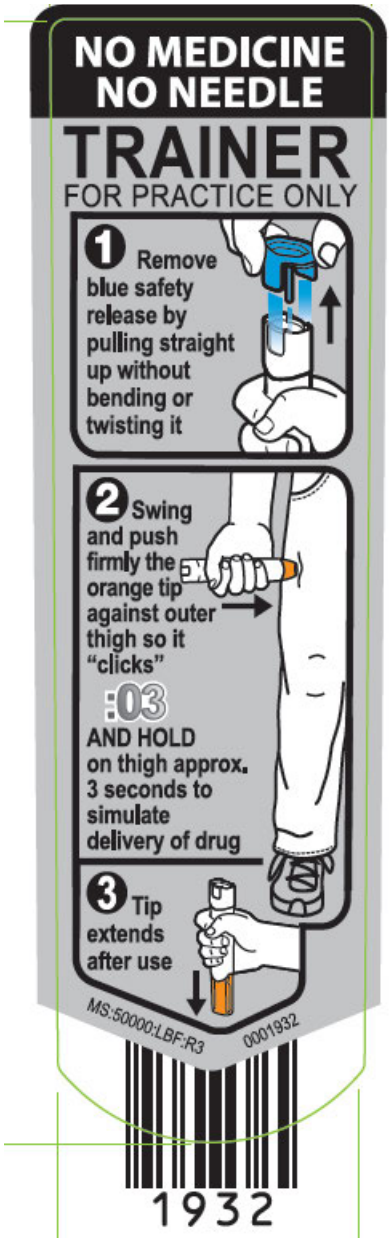



EPIPEN Jr® (epinephrine injection, USP)
Auto-Injector 0.15 mg
See other side for instructions
1 Remove blue safety release by pulling straight up without bending or twisting it
2 Swing and push firmly the orange tip against outer thigh so it "clicks"
03
Hold firmly in place for 3 seconds to deliver drug
3 GET EMERGENCY MEDICAL HELP
NEEDLE END
EpiPen Jr® Auto-Injector utilizes Trujject® technology.
US Patent 7,449,012 • 0001931 • MS-50101-LBR3
3 NDC 49502 50101 2
Rx only
After use, most of liquid stays in auto-injector and can't be reused.
Delivers 0.15 mg intramuscular dose of epinephrine from epinephrine injection 1:2000 USP (0.3 mL).
Each 0.3 mL also contains 1.8 mg sodium chloride and 0.5 mg sodium metabisulfite.
EPIPEN Jr®
(epinephrine injection, USP)
Auto-Injector 0.15 mg
for Allergic Emergencies (Anaphylaxis)
REPLACE
IF SOLUTION IS DISCOLORED
STORE AT 68° TO 77° F
(20° TO 25° C)
DO NOT REFRIGERATE
PROTECT FROM LIGHT
Mylan®
Mfd. for Mylan Specialty L.P., Morgantown, WV 26505, USA
by Meridian Medical Technologies, Inc.
Columbia, MD 21046, USA, a Pfizer company
Copyright © 2016 Meridian Medical Technologies.
All rights reserved.
Made in U.S.A.
EpiPen Jr® is a registered trademark of Mylan Inc. licensed exclusively to its wholly-owned affiliate, Mylan Specialty L.P. of Morgantown, WV 26505, USA
NEEDLE END



(Front remains the same)

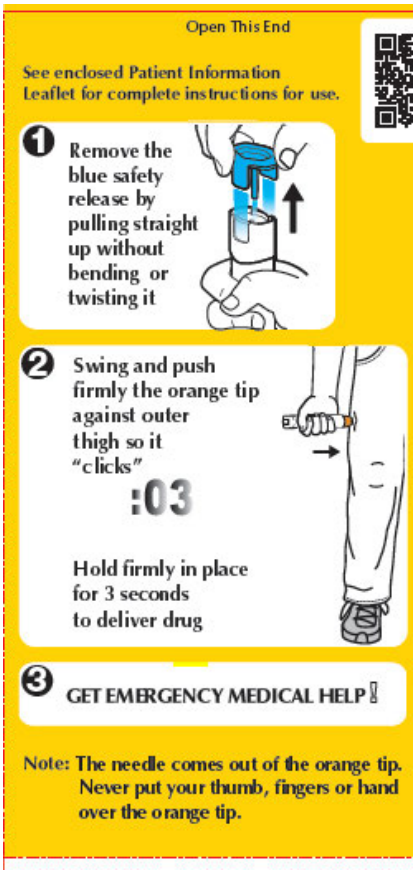
Source: NDA 019430/S-058



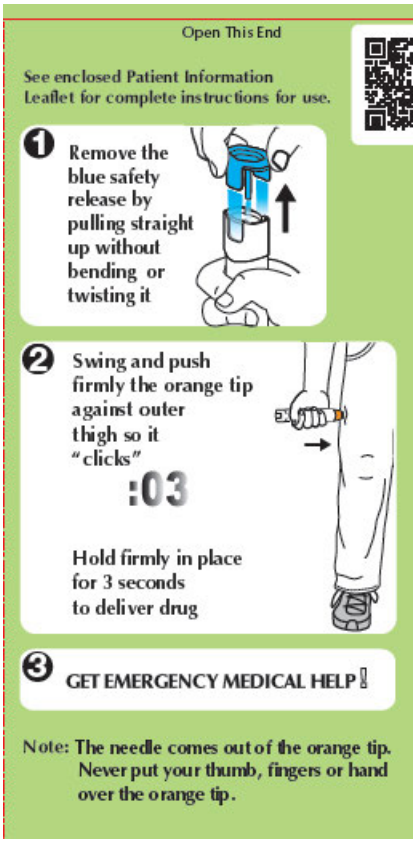
(Back modified – step 2)

Source NDA 19430/S-061


EPIPEN 2-PAK®
(epinephrine injection, USP)
Auto-Injectors 0.3 mg
Never put thumb, fingers or hand over orange tip.
Do not remove blue safety release until ready to use.
EpiPen 2-Pak® contains 2 EpiPen® Auto-Injectors and 1 Trainer.
Each EpiPen® Auto-Injector delivers one 0.3 mg intramuscular dose of epinephrine from epinephrine injection 1:1000 USP (0.3 mL).
Discard unit after use. The Trainer contains no medicine and no needle.
Read enclosed patient package insert carefully before using.
NDC 49502-500-02
For Allergic Emergencies (Anaphylaxis)
Rx only
EPIPEN 2-PAK®
(epinephrine injection, USP)
Auto-Injectors 0.3 mg
Each carton contains:
Two yellow EpiPen® Auto-Injectors
One grey Trainer
Register your EpiPen® Auto-Injectors at www.epipen.com to receive free refill reminders
Mylan®
Replace if discolored. Store at 68° to 77°F (20° to 25°C). Do not refrigerate.
Protect from light.
Manufactured for Mylan Specialty L.P., Morgantown, WV 26505, USA by Meridian Medical Technologies, Inc., Columbia, MD 21046, USA, a Pfizer company
EpiPen® and EpiPen Jr® are registered trademarks of Mylan Inc. licensed exclusively to its wholly-owned affiliate, Mylan Specialty L.P. of Morgantown, WV 26505, USA
Copyright © 2016 Meridian Medical Technologies. All rights reserved.
3 49502 50002 2
EPIPEN 2-PAK®
(epinephrine injection, USP)
Auto-Injectors 0.3 mg
Mylan®
1 Remove the blue safety release by pulling straight up without bending or twisting it
2 Swing and push firmly the orange tip against outer thigh so it "clicks"
:03
Hold firmly in place for 3 seconds to deliver drug
3 GET EMERGENCY MEDICAL HELP
Note: The needle comes out of the orange tip. Never put your thumb, fingers or hand over the orange tip.
See enclosed Patient Information Leaflet for complete instructions for use.
Open This End
EPIPEN 2-PAK®
(epinephrine injection, USP)
Auto-Injectors 0.3 mg
Mylan®
Scan here to learn more


Open This End
See enclosed Patient Information Leaflet for complete instructions for use.
1 Remove the blue safety release by pulling straight up without bending or twisting it
2 Swing and push firmly the orange tip against outer thigh so it "clicks"
:03
Hold firmly in place for 3 seconds to deliver drug
3 GET EMERGENCY MEDICAL HELP
Note: The needle comes out of the orange tip. Never put your thumb, fingers or hand over the orange tip.


EPIPEN Jr 2-PAK®
(epinephrine injection, USP)
Auto-Injectors 0.15 mg
Never put thumb, fingers or hand over orange tip.
Do not remove blue safety release until ready to use.
EpiPen Jr 2-Pak® contains 2 EpiPen Jr® Auto-Injectors and 1 Trainer.
Each EpiPen Jr® Auto-Injector delivers one 0.15 mg intramuscular dose of epinephrine from epinephrine injection 1:2000 USP (0.3 mL).
Discard unit after use. The Trainer contains no medicine and no needle.
Read enclosed patient package insert carefully before using.
NDC 49502-501-02
For Allergic Emergencies (Anaphylaxis)
Rx only
EPIPEN Jr 2-PAK®
(epinephrine injection, USP)
Auto-Injectors 0.15 mg
Each carton contains:
Two green EpiPen Jr® Auto-Injectors
One grey Trainer
Register your EpiPen Jr® Auto-Injectors at www.epipen.com to receive free refill reminders
Mylan®
Replace if discolored. Store at 68° to 77°F (20° to 25°C). Do not refrigerate. Protect from light.
Manufactured for Mylan Specialty LP, Morgantown, WV 26505, USA by Meridian Medical Technologies, Inc., Columbia, MD 21046, USA, a Pfizer company
EpiPen® and EpiPen Jr® are registered trademarks of Mylan Inc. licensed exclusively to its wholly-owned affiliate, Mylan Specialty L.P. of Morgantown, WV 26505, USA
Copyright © 2016 Meridian Medical Technologies. All rights reserved.
3 49502 50102 9
EPIPEN Jr 2-PAK®
(epinephrine injection, USP)
Auto-Injectors 0.15 mg
Mylan®
Open This End
See enclosed Patient Information Leaflet for complete instructions for use.
1 Remove the blue safety release by pulling straight up without bending or twisting it
2 Swing and push firmly the orange tip against outer thigh so it "clicks"
:03
Hold firmly in place for 3 seconds to deliver drug
3 GET EMERGENCY MEDICAL HELP
Note: The needle comes out of the orange tip. Never put your thumb, fingers or hand over the orange tip.
EPIPEN Jr 2-PAK®
Mylan®
Scan here to learn more


Open This End
See enclosed Patient Information Leaflet for complete instructions for use.
1 Remove the blue safety release by pulling straight up without bending or twisting it
2 Swing and push firmly the orange tip against outer thigh so it "clicks"
:03
Hold firmly in place for 3 seconds to deliver drug
3 GET EMERGENCY MEDICAL HELP
Note: The needle comes out of the orange tip. Never put your thumb, fingers or hand over the orange tip.

3.4 UNITED STATES PHARMACOPEIA (USP) & PHARMACOPEIA FORUM (PF)

We searched the USP and PF to determine if the drug product under review is the subject of a USP monograph or proposed USP monograph.

Table 2: USP and PF Search Results				
	Date Searched	**Monograph ? YES or NO**	**Monograph Title (NA if no monograph)**	**Packaging and Storage/Labeling Statements (NA if no monograph)**
USP	12/11/2015	YES	Epinephrine Injection	**Packaging and storage**— Preserve in single-dose or multiple-dose, light-resistant containers, preferably of Type I glass. **Labeling**— The label indicates that the Injection is not to be used if its color is pinkish or darker than slightly yellow or if it contains a precipitate.
PF	12/11/2015	YES	31(1) In-Process Revision: Epinephrine Injection	Same as above

Reviewer Comments:

Product is subject of a USP monograph with labeling requirement as stated above.

3.5 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 12/11/2015.

Table 3 provides Orange Book patents for the Model Labeling and ANDA patent certifications.

(For applications that have no patents, N/A is entered in the patent number column)

Table 3: Impact of Model Labeling Patents on ANDA Labeling						
Patent Number	**Patent Expiration**	**Patent Use Code**	**Patent Use Code Definition**	**Patent Certification**	**Date of Patent Cert Submission**	**Labeling Impact**
7449012	9/11/2025			IV	12/30/2014	None
7794432	9/11/2025			IV	12/30/2014	None
8048035	9/11/2025			IV	12/30/2014	None
8870827	9/11/2025			IV	12/30/2014	None

Reviewer Assessment:

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

Reviewer Comments:

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

Table 4: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling					
Exclusivity Code	**Exclusivity Expiration**	**Exclusivity Code Definition**	**Exclusivity Statement**	**Date of Exclusivity Submission**	**Labeling Impact**
NA					

Reviewer Assessment:

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

Reviewer Comments:

4. DESCRIPTION, HOW SUPPLIED AND MANUFACTURED BY STATEMENT

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

Reviewer Assessment:

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

Table 5: Comparison of DESCRIPTION Section or Inactive Ingredients Subsection (OTC)		
Previous Labeling Review	**Currently Proposed**	**Assessment**
Each 0.3 mL in the Epinephrine Injection USP, 0.3 mg (Auto-Injector) contains 0.3 mg epinephrine, USP, 1.8 mg sodium chloride, 0.4 mg sodium metabisulfite, 0.4 mg sodium tartrate (dihydrate), hydrochloric acid to adjust pH, and water for injection. The pH range is 2.2 to 5.0. Each 0.3 mL in the Epinephrine Injection USP, 0.15 mg (b) (4) Auto-Injector) contains 0.15 mg epinephrine, USP, 1.8 mg sodium chloride, 0.4 mg sodium metabisulfite, 0.2 mg sodium tartrate (dihydrate), hydrochloric acid to adjust pH, and water for injection. The pH range is 2.2 to 5.0.	Each 0.3 mL in the Epinephrine Injection USP, 0.3 mg (Auto-Injector) contains 0.3 mg epinephrine, USP, 1.8 mg sodium chloride, 0.4 mg sodium metabisulfite, 0.4 mg sodium tartrate (dihydrate), hydrochloric acid to adjust pH, and water for injection. The pH range is 2.2 to 5.0. Each 0.3 mL in the Epinephrine Injection USP, 0.15 mg (Auto-Injector) contains 0.15 mg epinephrine, USP, 1.8 mg sodium chloride, 0.4 mg sodium metabisulfite, 0.2 mg sodium tartrate (dihydrate), hydrochloric acid to adjust pH, and water for injection. The pH range is 2.2 to 5.0.	**Acceptable**

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

Table 6: Comparison of HOW SUPPLIED Section or Packaging Sizes for OTC Products		
Epinephrine Injection USP, 0.3 mg (Auto-Injectors) (epinephrine njections USP, 1:1000, 0.3 mL) are available as Epinephrine Injection USP, 0.3 mg (Auto-Injectors) 2-Pack, NDC 0093-5986-27, a pack that contains two Epinephrine Injection USP, 0.3 mg (Auto-Injectors) (epinephrine injections USP, 1:1000, 0.3 mL) and one Epinephrine Injection USP (Auto-Injector) trainer device. **Epinephrine Injection USP, 0.15 mg ((b) (4) Auto-Injectors) (epinephrine njections USP, 1:2000, 0.3 mL) are available as** Epinephrine Injection USP, 0.15 mg (Jr. Auto-Injectors) 2-Pack, NDC 0093-5985-27, a pack that contains two Epinephrine Injection USP, 0.15 mg (Jr. Auto-Injectors) (epinephrine injections USP, 1:2000, 0.3 mL) and one Epinephrine Injection USP (Auto-Injector) trainer device. Epinephrine Injection USP, 0.3 mg (Auto-Injectors) 2-Pack and Epinephrine Injection USP, 0.15 mg ((b) (4) Auto-Injectors) 2-Pack also includes a W-clip to clip two auto-injectors together.	**Epinephrine Injection USP, 0.3 mg (Auto-Injectors) (epinephrine njections USP, 1:1000, 0.3 mL) are available as** Epinephrine Injection USP, 0.3 mg 2-Pack, NDC 0093-5986-27, a pack that contains two Epinephrine Injection USP, 0.3 mg (Auto-Injectors) (epinephrine injections USP, 1:1000, 0.3 mL) and one Epinephrine Injection (Auto-Injector) trainer device. **Epinephrine Injection USP, 0.15 mg (Auto-Injectors) (epinephrine njections USP, 1:2000, 0.3 mL) are available** as Epinephrine Injection USP, 0.15 mg 2-Pack, NDC 0093-5985-27, a pack that contains two Epinephrine Injection USP, 0.15 mg (Auto-Injectors) (epinephrine injections USP, 1:2000, 0.3 mL) and one Epinephrine Injection (Auto-Injector) trainer device. Epinephrine Injection USP, 0.3 mg 2-Pack and Epinephrine Injection USP, 0.15 mg 2-Pack also includes an Wclip to clip two auto-injectors together.	**Acceptable** **((b) (4) is removed for the lower strength auto-injector (0.15 mg)**

Table 7: Manufacturer/Distributor/Packer Statements		
Previous Labeling Review	**Currently Proposed**	**Assessment**
Manufactured For: **TEVA PHARMACEUTICALS USA, INC.** North Wales, PA 19454	Manufactured For: TEVA PHARMACEUTICALS USA, INC. North Wales, PA 19454 Iss. 11/2015	**Same**

5. COMMENTS FOR CHEMISTRY REVIEWER

Describe issue(s) sent to and/or received from the chemistry (also known as drug product quality) reviewer:

Reviewer Comments:

6. COMMENTS FOR OTHER REVIEW DISCIPLINES

Describe questions/issue(s) sent to and/or received from other discipline reviewer(s):

Reviewer Comments:

DMEPA (Division of Medication Error Prevention and Analysis) will be consulted with following concerns on the proposed product:

- NDA 19430/S-61 (EpiPen and EpiPen Jr) approved on May 18, 2016, provides for new safety information that modifies the instruction for use of the drug product. Specifically, in order to address the reports of the laceration and embedded needles caused by the auto-injector used in the children, the container label, carton labeling, and the Instruction for Use leaflet are revised (step #2 in the instruction) and the "hold" time for the injection is decreased from 10 seconds to 3 seconds. Please indicate if additional information is needed from Teva to support these revisions to their labeling.
-
- In addition, we would like to consult on the presentation of the established name between the adult and the pediatric strength for ANDA 90589 so that the two strengths are adequately differentiated for safe use by the two population groups. The established name is "Epinephrine Injection USP, 0.3 mg (Auto-Injector)" for the adult strength and "Epinephrine Injection USP, 0.15 mg (Auto-Injector)" for the pediatric strength. In addition to using different carton color, RLD further differentiates the adult dose from the pediatric dose by adding (b) (4) after the product name for the lower dose. However we note that (b) (4) cannot be used for the generic product as (b) (4) is part of registered trademark for the RLD EpiPen Jr. We would like to consult on any alternative approach to differentiating the two strengths. Will it be acceptable to add statements such as "Adult dose" and " Pediatric dose"; "Adult Auto Injector" or "Pediatric Auto Injector" after the established name or would it be allowable/acceptable to include weight requirement on the carton labeling to provide differentiation between the two doses. For an example, please note that Auvi-Q (epinephrine injection USP, NDA 201739; TE code BX) uses same proprietary name on both strengths. The two strengths are differentiated by use of different carton color (blue for 0.3mg and orange for 0.15 mg strength) and further differentiated by adding the patient weight requirement on the PDP of the carton.

- Lastly, please evaluate our labeling comment to the applicant and provide any comment related to the safe use of the product.
  [Attach labeling comments in section 1.1 on the consult request form]

7. OVERALL ASSESSMENT OF MATERIALS REVIEWED

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

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

Table 8: Review Summary of Container Label and Carton Labeling

	Final or Draft or NA	Packaging Sizes	Submission Received Date	Recommendation
Container	Final	0.15 mg/ 0.3mL 0.3 mg/ 0.3 mL	11/18/2015	Revise
Blister	NA			
Carton	Final	2 Pak (two injections and one trainer device)	11/18/2015	Revise
(Other – specify)	NA			
Table 9 Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	**Revision Date and/or Code**	**Submission Received Date**	**Recommendation**
Prescribing Information	Final	Iss. 11/2015	11/18/2015	Revise
Trainer Instruction for Use	Final	Iss. 11/2015	11/18/2015	Revise
Patient Information and Instruction for Use	Final	Iss. 11/2015	11/18/2015	Revise
SPL Data Elements		Revised: 12/2014	11/18/2015	Satisfactory

Esther Chuh

Digitally signed by Esther Chuh
Date: 10/06/2016 01:58 54PM
GUID: 508da70700028b78f2f9ebd95bfb4a18
Comments: review revised.

Thuyanh Vu

Digitally signed by Thuyanh Vu
Date: 10/06/2016 03:49 25PM
GUID: 508da70a00028d70c2922eb0a0e2dbbe

LABELING REVIEW

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

Date of This Review	12/10/2015
ANDA Number(s)	090589
Review Number	5
Applicant Name	Teva Pharmaceuticals USA
Established Name & Strength(s)	Epinephrine Injection USP, 0.3 mg (Auto-Injector) and Epinephrine Injection USP, 0.15 mg (Auto-Injector)
Proposed Proprietary Name	N/A
Submission Received Date	11/18/2015
Labeling Reviewer	Eunjung Esther Chuh
Labeling Team Leader	John Grace

Review Conclusion

☐ ACCEPTABLE – No Comments.

☐ ACCEPTABLE – Include Post Approval Comments

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

*Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Easily Correctable Deficiency if all other OGD reviews are acceptable. Otherwise, the labeling minor deficiencies will be included in the Complete Response (CR) letter to the applicant.

☐ On Policy Alert List

1. LABELING COMMENTS

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT

Labeling Deficiencies determined on December 11, 2015, based on your submission dated November 18, 2015.

1. GENERAL COMMENTS

   Please be advised that if any additional labeling concerns are raised upon Agency's evaluation of your response to the comments related to the auto-injector device and its safe use, we may have further labeling comments.

2. CONTAINER LABEL(0.30 mg and 0.15 mg)

   We recommend further increasing the prominence of the established name and the strength.

3. CARTON LABELING (0.30 mg and 0.15 mg)
   a. Please ensure that the established name and the strength are the most prominent information on the label. We refer you to the draft guidance, "Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors". http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm349009.pdf
   b. We recommend further differentiation between the two strengths. We recommend using colors that provide sufficient contrast for the strength statements or using other means to differentiate the two strengths (e.g., boxing, highlighting, etc.).
   c. To decrease clutter on the principal display panel (PDP), you may consider relocating "Register your… to receive free refill reminders.." statement to the side panel.
   d. Delete the duplicate statement ("Each Carton Contains….") on the side panel, immediately below "(Auto-Injectors) 2 Pack.
4. PRESCRIBING INFORMATION (Insert Labeling, Patient Information and Instruction for Use)

   Throughout your labeling, delete "(auto-injector)" where you state "epinephrine injection, 0.3 mg and epinephrine injection, 0.15 mg (auto-injector)". You may choose to add "(auto-injector)" after the "0.3 mg" instead.

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

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with your last submitted labeling with all differences annotated and explained.

Prior to the submission of your amendment, please check labeling resources, including DRUGS@FDA, the electronic Orange Book and the NF-USP online, for recent updates and make any necessary revisions to your labels and labeling.

In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address –

http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE

The Division of Labeling has no further questions/comments at this time based on your labeling submission (s) dated (add date)

1.3 POST APPROVAL REVISIONS

These comments will NOT be sent to the applicants at this time.
These comments will be addressed post approval (in the first labeling supplement review).

None

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

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

REVIEW HISTORY

12/21/2007	Original ANDA 090589 submitted to FDA
11/21/2008	Original ANDA 090589 received to FDA for filing
6/4/2009	Labeling Review #1 completed
10/12/2010	Labeling Amendment, response to deficiencies issued on 6/4/2009
2/2/2011	Labeling Review #2 completed
8/1/2014	Labeling Amendment. Response to deficiencies issued on 2/2/2011. Also provides for update to be in accordance with the innovator labeling update approved on 4/30/2014.
9/26/2013	Labeling Review #3. ***(Deficiencies to this review is not yet sent out as Complete Response Letter is pending Agency. The comments issued to the applicant from review #4 will supersede the comments that were prepared for the applicant on review #3.)***
12/30/2014	Quality Minor Amendment and Unsolicited Amendment to provide for change in the manufacturing and testing site, formulation and device. Specifically the application provides for following change: drug product manufacturing site and device assembly site change; formulation change to (b) (4) sodium metabisulfite (b) (4) and (b) (4) of sodium tartrate (b) (4) in accordance with CFR 314.94(a)(9)(iii); and change to the device to improve the design to ensure the user will not be presented with a device that has delivered the drug product but has not engaged the safety guard. This amendment also provides for a Human Factor Study.
11/18/2015	Easily Correctable Deficiency(ECD) Amendment, response to ECD sent to the applicant on 11/3/2015. *This amendment is subject of this review.*

PREVIOUS DEFICIENCY AND FIRM'S RESPONSE

The below comments are from the labeling review C4 based on the submission dated 12/30/2014"

The Agency's original comment is presented below in bold, followed by Teva's response.

Labeling Comments:

1. GENERAL COMMENTS

a. The drug product name should be expressed consistently throughout the labeling. For an example you refer to your product as "Epinephrine 0.3 mg (auto-injector)", "Epinephrine Auto-Injector (0.3 mg)" and also as "epinephrine auto-injector". Please revise. We refer you to the established name of the drug product, "Epinephrine Injection USP, 0.3 mg" and "Epinephrine Injection USP, 0.15 mg".

Response:

For consistency, we have expressed our drug product name as Epinephrine Injection USP, 0.3 mg" and "Epinephrine Injection USP, 0.15 mg". Also, for consistency we called out the term "auto-injector" throughout the labeling to match the RLD.

b. **We note that you refer to your lower strength auto-injector as '(b) (4) Auto-Injector". (b) (4) is not a conventional way of expressing lower dose strength of a drug product and (b) (4) found in the name from the Reference Listed Drug (RLD) is part of a registered trademark. Please comment.**

Response:

We have removed all reference to '(b) (4) from our labeling and we refer to the lower strength as "Epinephrine Injection USP, 0.15 mg".

2. CARTON LABEING

a. **Revise, "I.M. use" to "Intramuscular use".**

Response:

We have revised "I.M. use" to "Intramuscular use".

b. **Revise, "Replace if discolored." to correspond to the USP 37-NF 32 (8/1/2014-11/30/2014) labeling statement below:**
"The label indicates that the Injection is not to be used if its color is pinkish or darker than slightly yellow or if it contains a precipitate."

Response:

We have revised our discolored solution statement to comply with USP 37-NF 32 (8/2/2014-11/30/2014). The discolored solution statement now reads, "Replace if the epinephrine solution appears discolored) pinkish or darker than slightly yellow) or if it contains a precipitate."

c. **The color bands with "TEVA" are more prominent than the color bands that distinguish the strengths of the two products. Revise the presentations so that the green color bands representing the auto-injector for the 0.15 mg and the yellow color bands representing the 0.3 mg strength are the most prominent color bands on each label respectively.**

Response:

We have increased the color bands on the labeling as request. When we submit final printed labeling we will further distinguish the product strengths by using data matrix scanning verification however,

3. PRESCRIBING INFORMATION

a. **HIGHLIGHTS OF PRESCRIBING INFORMATION Highlights Limitation Statement: Revise "Epinephrine Injection" to read "EPINEPHRINE INJECTION" (all in capital letters) to comply with the PLR format.**

Response:

We have revised the product name to all capital letters in the HIGHLIGHTS section to comply with the PLR format.

b. **The "Epinephrine" in the product title, immediately above the U. S. approval date, should be revised to all capital letters "EPINEPHRINE" to comply with the RLR format requirements.**

Response:

We have revised the product name in the product title to all capital letters to comply with the PLR format requirements.

c. **Revise the description of the discolored solution in applicable sections to correspond to the USP 37-NF 32 (8/1/2014-11/30/2014) labeling statement below:**
"The label indicates that the Injection is not to be used if its color is pinkish or darker than slightly yellow or if it contains a precipitate."

Response:

We have revised our discolored solution statement to comply with USP 37-NF 32 (8/2/2014-11/30/2014). The discolored solution statement now reads, "Replace if the epinephrine solution appears discolored) pinkish or darker than slightly yellow) or if it contains a precipitate."

4. PATIENT INFORMATON AND INSTRUCTION FOR USE

1.11.4 Response to FDA Request for Information - Multiple Module

a. **Under "How should I store.." after 4th bullet, we note that you have deleted the fourth bullet provided under the RLD. Please add this bullet which instructs the patients to protect the device from damage and water. Revise the statement to fit your drug product (no carrier tube).**

Response:

We have added the 4th bullet to our labeling to instruct the patients to protect the device from damage and water.

b. **Revise "Epinephrine Trainer" to Epinephrine Injection Trainer".**

Response:

We have revised the Epinephrine Trainer to read "Epinephrine Injection Trainer".

5. TRAINING INSTRUCTION

a. We encourage you to align the three steps under the Practice Instruction as with RLD.

Response:

We have revised Trainer Practice Instructions to align with the three steps of the RLD Trainer Practice Instructions. We believe that the Practice Instructions are now equivalent from a user perspective and that the steps included in the revised Practice Instructions fully simulate the auto-injector experience drug training.

b. We encourage you to make the headings (i.e.: "Practice Instruction", "Practice Session Information") more prominent such as by highlighting them as seen with the RLD.

Response:

We have made the heading "Practice Instruction" and "Practice Session Information" more prominent by revising them to match the RLD.

6. STRUCTURED PRODUCT LABELING (SPL)

Revise the total volume in the Strength Statement to read as "0.3 mg in 0.3 mL" (from "0.3 mg in 1 mL") and to read as "0.15 mg in 0.3 mL" (from 0.15 mg in 1 mL") for the lower strength auto-injector.

Response:

We have revised the total volume in the strength statement to read as 0.3 mg in 0.3 mL and 0.15 mg in 0.3 mL. Also, the dosage form was changed to "Injection".

Reviewer Comments to the applicant's response submitted on November 18, 2015:

Applicant's response to the deficiencies is acceptable. Product name is revised to remove (b) (4) for the lower strength (0.15 mg) and the established name is expressed consistently throughout the labeling as requested. Labeling statement regarding the discoloration/precipitation of the solution required by the USP is properly placed on all labeling.

Further comments need to be communicated to the applicant.

-Carton and Container - Applicant need to ensure that the product name and the strength are most prominently placed on the container and the carton. Also, recommend further differentiation between the two strengths by use of color, etc.

Insert Labeling – Throughout the insert, the proposed products are sometimes expressed as "epinephrine injection, 0.3 mg and epinephrine injection, 0.15 mg (auto-injector)". As both strengths are auto-injectors, the two products should be expressed consistently. Recommend deleting the "(auto-injector)" after the 0.15 mg or adding the "(auto-injector)" after the 0.3 mg.

2.1 CONTAINER AND CARTON LABELS

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

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

Reviewer Comments:

2.2 ADDITIONAL BACKGROUND INFORMATION PERTINENT TO THE REVIEW

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

Reviewer Comments:

Following are from previous review cycle #4:

Notes for the record

1)The labels and labeling provided on this unsolicited amendment was reviewed and comments are under section 1.Labeling Comments. However complete analysis of the labeling on the drug product is deferred until the evaluation of the device and the human factor study provided on this amendment is complete. The human factor study was requested by CDRH for the applicant to demonstrate that the device can be used by the representative users under simulated use conditions without producing patterns of failures that could result in negative clinical impact to patients or injury to the device users.

2)There is a Citizen's Petition submitted to the Agency on 1/16/2015 by Mylan which requests Agency to refrain from approving this ANDA "unless, after conducting an appropriately rigorous review under the established standards for proposed generic emergency use auto-injectors, the agency concludes that the proposed product is the "same as" the EpiPen® auto-injector". Much of their concern is related to the proper use of the auto-injector in an emergency situation. This reviewer also notes the difference in the device, such as the "twist off" function of the cap for the proposed product versus the "pull out" of the cap from a carrier tube on the RLD. At this time, the evaluation on the functionality and safe use of the device as a generic equivalent to RLD is pending with the subject experts in the Agency

3) Teva refers the lower dose epinephrine injection as (b) (4) Auto-Injector". As RLD name is trademarked as following: Epipen®, Epipen JR®, Epipen JR2-Pak®, this reviewer finds that the generic of Epipen Jr should not be referred as the (b) (4) Auto- Injector". Even if the (b) (4) is not trademarked, the terminology of (b) (4) Auto- Injector" is not a conventional way of referring to a lower strength auto-injector. This reviewer finds that (b) (4) may be proposed as a part of a proprietary name or the applicant may indicate the lower strength without the designation of (b) (4)

NOTE ON PREVIOUS CONSULTS ON THE ANDA:

11/13/2008 OGD consulted OND (Division of Pulmonary and Allergy Products) for a comparative review between the MOA of the Innovator's Auto-Injector versus TEVA's proposed Auto Injector. Per the consult response, it was concluded that the mechanism of action (mechanism of release) is the same between the TEVA's and the innovator's product and that Teva's product should be filed under the 505(j) pathway.

5/29/2009 Consult to CDRH on the device master file. CDRH requested that the applicant submit a Human Factors Study as part of the demonstration that generic device use is the same as the RLD device use. *Human Factor Study submitted on 12/30/2014 is pending review.*

4/29/2013 Consult to Division of Clinical Review on the difference on the length of the needle. Per the consult, slightly longer needle length of Teva's product compared to the RLD is not clinically significant, and should not be a factor in the approval of ANDA 90589 as a generic to EpiPen.

Update on the consults:

Consults to CDRH(device), DCR (formulation) OSE(human factor study) are completed and deficiency comments are incorporated by appropriate review disciplines. Refer to the Complete Response Deficiency letter that will be issued for the comments.

It is noted that OSE/DMEPA concluded that the Human Factor Study did not show that the end users who are switching from the reference listed product (RLD) to the proposed product can safely and effectively use the proposed product in accordance with the product's Instructions for Use (IFU) without the prescribing health care provider's intervention or training prior to use, and that the difference in the steps between the two devices may lead to errors if the product is substituted for the EpiPen (RLD) without additional training. DMEPA's review also noted that the approval of the proposed product as a generic substitution for the EpiPen may result in detrimental error due to confirmation bias with current EpiPen users.

2015-1409
Epinephrine Human Fa

[Review of Human Factor Study (DMEPA/OSE)]

ANDA90589.TEVA.Epi Pen.CDRH Engineering

[Review of the Device– CDRH]

CP citizen petition (Docket No: FDA-2015-P-0181): Agency has denied the petition to refrain from approving the current application by Teva (ANDA 090589) unless a rigorous review under the established standards for proposed generic emergency use auto-injectors was performed and the Agency concludes that the proposed product is the same as the EpiPen auto-injectors. CP was denied on 6/15/2015.

CP.pdf

[CP Response]

3. LABELING REVIEW INFORMATION AND REVIEWER ASSESSMENT

3.1 REGULATORY INFORMATION

Are there any pending issues in DLR's Repository files? NO If Yes, please explain in section 2.2 Additional Background Information Pertinent to the Review
Are there any pending issues in DLR's SharePoint Drug Facts? NO If Yes, please explain.
Is the drug product listed in the Policy Alert Tracker on OGD's SharePoint? NO If Yes, please explain.

3.2 MODEL PRESCRIBING INFORMATION

Table 1: Review Model Labeling for Prescribing Information and Patient Labeling (Check the box used as the Model Labeling)
☒ **MOST RECENTLY APPROVED NDA MODEL LABELING** *(If NDA is listed in the discontinued section of the Orange Book, also enter ANDA model labeling information.)* **NDA# /Supplement# (S-000 if original):** NDA 019430/S-059 **Supplement Approval Date:** 4-30-2014 **Proprietary Name:** EpiPen Auto-Injector and EpiPen Jr Auto-Injector **Established Name:** epinephrine **Description of Supplement:** This prior approval supplemental new drug application proposes to update the labeling to incorporate the format and content of the Physician Label Rule (PLR) in compliance with governing regulations 21 CFR 201.56 and 21 CFR 201.57. **NOTE: S-058 approved on 7/17/2014 was for update on the carton, container, and trainer label. [PAS was to update the carton labels to provide a visual summary of the three steps (Prepare, Administer, and Finalize) used to administer EpiPen, and to ensure that the administration summaries on the carton, container, and trainer labels match the three steps for administration of EpiPen in the approved instructions for use.]**

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

Reviewer Assessment:

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

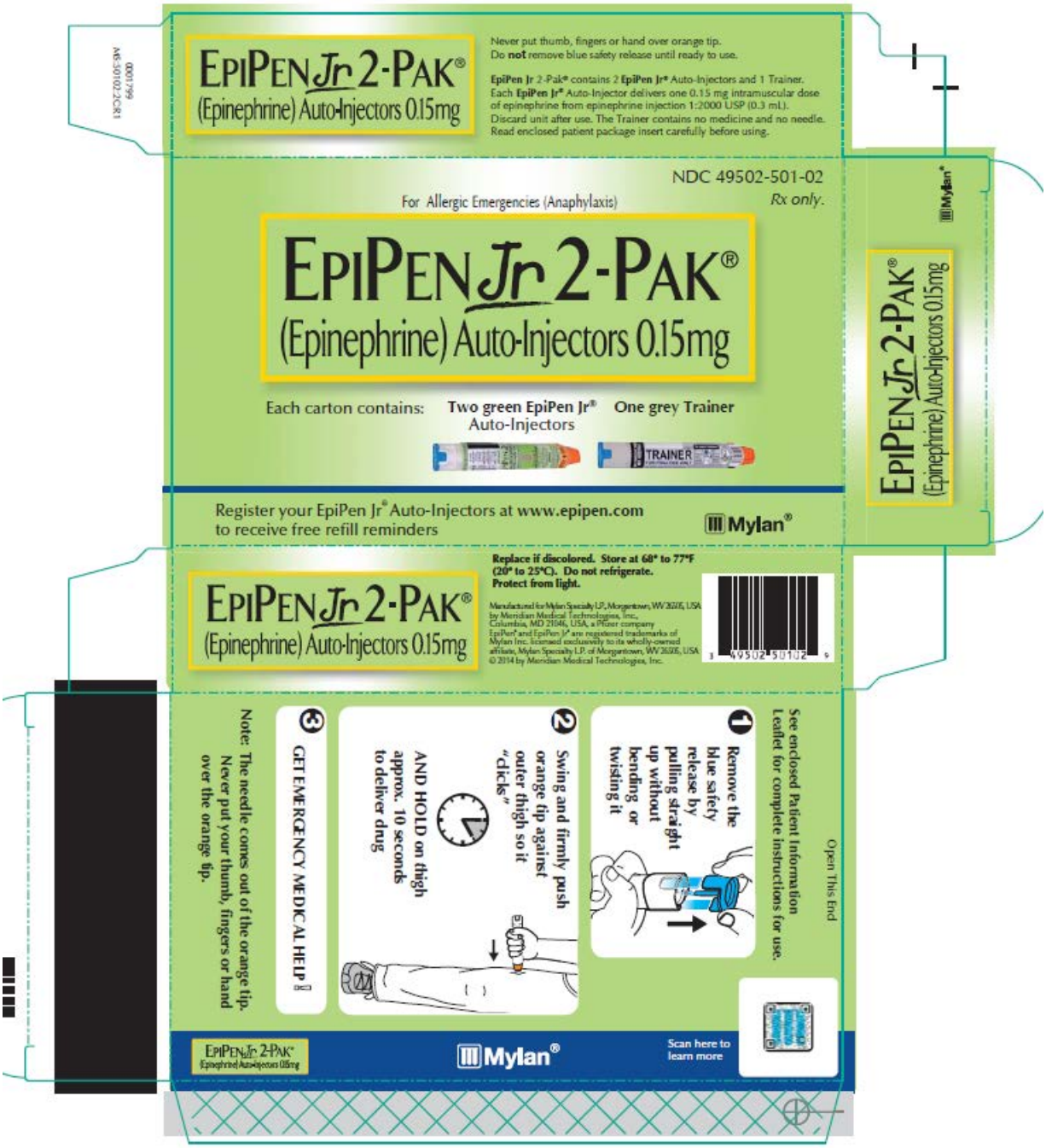
Reviewer Comments:

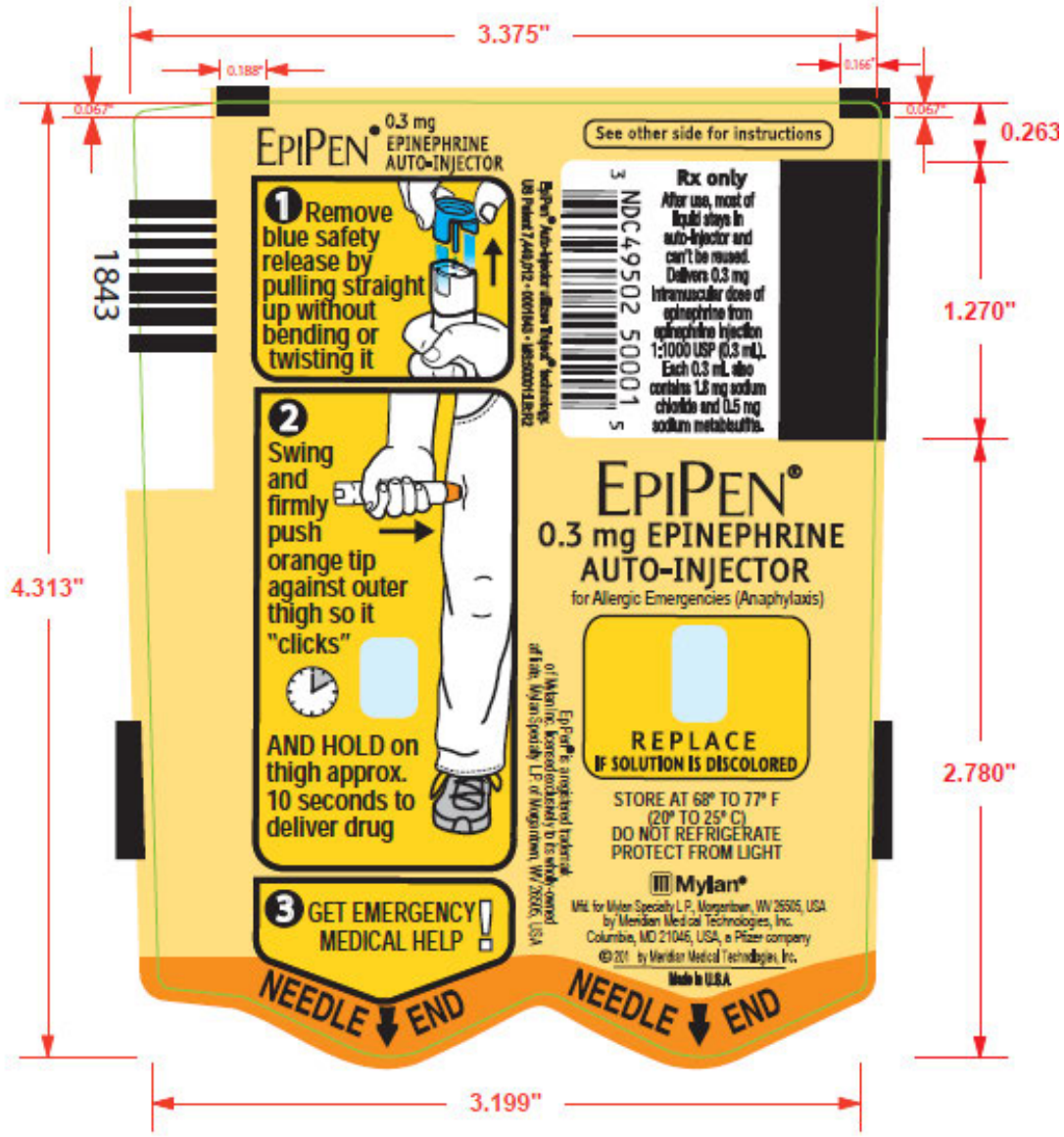
Insert labeling which includes the Patient Information and Instructions for Use are acceptable except one comment on the product name (see labeling comments). **HOWEVER**, please note that further evaluation of the inserts may be needed based on any change to the device made per the OSE's recommendation from the review of the Human Factor Study, Per the review by OSE (2015-1409), "DMEPA concludes that the validation study results do not show that end users who are switching from the reference listed product to the AJE can safely and effectively use the proposed product in accordance with the product's Instructions for Use (IFU) without the prescribing health care provider's intervention or training prior to use.". Refer to Additional Background section 2.2 for further information on the consult review.

3.3 MODEL CONTAINER LABELS

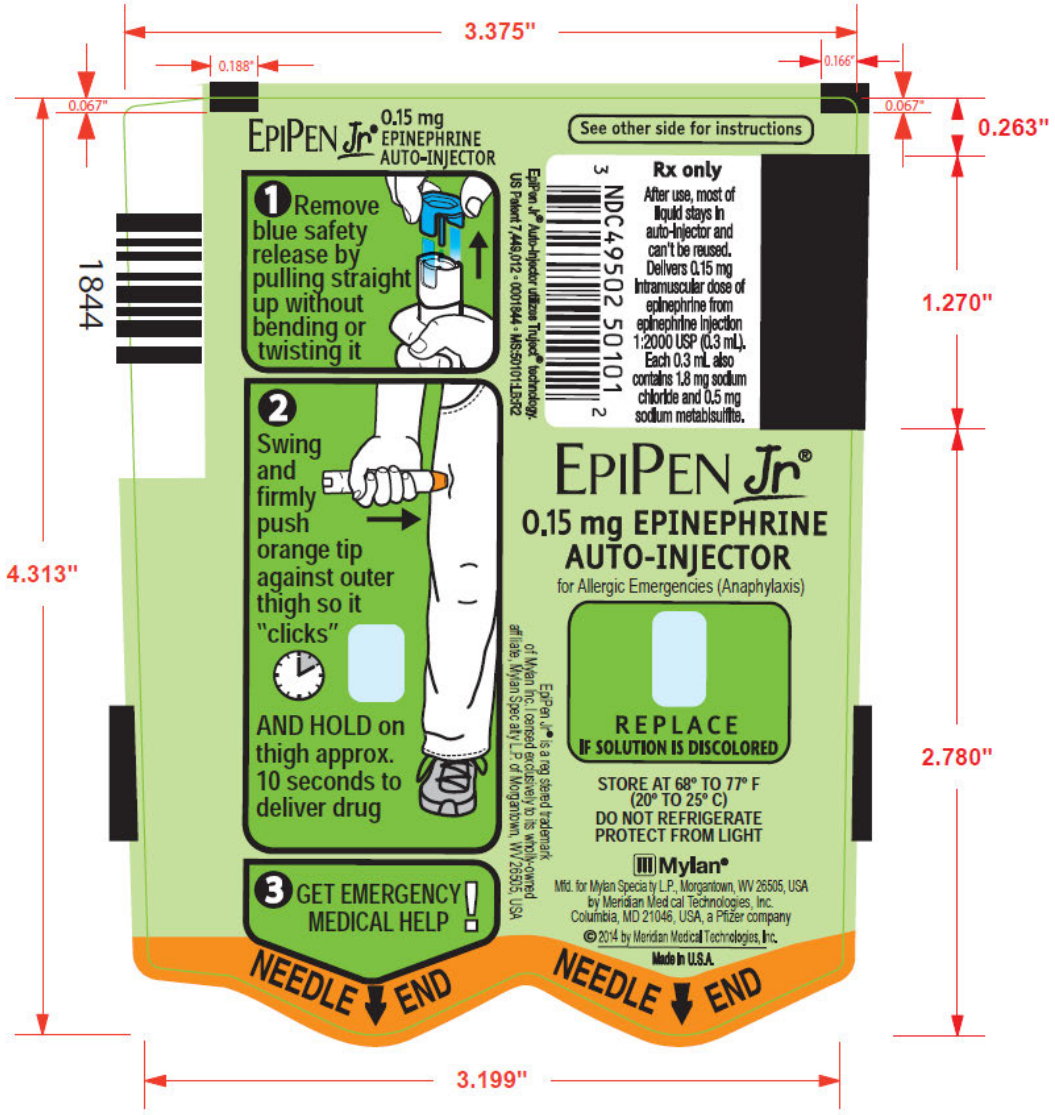
Model container/carton/blister labels [Source: NDA 019430/S-058, approved on 7/17/2014]


EPIPEN 2-PAK®
(Epinephrine) Auto-Injectors 0.3 mg
Never put thumb, fingers or hand over orange tip.
Do not remove blue safety release until ready to use.
EpiPen 2-Pak® contains 2 EpiPen® Auto-Injectors and 1 Trainer.
Each EpiPen® Auto-Injector delivers one 0.3 mg intramuscular dose of epinephrine from epinephrine injection 1:1000 USP (0.3 mL).
Discard unit after use. The Trainer contains no medicine and no needle.
Read enclosed patient package insert carefully before using.
NDC 49502-500-02
For Allergic Emergencies (Anaphylaxis)
Rx only.
EPIPEN 2-PAK®
(Epinephrine) Auto-Injectors 0.3 mg
Each carton contains:
Two yellow EpiPen® Auto-Injectors
One grey Trainer
TRAINER
Register your EpiPen® Auto-Injectors at www.epipen.com to receive free refill reminders
Mylan®
Replace if discolored. Store at 68° to 77°F (20° to 25°C). Do not refrigerate. Protect from light.
Manufactured for Mylan Specialty L.P., Morgantown, WV 26505, USA by Meridian Medical Technologies, Inc., Columbia, MD 21046, USA, a Pfizer company
EpiPen® and EpiPen Jr® are registered trademarks of Mylan Inc. licensed exclusively to its wholly-owned affiliate, Mylan Specialty L.P. of Morgantown, WV 26505, USA
© 2014 by Meridian Medical Technologies, Inc.
Open This End
See enclosed Patient Information Leaflet for complete instructions for use.
1 Remove the blue safety release by pulling straight up without bending or twisting it
2 Swing and firmly push orange tip against outer thigh so it "clicks"
AND HOLD on thigh approx. 10 seconds to deliver drug
3 GET EMERGENCY MEDICAL HELP!
Note: The needle comes out of the orange tip. Never put your thumb, fingers or hand over the orange tip.
Scan here to learn more
EPIPEN 2-PAK®
Mylan®

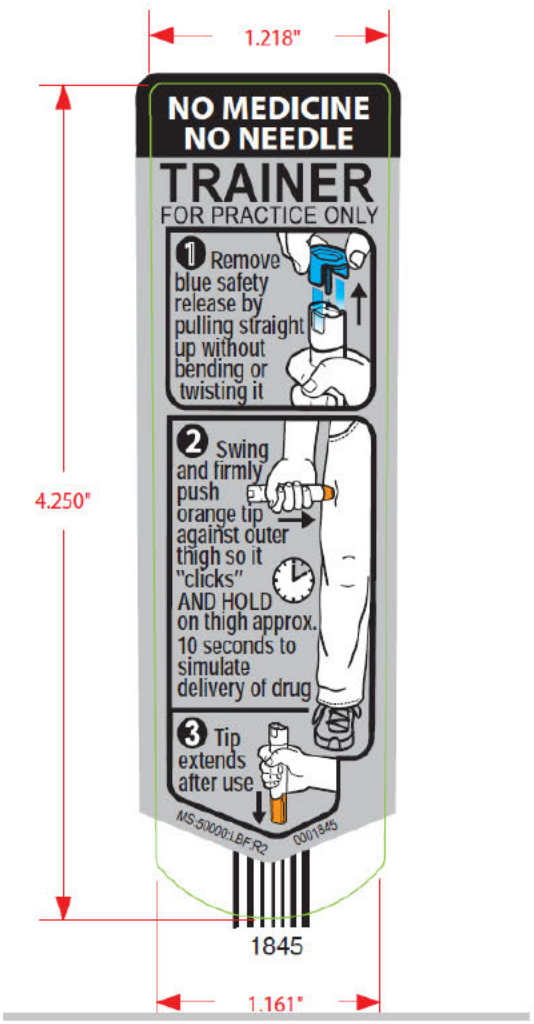

EPIPEN Jr 2-PAK®
(Epinephrine) Auto-Injectors 0.15mg
Never put thumb, fingers or hand over orange tip.
Do not remove blue safety release until ready to use.
EpiPen Jr 2-Pak® contains 2 EpiPen Jr® Auto-Injectors and 1 Trainer.
Each EpiPen Jr® Auto-Injector delivers one 0.15 mg intramuscular dose of epinephrine from epinephrine injection 1:2000 USP (0.3 mL).
Discard unit after use. The Trainer contains no medicine and no needle.
Read enclosed patient package insert carefully before using.
NDC 49502-501-02
Rx only.
For Allergic Emergencies (Anaphylaxis)
EPIPEN Jr 2-PAK®
(Epinephrine) Auto-Injectors 0.15mg
Each carton contains: Two green EpiPen Jr® Auto-Injectors One grey Trainer
TRAINER
Register your EpiPen Jr® Auto-Injectors at www.epipen.com to receive free refill reminders
Mylan®
Replace if discolored. Store at 68° to 77°F (20° to 25°C). Do not refrigerate. Protect from light.
Manufactured for Mylan Specialty LP, Morgantown, WV 26505, USA by Meridian Medical Technologies, Inc., Columbia, MD 21046, USA, a Pfizer company
EpiPen® and EpiPen Jr® are registered trademarks of Mylan Inc. licensed exclusively to its wholly-owned affiliate, Mylan Specialty L.P. of Morgantown, WV 26505, USA
© 2014 by Meridian Medical Technologies, Inc.
49502-501-02
Open This End
See enclosed Patient Information Leaflet for complete instructions for use.
1 Remove the blue safety release by pulling straight up without bending or twisting it
2 Swing and firmly push orange tip against outer thigh so it "clicks"
AND HOLD on thigh approx. 10 seconds to deliver drug
3 GET EMERGENCY MEDICAL HELP
Note: The needle comes out of the orange tip. Never put your thumb, fingers or hand over the orange tip.
Scan here to learn more
EPIPEN Jr 2-PAK®
(Epinephrine) Auto-Injectors 0.15mg
Mylan®

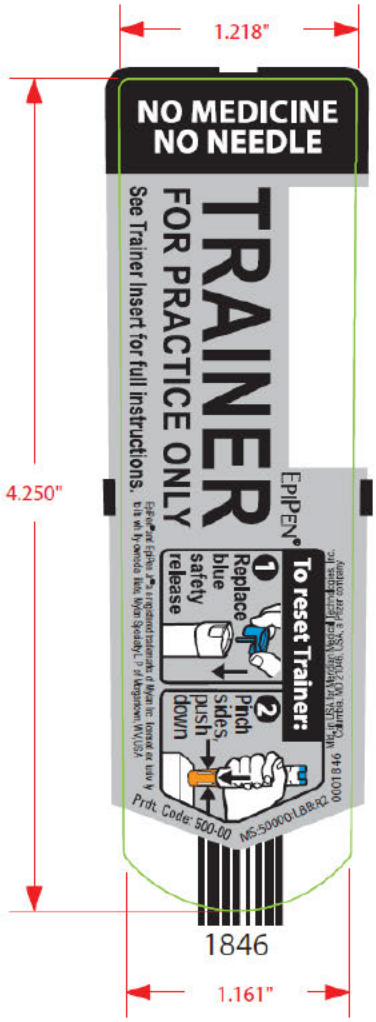


U.S. EpiPen Label
26JUN2014



U.S. EpiPen Jr Label
26JUN2014





3.4 UNITED STATES PHARMACOPEIA (USP) & PHARMACOPEIA FORUM (PF)

We searched the USP and PF to determine if the drug product under review is the subject of a USP monograph or proposed USP monograph.

Table 2: USP and PF Search Results

	Date Searched	Monograph? YES or NO	Monograph Title (NA if no monograph)	Packaging and Storage/Labeling Statements (NA if no monograph)
USP	12/11/2015	YES	Epinephrine Injection	**Packaging and storage**— Preserve in single-dose or multiple-dose, light-resistant containers, preferably of Type I glass. **Labeling**— The label indicates that the Injection is not to be used if its color is pinkish or darker than slightly yellow or if it contains a precipitate.
PF	12/11/2015	YES	31(1) In-Process Revision: Epinephrine Injection	Same as above

Reviewer Comments:

Product is subject of a USP monograph with labeling requirement as stated above.

3.5 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 12/11/2015.

Table 3 provides Orange Book patents for the Model Labeling and ANDA patent certifications.

(For applications that have no patents, N/A is entered in the patent number column)

Table 3: Impact of Model Labeling Patents on ANDA Labeling						
Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact
7449012	9/11/2025			IV	12/30/2014	None
7794432	9/11/2025			IV	12/30/2014	None
8048035	9/11/2025			IV	12/30/2014	None
8870827	9/11/2025			IV	12/30/2014	None

Reviewer Assessment:

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

Reviewer Comments:

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

Table 4: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling					
Exclusivity Code	Exclusivity Expiration	Exclusivity Code Definition	Exclusivity Statement	Date of Exclusivity Submission	Labeling Impact
NA					

Reviewer Assessment:

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

Reviewer Comments:

4. DESCRIPTION, HOW SUPPLIED AND MANUFACTURED BY STATEMENT

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

Reviewer Assessment:

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

Table 5: Comparison of DESCRIPTION Section or Inactive Ingredients Subsection (OTC)		
Previous Labeling Review	Currently Proposed	Assessment

Table 5: Comparison of DESCRIPTION Section or Inactive Ingredients Subsection (OTC)		
Each 0.3 mL in the Epinephrine Injection USP, 0.3 mg (Auto-Injector) contains 0.3 mg epinephrine, USP, 1.8 mg sodium chloride, 0.4 mg sodium metabisulfite, 0.4 mg sodium tartrate (dihydrate), hydrochloric acid to adjust pH, and water for injection. The pH range is 2.2 to 5.0. Each 0.3 mL in the Epinephrine Injection USP, 0.15 mg (b) (4) Auto-Injector) contains 0.15 mg epinephrine, USP, 1.8 mg sodium chloride, 0.4 mg sodium metabisulfite, 0.2 mg sodium tartrate (dihydrate), hydrochloric acid to adjust pH, and water for injection. The pH range is 2.2 to 5.0.	Each 0.3 mL in the Epinephrine Injection USP, 0.3 mg (Auto-Injector) contains 0.3 mg epinephrine, USP, 1.8 mg sodium chloride, 0.4 mg sodium metabisulfite, 0.4 mg sodium tartrate (dihydrate), hydrochloric acid to adjust pH, and water for injection. The pH range is 2.2 to 5.0. Each 0.3 mL in the Epinephrine Injection USP, 0.15 mg (Auto-Injector) contains 0.15 mg epinephrine, USP, 1.8 mg sodium chloride, 0.4 mg sodium metabisulfite, 0.2 mg sodium tartrate (dihydrate), hydrochloric acid to adjust pH, and water for injection. The pH range is 2.2 to 5.0.	**Acceptable**

Table 6: Comparison of HOW SUPPLIED Section or Packaging Sizes for OTC Products		
Previous Labeling Review	**Currently Proposed**	**Assessment**
Epinephrine Injection USP, 0.3 mg (Auto-Injectors) (epinephrine injections USP, 1:1000, 0.3 mL) are available as Epinephrine Injection USP, 0.3 mg (Auto-njectors) 2-Pack, NDC 0093-5986-27, a pack that contains two Epinephrine njection USP, 0.3 mg (Auto-Injectors) (epinephrine injections USP, 1:1000, 0.3 mL) and one Epinephrine Injection USP (Auto-Injector) trainer device. **Epinephrine Injection USP, 0.15 mg ((b) (4) Auto-Injectors) (epinephrine injections USP, 1:2000, 0.3 mL) are available as** Epinephrine Injection USP, 0.15 mg (Jr. Auto-njectors) 2-Pack, NDC 0093-5985-27, a pack that contains two Epinephrine Injection USP, 0.15 mg (Jr. Auto-njectors) (epinephrine injections USP, 1:2000, 0.3 mL) and one Epinephrine Injection USP (Auto-Injector) trainer device. Epinephrine Injection USP, 0.3 mg (Auto-njectors) 2-Pack and Epinephrine Injection USP, 0.15 mg (b) (4) Auto-Injectors) 2-Pack also includes a W-clip to clip two auto-injectors together.	**Epinephrine Injection USP, 0.3 mg (Auto-Injectors) (epinephrine injections USP, 1:1000, 0.3 mL) are available as** Epinephrine Injection USP, 0.3 mg 2-Pack, NDC 0093-5986-27, a pack that contains two Epinephrine Injection USP, 0.3 mg (Auto-njectors) (epinephrine injections USP, 1:1000, 0.3 mL) and one Epinephrine njection (Auto-Injector) trainer device. **Epinephrine Injection USP, 0.15 mg (Auto-Injectors) (epinephrine injections USP, 1:2000, 0.3 mL) are available** as Epinephrine Injection USP, 0.15 mg 2-Pack, NDC 0093-5985-27, a pack that contains two Epinephrine Injection USP, 0.15 mg (Auto-njectors) (epinephrine injections USP, 1:2000, 0.3 mL) and one Epinephrine Injection (Auto-njector) trainer device. Epinephrine Injection USP, 0.3 mg 2-Pack and Epinephrine Injection USP, 0.15 mg 2-Pack also ncludes an Wclip to clip two auto-injectors together.	**Acceptable** (**“ (b) (4) is removed for the lower strength auto-injector (0.15 mg))**

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

Table 7: Manufacturer/Distributor/Packer Statements		
Manufactured For: **TEVA PHARMACEUTICALS USA, INC.** North Wales, PA 19454	Manufactured For: TEVA PHARMACEUTICALS USA, INC. North Wales, PA 19454 Iss. 11/2015	**Same**

5. COMMENTS FOR CHEMISTRY REVIEWER

Describe issue(s) sent to and/or received from the chemistry (also known as drug product quality) reviewer:

Reviewer Comments:

6. COMMENTS FOR OTHER REVIEW DISCIPLINES

Describe questions/issue(s) sent to and/or received from other discipline reviewer(s):

Reviewer Comments:

7. OVERALL ASSESSMENT OF MATERIALS REVIEWED

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

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

Table 8: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	**Packaging Sizes**	**Submission Received Date**	**Recommendation**
Container	Final	0.15 mg/ 0.3mL 0.3 mg/ 0.3 mL	11/18/2015	Revise
Blister	NA			
Carton	Final	2 Pak (two injections and one trainer device)	11/18/2015	Revise
(Other – specify)	NA			
Table 9 Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	**Revision Date and/or Code**	**Submission Received Date**	**Recommendation**
Prescribing Information	Final	Iss. 11/2015	11/18/2015	Revise
Trainer Instruction for Use	Final	Iss. 11/2015	11/18/2015	Revise
Patient Information and Instruction for Use	Final	Iss. 11/2015	11/18/2015	Revise
SPL Data Elements		Revised: 12/2014	11/18/2015	Satisfactory

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

LABELING REVIEW

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

Date of This Review	5/4/2015
ANDA Number(s)	090589
Review Number	4
Applicant Name	Teva Pharmaceuticals USA
Established Name & Strength(s)	Epinephrine Injection USP, 0.3 mg/0.3 mL (Auto-Injector) and Epinephrine Injection USP, 0.15 mg/0.3mL (Auto-Injector)
Proposed Proprietary Name	N/A
Submission Received Date	12/30/2014
Labeling Reviewer	Eunjung Esther Chuh
Labeling Team Leader	John Grace

Review Conclusion

☐ ACCEPTABLE – No Comments.

☐ ACCEPTABLE – Include Post Approval Comments

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

*Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Easily Correctable Deficiency if all other OGD reviews are acceptable. Otherwise, the labeling minor deficiencies will be included in the Complete Response (CR) letter to the applicant.

1. LABELING COMMENTS ***

***** THIS COMMENT SECTION SUPERSEDES THE COMMENTS PROVIDED IN LABELING REVIEW #3 COMPLETED ON 9/16/2013 *****

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT

1. GENERAL COMMENTS
   a. The drug product name should be expressed consistently throughout the labeling. For an example you refer to your product as "Epinephrine 0.3 mg (auto-injector)", "Epinephrine Auto-Injector (0.3 mg)" and also as "epinephrine auto-injector". Please revise. We refer you to the established name of the drug product, "Epinephrine Injection USP, 0.3 mg" and "Epinephrine Injection USP, 0.15 mg".

   b. We note that you refer to your lower strength auto-injector as (b) (4) Auto-Injector". (b) (4)" is not a conventional way of expressing lower dose strength of a drug product and "Jr" found in the name from the Reference Listed Drug (RLD) is part of a registered trademark. Please comment.

   c. We acknowledge comments in your communication dated 12/30/2014, that you propose a change to the device to improve design and we acknowledge that you have submitted a human factor study to support this new device. Upon Agency's evaluation of the device and the human factor study, we will communicate to you any comments related to labeling. Currently, the evaluation is pending review by subject experts within the Agency.

2. CARTON LABELING
   a. Revise, "I.M. use" to "Intramuscular use".

   b. Revise, "Replace if discolored." to correspond to the USP 37-NF 32 (8/1/2014- 11/30/2014) labeling statement below:
   "The label indicates that the Injection is not to be used if its color is pinkish or darker than slightly yellow or if it contains a precipitate."

   c. The color bands with "TEVA" are more prominent than the color bands that distinguish the strengths of the two products. Revise the presentations so that the green color bands representing the auto-injector for the 0.15 mg and the yellow color bands representing the 0.3 mg strength are the most prominent color bands on each label respectively.

3. PRESCRIBING INFORMATION
   a. HIGHLIGHTS OF PRESCRIBING INFORMATION
   Highlights Limitation Statement: Revise "Epinephrine Injection" to read "EPINEPHRINE INJECTION" (all in capital letters) to comply with the PLR format.

   b. The "Epinephrine" in the product title, immediately above the U. S. approval date, should be revised to all capital letters "EPINEPHRINE" to comply with the RLR format requirements.

   c. Revise the description of the discolored solution in applicable sections to correspond to the USP 37-NF 32 (8/1/2014-11/30/2014) labeling statement below:
   "The label indicates that the Injection is not to be used if its color is pinkish or darker than slightly yellow or if it contains a precipitate."

4. PATIENT INFORMATON AND INSTRUCTION FOR USE
   a. Under "How should I store.." after 4th bullet, we note that you have deleted the fourth bullet provided under the RLD. Please add this bullet which instructs the patients to protect the device from damage and water. Revise the statement to fit your drug product (no carrier tube).

   b. Revise "Epinephrine Trainer" to Epinephrine Injection Trainer".

5. TRAINING INSTRUCTION
   a. We encourage you to align the three steps under the Practice Instruction as with RLD.

   b. We encourage you to make the headings (ie: "Practice Instruction", "Practice Session Information") more prominent such as by highlighting them as seen with the RLD.

6. STRUCTURED PRODUCT LABELING (SPL)
   Revise the total volume in the Strength Statement to read as "0.3 mg in 0.3 mL" (from "0.3 mg in 1 mL") and to read as "0.15 mg in 0.3 mL" (from 0.15 mg in 1 mL") for the lower strength auto-injector.

Submit your revised labeling electronically in final print format.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with your last submitted labeling with all differences annotated and explained.

Prior to the submission of your amendment, please check labeling resources, including DRUGS@FDA, the electronic Orange Book and the NF-USP online, for recent updates and make any necessary revisions to your labels and labeling.

In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address –

http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

1.2 POST APPROVAL REVISIONS

These comments will NOT be sent to the applicants at this time.
These comments will be addressed post approval (in the first labeling supplement review).

None

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

In this section, we include any previous labeling review deficiencies, the firm's response and reviewer's assessment. Include the previous review(s) finalized date(s).

REVIEW HISTORY

12/21/2007	Original ANDA 090589 submitted to FDA
11/21/2008	Original ANDA 090589 received to FDA for filing
6/4/2009	Labeling Review #1 completed
10/12/2010	Labeling Amendment, response to deficiencies issued on 6/4/2009
2/2/2011	Labeling Review #2 completed
8/1/2014	Labeling Amendment. Response to deficiencies issued on 2/2/2011. Also provides for update to be in accordance with the innovator labeling update approved on 4/30/2014.
9/26/2013	Labeling Review #3. ***(Deficiencies to this review is not yet sent out as Complete Response Letter is pending Agency. The comments issued to the applicant from review #4 will supersede the comments that were prepared for the applicant on review #3.)***
12/30/2014	Quality Minor Amendment and Unsolicited Amendment to provide for change in the manufacturing and testing site, formulation and device. Specifically the application provides for following change: drug product manufacturing site and device assembly site change; formulation change [redacted] (b) (4) sodium metabisulfite [redacted] (b) (4) and [redacted] (b) (4) sodium tartrate [redacted] (b) (4) in accordance with CFR 314.94(a)(9)(iii); and change to the device to improve the design to ensure the user will not be presented with a device that has delivered the drug product but has not engaged the safety guard. This amendment also provides for a Human Factor Study. ***This amendment is subject of this review #4.***

Reviewer Comments:

Below comments from previous labeling review (rev #3) will be communicated to the applicant:

1. CARTON
   a. Revise, "I.M. use" to "Intramuscular use".
   b. Revise, "Replace if discolored." to correspond to the USP 37-NF 32 (8/1/2014-11/30/2014) labeling statement below: "The label indicates that the Injection is not to be used if its color is pinkish or darker than slightly yellow or if it contains a precipitate."
   c. The color bands with "TEVA" are more prominent than the color bands that distinguish the strengths of the two products. Revise the presentations so that the green color bands representing the (b) (4) Auto-Injectors) and the yellow color bands representing the (Auto-Injectors) are the most prominent color bands on each label respectively.

2. PRESCRIBING INFORMATION
   c. Revise the description of the discolored solution in applicable sections to correspond to the USP 37-NF 32 (8/1/2014-11/30/2014) labeling statement below: "The label indicates that the Injection is not to be used if its color is pinkish or darker than slightly yellow or if it contains a precipitate."

Notes for the record

1)The labels and labeling provided on this unsolicited amendment was reviewed and comments are under section 1.Labeling Comments. However complete analysis of the labeling on the drug product is deferred until the evaluation of the device and the human factor study provided on this amendment is complete. The human factor study was requested by CDRH for the applicant to demonstrate that the device can be used by the representative users under simulated use conditions without producing patterns of failures that could result in negative clinical impact to patients or injury to the device users.

2)There is a Citizen's Petition submitted to the Agency on 1/16/2015 by Mylan which requests Agency to refrain from approving this ANDA "unless, after conducting an appropriately rigorous review under the established standards for proposed generic emergency use auto-injectors, the agency concludes that the proposed product is the "same as" the EpiPen® auto-injector". Much of their concern is related to the proper use of the auto-injector in an emergency situation. This reviewer also notes the difference in the device, such as the "twist off" function of the cap for the proposed product versus the "pull out" of the cap from a carrier tube on the RLD. At this time, the evaluation on the functionality and safe use of the device as a generic equivalent to RLD is pending with the subject experts in the Agency

3) Teva refers the lower dose epinephrine injection as " (b) (4) Auto-Injector". As RLD name is trademarked as following: Epipen ®, Epipen JR®, Epipen JR2-Pak®, this reviewer finds that the generic of Epipen Jr should not be referred as the " (b) (4) Auto- Injector". Even if the (b) (4)" is not trademarked, the terminology of (b) (4). Auto- Injector" is not a conventional way of referring to a lower strength auto-injector. This reviewer finds that (b) (4) may be proposed as a part of a proprietary name or the applicant may indicate the lower strength without the designation of " (b) (4).

2.1 CONTAINER AND CARTON LABELS

Did the firm submit container and/or carton labels that were **NOT** requested in the previous labeling review?
YES

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

Reviewer Comments:

Firm submitted an unsolicited amendment to provide for update to the device. Firm also provided for Human Factor Study per request from CDRH. DLR's further evaluation on the container/carton label is deferred until the device and the Human Factor Study is completed.

2.2 ADDITIONAL BACKGROUND INFORMATION PERTINENT TO THE REVIEW

In this section, include any correspondence or internal information pertinent to the review. Include the correspondence(s) and/or information date(s).

NOTE ON PREVIOUS CONSULTS ON THE ANDA:

11/13/2008 OGD consulted OND (Division of Pulmonary and Allergy Products) for a comparative review between the MOA of the Innovator's Auto-Injector versus TEVA's proposed Auto Injector. Per the consult response, it was concluded that the mechanism of action (mechanism of release) is the same between the TEVA's and the innovator's product and that Teva's product should be filed under the 505(j) pathway.

5/29/2009 Consult to CDRH on the device master file. CDRH requested that the applicant submit a Human Factors Study as part of the demonstration that generic device use is the same as the RLD device use. *Human Factor Study submitted on 12/30/2014 is pending review.*

4/29/2013 Consult to Division of Clinical Review on the difference on the length of the needle. Per the consult, slightly longer needle length of Teva's product compared to the RLD is not clinically significant, and should not be a factor in the approval of ANDA 90589 as a generic to EpiPen.

3. LABELING REVIEW INFORMATION AND REVIEWER ASSESSMENT

3.1 REGULATORY INFORMATION

Are there any pending issues in DLR's SharePoint Repository files? NO
If Yes, please explain in section 2.2 Additional Background Information Pertinent to the Review

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

If Yes, please explain.

There a pending CP per the OGD Policy Alert List dated 4/24/2015.

OGDP Policy Alert List

Docket #	Petitioner or Requester	Brand Name	Generic Name / Dosage Form	Action Requested or Issue Description	RLD#	Affected ANDAs	Policy Alert (Y,N/A,R)	Policy Alert Level of Affected Review	Policy Alert Basis	Policy Alert Notes	OGD Policy Lead
FDA-2015-P-0181	Mylan	EpiPen	Epinephrine Injection	Refrain from approving the Teva ANDA unless, after conducting an appropriately rigorous review under the established standards for proposed generic emergency use auto-injectors, the agency concludes that the proposed product is the "same as" the EpiPen® auto-injector	019430	090589	Yes	Clinical and Labeling Reviews	CP	No Action (CR, TA or AP) should be sent to Sponsor prior to contacting Policy	James Myers

3.2 MODEL PRESCRIBING INFORMATION

Table 1: Review Model Labeling for Prescribing Information and Patient Labeling (Check the box used as the Model Labeling)

☒ **MOST RECENTLY APPROVED NDA MODEL LABELING**

(If NDA is listed in the discontinued section of the Orange Book, also enter ANDA model labeling information.)

NDA# /Supplement# (S-000 if original): NDA 019430/S-059

Supplement Approval Date: 4-30-2014

Proprietary Name: EpiPen Auto-Injector and EpiPen Jr Auto-Injector

Established Name: epinephrine

Description of Supplement: This prior approval supplemental new drug application proposes to update the labeling to incorporate the format and content of the Physician Label Rule (PLR) in compliance with governing regulations 21 CFR 201.56 and 21 CFR 201.57.

☐ **MOST RECENTLY APPROVED ANDA MODEL LABELING**

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

Supplement Approval Date: Click here to enter text.

Proprietary Name: Click here to enter text.

Established Name: Click here to enter text.

Description of Supplement: Click here to enter text.

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

☐ OTHER (Describe):

NOTE: S-058 approved on 7/17/2014 was for update on the carton, container, and trainer label. [PAS was to update the carton labels to provide a visual summary of the three steps (Prepare, Administer, and Finalize) used to administer EpiPen, and to ensure that the administration summaries on the carton, container, and trainer labels match the three steps for administration of EpiPen in the approved instructions for use.]

Reviewer Assessment:

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

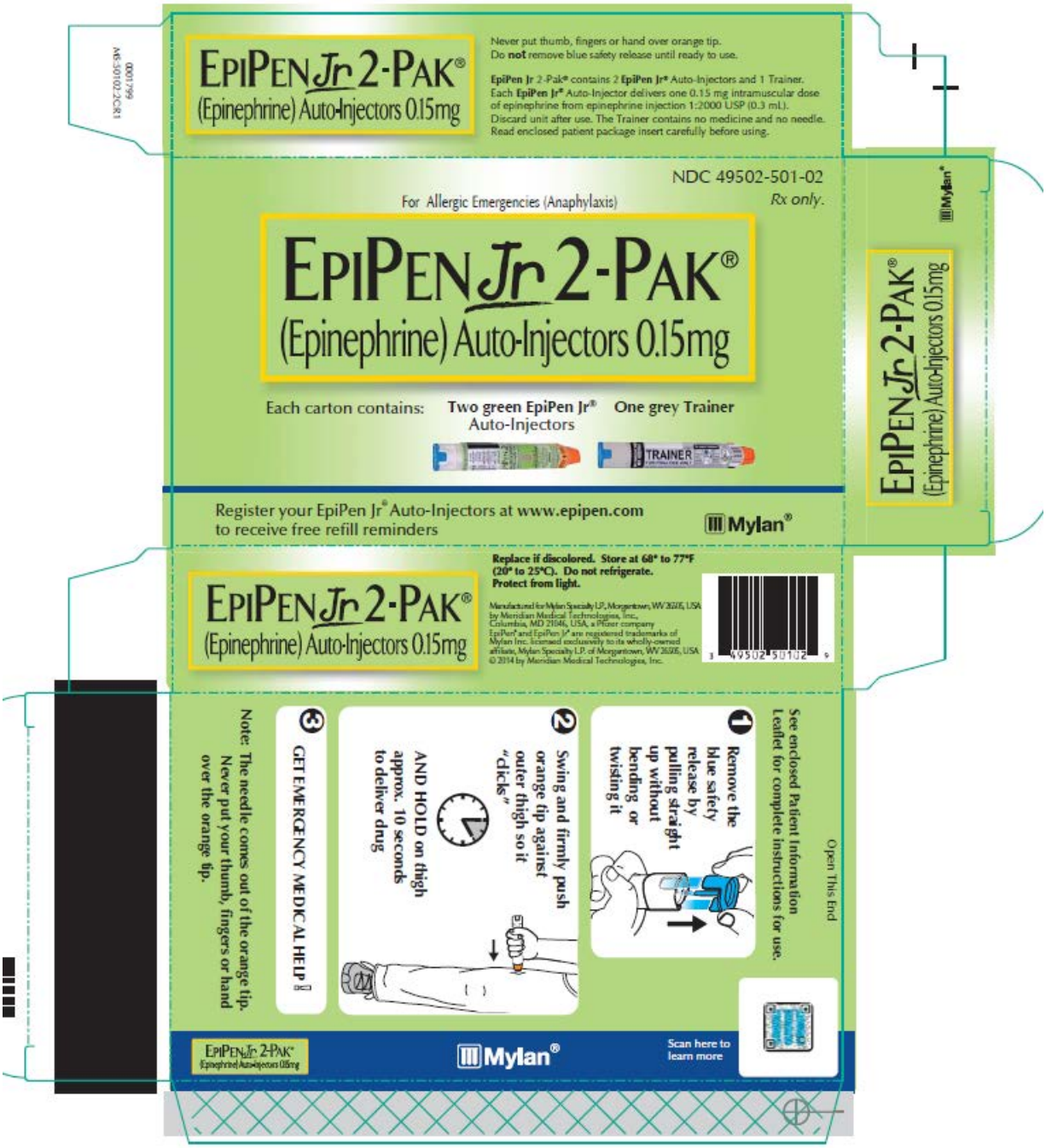
Reviewer Comments:

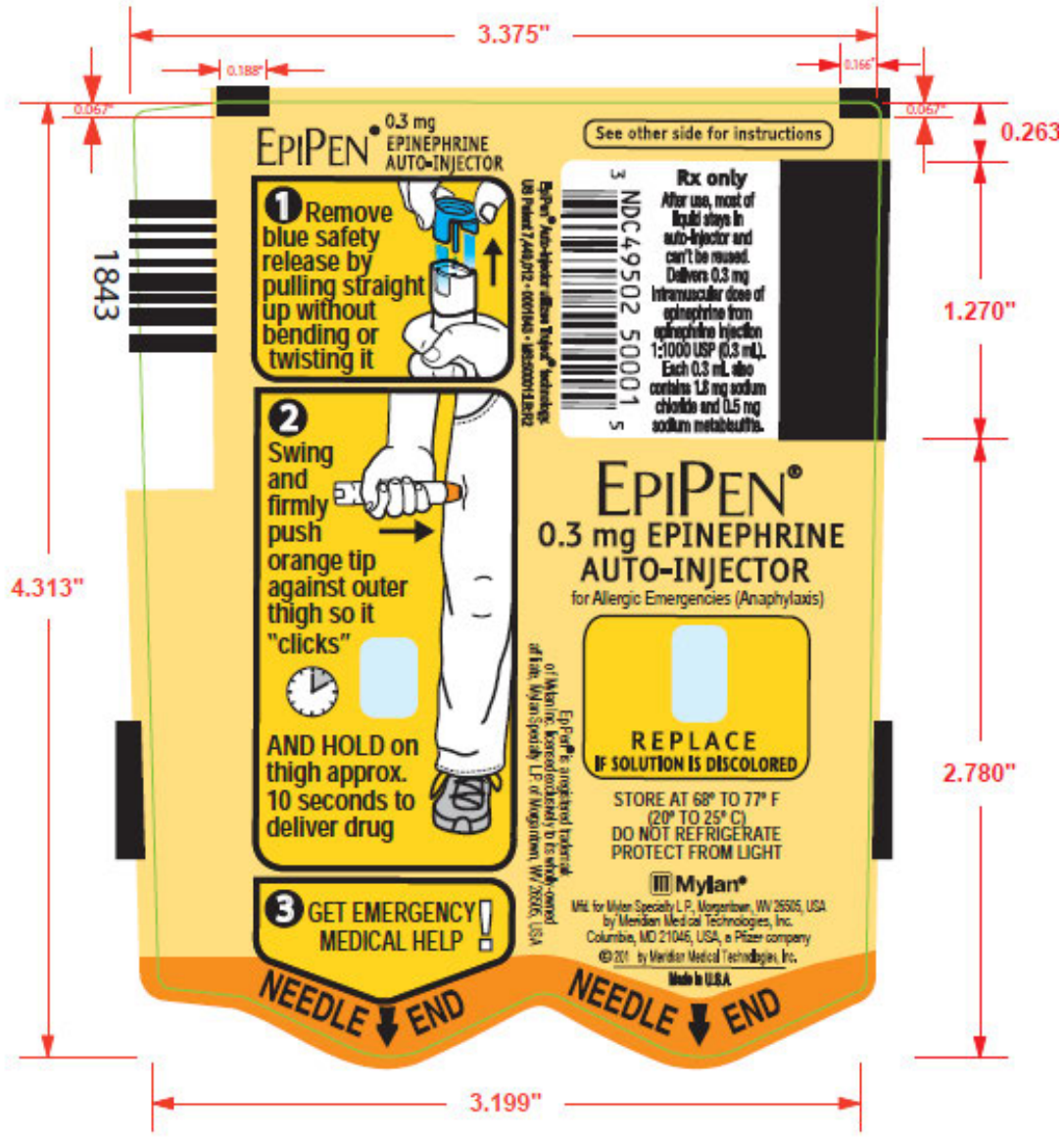
TEVA's labeling was based on the most recently approved NDA supplement S-059. Refer to Labeling Comments Section 1 for comments to applicant.

3.3 MODEL CONTAINER LABELS

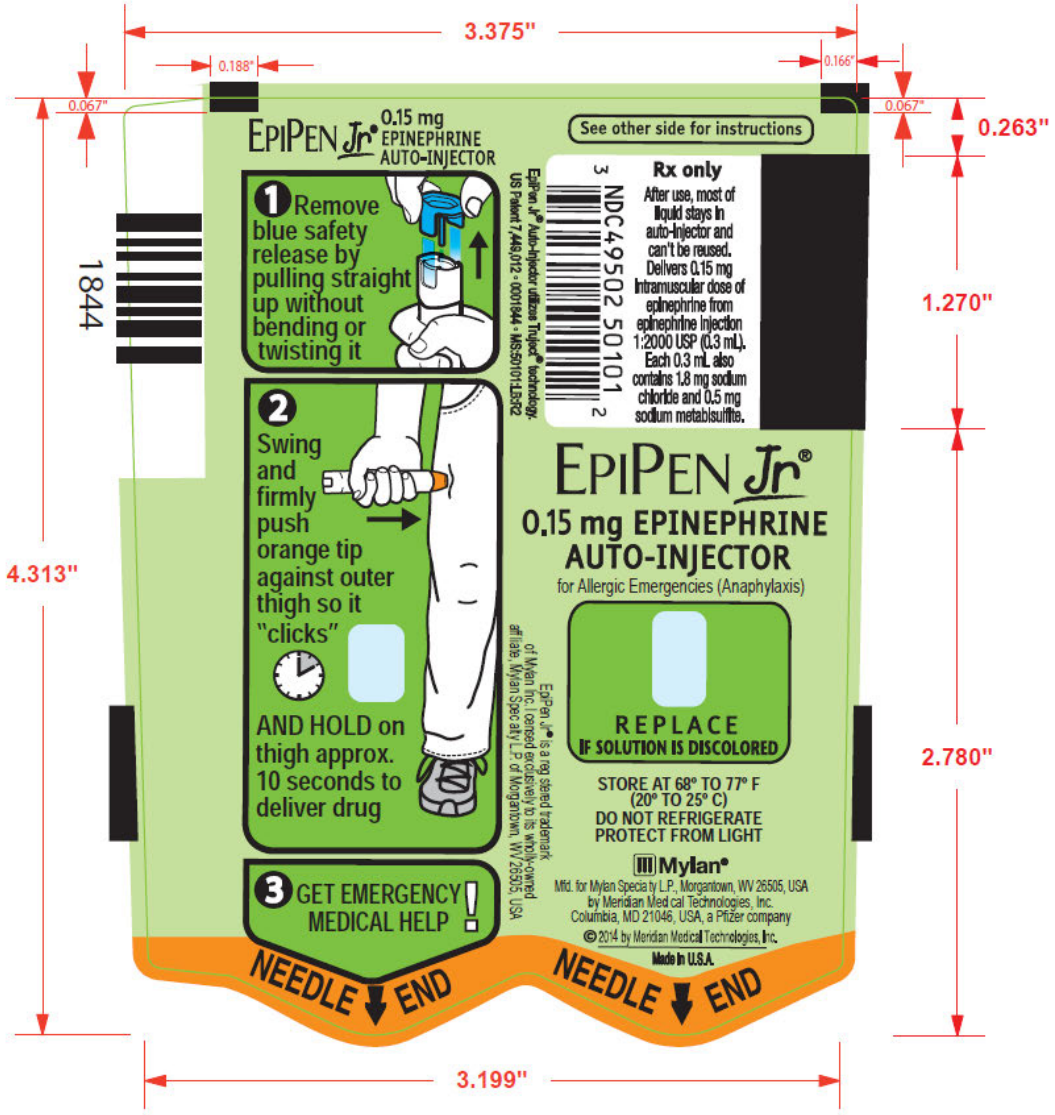
Model labels and carton labeling. [Source: NDA **019430/S-058, approved on 7/17/2014**]


EPIPEN 2-PAK®
(Epinephrine) Auto-Injectors 0.3 mg
Never put thumb, fingers or hand over orange tip.
Do not remove blue safety release until ready to use.
EpiPen 2-Pak® contains 2 EpiPen® Auto-Injectors and 1 Trainer.
Each EpiPen® Auto-Injector delivers one 0.3 mg intramuscular dose of epinephrine from epinephrine injection 1:1000 USP (0.3 mL).
Discard unit after use. The Trainer contains no medicine and no needle.
Read enclosed patient package insert carefully before using.
NDC 49502-500-02
For Allergic Emergencies (Anaphylaxis)
Rx only.
EPIPEN 2-PAK®
(Epinephrine) Auto-Injectors 0.3 mg
Each carton contains:
Two yellow EpiPen® Auto-Injectors
One grey Trainer
TRAINER
Register your EpiPen® Auto-Injectors at www.epipen.com to receive free refill reminders
Mylan®
Replace if discolored. Store at 68° to 77°F (20° to 25°C). Do not refrigerate. Protect from light.
Manufactured for Mylan Specialty L.P., Morgantown, WV 26505, USA by Meridian Medical Technologies, Inc., Columbia, MD 21046, USA, a Pfizer company
EpiPen® and EpiPen Jr® are registered trademarks of Mylan Inc. licensed exclusively to its wholly-owned affiliate, Mylan Specialty L.P. of Morgantown, WV 26505, USA
© 2014 by Meridian Medical Technologies, Inc.
Open This End
See enclosed Patient Information Leaflet for complete instructions for use.
1 Remove the blue safety release by pulling straight up without bending or twisting it
2 Swing and firmly push orange tip against outer thigh so it "clicks"
AND HOLD on thigh approx. 10 seconds to deliver drug
3 GET EMERGENCY MEDICAL HELP!
Note: The needle comes out of the orange tip. Never put your thumb, fingers or hand over the orange tip.
Scan here to learn more

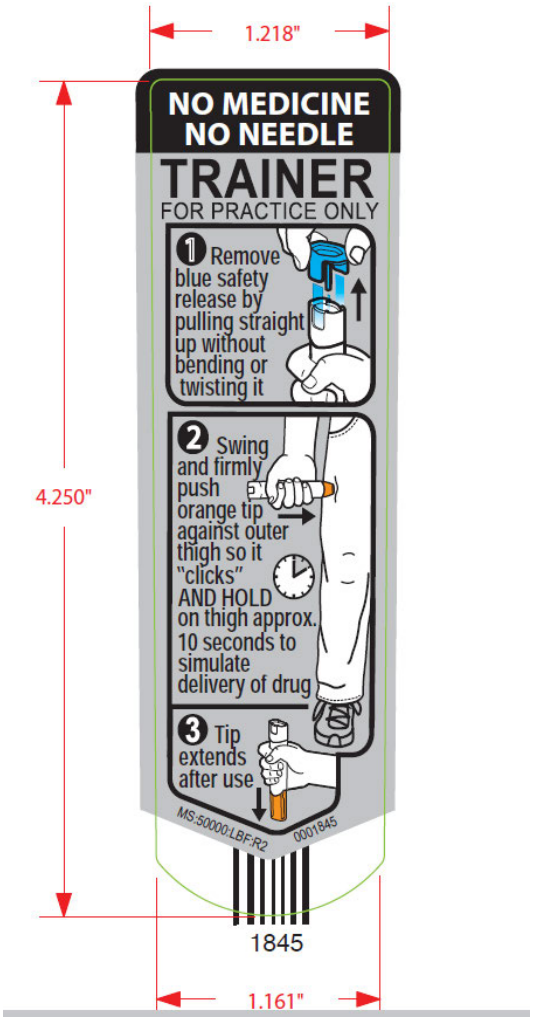

EPIPEN Jr 2-PAK®
(Epinephrine) Auto-Injectors 0.15mg
Never put thumb, fingers or hand over orange tip.
Do not remove blue safety release until ready to use.
EpiPen Jr 2-Pak® contains 2 EpiPen Jr® Auto-Injectors and 1 Trainer.
Each EpiPen Jr® Auto-Injector delivers one 0.15 mg intramuscular dose of epinephrine from epinephrine injection 1:2000 USP (0.3 mL).
Discard unit after use. The Trainer contains no medicine and no needle.
Read enclosed patient package insert carefully before using.
NDC 49502-501-02
Rx only.
For Allergic Emergencies (Anaphylaxis)
EPIPEN Jr 2-PAK®
(Epinephrine) Auto-Injectors 0.15mg
Each carton contains: Two green EpiPen Jr® Auto-Injectors One grey Trainer
TRAINER
Register your EpiPen Jr® Auto-Injectors at www.epipen.com to receive free refill reminders
Mylan®
Replace if discolored. Store at 68° to 77°F (20° to 25°C). Do not refrigerate. Protect from light.
Manufactured for Mylan Specialty LP, Morgantown, WV 26505, USA by Meridian Medical Technologies, Inc., Columbia, MD 21046, USA, a Pfizer company
EpiPen® and EpiPen Jr® are registered trademarks of Mylan Inc. licensed exclusively to its wholly-owned affiliate, Mylan Specialty L.P. of Morgantown, WV 26505, USA
© 2014 by Meridian Medical Technologies, Inc.
49502-501-02
Open This End
See enclosed Patient Information Leaflet for complete instructions for use.
1 Remove the blue safety release by pulling straight up without bending or twisting it
2 Swing and firmly push orange tip against outer thigh so it "clicks"
AND HOLD on thigh approx. 10 seconds to deliver drug
3 GET EMERGENCY MEDICAL HELP
Note: The needle comes out of the orange tip. Never put your thumb, fingers or hand over the orange tip.
Scan here to learn more

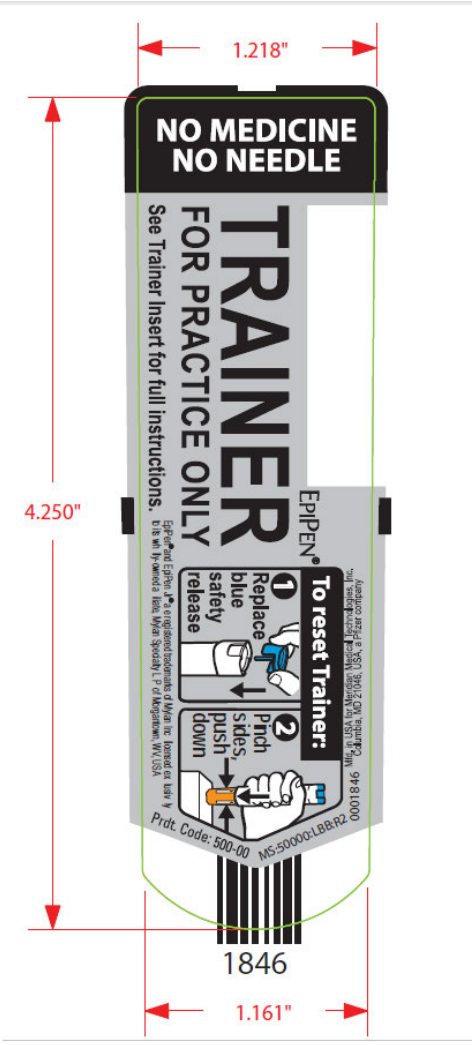


U.S. EpiPen Label
26JUN2014



U. S. EpiPen Jr Label
26JUN2014


1.218"
NO MEDICINE
NO NEEDLE
TRAINER
FOR PRACTICE ONLY
1 Remove blue safety release by pulling straight up without bending or twisting it
2 Swing and firmly push orange tip against outer thigh so it "clicks" AND HOLD on thigh approx. 10 seconds to simulate delivery of drug
3 Tip extends after use
MS:50000:LBF:R2
0001845
4.250"
1845
1.161"


1.218"
NO MEDICINE
NO NEEDLE
TRAINER
FOR PRACTICE ONLY
See Trainer Insert for full instructions.
EpiPen
To reset Trainer:
1 Replace blue safety release
2 Pinch sides, push down
Prdt. Code: 500-00
MS:50000:LBB:R2
0001846
4.250"
1846
1.161"

3.4 UNITED STATES PHARMACOPEIA (USP) & PHARMACOPEIA FORUM (PF)

We searched the USP and PF to determine if the drug product under review is the subject of a USP monograph or proposed USP monograph.

Table 2: USP and PF Search Results				
	Date Searched	Monograph? YES or NO	Monograph Title (NA if no monograph)	Packaging and Storage/Labeling Statements (NA if no monograph)
USP	5/4/2015	Yes	Epinephrine Injection	**Packaging and storage—** Preserve in single-dose or multiple-dose, light-resistant containers, preferably of Type I glass. **Labeling—** The label indicates that the Injection is not to be used if its color is pinkish or darker than slightly yellow or if it contains a precipitate.
PF	5/4/2015	YES	Epinephrine Injection, *USP*	**Packaging and storage—** Preserve in single-dose or in multiple-dose, light-resistant containers, preferably of Type I glass. **Labeling—** The label indicates that the Injection is not to be used if its color is pinkish or darker than slightly yellow or if it contains a precipitate.

Reviewer Comments:

None

3.5 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 5/4/2015.

Table 3 provides Orange Book patents for the Model Labeling and ANDA patent certifications.

(For applications that have no patents, N/A is entered in the patent number column)

Table 3: Impact of Model Labeling Patents on ANDA Labeling						
Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact
7449012	9/11/2025			IV	12/30/2014	None
7794432	9/11/2025			IV	12/30/2014	None
8048035	9/11/2025			IV	12/30/2014	None
8870827	9/11/2025			IV	12/30/2014	None

Reviewer Assessment:

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

Reviewer Comments:

None

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

Table 4: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling					
Exclusivity Code	Exclusivity Expiration	Exclusivity Code Definition	Exclusivity Statement	Date of Exclusivity Submission	Labeling Impact
NA					

Reviewer Assessment:

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

Reviewer Comments:

None

4. DESCRIPTION, HOW SUPPLIED AND MANUFACTURED BY STATEMENT

Tables 5, 6, and 7 describe any changes in the DESCRIPTION section, HOW SUPPLIED section and manufacturing statements of the Prescribing Information when compared to the previous labeling review.

Reviewer Assessment:

Are there changes to the inactives in the DESCRIPTION section? **YES**
Are there changes to the dosage form description(s) or package size(s) in HOW SUPPLIED? **NO**
Are there changes to the manufacturing statements? **YES**
If yes, then comment below in Tables 5, 6, and 7.

Table 5: Comparison of DESCRIPTION Section

Previous Labeling Review	Currently Proposed	Assessment
From previous review (Review #3): The description of the inactive ingredients in the insert labeling appears accurate according to the composition statement. [Vol. 1.1, pg. 117] same as the RLD. Contains metabisulfite and NaCL. **Source: Submission dated 8/1/2014 (basis of rev #3)** (b) (4)	Each 0.3 mL in the Epinephrine Injection USP, 0.3 mg (Auto-Injector) contains 0.3 mg epinephrine, USP, 1.8 mg sodium chloride, 0.4 mg sodium metabisulfite, 0.4 mg sodium tartrate (dihydrate), hydrochloric acid to adjust pH, and water for injection. The pH range is 2.2 to 5.0. Each 0.3 mL in the Epinephrine njection USP, 0.15 mg (Jr. Auto-njector) contains 0.15 mg epinephrine, USP, 1.8 mg sodium chloride, 0.4 mg sodium metabisulfite, 0.2 mg sodium tartrate (dihydrate), hydrochloric acid to adjust pH, and water for injection. The pH range is 2.2 to 5.0.	**The list of inactive ingredients is consistent with CMC Module 3.2.P.1.** (b) (4) **sodium metabisulfite (** (b) (4) (b) (4) **0.4 mg) and** (b) (4) **al inactive ingredient - sodium tartrate (dehydrate) in the currently proposed PI. This is consistent with the cover page of the amendment dated 12/30/14 (subject of this review).** (b) (4)

Table 6: Comparison of HOW SUPPLIED Section		
Previously Labeling Review	**Currently Proposed**	**Assessment**
(b) (4)	**Epinephrine Injection USP, 0.3 mg (Auto-Injectors) (epinephrine injections USP, 1:1000, 0.3 mL) are available as** Epinephrine Injection USP, 0.3 mg (Auto-njectors) 2-Pack, NDC 0093-5986-27, a pack that contains two Epinephrine njection USP, 0.3 mg (Auto-Injectors) (epinephrine injections USP, 1:1000, 0.3 mL) and one Epinephrine Injection USP Auto-Injector) trainer device. **Epinephrine Injection USP, 0.15 mg (Jr. Auto-Injectors) (epinephrine injections USP, 1:2000, 0.3 mL) are available as** Epinephrine Injection USP, 0.15 mg (Jr. Auto-Injectors) 2-Pack, NDC 0093-5985-27, a pack that contains two Epinephrine Injection USP, 0.15 mg (Jr. Auto-Injectors) (epinephrine injections USP, 1:2000, 0.3 mL) and one Epinephrine Injection USP (Auto-Injector) trainer device. Epinephrine Injection USP, 0.3 mg (Auto-njectors) 2-Pack and Epinephrine Injection USP, 0.15 mg (Jr. Auto-Injectors) 2-Pack also includes a W-clip to clip two auto-njectors together.	**Same**

Table 7: Manufactured by statement		
Previously Labeling Review	**Currently Proposed**	**Assessment**
(b) (4)	Manufactured For: **TEVA PHARMACEUTICALS USA, INC.** North Wales, PA 19454	**Per submission dated 12/30/2014, the drug product manufacturer is changed to** (b) (4) **Currently proposed manufacturer statement is acceptable.**

5. COMMENTS FOR CHEMISTRY REVIEWER

Describe issue(s) sent to and/or received from the chemistry (also known as drug product quality) reviewer:

Reviewer Comments:

1. Please comment if there is any labeling concern with the changed amount of sodium metabisulfate and addition of sodium tartrate provided on the amendment 12/30/14.

2. The amendment dated 12/30/14 provided Human Factor Study and an update to the device. Please notify this labeling reviewer if any labeling concern is identified on the study and/or the device.
3. We note that the fill volume differs between this drug product and the RLD. RLD has 2 mL fill volume versus ANDA has 1 mL. Therefore after administration of the dose, the remaining volume in the injection will differ (1.7 mL vs 0.7 mL). Please comment if there is any concern on this difference.

6. COMMENTS FOR OTHER REVIEW DISCIPLINES

Describe questions/issue(s) sent to and/or received from other discipline reviewer(s):

Reviewer Comments:

7. OVERALL ASSESSMENT OF MATERIALS REVIEWED

Tables 8 and 9 provide a summary of recommendations for each material analyzed in this review.

If this review is acceptable, then all pertinent labeling pieces must be entered for both tables.

For each row, if you enter "NA" under the second column, you do NOT need to enter "NA" for the remaining columns.

Table 8: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	**Packaging Sizes**	**Submission Date**	**Recommendation**
Container	Draft	0.15 mg/ 0.3mL 0.3 mg/ 0.3 mL	12/30/2014	Revise
Carton	Draft	2 Pak	12/30/2014	Revise
	Final or Draft or NA	**Revision Date and/or Code**	**Submission Date**	**Recommendation**
Prescribing Information	Draft	12/2014	12/30/2014	Revise
Trainer Instruction for Use	Draft	12/2014	12/30/2014	Revise
Patient Information and Instruction for Use	Draft	12/2014	12/30/2014	Revise
SPL Data Elements		12/2014	12/30/2014	Revise

* Post-approval revision

REVIEW OF PROFESSIONAL LABELING #3
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number:	090589
Date of Submission:	August 1, 2014
Applicant's Name:	Teva Pharmaceuticals
Established Name:	Epinephrine Injection USP, **0.15 mg**/0.3 mL (b) (4) Auto-Injector) and **0.3 mg**/0.3 mL (Auto-Injector)

Labeling Comments below are considered:

☒ Minor Deficiency *
* Please note that the RPM may change the status from Minor Deficiency to Easily Correctable Deficiency if other disciplines are acceptable.

☐ No Comments (Labeling Approval Summary or Tentative Approval Summary)

RPM Note - Labeling comments to be sent to the firm start below:

1. CARTON
   a. Revise, "I.M. use" to "Intramuscular use".
   b. Revise, "Replace if discolored." to correspond to the USP 37-NF 32 (8/1/2014-11/30/2014) labeling statement below: "The label indicates that the Injection is not to be used if its color is pinkish or darker than slightly yellow or if it contains a precipitate."
   c. The color bands with "TEVA" are more prominent than the color bands that distinguish the strengths of the two products. Revise the presentations so that the green color bands representing the (b) (4) Auto-Injectors) and the yellow color bands representing the (Auto-Injectors) are the most prominent color bands on each label respectively.

2. PRESCRIBING INFORMATION
   a. The presentation of the manufacturer information is inconsistent across labeling pieces including the prescribing information, instructions for use for the commercial devices, and the instructions for use for the trainer device. Revise the information to consistently read, (b) (4) (b) (4), Manufactured For: TEVA PHARMACEUTICALS USA, Sellersville, PA 18960"
   b. Revise the statement, "Epinephrine, USP solution" to "Epinephrine solution" in

the DESCRIPTION section to correspond to the RLD.

c. Revise the description of the discolored solution in applicable sections to correspond to the USP 37-NF 32 (8/1/2014-11/30/2014) labeling statement below: "The label indicates that the Injection is not to be used if its color is pinkish or darker than slightly yellow or if it contains a precipitate."

Submit your revised labeling electronically in final print format.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with the reference listed drug's labeling with all differences annotated and explained.

Prior to the submission of your amendment, please check labeling resources, including DRUGS@FDA, the Electronic Orange Book and the NF-USP online, for recent updates and make any necessary revisions to your labels and labeling.

In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17.

Note RPM - Labeling comments end here

FOR THE RECORD
LABELING REVIEW BRANCH

1. APPLICANT INFORMATION

Labels and Labeling Summary (Draft)	Revise	Acceptable
Container Labels Single labels for 0.15 mg/0.30mL and 0.3 mg/0.30 mL Trainer label	X	
Carton Labels 2 pak - 0.15 mg, 0.3 mg	X	
Package Insert Labeling Patient instruction sheet AND Trainer sheet	X	

REFERENCE LISTED DRUG:

Patent Data for NDA 19-430 (updated Cycle 3)

Patent No	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
7449012	Sep 11, 2025			PIV	None
7794432	Sep 11, 2025				
8048035	Sep 11, 2025				

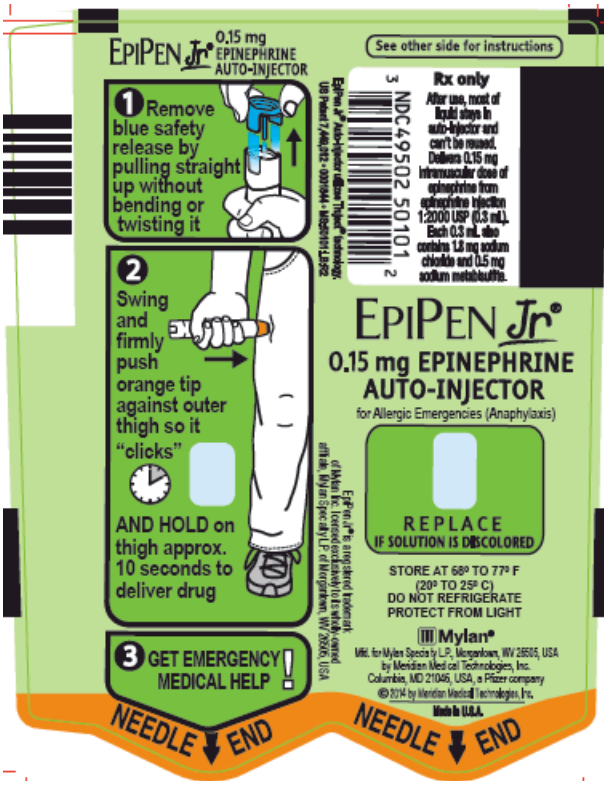
Exclusivity Data for NDA 019430

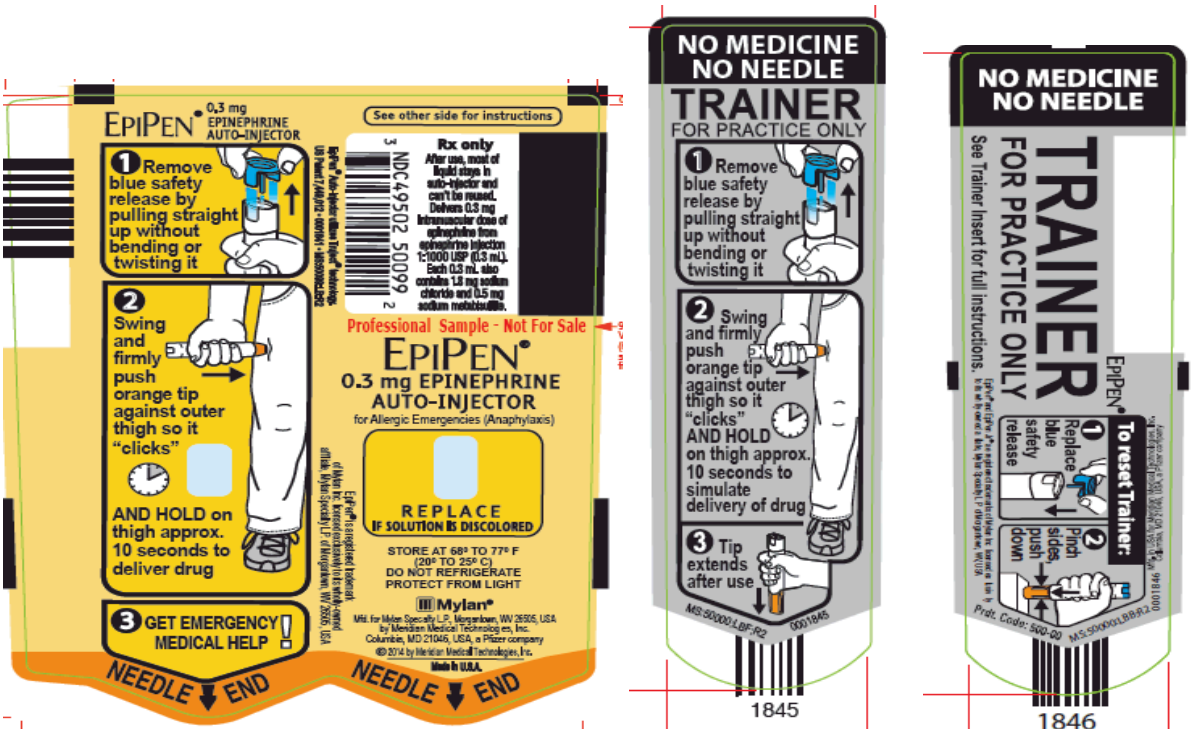
Code/sup	Expiration	Description	*Labeling impact*
None			

Model Labeling

RLD: EPI-Pen JR and Epi-pen	Cycle 2	Cycle 3	
NDA: 19430			
Firm:	Meridian medical Tech	Mylan	
Currently approved PI	S-047- tip, cover, safety cap color change and noted changes to PI and PI	S-059 -PLR conversion	S-058 update Container, carton, and trainer labels
AP Date	5/19/2009	4/30/14	7/17/2014

RLD labeling (representative sample-each strength is provided in a commercial label and a Physician Sample




EPIPEN® 0.3 mg EPINEPHRINE AUTO-INJECTOR
See other side for instructions
1 Remove blue safety release by pulling straight up without bending or twisting it
2 Swing and firmly push orange tip against outer thigh so it "clicks"
AND HOLD on thigh approx. 10 seconds to deliver drug
3 GET EMERGENCY MEDICAL HELP
NEEDLE END
NEEDLE END
Rx only
After use, most of liquid stays in auto-injector and can't be reused. Delivers 0.3 mg intramuscular dose of epinephrine from epinephrine injection 1:1000 USP (0.3 mL). Each 0.3 mL also contains 1.8 mg sodium chloride and 0.5 mg sodium metabisulfite.
NDC 49502 509 02
Professional Sample - Not For Sale
EPIPEN®
0.3 mg EPINEPHRINE AUTO-INJECTOR
for Allergic Emergencies (Anaphylaxis)
REPLACE IF SOLUTION IS DISCOLORED
STORE AT 68° TO 77° F (20° TO 25° C)
DO NOT REFRIGERATE
PROTECT FROM LIGHT
Mylan®
Made in U.S.A.
NO MEDICINE NO NEEDLE
TRAINER
FOR PRACTICE ONLY
1 Remove blue safety release by pulling straight up without bending or twisting it
2 Swing and firmly push orange tip against outer thigh so it "clicks" AND HOLD on thigh approx. 10 seconds to simulate delivery of drug
3 Tip extends after use
1845
NO MEDICINE NO NEEDLE
TRAINER
FOR PRACTICE ONLY
See Trainer Insert for full instructions.
EPIPEN®
To reset Trainer:
1 Replace blue safety release
2 Pinch sides, push down
1846


EPIPEN 2-PAK®
(Epinephrine) Auto-Injectors 0.3 mg
Never put thumb, fingers or hand over orange tip.
Do not remove blue safety release until ready to use.
EpiPen 2-Pak® contains 2 EpiPen® Auto-Injectors and 1 Trainer.
Each EpiPen® Auto-Injector delivers one 0.3 mg intramuscular dose of epinephrine from epinephrine injection 1:1000 USP (0.3 mL).
Discard unit after use. The Trainer contains no medicine and no needle.
Read enclosed patient package insert carefully before using.
NDC 49502-500-02
For Allergic Emergencies (Anaphylaxis)
Rx only.
EPIPEN 2-PAK®
(Epinephrine) Auto-Injectors 0.3 mg
Each carton contains: Two yellow EpiPen® Auto-Injectors
One grey Trainer
TRAINER
Register your EpiPen® Auto-Injectors at www.epipen.com to receive free refill reminders
Mylan®
EPIPEN 2-PAK®
(Epinephrine) Auto-Injectors 0.3 mg
Replace if discolored. Store at 68° to 77°F (20° to 25°C). Do not refrigerate. Protect from light.
Manufactured for Mylan Specialty L.P., Morgantown WV 26505, USA by Meridian Medical Technologies, Inc., Columbia, MD 21045, USA, a Pfizer company.
EpiPen® and EpiPen Jr® are registered trademarks of Mylan Inc. licensed exclusively to its wholly-owned affiliate, Mylan Specialty L.P. of Morgantown, WV 26505, USA
© 2014 by Meridian Medical Technologies, Inc.
EPIPEN 2-PAK®
(Epinephrine) Auto-Injectors 0.3 mg
Mylan®
EPIPEN 2-PAK®
(Epinephrine) Auto-Injectors 0.3 mg
Open This End
See enclosed Patient Information Leaflet for complete instructions for use.
1 Remove the blue safety release by pulling straight up without bending or twisting it
2 Swing and firmly push orange tip against outer thigh so it "clicks"
AND HOLD on thigh approx. 10 seconds to deliver drug
3 GET EMERGENCY MEDICAL HELP
Note: The needle comes out of the orange tip. Never put your thumb, fingers or hand over the orange tip.
EPIPEN 2-PAK®
Mylan®
Scan here to learn more

*Note the RLD container and carton labels provided in the application are not the most recently approved.

2. NOTE TO CHEMIST: I am not sure what the firing mechanism consist of but I believe it has to be the same as the RLD or it may be considered a new device and perhaps can not be approved as ANDA. The applicant should also provide a case/tube for the container that should protect the product from light and to be used to safely store and transport the product. This ANDA may also need a usability test (b) (4) (b) (4) The applicant has submitted mechanism firing information and use test to CDRH and in this submission 6/10. There is a CP in house regarding Teva's product having more steps (remove cap and safety clip) to initiate the firing while the brand has only one. The innovator has a sleeve that the auto-injector fits into that has to be removed before the product can be used. There were many significant differences noted in the labeling that could require the customer to have to relearn how to use this new device. I have unlabeled samples of the autoinjector in my office if you wish to view them.
Please note the fill volume for the ANDA and RLD are different. The ANDA has less.

Cycle 3
Per a consult with OND, Division of Pulmonary and Allergy Products provided on November 13, 2008, Teva's product should be filed under the 505(j) pathway and is not

significantly different that the RLD. Per consult with CDRH dated 5/7/12, usability guidance and recommendations were forwarded to the firm. Defer to CDRH for the outcome on usability studies.

3. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM – Cycle 3 update
   a. Containers, Instructions for use Commercial device, and Trainer device: Manufactured For: TEVA PHARMACEUTICALS USA, Sellersville, PA 18960

   d. Carton- Manufactured [redacted] for TEVA PHARMACEUTICALS USA, Sellersville, PA 18960

   e. Package Insert: [redacted] Manufactured For: TEVA PHARMACEUTICALS USA, Sellersville, PA 18960

Inconsistent presentations of the manufacturer's information among the different pieces of labeling. Will ask the firm to make all presentations of the manufacturing information consistent.

4. CONTAINER/CLOSURE and packaging configurations

RLD: 0.3 mL dispensed /1.7 mL remains left- for total of 2 mL total volume
ANDA: 0.3 mL dispensed / 0.7 ml remains left - for a total of 1 mL total volume
Cycle 3:
Epinephrine Injection USP, 0.3 mg (Auto-Injectors) (epinephrine injections USP, 1:1000, 0.3 mL) are available as Epinephrine Injection USP, 0.3 mg (Auto-Injectors) 2-Pack, NDC 0703-9350-20, a pack that contains two Epinephrine Injection USP, 0.3 mg (Auto-Injectors) (epinephrine injections USP, 1:1000, 0.3 mL) and one Epinephrine Injection USP (Auto-Injector) trainer device.

Epinephrine Injection USP, 0.15 mg ([redacted] Auto-Injectors) (epinephrine injections USP, 1:2000, 0.3 mL) are available as Epinephrine Injection USP, 0.15 mg ([redacted]. Auto-Injectors) 2-Pack, NDC 0703-9400-20, a pack that contains two Epinephrine Injection USP, 0.15 mg ([redacted] Auto-Injectors) (epinephrine injections USP, 1:2000, 0.3 mL) and one Epinephrine Injection USP (Auto-Injector) trainer device.

Epinephrine Injection USP, 0.3 mg (Auto-Injectors) 2-Pack and Epinephrine Injection USP, 0.15 mg [redacted] Auto-Injectors) 2-Pack also includes an S-clip to clip two auto-injectors together.

5. Active and INACTIVE INGREDIENTS

The description of the inactive ingredients in the insert labeling appears accurate according to

the composition statement. [Vol. 1.1, pg. 117] same as the RLD. Contains metabisulfite and NaCL

6. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

USP: Preserve in single-dose or multiple-dose, light-resistant containers, preferably of Type I glass.
RLD: store at 25 (77F). See USP CRT protect from light, Do not Freeze
ANDA: Store at 20-25C (68-77F). [See USP CRT]. Store upright protect from light. Do not freeze

Cycle 3- Update
Epinephrine is light sensitive and the auto-injector is manufactured from transparent UV stabilized polycarbonate to protect it from light. Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30° (59° to 86°F) [See USP Controlled Room Temperature].
PROTECT FROM LIGHT.
DO NOT REFRIGERATE.
Before using, check to make sure the solution in the auto-injector is clear and colorless. Replace the auto-injector if the solution is discolored (pinkish or brown color), cloudy, or contains particles.
KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

7. DISPENSING STATEMENTS COMPARISON

USP: Not a USP item
RLD: Epinephrine Injection 1:2000 (JR) and 1:1000 autoinjector
ANDA (*Insert*): plastic unit dose ampules

Update Cycle 3:
USP: The label indicates that the Injection is not to be used if its color is pinkish or darker than slightly yellow or if it contains a precipitate.
ANDA:
Epinephrine Injection USP, 0.3 mg (Auto-Injectors) (epinephrine injections USP, 1:1000, 0.3 mL
Epinephrine Injection USP, 0.15 mg ([(b) (4)] Auto-Injectors) (epinephrine injections USP, 1:2000, 0.3 mL

8. BIOAVAILABILITY/BIOEQUIVALENCE**.** Pending.\
Cycle 3 update- Inadequate per review dated 3/11/2010

9. Comments were sent to the firm on February 2, 2011 for the second review cycle. The firm provided the following responses on August 1, 2014:

1. C**ONTAINER**-

a. Is the [redacted] noticeably different than the orange barrel that appears in the window prior to use, such that the orange color cannot be confused with being a [redacted] color?

Response:
The [redacted] has been changed to a black dot to better contrast with the orange barrel as well as to match the referenced listed drug. Prior to use the window is clear allowing visibility of the drug product and becomes black following activation.

b. How does the [redacted] appear in the window viewer? [redacted] I almost missed seeing the [redacted] in the diagram. It would be better to locate the text in the area where the [redacted] is going to appear. Please provide an auto injector with your draft label placed on it. Please use the reference for guidance.

Response:
The [redacted] has been changed to a black dot. The black dot will appear in the window following activation of the device. The window turns black when an internal black component is moved from one position to another during the activation process. [redacted]. The autoinjectors with the draft labels placed on them will be provided concomitantly under separate cover.

c. Upon further review, please revise Auto-Injector [redacted] to read [redacted] Auto- injector). This is so that [redacted] will not be missed when looking at the name of the injections and this is also in keeping with the naming for the innovator products reading Epi-Pen Jr. Auto- Injector for the 0.15 mg product. Please revise on all labels and labeling.

Response:
We have revised "Auto-Injector [redacted]." to read "[redacted]. Auto-Injector" on all labels and labeling.

2. **CARTON** - "Open immediately" stands alone on the carton. Please add "… immediately- To complete Teva's Epinephrine Injection USP Auto- Injectors for Anaphylactic Support- FREE MEMBERSHIP- Details inside.

Response:
We have revised the text on the carton to read "**Open immediately – To complete Teva's Epinephrine Injection USP (Auto-Injectors) for Anaphylactic Support FREE MEMBERSHIP – Details inside**."

3. PROFESSIONAL INSERT- See comment regarding naming.

Response:
We have revised "Auto-Injector [redacted]." to read [redacted]. Auto-Injector" throughout the professional insert labeling.

4. **PATIENT INSTRUCTIONS** -

a. Rather than "contain no latex" revise to read "contains no natural rubber latex" where that

statement appears in the labeling.

Response:
The statement "contain no latex" which appeared in the carton labeling, was revised to read, "Contains no natural rubber latex."

b. The storage statement reads … protect from light. What part of your injector will protect the product from light? The innovatory encloses the auto-injector in to an amber sleeve outer carrying case?

Response:
The latest innovator device is housed within a transparent UV stabilized polycarbonate carrying case. The outer housing of our auto-injectors is manufactured from transparent UV stabilized polycarbonate. In addition, within the outer housing, the prefilled syringe is contained within a sleeve which is also manufactured from transparent UV stabilized polycarbonate. (b) (4) (b) (4) (b) (4)

c. Complete the sentence " See other side for Directions for Use and for Teva's Epinephrine auto-injector

Response:
We are submitting draft labeling at this time to match the reference listed drug. When we prepare final print labeling, and if necessary, we will add the statement (b) (4) (b) (4) This statement does not appear in the reference listed drug however, this statement did appear in the last submitted labeling.

d. We note the following does not appear in the reference product: (b) (4) (b) (4) and should be deleted.

Response:
We have revised our labeling to comply with the reference listed drug. The statements, (b) (4) (b) (4) have been removed from our labeling.

e. Add "for Teva's Epinephrine Injections USP Auto- Injector for Anaphylactic Support- to (b) (4) ….. as seen in the referenced product.

Response:
We are submitting draft labeling at this time. When we prepare final print labeling, if necessary, we will add the statement (b) (4) (b) (4). This statement no longer appears in the reference listed drug labeling.

f. Steps 1, 2, 3, and 4 should be rotated so that the panels are visible in a vertical position and as the patient holds the product container.

Response:
We have rotated "Steps 1, 2, and 3" on the container label so that the panels are visible in a vertical position and as the patient holds the product container. Due to redesign, we no longer have a Step 4 on the container label.

g. DIRECTIONS FOR USE- your proposed section is missing some billets. First billet… you will have to say "a carrying case is NOT provided as seen with other products". Move "Do not use if solution is discolored up so that it follows Do not remove blue safety release…. The two sentences with the yellow or green cap statement were not seen in the referenced product.

Response:
We have revised our "INSTRUCTIONS FOR USE" labeling to comply with the reference listed drug. Also, we have added the statement "A CARRYING TUBE IS NOT PROVIDED AS SEEN WITH OTHER PRODUCTS". Due to the latest RLD update our labeling does not include as bullets, "DO NOT use if solution is discolored" and "DO not remove blue safety release" in this section of our Instructions for Use labeling. The two sentences with the yellow or green cap statement were not seen in the reference product and have been removed from our Instructions for Use labeling.

h. TO USE AUTO INJECTOR- Please revisit this section.

This section does not read the same as the innovator. It was difficult to follow and to ensure that the sequence of steps match the innovator. This section may present confusion for customers that have used the innovator's product. Thus your proposed section, as written, will require new learning and teaching for the previous customers and physicians.

(b) (4)

Again, your proposal has major operational differences from the innovator and would required additional training on your product. To avoid having to re-teach patients, your product should read the same as the innovator with only minor differences.

Response:
We have revised our instructions to follow the reference listed drug label instructions for both content and sequence. We also now have the same number of steps as the innovator.

Your labeling goes on to ask the patient to twist and then pull off the cap while the innovator cap is a (b) (4) cap. I had difficulty twisting the cap and getting it off in a timely manner. Asking the customer to twist and met with more than one direction to twist the cap is not what we would want the patient to have to figure out or experience through trial and error. Is there a way that the cap could be secured to the device and still allow for popped off action rather than twist? The patient will be face with question… how far do I twist, Do I twist in one direction and then again in the other direction following both arrows that are near the word twist, or do I twist the cap all the way around. In addition, the customer will have to recognize first that the cap has to be twisted before it can come off.

Response:
The cap has been redesigned so that it can be easily twisted in only one direction. Additionally, a printed twist arrow has been added to the cap showing which direction to twist the cap for removal. The trainer device, which will be included in each kit, also includes a cap

with the identical geometry, function and markings as the actual device.

Your product has two steps ([(b) (4)] safety clip and [(b) (4)] yellow cap) while the innovator has one (safety clip) for the actual device.

Response:

The labeling has been revised to have one step and no longer contains numbers on the device to align with the innovator.

Your product has more than one window and you instruct the patient to view for [(b) (4)] and also discoloration. Please explain how this will be accomplished so the patient would know which window to view the [(b) (4)] an which to view for discoloration.

Response:

The labeling has been revised to highlight the viewing window and the text that relates to the window. The see through window is symmetrical and will indicate the device state when viewed from either side of the device. The [(b) (4)] is also now a black dot for better contrast and to align with the innovator. The innovator has 3 steps while you have 4. [(b) (4)] [(b) (4)] More importantly, the statements should appear on the window where the [(b) (4)] will appear. Please provide a labeled autoinjector.

Response:

We have revised the auto-injector to have the same number of steps as the innovator. The [(b) (4)] [(b) (4)] is now a black dot which matches the innovator. The statement regarding the black dot is now located near the viewing window. The auto-injectors with the draft labels placed on them will be provided under separate cover.

5. **TRAINER LEAFLET -**

a. The innovator has the following sentence in two locations and you have use the statement in only one location. Please add "The Trainer does NOT contain any medication and does NOT have a needle".

Response:

We have revised our trainer labeling to comply with the reference listed drug. We have also added the statement “The Trainer does NOT contain any medication and does NOT have a needle”.

b. Add specific location the following seeing your auto-injector is designed different than the reference- Never put thumb, other fingers, or hand over orange tip (below gray safety cap).

Response:

For the purpose of specific location, we have added the following [(b) (4)] to the statement “Never put thumb, other fingers, or hand over orange tip” to our Trainer Instructions for Use labeling.

c. We do not think your sentence added to the trainer labeling is necessary. Please delete the following sentence: [(b) (4)] [(b) (4)]

Response:
We have removed, [redacted] (b) (4)

d. Steps 1, 2, 3, and 4 are different from the reference and should not be. Please revisit the operational aspect of your container for difference. We refer you to our comments above under TO USE AUTO INJECTOR.

Response:
We have revised our trainer label to comply with the reference listed drug. We have rotated "Steps 1, 2, and 3" on the trainer label so that the panels are visible in a vertical position and as the patient holds the product container. Also, due to the redesign, we no longer have a Step 4 on the trainer label.

e. Under CAUTION section- revise to read as the reference listed drug. Do not add your own text. Example: "drug product" should read medication and Ok should read okay. In addition, the question that asks about pressure needed for the trainer device yours say moderate while the reference product says strong.

Response:
We have revised our "CAUTION" labeling text to read as the reference listed drug.

f. Title- Place the comma behind USP rather than in front of USP.

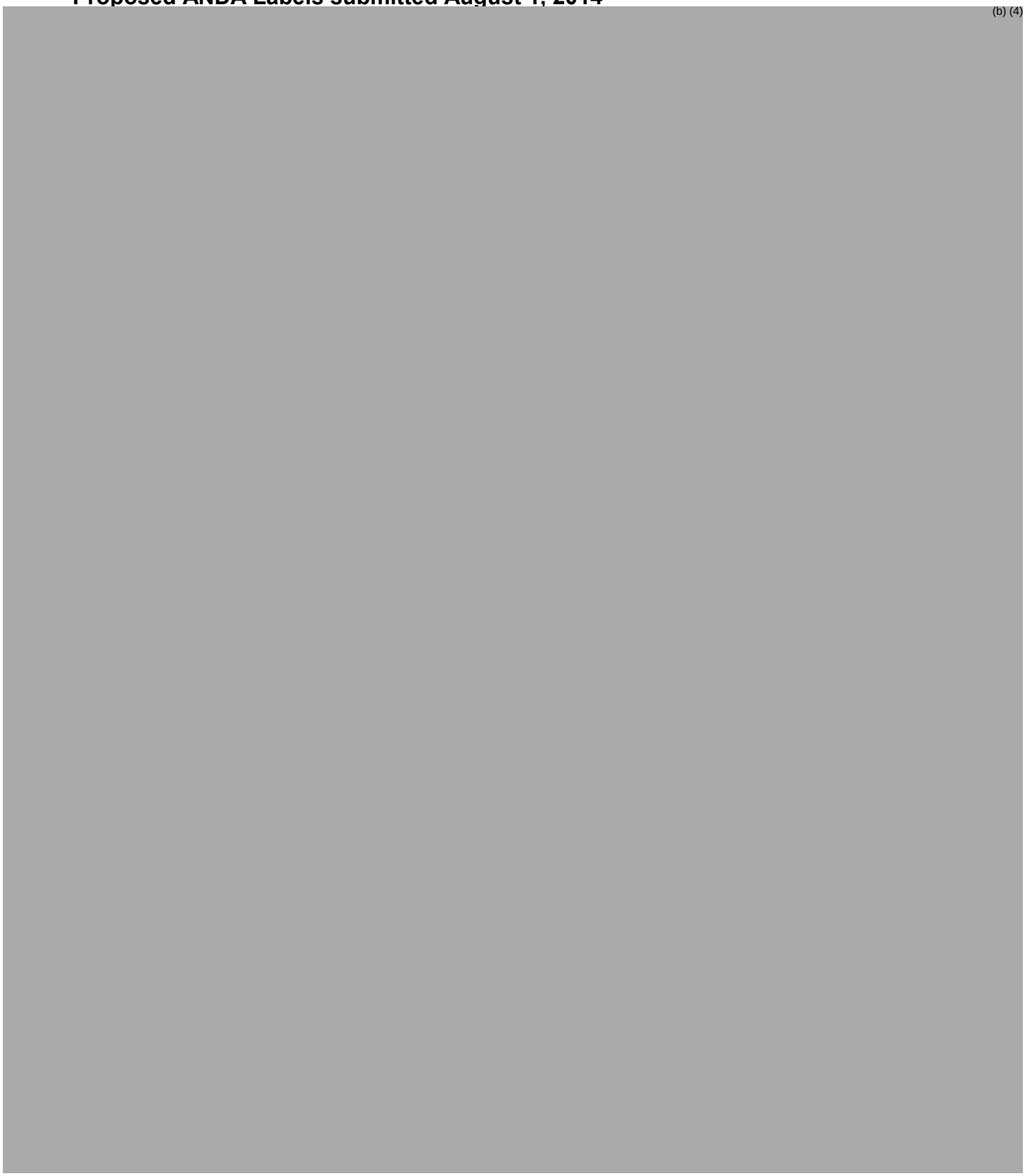
Response:
In the title, we have placed the comma behind USP rather than in front of USP.

Assessment:

The responses submitted by the firm in response to the comments sent based on the second review cycle, to be acceptable form a labeling perspective; however I defer to the CDRH for human factor and functional features of the device.

Proposed ANDA Labels submitted August 1, 2014

(b) (4)



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

/s/

KIMBERLY M RAINS
09/26/2014

JOHN F GRACE
09/26/2014

REVIEW OF PROFESSIONAL LABELING #2
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 090589 Date of Submission: 12 OCT 2010

Applicant's Name: Teva Pharmaceuticals.

Established Name: Epinephrine Injection USP, **0.15 mg**/0.3 mL ((b) (4) Auto Injector) and **0.3 mg**/0.3 mL (Adult- auto injector)

Labeling Comments:

1. C**ONTAINER**-

   a. Is the (b) (4) noticeably different than the orange barrel that appears in the window prior to use, such that the orange color can not be confused with being a reddish color?

   b. How does the (b) (4) appear in the window viewer? In diagram 4, please use an arrow to indicate the location of the (b) (4). I almost missed seeing the (b) (4) in the diagram. It would be better to locate the text in the area where the red dot is going to appear. Please provide an auto injector with your draft label placed on it. Please use the reference for guidance.

   c. Upon further review, please revise Auto-Injector (b) (4) to read ((b) (4) Auto- injector). This is so that (b) (4) will not be missed when looking at the name of the injections and this is also in keeping with the naming for the innovator products reading Epi-Pen Jr. Auto- Injector for the 0.15 mg product. Please revise on all labels and labeling.

2. **CARTON -** "Open immediately" stands alone on the carton. Please add "… immediately- To complete Teva's Epinephrine Injection USP Auto- Injectors for Anaphylatic Support- FREE MEMBERSHIP- Details inside.

3. **PROFESSIONAL INSERT-** See comment regarding naming.

4. **PATIENT INSTRUCTIONS** -

   a. Rather than "contain no latex" revise to read "contains no natural rubber latex" where that statement appears in the labeling.

   b. The storage statement reads … protect from light. What part of your injector will protect the product from light? The innovatory encloses the auto-injector in to an amber sleeve outer carrying case?

   c. Complete the sentence " See other side for Directions for Use and for Teva's Epinephrine auto-injector

   d. We note the following does not appear in the reference product: (b) (4) and should be deleted.

   e. Add "for Teva's Epinephrine Injections USP Auto- Injector for Anaphylatic Support- to SEE OTHER SIDE FOR "DIRECTIONS FOR USE" AND TEVA'S….. as seen in the referenced product.

   f. Steps 1, 2, 3, and 4 should be rotated so that the panels are visible in a vertical position and as the patient holds the product container.

g. DIRECTIONS FOR USE- your proposed section is missing some billets. First billet… you will have to say "a carrying case is NOT provided as seen with other products". Move "Do not use if solution is discolored up so that it follows Do not remove blue safety release…. The two sentences with the yellow or green cap statement were not seen in the referenced product.

h. TO USE AUTO INJECTOR- Please revisit this section.

This section does not read the same as the innovator. It was difficult to follow and to ensure that the sequence of steps match the innovator. This section may present confusion for customers that have used the innovator's product. Thus your proposed section, as written, will require new learning and teaching for the previous customers and physicians (b) (4) (b) (4)

Again, your proposal has major operational differences from the innovator and would required additional training on your product. To avoid having to re-teach patients, your product should read the same as the innovator with only minor differences.

Your labeling goes on to ask the patient to twist and then pull off the cap while the innovator cap is a (b) (4) cap. I had difficulty twisting the cap and getting it off in a timely manner. Asking the customer to twist and met with more than one direction to twist the cap is not what we would want the patient to have to figure out or experience through trail and error. Is there a way that the cap could be secured to the device and still allow for popped off action rather than twist? The patient will be face with question… how far do I twist, Do I twist in one direction and then again in the other direction following both arrows that are near the word twist, or do I twist the cap all the way around. In addition, the customer will have to recognize first that the cap has to be twisted before it can come off.

Your product has two steps ((b) (4) safety clip and (b) yellow cap) while the innovator has one (safety clip) for the actual device.

Your product has more than one window and you instruct the patient to view for (b) (4) and also discoloration. Please explain how this will be accomplished so the patient would know which window to view the (b) (4) an which to view for discoloration.

The innovator has 3 steps while you have 4. The fourth diagram displays a (b) (4) that is barely seen please place a black arrow indicating the (b) (4). More importantly, the statements should appear on the window where the red dot will appear. Please provide a labeled autoinjector

5. **TRAINER LEAFLET -**

a. The innovator has the following sentence in two locations and you have use the statement in only one location. Please add "The Trainer does NOT contain any medication and does NOT have a needle".

b. Add specific location the following seeing your auto-injector is designed different than the reference- Never put thumb, other fingers, or hand over orange tip (below gray safety cap).

c. We do not think your sentence added to the trainer labeling is necessary. Please delete the following sentence: (b) (4)

d. Steps 1, 2, 3, and 4 are different from the reference and should not be. Please revisit the operational aspect of your container for difference. We refer you to our comments above under TO USE AUTO INJECTOR.

e. Under CAUTION section- revise to read as the reference listed drug. Do not add your own text. Example: "drug product" should read medication and Ok should read okay. In addition, the question that asks about pressure needed for the trainer device yours say moderate while the reference product says strong.

f. Title- Place the comma behind USP rather than in front of USP.

Revise your labels and labeling, as instructed above, and submit DRAFT (or final print if prefer) electronically.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling and the latest approved labeling for the reference listed drug (or your last submission) with all differences annotated and explained.

FOR THE RECORD
LABELING REVIEW BRANCH

REMS required? NO

MedGuides and/or PPIs (505-1(e)) ☐ Yes ☐ No

Communication plan (505-1(e)) ☐ Yes ☐ No

Elements to assure safe use (ETASU) (505-1(f)(3)) ☐ Yes ☐ No

Implementation system if certain ETASU (505-1(f)(4)) ☐ Yes ☐ No

Timetable for assessment (505-1(d)) ☐ Yes ☐ No

ANDA REMS acceptable?
☐ Yes ☐ No X n/a

1. APPLICANT INFORMATION.

ANDA Number	90-589
Date of Submission	
Applicant	Teva
Drug Name	Epinephrine Auto Injector
Strength(s)	0.15 mg/o.3 mL and 0.3 mg/0.3 mL

Labels and Labeling Summary
Container Labels 1 pak - 0.15 mg and 0.3 mg 2 pak - 0.15 mg, 0.3 mg and trainer Pouches (NOT USED)
Carton Labels 1 pak - 0.15 mg and 0.3 mg 2 pak - 0.15 mg, 0.3 mg and trainer Package Insert Labeling Patient instruction sheet AND Trainer sheet

REFERENCE LISTED DRUG:

Patent Data For NDA 19-430

Patent No	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
None				PII	Labeling Impact

Exclusivity Data For NDA 19-430 Jr

Code/sup	Expiration	Description	*Labeling impact*

None			

Reference Listed Drug

RLD on the 356(h) form	EPI-Pen JR and Epi-pen
NDA Number	19-430
RLD established name	Epinephrine auto injector
Firm	Meridian medical Techn
Currently approved PI	S-047- tip, cover, safety cap color change and noted changes to PI and PI
AP Date	19 MAY 2009

Note:

2. NOTE TO CHEMIST: I am not sure what the firing mechanism consist of but I believe it has to be the same as the RLD or it may be considered a new device and perphaps can not be approved as ANDA. The applicant should also provide a case/tube for the container that should protect the product from light and to be used to safely store and transport the product. This ANDA may also need a usability test as was the case for another generic seeing the needle has to go through the customers clothing during administration. The applicant has submitted mechanism firing information and use test to CDRH and in this submission 6/10. There is a CP in house regarding Teva's product having more steps (remove cap and safety clip) to initiate the firing while the brand has only one. The innovator has a sleeve that the auto-injector fits into that has to be removed before the product can be used. There were many significant differences noted in the labeling that could require the customer to have to relearn how to use this new device. I have unlabeled samples of the autoinjector in my office if you wish to view them.

   Please note the fill volume for the ANDA and RLD are different. The ANDA has less.

3. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM -

4. CONTAINER/CLOSURE and packaging configurations

   RLD: 0.3 mL dispensed /1.7 mL remains left- for total of 2 mL total volume
   ANDA: 0.3 mL dispensed / 0.7 ml remains left - for a total of 1 mL total volume

5. Active and INACTIVE INGREDIENTS

   The description of the inactive ingredients in the insert labeling appears accurate according to the composition statement. [Vol. 1.1, pg. 117] same as the RLD. Contains metabisulfite and NaCL

6. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

   USP: store in tight containers
   RLD: store at 25 (77F). See USP CRT protect from light, Do not Freeze
   ANDA: Store at 20-25C (68-77F).[See USP CRT]. Store upright protect from light. Do not freeze

7. DISPENSING STATEMENTS COMPARISON

   USP: Not a USP item
   RLD: Epinephrine Injection 1:2000 (JR) and 1:1000 autoinjector
   ANDA (*Insert*): plastic unit dose ampules

8. BIOAVAILABILITY/BIOEQUIVALENCE**.** Pending.

9. **PROFESSIONAL INSERT-** The first review has extensive comments for the applicant. Below is just a few that has been updated with the firms response.

   a. WARNINGS- The product is light sensitive and the innovator products a tube to store the product. Please do the same. This will also help with transporting the product to the emergency room visit as instructed in the labeling. Firm states container is light resistence.

   b. HOW SUPPLIED- The innovator provides individual carrying cases (tube sleeves) that provides built-in needle protection after use. The also provide a clip for the 2 pack. Please provide similar cases. Please explain how are you proposing to protect the build in needle? Firm states they do not provide a carrying sleeve because their product needle is covered by the shield using the suresafe mechanism covering the needle.

   PATIENT INSTRUCTIONS -Please use the innovators patient insert to ensure that your leaflet reads the same. Important information is missing from your labeling. Just to name a few areas - Add-Examine content, Support center enrollment form, four billets should follow immediately after Directions for use,

   a. DIRECTIONS FOR USE - Please revisit this entire section it is not similar or the same as the reference listed drug. Important information was omitted just to mention a few: Indicate lot number and expiration date position as seen on the reference product. The outer package information must be revisited. In addition color of caps must also be changed. Diagram should look like the innovators. (b) (4)

   b. TRAINER- Revisit this entire section to comply with sameness.

Date of Review: 1/26/11 Date of Submission: 12 OCT 2010

---

cc:

ANDA: 90-589
DUP/DIVISION FILE
HFD-613/APayne/JGrace (no cc)
v:\firmsnz\teva\lets&rev\90589na2labdfsreview
Review

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

/s/

ANGELA M PAYNE
01/28/2011

JOHN F GRACE
02/02/2011

REVIEW OF PROFESSIONAL LABELING #1
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 90-589 Dates of Submission: 21 DEC 2007 and 24 NOV 2008

Applicant's Name: Teva Pharmaceuticals.

Established Name: Epinephrine Injection USP, 0.15 mg/0.3 mL ((b) (4) auto Injector) and 0.3 mg/0.3 mL

Labeling Deficiencies:

1. C**ONTAINER**-

a. We were able to make only limited comments because the innovators labels you submitted lack resolution. Please resubmit.

b. The layout of the label is not acceptable. It will cause a customer to have to turn the container in three different directions. Please realign the text so that it will flow with easy in one direction.

c. There is an USP monograph for this product. The established name should appear on all labels and labeling expressed as "Epinephrine Injection USP, 0.15 mg (Auto Injector JR)" or "Epinephrine Injection USP, 0.3 mg (Auto Injector)" in conjunction to the trade name (if there is one) on the principal display panel. You may also elect to retain "Epinephrine Auto-Injector" but add the established name (Epinephrine Injection USP). Please ensure that the route of administration is also displayed on the main panel "For IM Use" or "intramuscular Use". Note; also relocate the comma it should appear after USP rather than after injection.

d. It is important that the tip color, safety clip, and label are the same colors as the innovator's product for both the pediatric and adult versions. This will lessen confusion for the consumer who is use to the looking at the innovators product. Currently you have a gray tip and black safety clip while the innovator has a black tip and gray safety clip. Please reverse the color for your product so that it is the same as the reference listed drug. Correct your labeled diagrams and text to be consistent to the changes you make. Please explain whether the exposed needle extends beyond or protrudes beyond the container rim once the cap is removed. Please submit samples to the labeling branch.

e. Revise "Window blocked if unit used"…" to read "A ___ window..." or restate the sentence exactly like the innovator has it. In addition, the text should be placed around the window as seen with the RLD.

f. (b) (4)

g. Diagram 3 - Will the customer hear a click? If so, please state that as does the innovator. You state "… (b) (4) ...". . Please explain the firing mechanism. Will the patient have to push something to operate the tube? The diagram is too crowded. Please use the same picture of the thigh with cloths as seen with the innovator's label. It appears that your product can not go through clothing. Please revise and or verify. Also, a usability test may be required.

h. Diagram 2- Was not seen in the innovator's labeling. Please delete. In addition, you should cite the color of the caps as does the innovator. We are concerned that the twist and pull method may cause a slight time delay in an emergency. Quick retrieval and safety are the goals.

i. Diagram 1- Will the number be printed on the actual cap. Also, give the color. Please consider the innovators naming system for consistency. Cap 1 and Cap 2 are confusing. It is important that

your caps are label and colored the same as the reference listed drug for consistency across this product line.

j. Relocate "replace if solution is discolored" so that it appears below the window area.

k. .Trainer Device- Please submit for review. To prevent potential for confusion with the auto-injector containing active drug product and the training device, increase the font size of “Training Device for” .

l. Please include all inactive ingredients found in your component/composition statement on your labels.

m. The innovator places the auto-injector in an outer case that protects the needle and injector for safety reasons and from light. How will the customer safely and securely take the used syringe to the emergency room visit as instructed in the labeling? Please comment on what you are providing to do the same.

n. The route of administration is not clearly stated on the label and is included only to refer how much epinephrine is delivered. Include the route of administration as a stand alone statement outside the text (i.e. for intramuscular use only) per 21 CFR 201.100(b)(3).

o. Include a “For One Time Use” statement so that the user is clear there is only one dose per injection.

p. Epinephrine is most often used in emergent situations that preclude the removal of clothing. The EpiPen and EpiPen Jr labels and labeling depict the device being injected into a person who is fully clothed; the Anapen pictures do not convey this same message and instead it appears that the Anapen device is pressed directly upon the skin. Revise the pictures to reflect that Anapen may be injected through clothing.

q. We note that the label directions on the trainer device are positioned horizontally instead of vertically like the Anapen/Anapen Jr devices. Revise the orientation of the labels so that it is consistent with the actual device. Also, ensure that the directions are oriented so that the user will find it easy to read while holding the auto-injector.

r. Identify the needle end clearly by changing the color from (b) (4) to orange or red and include an information label that reads “Needle End” on the label and to the protective tube.

s. Bold the “10 seconds” statement so that this instruction is more visible to users.

t. Place an instruction to “pull off to use” on the safety release to increase the likelihood that users will quickly understand what needs to be removed to use the auto-injector.

2. **CARTON -** We are unable to complete comments on this section at this time. Please resubmit clearer innovators labeling.

a. Include the following statements "open immediately…" and we refer you to the RLD labeling for guidance.

b. A picture of the contents should be placed on the cartons as seen with the listed drug product.

3. PROFESSIONAL INSERT-

.a. WARNINGS- The product is light sensitive and the innovator products a tube to store the product. Please do the same. This will also help with transporting the product to the emergency

room visit as instructed in the labeling.

b. HOW SUPPLIED- The innovator provides individual carrying cases (tube sleeves) that provides built-in needle protection after use. The also provide a clip for the 2 pack. Please provide similar cases. Please explain how are you proposing to protect the build in needle?

4. **PATIENT INSTRUCTIONS** -Please use the innovators patient insert to ensure that your leaflet reads the same. Important information is missing from your labeling. Just to name a few areas - Add- Examine content, Support center enrollment form, four billets should follow immediately after Directions for use,

   a. DIRECTIONS FOR USE - Please revisit this entire section it is not similar or the same as the reference listed drug. Important information was omitted just to mention a few: Indicate lot number and expiration date position as seen on the reference product. The outer package information must be revisited. In addition color of caps must also be changed. Diagram should look like the innovators.. (b) (4)

   b. WARNINGS: - revisit cap colors.

   c. Expiration Reminder Program- Provide a phone number in addition to the web in case a customer has not access to the web. Must include the center for anaphylactic support information.

   d. Please combine the patient instructions sheet for both products rather than providing separate instructions sheets

5. **TRAINER LEAFLET -** This section is missing from your submission. However, we have included a few general comments.

   a. Add "Directions for use" just below the title. Just after the table add "Practice Instructions". Re-label needle cap and safety cap based on comments under CONTAINER above. You provide 5 steps while the RLD site 9. Please revisit this section. We refer you the RLD labeling. Please ensure that you cite the color of the trainer.

   b. Under "Resetting the trainer" and the last portion of this leaflet you are not consistent with stating the color of the needle cap and safety cap. You also state moderate pressure needed versus strong for the RLD. Is your needle stable if the pressure is strong because need must also travel through fabric.

Revise your labels and labeling, as instructed above, and submit final printed (or draft if you prefer) electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – ANDA.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://www.fda.gov/cder/cdernew/listserv.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling and the latest approved labeling for the reference listed drug (or your last submission) with all differences annotated and explained.

FOR THE RECORD
LABELING REVIEW BRANCH

1. APPLICANT INFORMATION.

ANDA Number	90-589
Date of Submission	
Applicant	Teva
Drug Name	Epinephrine Auto Injector
Strength(s)	0.15 mg/o.3 mL and 0.3 mg/0.3 mL

Labels and Labeling Summary
Container Labels
Pouches
Carton Labels
Package Insert Labeling
Patient instruction sheet

REFERENCE LISTED DRUG:

Patent Data For NDA 19-430

Patent No	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
None				PII	Labeling Impact

Exclusivity Data For NDA 19-430 Jr

Code/sup	Expiration	Description	*Labeling impact*
None			

Reference Listed Drug

RLD on the 356(h) form	EPI-Pen JR and Epi-pen
NDA Number	19-430
RLD established name	Epinephrine auto injector
Firm	Meridian medical Techn
Currently approved PI	S-044
AP Date	26 SEP 2008

Note: Several pending supplements

NOTE TO CHEMIST: I am not sure what the firing mechanism consist of but I believe it has to be the same as the RLD or it may be consider a new device and there can not be approved as ANDA. The applicant must also provide a case/tub for the container that should protect the product from light and is used to safely store and transport the product. This ANDA product may also need a usability test as was the case for another generic and seeing that is product may have to go through the customers clothing during a reaction.

FOR THE RECORD:

1. MODEL LABELING

   This review was based on the labeling NDA- see above.

2. PATENTS/EXCLUSIVITIES: See above [Vol. A1.1 pg. 7]

3. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM -

4. CONTAINER/CLOSURE and packaging configurations

   RLD: 0.3 mL dispensed /1.7 mL remains left- for total of 2 mL total volume
   ANDA: 0.3 mL dispensed / 0.7 ml remains left - for a total of 1 mL total volume

5. Active and INACTIVE INGREDIENTS

   The description of the inactive ingredients in the insert labeling appears accurate according to the composition statement. [Vol. 1.1, pg. 117] same as the RLD. Contains metabisulfite and NaCL

6. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

   USP: store in tight containers
   RLD: store at 25 (77F). See USP CRT protect from light, Do not Freeze
   ANDA: Store at 20-25C (68-77F).[See USP CRT]. Store upright protect from light. Do not freeze

7. DISPENSING STATEMENTS COMPARISON

   USP: Not a USP item
   RLD: Epinephrine Injection 1:2000 (JR) and 1:1000 autoinjector
   ANDA (*Insert*): plastic unit dose ampules

8. BIOAVAILABILITY/BIOEQUIVALENCE:

Date of Review: 5/26/09 Date of Submission: 21 DEC 2007 and 24 NOV 2008

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cc:

ANDA: 90-589
DUP/DIVISION FILE
HFD-613/APayne/JGrace (no cc)
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Review

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

/s/

Angela Payne
5/28/2009 09:12:00 AM
LABELING REVIEWER

John Grace
6/4/2009 10:37:40 AM
LABELING REVIEWER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 090589

CHEMISTRY REVIEW(S)

Approvability – CMC Adequate

ANDA 090589

Epinephrine Injection, USP (Auto-Injector)
0.15 mg/0.3 mL and 0.3 mg/0.3 mL

Teva Pharmaceuticals USA, Inc.

Xiaohua Huang
Division of Immediate Release Products II

Chemistry Review Data Sheet

1. ANDA 090589

2. REVIEW #: 4c

3. REVIEW DATE: 6/1/2018

4. REVIEWER: Xiaohua Huang

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original Application (SD #1)	21-Dec-2007
Amendment (SD #2)	30-May-2008
Chemistry Review #1	04/30/2009
Amendment (SD #5)	23-May-2009
Amendment (SD #6)	12-Jun-2009
Chemistry Review #2	03/02/2010
Chemistry Review #2a	05/16/2011
Amendment (SD#16) (change of ownership)	18-Jul-2011
Amendment (SD#19)	20-Jan-2012
Chemistry Review #2b	12/20/2012
Amendment (SD #25)-Response to IR and Formulation Change	12/30/2014
Amendment (SD #27)-Response to IR	05/20/2015
Amendment (SD #28)-Response to IR	05/21/2015
Amendment (SD #29)-Response to IR	06/12/2015
Chemistry Review #3	06/24/2016
Amendment (SD #33)-Response to IR	09/08/2016
Chemistry Review #3a	11/07/2016
Amendment (SD #40)-Response to IR	12/07/2016
Chemistry Review #3b	03/10/2017

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment (SD #46)-Response to IR and Gratuitous Information	04/04/2017
Amendment (SD #47)-Response to IR	04/04/2017
Chemistry Review #4	09/05/2017
Amendment (SD #57)-Response to IR	10/06/2017
Chemistry Review #4a	01/30/2018
Amendment (SD #62)-Response to IR	02/28/2018

Chemistry Review #4b	5/14/2018
Amendment (SD #66)-Response to IR	5/30/2018

7. NAME & ADDRESS OF APPLICANT:

Name:	Teva Pharmaceuticals USA, Inc.
Address:	425 Privet Road, Horsham, PA 19044
Representative:	Cory Wohlbach, Senior Director, US Generics Regulatory Affairs
Telephone:	215-293-6519
Fax:	215-591-8812

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Epinephrine Injection USP

9. LEGAL BASIS FOR SUBMISSION:

The basis for Teva Parenteral Medicines, Inc proposed ANDA for Epinephrine Injection USP, Auto-Injector 0.15 mg and 0.3 mg is the approved reference listed drug (RLD) EpiPen®, EpiPen® Jr, the subject of NDA No. 19-430 held by MYLAN SPECLT (Approved December 22, 1987). The RLD is in 0.15 mg and 0.3 mg strengths.

The ANDA sponsor filed a Paragraph IV certification for U.S. Patent 7,449,012, 7,794,432, 8,048,035, and 8,870,827 that will expire on September 11, 2025. The RLD holder filed the citizen petition on January 16 of 2015 and April 28 of 2015, which were denied on June 15 of 2015 without comment.

10. PHARMACOL. CATEGORY: sympathomimetic catecholamine.

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 0.15 mg/0.3 mL and 0.3 mg/0.3 mL

13. ROUTE OF ADMINISTRATION: intramuscular & subcutaneous

14. Rx/OTC DISPENSED: _X_ Rx ____ OTC

15a. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

☐ SPOTS product – Form Completed

☒ Not a SPOTS product

15b. NANOTECHNOLOGY PRODUCT TRACKING:

☐ NANO product – Form Completed (See Appendix A.4)

☒ Not a NANO product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical name: (-)-3,4-Dihydroxy-alpha-((methylamino)methyl)benzyl alcohol

or

1,2-Benzenediol, 4-(1-hydroxy-2-(methylamino)ethyl)-, (R)-

or

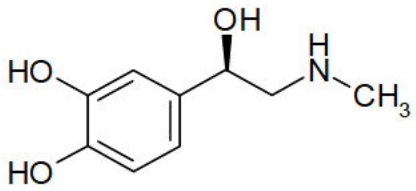
1-1-(3,4-Dihydroxyphenyl)-2-methylaminoethanol

Molecular formula: $C_9H_{13}NO_3$

Formula weight: 183.206 g/mol

CAS RN: [51-43-4]

Structural formula:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

(b) (4)

DMF	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)		3	Adequate	06/01/2016	SKANCHY, DAVID J
	III			3	Adequate	1/24/2018	Koushik Paul
	III			3	Adequate	2/13/2018	Erika Englund
	V			3	Adequate	12/20/2017	David Bateman
	V			3	Adequate	12/20/2017	David Bateman
	V			3	Adequate	3/5/2018	Yan Zheng
				3	Adequate	1/30/2018	John McMichael
				3	Adequate	1/30/2018	John McMichael

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 – Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")
[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	Consult No:	DESCRIPTION
Consult	2008-0229	Consult request to DACCADP re Mechanism of Action
Consult	2009-0320 2010-0383	Consult request to CDRH re MAF (b) (4)
Consult	2010-0382	Pharm/Tox consult re the impurity ESA
Consult	Consult date: 04Apr2012 Response Date: 07May2012	Consult request to CDRH re human factor study
Consult	2013-0786	Consult request to OGD/DCR re needle length

Consult	Consult date: 6/5/2015	Consult for MAFs (b) (4)
Consult	Consult date: 6/10/2015	Consult for Human Factor Study
Consult	Consult date: 6/25/2015	Consult request from DB III to DCR re clinical safety of sodium tartrate dihydrate as an inactive ingredient in the proposed drug product when injected subcutaneously
Respond to Consult request	Response Date: 8/10/16	Respond to Consult request from Division of Bioequivalence III (DBIII) regarding the justification of the excipient sodium tartrate dihydrate for subcutaneous administration
Respond to Consult request	Response Date: 8/19/16	Respond to Consult request from DCR regarding the justification of the excipient sodium tartrate dihydrate for subcutaneous administration
Consult	Consult date: 09/02/2016	Consult to CDRH --- cGMP compliance of the device manufacturing facility (b) (4) Recommendation: PAI at the device assembly facility, (b) (4)
Consult	Consult date: 09/16/2016	Consult to DCR --- Impurity qualification. Recommendation: Adequate
Consult	Consult date: 10/06/2016	Consult to OSE\DMEPA-human factor study Recommendation: Pending
Consult	Consult date: 11/16/2016	Consult to CDRH-Response to device deficiencies Recommendation: Adequate
Consult	Consult date: 3/15/2018	Consult to CDRH- Gratuitous amendment dated 03/05/2018 Recommendation: Adequate

18. STATUS:

CONSULTS / CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Adequate	6/14/2017	Eric Adeeku
Methods Validation	N/A		
Labeling	Inadequate	12/12/2016	Esther Chuh
Bioequivalence	Adequate	11/22/2017	Harikrishna Devalapally
EA	Categorical Exclusion	30-Nov-2015	Xiaohua Huang
Radiopharmaceutical	N/A		
Sample requested	Yes	June 15, 2015 October 6, 2016	Xiaohua Huang Mike Darj

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. ___ Yes _x_ No If no, explain reason(s) below:

High priority because of the drug shortage status for Epinephrine Injection Auto-Injector and the urgent public health need of a more affordable generic product.

20. EES INFORMATION

Overall Recommendation: Approve

Drug Substance			
Function	**Site Information**	**FEI #**	**Status**
[redacted]	[redacted]	(b) (4)	Adequate
[redacted]	[redacted]	[redacted]	Adequate
[redacted]	[redacted]	[redacted]	**Status**
[redacted]	[redacted]	[redacted]	Adequate
[redacted]	[redacted]	[redacted]	Adequate
[redacted]	[redacted]	[redacted]	Adequate
[redacted]	[redacted]	[redacted]	N/A
[redacted]	[redacted]	[redacted]	N/A
[redacted]	[redacted]	[redacted]	N/A

Chemistry Review Data Sheet

(b) (4)

	N/A
	N/A
	Withdrawn
	Withdrawn
	Adequate
	Adequate

(b) (4)

1.

2.

3. Reported in the amendment dated 4/4/2017, but not in Panorama. RBPM notified.
4. Withdrawn in the amendments dated 4/4/2017, but not reported in previous submissions.

The Chemistry Review for ANDA 090589

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

CMC Adequate. DMEPA consult and labeling review are pending.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Not Applicable

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance

Epinephrine, also known as Adrenaline, is a white to off-white crystalline powder. The molecule is optically active due to a chiral center. It exists as D- and L- optical isomers, (b) (4) (b) (4) It has aqueous solubility of less than 0.01 grams in 100 mL. However, solubility increases as the solution becomes more acidic. It is prone to oxidation and photo-degradation. (b) (4) (b) (4) The USP monograph for the drug substance is available.

Drug Product

The drug product is Epinephrine Injection USP 0.15 mg/0.3 mL and 0.3 mg/0.3 mL. The product is packaged in an autoinjector device. The drug product is intended for the treatment of severe allergic reactions (Type I) to insect stings or bites, foods, drugs, and other allergens. It can also be used in the treatment of exercise-induced anaphylaxis. According to the labeling, the usual adult dose is 0.3 mg. However, with severe persistent anaphylaxis, repeat injections with an additional Epinephrine Injection, USP auto-injector may be necessary. (b) (4) (b) (4)

(b) (4)

Exhibit batch number placed on stability	Bio batch number for in-vivo studies
021A16A (0.15 mg/0.3 mL) 020A16A (0.3 mg/0.3 mL)	N/A

B. Description of How the Drug Product is Intended to be Used

Inject epinephrine injection, 0.3 mg or epinephrine injection, 0.15 mg intramuscularly or subcutaneously into the anterolateral aspect of the thigh, through clothing if necessary. Selection of the appropriate dosage strength (epinephrine injection, 0.3 mg or epinephrine injection, 0.15 mg) is determined according to patient body weight.

- Patients greater than or equal to 30 kg (approximately 66 pounds or more): Epinephrine injection, 0.3 mg
- Patients 15 to 30 kg (33 pounds to 66 pounds): Epinephrine injection, 0.15 mg

C. Basis for Approvability or Not-Approval Recommendation

Adequate pending DMEPA consult and labeling review.

Summary of Proposed Changes as Provided in SD# 46 and SD# 47 dated 4/4/2017 – Major Amendment

- (b) (4)

Chemistry Assessment

I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data

S DRUG SUBSTANCE:

S.1 General Information

S.1.1 Nomenclature:

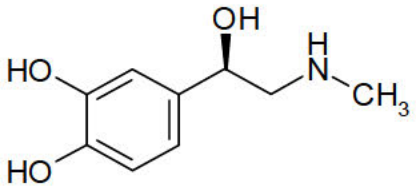
Chemical Name: (-)-3,4-Dihydroxy-alpha-((methylamino)methyl)benzyl alcohol
or
1,2-Benzenediol, 4-(1-hydroxy-2-(methylamino)ethyl)-, (R)-
or
1-1-(3,4-Dihydroxyphenyl)-2-methylaminoethanol

Other nonproprietary name: Adrenaline

Molecular Formula: $C_9H_{13}NO_3$

Molecular Weight: 183.20

S.1.2 Structure:



S 1.3 General Properties:

Physical Description: White to off-white crystalline powder
pKa: $pK_1 = 8.71$ at 20 °C, $pK_2 = 9.90$ at 20 °C
Polymorphism: Does not exist in different crystalline forms
Stereochemistry: Epinephrine exists as D- and L- optical isomers. (b) (4)
(b) (4)
Solubility Characteristics: <0.01 g / 100 mL of water at 18 °C; very slightly soluble in alcohol, insoluble in chloroform, ether, acetone, and oils. Soluble in mineral acids. Solubility increases as a function of decreasing pH.
Hygroscopicity: Epinephrine is not reported in the literature as being hygroscopic.
Melting Point: 211-212 °C
Partition Coefficient: Log P (octanol-water) = -1.37
Other Physicochemical Characteristics: Vapor pressure at 25 °C = 7.37×10^{-7} mm Hg

S.2 Manufacture

S.2.1 Manufacturers:

Who manufactures the drug substance?

See item 20 in Chemistry Review Data Sheet.

S.2.2 Description of Manufacturing Process and Process Controls:

Refer to DMF (b) (4)

S.2.3 Control of Materials

Refer to DMF (b) (4)

S.2.4 Controls of Critical Steps and Intermediates

Refer to DMF (b) (4)

S.2.5 Process Validation and/or Evaluation

Refer to DMF (b) (4)

S.2.6 Manufacturing Process Development

Refer to DMF (b) (4)

S.3 Characterization

S.3.1 Elucidation of Structure and other Characteristics

Refer to DMF (b) (4)

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

A APPENDICES

A.1 Facilities and Equipment (biotech only) Provided

A.2 Adventitious Agents Safety Evaluation None.

A.3 Novel Excipients None

R REGIONAL INFORMATION

R1 Executed Batch Records Provided

R2 Comparability Protocols None

R3 Methods Validation Package Provided

Appendix D: Chemistry Review Template – Labeling section

II. Review of Common Technical Document-Quality (Ctd-Q) Module 1

A. Labeling & Package Insert

a) DESCRIPTION section

i) Is the information accurate? ☒ Yes ☐ No

If "No," explain.

ii) Is the drug product subject of a USP monograph? ☒ Yes ☐ No

If "Yes," state if labeling needs a special USP statement in the Description. (e.g., USP test pending. Meets USP assay test 2. Meets USP organic impurities test 3.) No.

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

b) HOW SUPPLIED section

i) Is the information accurate? ☒ Yes ☐ No
If "No," explain.

ii) Are the storage conditions acceptable? ☒ Yes ☐ No
If "No," explain.

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

Did the applicant provide quality data to support in-use conditions (e.g. diluent compatibility studies)? ☐ Yes ☐ No ☒ N/A
If "No," explain.

d) For OTC Drugs and Controlled Substances: N/A

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

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

ANDA Strength	Length (mm)	Imprint Code

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

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1

Documents
Patent Certification: Yes

Exclusivity: Yes

Debarment Certification: Yes

cGMP Statement: Yes

Reprocessing Statement: Yes

Letters of Authorization: Yes

Request for Bio-waiver: Yes

Citizen Petition and/or Control Request Linked to the Application:
Citizen Petitions were filed by RLD holder–Mylan on January 16 of 2015 and April 28 of 2015, and denied on June 15 of 2015 without comment.

Environmental Impact Considerations/Categorical Exclusions: Yes

III. List Of Deficiencies To Be Communicated

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 090589 APPLICANT: Teva Pharmaceuticals USA

DRUG PRODUCT: Epinephrine Injection USP, Autoinjector 0.15mg/0.3mL and 0.3mg/0.3mL

A. Deficiencies:

None.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

None.

ADMINISTRATIVE

A. Reviewer's Signature

B. Endorsement Block

Chemist Name/Date: Xiaohua Huang, 6/1/2018
Quality Assessment Lead Name/Date: M. Darj, 14Jun2018
Regulatory Business Process Manager Name/Date:

TYPE OF LETTER:

Mike Darj

Digitally signed by Mike Darj
Date: 6/14/2018 03:03:30PM
GUID: 508da70000028695fe9776e1e3e9234c

Xiaohua Huang

Digitally signed by Xiaohua Huang
Date: 6/14/2018 03:03:25PM
GUID: 542052230001985d194bf82bb7ee9157

Addendum to Chemistry Review 4c

Approvability – CMC Adequate

ANDA 090589

Epinephrine Injection, USP (Auto-Injector)
0.15 mg/0.3 mL and 0.3 mg/0.3 mL

Teva Pharmaceuticals USA, Inc.

Xiaohua Huang
Division of Immediate Release Products II

Purpose

The purpose of this addendum is to update Section 5 (Previous Documents), Section 6 (Submission(s) Being Reviewed), Section 17.A. (Related/Supporting Documents: DMFs), and Section 18 (Status) of the Chemistry Review Data Sheet to include all Quality Amendments for this ANDA as well as correcting review information for DMFs that pertain to Microbiology review. The DMF information was taken from the Microbiology review signed on 15Jun2017. Information below supersedes the corresponding information provided in the quality review dated/signed 14Jun2018.

Chemistry Review Data Sheet

1. ANDA 090589

2. REVIEW #: 4c - Addendum

3. REVIEW DATE: 15Aug2018

4. REVIEWER: Xiaohua Huang

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original Application (SD #1)	21-Dec-2007
Amendment (SD #2)	30-May-2008
Chemistry Review #1	04/30/2009
Amendment (SD #5)	23-May-2009
Amendment (SD #6)	12-Jun-2009
Chemistry Review #2	03/02/2010
Chemistry Review #2a	05/16/2011
Amendment (SD#16) (change of ownership)	18-Jul-2011
Amendment (SD#19)	20-Jan-2012
Chemistry Review #2b	12/20/2012
HFS/DMEPA Consult IR Response	08/29/2013
Amendment (SD #25)-Response to IR and Formulation Change	12/30/2014
Amendment (SD #27)-Response to IR	05/20/2015
Amendment (SD #28)-Response to IR	05/21/2015
Amendment (SD #29)-Response to IR	06/12/2015
Chemistry Review #3	06/24/2016
Amendment (SD #33)-Response to IR	09/08/2016
HFS/DMEPA Consult IR Response	09/09/2016
HFS/DMEPA consult (additional information provided after F2F meeting)	09/26/2016
Samples Received	10/06/2016
Acknowledgement that Teva can respond to CRL on rolling basis	10/28/2016
Chemistry Review #3a	11/07/2016
Amendment (SD #40)-Response to IR	12/07/2016
Micro and Drug Product CR response	01/31/2017
Chemistry Review #3b	03/10/2017

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
CDRH Compliance consult IR Response	03/27/2017
CDRH Device consult IR Response	03/31/2017

Amendment (SD #46)-Response to IR and Gratuitous Information	04/04/2017
Amendment (SD #47)-Response to IR	04/04/2017
CDRH Device consult IR Response	05/04/2017
CDRH Device consult IR Response	05/22/2017
Micro IR Response	06/02/2017
CDRH Compliance consult IR Response	07/12/2017
CDRH Device consult IR Response	07/28/2017
Chemistry Review #4	09/05/2017
Amendment (SD #57)-Response to IR	10/06/2017
CDRH Device consult IR Response	12/01/2017
CDRH Device consult IR Response	01/11/2018
CDRH Device consult IR Response	01/29/2018
Chemistry Review #4a	01/30/2018
Amendment (SD #62)-Response to IR	02/28/2018
Samples received	03/01/2018
Updated facility info	03/02/2018
Chemistry Review #4b	5/14/2018
Amendment (SD #66)-Response to IR	5/30/2018

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

(b) (4)

DMF	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)		3	Adequate	06/01/2016	SKANCHY, DAVID J
	III			3	Adequate	09/14/2017	E. Adeeku
	III			3	Adequate	2/13/2018	Erika Englund
	V			3	Adequate	06/29/2015	David Bateman
	V			3	Adequate	10/16/2016	David Bateman
	V			3	Adequate	02/15/2017	E. Adeeku
				3	Adequate	1/30/2018	John McMichael
				3	Adequate	1/30/2018	John McMichael

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 – Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")
[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

18. STATUS:

CONSULTS / CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Adequate	6/14/2017	Eric Adeeku
Methods Validation	N/A		
Labeling	Adequate	06/26/2018	Esther Chuh
Bioequivalence	Adequate	11/22/2017	Harikrishna Devalapally
EA	Categorical Exclusion	30-Nov-2015	Xiaohua Huang
Radiopharmaceutical	N/A		
Sample requested	Yes	June 15, 2015 October 6, 2016	Xiaohua Huang Mike Darj

Comparative Human Factors review was found adequate on 14Aug2018

Mike Darj

Digitally signed by Mike Darj
Date: 8/15/2018 11:28:53AM
GUID: 508da70000028695fe9776e1e3e9234c

Xiaohua Huang

Digitally signed by Xiaohua Huang
Date: 8/15/2018 11:28:18AM
GUID: 542052230001985d194bf82bb7ee9157

Approvability – CMC Adequate

ANDA 090589

Epinephrine Injection, USP (Auto-Injector)
0.15 mg/0.3 mL and 0.3 mg/0.3 mL

Teva Pharmaceuticals USA, Inc.

Xiaohua Huang
Division of Immediate Release Products II

Chemistry Review Data Sheet

1. ANDA 090589

2. REVIEW #: 4c

3. REVIEW DATE: 6/1/2018

4. REVIEWER: Xiaohua Huang

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original Application (SD #1)	21-Dec-2007
Amendment (SD #2)	30-May-2008
Chemistry Review #1	04/30/2009
Amendment (SD #5)	23-May-2009
Amendment (SD #6)	12-Jun-2009
Chemistry Review #2	03/02/2010
Chemistry Review #2a	05/16/2011
Amendment (SD#16) (change of ownership)	18-Jul-2011
Amendment (SD#19)	20-Jan-2012
Chemistry Review #2b	12/20/2012
Amendment (SD #25)-Response to IR and Formulation Change	12/30/2014
Amendment (SD #27)-Response to IR	05/20/2015
Amendment (SD #28)-Response to IR	05/21/2015
Amendment (SD #29)-Response to IR	06/12/2015
Chemistry Review #3	06/24/2016
Amendment (SD #33)-Response to IR	09/08/2016
Chemistry Review #3a	11/07/2016
Amendment (SD #40)-Response to IR	12/07/2016
Chemistry Review #3b	03/10/2017

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment (SD #46)-Response to IR and Gratuitous Information	04/04/2017
Amendment (SD #47)-Response to IR	04/04/2017
Chemistry Review #4	09/05/2017
Amendment (SD #57)-Response to IR	10/06/2017
Chemistry Review #4a	01/30/2018
Amendment (SD #62)-Response to IR	02/28/2018

Chemistry Review #4b	5/14/2018
Amendment (SD #66)-Response to IR	5/30/2018

7. NAME & ADDRESS OF APPLICANT:

Name:	Teva Pharmaceuticals USA, Inc.
Address:	425 Privet Road, Horsham, PA 19044
Representative:	Cory Wohlbach, Senior Director, US Generics Regulatory Affairs
Telephone:	215-293-6519
Fax:	215-591-8812

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Epinephrine Injection USP

9. LEGAL BASIS FOR SUBMISSION:

The basis for Teva Parenteral Medicines, Inc proposed ANDA for Epinephrine Injection USP, Auto-Injector 0.15 mg and 0.3 mg is the approved reference listed drug (RLD) EpiPen®, EpiPen® Jr, the subject of NDA No. 19-430 held by MYLAN SPECLT (Approved December 22, 1987). The RLD is in 0.15 mg and 0.3 mg strengths.

The ANDA sponsor filed a Paragraph IV certification for U.S. Patent 7,449,012, 7,794,432, 8,048,035, and 8,870,827 that will expire on September 11, 2025. The RLD holder filed the citizen petition on January 16 of 2015 and April 28 of 2015, which were denied on June 15 of 2015 without comment.

10. PHARMACOL. CATEGORY: sympathomimetic catecholamine.

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 0.15 mg/0.3 mL and 0.3 mg/0.3 mL

13. ROUTE OF ADMINISTRATION: intramuscular & subcutaneous

14. Rx/OTC DISPENSED: _X_ Rx ____ OTC

15a. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

☐ SPOTS product – Form Completed

☒ Not a SPOTS product

15b. NANOTECHNOLOGY PRODUCT TRACKING:

☐ NANO product – Form Completed (See Appendix A.4)

☒ Not a NANO product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical name: (-)-3,4-Dihydroxy-alpha-((methylamino)methyl)benzyl alcohol

or

1,2-Benzenediol, 4-(1-hydroxy-2-(methylamino)ethyl)-, (R)-

or

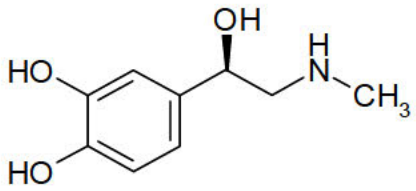
1-1-(3,4-Dihydroxyphenyl)-2-methylaminoethanol

Molecular formula: $C_9H_{13}NO_3$

Formula weight: 183.206 g/mol

CAS RN: [51-43-4]

Structural formula:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

(b) (4)

DMF	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	3	Adequate	06/01/2016	SKANCHY, DAVID J
	III			3	Adequate	1/24/2018	Koushik Paul
	III			3	Adequate	2/13/2018	Erika Englund
	V			3	Adequate	12/20/2017	David Bateman
	V			3	Adequate	12/20/2017	David Bateman
	V			3	Adequate	3/5/2018	Yan Zheng
				3	Adequate	1/30/2018	John McMichael
				3	Adequate	1/30/2018	John McMichael

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 – Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")
[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	Consult No:	DESCRIPTION
Consult	2008-0229	Consult request to DACCADP re Mechanism of Action
Consult	2009-0320 2010-0383	Consult request to CDRH re MAF (b) (4)
Consult	2010-0382	Pharm/Tox consult re the impurity ESA
Consult	Consult date: 04Apr2012 Response Date: 07May2012	Consult request to CDRH re human factor study
Consult	2013-0786	Consult request to OGD/DCR re needle length

Consult	Consult date: 6/5/2015	Consult for MAFs (b) (4)
Consult	Consult date: 6/10/2015	Consult for Human Factor Study
Consult	Consult date: 6/25/2015	Consult request from DB III to DCR re clinical safety of sodium tartrate dihydrate as an inactive ingredient in the proposed drug product when injected subcutaneously
Respond to Consult request	Response Date: 8/10/16	Respond to Consult request from Division of Bioequivalence III (DBIII) regarding the justification of the excipient sodium tartrate dihydrate for subcutaneous administration
Respond to Consult request	Response Date: 8/19/16	Respond to Consult request from DCR regarding the justification of the excipient sodium tartrate dihydrate for subcutaneous administration
Consult	Consult date: 09/02/2016	Consult to CDRH --- cGMP compliance of the device manufacturing facility ((b) (4) Recommendation: PAI at the device assembly facility, (b) (4)
Consult	Consult date: 09/16/2016	Consult to DCR --- Impurity qualification. Recommendation: Adequate
Consult	Consult date: 10/06/2016	Consult to OSE\DMEPA-human factor study Recommendation: Pending
Consult	Consult date: 11/16/2016	Consult to CDRH-Response to device deficiencies Recommendation: Adequate
Consult	Consult date: 3/15/2018	Consult to CDRH- Gratuitous amendment dated 03/05/2018 Recommendation: Adequate

18. STATUS:

CONSULTS / CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Adequate	6/14/2017	Eric Adeeku
Methods Validation	N/A		
Labeling	Inadequate	12/12/2016	Esther Chuh
Bioequivalence	Adequate	11/22/2017	Harikrishna Devalapally
EA	Categorical Exclusion	30-Nov-2015	Xiaohua Huang
Radiopharmaceutical	N/A		
Sample requested	Yes	June 15, 2015 October 6, 2016	Xiaohua Huang Mike Darj

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. ___ Yes _x_ No If no, explain reason(s) below:

High priority because of the drug shortage status for Epinephrine Injection Auto-Injector and the urgent public health need of a more affordable generic product.

20. EES INFORMATION

Overall Recommendation: Approve

Drug Substance			
Function	**Site Information**	**FEI #**	**Status**
		(b) (4)	Adequate
			Adequate
			Status
			Adequate
			Adequate
			Adequate
			N/A
			N/A
			N/A

Chemistry Review Data Sheet

[redacted] (b) (4)	
	N/A
	N/A
	Withdrawn
	Withdrawn
	Adequate
	Adequate

1. [redacted] (b) (4)

2. [redacted]

3. Reported in the amendment dated 4/4/2017, but not in Panorama. RBPM notified.
4. Withdrawn in the amendments dated 4/4/2017, but not reported in previous submissions.

The Chemistry Review for ANDA 090589

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

CMC Adequate. DMEPA consult and labeling review are pending.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Not Applicable

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance

Epinephrine, also known as Adrenaline, is a white to off-white crystalline powder. The molecule is optically active due to a chiral center. It exists as D- and L- optical isomers, (b) (4) (b) (4) It has aqueous solubility of less than 0.01 grams in 100 mL. However, solubility increases as the solution becomes more acidic. It is prone to oxidation and photo-degradation. (b) (4) (b) (4) The USP monograph for the drug substance is available.

Drug Product

The drug product is Epinephrine Injection USP 0.15 mg/0.3 mL and 0.3 mg/0.3 mL. The product is packaged in an autoinjector device. The drug product is intended for the treatment of severe allergic reactions (Type I) to insect stings or bites, foods, drugs, and other allergens. It can also be used in the treatment of exercise-induced anaphylaxis. According to the labeling, the usual adult dose is 0.3 mg. However, with severe persistent anaphylaxis, repeat injections with an additional Epinephrine Injection, USP auto-injector may be necessary. (b) (4) (b) (4)

(b) (4)

Exhibit batch number placed on stability	Bio batch number for in-vivo studies
021A16A (0.15 mg/0.3 mL) 020A16A (0.3 mg/0.3 mL)	N/A

B. Description of How the Drug Product is Intended to be Used

Inject epinephrine injection, 0.3 mg or epinephrine injection, 0.15 mg intramuscularly or subcutaneously into the anterolateral aspect of the thigh, through clothing if necessary. Selection of the appropriate dosage strength (epinephrine injection, 0.3 mg or epinephrine injection, 0.15 mg) is determined according to patient body weight.

- Patients greater than or equal to 30 kg (approximately 66 pounds or more): Epinephrine injection, 0.3 mg
- Patients 15 to 30 kg (33 pounds to 66 pounds): Epinephrine injection, 0.15 mg

C. Basis for Approvability or Not-Approval Recommendation

Adequate pending DMEPA consult and labeling review.

Summary of Proposed Changes as Provided in SD# 46 and SD# 47 dated 4/4/2017 – Major Amendment

- (b) (4)

Chemistry Assessment

I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data

S DRUG SUBSTANCE:

S.1 General Information

S.1.1 Nomenclature:

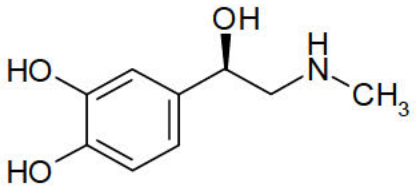
Chemical Name: (-)-3,4-Dihydroxy-alpha-((methylamino)methyl)benzyl alcohol
or
1,2-Benzenediol, 4-(1-hydroxy-2-(methylamino)ethyl)-, (R)-
or
1-1-(3,4-Dihydroxyphenyl)-2-methylaminoethanol

Other nonproprietary name: Adrenaline

Molecular Formula: $C_9H_{13}NO_3$

Molecular Weight: 183.20

S.1.2 Structure:



S 1.3 General Properties:

Physical Description: White to off-white crystalline powder
pKa: $pK_1 = 8.71$ at 20 °C, $pK_2 = 9.90$ at 20 °C
Polymorphism: Does not exist in different crystalline forms
Stereochemistry: Epinephrine exists as D- and L- optical isomers. (b) (4)
(b) (4)
Solubility Characteristics: <0.01 g / 100 mL of water at 18 °C; very slightly soluble in alcohol, insoluble in chloroform, ether, acetone, and oils. Soluble in mineral acids. Solubility increases as a function of decreasing pH.
Hygroscopicity: Epinephrine is not reported in the literature as being hygroscopic.
Melting Point: 211-212 °C
Partition Coefficient: Log P (octanol-water) = -1.37
Other Physicochemical Characteristics: Vapor pressure at 25 °C = 7.37×10^{-7} mm Hg

S.2 Manufacture

S.2.1 Manufacturers:

Who manufactures the drug substance?

See item 20 in Chemistry Review Data Sheet.

S.2.2 Description of Manufacturing Process and Process Controls:

Refer to DMF (b) (4)

S.2.3 Control of Materials

Refer to DMF (b) (4)

S.2.4 Controls of Critical Steps and Intermediates

Refer to DMF (b) (4)

S.2.5 Process Validation and/or Evaluation

Refer to DMF (b) (4)

S.2.6 Manufacturing Process Development

Refer to DMF (b) (4)

S.3 Characterization

S.3.1 Elucidation of Structure and other Characteristics

Refer to DMF (b) (4)

A APPENDICES

A.1 Facilities and Equipment (biotech only) Provided

A.2 Adventitious Agents Safety Evaluation None.

A.3 Novel Excipients None

R REGIONAL INFORMATION

R1 Executed Batch Records Provided

R2 Comparability Protocols None

R3 Methods Validation Package Provided

Appendix D: Chemistry Review Template – Labeling section

II. Review of Common Technical Document-Quality (Ctd-Q) Module 1

A. Labeling & Package Insert

a) DESCRIPTION section

i) Is the information accurate? ☒ Yes ☐ No

If "No," explain.

ii) Is the drug product subject of a USP monograph? ☒ Yes ☐ No

If "Yes," state if labeling needs a special USP statement in the Description. (e.g., USP test pending. Meets USP assay test 2. Meets USP organic impurities test 3.) No.

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

b) HOW SUPPLIED section

i) Is the information accurate? ☒ Yes ☐ No
If "No," explain.

ii) Are the storage conditions acceptable? ☒ Yes ☐ No
If "No," explain.

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

Did the applicant provide quality data to support in-use conditions (e.g. diluent compatibility studies)? ☐ Yes ☐ No ☒ N/A
If "No," explain.

d) For OTC Drugs and Controlled Substances: N/A

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

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

ANDA Strength	Length (mm)	Imprint Code

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

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1

Documents
Patent Certification: Yes

Exclusivity: Yes

Debarment Certification: Yes

cGMP Statement: Yes

Reprocessing Statement: Yes

Letters of Authorization: Yes

Request for Bio-waiver: Yes

Citizen Petition and/or Control Request Linked to the Application:
Citizen Petitions were filed by RLD holder–Mylan on January 16 of 2015 and April 28 of 2015, and denied on June 15 of 2015 without comment.

Environmental Impact Considerations/Categorical Exclusions: Yes

III. List Of Deficiencies To Be Communicated

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 090589 APPLICANT: Teva Pharmaceuticals USA

DRUG PRODUCT: Epinephrine Injection USP, Autoinjector 0.15mg/0.3mL and 0.3mg/0.3mL

A. Deficiencies:

None.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

None.

ADMINISTRATIVE

A. Reviewer's Signature

B. Endorsement Block

Chemist Name/Date: Xiaohua Huang, 6/1/2018
Quality Assessment Lead Name/Date: M. Darj, 14Jun2018
Regulatory Business Process Manager Name/Date:

TYPE OF LETTER:

Mike Darj

Digitally signed by Mike Darj
Date: 6/14/2018 03:03:30PM
GUID: 508da70000028695fe9776e1e3e9234c

Xiaohua Huang

Digitally signed by Xiaohua Huang
Date: 6/14/2018 03:03:25PM
GUID: 542052230001985d194bf82bb7ee9157

A. Check List

Solid IR/Oral Sol. RPN < 60 or Injection/Ophthalmic Q1/Q2 = RLD – 2 Tier to QAL ☐

First Generic – 2 Tier to BC ☐

Other Criteria under "Exceptions List" for Table 1 of SOP – 2 Tier to BC ☐

B. Approvability: –No, ***Minor Deficiency***

ANDA 090589

Epinephrine Injection, USP (Auto-Injector)
0.15 mg/0.3 mL and 0.3 mg/0.3 mL

Teva Pharmaceuticals USA, Inc.

Xiaohua Huang
Division of Immediate Release Products II

Table of Contents

Chemistry Review Data Sheet

1. ANDA 090589

2. REVIEW #: 4

3. REVIEW DATE: 05/20/2016

4. REVIEWER: Xiaohua Huang

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original Application (SD #1)	21-Dec-2007
Amendment (SD #2)	30-May-2008
Amendment (SD #5)	23-May-2009
Amendment (SD #6)	12-Jun-2009

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment (SD #25)	12/30/2014
Amendment (SD #27)	05/20/2015
Amendment (SD #28)	05/21/2015
Amendment (SD #29)	06/12/2015

7. NAME & ADDRESS OF APPLICANT:

Name:	Teva Pharmaceuticals USA, Inc.
Address:	425 Privet Road, Horsham, PA 19044
Representative:	Cory Wohlbach, Director, US Generics Regulatory Affairs
Telephone:	215-293-6519
Fax:	215-591-8812

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Epinephrine Injection, USP

9. LEGAL BASIS FOR SUBMISSION:

The basis for Teva Parenteral Medicines, Inc proposed ANDA for Epinephrine Injection USP, Auto-Injector 0.15 mg and 0.3 mg is the approved reference listed drug (RLD) EpiPen®, EpiPen® Jr, the subject of NDA No. 19-430 held by

MYLAN SPECLT (Approved December 22, 1987). The RLD is in 0.15 mg and 0.3 mg strengths.
The ANDA sponsor filed a Paragraph IV certification for U.S. Patent 7,449,012, 7,794,432, 8,048,035, and 8,870,827 that will expire on September 11, 2025. The RLD holder filed the citizen petition on January 16 of 2015 and April 28 of 2015, which were denied on June 15 of 2015 without comment.

10. PHARMACOL. CATEGORY: sympathomimetic catecholamine.

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 0.15 mg/0.3 mL and 0.3 mg/0.3 mL

13. ROUTE OF ADMINISTRATION: intramuscular & subcutaneous

14. Rx/OTC DISPENSED: _X_ Rx ____ OTC

15a. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

☐ SPOTS product – Form Completed

☒ Not a SPOTS product

15b. NANOTECHNOLOGY PRODUCT TRACKING:

☐ NANO product – Form Completed (See Appendix A.4)

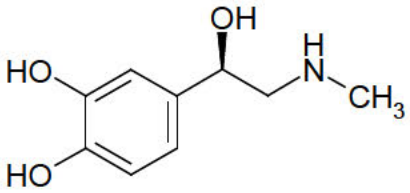
☒ Not a NANO product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical name: (-)-3,4-Dihydroxy-alpha-((methylamino)methyl)benzyl alcohol
or
1,2-Benzenediol, 4-(1-hydroxy-2-(methylamino)ethyl)-, (R)-
or
1-1-(3,4-Dihydroxyphenyl)-2-methylaminoethanol

Molecular formula: $C_9H_{13}NO_3$
Formula weight: 183.206 g/mol
CAS RN: [51-43-4]

Structural formula:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)		1	Adequate	01Jun2016	NAI'd by D. Skanchy
	III			1	Inadequate	July 1, 2015	Eric K. Adeeku
	V			1	Inadequate	July 1, 2015	Eric K. Adeeku
	III			1	Inadequate	July 1, 2015	Eric K. Adeeku
				1	Inadequate	July 2, 2015	Eric K. Adeeku
				1	Inadequate	October 23, 2015	Alan Stevens
				1	Inadequate	October 23, 2015	Alan Stevens

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 – Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	Consult No:	DESCRIPTION
Consult	2008-0229	Consult request to DACCADP re Mechanism of Action
Consult	2009-0320 2010-0383	Consult request to CDRH re MAF (b) (4)
Consult	2010-0382	Pharm/Tox consult re the impurity ESA
Consult	Consult date: 04Apr2012	Consult request to CDRH re human factor study

	Response Date: 07May2012	
Consult	2013-0786	Consult request to OGD/DCR re needle length
Consult	Consult date: 6/5/2015	Consult for MAFs (b) (4)
Consult	Consult date: 6/10/2015	Consult for Human Factor Study
Consult	Consult date: 6/25/2015	Clinical safety of sodium tartrate dihydrate as an inactive ingredient in the proposed drug product when injected subcutaneously

18. STATUS:

CONSULTS / CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Inadequate	19-Feb-2016	Eric Adeeku
Methods Validation	N/A		
Labeling	Inadequate	11-Dec-2015	Esther Chuh
Bioequivalence	Adequate	13-May-2016	Ke Ren
EA	Categorical Exclusion	30-Nov-2015	Xiaohua Huang
Radiopharmaceutical	N/A		
Sample requested	Yes	June 15, 2015	Xiaohua Huang

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. __X__ Yes ___ No If no, explain reason(s) below:

20. EES INFORMATION

Overal Recommendation: Adequate

Drug Substance	
(b) (4)	**Status**
	Adequate
	Adequate
	Status
	Adequate
	Adequate

Chemistry Review Data Sheet

(b) (4)	
	Adequate
	N/A
	N/A
	N/A
	N/A
	N/A
	N/A
	N/A
	N/A

The Chemistry Review for ANDA 090589

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This ANDA is not approvable.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Not Applicable

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance

Epinephrine, also known as Adrenaline, is a white to off-white crystalline powder. The molecule is optically active due to a chiral center. It exists as D- and L- optical isomers, (b) (4) (b) (4) It is not known to exhibit polymorphism. It has aqueous solubility of less than 0.01 grams in 100 mL. However, solubility increases as the pH becomes more acidic. It is prone to oxidation and photo-degradation. (b) (4) The USP monograph for the drug substance is available.

Drug Product

The drug product is Epinephrine Injection USP 0.15 mg/0.3 mL and 0.3 mg/0.3 mL. The product is packaged in an autoinjector device. The drug product is intended for the treatment of severe allergic reactions (Type I) to insect stings or bites, foods, drugs, and other allergens. It can also be used in the treatment of exercise-induced anaphylaxis. According to the labeling, the usual adult dose is 0.3 mg. However, with severe persistent anaphylaxis, repeat injections with an additional Epinephrine Injection, USP auto-injector may be necessary. (b) (4) (b) (4)

(b) (4)

Exhibit batch number placed on stability	Bio batch number for in-vivo studies
R1014TPD-124 (0.15 mg/0.3 mL) R1014SX6-124 (0.3 mg/0.3 mL)	Bio waiver granted

B. Description of How the Drug Product is Intended to be Used

Inject epinephrine injection, 0.3 mg or epinephrine injection, 0.15 mg intramuscularly or subcutaneously into the anterolateral aspect of the thigh, through clothing if necessary. Selection of the appropriate dosage strength (epinephrine injection, 0.3 mg or epinephrine injection, 0.15 mg) is determined according to patient body weight.

☐ Patients greater than or equal to 30 kg (approximately 66 pounds or more): Epinephrine injection, 0.3 mg

☐ Patients 15 to 30 kg (33 pounds to 66 pounds): Epinephrine injection, 0.15 mg

C. Basis for Approvability or Not-Approval Recommendation

The recommendation of Not-Approvability is based on the cited deficiencies (see review for more details).

Chemistry Assessment

I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data

S DRUG SUBSTANCE:

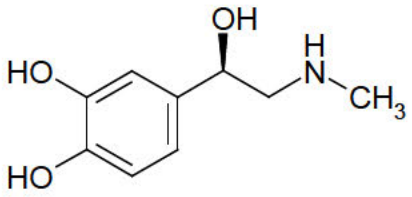
S.1 General Information

S.1.1 Nomenclature:

Chemical Name: (-)-3,4-Dihydroxy-alpha-((methylamino)methyl)benzyl alcohol
or
1,2-Benzenediol, 4-(1-hydroxy-2-(methylamino)ethyl)-, (R)-
or
1-1-(3,4-Dihydroxyphenyl)-2-methylaminoethanol

Other nonproprietary name: Adrenaline

S.1.2 Structure:



S 1.3 General Properties:

Physical Description: White to off-white crystalline powder
pKa: $pK_1 = 8.71$ at 20 °C, $pK_2 = 9.90$ at 20 °C
Polymorphism: Does not exist in different crystalline forms
Stereochemistry: Epinephrine exists as D- and L- optical isomers. (b) (4) (b) (4).
Solubility Characteristics: <0.01 g / 100 mL of water at 18 °C; very slightly soluble in alcohol, insoluble in chloroform, ether, acetone, and oils. Soluble in mineral acids. Solubility increases as a function of decreasing pH.
Hygroscopicity: Epinephrine is not reported in the literature as being hygroscopic.
Melting Point: 211-212 °C
Partition Coefficient: Log P (octanol-water) = -1.37
Other Physicochemical Characteristics:Vapor pressure at 25 °C = 7.37×10^{-7} mm Hg

Reviewer's Assessment (Review #4): Satisfactory
The melting point, partition coefficient logP and pKa agree with the information in DrugBank. See below. (b) (4)

(b) (4)

[redacted]

S.2.2 Description of Manufacturing Process and Process Controls:

Refer to DMF (b) (4)

S.2.3 Control of Materials

Refer to DMF (b) (4)

S.2.4 Controls of Critical Steps and Intermediates

Refer to DMF (b) (4)

S.2.5 Process Validation and/or Evaluation

Refer to DMF (b) (4)

S.2.6 Manufacturing Process Development

Refer to DMF (b) (4)

Reviewer's Assessment (Review #4): Satisfactory

(b) (4)

S.3 Characterization

S.3.1 Elucidation of Structure and other Characteristics

Refer to DMF (b) (4)

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

A APPENDICES

A.1 Facilities and Equipment (biotech only) Provided

A.2 Adventitious Agents Safety Evaluation None.

A.3 Novel Excipients None

R REGIONAL INFORMATION

R1 Executed Batch Records Provided

R2 Comparability Protocols None

R3 Methods Validation Package Provided

Appendix D: Chemistry Review Template – Labeling section

II. Review of Common Technical Document-Quality (Ctd-Q) Module 1

A. Labeling & Package Insert

a) DESCRIPTION section

i) Is the information accurate? ☒ Yes ☐ No

If "No," explain.

ii) Is the drug product subject of a USP monograph? ☒ Yes ☐ No

If "Yes," state if labeling needs a special USP statement in the Description. (e.g., USP test pending. Meets USP assay test 2. Meets USP organic impurities test 3.) No.

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

b) HOW SUPPLIED section

i) Is the information accurate? ☒ Yes ☐ No
If "No," explain.

ii) Are the storage conditions acceptable? ☒ Yes ☐ No
If "No," explain.

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

Did the applicant provide quality data to support in-use conditions (e.g. diluent compatibility studies)? ☒ Yes ☐ No ☐ N/A
If "No," explain.

d) For OTC Drugs and Controlled Substances:

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

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

ANDA Strength	Length (mm)	Imprint Code

f) Describe issue(s) sent to and/or received from the OGD Labeling Reviewer:

1. Please comment if there is any labeling concern with the changed amount of sodium metabisulfate and addition of sodium tartrate provided on the amendment 12/30/14.

   Comment: The ANDA product does not meet Q1 and Q2 requirements for the drug product of parenteral use. CFR 314.94(a)(9)(iii) accepts these difference in (b) (4) (b) (4) provided that the applicant identifies and characterizes the differences AND provides information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product.

   Sodium tartrate is a newly added excipient in the ANDA formulation, and the firm claims its only function (b) (4) which is acceptable by CFR and the USP monograph of the drug product (b) (4) (b) (4) Deficiency was issued to ask for the clarification. The firm also claims the submission of toxicity study for sodium tartrate via proposed subcutaneous administration. However, such study could not be found and was requested in the deficiency. Further evaluation will be made subsequent to firm's response to these deficiencies.

2. The amendment dated 12/30/14 provided Human Factor Study and an update to the device. Please notify this labeling reviewer if any labeling concern is identified on the study and/or the device.
   Comment: Consult requests for Human Factor Study and Device MAFs were sent to OSE\DEMPA and CDRH respectively, and will update if labeling concern is identified.

3. We note that the fill volume differs between this drug product and the RLD. RLD has 2 mL fill volume versus ANDA has 1 mL. Therefore after administration of the dose, the remaining volume in the injection will differ (1.7 mL vs 0.7 mL). Please comment if there is any concern on this difference.

   Comment: There is no guidance on the allowable remaining volume for the pre-filled syringe, and the ANDA product has less in excess than RLD. Acceptable.

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1

Documents

Patent Certification: Yes

Exclusivity: Yes

Debarment Certification: Yes

cGMP Statement: Yes

Reprocessing Statement: Yes

Letters of Authorization: Yes

Request for Bio-waiver: Yes

Citizen Petition and/or Control Request Linked to the Application:
Citizen Petitions were filed by RLD holder–Mylan on January 16 of 2015 and April 28 of 2015, and denied on June 15 of 2015 without comment.

Environmental Impact Considerations/Categorical Exclusions: Yes

III. List Of Deficiencies To Be Communicated

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 90589 APPLICANT: Teva Pharmaceuticals USA

DRUG PRODUCT: Epinephrine Injection USP, Autoinjector 0.15mg/0.3mL and 0.3mg/0.3mL

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

(b) (4)

1.

2.

3.

4.

5.

6.

(b) (4)

7.

8.

9.

10

11

(b) (4)

12

13

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B.

1. Please provide all available long term stability data.

ADMINISTRATIVE

A. Reviewer's Signature

B. Endorsement Block

Chemist Name/Date: Xiaohua Huang-05/20/2016, 6/23/2016, 6/24/2016
Quality Assessment Lead Name/Date: M. Darj, 22Jun2016/24Jun2016/
Regulatory Business Process Manager Name/Date:

TYPE OF LETTER: Minor deficiency

First Generic
Not Approvable – Major Deficiency

ANDA 090589

Epinephrine Injection, USP
Autoinjector 0.15 mg/0.3 mL and 0.3 mg/0.3 mL

Teva Pharmaceuticals USA

CR#3

Xiaohua Huang
Division of Immediate Release Products II

Table of Contents

Chemistry Review Data Sheet

1. ANDA 090589

2. REVIEW #: 3

3. REVIEW DATE: July 2, 2015

4. REVIEWER: Xiaohua Huang

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original Application (SD #1)	21-Dec-2007
Amendment (SD #2)	30-May-2008
Amendment (SD #5)	23-May-2009
Amendment (SD #6)	12-Jun-2009

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment (SD #25)	12/30/2014
Amendment (SD #27)	05/20/2015
Amendment (SD #28)	05/21/2015
Amendment (SD #29)	06/12/2015

7. NAME & ADDRESS OF APPLICANT:

Name:	Teva Pharmaceuticals USA
Address:	425 Privet Road, Horsham, PA 19044
Representative:	Cory Wohlbach, Director, US Generics Regulatory Affairs
Telephone:	215-293-6519
Fax:	215-591-8812

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Epinephrine Injection, USP

9. LEGAL BASIS FOR SUBMISSION:

The basis for Teva Parenteral Medicines, Inc proposed ANDA for Epinephrine Injection USP, Auto-Injector 0.15 mg and 0.3 mg is the approved reference listed drug (RLD) EpiPen®, EpiPen® Jr, the subject of NDA No. 19-430 held by

MYLAN SPECLT (Approved December 22, 1987). The RLD is in 0.15 mg and 0.3 mg strengths.
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10. PHARMACOL. CATEGORY: sympathomimetic catecholamine.

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 0.15 mg/0.3 mL and 0.3 mg/0.3 mL

13. ROUTE OF ADMINISTRATION: intramuscular & subcutaneous

14. Rx/OTC DISPENSED: _X_ Rx ____ OTC

15a. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

☐ SPOTS product – Form Completed

☒ Not a SPOTS product

15b. NANOTECHNOLOGY PRODUCT TRACKING:

☐ NANO product – Form Completed (See Appendix A.4)

☒ Not a NANO product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

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or
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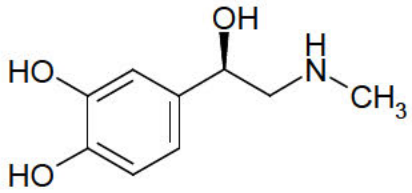
or
1-1-(3,4-Dihydroxyphenyl)-2-methylaminoethanol

Molecular formula: $C_9H_{13}NO_3$
Formula weight: 183.206 g/mol
CAS RN: [51-43-4]

Structural formula:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)		3	Adequate	10/07/2015	NAI'd by D. Skanchy
	III			1	Inadequate	17-Jun-2015	Eric K. Adeeku
	V			1	Inadequate	17-Jun-2015	Eric K. Adeeku
	III			1	Inadequate	17-Jun-2015	Eric K. Adeeku
				1	Inadequate	17-Jun-2015	Eric K. Adeeku
				1	Inadequate	October 23, 2015	Alan Stevens
				1	Inadequate	October 23, 2015	Alan Stevens

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
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4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	Consult No:	DESCRIPTION
Consult	2008-0229	Consult request to DACCADP re Mechanism of Action
Consult	2009-0320 2010-0383	Consult request to CDRH re MAF (b) (4)
Consult	2010-0382	Pharm/Tox consult re the impurity ESA
Consult	Consult date: 04Apr2012	Consult request to CDRH re human factor study

	Response Date: 07May2012	
Consult	2013-0786	Consult request to OGD/DCR re needle length
Consult	Consult date: 6/5/2015	Consult for MAFs (b) (4)
Consult	Consult date: 6/10/2015	Consult for Human Factor Study
Consult	Consult date: 6/25/2015	Clinical safety of sodium tartrate dihydrate as an inactive ingredient in the proposed drug product when injected subcutaneously

18. STATUS:

CONSULTS / CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Deficient	17-Jun-2015	Eric Adeeku
Methods Validation	N/A		
Labeling	Deficient	01-Jun-2015	Esther Chuh
Bioequivalence	Deficient	16-Nov-2015	Suman Dandamudi
EA	Acceptable	30-Nov-2015	Xiaohua Huang
Radiopharmaceutical	N/A		
Sample requested	Yes and acceptable	June 15, 2015	Xiaohua Huang

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. __X__ Yes ___ No If no, explain reason(s) below:

20. EES INFORMATION

Overal Recommendation: Adequate

Drug Substance			
Function	**Site Information**	**FEI #**	**Status**
(b) (4)			Adequate
			Adequate
			Status
			Adequate

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

B. Description of How the Drug Product is Intended to be Used

The drug product is an injectable solution that is administered intramuscularly or subcutaneously.

C. Basis for Approvability or Not-Approval Recommendation

The recommendation of Not-Approvability is based on the cited deficiency by the Division of Bioequivalence for either reformulating the drug product to remove Sodium Tartrate or provide clinical data. If the firm provides clinical data, then the application may no longer qualify as a 505(j) submission. As such, CMC deficiencies will not be communicated to the firm until the bioequivalence deficiency regarding reformulation is resolved.

III. List Of Deficiencies To Be Communicated

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 90589 APPLICANT: Teva Pharmaceuticals USA

DRUG PRODUCT: Epinephrine Injection USP, Autoinjector 0.15mg/0.3mL and 0.3mg/0.3mL

The deficiencies presented below represent MAJOR deficiencies.

A. Deficiencies:

The review of the Chemistry, Manufacturing and Control of your application can not be completed at this time due to the deficiency cited by the Division of Bioequivalence pertaining to reformulation of the drug product. Please refer to the deficiencies under the Bioequivalence portion of this letter.

The following section from the CDRH consult contains information requests for the ANDA sponsor.

Information Requests for the ANDA HOLDER

1. The release specifications for the epinephrine autoinjectors and the trainer device do not appear adequately complete. The release specifications for the epinephrine auto-injectors do not include essential performance requirements, such as needle dimensions, needle injection depth, needle resistance to bending or breakage, injection does not initiate until the needle reaches intended injection depth, injection completion prior to needle retraction, needle bevel attributes, drug injection pathway patency, physical stability of needle / syringe junction, visual / audible indicator for end of injection, etc. Similarly, the trainer device release specifications do not include essential performance attributes, such as break force, trigger force, injection confirmation, etc. Provide a revised release specification to assure that the release specifications include the essential performance specifications for epinephrine injection with each auto-injector presentation and the trainer device.

2. The ANDA describes two epinephrine combination product presentations (e.g., 0.3mg and 0.15mg). However, the Agency was unable to locate a complete comparison of design and performance specifications for the two epinephrine combination product presentations included in ANDA 90589. Provide a complete comparison of the differences between the two product presentations.

3. The ANDA does not provide a design control document that identifies the design requirements for the device constituent parts of the combination product. The combination product developer is responsible for specifying the design and performance of the device constituent parts of

combination product and assuring that those requirements are verified and validated. If you choose to rely on third party contract manufacturers or designers, it is expected that you, as the combination product developer, will communicate design requirements to those suppliers and assure that they have been completely and comprehensively implemented. . The ANDA submission should contain sufficient details regarding design controls that the Agency can be confident that you, as the ANDA sponsor, have developed product requirements and assured their verification and validation. Provide the design requirements document for the epinephrine auto-injector combination product and provide evidence validating that the design specifications developed by the master file holder have met your design requirements.

4. The labeling states that injection may occur through clothing. Review of the ANDA does not identify any design requirements for the injector, needle, or assembled combination product to specify adequately reliable injection through clothing. In addition to having explicit requirements for injection through clothing, the requirements document should specify adequately valid requirements for the needle to assure that the needle will not bend, break or separate from the syringe during injection through clothing. Additionally, FDA was unable to locate any performance data to verify and validate that the combination product will reliably inject epinephrine to the target injection site when injected through clothing. Clothing attributes might include material type, density, thickness, etc. Provide evidence that the combination product will reliably inject epinephrine to the target injection when the injection occurs through clothing. The evidence should include design requirements and performance data with adequately challenging conditions (e.g., sample size, clothing types, injection angles, transversely applied stress (transverse to injection angle), etc.).

5. The ANDA does not include a device hazards analysis confirming that reasonably foreseeable delivery error hazards have been identified and mitigated. To assure the safety and effectiveness of the delivery system, we need to review documentation demonstrating that potential causes, failure mechanisms, and / or events that could result in failure to deliver epinephrine to the intended injection site have been identified and mitigated. We have identified some potential hazards that need to be addressed, which include:

- Device fluid path occlusion
- Failure to inject or incomplete injection
- Unexpected separation of components
- Excessive drug delivery
- Component failure
- Inadequate container dimensions
- Inadequate or Insufficient device activation
- Device aging, shipping, storage and / or use conditions resulting in device malfunction prior to expiry
- Injection initiates prior to needle reaching the intended injection site.
- Premature retraction of needle before injection is completed.
- Needle bend or fracture (e.g., injection through clothing, skin tissue)
- Needle unable to penetrate to correct depth of penetration (clothing, skin, etc)

Your own analyses may have identified additional device hazards. Please provide a hazard analysis (e.g. fault tree analysis) identifying the potential causes of the device hazards we have

identified from our review and any additional system hazards you may have identified. For each identified cause, provide the following:

a. Describe the control method or mitigation for each identified cause.

b. For each cause, provide an explanation justifying the adequacy of the control to mitigate the respective system hazard.

c. Provide evidence verifying the control method or mitigations adequately address the respective cause / hazard under conditions of use that are reasonably challenging.

6. The intended use of your product involves the delivery of medication to treat a potentially life threatening condition within use environments that may offer limited opportunity for alternative treatments. As such, the Agency believes that it is essential for your product to perform reliably. The ANDA does not include adequate documentation to verify that the combination product will reliably inject epinephrine throughout the expiry period. Product reliability should be supported by explicit reliability specifications, hazard analysis, and performance data. Therefore, we are requesting your commitment to establish reliability requirements for the combination product and complete testing which verifies combination product reliability.

Provide the following:

a. Establish reliability requirements for your combination product. It is recommended that reliability be directly specified as R(t) = x%, where t = time and x% = probability of meeting essential performance requirements. These requirements should be objective and relate to the ability of a population of devices to meet essential performance requirements after pre-conditioning to elements outlined within c, below. The reliability requirements should be verified with a high degree of statistical confidence.

b. Provide rationale and justification supporting the clinical acceptability of the established reliability requirements.

c. Provide protocols and data to verify the reliability requirements specified have been met.

d. Final assembled combination products that are assessed within the reliability test should be preconditioned to worst-case reasonably foreseeable conditions. The Agency has conceived the following recommended preconditioning activities, however you should provide rationale supporting the final precondition elements chosen, and the order in which the products are conditioned. Your assessment of the preconditioning parameters should be based on your own failure analyses (e.g., fault tree analysis) in order to assure that the scope of preconditions and their boundary values are adequately correct and complete. It is noted that preconditioning requirements in international standards, such as ISO 11608-1, that are typically used for evaluation of auto-injectors, might be considered inadequate to verify and validate high reliability needed for an epinephrine auto-injector. Therefore, all preconditioning and test methodologies should be validated per your hazard analysis and reliability requirements.

i. Shipping

ii. Aging
iii. Storage orientation and conditions
iv. Vibration
v. Shock (e.g., resistance to random impacts, such as being dropped)

e. Devices assessed within the reliability analysis should be activated under worst-case reasonably foreseeable conditions. The Agency has conceived the following recommended circumstances of activation; however you should provide rationale supporting the final circumstances of activation chosen.

i. Activation orientation
ii. Environmental temperature
iii. Injection site conditions (clothing type, skin type, etc.)

f. Provide a revised post-approval commitment protocol to include evaluation of the reliability performance specifications for each auto-injector presentation.

7. Batch Analysis records provided in Section 3.2.P.5.4 describe delivery volume testing. However, the referenced method (b) (4) does not appear to describe testing to verify specifications for delivery volume. (see section 3.2.P.5.4 COA references). Please update the batch analysis records with the reference to the auto-injector delivery volume verification data, and provide the record of the testing.

8. There are various requirements for shelf life, storage, expiry, etc. for the device constituent parts and the final combination product found within the ANDA and device master file. The Agency is unable to verify from the documentation provided that the various shelf life dates for device constituents and the final combination product have been evaluated to assure that the shelf life of a constituent part will not be reached prior to the combination product expiry. Provide information to assure that no device constituent part will reach its shelf life prior to the combination product expiry.

9. Given the sameness in design of the epinephrine autoinjectors and trainer devices, it is important to assure that the products are not mislabeled or otherwise mistaken during the manufacturing of the products. Provide information to assure that the risks associated with mixing the epinephrine autoinjectors and the training device has been adequately mitigated during manufacturing of the combination products.

10. The autoinjector package component specifications (Section 3.2.P.7) include dimensional specifications for the autoinjector package, which includes the statement "For Reference Only". This statement is not understood in the context of the specification. Clarify the statement "For Reference Only" and clarify the dimensional specifications for the autoinjector components.

11. Please be advised that the Agency has communicated deficiencies regarding content found within MAF (b) (4) directly to the master file holder(s). The Agency in unable to provide details of these deficiencies to you as the documentation is not contained directly within the ANDA. Approval of the ANDA depends on resolution of the deficiencies communicated to the master file holder. Please work with the master file holder to resolve these concerns and

provide responses to MAF (b) (4) record. Alternatively, and if appropriate, you may provide responses to these questions and supporting documentation to the ANDA record.

12. Please note that if the drug product is reformulated, the ANDA should be amended to include design verification evidence showing that the final, finished combination product will perform as specified. Where device constituent review issues identified in this letter rely on a demonstration of injection performance, the testing should be conducted on samples from design verification batches that represent the final, finished product.

ADMINISTRATIVE

A. Reviewer's Signature

B. Endorsement Block

Chemist Name/Date: Xiaohua Huang/07-02-2015, 11/13/2015, 12/1/2015
Quality Assessment Lead Name/Date: M. Darj, 25Nov2015/10Dec2015/
Regulatory Business Process Manager Name/Date:

TYPE OF LETTER: Major Deficiency

090589R02_adden2_101012

ANDA 090589

Epinephrine Injection, USP
Autoinjector 0.15 mg/0.3 mL and 0.3 mg/0.3 mL

Teva Pharmaceuticals USA

Addendum 2 to CR#2

Mike Darj
Office of Generic Drugs
Division of Chemistry I

Chemistry Review Data Sheet

1. ANDA 90-589

2. REVIEW #: 2 Addendum 2

3. REVIEW DATE: 10OCT2012

4. REVIEWER: Mike Darj, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original Application (SD #1)	21-Dec-2007
Amendment (SD #2)	30-May-2008
Amendment (SD #5)	23-May-2009*
Amendment (SD #6)	12-Jun-2009

* Firm's letter is dated 22May2009, but DARRTS show 23May2009

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment (SD#19)	20-Jan-2012
Amendment (SD#16) (change of ownership)	18-Jul-2011

7. NAME & ADDRESS OF APPLICANT:

Name:	Teva Pharmaceuticals USA
Address:	1090 Horsham Road PO Box 1090 North Wales, PA 19454
Representative:	Philip Erickson
Telephone:	(215) 591-3141
Fax:	(215) 591-8812

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Epinephrine Injection, USP

9. LEGAL BASIS FOR SUBMISSION:

The basis for Teva Parenteral Medicines, Inc proposed ANDA for Epinephrine Injection USP, Auto-Injector 0.15 mg and 0.3 mg is the approved reference listed drug (RLD) EpiPen®, EpiPen® Jr, the subject of NDA No. 19-430 held by Meridian Medical Technologies, Inc (Approved December 22, 1987). The RLD is in 0.15 mg and 0.3 mg strengths.

10. PHARMACOL. CATEGORY: sympathomimetic catecholamine.

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 0.15 mg/0.3 mL and 0.3 mg/0.3 mL

13. ROUTE OF ADMINISTRATION: Intramuscular

14. Rx/OTC DISPENSED: __X__ Rx ____ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

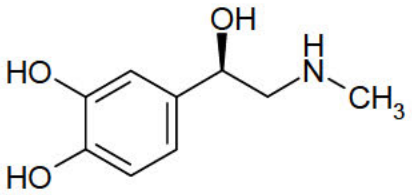
_____SPOTS product – Form Completed

__X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical name: (-)-3,4-Dihydroxy-alpha-((methylamino)methyl)benzyl alcohol
or
1,2-Benzenediol, 4-(1-hydroxy-2-(methylamino)ethyl)-, (R)-
or
1-1-(3,4-Dihydroxyphenyl)-2-methylaminoethanol

Molecular formula: $C_9H_{13}NO_3$
Formula weight: 183.206 g/mol
CAS RN: [51-43-4]
Structural formula:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	7			This is an addendum 2 to CR#2. When the firm respond to the CMC deficiencies, this DMF will be evaluated.
	III			4	N/A		
				3	Adequate	28Jun2010 (in DARRTS: 06Jul2010)	Reviewed by CDRH

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Consult	2008-0229	Consult request dated 6/20/2008 to DACCADP
Consult	2009-0320 2010-0383	Consult request to CDRH re MAF (b) (4)
Consult	2010-0382	Pharm/Tox consult
Consult	Consult date: 04Apr2012	Consult request to CDRH re

	Response Date: 07May2012	human factor study

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Acceptable	25Sep2009	Eric Adeeku
EES	Withhold	02Sep2011	D. Smith
Methods Validation	N/A (per current OGD policy)		
Labeling	Deficient	02Feb2011	Angela Payne
Bioequivalence	Deficient	29Mar2010	Nilufer Tampal
EA	Acceptable	31Mar2009	M. Darj
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. ___ Yes __X__ No If no, explain reason(s) below:

Addendum 2 to Review #2

Chemistry Assessment Section

Addendum 2 To Chemistry Review #2

The purpose of this addendum is to convey to the firm the deficiencies identified by the CDRH reviewer in reviewing of the firm's human factor study protocol.

Below is the review of the CDRH along with identified deficiencies as provided to the Office of Generic Drugs.

CDRH Human Factors Review

Overview

The Office of Generic Drugs, Office of Pharmaceutical Science, Center for Drugs Research and Evaluation, requested a Human Factors consultative review of the ANDA 90589 submitted by Teva Pharmaceutical, USA. This review provides CDRH's review and recommendations on the Human Factors related information contained in the ANDA specifically the draft Human Factors/usability validation study protocol. In addition to seeking FDA's assessment of the protocol, Teva Pharmaceuticals also would like to request FDA's guidance in three specific areas: (1) selection of user groups to study; (2) endpoints; and (3) training. Please see the recommendation section for comments to be transmitted to Teva Pharmaceuticals, USA.

Review Materials

CDRH Human Factors Review

Combination Product Device Information

Submission Number: ANDA 90580
Applicant: Teva Pharmaceuticals, USA
Drug Constituent: Epinephrine
Device Constituent: Peninjectors
Intended treatment: Allergic Reactions

CDRH Human Factors Involvement History

4-APR-2012: CDRH HF was requested to review a final Human Factors/usability validation (summative) study protocol

Review of Human Factors Related Information

Device and User Interface Description

The product is cylindrical in shape. It has a twist-off yellow (AJE Adult) or green (AJE Jr.) cap. Once the twist-off cap is removed, the auto-injector has an orange needle guard at one end, and a blue safety release at the other end. There are graphic Instructions for Use along the side of the Device (i.e., on-device IFU).

To administer a successful simulated injection, the user must perform the following tasks:
1. Twist off the yellow cap (AJE Adult) or green cap (AJE Jr.) of the Auto-Injector.
2. Pull off the blue safety release.
3. Swing and firmly push the orange tip against the outer thigh until it clicks.
4. Hold firmly against the thigh for 1.0 second (labeled IFU states approximately 10 seconds, but device delivers full dose in about 1/3 of a second).
5. Remove the device from the injection site.

Summary of Known Problems

Potential problems with AJE device use have been identified through the execution of multiple user studies (two sharps protection evaluation studies and two usability studies). In these studies the following problems were identified:

- Users not pressing the device against the skin with sufficient force to trigger the injection - this was improved with a change to device design
- Holding the device in the incorrect orientation
- Not holding the device at the injection site long enough

Table 7, page 103 of the electronic submission, provides a list of additional use errors/hazards identified for similar devices. The table also includes how the proposed Epi-Pen is designed to address the potential hazards.

In addition, Table 11, page 113 of the electronic submission shows a summary of all exploratory (formative) studies that have been conducted with the proposed Epi Pen. The table also provides a discussion of key results, and subsequent design medications that have been implemented based on the study results.

Summary of Human Factors Study Protocol

User Population

The Antares AJE Auto-injector" is intended specifically for self-injection of epinephrine by, patients who have been prescribed the drug, for immediate emergency supportive therapy only of severe allergic reactions (and are not substitute for immediate medical care). Injections may also be performed for the patient by laypersons or healthcare professionals.

Testing will be conducted with 30 participants in each of the 5 different user groups, with 15 will use the proposed AJE pen and 15 will use the current EpiPen (Table 28, page 131 of the electronic submission)

- Current adult Epi Pen owners
- Current teenage Epi Pen owners
- Adult non-Epi Pen owners
- Teenage non-Epi Pen owners
- Trained Epi-Pen roviders

Intended Use

The product is an automated drug delivery device for intramuscular or subcutaneous administration of epinephrine (0.15 mg/0.3 mL or 0.3 mg/0.3 mL via a pre-filled syringe), a drug used to treat severe allergic reactions. It is a singleshot, fixed dose, (b) (4) disposable device.

The product is intended for immediate self-administration as emergency supportive therapy only by patients or their trained providers/caregivers (i.e. parents, school nurses or applicable school staff). The drug, epinephrine, is a prescription drug indicated for the emergency treatment of severe allergic reactions (i.e. anaphylaxis).

Use Environments

The product is intended for use in the home, public settings and other non-clinical locations by patients or their trained providers/caregivers.

Acceptance Criteria

The AJ E device model will pass this evaluation if the Sponsor determines that:

The AJ E device use errors, near misses, or operational difficulties (if any are observed) occur with the AJ E device at a frequency and/or level that is no more than 10% greater than the frequency/level of use errors observed for the Epi Pen.

Materials

The devices used in this study will consist of devices that have no needles, and the devices will not be filled with any liquid (i.e., air filled only and/or no drug cartridge - as applicable). Except for the above listed modifications, the study devices will be designed to be equivalent to the commercial product.

Expected Training

Because this device is intended to be a generic substitutable device for the Epi Pen® and Epi Pen Jr.® auto-injectors currently on the market, the Sponsor anticipates that users will not receive any training from a health care professional specific to the use of the AJ E device. In order to replicate users who were not trained on the use of the device by a health care professional, and actual real-life situations of use as closely as possible, all test participants will have access only to the on-device IFU during the simulated use testing. !No device training will be given to study participants

(by a health care professional or study personnel); nor will the written IFU package insert be provided to study participants.

Task Analysis, Characterization, and Prioritization

Table 3 of the protocol provides an analysis of user tasks, potential use errors, clinical consequences, and mitigations. This will be evaluated by having the participants use the product indenpendently, and as realistic a manner as possible. Both behavioral (direct observation of behavior) and qualitative (subjective participant assessments) data will be collected.

Different user groups (Current Epi Pen Users, Non Epi Pen Owners, Trained Epi Pen Providers – as described above) will participate in a session simulating the

participants' normal use of the of the device. During the behavioral trials, the study facilitator will observe when and how participants consult the on-device Instructions for Use. Following each trial, the Study Facilitator will interview the participant regarding his/her understanding of the on-device instructions. Participants will be asked their subjective opinions concerning any parts of the instructions that are unclear or could be improved.

Data Analysis

This study is intended to collect both behavioral and qualitative data. The data will be coded using the following coding scheme:

- •Unassisted ("U"): Successful completion of the task without any observed use errors, close calls, or assistance from the facilitator/observer. Participant completed the scenario successfully without making any errors.
- •Resolved ("R"): Successful completion of the task with an observed close call or apparent operational difficulty.
- •Assisted ("A"): Successful completion ofthe task was only possible with assistance from the facilitator/observer.
- •Unresolved ("X"): Unsuccessful (incomplete and/or incorrect) completion of the task. Participant was unable to complete the scenario successfully.
- •No Time ("N/T"): Participant was unable to complete the scenario because session time was limited.

The Sponsor will analyze all AJ E device use errors, near misses, and operational difficulties to determine if the device and associated labeling is safe as-is, or if it requires further risk mitigations.

CDRH Human Factors Review Recommendations

Overall, this reviewer believe that the proposed protocol demonstrates how Teva Pharmaceutical has systematically evaluated use-related risk and how they would validate user-performance based on performance of the highest priority task pertinent to their device.

However, there are several specific sections in the protocol that are of concern and will require additional clarification/information. These specific sections are mostly aligned with Teva's questions in their cover letter. As a result, this reviewer will provide comments to those questions.

Please transmit the following response (in blue) to Teva Pharmaceuticals:

1. Selection of User Groups to Study

Per the instructions in the review letter, our goal is to select test participants that are representative of our intended end-user population as described in our indications for use statement. We have identified the following 5 groups to study:

- Current Epi Pen Owners (Adults)
- Current Epi Pen Owners (Teenagers 13-17)
- Non-Epi Pen Owners (Adults)
- Non-Epi Pen Owners (Teenagers 13-17)
- Trained Epi Pen Providers

The detailed description of these groups is contained on page 5-6 of the draft protocol. We plan to study 15 subjects per group (with an additional 3 per group to account for any dropouts). We believe that these groups will provide users with distinctly different characteristics.

- Do you agree with our selection of Study Groups?
- Are 15 subjects per group (with 3 added for dropouts) adequate for analysis?

Proposed FDA Response from CDRH HF:

The Agency agrees with your proposed study population selection. However, please provide a clarification regarding the number of study participants. In Table 28 of the submission, you indicated that a total of 150 participants will be included in the study with a total of 30 participants in each of the 5 major user groups. And in each of the 5 major user groups, you will have 15 participants use the proposed AJE peninjectors, and 15 use the EpiPen. It appears that you intend to provide a direct comparison for the proposed AJE pen injectors and the current EpiPens. Please note that this type of comparative study is useful in the exploratory phase whereas in a validation study, the Agency recommends that you focus your effort on the proposed AJE pen injectors, and provide the necessary data that demonstrate that the AJE pen injectors can be used safely and effectively by representative users in representative use environment. Alternatively, you might consider studying the AJE pen injectors first in your study, and collect the necessary data before studying the EpiPens.

2. Endpoints

Our current proposed acceptance criteria on page 29 of the draft protocol state the following:
The AJE device model will pass this evaluation if the Sponsor determines that:
The AJE device use errors, near misses, or operational difficulties (if any are observed) occur with the AJE device at a frequency and/or level that is no more than 10% greater than the frequency/level of use errors observed for the Epi Pen.

- Do you agree that this an acceptable endpoint?

Proposed FDA Response from CDRH HF:

The Agency does not agree with the endpoint that you proposed. Please note that we are not so much concerned with the achievement of a certain percentage of success based on a pre-

established criterion value as with the nature of the failures and use errors that are found. Describe the performance criteria and clearly state what the results mean in terms of failures, and use errors that could correspond to potential harm to patients. Your analysis of performance and subjective data should be directed toward understanding user performance and particularly task failures, use errors, close calls, and operational difficulties, and their associated root cause. Also, as indicated in our response to question 1, the Agency recommends that you focus your effort on the proposed AJE pen injectors.

Since our application is an Abbreviated New Drug Application for a critical need rescue device, we recognize that, to simulate real-life situations, our study should provide information on the interchangeability of our device with the reference listed drug (Epi Pen). Our draft protocol, therefore, proposes (among other parameters) to compare the time it takes each subject to use our product to the time it takes the same subjects to use an Epi Pen. We believe that our device is a close copy of the Epi Pen, having only minor differences. We recognize, however, that three of our user groups consist of individuals who have experience in using an actual Epi Pen. This familiarity with the product would enable them to more easily (and quickly) administer the Epi Pen than our device. We are concerned about how to structure time endpoints for the study that would take into account this familiarity bias with the Epi Pen device.

- Can the endpoint be an acceptable time range (rather than a direct time comparison) during which a certain percentage of subjects would be able to administer product (90% of subjects administered the drug within 5 minutes)?

Proposed FDA Response from CDRH HF:

While for epinephrine pen-injectors, timing to deliver a successful dose is clinically critical, we do not agree with your proposed 90% of subjects successfully administering the drug in 5 minutes criterion. We would be concerned with the 10% subjects who failed to administer the drug in 5 minutes and why they failed and whether remaining use-related risks should be considered acceptable. Again, we are not so much concerned with the achievement of a certain percentage of success based on a pre-established criterion value as with the nature of the failures and use errors that are found. We recommend that you include an analysis of residual risk of the use failures/errors as well as close calls and operational difficulties identified in the study to determine if additional design and/or labeling modifications are indicated or if not. This analysis should address the possibility or practicality of reducing safety-critical risks further and address whether the residual risk is outweighed by the advantages offered by the device.

3. Training

Because our product is designed to be substituted for the Epi Pen product, we recognize that many patients who get our device will not receive specific oral instructions for use from their physician. To replicate a true to life scenario, we have not proposed to train the subjects on the use of our device before giving it to them, and will rely on only the instructions for use on the device itself. (We have incorporated a separate study to evaluate our written instructions for use.)

- Do you agree with our proposal to not train subjects before the study?

Proposed FDA Response from CDRH HF:

The Agency agrees with your proposal not to train subjects before the study.

Guidance on human factors procedures to follow can be found in *Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management,* available online at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094460.htm. Note that we recently published a draft guidance document that, while not yet in effect, might also be useful in understanding our current thinking and our approach to human factors. It is titled, *Applying Human Factors and Usability Engineering to Optimize Medical Device Design* and can be found online at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259748.htm

Note
As per RPM, the CMC deficiencies that were faxed to the firm on 02Mar2010, are being sent again as part of current OGD practice of issuance of Complete Response Letter.

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 090589 APPLICANT: Teva Pharmaceuticals USA

DRUG PRODUCT: Epinephrine Injection USP, Autoinjector 0.15mg/0.3mL and 0.3mg/0.3mL

The deficiencies presented below represent MINOR deficiencies.

The following deficiencies pertain to the Human Factor Study:

1. **Selection of User Group to Study**
   The Agency agrees with your proposed study population selection. However, please provide a clarification regarding the number of study participants. In Table 28 of the submission, you indicated that a total of 150 participants will be included in the study with a total of 30 participants in each of the 5 major user groups. And in each of the 5 major user groups, you will have 15 participants use the proposed AJE peninjectors, and 15 use the EpiPen. It appears that you intend to provide a direct comparison for the proposed AJE pen injectors and the current EpiPens. Please note that this type of comparative study is useful in the exploratory phase whereas in a validation study, the Agency recommends that you focus your effort on the proposed AJE pen injectors, and provide the necessary data that demonstrate that the AJE pen injectors can be used safely and effectively by representative users in representative use environment. Alternatively, you might consider studying the AJE pen injectors first in your study, and collect the necessary data before studying the EpiPens.

2. **End Points**
   a. The Agency does not agree with the endpoint that you proposed. Please note that we are not so much concerned with the achievement of a certain percentage of success based on a pre- established criterion value as with the nature of the failures and use errors that are found. Describe the performance criteria and clearly state what the results mean in terms of failures, and use errors that could correspond to potential harm to patients. Your analysis of performance and subjective data should be directed toward understanding user performance and particularly task failures, use errors, close calls, and operational difficulties, and their associated root cause. Also, as indicated in our response to question 1, the Agency recommends that you focus your effort on the proposed AJE pen injectors.

   b. While for epinephrine pen-injectors, timing to deliver a successful dose is clinically critical, we do not agree with your proposed 90% of subjects successfully administering the drug in 5 minutes criterion. We would be concerned with the 10% subjects who failed to administer the drug in 5 minutes and why they failed and whether remaining use-related risks should be

considered acceptable. Again, we are not so much concerned with the achievement of a certain percentage of success based on a pre-established criterion value as with the nature of the failures and use errors that are found. We recommend that you include an analysis of residual risk of the use failures/errors as well as close calls and operational difficulties identified in the study to determine if additional design and/or labeling modifications are indicated or if not. This analysis should address the possibility or practicality of reducing safety-critical risks further and address whether the residual risk is outweighed by the advantages offered by the device.

3. **Training**
The Agency agrees with your proposal not to train subjects before the study.

Guidance on human factors procedures to follow can be found in *Medical Device Use-Safety:*
Incorporating Human Factors Engineering into Risk Management, available online at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094460.htm. Note that we recently published a draft guidance document that, while not yet in effect, might also be useful in understanding our current thinking and our approach to human factors. It is titled, *Applying Human Factors and Usability Engineering to Optimize Medical Device Design* and can be found online at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259748.htm

The following are the CMC deficiencies that were faxed on March 2, 2010:

A. Deficiencies:

1. (b) (4)

2.

3. [redacted] (b) (4)

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comment in your response:

1. [redacted] (b) (4)
2.
3.

Sincerely yours,

{See appended electronic signature page}

Andre Raw, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 090589
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-620/M. Darj, Ph.D., RC/10Oct2012/

HFD-620/B. M. Azarm, M.S., TL/10/10/12

HFD-617/S.Eng, Pharm.D., PM/12/19/12

TYPE OF LETTER: NOT APPROVABLE - MINOR

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

/s/

MIKE DARJ
12/19/2012

SIMON S ENG
12/19/2012

BITA MIRZAI AZARM
12/20/2012

ANDRE S RAW
12/20/2012

ANDA 090589

Epinephrine Injection, USP
Autoinjector 0.15 mg/0.3 mL and 0.3 mg/0.3 mL

Teva Parenteral Medicines, Inc.

Addendum to CR#2

Mike Darj
Office of Generic Drugs
Division of Chemistry I

Chemistry Review Data Sheet

1. ANDA 90-589

2. REVIEW #: 2 Addendum

3. REVIEW DATE: 11MAY2011

4. REVIEWER: Mike Darj, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original Application (SD #1)	21-Dec-2007
Amendment (SD #2)	30-May-2008
Amendment (SD #5)	23-May-2009*
Amendment (SD #6)	12-Jun-2009

* Firm's letter is dated 22May2009, but DARRTS show 23May2009

6. SUBMISSION(S) BEING REVIEWED: N/A

Submission(s) Reviewed	Document Date

NOTE: This addendum is created because of Human Factors Deficiency issues.

7. NAME & ADDRESS OF APPLICANT:

Name:	Teva Parenteral Medicines, Inc.
Address:	19 Hughes Irvine, CA 92618
Representative:	Susan O'Brien
Telephone:	(949) 455-4724
Fax:	(949) 583-7351

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Epinephrine Injection, USP

9. LEGAL BASIS FOR SUBMISSION:

The basis for Teva Parenteral Medicines, Inc proposed ANDA for Epinephrine Injection USP, Auto-Injector 0.15 mg and 0.3 mg is the approved reference listed drug (RLD) EpiPen®, EpiPen® Jr, the subject of NDA No. 19-430 held by Meridian Medical Technologies, Inc (Approved December 22, 1987). The RLD is in 0.15 mg and 0.3 mg strengths.

10. PHARMACOL. CATEGORY: sympathomimetic catecholamine.

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 0.15 mg/0.3 mL and 0.3 mg/0.3 mL

13. ROUTE OF ADMINISTRATION: Intramuscular

14. Rx/OTC DISPENSED: __X__ Rx ____ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

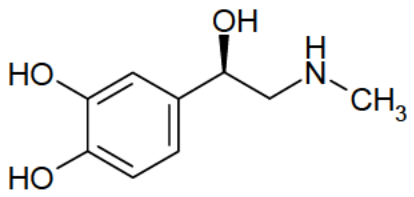
_____SPOTS product – Form Completed

__X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical name: (-)-3,4-Dihydroxy-alpha-((methylamino)methyl)benzyl alcohol
or
1,2-Benzenediol, 4-(1-hydroxy-2-(methylamino)ethyl)-, (R)-
or
1-1-(3,4-Dihydroxyphenyl)-2-methylaminoethanol

Molecular formula: $C_9H_{13}NO_3$
Formula weight: 183.206 g/mol
CAS RN: [51-43-4]
Structural formula:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)		7			This is an addendum to CR#2. When the firm respond to the deficiencies, this DMF will be evaluated.
	III			4	N/A		
				3	Inadequate	09Jul2009	Reviewed by CDRH

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Consult	2008-0229	Consult request dated 6/20/2008 to DACCADP
Consult	2009-0320	Consult request dated 3/27/2009 to CDRH re MAF (b) (4)

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Acceptable	25Sep2009	Eric Adeeku

EES	Withhold (WL issued)	23Feb2011	EES-Prod
Methods Validation	N/A (per current OGD policy)		
Labeling	Deficient	02Feb2011	Angela Payne
Bioequivalence	Deficient	29Mar2010	Nilufer Tampal
EA	Acceptable	31Mar2009	M. Darj
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. ___ Yes __X__ No If no, explain reason(s) below:

Addendum to Review #2

Chemistry Assessment Section

Addendum To Chemistry Review #2

The purpose of this addendum is to convey to the firm that a human factor study is required as part of the demonstration that the generic device use is the same as the RLD device use. The following deficiency is recommended by the CDRH and it is being sent to the firm **without modifications**. The firm's response to this deficiency will be submitted to the CDRH for evaluation.

Please conduct a design validation (human factors) study. We recommend that you submit a draft of the test protocol before you implement it for our review and feedback to ensure that your methods will be acceptable.

The purpose of a design validation (human factors) study is to demonstrate that the device can be used by representative users under simulated use conditions without producing patterns of failures that could result in negative clinical impact to patients or injury to device users. Tasks included in the study should be those identified through completion of a risk assessment of hazards that may be associated with use-related problems and represent greater than minimal risk to users. The study should collect sufficient and appropriate data to facilitate identification and understanding of the root causes of any use failures or problems that do occur. The causes may be related to the design of the device, the device labeling (including instructions for use), and/or the training of test participants. The test report should present a summary of your test results, data analysis, and conclusions regarding safe and effective use and including whether any modifications are indicated; if they are, these modifications should be described and if significant, the modifications should also be validated.

Your validation study protocol should include the items listed below.

Devices and Labeling Used and Training

For design validation, the devices used in your testing should represent the final design, which includes instructions for use, or any other labeling materials.

The training you provide to your test participants should approximate the training that your actual end users will receive. Please describe the training you plan to provide in your validation study and how it corresponds to realistic training levels.

Your participants should assess the clarity of the instructions for use and you should assess the extent to which the instructions support safe and effective use of your device. If any of the other labeling (e.g., packaging, inserts) is critical to use, include them in your validation testing as well. You may include these assessments in your validation testing or conduct them in a separate study.

If you decide to include the assessment of clarity of instructions for use and training as part of the validation study, the Agency expects that the results demonstrating effectiveness of your training and instructions for use are analyzed separately from the results of use performance.

User Tasks and Use-Related Risks Analysis

FDA expects to see a clear description of how you determined which user tasks would be included in the testing and how many trials each participant would complete. In order to adequately assess user performance and safety, the tasks selected for testing should be derived from the results of a comprehensive assessment of use-related hazards and risks that consider all functions of the device. The tasks should be prioritized to reflect the relative magnitude and severity of the potential impact of inadequate task performance on the safety of the device and the user.

Please provide a use-related risks analysis, describe and provide a rationale for the tasks you include in your testing and their relative priority. Please also describe all activities in which your test participants will engage during the test.

Use Environment and Conditions

You should conduct your validation testing in an environment that includes or simulates all key aspects of the real-world environments in which you anticipate your device would be used.

Identification of potentially challenging use conditions should be derived through analyses of use hazards prior to conducting validation testing and aspects of use that can be reasonably anticipated, such as use with gloves or wet fingers, dim lighting, noisy situations, etc., should be included in your testing. Please evaluate use of your device under whatever conditions you identify as potentially occurring and hazardous.

Please describe the testing environment and realism of the simulated use in sufficient detail for us and justify how they were appropriate for validation testing.

Study Participants

FDA expects you to test a minimum of 15 participants from each major user group for validation of device use. Your test participants should be representative of your intended end-user populations, as described in your indications for use statement. If users with distinctly different characteristics (e.g., age ranges, skill sets, or experience levels, level of disabilities/impairments) will use your device, you should include 15 from each distinct group.

Regardless of the number of groups you test, please provide a rationale that these groups are representative the overall population of users for your device. Note that study participants should not be your own employees, or those that have been exposed to the products prior to the testing.

Data Collection

Any data collected and analyzed in a validation study should be described in terms of how it supports the safety case claim that your device can be used safely and effectively by the

indicated users. FDA expects you to collect both empirical and qualitative data in a design validation study.

Empirical Data – Your test participants should be given an opportunity to use the device independently and in as realistic a manner as possible, without guidance, coaching, praise or critique from the test facilitator/moderator. Some data, such as successful or failed performance of key tasks or time taken to perform tasks – if time is a safety-critical criterion – should be measured directly rather than soliciting participant opinions. Observing participant behavior during the test is also important, in order to assess participants' adherence to protocol and proper technique and especially to assess and understand the nature of any errors or problems that occur.

Qualitative Data – The Agency expects you to ask open-ended questions of participants at the end of a usability validation, such as, "Did you have any difficulty using this device? [If so] can you tell me about that?" The questions should explore performance of each critical task involved in the use of the device and any problems encountered. Note that since the labeling and instructions for use are considered part of the user interface for your device, the questions should cover those components as well.

Your analysis of performance and subjective data should be directed toward understanding user performance and particularly task failures. The analysis should determine the nature of failures, the causes of failures, and the clinical impact. Every test participant who experiences a "failure" (does something that would have led to harm under actual conditions of use), should be interviewed about that failure to determine the cause of the failure from the perspective of the participant.

Please describe and provide a rationale for including each type of data you collect.

Please provide a proposed protocol for the Agency to review prior to conducting the study.

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 90589 APPLICANT: Teva Parenteral Medicines, Inc.

DRUG PRODUCT: Epinephrine Injection USP, Autoinjector 0.15mg/0.3mL and 0.3mg/0.3mL

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

Please conduct a design validation (human factors) study. We recommend that you submit a draft of the test protocol before you implement it for our review and feedback to ensure that your methods will be acceptable.

The purpose of a design validation (human factors) study is to demonstrate that the device can be used by representative users under simulated use conditions without producing patterns of failures that could result in negative clinical impact to patients or injury to device users. Tasks included in the study should be those identified through completion of a risk assessment of hazards that may be associated with use-related problems and represent greater than minimal risk to users. The study should collect sufficient and appropriate data to facilitate identification and understanding of the root causes of any use failures or problems that do occur. The causes may be related to the design of the device, the device labeling (including instructions for use), and/or the training of test participants. The test report should present a summary of your test results, data analysis, and conclusions regarding safe and effective use and including whether any modifications are indicated; if they are, these modifications should be described and if significant, the modifications should also be validated.

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Please describe the testing environment and realism of the simulated use in sufficient detail for us and justify how they were appropriate for validation testing.

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Please describe and provide a rationale for including each type of data you collect.

Please provide a proposed protocol for the Agency to review prior to conducting the study.

B. In addition to responding to the deficiency presented above, please note and acknowledge the following comment in your response:

1. The labeling, bioequivalence and CMC portions of your application have been found to be deficient. Your responses to the deficiencies should be sent to each division under separate covers.

2. A satisfactory cGMP compliance evaluation for the firms referenced in the ANDA is required for approval. The Division of Manufacturing and Product Quality currently recommends that we withhold approval.

Sincerely yours,

{See appended electronic signature page}

Paul Schwartz, Ph.D.
Acting Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 90-589
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-620/M. Darj, Ph.D., RC/11May2011/

HFD-620/B. M. Azarm, M.S., TL/05/12/11

HFD-617/K. Kirby, Pharm.D., PM/12MAY2011

TYPE OF LETTER: NOT APPROVABLE - MINOR

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

/s/

MIKE DARJ
05/16/2011

CHRISTINA L KIRBY
05/16/2011

BITA MIRZAI AZARM
05/16/2011

ANDA 090589

Epinephrine Injection, USP
Autoinjector 0.15 mg/0.3 mL and 0.3 mg/0.3 mL

Teva Parenteral Medicines, Inc.

CR#2

Mike Darj
Office of Generic Drugs
Division of Chemistry I

Table of Contents

Chemistry Review Data Sheet

1. ANDA 090589

2. REVIEW #: 2

3. REVIEW DATE: 31OCT2009
   REVISION DATE: 05JAN2010

4. REVIEWER: Mike Darj, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original Application (SD #1)	21-Dec-2007
Amendment (SD #2)	30-May-2008

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment (SD #5)	23-May-2009*
Amendment (SD #6)	12-Jun-2009

* Firm's letter is dated 22May2009, but DARRTS show 23May2009

7. NAME & ADDRESS OF APPLICANT:

Name:	Teva Parenteral Medicines, Inc.
Address:	19 Hughes Irvine, CA 92618
Representative:	Susan O'Brien
Telephone:	(949) 455-4724
Fax:	(949) 583-7351

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Epinephrine Injection, USP

9. LEGAL BASIS FOR SUBMISSION:

The basis for Teva Parenteral Medicines, Inc proposed ANDA for Epinephrine Injection USP, Auto-Injector 0.15 mg and 0.3 mg is the approved reference listed drug (RLD) EpiPen®, EpiPen® Jr, the subject of NDA No. 19-430 held by Meridian Medical Technologies, Inc (Approved December 22, 1987). The RLD is in 0.15 mg and 0.3 mg strengths.

10. PHARMACOL. CATEGORY: sympathomimetic catecholamine.

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 0.15 mg/0.3 mL and 0.3 mg/0.3 mL

13. ROUTE OF ADMINISTRATION: Intramuscular

14. Rx/OTC DISPENSED: __X__ Rx ____ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

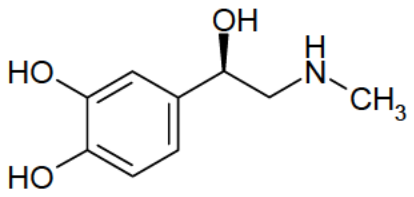
_____SPOTS product – Form Completed

__X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical name: (-)-3,4-Dihydroxy-alpha-((methylamino)methyl)benzyl alcohol
or
1,2-Benzenediol, 4-(1-hydroxy-2-(methylamino)ethyl)-, (R)-
or
1-1-(3,4-Dihydroxyphenyl)-2-methylaminoethanol

Molecular formula: $C_9H_{13}NO_3$
Formula weight: 183.206 g/mol
CAS RN: [51-43-4]
Structural formula:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	7			See section "S" for explanation
	III			4	N/A		
				3	Inadequate	09Jul2009	Reviewed by CDRH

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Consult	2008-0229	Consult request dated 6/20/2008 to DACCADP
Consult	2009-0320	Consult request dated 3/27/2009 to CDRH re MAF (b) (4)

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Acceptable	25Sep2009	Eric Adeeku
EES	Pending		
Methods Validation	N/A (per current OGD policy)		
Labeling	Deficient	04Jun2009	Angela Payne
Bioequivalence	Pending		

EA	Acceptable	31Mar2009	M. Darj
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. ___ Yes __X__ No If no, explain reason(s) below:

Minor amendment

The Chemistry Review for ANDA 090589

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The ANDA is Not Approvable

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Not Applicable

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance

Epinephrine, also known as Adrenaline, is a white to off-white crystalline powder. The molecule is optically active due to a chiral center. It exists as D- and L-optical isomers, (b) (4). It is not known to exhibit polymorphism. It has aqueous solubility of less than 0.01 grams in 100 mL. However, solubility increases as the pH becomes more acidic. It is prone to oxidation and photo-degradation. (b) (4) (b) (4).

Drug Product

The drug product is Epinephrine Injection USP 0.15mg and 0.3mg. The product is packaged in an autoinjector device. The drug product is intended for the treatment of severe allergic reactions (Type I) to insect stings or bites, foods, drugs, and other allergens. It can also be used in the treatment of exercise-induced anaphylaxis. According to the labeling, the usual adult dose is 0.3 mg. However, with severe persistent anaphylaxis, repeat injections with an additional Epinephrine Injection, USP auto-injector may be necessary. For the purpose of assessing the impurities limits, usual **daily dose of 0.3 mg** will be used (b) (4) (b) (4)

B. Description of How the Drug Product is Intended to be Used

The drug product is an injectable solution that is administered intramuscularly.

C. Basis for Approvability or Not-Approval Recommendation

The recommendation of Not-Approvability is based on the cited deficiencies (see review for more details).

In addition to the above CMC issues, the bioequivalence review is pending, labeling is deficient, and establishment evaluation is pending assessment by DMPQ. Information of microbiology is acceptable

The drug product, Epinephrine Injection USP, Autoinjector 0.15mg and 0.3 mg cannot be approved in this review based on the deficiencies described above.

Chemistry Assessment

I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data

S DRUG SUBSTANCE:

LOA dated 9Nov2007 is provided. DMF [(b) (4)] was reviewed on 19Mar2009 and found to be adequate. The review of this ANDA amendment was completed on 31Oct2009. Since this review date, an amendment to DMF [(b) (4)] dated 30Oct2009, which was stamped by the Central Document Room on 05Nov2009 was received. Since this ANDA remains deficient, the review of the DMF will be completed when the response to the ANDA deficiencies are received.

S.1 General Information

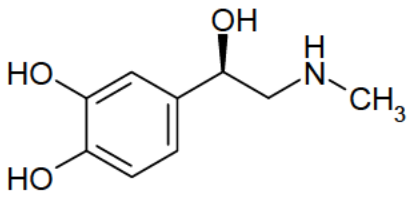
Name: Epinephrine USP

[(b) (4)]

S.1.1 Nomenclature:

Chemical Name: (-)-3,4-Dihydroxy-alpha-((methylamino)methyl)benzyl alcohol
or
1,2-Benzenediol, 4-(1-hydroxy-2-(methylamino)ethyl)-, (R)-
or
1-1-(3,4-Dihydroxyphenyl)-2-methylaminoethanol

S.1.2 Structure:



S 1.3 General Properties:

Physical Description: White to off-white crystalline powder
pKa: $pK_1 = 8.71$ at 20°C, $pK_2 = 9.90$ at 20°C
Polymorphism: Does not exist in different crystalline forms
Stereochemistry: Epinephrine exists as D- and L- optical isomers. [(b) (4)]
[(b) (4)]
Solubility Characteristics: <0.01 g / 100 mL of water at 18°C; very slightly soluble in alcohol, insoluble in chloroform, ether, acetone, and oils. Soluble in mineral acids. Solubility increases as a function of decreasing pH.
Hygroscopicity: Epinephrine is not reported in the literature as being hygroscopic.

Melting Point: 211-212°C
Partition Coefficient: Log P (octanol-water) = -1.37
Other Physicochemical Characteristics: Vapor pressure at 25°C = 7.37 X 10^{-7} mm Hg

S.2 Manufacture

(b) (4)

[redacted]

S.2.2 Description of Manufacturing Process and Process Controls:

Refer to DMF (b) (4)

S.2.3 Control of Materials

Refer to DMF (b) (4)

S.2.4 Controls of Critical Steps and Intermediates

Refer to DMF (b) (4)

S.2.5 Process Validation and/or Evaluation

Refer to DMF (b) (4)

S.2.6 Manufacturing Process Development

Refer to DMF (b) (4)

S.3 Characterization

S.3.1 Elucidation of Structure and other Characteristics

Refer to DMF (b) (4)

S.3.2 Impurities:

Refer to DMF (b) (4)

S.4 Control of Drug Substance

S.4.1 Specification Satisfactory

Specifications and results for the drug substance are provided below.

(b) (4)

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

cc: ANDA 90-589
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-620/M. Darj, Ph.D., RC/31Oct2009/05Jan2010

HFD-620/B. Cai, Ph.D., TL/

HFD-617/E. Chuh, PM/

Temporary location of the review file:

V:\CHEMISTRY DIVISION I\TEAM 2\TL FOLDER\ANDA\Draft_Under Process\90589CR2.DOC

TYPE OF LETTER: NOT APPROVABLE - MINOR

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-90589	ORIG-1	TEVA PARENTERAL MEDICINES INC	EPINEPHRINE

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

/s/

MIKE DARJ
02/26/2010

BING CAI
02/26/2010

EUNJUNG E CHUH
03/02/2010

ANDA 90-589

Epinephrine Injection, USP
Autoinjector 0.15 mg/0.3 mL and 0.3 mg/0.3 mL

Teva Parenteral Medicines, Inc.

Mike Darj
Office of Generic Drugs
Division of Chemistry I

Table of Contents

Chemistry Review Data Sheet

1. ANDA 90-589

2. REVIEW #: 1

3. REVIEW DATE: 31MAR2009
   REVISION DATE: 12APR2009, 27APR2009

4. REVIEWER: Mike Darj, Ph.D.

5. PREVIOUS DOCUMENTS: None

Previous Documents	Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Application	21-Dec-2007
Amendment	30-May-2008

7. NAME & ADDRESS OF APPLICANT:

Name:	Teva Parenteral Medicines, Inc.
Address:	19 Hughes Irvine, CA 92618
Representative:	Susan O'Brien
Telephone:	(949) 455-4724
Fax:	(949) 583-7351

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Epinephrine Injection, USP

9. LEGAL BASIS FOR SUBMISSION:

The basis for Teva Parenteral Medicines, Inc proposed ANDA for Epinephrine Injection USP, Auto-Injector 0.15 mg and 0.3 mg is the approved reference listed drug (RLD) EpiPen®, EpiPen® Jr, the subject of NDA No. 19-430 held by Meridian Medical Technologies, Inc (Approved December 22, 1987). The RLD is in 0.15 mg and 0.3 mg strengths.

10. PHARMACOL. CATEGORY: Epinephrine is a sympathomimetic catecholamine.

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 0.15 mg/0.3 mL and 0.3 mg/0.3 mL

13. ROUTE OF ADMINISTRATION: Intramuscular

14. Rx/OTC DISPENSED: __X__ Rx ____ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__X__Not a SPOTS product

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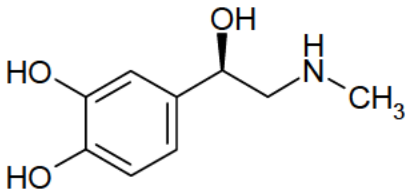
or
1-1-(3,4-Dihydroxyphenyl)-2-methylaminoethanol

Molecular formula: $C_9H_{13}NO_3$
Formula weight: 183.206 g/mol
CAS RN: [51-43-4]
Structural formula:



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	III			4	N/A		
				7	Pending		Pending review by CDRH

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: N/A

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER

Microbiology	Pending		
EES	Pending		
Methods Validation	N/A (per current OGD policy)		
Labeling	Pending		
Bioequivalence	Pending		
EA	Acceptable	31Mar2009	M. Darj
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. __X__ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 90-589

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The ANDA is Not Approvable

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Not Applicable

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance

Epinephrine, also known as Adrenaline, is a white to off-white crystalline powder. The molecule is optically active due to a chiral center. It exists as D- and L-optical isomers, (b) (4). It is not known to exhibit polymorphism. It has aqueous solubility of less than 0.01 grams in 100 mL. However, solubility increases as the pH becomes more acidic. It is prone to oxidation and photo-degradation. (b) (4)

(b) (4)

Drug Product

The drug product is Epinephrine Injection USP 0.15mg and 0.3mg. The product is packaged in an autoinjector device. The drug product is intended for the treatment of severe allergic reactions (Type I) to insect stings or bites, foods, drugs, and other allergens. It can also be used in the treatment of exercise-induced anaphylaxis. According to the labeling, the usual adult dose is 0.3 mg. However, with severe persistent anaphylaxis, repeat injections with an additional Epinephrine Injection, USP auto-injector may be necessary. For the purpose of assessing the impurities limits, usual daily dose of 0.3 mg will be used. (b) (4)

(b) (4)

B. Description of How the Drug Product is Intended to be Used

The drug product is an injectable solution that is administered intramuscularly.

C. Basis for Approvability or Not-Approval Recommendation

The recommendation of Not-Approvability is based on the cited deficiencies (see review for more details).

In addition to the above CMC issues, the bioequivalence, labeling and microbiology portions are pending review, and establishment evaluation is pending assessment by DMPQ.

The drug product, Epinephrine Injection USP, Autoinjector 0.15mg and 0.3 mg cannot be approved in this review based on the deficiencies described above.

Chemistry Assessment

I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data

S DRUG SUBSTANCE: Not Satisfactory

LOA dated 9Nov2007 is provided. DMF [redacted] (b) (4) was reviewed on 19Mar2009 and found to be adequate.

S.1 General Information

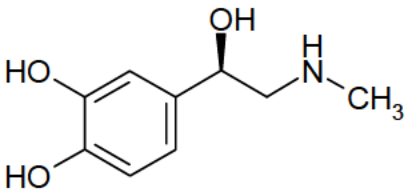
Name: Epinephrine USP

[redacted] (b) (4)

S.1.1 Nomenclature:

Chemical Name: (-)-3,4-Dihydroxy-alpha-((methylamino)methyl)benzyl alcohol
or
1,2-Benzenediol, 4-(1-hydroxy-2-(methylamino)ethyl)-, (R)-
or
1-1-(3,4-Dihydroxyphenyl)-2-methylaminoethanol

S.1.2 Structure:



S 1.3 General Properties:

Physical Description: White to off-white crystalline powder
pKa: $pK_1 = 8.71$ at 20°C, $pK_2 = 9.90$ at 20°C
Polymorphism: Does not exist in different crystalline forms
Stereochemistry: Epinephrine exists as D- and L- optical isomers. [redacted] (b) (4)
[redacted] (b) (4)
Solubility Characteristics: <0.01 g / 100 mL of water at 18°C; very slightly soluble in alcohol, insoluble in chloroform, ether, acetone, and oils. Soluble in mineral acids. Solubility increases as a function of decreasing pH.
Hygroscopicity: Epinephrine is not reported in the literature as being hygroscopic.
Melting Point: 211-212°C
Partition Coefficient: Log P (octanol-water) = -1.37
Other Physicochemical Characteristics: Vapor pressure at 25°C = 7.37×10^{-7} mm Hg

S.2 Manufacture

S.2.1 Manufacturers:

(b) (4)

[redacted]

S.2.2 Description of Manufacturing Process and Process Controls:

Refer to DMF (b) (4)

S.2.3 Control of Materials

Refer to DMF (b) (4)

S.2.4 Controls of Critical Steps and Intermediates

Refer to DMF (b) (4)

S.2.5 Process Validation and/or Evaluation

Refer to DMF (b) (4)

S.2.6 Manufacturing Process Development

Refer to DMF (b) (4)

S.3 Characterization

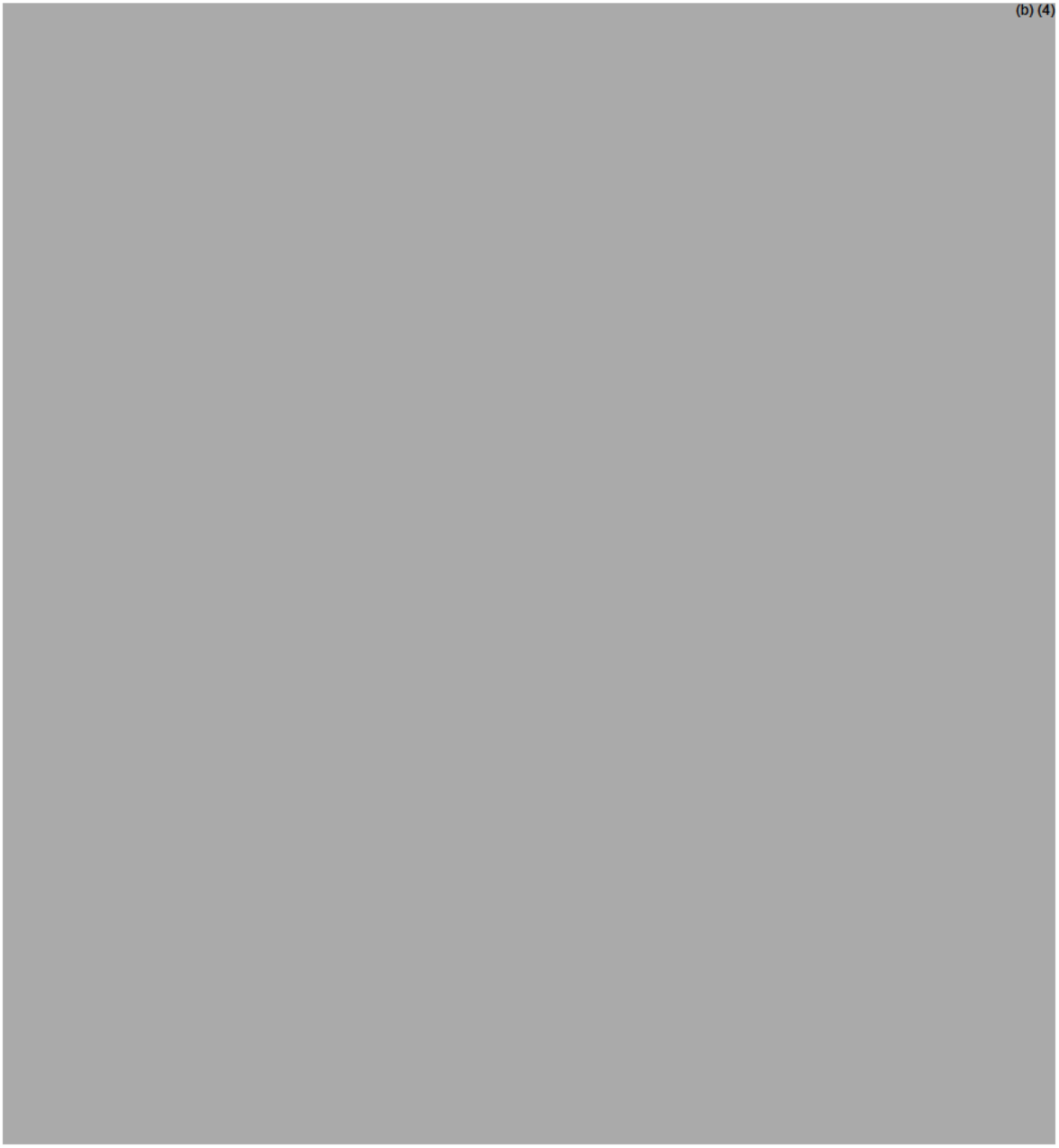
S.3.1 Elucidation of Structure and other Characteristics

Refer to DMF (b) (4)

S.3.2 Impurities:

Refer to DMF (b) (4)

(b) (4)



13. Please provide the protocol followed and the test data for the clinical study of the container/closure system.

14. Please add the orientation of the container/closure system to the stability data tables.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comment in your response:

Chemistry Assessment Section

1. (b) (4)
2.
3.
4.
5.

Sincerely yours,

{See appended electronic signature page}

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

Temporary location of review file before checking into DFS:

V:\CHEMISTRY DIVISION I\TEAM 2\TL FOLDER\ANDA\90589CR1.DOC

TYPE OF LETTER: NOT APPROVABLE - MINOR

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

/s/

Mike Darj
4/28/2009 05:47:31 PM
CHEMIST

Esther Chuh
4/30/2009 01:09:03 PM
CHEMIST

Ramnarayan Randad
4/30/2009 03:05:03 PM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 090589

BIOEQUIVALENCE REVIEW(S)

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	090589		
Drug Product Name	Epinephrine Injection USP (Auto-Injector)		
Strength(s)	0.15 mg/0.3 mL, 0.3 mg/0.3 mL		
Applicant Name	Teva Pharmaceuticals USA		
Applicant Address	425 Privet Road, Horsham, PA 19044		
Applicant's Point of Contact	Cory Wohlbach Senior Director, Regulatory Affairs, US Generics		
Contact's Telephone Number	215-293-6519		
Contact's Fax Number	215-591-8812		
Contact's Email Address	Cory.wohlbach@tevapharm.com		
Original Submission Date(s)	December 21, 2007 May 30, 2008 (Amendment), May 22, 2009 (Amendment) July 31, 2013 (in vitro), December 30, 2014 (re-formulation) and May 20, 2015 (Amendment)		
Submission Date(s) of Amendment(s) Under Review	March 18, 2016 (Post Complete Response Meeting Request)		
Reviewer	Harikrishna Devalapally, Ph. D.		
OVERALL REVIEW RESULT	**ADEQUATE**		
REVISED/NEW DRAFT GUIDANCE INCLUDED	**NO**		
COMMUNICATION	☐ **ECD** ☐ **IR** ☒ **NOT APPLICABLE**		
BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	**STUDY/TEST TYPE**	**STRENGTH**	**REVIEW RESULT**
21, 25, 32, 38, 39, 48	**Waiver**	**0.3 mg/0.3 mL & 0.15 mg/0.3 mL**	**ADEQUATE**

ADDENDUM: Review of Superseding Consult Responses

This is an addendum to a previous review,[1] dated October 19, 2016, which reviewed a consult response from the Division of Clinical Review (DCR)[2] regarding "*whether the* (b) (4) *sodium tartrate should be of a safety concern when administered population,*" and a consult response from the Office of Pharmaceutical Quality (OPQ)[3] regarding "*the acceptability of firm's justification that sodium tartrate dissociates in* (b) (4) (b) (4) DCR and OPQ have subsequently completed superseding consult responses

[1] ANDA 090589, Division of Bioequivalence Review (Oct. 19, 2016).
[2] ANDA 090589, Division of Clinical Review Consultation (Sept. 7, 2016).
[3] ANDA 090589, Comment to Consult Request from Division of Clinical Review (Aug, 19, 2016).

to provide clarification regarding the information relied upon by DCR and OPQ in making the conclusions set forth in their respective consult responses.[4] We note that the conclusions set forth in the superseding DCR consult response and superseding OPQ consult response are consistent with the conclusions set forth in the earlier versions of these consult responses. We have reviewed the superseding DCR consult response and superseding OPQ consult response, and the Division of Bioequivalence III (DBIII) agrees with DCR's and OPQ's conclusions regarding Teva Pharmaceuticals USA's (Teva's) justification for the use of sodium tartrate dihydrate in the formulation of Teva's epinephrine injection, 0.3 mg/0.3 mL and 0.15 mg/0.3 mL.

Further, in the October 19, 2016 review, DBIII concluded that the information submitted by Teva demonstrates that epinephrine injection, 0.3 mg/mL and 0.15 mg/mL, meets the requirements of 21 CFR 320.24(b)(6), and that Teva's waiver request of in vivo bioequivalence study requirements for the test product is granted. This addendum clarifies that Teva's request for a waiver under section 21 CFR 320.22(b)(1) was not granted, but rather that DBIII deems the approach taken by Teva to be adequate to establish bioequivalence pursuant to 21 CFR 320.24(b)(6).

The BE portion of the application remains **adequate**.

[4] See ANDA 090589, OPQ's Superseding Response to Consult Request from Division of Clinical Review (Aug. 14, 2018); see also ANDA 090589, DCR's Division of Clinical Review Superseding Consultation (Aug. 15, 2018).

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	090589
Drug Product Name	Epinephrine Injection USP (Auto-Injector)
Strength(s)	0.15 mg/0.3 mL, 0.3 mg/0.3 mL
Applicant Name	Teva Pharmaceuticals USA, Inc.
Address	425 Privet Road, Horsham, PA 19044
Applicant's Point of Contact	Cory Wohlbach
Contact's Telephone Number	215-293-6519
Contact's Fax Number	215-591-8812
Original Submission Dates	December 21, 2007 May 30, 2008 (Amendment) May 22, 2009 (Amendment) July 31, 2013 (in vitro) December 30, 2014 (re-formulation) May 20, 2015 (Amendment) March 08, 2016 (Post Complete Response Meeting Request)
Submission Date of Amendment Under Review	April 19, 2017
First Generic	**Yes**
Reviewer	Harikrishna Devalapally, Ph. D.
Secondary Reviewer	Suman Dandamudi, Ph. D.
Tertiary Reviewer	Ke Ren, Ph. D.
Overall Review Result	**Adequate**
Revised/New Draft Guidance Generated as Part of Current Review	**Yes**
Deficiency Classification	☐ **Major** ☐ **Minor** ☒ **Not Applicable (Review is adequate)**

Bioequivalence study tracking/supporting document #	**Study/test type**	**Strength**	**Review Result**
48	**In Vitro Tests**	**0.3 mg/0.3 mL and 0.15 mg/0.3 mL**	**Adequate**

Review of a Consult Response

I. EXECUTIVE SUMMARY

This is a review of the consult response from the Division of Clinical Research (DCR) in Office of Bioequivalence (OB) to a consult request seeking expert opinion on *whether the slightly greater force needed to activate the test device compared to reference device raise any safety or efficacy concern for the test product?*

The reference listed drug product (RLD) is Mylan Speclt's EpiPen® (epinephrine) Injection (Auto-Injector), 0.15 mg/0.3 mL and 0.3 mg/0.3 mL (NDA 019430, approved on December 22, 1987). It is indicated in the emergency treatment of allergic reactions (Type I) including anaphylaxis.

Per current product specific guidance for Epinephrine Injection (Auto-injector)[1], to demonstrate bioequivalence between the test and RLD (EpiPen®) products, in vitro comparative device performance studies are recommended. Delivered volume and extended needle length passed PBE analysis. However, PBE analysis results of ejection time and trigger force (activation force) data showed that the test device is not statistically equivalent to the reference device[2].

The Division of Bioequivalence III (DBIII) had an internal meeting with the management of Office of Bioequivalence (OB) and Office of Research and Standards (ORS) to discuss in vitro study results submitted by the applicant specifically Ejection Time and Trigger Force studies. In this meeting dated 06/12/2017, attendees concluded that small differences in mean fluid ejection time (approximately 30- 40 milliseconds) and shorter ejection time of test product will not have impact on clinical outcome, and recommended ejection time study to be acceptable from BE perspective. However, clinical significance of the observed statistical difference in trigger force should be further evaluated by a medical officer[3].

Therefore, DBIII sent a consult to the DCR to evaluate if the slightly greater force needed to activate the test device compared to reference device raise any safety or efficacy concern for the test product?[4]

(b) (4)

(b) (4) The DCR has evaluated the applicant's comparative trigger (activation) force study results, overviewed other epinephrine autoinjector's data and referred the results of in-vitro testing of EpiPen injectors published in the literature and concluded that slightly greater force needed to activate the test device compared to the reference device does not raise any safety or efficacy concerns regarding the test product[5].

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[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM534133.pdf, Recommended December 2016

[2] GDRP, ANDA-090589-ORIG-1-AMEND-6, http://panorama.fda.gov/task/view?ID=5420f1160002bc9df9be4d40027ff2e6&activeTab=list-task-documents, Ke Ren, Date Completed: 9/21/2017

[3] GDRP, ANDA-090589-ORIGI-1-AMEND-6, Meeting minutes review, http://panorama.fda.gov/task/view?ID=5420f1160002bc9df9be4d40027ff2e6, Suman Dandamudi, 10/15/2017

[4] GDRP, ANDA-090589-ORIG-1-AMEND-6, http://panorama.fda.gov/task/view?ID=5420f1160002bc9df9be4d40027ff2e6&activeTab=list-task-documents, Suman Dandamudi, Date Completed: 10/5/2017 (A090589DB_C09072017)

[5] GDRP, ANDA-090589-ORIG-1-AMEND-6, http://panorama.fda.gov/task/view?ID=599451230042d5a0ed0907431a6d15ce, Nitin K. Patel, Date Completed: 11/8/2017

For more details on this conclusion and scientific evaluation of comparative trigger (activation) force study results in drawing this conclusion, please see section VI Appendix I for details of the OGD DCR consult response.

The BE reviewer agrees with DCR's conclusions. Based on the above information including the fact that all in vitro equivalence studies submitted meet bioequivalence requirement as per current drug product guidance on Epinephrine Injection, the DBIII considers the applicant's proposed test formulations to be acceptable from BE perspective.

The BE portion of the application is **adequate**.

II. TABLE OF CONTENTS

III. REVIEW OF CONSULT RESPONSE

Consult request: DBIII requested DCR's expert opinion on the following question in the consult request[4].

> **Does the slightly greater force needed to activate the test device compared to reference device raise any safety or efficacy concern for the test product?**

The DCR evaluated the applicant's comparative trigger (activation) force study results, overviewed other epinephrine autoinjector's data and referred the results of in-vitro testing of EpiPen injectors published in the literature and made the following conclusions[5]:

Summary of DCR's Response:
Slightly greater force needed to activate the test device compared to the reference device does not raise any safety or efficacy concerns regarding the test product, based on the following:

1) given that EpiPen/EpiPen Jr labeling only specifies to "push firmly," it is likely that an imprecise and relatively wide range of activation forces would be observed, and that the range would include the activation force numbers observed with the test and RLD devices;

2) average activation force values for the test products are consistent with the range considered acceptable based on the literature (e.g., 5-10 lbf), and are consistent with published results for other approved epinephrine autoinjectors (b) (4)

3) the average activation force for the test products is well within the capability of expected users of the products, even younger self-administrators (e.g., 8-12 year old can generate [redacted] *);*
4) small differences in activation forces between the test and RLD would not be particularly notable to the user given that the context of use is typically infrequent emergency-use; and
5) activation force specification ranges for approved epinephrine autoinjectors reflect the lack of precision needed within a clinically acceptable range. Within that range, a difference of [redacted] *would not be a concern.*

Reviewer's Comments:

- Per current product specific guidance on Epinephrine Injection (Auto-injector), to demonstrate bioequivalence between test and RLD (EpiPen®) products, following in vitro comparative device performance studies are recommended.

  Delivered Volume
  Ejection Time
  Trigger Force
  Extended Needle Length
  Needle integrity post-injection

- Delivered volume and extended needle length passed PBE analysis. However, PBE analysis results of ejection time and trigger force (activation force) data showed that the test device is not statistically equivalent to the reference device.

- Since both ejection time and trigger force data failed to meet PBE analysis criteria, DBIII requested a meeting with the management of the Office of Bioequivalence (OB) and Office of Research and Standards (ORS) to discuss whether to accept or ask the applicant to repeat these two in vitro studies.

- [redacted] and shorter ejection time of test product will not have impact on clinical outcome, meeting attendees recommended ejection time study to be acceptable from BE perspective. However, the clinical significance of the statistical difference in the trigger force between the test and reference product needed further evaluation by a medical officer.

- The DCR has evaluated the applicant's comparative trigger (activation) force study results, overviewed other epinephrine autoinjector's data and referred the results of in-vitro testing of EpiPen injectors published in the literature and concluded that slightly greater force needed to activate the test device compared to the reference device does not raise any safety or efficacy concerns regarding the test product.

The reviewer agrees with the recommendation of DCR on considering the differences in mean trigger force of test and reference product to be clinically insignificant.

IV. DEFICIENCY COMMENT

None

V. RECOMMENDATIONS

The Division of Bioequivalence III (DBIII) agrees that the information submitted by Teva Pharmaceutical demonstrates that Epinephrine Injection USP, 0.3 mg/mL and 0.15 mg/mL, pre-filled syringe with auto-injector meets the requirements of Section 21 CFR § 320.24 (b) (6). The waivers of in vivo bioequivalence testing for the test products granted.

VI. APPENDIX

Consult Request

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	**REQUEST FOR CONSULTATION**

TO (*Division/Office*):	FROM:
Sarah Yim, M.D. Division of Clinical Review Office of Bioequivalence Office of Generic Drugs	Harikrishna Devalapally, Ph.D. Through Nilufer M. Tampal, Ph.D. Director, Division of Bioequivalence III (DBIII) Office of Bioequivalence Office of Generic Drugs

DATE	IND NO.	ANDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
September 25, 2017	N/A	090589	Bioequivalence Review	April 19, 2017

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Epinephrine Injection USP (Auto-Injector) 0.15 mg/0.3 mL & 0.3 mg/0.3 mL	High	Bronchodilator	November 30, 2017

NAME OF FIRM: Teva Pharmaceuticals USA, Inc.

REASON FOR REQUEST

I. GENERAL

☐ NEW PROTOCOL	☐ PRE--NDA MEETING	☐ RESPONSE TO DEFICIENCY LETTER
☐ PROGRESS REPORT	☐ END OF PHASE II MEETING	☐ FINAL PRINTED LABELING
☐ NEW CORRESPONDENCE	☐ RESUBMISSION	☐ LABELING REVISION
☐ DRUG ADVERTISING	☒ SAFETY/EFFICACY	☐ ORIGINAL NEW CORRESPONDENCE
☐ ADVERSE REACTION REPORT	☐ PAPER NDA	☐ FORMULATIVE REVIEW
☐ MANUFACTURING CHANGE/ADDITION	☐ CONTROL SUPPLEMENT	☐ OTHER (*SPECIFY BELOW*):
☐ MEETING PLANNED BY		

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

☐ DISSOLUTION	☐ DEFICIENCY LETTER RESPONSE
☐ BIOAVAILABILTY STUDIES	☐ PROTOCOL-BIOPHARMACEUTICS
☐ PHASE IV STUDIES	☒ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL	☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES	☐ SUMMARY OF ADVERSE EXPERIENCE
☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)	☐ POISON RISK ANALYSIS
☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP	

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Background:

DBIII is reviewing the generic application submitted by Teva Pharmaceuticals USA, Inc. for Epinephrine Injection USP (Auto-Injector), 0.15 mg/0.3 mL, 0.3 mg/0.3 mL (ANDA 090589) referencing EpiPen® (epinephrine) Injection (Auto-Injector), for intramuscular and subcutaneous use. There are no approved generics and pending applications referencing this RLD.

In the original submission dated 12/21/2007, the firm requested the waiver of *in vivo* bioequivalence (BE) study requirements under 21 CFR § 320.22(b)(1) for its test product, Epinephrine Injection USP, 0.15 mg/0.3 mL (Auto Injector Jr.) and 0.3 mg/0.3 mL (Auto Injector). Since the drug product is an autoinjector, in addition to the formulation comparison, the firm was asked to demonstrate device similarity by *in vitro* comparative performance tests for approval of this drug product[1]. The firm has provided the comparative summary results of the performance parameters between the test and RLD devices on 5/30/2008. In 2014, the firm reformulated its test product and submitted the component and composition of the re-formulated test product in the amendment dated 12/30/2014. The firm has also submitted the results of *in vitro* BE studies comparing the reformulated test product lot and RLD product lots. The *in vitro* study results that were submitted by Teva were conducted on single lot (30 units) of test product and 3 lots (10 units of each lot) of reference product. At the time of the review of the *in vitro* study results, Agency did not have specific recommendations for the statistical criteria of the *in vitro* study data. Therefore, the BE statistical analysis was based on the 90% confidence intervals of the T/R ratios being within the limits of 80.00%-120.00% (since the data from the multiple lots of the test product are needed to determine the 'between-lot variability' for PBE analysis, the reviewer did not perform PBE analysis at that time)[2]. The test and RLD devices comparison data submitted for different tests were deemed acceptable from the bioequivalence perspective prior to the posting of the product-specific guidance on Epinephrine Injection (Auto-Injector)[3].

In December 2016, the Agency drafted new product-specific guidance on Epinephrine Injection[4]. As per the current draft guidance recommendation for this drug product, the following *in vitro* studies should be conducted for the demonstration of bioequivalence between the test and reference products:

- Delivered Volume
- Ejection Time
- Trigger Force
- Extended Needle Length
- Needle integrity post-injection

At least three batches each of the test and reference products, with no fewer than 10 units from each batch should be used in conducting the above in vitro tests. Therefore, based on the current bioequivalence recommendations for this drug product, the firm's *in vitro* studies were deemed inadequate. The firm was asked to re-conduct *in vitro* tests to document the performance characteristics and submit the data for evaluation through information request[5]. In response to the information request,

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[1] DARRTS for ANDA 090589: TAMPAL, NILUFER M 03/11/2010 N/A 03/11/2010 REV-BIOEQ-01(General Review) Original-1 Archive

[2] GDRP for ANDA 090589- Bioequivalence Review- http://panorama.fda.gov/PanoramaDocMgmt/document/download/090026f880ae507f , Suman Dandamudi, 7/2/2015

[3] GDRP for ANDA 090589- Bioequivalence Review- http://panorama.fda.gov/PanoramaDocMgmt/document/download/090026f880ae507f , Suman Dandamudi, 7/2/2015

[4] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM534133.pdf, Recommended December 2016

[5] GDRP ANDA-090589-ORIG-1-AMEND-6, BE review: http://panorama.fda.gov/task/view?ID=3420f1160002bc9df9be4d40027ff2a6, Suman Dandamudi, A09058N006DB_ADD12302014; Date uploaded 1/25/2017

the firm conducted studies as per the guidance and submitted the results of the comparative performance testing of the test and RLD devices in the amendment dated April 19th, 2017. The in vitro equivalence tests were conducted using three lots of the test and RLD products with 20 units from each lot of both strengths. Delivered volume and extended needle length passed PBE analysis. However, PBE analysis results of ejection time and trigger force (activation force) data shows that the test device is not statistically equivalent to the reference device.

Since both ejection time and trigger force data failed to meet PBE analysis criteria, DBIII requested a meeting with the management of the Office of Bioequivalence (OB) and Office of Research and Standards (ORS) to discuss whether to accept or ask the firm to repeat these two in vitro studies[6].

(b) (4)

(b) (4) The fluid ejection time (dispense time) of the test product is within the RLD specification (NMT (b) (4)) for both the adult and junior devices. The difference in ejection time between the test and reference devices is (b) (4) As the mean fluid ejection time differences are small and also shorter ejection time of test product will not have impact on clinical outcome, meeting attendees recommended ejection time study to be acceptable from BE perspective.

Issue:

(b) (4)

Based on the reviewer's PBE analysis, the 95% upper bound of trigger force for adult (b) (4) and junior (b) (4) device are greater than 0 (PBE criterion is 95% upper bound must be ≤0).

(b) (4)

It should be noted that the trigger force (activation force) of the test product is within the RLD specification (b) (4) for both the adult and junior devices. The firm provided the following justification for considering the trigger force to be acceptable inspite of the observed differences between the test and reference products: *Irrespective of statistic equivalence, when used as intended, a* (b) (4) *difference in activation force will be imperceptible to the user. The test device distributions fall well within the historical reference device distribution. From the user perspective, a small difference in activation force does not prevent use of the product and therefore the test and reference product are considered equivalent.*

The firm further justified stating that there is variability in the RLD lots:
"The reference product, when compared to itself using data taken from a 2015 bioequivalence study (TR1421, this data were not submitted for Agency's review), also does not demonstrate bioequivalence

[6] GDRP, ANDA-090589-ORIGI-1-AMEND-6, Meeting minutes review, http://panorama.fda.gov/task/view?ID=5420f1160002bc9df9be4d40027ff2e6, Suman Dandamudi, 9/15/2017

(b) (4)

[redacted]

It should be noted that the DBIII had a meeting with the management of OB and ORS to discuss in vitro study results submitted by the firm specifically Ejection Time and Trigger Force studies. In this meeting dated 06/12/2017, attendees concluded that the clinical significance of the observed statistical difference in trigger force should be further evaluated by a medical officer.

Consult Request:

Based on the above-mentioned information, the Division of Bioequivalence III (DBIII) is seeking expert opinion from the Division of Clinical Review (DCR) in the Office of Bioequivalence (OB) on the following:

> Does the slightly greater force needed to activate the test device compared to reference device raise any safety or efficacy concern for the test product?

Attachment:
In Vitro BE Study Report

PD-RPT-0142_
PD-PLN-0015_ETeva™

Thank you for your consideration. Please address comments/questions to nilufer.tampal@fda.hhs.gov

SIGNATURE OF REQUESTER Harikrishna Devalapally, Ph.D.	METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

[7] GDRP, ANDA-090589-ORIGI-1-AMEND-6, http://panorama.fda.gov/task/view?ID=5420f1160002bc9df9be4d40027ff2e6, A090589DB_NA04192017.doc, Uploaded by Suman Dandamudi on 09/15/2017

Consult Response

CLINICAL CONSULTATION REVIEW
Division of Clinical Review (DCR)
Office of Bioequivalence (OB), Office of Generic Drugs (OGD)
Center for Drug Evaluation & Research (CDER)

Drug Product:	Epinephrine Injection USP (Auto-Injector), 0.15 mg/0.3 mL & 0.3 mg/0.3 mL
ANDA#/Applicant:	ANDA 090589 / Teva Pharmaceuticals USA, Inc.
RLD#/Approval Date: **Sponsor:**	EpiPen® (0.3 mg), EpiPen Jr.® (0.15mg) NDA 019430 / December 22, 1987 Mylan Specialty LP
Clinical Primary Reviewer:	Sarah Yim, M.D. Director, Division of Clinical Review (DCR)
Tertiary Reviewer:	Same
To:	Division of Bioequivalence III
Reason for Consult:	Does the slightly greater force needed to activate the test device compared to reference device raise any safety or efficacy concern for the test product?
Date of Submission:	April 19, 2017
Date Consult Received:	October 11, 2017
Date of Completion:	November 7, 2017
Conclusion:	(b) (4) (b) (4) Given that EpiPen/EpiPen Jr labeling only specifies to "push firmly," it is likely that an imprecise and relatively wide range of activation forces would be observed, and that the range would include the activation force numbers observed with the test and RLD devices. Both sets of activation force numbers are well within the capability of likely users of the devices; and both sets of numbers are in the typical range of activation forces for this type of autoinjector. Therefore, DCR concludes the slightly greater force needed to activate the test device compared to the reference device does not raise any safety or efficacy concerns regarding the test product.
Deficiency Classification:	☐ Major ☐ Minor ☒ N/A (Review is Adequate)

1 Executive Summary:

DCR concludes that the slightly greater force needed to activate the test device compared to the reference device does not raise any safety or efficacy concerns regarding the test product, based on the following: 1) given that EpiPen/EpiPen Jr labeling only specifies to "push firmly," it is likely that an imprecise and relatively wide range of activation forces would be observed, and that the range would include the activation force numbers observed with the test and RLD devices; 2) average activation force values for the test products are consistent with the range considered acceptable based on the literature (e.g., 5-10 lbf), and are consistent with published results for other approved epinephrine autoinjectors (b) (4) 3) the average activation force for the test products is well within the capability of expected users of the products, even younger self-administrators (e.g., 8-12 year olds can generate (b) (4); 4) small differences in activation forces between the test and RLD would not be particularly notable to the user given that the context of use is typically infrequent emergency-use; and 5) activation force specification ranges for approved epinephrine autoinjectors reflect the lack of precision needed within a clinically acceptable range. Within that range, a difference of (b) (4) would not be a concern.

2 Regulatory Background:

The regulatory background of the RLD and ANDA is extensive and is beyond the scope of this consultation. DCR has provided previous consults for ANDA 090589 on 4/25/13 regarding the difference in needle length and on 9/6/16 and 10/29/15 regarding the level of inactive ingredient sodium tartrate dihydrate.

2.1 Orange Book Information

EpiPen and EpiPen Jr is one of three marketed brands of epinephrine autoinjectors in the Orange Book that come in the 0.3 mg and 0.15 mg strengths per delivery, and all are Reference Listed Drugs (RLD) (see Table 1 below). No generic epinephrine autoinjectors are currently approved.

Table 1: Orange Book Currently Approved Applications for Epinephrine Autoinjectors

Active ingredient	Proprietary Name	Application No. / Holder	Dosage Form	Route	Strength		
Epinephrine	EpiPen	NDA 019430 Mylan Specialty LP	Injectable	IM; SC	EQ 0.3 mg / delivery	RLD	RS
Epinephrine	EpiPen Jr	NDA 019430 Mylan Specialty LP	Injectable	IM; SC	EQ 0.15 mg / delivery	RLD	RS
Epinephrine	Adrenaclick	NDA 020800 Impax Laboratories Inc.*	Injectable	IM; SC	EQ 0.3 mg / delivery	RLD	RS
Epinephrine	Adrenaclick	NDA 020800 Impax Laboratories Inc.	Injectable	IM; SC	EQ 0.15 mg / delivery	RLD	RS
Epinephrine	Auvi-Q	NDA 201739 Kaleo Inc.	Injectable	IM; SC	EQ 0.3 mg / delivery	RLD	RS
Epinephrine	Auvi-Q	NDA 201739 Kaleo Inc.	Injectable	IM; SC	EQ 0.15 mg / delivery	RLD	RS

Source: Search on 10/22/17, website: https://www.accessdata.fda.gov/scripts/cder/ob/search_product.cfm
RLD=Reference Listed Drug; RS=Reference Standard. All of the above are currently rated "BX."
*NDA 020800 also previously included Twinject 0.3 mg and 0.15 mg epinephrine autoinjectors, which have been discontinued.

2.2 Labeling

The currently approved prescribing information[1] and patient/caregiver instructions for use[2] for EpiPen and EpiPen Jr were reviewed and are notable for the following:

1) Although there is a tiered weight-based dosing recommendation that separates the target patient population of EpiPen 0.3 mg (patients greater than or equal to 30 kg/66 lbs) from EpiPen Jr 0.15 mg (patients 15 to 30 kg/33 to 66 lbs), the label is silent regarding the abilities or characteristics of the person administering/self-administering the injection.
2) The patient/caregiver instructions for use are also silent regarding the abilities or characteristics of the person administering/self-administering the injection. The instruction is to "Swing and push the auto-injector **firmly** until it 'clicks'."

The lack of specificity regarding strength requirements for using the EpiPen and EpiPen Jr, as well as the lack of specificity regarding how "firmly" one must push the auto-injector, suggests a lack of precision and implies the acceptability of activation forces within a certain range; i.e., what an average person mature enough to use one of these injectors might consider to be pushing "firmly." What this range might encompass is considered further in Section 3 below.

3 Review

General expectations for activation force range for epinephrine autoinjectors

Like the other currently approved epinephrine autoinjectors in the U.S., EpiPen is a cartridge-based autoinjector. With this type of device, after the safety cap has been removed, the injector is activated by holding the outer housing and pressing the device tip onto the tissue, allowing the outer housing to move against the inner housing. After activation, the released spring moves the cartridge and the attached needle to its end position, which then pierces through the closure and into the tissue. Application of an adequate activation force and maintaining this throughout the injection compresses subcutaneous tissue, which facilitates intramuscular delivery.[3] While subcutaneous delivery is an approved route of administration, intramuscular delivery of epinephrine is more desirable in that achieves peak concentrations faster.[4] The activation force of the typical epinephrine autoinjector is generally designed to be in the range of 5 to 10 lbs.[5] The main consideration in the decision to allow self-administration of autoinjectors with children is not the ability to generate the force needed to activate the autoinjector or control the recoil, but rather, judgment and maturity factors, and thus there are no standardized age recommendations.[4] In fact, children as young as 8 to 12 years of age can generate more than adequate forces, e.g., in the range of 38 to 43 N (b) (4)[6], depending on the shape of the grip. Therefore, junior version autoinjectors typically do not differ in activation or recoil forces compared to adult

[1] https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/019430s067lbl.pdf , supplement 67, approved 4/28/17
[2] https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/019430s061lbl.pdf , supplement 61, approved 5/18/16
[3] Frew AJ, "What are the 'ideal' features of an adrenaline (epinephrine) auto-injector in the treatment of anaphylaxis?" Allergy 2011; 66:15-24
[4] Sicherer SH, Simons FER, AAP Section on Allergy and Immunology. Epinephrine for First-aid Management of Anaphylaxis. Pediatrics. 2017; 139(3):e20164006
[5] Dennerlein JT, "Anaphylaxis Treatment: Ergonomics of Epinephrine Autoinjector Design." The American Journal of Medicine (2014) 127, S12-S16.
[6] Barbir A et al., "Designing Auto-Injectors for Children: Effect of Form Factor on the Human Factors of Efficient Drug Delivery." J Allergy and Clin Immunol February 2015, 135 (2): supplement AB210. Abstract 678.

version autoinjectors, though needle length is a unique consideration, and has been addressed in a separate DCR consult.

The results of in-vitro testing of EpiPen injectors published in the literature have generally ranged closer to [redacted] in one article and at an average of 23.4 N (5.26 lbf)[8] in another. Similar activation forces were observed with Adrenaclick and Twinject injectors, as shown in Table 2 below. Activation forces are lower with syringe-based injectors (e.g. 8-[redacted])[7], but no epinephrine syringe-based injectors are approved in the U.S.

Table 2
TABLE E1. Descriptive statistics for EAIs and EAITDs

	Actual				Trainer			
Injector	No.	Mean	SD	95% CI	No.	Mean	SD	95% CI
EpiPen								
Activation	5	23.4 N	1.9	21.7-25.1	5	28.0 N	5.8	22.9-33.1
Recoil	5	42.2 N	4.0	38.7-45.7	5	13.3 N	3.2	10.5-16.1
Adrenaclick								
Activation	5	22.6 N	5.7	17.6-27.6	5	16.0 N	0.6	15.5-16.5
Recoil	5	15.4 N	4.3	11.6-19.2	5	13.1 N	1.4	11.9-14.3
Twinject								
Activation	5	27.1 N	2.6	24.8-29.4	5	16.5 N	0.9	15.7-17.3
Recoil	5	18.9 N	1.9	17.2-20.6	5	13.7 N	1.0	12.8-14.6

Source: Jacobsen et al., J Allergy Clin Immunol., 129(4):1143-5. Conversion factor: 1 N = 0.22481 lbf.

Teva proposed epinephrine autoinjector results vs. RLD

As noted in the consult request, the [redacted]

Based on the population bioequivalence (PBE) analysis performed by the Division of Bioequivalence III (DBIII) reviewer, the 95% upper bound of trigger force for adult [redacted] and junior [redacted] device are greater than 0 (PBE criterion is 95% upper bound must be ≤0), which is not passing, as shown in Table 3 below.

[redacted]

[7] Schwirtz A and H Seeger, "Are adrenaline autoinjectors fit for purpose? A pilot study of the mechanical and injection performance characteristics of a cartridge versus a syringe-based autoinjector." Journal of Asthma and Allergy 2010 (3):159-167

[8] Jacobsen RC et al. "Comparing activation and recoil forces generated by epinephrine autoinjectors and their training devices." J Allergy Clin Immunol 2012, 129 (4): 1143-5

However, the firm provided justification for the slightly higher average trigger/activation force for the test product, which included: 1) that a (b) (4) difference in force would not be clinically meaningful to the user, and 2) that there is variability in the RLD lots, as shown by their own activation force data on the RLD in 2015 and 2017 BE studies (see Table 4 below). They reason that if the 2015 RLD would not pass PBE compared to the 2017 RLD, then their test product would not pass either, since they developed their product to be equivalent to the 2015 RLD product. They also conclude that as both 2015 and 2017 RLD versions were approved to be marketed, that any differences between them would not be considered clinically significant.

As discussed at an FDA internal meeting between Office of Bioequivalence (OB) and Office of Research and Standards (ORS) on 6/12/17, the RLD activation force specification for both the adult and junior devices is (b) (4) and specifications for other epinephrine autoinjectors are also similarly broad (b) (4) so the variability in RLD activation force noted by the ANDA sponsor would fall well within this range and would not be unexpected. This lends further credence to the ANDA sponsor's data on the RLD.

(b) (4)

Other clinical considerations:

Other considerations that impact the potential acceptability of the proposed difference in activation force pertain to the context of use. Specifically, EpiPen and EpiPen Jr are not chronically administered products, so their activation forces are not forces to which patients or caregivers would likely become very accustomed. These are emergency-use medications that are used infrequently and sporadically, so it is unlikely that a patient or caregiver would be highly attuned to a specific activation force, as long as activation does not require a very large or very small amount of effort.

4 Conclusions:

(b) (4)

(b) (4) DCR concludes that the slightly greater force needed to activate the test device compared to the reference device does not raise any safety or efficacy concerns regarding the test product.

The rationale for this conclusion is based on the following:

1) Given that EpiPen/EpiPen Jr labeling only specifies to "push firmly," it is likely that an imprecise and relatively wide range of activation forces would be observed, and that the range would include the activation force numbers observed with the test and RLD devices;
2) The average activation force for the test products are well within the range considered acceptable based on the literature (b) (4) and are consistent with published results for other approved epinephrine autoinjectors (b) (4)
3) The average activation force for the test products are well within the capability of expected users of the products, even younger self-administrators (e.g., 8-12 year olds can generate (b) (4).
4) Small differences in activation forces between the test and RLD would not be particularly notable to users given that the product is used infrequently/sporadically in emergency use situations.
5) Acceptable activation force specification ranges for approved epinephrine autoinjectors reflect the lack of precision needed within a clinically acceptable range. Within that range, a difference of (b) (4) would not be a concern.

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 090589

APPLICANT: Teva Pharmaceuticals USA

DRUG PRODUCT: Epinephrine Injection USP (Auto-Injector), 0.3 mg/0.3 mL and 0.15 mg/0.3 mL

The Division of Bioequivalence III (DBIII) has completed its review of your submission(s) acknowledged on the cover sheet and has no further questions at this time.

The bioequivalence comments provided in this communication are comprehensive as of issuance. However, these comments are subject to revision if additional concerns raised by chemistry, manufacturing and controls, microbiology, labeling, other scientific or regulatory issues or inspectional results arise in the future. Please be advised that these concerns may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

{See appended electronic signature page}

Nilufer M. Tampal, Ph.D.
Director, Division of Bioequivalence III
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

VII. OUTCOME

http://cdsogd1/bioprod

Reviewer: Harikrishna Devalapally **Date Completed:**
Verifier: , **Date Verified:**
Division: Division of Bioequivalence
Description: Epinephrine Injection (Auto-Injector)

Items:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Score*	*Subtotal*
32946	11/8/2017	BIO	Consult Review (For Consults to DBs) [1]	1	1
32946	11/8/2017	Parallel	Review of the Consult Response and Formal Consult to DB [1]	1	1
32946	11/13/2017	BIOQUALITY	Quality Assessment [1-5]	5	5

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	090589		
Drug Product Name	Epinephrine Injection USP (Auto-Injector)		
Strength(s)	0.15 mg/0.3 mL, 0.3 mg/0.3 mL		
Applicant Name	Teva Pharmaceuticals USA, Inc.		
Address	425 Privet Road, Horsham, PA 19044		
Applicant's Point of Contact	Cory Wohlbach		
Contact's Telephone Number	215-293-6519		
Contact's Fax Number	215-591-8812		
Original Submission Dates	December 21, 2007 May 30, 2008 (Amendment) May 22, 2009 (Amendment) July 31, 2013 (in vitro) December 30, 2014 (re-formulation) May 20, 2015 (Amendment) March 08, 2016 (Post Complete Response Meeting Request)		
Submission Date of Amendment Under Review	April 19, 2017		
First Generic	**Yes**		
Reviewer	Harikrishna Devalapally, Ph. D.		
Secondary Reviewer	Suman Dandamudi, Ph. D.		
Tertiary Reviewer	Ke Ren, Ph. D.		
Overall Review Result	**Inadequate (Pending Clinical Consult Response)**		
Revised/New Draft Guidance Generated as Part of Current Review	**Yes**		
Deficiency Classification	☐**Major** ☐**Minor** ☒**Not Applicable**		
Bioequivalence study tracking/supporting document #	**Study/test type**	**Strength**	**Review Result**
48	**In Vitro Tests**	**0.3 mg/0.3 mL and 0.15 mg/0.3 mL**	**Inadequate pending outcome of clinical consult**

REVIEW OF AN AMENDMENT

1 EXECUTIVE SUMMARY

This is a review of the BE study amendment dated 04/19/2017 (supporting document # 48).

In the original submission, the firm requested a waiver of *in vivo* bioequivalence study requirements under 21 CFR § 320.22(b)(1) for its test products, Epinephrine Injection

USP, 0.15 mg/0.3 mL (Auto Injector Jr.) and 0.3 mg/0.3 mL (Auto Injector). The submission references NDA 019430, EpiPen® and EpiPen® Jr (epinephrine) Auto-Injector, 0.3 mg/0.3 mL and 0.15 mg/0.3 mL by Mylan Speclt. Since the drug product is an auto-injector, in addition to the formulation comparison, device similarity by *in vitro* comparative performance should be demonstrated for approval of this drug product. Since the firm did not provide the individual data for the in vitro tests to demonstrate comparable performance between the test and RLD devices, the firm was asked to conduct in vitro tests to document the performance characteristics and submit the data for evaluation[1].

In the amendment dated 12/30/2014, the firm has submitted the re-formulated test product. The re-formulated test product was NOT qualitatively (Q1) and quantitatively (Q2) the same as RLD product. The test product contains Sodium Tartrate Dihydrate as (b) (4) whereas the RLD product contains no (b) (4). In addition, the firm's re-formulated test product (0.4 mg) contains considerably lower quantity of Sodium Metabisulfite than in the RLD formulation (0.5 mg). Based on the response from DCR and OPQ consult requests, DBIII considered the firm's proposed test formulations to be adequate.

The firm has also submitted the results of in vitro bioequivalence (BE) studies comparing the test and RLD product devices. The test and RLD devices comparison data submitted for different tests were deemed acceptable prior to posting the product-specific guidance for Epinephrine Injection (Auto Injector).

In December 2016, the Agency drafted new product-specific guidance on Epinephrine Injection[2]. As per the current draft guidance recommendation for this drug product, the following in vitro studies should be conducted for the demonstration of bioequivalence between the test and reference products:

- Delivered Volume
- Ejection Time
- Trigger Force
- Extended Needle Length
- Needle integrity post-injection

The in vitro study results that were submitted by the firm were conducted on single lot (30 units) of test product and 3 lots (10 units of each lot) of reference product. At the time of the review of the in vitro study results, Agency did not have specific recommendations for the statistical criteria of the in vitro study data. Therefore, the BE statistical analysis was based on the 90% confidence intervals of the T/R ratios being within the limits of 80.00%-120.00% (since the data from the multiple lots of the test product are needed to determine the 'between-lot variability' for PBE analysis, the PBE analysis did not perform at that time). In addition, the firm used the test device to conduct pre-study

[1] DARRTS for ANDA 090589: TAMPAL, NILUFER M 03/11/2010 N/A 03/11/2010 REV-BIOEQ-01(General Review) Original-1 Archive

[2] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM534133.pdf, Recommended December 2016

method validations for all the in vitro studies. Therefore, based on the current bioequivalence recommendations for this drug product, the firm's in vitro studies were deemed inadequate. The firm was asked to conduct in vitro tests to document the performance characteristics and submit the data for evaluation.

Teva Pharmaceuticals submitted its responses to the deficiency comments made by the Division of Bioequivalence III (DBIII) in the Information Request (IR) via email dated February 1st, 2017[3]. In response to the IR, in the current amendment dated April 19th, 2017, the firm re-submitted the results of the comparative performance testing of the test and RLD devices. As requested, the firm also conducted pre-study method validations for all the in-vitro tests using the reference product as per the current draft guidance on Epinephrine Injection. The in vitro equivalence tests were conducted using three lots of the test and RLD devices with 20 units from each lot of both strengths. PBE analyses were performed for delivered volume, ejection time, trigger force and extended needle length as per the recommendations in the draft guidance. The test and RLD devices are considered to be bioequivalent with respect to delivered volume and exposed needle length. Needle integrity post injection test was conducted at a maximum of (b) (4) from the labeled injection angle and is considered the reasonable worst case along with (b) (4) and (b) (4) from the labeled injection angle. Based on the results, it is evident that all the test adult and junior devices triggered successfully at all combinations of angles and materials. Therefore all aspects of needle integrity are considered acceptable. However, the test product failed to meet PBE criteria for ejection time and trigger force.

Since both fluid ejection time and trigger force data failed to meet PBE analysis criteria, the DBIII requested a meeting with the management of the Office of Bioequivalence (OB) and Office of Research and Standards (ORS) to discuss whether to accept or ask the firm to repeat these in vitro studies. (b) (4) (b) (4) and also shorter ejection time of test product will not have impact on clinical outcome, meeting attendees recommended ejection time study to be acceptable from BE perspective. Since the test devices required slightly higher force needed to trigger the device, based on the recommendation from meeting attendees, DBIII sent consult request to DCR to evaluate the impact of this trigger force difference on the safety and efficacy of the test device[4].

The BE portion of the application is **inadequate** pending clinical consult response from DCR.

NOTE TO REGULATORY PROJECT MANAGER (RPM): Currently there is a pending clinical consult with DCR.

[3] DARRTS for ANDA 090589: SOLANA-SODEINDE, DIANA A 03/29/2010 FAX 03/29/2010 COR-ANDADE-01(Bio Incomplete Deficiencies) Original-1 Archive
[4] GDRP ANDA 090589 http://panorama.fda.gov/document/view?ID=59944fff0042b3b1160e5afd96e3d808

2 TABLE OF CONTENTS

3 BACKGROUND

1. Teva Pharmaceuticals USA submitted ANDA 090589 for its test product, Epinephrine Injection (auto-injector) 0.15 mg/0.3 mL and 0.3 mg/0.3 mL. The submission references NDA 019430, EpiPen® (epinephrine) Injection Auto-Injector, 0.3 mg and EpiPen Jr® (epinephrine) Injection Auto-Injector, 0.15 mg from Mylan Speclt.

2. In the original submission dated 12/21/2007, the firm requested the waiver of in vivo bioequivalence study requirements under 21 CFR § 320.22(b)(1) for its test products, Epinephrine Injection USP, 0.15 mg/0.3 mL (Auto Injector Jr.) and 0.3 mg/0.3 mL (Auto Injector).

3. Since the drug product is an autoinjector, in addition to the formulation comparison, device similarity by *in vitro* comparative performance should be demonstrated for approval of this drug product. The firm has provided the comparative summary results of the performance parameters between the test and RLD devices on 5/30/2008. The original application was accepted for filing on 11/21/2008[5].

[5] DARRTS for ANDA 090589: MARGAND, IAIN, 01/02/2009, MAIL, 01/02/2009, COR-ANDAFILE-01(Filing Acknowledgment (General)), Original-1

4. The OGD has requested the division of pulmonary and allergy products (DPAP)'s feedback regarding the mechanism of action (MOA) of the innovator's autoinjector compared to TEVA's proposed auto-injector[6]. On 11/13/2008, DPAP reviewed OGD's request and concluded that mechanism of action of the TEVA auto-injector product and the EpiPen® auto-injector product is the same[7].

5. In the CR letter dated 4/30/2009, the Agency communicated the firm that the information and data provided in the original submission dated December 21, 2007, and in the addendum dated May 30, 2008 do not support claim that the TEVA' s proposed auto-injector intended for subcutaneous delivery of epinephrine is comparable to the EpiPen® Autoinjector[8].

6. Since the firm did not provide the individual data for the in vitro tests to demonstrate comparable performance between the test and RLD devices, the firm was asked to conduct suitable in vitro tests to document the performance characteristics and submit the data for evaluation[9].

7. On 04/04/2012, an inter-center consultation request was submitted to CDRH for the review of the firm's submitted protocol[10]. In the amendment dated 1/20/2012, the firm has submitted the protocol for the human factors study. The CDRH has conducted the review of this protocol and provided its recommendations[11]. The recommendations were conveyed to the firm by Division of Chemistry[12].

8. In the amendment dated 12/30/2014, the firm has submitted the Human Factor Study results on the re-designed device. On 06/25/2015, an inter-center consultation request was submitted to CDRH and OSE for the review of the firm's submitted results[13]. OSE has reviewed and provided comments on the submitted human factor study results on 2/11/2016[14].

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[6] DARRTS for ANDA 090589: LIU, THERESA C, 10/15/2008, N/A, 10/15/2008, FRM-CONSULT-01(General Consult Request), Original-1

[7] DARRTS for ANDA 090589: GILBERT MCCLAIN, LYDIA I, 11/13/2008, N/A, 11/13/2008, REV-CLINICAL-03(General Review), Original-1

[8] DARRTS for ANDA 090589: CHUH, EUNJUNG E, 04/30/2009, MAIL, 04/30/2009, COR-ANDAACTION-09(Complete Response), Original-1

[9] DARRTS for ANDA 090589: TAMPAL, NILUFER M 03/11/2010 N/A 03/11/2010 REV-BIOEQ-01(General Review) Original-1 Archive

[10] DARRTS for ANDA 090589: DARJ, MIKE 04/04/2012 N/A 04/04/2012 FRM-CONSULT-02 (Inter-center/Combination Products Consult) Original-1 Archive

[11] DARRTS for ANDA 090589: TRAN, TRANG Q 05/07/2012 N/A 05/07/2012 FRM-ADMIN-01(Memorandum to File) Original-1 Archive

[12] DARRTS for ANDA 090589: DARJ, MIKE 12/20/2012 N/A 12/20/2012 REV-QUALITY-03(General Review) Original-1 Archive

[13] DARRTS for ANDA 090589: HUANG, XIAOHUA 06/25/2015 N/A 06/25/2015 FRM-CONSULT-06(OSE Consult (Except Proprietary Name Reviews)) Original-1 Archive

[14] DARRTS for ANDA 090589: OWENS, LISSA C, 02/11/2016, N/A, 02/11/2016, REV-SURVEPI-24(Human Factors Review), Original-1

9. In the amendment dated 9/26/2016, the firm has submitted the Human Factor Study results. On 10/6/2016, an consultation request was submitted to CDRH and OSE for the review of the firm's submitted results[15,16]. OSE has reviewed and deemed adequate on 3/10/2017[17].

10. On 3/20/2013, OPQ requested DCR to assess if there is a clinical concern regarding the longer needle length of Teva Pharmaceuticals' proposed generic epinephrine auto-injector, compared to the needle length of the RLD, EpiPen®[18]. DCR reviewed and concluded that the slightly longer needle length of Teva's product compared to the RLD is not clinically significant, and should not be a factor in the approval of ANDA 90589 as a generic to EpiPen®[19].

11. In the amendment dated 12/30/2014, the firm has submitted the re-formulated test product. The re-formulated test product is NOT qualitatively (Q1) and quantitatively (Q2) the same as RLD product. The test product contains sodium tartrate dihydrate as (b) (4) whereas the RLD product contains no (b) (4) In addition, the firm's re-formulated test product (0.4 mg) contained considerably lower quantity of Sodium Metabisulfite than in the RLD formulation (0.5 mg). The firm has also submitted the results of in vitro bioequivalence (BE) studies comparing the test and RLD product devices. The test and RLD devices comparison data submitted for different tests were acceptable from the bioequivalence perspective[20].

12. On 6/25/2015 a consultation request was submitted to DCR to determine whether the amount of sodium tartrate dihydrate used in the formulation of Teva's Epinephrine Injection, 0.3 mg/0.3 mL and 0.15 mg/0.3 mL should be a safety concern when administered subcutaneously[21].

13. DCR has concluded that the firm should consider re-formulating its test product since sodium tartrate dihydrate is considered as a novel excipient for the subcutaneous

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[15] DARRTS for ANDA 090589: HUANG, XIAOHUA 10/06/2016 N/A 10/06/2016 FRM-CONSULT-06 (OSE Consult (Except Proprietary Name Reviews)) Original-1 Archive
[16] DARRTS for ANDA 090589: SINKS, MICHAEL A, 10/07/2016, N/A, 10/07/2016, FRM-CONSULT-01 (General Consult Request), Original-1
[17] DARRTS for ANDA 090589: WANG, YIFAN, 03/10/2017, N/A, 03/10/2017, CONSULT REV-BIOMETRICS-01(General Consult Review) , Original-1
[18] DARRTS for ANDA 090589: DARJ, MIKE, 03/20/2013, N/A, 03/20/2013, FRM-CONSULT-01 (General Consult Request), Original-1
[19] SEIBEL, DEBORAH J, 04/29/2013, N/A, 04/29/2013, CONSULT REV-CLINICAL-01(General Consult Review), Original-1
[20] GDRP for ANDA 090589- Bioequivalence Review- http://panorama.fda.gov/PanoramaDocMgmt/document/download/090026f880ae507f , Suman Dandamudi, 7/2/2015
[21] GDRP for ANDA 090589, Clinical Consult Request: http://panorama.fda.gov/PanoramaDocMgmt/document/download/090026f880ae5418, Suman Dandamudi, 7/2/2015

route of administration and there were no approved drug products administered subcutaneously that contain sodium tartrate dihydrate as an excipient[22].

14. On February 23, 2016 the deficiency related to the inactive ingredient, sodium tartrate dihydrate was conveyed to the firm through a Complete Response Letter[23] and DBIII deemed the application to be inadequate[24].

15. The OPQ has submitted inter-center consultation request to CDRH on 6/25/2015 for the evaluation of the Teva's re-designed auto-injector device (Vibex (b) (4)[25].On 10/27/2015, CDRH has provided its response to the consultation request regarding the review of the device. The CDRH has conducted thorough review of the device and its components and listed the deficiencies to be conveyed to the firm[26]. The deficiencies related to the device were sent to the firm in the Complete Response letter dated April 20, 2016 by Office of Pharmaceutical Quality.

16. The OPQ has submitted inter-center consultation request to CDRH on 9/2/2016 to assess the cGMP compliance of the device manufacturing facility (b) (4) (b) (4) and determine whether inspection is needed or if the facility is acceptable[27]. On 1/4/2017, Office of Compliance (OC) has provided its response to the consultation request regarding the inspection status of the site. Inspectional History –An analysis of the firm's inspection history over the past 2 years showed that an inspection conducted on (b) (4). The inspection covered medical device QS requirements and was classified NAI[28].

17. In amendment dated 3/8/2017, the firm proposed proprietary names (b) (4) (epinephrine injection, USP) 0.3 mg and (b) (4) (epinephrine injection, USP) 0.15 mg. On 3/22/2017, the firm's proposed names were evaluated by Office of Prescription Drug Promotion (OPDP) and determined that the proposed proprietary names were not acceptable as they would misbrand the proposed products[29].

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[22] GDRP for ANDA 090589, Consult Response: http://panorama.fda.gov/task/view?ID=5420f1160002bcdbd808308629e66727, 9/7/2016 (reviewed on 10/29/2015)
[23] GDRP for ANDA 090589: Final Decision- http://panorama.fda.gov/task/view?ID=56e1db890065a9c90d34d6a8b5cf6e6e, Jessica Kreger, 4/20/2016.
[24] GDRP for ANDA 090589: Consult Response Review- http://panorama.fda.gov/PanoramaDocMgmt/webhooks/viewdownload?id=090026f880c1b943, Suman Dandamudi, 11/16/2015
[25] DARRTS for ANDA 090589: HUANG, XIAOHUA 06/25/2015 N/A 06/25/2015 FRM-CONSULT-02 (Inter-center/Combination Products Consult) Original-1
[26] GDRP for ANDA 090589: ANDA 090589.TEVA.Epipen.CDRH Engineering Evaluation. Stervens.pdf, Date uploaded 10/27/2015. http://panorama.fda.gov/task/view?ID=5420f1160002bbfe419982883f9a1a75
[27] DARRTS for ANDA 090589: HUANG, XIAOHUA 09/02/2016 N/A 06/25/2015 FRM-CONSULT-02 (Inter-center/Combination Products Consult) Original-1
[28] DARRTS for ANDA 090589: NGUYEN, JENNIFER H, 01/04/2017, N/A, 01/04/2017, FRM-ADMIN-01(Memorandum to File), Original-1
[29] DARRTS for ANDA 090589: OWENS, LISSA C, 03/23/2017, N/A, 03/23/2017, REV-SURVEPI-10(Proprietary Name Review), Original-1

18. On March 8, 2016, the firm submitted a request for a Post Complete Response Meeting Request (post CR MR) with the OGD for clarification of sodium tartrate dihydrate to be considered as novel excipient for the subcutaneous route of administration[30]. Agency has accepted firm's meeting request and determined that written response would be the most appropriate to discuss the deficiencies noted in CR[31].

19. In the CR letter, the firm has provided the justification for the use of sodium tartrate dehydrate in the test formulation that included: Toxicity Study Report DS-2014-062, Inactive Ingredient Database (IID) reference for (b) (4) in an approved product, Signifor and thus request the Agency to not consider as a novel excipient for subcutaneous route of administration.

20. Based on the information provided by the firm in their submission dated March 8, 2016, the DBIII re-evaluated the amount of sodium tartrate dihydrate in the test formulation and agrees with the firm that the amount of this ingredient is within the acceptable limits for subcutaneous administration based on the FDA's Inactive Ingredient database[32].

21. However, the listed drug product Signifor® (pasireotide diasparate) Solution is indicated for the treatment of adult patients with Cushing's disease for whom pituitary surgery is not an option or has not been curative. As per the labeling, no studies have been performed and safety and effectiveness of Signifor® have not been established in pediatric patients[33]. Whereas the current test product Epinephrine Injection USP, 0.15 mg/0.3 mL (Auto Injector Jr.) and 0.3 mg/0.3 mL (Auto Injector) has pediatric use as per the labeling[34].

22. Based on the above-mentioned information, the DBIII requested expert opinion from the DCR[35] to evaluate if the amount of sodium tartrate dihydrate used in the formulation of Teva's Epinephrine Injection, 0.3 mg/0.3 mL and 0.15 mg/0.3 mL poses a safety concern for adult and pediatric patients, when administered subcutaneously?

23. (b) (4)

[30] GDRP for 090589: 03/08/2016: Meeting/Meeting Request General Information-1
[31] GDRP for 090589: http://panorama fda.gov/task/view?ID=56e1db890065a97a851fcca9c0431840, Jessica Kreger, 3/21/2016.
[32] GDRP for ANDA 090589: Post CR MR Review-http://panorama.fda.gov/PanoramaDocMgmt/webhooks/viewdownload?id=090026f880cf427c, Ke Ren, 5/13/2016
[33] Drugs@FDA, http://www.accessdata fda.gov/drugsatfda_docs/label/2015/200677s002lbl.pdf
[34] Drugs@FDA, http://www.accessdata fda.gov/drugsatfda_docs/label/2016/019430s061lbl.pdf
[35] GDRP for 090589: http://panorama fda.gov/task/view?ID=5420f1160002bc9df9be4d40027ff2e6, Ke Ren, 7/8/2016.

24 (b) (4)

25

26. In addition to the consult request submitted to the DCR, DBIII also requested the Office of Pharmaceutical Quality (OPQ) to comment whether firm's justification (b) (4) (b) (4) is acceptable[39].

27. In response to DBIII consult request, the OPQ reviewer has confirmed that at a test product (b) (4) (b) (4).

[36] GDRP for 090589: http://panorama fda.gov/task/view?ID=578d28ef0036c6f42415a8448c33752a, Nitin Patel, 7/18/2016.
[37] GDRP for 090589: http://panorama fda.gov/task/view?ID=578d28f00036c6fbfb5a80e1d2464177, Mike Darj, 8/19/2016.
[38] GDRP for 090589: http://panorama fda.gov/task/view?ID=5776aaa60042f92d3c68f61ac1cb4cd5, Karen Feibus, 9/7/2016.
[39] GDRP for 090589: http://panorama fda.gov/task/view?ID=5420f1160002bc9df9be4d40027ff2e6, Ke Ren, 7/7/2016.
[40] GDRP for 090589: http://panorama fda.gov/task/view?ID=5776a72d0042c7fbc115f020696f84cc, Mike Darj, 8/10/2016.

28. Based on the above information from consult responses, DBIII agrees with the DCR and OPQ recommendation and considered the firm's proposed test formulations to be adequate[41].

29. The in vitro study results that were submitted previously (on 12/30/2014) by Teva were conducted on single lot (30 units) of test product and 3 lots (10 units of each lot) of reference product. At the time of the review of the in vitro study results, Agency did not have specific recommendations for the statistical criteria of the in vitro study data. Therefore, the BE statistical analysis was based on the 90% confidence intervals of the T/R ratios being within the limits of 80.00%-120.00% (since the data from the multiple lots of the test product are needed to determine the 'between-lot variability' for PBE analysis, the PBE analysis did not perform at that time). In addition, the firm used the test device to conduct pre-study method validations for all the in vitro studies[16].

30. In December 2016, the Agency drafted new product-specific guidance on Epinephrine Injection[42]. As per the current draft guidance recommendation for this drug product, the following in vitro studies should be conducted for the demonstration of bioequivalence between the test and reference products:

    - Delivered Volume
    - Ejection Time
    - Trigger Force
    - Extended Needle Length
    - Needle integrity post-injection

    At least three batches each of the test and reference products, with no fewer than 10 units from each batch should be used in conducting the above in vitro tests. Method validation should be performed using the reference product, and the lot number(s) for the reference products used for the validation should be provided. Therefore, based on the current bioequivalence recommendations for this drug product, the firm's in vitro studies were deemed inadequate. The firm was asked to conduct in vitro tests to document the performance characteristics and submit the data for evaluation[43].

31. The BE deficiencies were communicated to the firm in IR format via email on February 1st, 2017[44].

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[41] GDRP ANDA-090589-ORIG-1-AMEND-6, BE review: http://panorama.fda.gov/task/view?ID=5420f1160002bc9df9be4d40027ff2e6 Suman Dandamudi, A09058N006DB_CRR03082016; Date uploaded 10/19/2016

[42] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM534133.pdf, Recommended December 2016

[43] GDRP ANDA-090589-ORIG-1-AMEND-6, BE review: http://panorama.fda.gov/task/view?ID=5420f1160002bc9df9be4d40027ff2e6, Suman Dandamudi, A09058N006DB_ADD12302014; Date uploaded 1/25/2017

[44] EDR, ANDA 090589, Application 090589 - Sequence 0043 - Information Request Dated February 01, 2017 - Ref #12908485, M.1.11.3, Date 4/19/2017.

32. In response to the IR, in the current amendment dated April 19th, 2017, the firm submitted the results of the comparative performance testing of the test and RLD devices. As requested, the firm also conducted pre-study method validations for all the in-vitro tests using the reference product as per the current draft guidance on Epinephrine Injection. Firm used 3 lots of the test and reference units with 20 units from each lot.

4 SUBMISSION SUMMARY

4.1 Drug Product Information, PK/PD Information, and Relevant DB History

See the review of the original submission[1].

4.2 OGD Recommendations for Drug Product

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM534133.pdf, *Recommended December 2016*

On January 16, 2015, the innovator has submitted a citizen petition (Docket No: FDA-2015-P-0181), requesting the Agency, to refrain from approving the current application by Teva (ANDA 090589) unless a rigorous review under the established standards for proposed generic emergency use auto-injectors was performed and the Agency concludes that the proposed product is the same as the EpiPen auto-injectors. After careful consideration, the Agency has denied the above stated citizen petition (See section 4.11 for citizen petition).

4.3 Review of Current Amendment

Deficiency Comment:
In December 2016, the Agency announced the availability of a new draft guidance entitled "Draft Guidance on Epinephrine Injection." This new draft guidance provides product-specific recommendations for proposed generic drug products citing EpiPen® (epinephrine) Auto-Injector, 0.3 mg and EpiPen® Jr (epinephrine) Auto-Injector, 0.15 mg (NDA 019430) as their reference listed drug (REFERENCE PRODUCT).

Specifically, the new draft guidance recommends that at least three batches each of the test and reference products should be used in all of the recommended in vitro studies. This helps ensure consistency of in vitro performance among the batches. A copy of this Draft Guidance on Epinephrine Injection is available on FDA's Drug guidance page: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM534133.pdf.

In the amendments to your application dated July 31, 2013 and December 30, 2014, you submitted in vitro study results that were conducted on a single lot (30 units) of test product and on three lots (10 units of each lot) of reference product. Please re-

conduct all of the recommended in vitro studies per the current Draft Guidance on Epinephrine Injection using three batches of the test and reference products with no fewer than 10 units from each batch. Please perform population bioequivalence analysis for the following studies: Delivered Volume, Ejection Time, Trigger Force, and Extended Needle Length as per the recommendations in the draft guidance. For details regarding the in vitro studies, please refer to the Draft Guidance on Epinephrine Injection referenced above.

In addition, in the amendments to your application dated July 31, 2013 and December 30, 2014, you also used the test product to conduct pre-study method validations for all of the in vitro tests. Because the test product is not an approved drug product, it is not appropriate to use the test product for method validations involving drug product performance. Please repeat all pre-study method validations related to the drug product performance using the reference product, per the current Draft Guidance on Epinephrine Injection.

Consistent with 21 CFR 320.24(a), the scientific recommendations reflected in the Draft Guidance on Epinephrine Injection represents FDA's determination of the most accurate, sensitive, and reproducible approach for conducting bioequivalence testing.

Firm's Response: For a historical perspective, please note the following summary for BE Studies completed prior to 2015 that were conducted under this application.

Historical Summary

- *2013 BE Analysis*

  The Amendment to the Application dated July 31, 2013 (Sequence #0016) was a response to a deficiency letter dated March 29, 2010, where the FDA requested a BE study be performed. The study was performed on the Test Article design current at that time and evaluated Delivered Volume, Residual Fluid Volume, Fluid Ejection Time, Trigger Force, Exposed Needle Length, Collar Lockout Override Force, Angled Entry Force of Injection, and Post-Injection Needle Integrity.[1] The Test Article results were compared with Reference Product (with the current EpiPen design) data generated in 2010. Due to subsequent changes for the Test Article device, the results from this study are no longer deemed representative of the current proposed test article.

- *2014 BE Analysis*

  An additional BE study was performed in 2014 and this study was submitted in the December 30, 2014 Unsolicited Amendment (Sequence #0020). Changes to the Test Article device (i.e., safety-related change to add an indication of unintended activation) were made after the 2013 BE study. The study evaluated the re-designed Test Article (with a sample size of n=30) versus Reference Product results generated in 2010. Testing was conducted for delivered volume, ejection time, exposed needle length, residual content, lockout override, trigger force, and angled entry.[1] Equivalence was evaluated using a two one-sided test (TOST). The results demonstrated equivalence for delivered volume, ejection time, exposed needle length, trigger force, and angle entry. (b) (4) (b) (4) these parameters do not result in any differences in the safety or the efficacy of the proposed combination drug product. (We refer the reviewer to the previously submitted report and 2017 BE Protocol which provide detailed information.)

- *2015 BE Analysis*

  Teva proactively completed another BE study in 2015 using a sample size of n=60 in line with comments seen for other applications with regard to sample sizes. New data was generated for both the Reference Product and the Test Article. Until now, that study information had not been submitted. The study evaluated equivalence for delivered volume, ejection time, exposed needle length, residual content, lockout override, trigger force, and angled entry. New equipment and methods (when compared to previously generated data) were used due to updates to equipment in the laboratory that performed analysis. Equivalence was evaluated using a TOST analysis. The results demonstrated equivalence for delivered volume, ejection time, exposed needle length, trigger force, and angle entry. (b) (4) (b) (4) these parameters do not result in any differences in the safety or the efficacy of the proposed

[1] Testing of the test article was done using equipment and methods current at the time of analysis.

combination drug product. (We refer the reviewer to the reports[2] TR-1418, TR-1419, TR-1420, TR-1421 and TR-1422 provided herein and to the 2017 BE Protocol which provide detailed information.)[3]

As requested, Teva has re-conducted the recommended in vitro studies in 2017 per the current Draft Guidance on Epinephrine using three batches of the test and reference products with no fewer than 10 units from each batch. Population bioequivalence (PBE) analyses were performed for delivered volume, ejection time, trigger force and extended needle length as per the recommendations in the draft guidance. Copies of the Draft Guidance on Epinephrine Injection and the Budesonide Inhalation Suspension Guidance (referenced by the Epinephrine Injection Draft Guidance for the PBE analysis) are provided in Module 5.4. Prior to study initiation, a Protocol (b) (4) was approved and is also provided in Module 5.3.1.3. Please note that for the Needle Integrity Post Injection Test, justification for the injection materials was provided in the Protocol. The test was conducted at a maximum of (b) (4) from the labeled injection angle and is considered the reasonable worst-case (based on design inputs) along with (b) (4) from the labeled injection angle. (The label indicates to administer the product at a right angle (perpendicular) to the thigh.)

As requested, pre-study method validations for all the in-vitro tests have also been performed using the reference product as per the current Draft Guidance on Epinephrine Injection. Table 1 below provides a summary of the methods, validation protocols, and reports that are provided in Module 5.3.1.3.

Table 1. Summary of Methods, Validation Protocols and Validation Reports Used in 2017 BE Study of Reference Product and Test Article.

(b) (4)

(b) (4)

Results for the 2017 BE analysis are provided in the report (b) (4) also provided in Module 5.3.1.3. The results demonstrate that the test article is bioequivalent to the reference product for Delivered Volume and Exposed Needle Length. Needle integrity post injection also met the bioequivalence requirements however no analysis was conducted due to both the Test Article and Reference Product demonstrating 100% acceptance.

The ejection time for the Test Article was slightly faster than for the Reference Product in the tested populations. When the 2017 data for ejection time are considered, the difference is extremely small (b) (4) while statistically significant in these populations, this difference is not of clinical significance for the intended and labeled use of the product. Prompt administration of epinephrine for pre-hospital self-management of anaphylaxis is of utmost importance to achieve successful outcomes. This fact has been supported with numerous clinical experiences and literature articles. From the data presented in this report, the Test Article ejection time is marginally shorter than the Reference Product. Given the fact that rapid treatment with epinephrine is a key component to successful patient outcomes, this extremely small difference, resulting in shorter ejection time, will not be clinically meaningful.

The activation force test data demonstrated the Test Article and Reference Product activation forces were each centered on slightly different values. The 2017 data analyzed for the Reference Product vs. the Test Article identified a difference in activation force that was not previously observed when performing a similar comparison study of the same sample size in the previous study conducted in 2015 (b) (4) Since previous studies determined that the Reference Product and the Test Article were bioequivalent, further evaluation of the Reference Product results was performed.[8] Reference Product data from 2015 and 2017 were analyzed for bioequivalence using the same PBE analysis as described in the Draft Guidance on Epinephrine dated Dec 2016. (b) (4)

(b) (4)

Pooling the data between the 2015 and 2017 studies allows for examination of equivalence over time and with an increased sample size; therefore, an additional analysis of that data was performed. The tests were executed (according to their respective protocols) using the same or equivalent validated methods, ensuring the data recorded can be pooled and analyzed. The retrospective pooled PBE analysis for activation force showed equivalence

(b) (4)

between the Test Article and Reference Product for both the 0.3mg and 0.15mg auto-injectors.[9]

(b) (4)

Based on the 2017 data presented herein, the Test Article is bioequivalent to the Reference Product for the parameters of Delivered Volume, Exposed Needle Length, and Needle Integrity Post Injection. Based on the pooled retrospective analysis of 2015/2017 data, which demonstrates a larger sample size and a reflection of the product over time, the Test Article is bioequivalent to the Reference Product with regard to Trigger Force. While there were slight differences seen with regard to Ejection Time between the Test Article and the Reference Product, with a slightly faster (b) (4) ejection time for the test article, this difference is not clinically meaningful.

In conclusion, the results of the 2017 Study demonstrate an (b) (4)

(b) (4)

Test Article and the Reference Product are essentially bioequivalent and are therefore substitutable.

(b) (4)

Reviewer's Comments:

- In the current amendment dated April 19, 2017, the firm has submitted the response to the deficiency comment made by DBIII regarding the performance testing of the devices[45]. The firms has re-conducted in vitro device performance tests specifically for delivered volume, ejection time, trigger force, extended needle length and needle integrity post-injection and submitted the data for Agency's evaluation.

- The firm has manufactured new exhibit test batches and re-conducted the recommended in vitro studies as per the new draft product-specific guidance on Epinephrine Injection using three batches of the test and reference products with 20 units from each batch. Population bioequivalence (PBE) analysis was performed for delivered volume, ejection time, trigger force and extended needle length as per the recommendations in the draft guidance.

- Per the current draft guidance on Epinephrine Injection, the firm has conducted pre-study method validations for all the in-vitro tests using the reference product.

4.4 In Vitro Studies

The firm has conducted in vitro studies comparing the test product device (Vibex (b) (4), with the reference product device (EpiPen and EpiPen Jr).

There were two groups of parameters of interest: four continuous parameters (Delivered Volume, Ejection Time, Trigger Force, and Extended Needle Length), and three dichotomous parameters (pass/fail) about needle integrity (ability to trigger the injection at the angle of incidence, ability of the needle to penetrate the material, and integrity of the needle post-injection).

Testing was performed using both strengths of the test and RLD devices (0.3 mg and 0.15 mg). For the test product, each strength of a single lot of solution was split-filled into three equal size sub-lots of product. The three lots of test product were prepared from three different lots of the same critical device components (b) (4) (See below Table). The RLD device was procured in 3 equal lots for the 0.3 mg and 0.15 mg strengths. BE testing for the RLD and test devices was conducted with a sample size of n=20 for each lot.

[45] EDR, ANDA 090589, Application 090589 - Sequence 0043 - Information Request Dated February 01, 2017 - Ref #12908485, M.1.11.3, Date 4/19/2017.

Dose Strength	PRODUCT	BATCH	Sample Size
0.15 mg	REF	RM17007	20
0.15 mg	REF	RM17008	20
0.15 mg	REF	RM17014	20
0.15 mg	TEST	RM17044	20
0.15 mg	TEST	RM17045	20
0.15 mg	TEST	RM17046	20
0.3 mg	REF	RM17009	20
0.3 mg	REF	RM17015	20
0.3 mg	REF	RM17017	20
0.3 mg	TEST	RM17041	20
0.3 mg	TEST	RM17042	20
0.3 mg	TEST	RM17043	20

For needle integrity a sample size of 90 per lot was tested. This was a result of three angles and three materials being tested for a total of 9 combinations, with 10 samples per combination. A total of three lots per product were tested.

PRODUCT	BATCH	Sample Size
REF	RM17007	90
REF	RM17008	90
REF	RM17014	90
TEST	RM17044	90
TEST	RM17045	90
TEST	RM17046	90

The firm conducted analysis of bioequivalence for the continuous parameters following the stepwise Population Bioequivalence (PBE) approach. For the three dichotomous parameters of needle integrity, qualitative comparison between test and RLD devices was performed. The protocol also provided a method for quantitative comparison but it was not used because of the 100% success rate.

Note: *Under the PBE method, for each comparative in vitro test described in the guidance for budesonide, FDA recommends the calculation of a 95 percent confidence interval as a measure of equivalence between the test and reference products that includes the ratio of the geometric means of the two products and the difference in variability between test and reference products. The confidence interval is compared to an acceptance limit that is based on fixed statistical parameters (i.e., the regulatory constants, SigmaT0 and Epsilon and takes into consideration the observed within-study variability of the test and reference products. Inherent in the PBE method is the principle that the acceptance limits for the confidence interval depend on the relative variability of the test and reference products observed in the study. In the case of low variability data for the reference product, the acceptance limits narrow, toward the 90-111 percent criteria used in the geometric mean method, enabling only test products with comparable variability to meet the criteria. Conversely, in the case of high variability data for the reference product, the acceptance limits might be slightly wider. This permits approval of generic products that are comparably or less variable than the reference product (even if the ratio of the geometric means falls slightly outside of the 90-111 criteria) and, guards against approval of generic products that are more variable than the reference product (even if the ratio of the geometric means falls within the 90-111 percent criteria).*

In summary, to test for population bioequivalence, 95% upper confidence bound of either the reference-scaled or constant-scaled linearized criterion are computed. For linearized theta P, if this upper bound is negative, conclude population bioequivalence. If the upper bound is positive, do not conclude population bioequivalence.

4.4.1 Delivered Volume

Testing was performed on 20 Adult and Junior epinephrine devices of three lots of both the test and reference products. The delivered volume was determined gravimetrically post-device triggering into a tared test beaker.

0.15mg Test Article		0.3mg Test Article		0.15mg Reference Product		0.3mg Reference Product	
Lot Number Antares/Teva	Qty	Lot Number Antares/Teva	Qty	Lot Number Antares/Mylan	Qty	Lot Number Antares/Mylan	Qty
RM17044/021A16AA	20	RM17041/020A16AA	20	RM17007/6FN718	20	RM17009/6FM771	20
RM17045/021A16AB	20	RM17042/020A16AB	20	RM17008/6FN721	20	RM17015/6FM722	20
RM17046/021A16AC	20	RM17043/020A16AC	20	RM17014/6FN719	20	RM17017/6FM716	20
-	60	-	60	-	60	-	60

Test Procedure: (b) (4)

(b) (4)

The AJ E and EpiPen® devices were tested per SOP (b) (4)

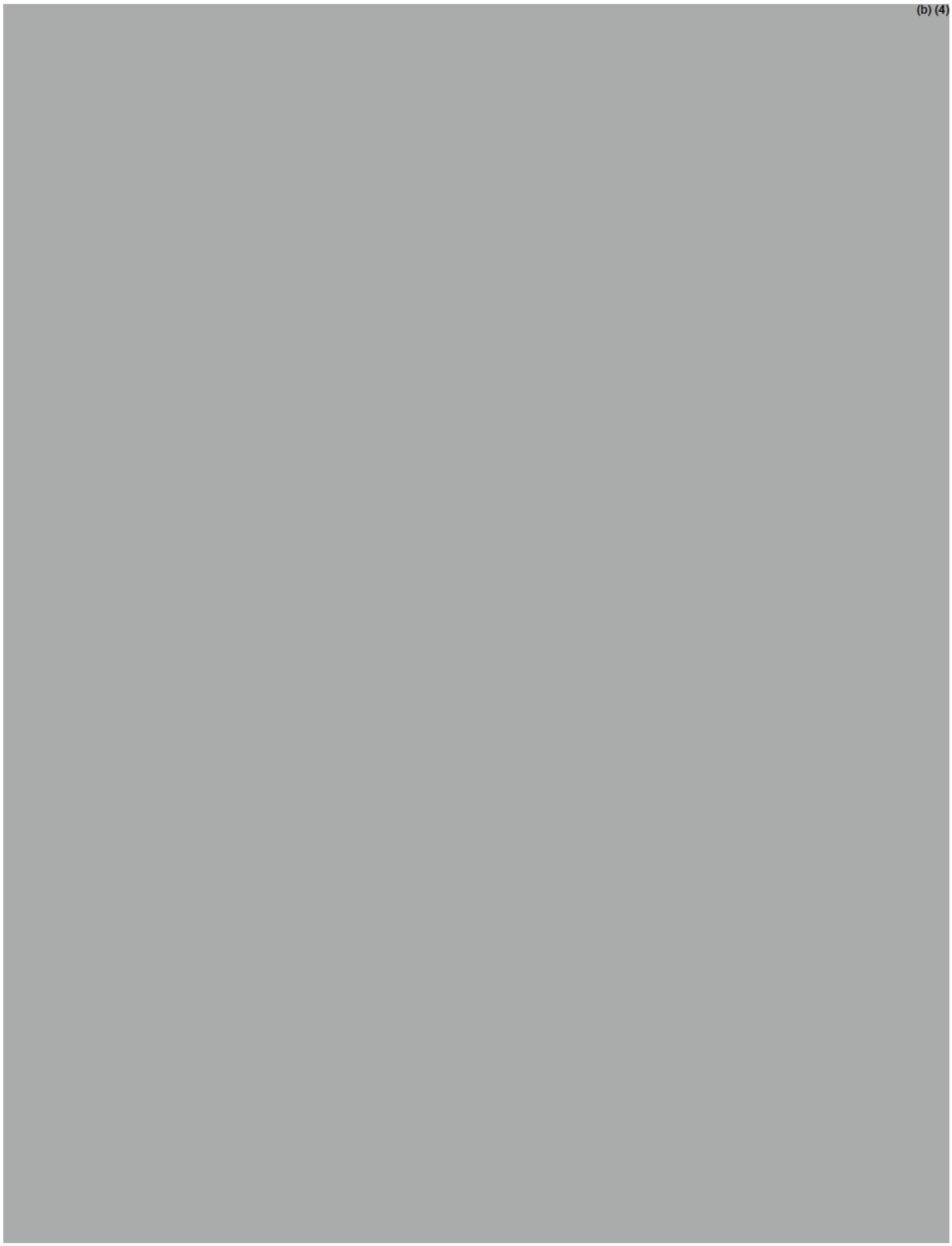
(b) (4)

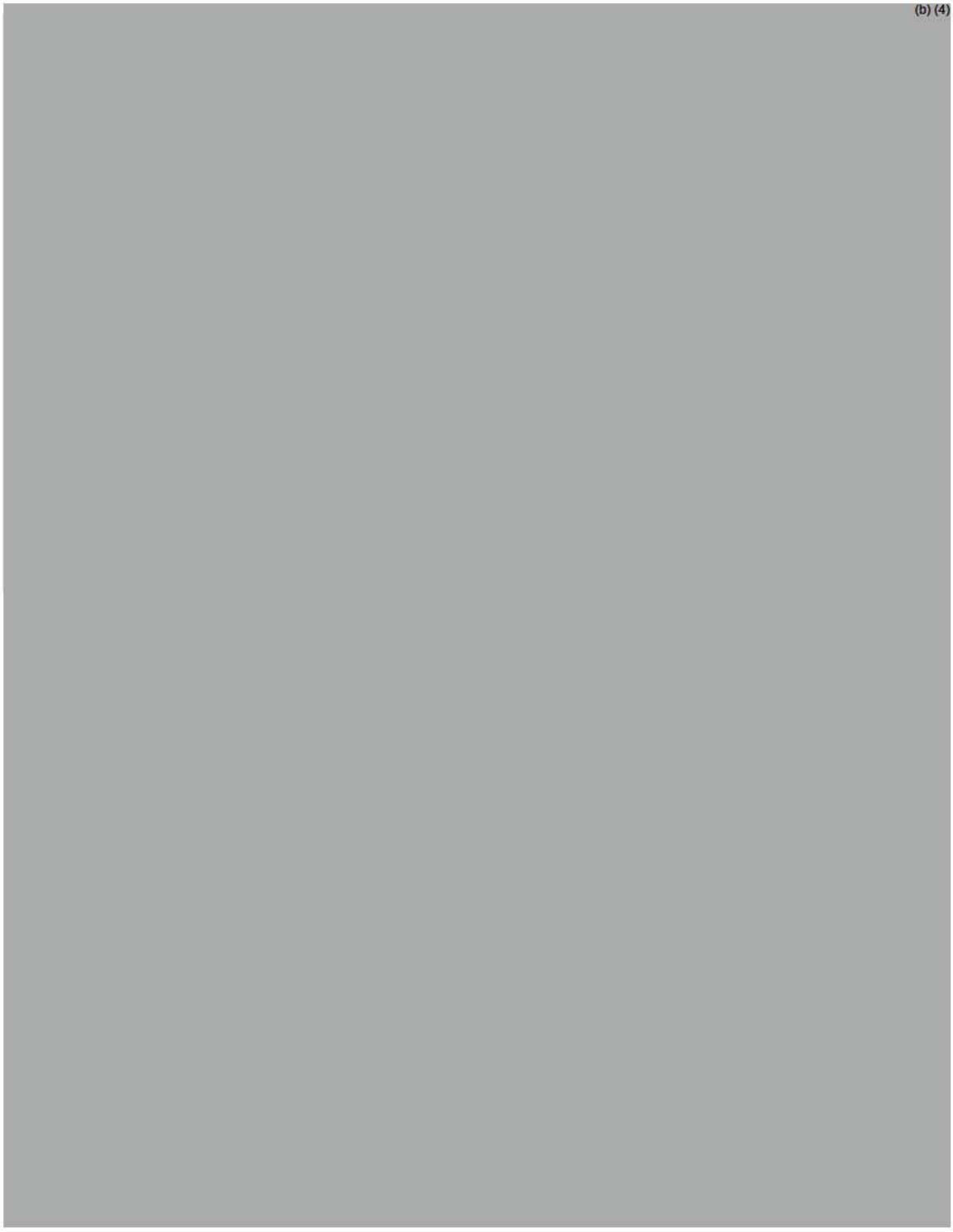
(b) (4)

The firm has validated the Balance (b) (4) methodology for the measurement of delivered volume and submitted the report (b) (4) The method was validated for repeatability and reproducibility per method validation protocol (b) (4) The validation results are as follows.

Gage R & R: The test was conducted using known weights on analytical balance which were weighed three times each by three separate operators and 10 units each time (total 90 devices were tested). Gage variability is defined as %tolerance variability for the total gage inclusive of equipment variability (repeatability) and operator variability (reproducibility).

(b) (4)


(b) (4)



Conclusion: The results (gage R & R and recovery efficiencies were 4.33% and 99.99%, respectively) indicate that all the data met the acceptance criteria and the firm has adequately demonstrated the repeatability and reproducibility of the (b) (4) in measuring "Delivered Volume" from Auto-Injectors. Thus method validation is acceptable.

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(b) (4)

Reviewer's Comments:

- As per the SOP (b) (4) the delivered volume from the injection device was measured using a (b) (4) balance. The delivered volume has been evaluated on 20 devices of three lots of test and reference products. The firm submitted the individual and mean results expressed as the weight in grams.

- In addition, the firm also submitted the statistical results comparing the mean delivered volumes of the test and reference products using the PBE analysis. Based on the above results, the firm has concluded that both the test and reference product devices are statistically equivalent with respect to delivered volume.

- The reviewer conducted PBE statistical analysis on the in vitro data as per the product-specific guidance. Since the values of SigmaR are less than 0.1(regulatory constant) for adult and junior devices, constant scaled approach was used in the statistical analysis. The 95% upper bound of delivered volume for adult ((b) (4) and junior (b) (4) device are less than 0 (PBE criterion is 95% upper bound must be ≤0). The delivered volume test passed PBE analysis.

- (b) (4)

- Thus, the test product auto-injector device is similar to the reference product auto-injector device for delivered volume.

[46] DARRTS for NDA 019430: KIM, CHONG HO 11/04/2009 N/A 11/04/2009 REV-QUALITY-03(General Review) Supplement-49 (Manufacturing (CMC)) Archive

- The Delivered Volume testing is **acceptable**.

4.4.2 Ejection Time

Testing was performed on 20 Adult and Junior epinephrine devices of three lots of both AJ E and EpiPen Devices for fluid ejection time. (b) (4)

(b) (4)

0.15mg Test Article		0.3mg Test Article		0.15mg Reference Product		0.3mg Reference Product	
Lot Number Antares/Teva	Qty	Lot Number Antares/Teva	Qty	Lot Number Antares/Mylan	Qty	Lot Number Antares/Mylan	Qty
RM17044/021A16AA	20	RM17041/020A16AA	20	RM17007/6FN718	20	RM17009/6FM771	20
RM17045/021A16AB	20	RM17042/020A16AB	20	RM17008/6FN721	20	RM17015/6FM722	20
RM17046/021A16AC	20	RM17043/020A16AC	20	RM17014/6FN719	20	RM17017/6FM716	20
-	60	-	60	-	60	-	60

Test Procedure: The AJ E and EpiPen devices were tested per SOP (b) (4)

(b) (4)

The firm has conducted the validation studies by verifying (b) (4)

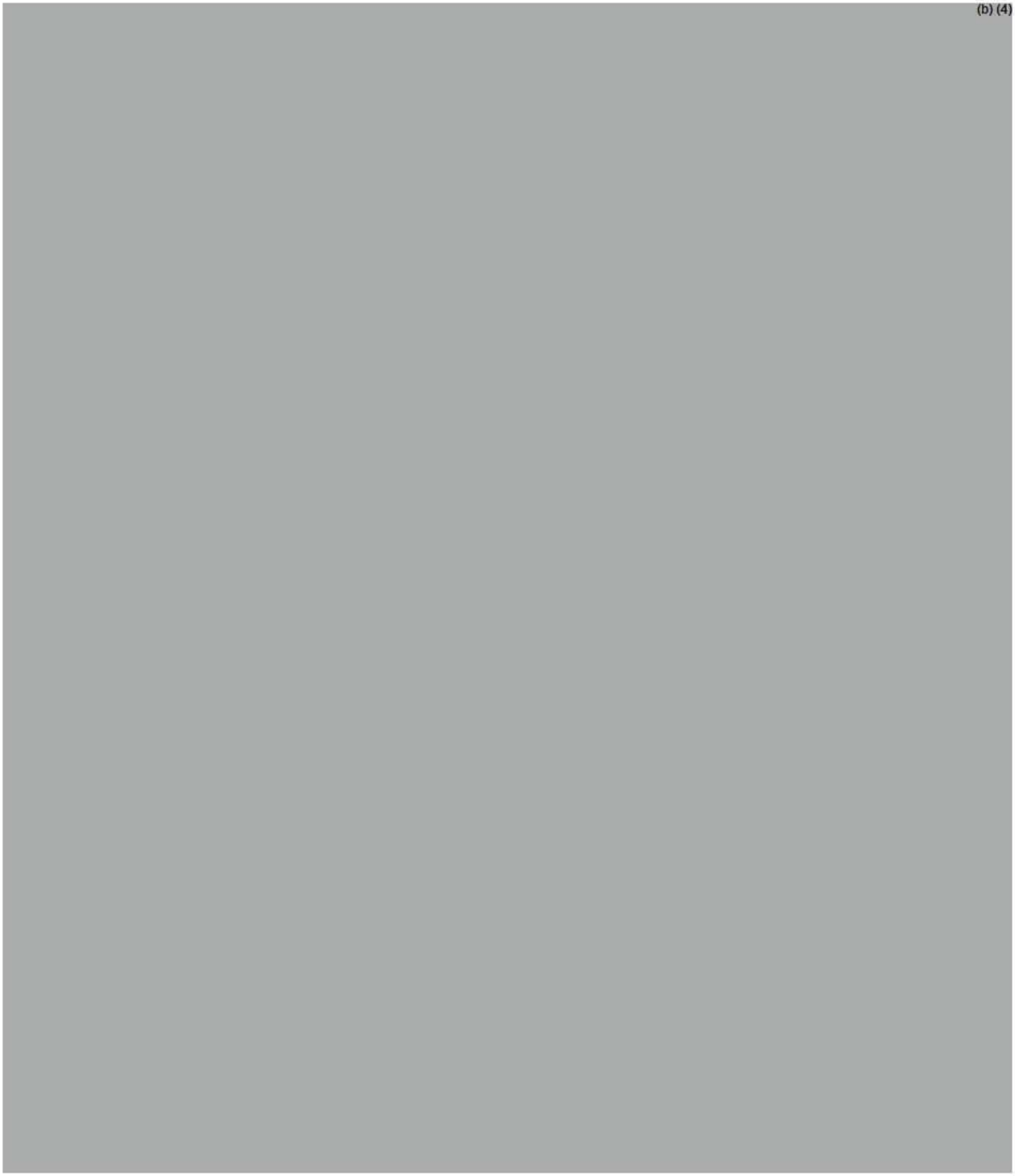
(b) (4) and by analyzing the fluid ejection time observed for 10 units of test and RLD devices and submitted the report ((b) (4)). The method was validated for repeatability and reproducibility per method validation protocol (b) (4) . The validation results are as follows.

Crossed Gage R & R: The test was conducted using a (b) (4)

(b) (4)

(b) (4) Gage variability is defined as %Tolerance variability for the total

gage inclusive of equipment variability (repeatability) and operator variability (reproducibility).



Conclusion: The results of the gage R&R produced a total gage variability of (b) (4) indicate that the data met the acceptance criteria. Thus the firm has adequately verified

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Reviewer's Comments:

- As per the SOP (b) (4) the fluid ejection time from the injection device was measured using a (b) (4). The fluid ejection time has been evaluated on 20 devices each of three lots of test and reference products. The firm submitted the individual and mean results expressed as milliseconds.

- (b) (4)

- (b) (4)

(b) (4) The fluid ejection time (dispense time) of the test product is within the RLD specification ((b) (4)) for both the adult and junior devices.

- Based on the reviewer's statistical analysis, since the values of SigmaR are less than 0.1(regulatory constant) for adult and junior devices, constant scaled approach was used in the statistical analysis. The 95% upper bound of fluid ejection time for adult (b) (4) and junior (b) (4) device are greater than 0 (PBE criterion is 95% upper bound must be ≤0). The fluid ejection time test **failed PBE analysis**.

  Firm's justification:

  (b) (4)

- Based on the data submitted, the ejection time of the test device is slightly faster than the reference device. The reviewer agrees with the firm that this small difference (b) (4) (b) (4) in the ejection time between test and reference device may not be clinically significant even though the PBE analysis failed.

- A meeting was held between OB and ORS to discuss the failed study results (For more details, see Meeting Minutes document uploaded in panorama [48]).

- As the mean fluid ejection time differences are small and also shorter ejection time of test product will not have impact on clinical outcome, meeting attendees

(b) (4)

[48] GDRP, ANDA-090589-ORIGI-1-AMEND-6, Meeting minutes review, http://panorama.fda.gov/task/view?ID=5420f1160002bc9df9be4d40027ff2e6, A090589DB_MM06122017, Suman Dandamudi, 9/19/2017

recommended ejection time study to be acceptable from BE perspective. Thus, the test product auto-injector device is considered similar to the reference product auto-injector device for fluid ejection time.

4.4.3 Trigger Force (Force Required to Discharge Actuator)

(b) (4)

Trigger force testing was performed on 20 Adult and Junior epinephrine devices each of three lots of both AJ E and EpiPen Devices. (b) (4)

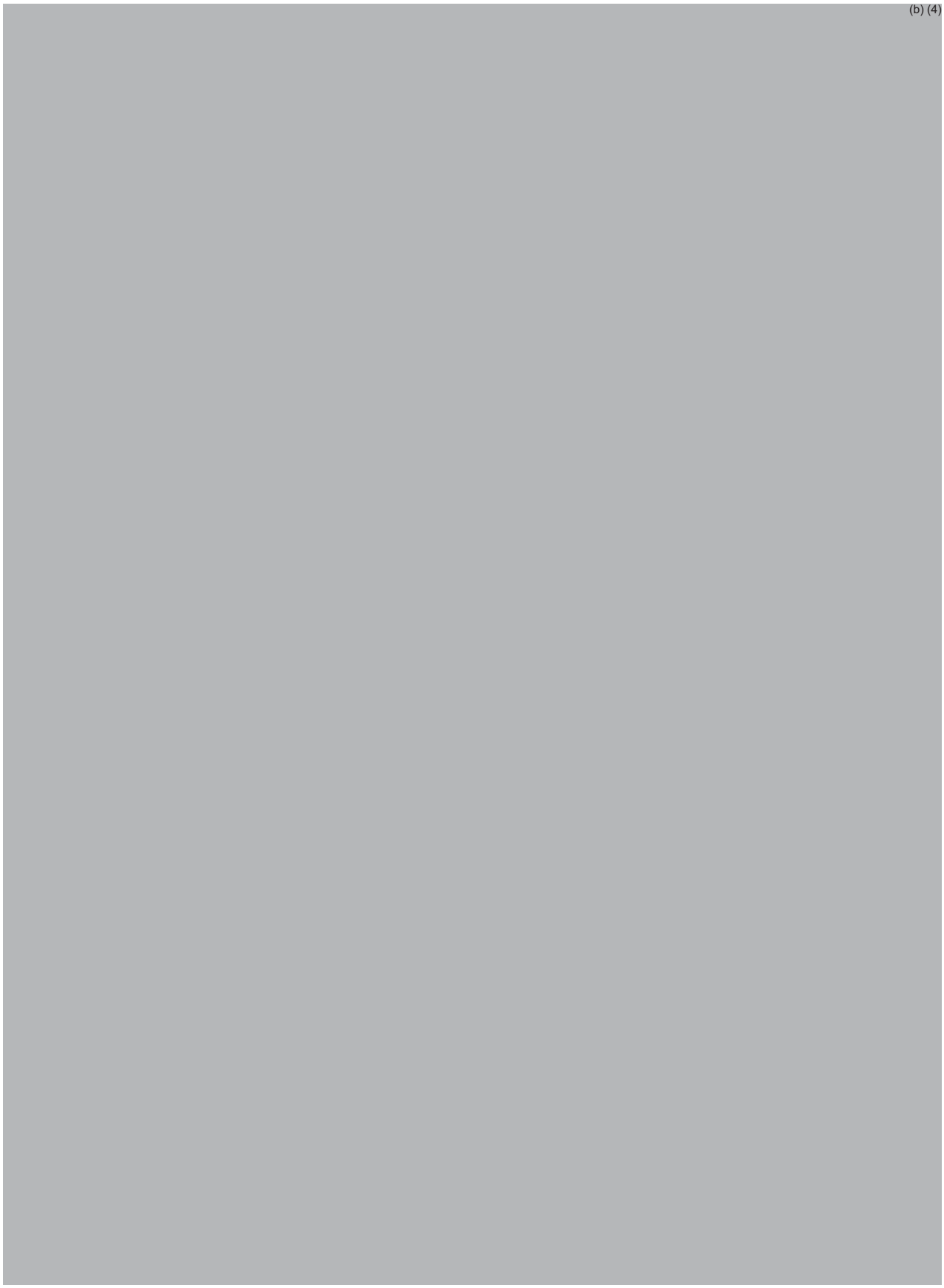
(b) (4)

0.15mg Test Article		0.3mg Test Article		0.15mg Reference Product		0.3mg Reference Product	
Lot Number Antares/Teva	Qty	Lot Number Antares/Teva	Qty	Lot Number Antares/Mylan	Qty	Lot Number Antares/Mylan	Qty
RM17044/021A16AA	20	RM17041/020A16AA	20	RM17007/6FN718	20[a]	RM17009/6FM771	20[a]
RM17045/021A16AB	20	RM17042/020A16AB	20	RM17008/6FN721	20[a]	RM17015/6FM722	20[a]
RM17046/021A16AC	20	RM17043/020A16AC	20	RM17014/6FN719	20[a]	RM17017/6FM716	20[a]
-	60	-	60	-	60	-	60

Test Procedure: The AJ E and EpiPen devices were tested per SOP (b) (4)

(b) (4)

[49] GDRP for ANDA 090589-ORIG-1-AMEND-6, CDRH Device Consult-Gratuitous Amend 46 IR, http://panorama.fda.gov/issue/view?ID=590799f700138de6623d49a4e0797d09, Jennifer Nguyen, 5/1/2017

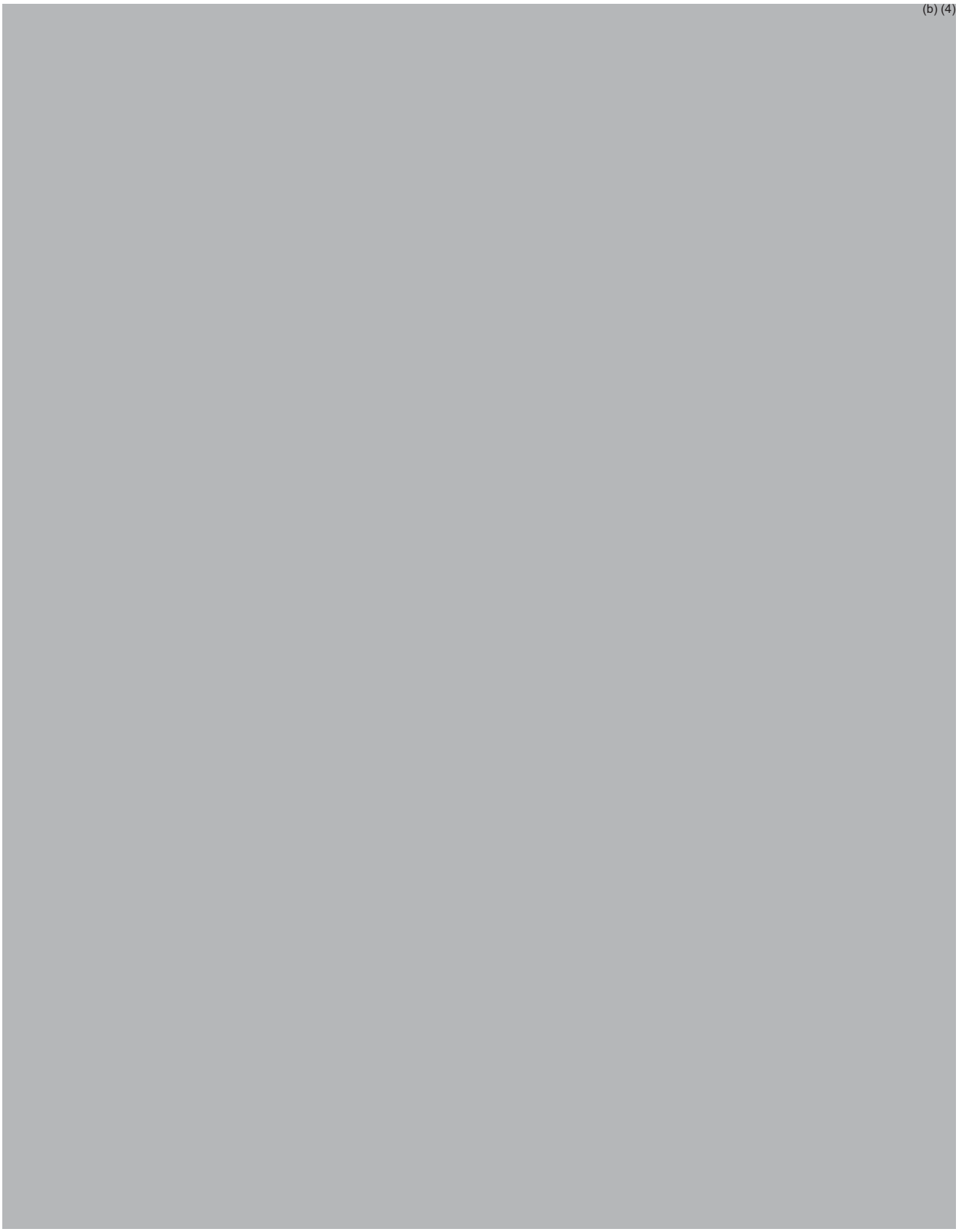

(b) (4)

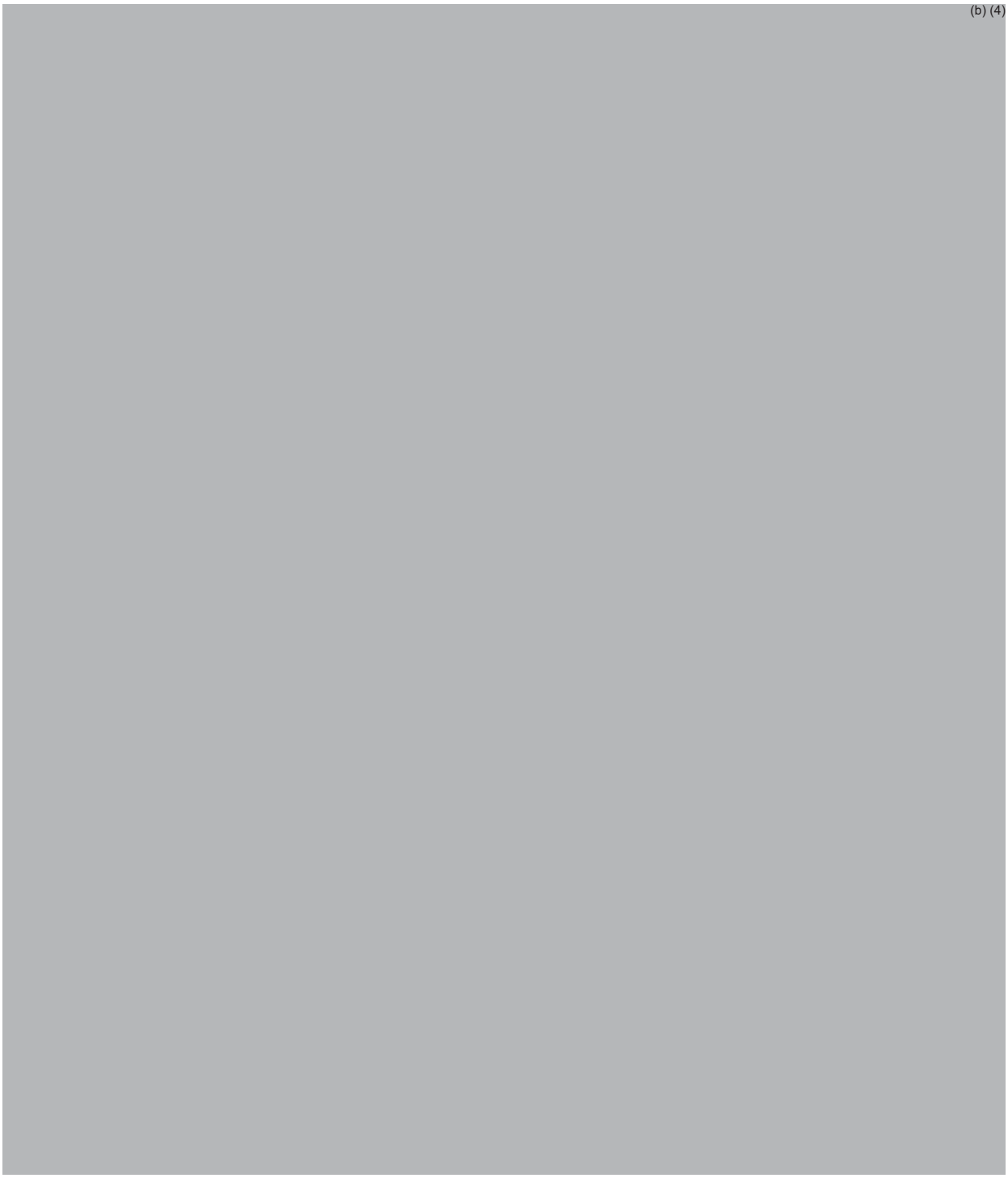
(b) (4)

Conclusion: The results of the gage R&R produced a total gage variability of (b) (4) indicate that the data met the acceptance criteria and the firm has adequately demonstrated the repeatability and reproducibility of the test method for measuring the trigger force. Thus method validation is acceptable.

Study Results:

(b) (4)


(b) (4)

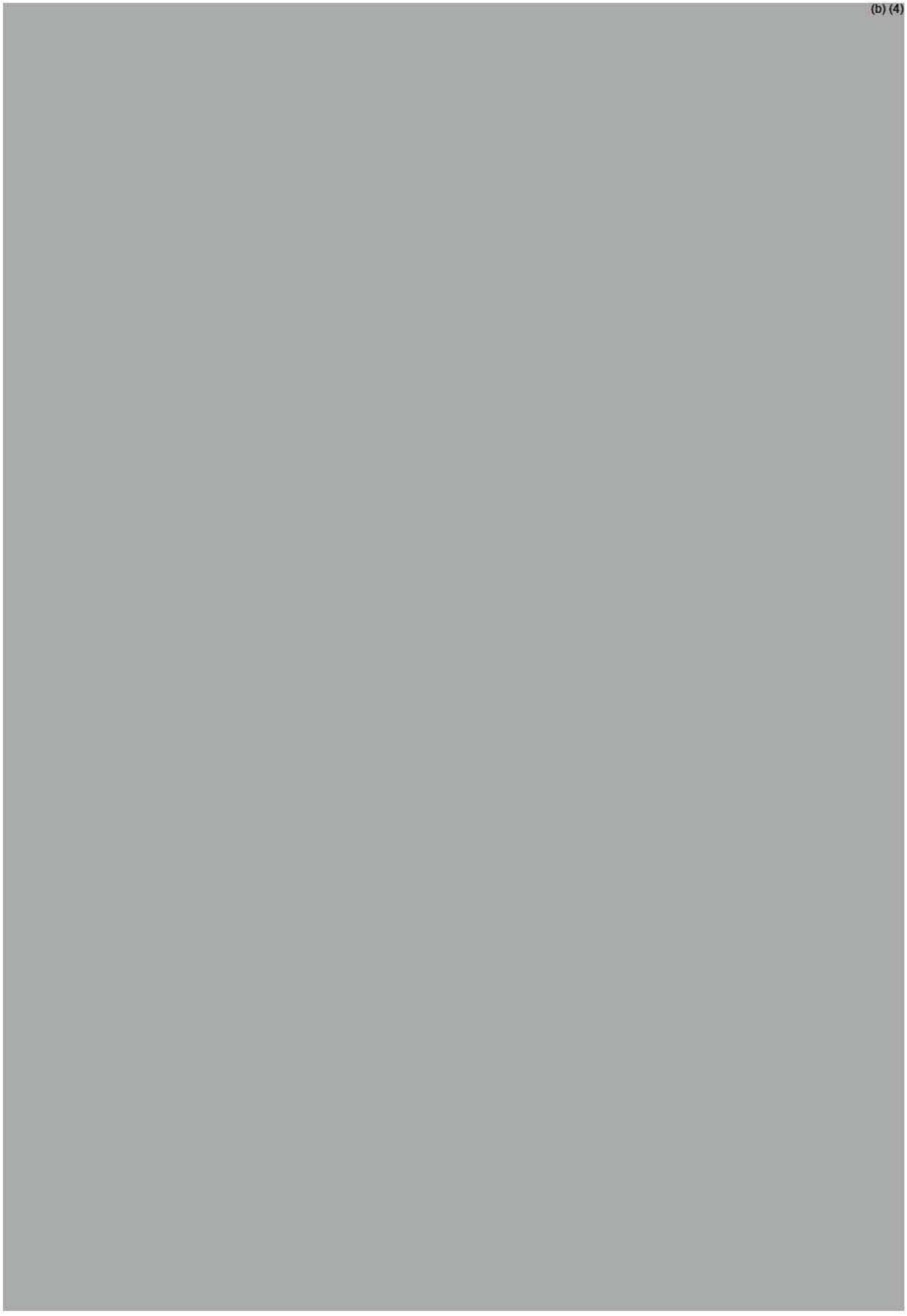


Reviewer's Comments:

- As per the SOP (b) (4), the trigger force of the injection device was measured. The trigger force has been evaluated on 20 devices of three lots of both test and reference products. The firm submitted the individual and mean results expressed as pounds per force (lbf).

- [redacted] The trigger force (activation force) of the test product is within the RLD specification [redacted] for both the adult and junior devices.
- [redacted] The 95% upper bound of trigger force for adult [redacted] and junior [redacted] device are greater than 0 (PBE criterion is 95% upper bound must be ≤0). Therefore, the trigger force test failed PBE analysis. In addition, the mean T/R ratios of trigger force for adult [redacted] and junior [redacted] devices are not within [redacted].

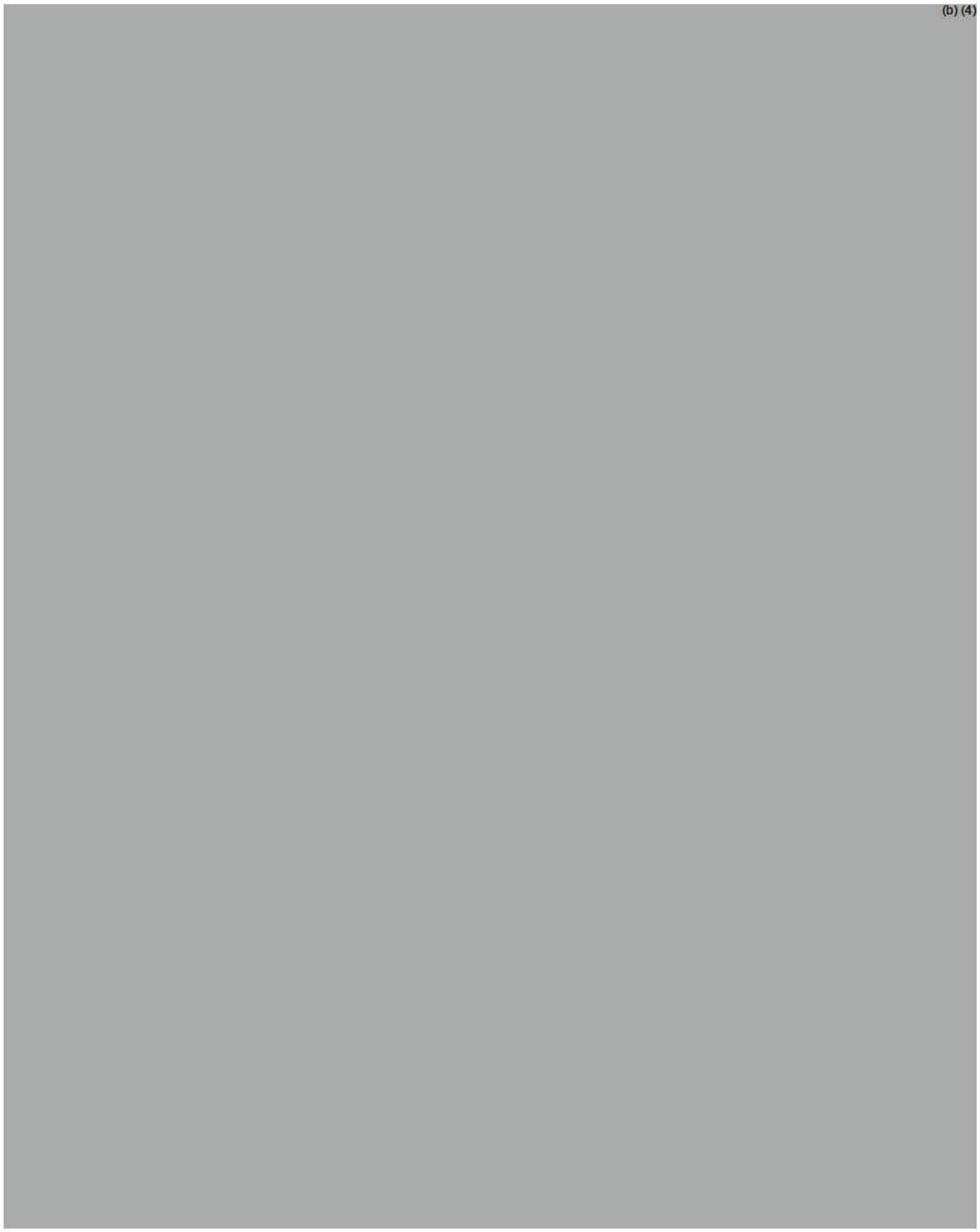
[redacted]


(b) (4)

The 2017 study was conducted as supplemental data to the 2015 study in order to demonstrate compliance with the December 2016 FDA Draft Guidance on Epinephrine. By pooling the data between the 2015 and 2017 studies, equivalence can be examined over time and with increased sample size. The tests that were executed (according to their respective protocols) utilized the same or equivalent validated methods between the two studies, ensuring the data recorded can be pooled and analyzed.

The pooled PBE analysis for activation force showed equivalence between the test article and reference product for both the 0.3 mg and 0.15 mg auto-injectors. Detailed analysis is located in ***Appendix B1****.*
In addition, the pooled analysis was conducted for the remaining variable test parameters. The pooled data demonstrates the test article is statistically bioequivalent to the reference product over time for delivered volume and extended (exposed) needle length. The 2015 data for delivered volume and extended (exposed) needle length was originally documented in ***TR1418****. Detailed analysis is located in* ***Appendix B1****. Raw data is located in* ***Appendix B2.***

EpiPen 2015 vs 2017 Data Analysis



Since both ejection time and trigger force data failed to meet PBE analysis criteria the Division of Bioequivalence III (DBIII) requested a meeting with the management of the Office of Bioequivalence (OB) and Office of Research and Standards (ORS) to discuss whether to accept or ask the firm to repeat these in vitro studies[48].

Reviewer compiled the RLD lots data from 2014, 2015, current submission and compared the ejection time and trigger force study results.

PBE Analysis				
	Adult		**Junior**	
	2014 vs 2017	**2015 vs 2017**	**2014 vs 2017**	**2015 vs 2017**
Ejection Time	FAIL	FAIL	FAIL	FAIL
Tigger Force	FAIL	FAIL	PASS	FAIL

Reviewer also compared the ejection time and trigger force data of the test lots from current submission with the RLD lots from 2015.

(b) (4)

- Trigger force data met PBE analysis when test device data of 2017 compared with the RLD device data submitted in 2015. When RLD lots data from 2014 and 2015 compared with 2017 trigger force data failed to meet PBE analysis (except Jr device 2014 vs 2017). Above data indicates that there is a lot to lot variability observed over time with reference device.

- The mean trigger force of the test product is within the RLD specification (b) (4)) for both the adult and junior devices.

- Since the test devices needed slightly higher force to trigger the device, based on the recommendation from meeting attendees, DBIII sent consult request to DCR to evaluate the impact of this trigger force difference on the safety and efficacy of the test device[50].

- Therefore, trigger force study is considered incomplete pending consult response from DCR at this time.

4.4.4 Extended Needle Length

Testing was performed on 20 Adult and Junior epinephrine devices of three lots of both AJ E and EpiPen Devices for exposed needle length. (b) (4)

(b) (4)

[50] GDRP, ANDA-090589-ORIGI-1-AMEND-6, http://panorama.fda.gov/task/view?ID=5420f1160002bc9df9be4d40027ff2e6,A090589DB_C09072017 Suman Dandamudi, 9/19/2017

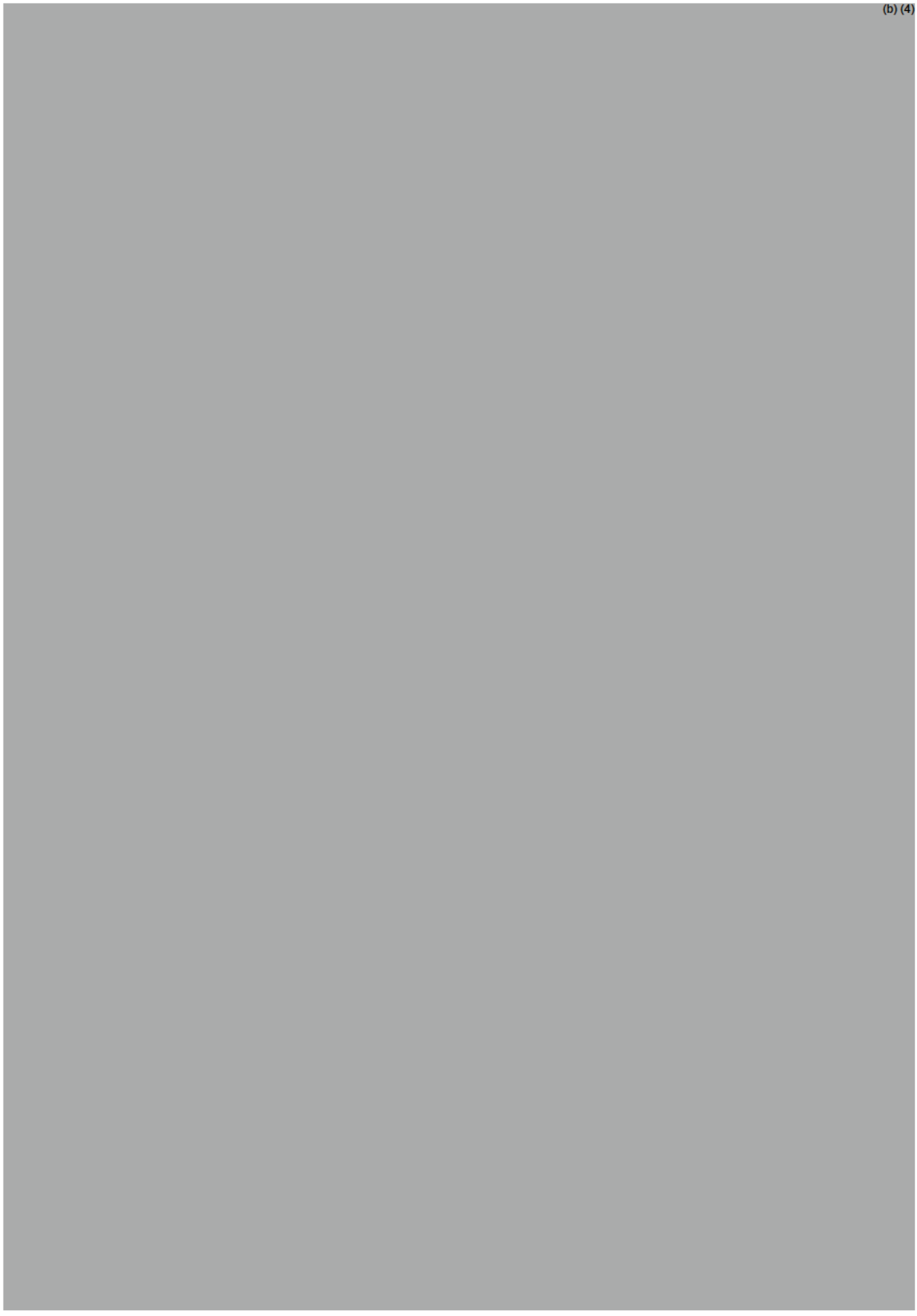
0.15mg Test Article		0.3mg Test Article		0.15mg Reference Product		0.3mg Reference Product	
Lot Number Antares/Teva	Qty	Lot Number Antares/Teva	Qty	Lot Number Antares/Mylan	Qty	Lot Number Antares/Mylan	Qty
RM17044/021A16AA	20	RM17041/020A16AA	20	RM17007/6FN718	20[a]	RM17009/6FM771	20[a]
RM17045/021A16AB	20	RM17042/020A16AB	20	RM17008/6FN721	20[a]	RM17015/6FM722	20[a]
RM17046/021A16AC	20	RM17043/020A16AC	20	RM17014/6FN719	20[a]	RM17017/6FM716	20[a]
-	60	-	60	-	60	-	60

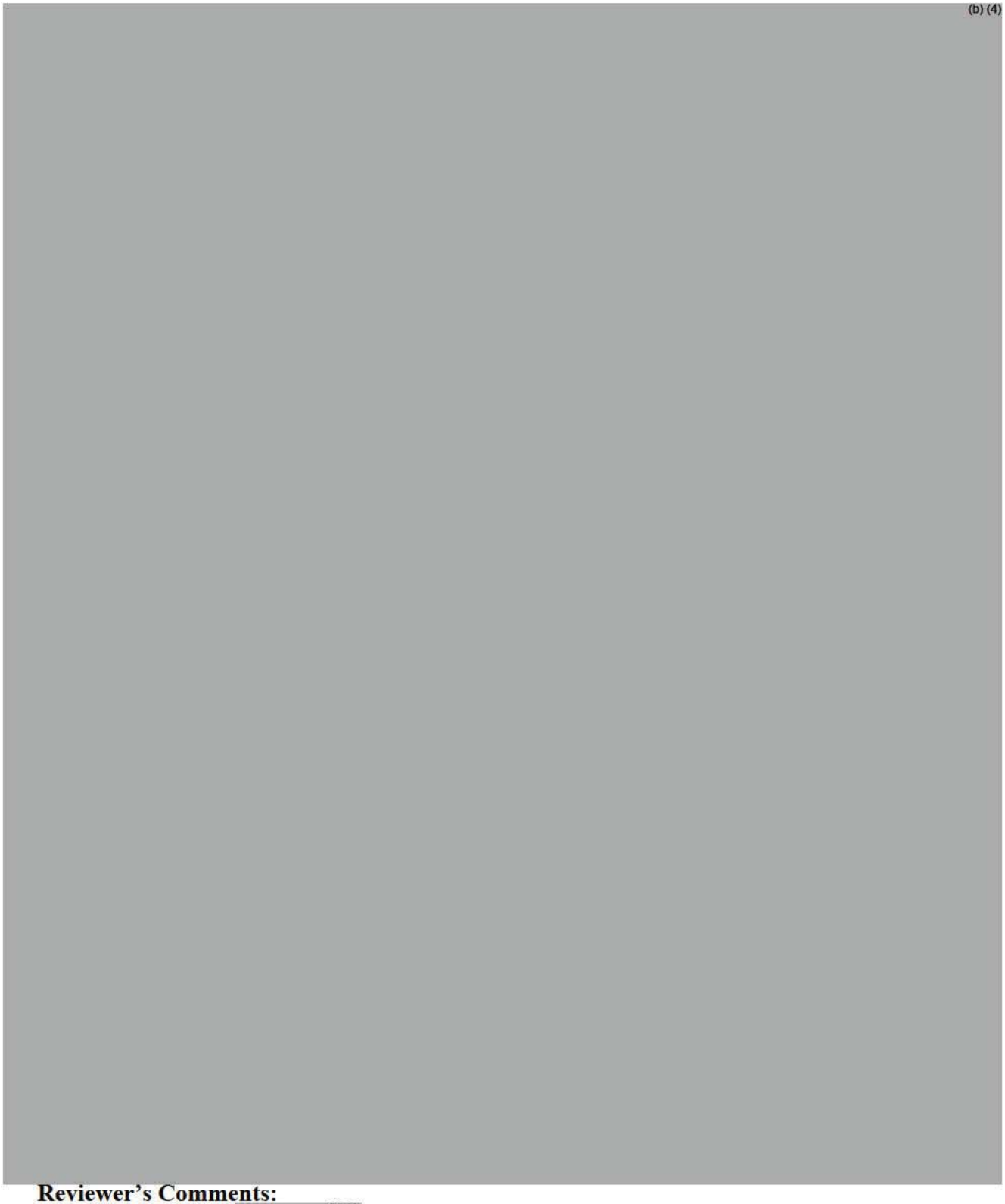
Test Procedure: The AJ E and EpiPen devices were tested per SO (b) (4)

(b) (4)

Conclusion: The results of the gage R&R produced a total gage variability of (b) (4) indicate that the data met the acceptance criteria and the firm has adeq demonstrated the repeatability and reproducibility of the test method for measuring the exposed needle length. Thus method validation is acceptable.

Study Results:


(b) (4)



Reviewer's Comments:

- As per the SOP (b) (4) the exposed needle length of the injection device was measured. The exposed needle length has been evaluated on 20 devices of three lots of test and reference products. The firm submitted the individual and mean results expressed as mm.

- [redacted] The exposed needle length of the test product is within the RLD specification (Adult: [redacted] Junior: [redacted] for both the adult and junior devices.

- [redacted]. The 95% upper bound of extended needle length for adult [redacted] and junior [redacted] device are less than 0 (PBE criterion is 95% upper bound must be ≤0). The extended needle length test passed PBE analysis.

- Thus, the test product auto-injector device is similar to the reference product auto-injector device for exposed needle length.

- The exposed needle length testing is **acceptable**.

4.4.5 Needle Integrity Post-Injection

Testing was performed on 90 Adult and Junior epinephrine devices of three lots of both AJ E and EpiPen Devices for angled entry and material penetration. The angled entry and material penetration capability was determined by attempting to trigger the device using a variety of angles of incidence and materials. Each device model was tested at three different angles from vertical [redacted] and through three cloth materials of differing penetration challenges [redacted] at each angle (ten devices were tested with each cloth material at each angle per device model). [redacted]

[redacted]

Test Procedure: The AJ E and EpiPen devices were tested per SOP [redacted]. The angled entry and material penetration capability of the device was obtained by testing each device model at three different incidence angles, and with three different material penetration challenges at each incidence angle, resulting in [redacted] different incidence angle and penetration material combinations. Each device model was tested using ten representative devices at each angle and material combination. Each representative device was tested for ability to trigger at the angle, ability of the device to penetrate the material, integrity of the needle after injection, and the ability of the device to lockout after being removed from the injection site.

(b) (4)

Validation: No validation studies were conducted on this testing, since it is visual inspection test.

Study Results:

	REF Article		TEST Article		
	Sample Size	Success	Sample Size	Success	**PBE**
Triggered	270	100%	270	100%	PASS
Needle Integrity	270	100%	270	100%	PASS
Device Locked Out	270	100%	270	100%	PASS
Material Penetrated	270	100%	270	100%	PASS

Reviewer's Comments:

- As per the SOP (b) (4) the angular and the penetration test of the injection device was conducted. The testing was performed on 90 devices of test and reference products. For each cloth and angle pair firm recorded whether the device successfully triggered, whether there were any post-triggering needle integrity issues (i.e. deformities, damage or bending), whether the device successfully locked out when removed from the site and whether the needle penetrated the cloth and injected.

- The firm submitted the results as "Pass" or "Fail". Pass indicated that all tested representative devices (i.e. 100%) in the set of ten passed the test/inspection, whereas fail indicate that at least one tested representative device in the set often failed the test /inspection.

- Based on the firm's results, it is evident that all the test adult and junior devices triggered successfully at all combinations of angles and materials. All devices successfully locked out after triggering and being removed from the injection site. All devices successfully penetrated the test material when triggered (Please see Appendix 4.11.5 for individual device results).

- The angled entry and post-injection needle integrity testing is acceptable.

4.5 Formulation

No change in formulation.

4.6 Deficiency Comments

Deficiency comments if any will be provided based on the outcome of the clinical consult with the DCR.

4.7 Recommendations

The Division of Bioequivalence III (DBIII) does not grant the waivers of in vivo bioequivalence testing requirements for the Teva's test product Epinephrine Injection USP, 0.3 mg/mL and 0.15 mg/mL, pre-filled syringe with auto-injector at this time pending the clinical consult response from DCR.

4.8 Comments for Other OGD Disciplines

Discipline	Comment
All	The final decision on the waiver request for Epinephrine Injection is currently pending the outcome of the consult request to the DCR.

4.9 Pending Consults

DBIII has submitted Consultation request to DCR for the evaluation of the trigger force of the test device on safety and efficacy.

4.10 Detailed Regulatory History

Citizen Petition: FDA-2015-P-0181[51]

[51] http://www regulations.gov/#!documentDetail;D=FDA-2015-P-0181-0009

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
10903 New Hampshire Avenue
Building #51
Silver Spring, MD 20993

JUN 1 5 2015

Frank Casty, M.D.
Mylan Specialty, L.P.
1000 Mylan Blvd.
Canonsburg, PA 15317

Re: Docket No. FDA-2015-P-0181

Dear Dr. Casty:

This letter responds to your citizen petition dated January 16, 2015 (Petition) and supplement dated April 28, 2015. In the Petition, you request that the Food and Drug Administration (FDA or the Agency) take certain actions with respect to abbreviated new drug application (ANDA) 090589, submitted by Teva Pharmaceuticals, for an epinephrine auto-injector (hereafter Teva application or product). Among other things, you ask that the Commissioner refrain from approving the Teva application unless, after conducting an appropriately rigorous review under the established standards for proposed generic emergency use auto-injectors, the Agency concludes that the proposed product is the "same as" the EpiPen auto-injector. You state that this includes the request that patients, caregivers, and other relevant user groups trained in the use of the EpiPen auto-injector who face an emergency situation be able to safely and effectively use the proposed product in accordance with the EpiPen auto-injector instructions for use, without additional physician interaction or training.

We have carefully considered the Petition and supplement. For the reasons stated below, the Petition is denied without comment on whether we will take the actions you request.

I. BACKGROUND

A. EpiPen

Mylan Specialty, L.P., holds approved new drug application (NDA) 019430 for EpiPen (epinephrine auto-injector). The product is indicated in the emergency treatment of allergic reactions (Type I) including anaphylaxis of various origins. It is available in two strengths, 0.3 milligram (mg)/delivery (0.3 mg/0.3 mL) (the EpiPen auto-injector) (yellow carrier cap and label) and 0.15 mg/delivery (0.15 mg/0.3 mL) (the EpiPen Jr auto-injector) (green carrier cap and label). EpiPen was initially approved on December 22, 1987.

B. Section 505(q) of the FD&C Act

Section 505(q) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) was added by section 914 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Pub. L. 110-85, 121 Stat. 823) and was amended by the Food and Drug Administration Safety and Innovation Act (FDASIA), which was signed into law on July 9, 2012 (Pub. L. 112-144, 126 Stat. 993). Section 505(q), as originally added by FDAAA, applies to certain citizen petitions and petitions for stay of Agency action that request that FDA take any form of action relating to a pending application submitted under section 505(b)(2) or (j) of the FD&C Act (21 U.S.C. 355(b)(2) or (j)) and governs the manner in which these petitions are treated. Among other things, section 505(q)(1)(F) of the FD&C Act governs the time frame for final Agency action on a petition subject to section 505(q). Under this provision, FDA must take final Agency action on a petition not later than 150 days after the date on which the petition is submitted. The 150-day period is not to be extended for any reason.

II. DISCUSSION

In the Petition, you request that FDA:

1. Refrain from approving the Teva application unless the Agency affirmatively finds that the proposed generic product is the same as the EpiPen auto-injector such that:

    a. Patients, caregivers, and other relevant user groups who were trained in the use of the EpiPen auto-injector and who face an emergency situation are able to safely and effectively use the Teva product in accordance with the instructions for the EpiPen auto-injector without additional retraining or physician interaction;

    b. No human factors or other clinical testing is required to demonstrate the Teva product's safety or effectiveness in actual use by patients or their caregivers who were trained in the use of the EpiPen auto-injector, or such that the Teva product has the same safety and effectiveness profile as the EpiPen auto-injector;

    c. The instructions for use and related aspects of the label and labeling of the Teva product do not differ from the EpiPen auto-injector label and labeling beyond differences permitted by the statute and applicable regulations, which require that a generic product generally have the same labeling as the reference listed drug (RLD);

    d. Considering the EpiPen auto-injector as a whole and its individual constituent parts, differences between the Teva product and the EpiPen auto-injector do not introduce new risks, taking into account both risks intrinsic to the Teva product and risks associated with switching from one epinephrine auto-injector to another without training or physician intervention; and

e. The Teva product is shown to be bioequivalent to the EpiPen auto-injector through appropriately designed bioequivalence testing to examine potential performance differences resulting from design differences and to assure equivalent clinical outcomes in the context of generic substitution.

2. Require Teva to provide the information necessary to make the above determinations, including specific information regarding product design and operating principles, as well as the results of comparative performance tests between the Teva product and the EpiPen auto-injector, as detailed in the Petition.

3. Require withdrawal of the ANDA and submission of an NDA under section 505(b)(2) of the FD&C Act because human factors or other clinical testing is required to demonstrate the Teva product's safety or effectiveness in actual use.

4. Not assign a therapeutic equivalence code to the Teva product indicating its therapeutic equivalence to the EpiPen auto-injector if the Teva product is approved under a 505(b)(2) NDA, unless the Agency finds that the two products are bioequivalent and can be expected to have the same clinical effect and safety profile when administered for the approved use and substituted without retraining.

5. Convene a joint meeting of the appropriate advisory committees to provide expert advice and clarity to the Agency on the complex scientific, technical, regulatory, and policy issues implicated by the data-driven evaluation of the "sameness" of the Teva proposed generic epinephrine auto-injector and the EpiPen auto-injector.

(Petition at 4-5.)

As grounds for your requests, your Petition cites previously issued Agency citizen petition responses[1] and guidances[2] that generally articulate Agency's thinking with regard to evaluating the approvability of an ANDA for a proposed generic auto-injector (Petition at 1-3, 10-13, 23-25), and states that this Petition is specific to the Teva product. You assert that application of the standards enumerated in the cited petition responses and guidances should lead FDA to not approve the Teva application, or to preclude a therapeutic equivalence rating if the product is approved under section 505(b)(2) of the FD&C Act.

You state that there are significant differences between the Teva product and the EpiPen that preclude the Teva product's approval under section 505(j) of the FD&C Act. You state that these include differences in design and operating principles, such as the manner in which the safety cap is released, preparation of the needle, and the method of injection (Petition at 9, 14-21). You assert that these differences would prevent a patient or caregiver trained on the EpiPen auto-injector from being able to use the Teva product safely and effectively in an emergency or in accordance with the EpiPen instructions for use (Petition at 14). For similar reasons, you assert that even under a 505(b)(2) approval, the product differences enumerated throughout the Petition preclude a designation of therapeutic equivalence.

As described in section I.B of this response, section 505(q)(1)(F) of the FD&C Act requires FDA to take final Agency action on the Petition within 150 days of submission. Therefore, we must take action on the Petition at this time. For the reasons explained below, we deny without comment the specific requests in your Petition regarding the approvability of any specific 505(j) application.

FDA has made no final determination on whether to approve or not approve any ANDA relying on EpiPen as the RLD. Therefore, we must determine whether it would be appropriate for us to take final Agency action on the approvability of a specific aspect of an application before taking final action on the approvability of the application as a whole. To make this determination, we believe it is appropriate to evaluate the statutory and regulatory provisions governing the content and review of 505(j) applications in connection with the statutory provision of section 505(q) of the FD&C Act governing the time frame for action on the Petition.

The FD&C Act and FDA regulations establish procedural protections for applicants in the context of application review. Section 505 of the FD&C Act and FDA's regulations at 21 CFR part 314 describe certain procedures by which the Agency reviews an NDA or ANDA and notifies an applicant if it determines that an application is approved (§ 314.105) or may not be approved (section 505(c) and (j) of the FD&C Act; §§ 314.125 and 314.127), or identifies the deficiencies in the application and the steps an applicant may take to respond to the deficiencies (§ 314.110). In addition, the statute and regulations describe a specific process through which an applicant whose application the Agency has found does not meet the requirements for approval may challenge the Agency's determination (section 505(c)(1)(B) and (d) of the FD&C Act; § 314.200). Under this process, the Agency will give the applicant notice of an opportunity for a hearing on whether the application is approvable, with a specific time frame and process, should the applicant request such a hearing (id.). These procedures ensure that applicants have an adequate opportunity to challenge a finding by the Agency that a product does not meet the requirements for approval.

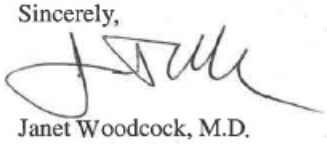
There is no evidence that in enacting section 505(q) of the FD&C Act, Congress intended to bypass the application review process or to lessen an ANDA or NDA applicant's procedural rights by requiring that the Agency make decisions that constitute final Agency action regarding the approvability of certain aspects of pending applications on a piecemeal basis outside of the

process established under the FD&C Act and FDA regulations.[3] Therefore, we do not interpret section 505(q) of the FD&C Act to require that the Agency render a final Agency decision within the statutory deadline on the approvability of a specific aspect of an application when a final decision on the approvability of any such application has not yet been made.[4] Accordingly, we are denying without comment your requests on the specific requirements for approval of an application relying on EpiPen as the RLD.

III. CONCLUSION

For the reasons described in this response, the Petition is denied.

Sincerely,



Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research

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

NOTE TO REGULATORY PROJECT MANAGER (RPM): Currently there is a pending clinical consult with DCR.

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA:	090589
APPLICANT:	Teva Pharmaceuticals USA
DRUG PRODUCT:	Epinephrine Injection USP (Auto-Injector), 0.3 mg/0.3 mL and 0.15 mg/0.3 mL

No letter is prepared at this time pending the response of the DCR consult request.

Sincerely yours,

{See appended electronic signature page}

Nilufer M. Tampal, Ph.D.
Director, Division of Bioequivalence III
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

5 OUTCOME PAGE

http://cdsogd1/bioprod

Reviewer: Suman Dandamudi **Date Completed:**
Verifier: , **Date Verified:**
Division: Division of Bioequivalence
Description: Epinephrine Injection (Auto-Injector)

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Score*	*Subtotal*
32363	4/19/2017	BIO	ANDA Amendment [1]	1	1
32363	4/19/2017	Parallel	Study Amendment [1]	1	1
32363	4/19/2017	Parallel	In-Vitro Study, Per Study [0.5]	0.5	0.5
32363	4/19/2017	Parallel	In-Vitro Study, Per Study [0.5]	0.5	0.5
32363	4/19/2017	Parallel	In-Vitro Study, Per Study [0.5]	0.5	0.5
32363	4/19/2017	Parallel	In-Vitro Study, Per Study [0.5]	0.5	0.5
32363	4/19/2017	Complexity	First Generic Drug Product Review [1]	1	1
32363	4/19/2017	Complexity	Formulation & Device [0.5]	0.5	0.5
32363	9/19/2017	BIOQUALITY	Quality Assessment [1-5]	4.75	4.75
				Total:	10.25

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	090589		
Drug Product Name	Epinephrine Injection USP (Auto-Injector)		
Strength(s)	0.15 mg/0.3 mL, 0.3 mg/0.3 mL		
Applicant Name	Teva Pharmaceuticals USA		
Applicant Address	425 Privet Road, Horsham, PA 19044		
Applicant's Point of Contact	Cory Wohlbach Senior Director, Regulatory Affairs, US Generics		
Contact's Telephone Number	215-293-6519		
Contact's Fax Number	215-591-8812		
Contact's Email Address	Cory.wohlbach@tevapharm.com		
Original Submission Date(s)	December 21, 2007 May 30, 2008 (Amendment), May 22, 2009 (Amendment) July 31, 2013 (in vitro), December 30, 2014 (re-formulation) and May 20, 2015 (Amendment) March 08, 2016 (Post Complete Response Meeting Request)		
Submission Date(s) of Amendment(s) Under Review	October 28, 2016 (Complete Response)		
First Generic	Yes		
Primary Reviewer	Harikrishna Devalapally, Ph. D.		
Secondary Reviewer	Suman Dandamudi, Ph. D.		
OVERALL REVIEW RESULT	**ADEQUATE**		
REVISED/NEW DRAFT GUIDANCE INCLUDED	**NO**		
COMMUNICATION	☐ **ECD** ☐ **IR** ☒ **NOT APPLICABLE**		
BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	**STUDY/TEST TYPE**	**STRENGTH**	**REVIEW RESULT**
21, 25, 26, 38	**Waiver**	**0.3 mg/0.3 mL & 0.15 mg/0.3 mL**	**ADEQUATE**

ADDENDUM: Post Complete Response (CR) Meeting Request (MR) Review

I. EXECUTIVE SUMMARY

This is an addendum to a previous bioequivalence review of post complete response (CR) meeting request (MR)[1] which contains review of a consult response from the Division of Clinical Review (DCR)[2] and Office of Pharmaceutical Quality (OPQ)[3]. In the previous review, the Division of Bioequivalence III (DBIII) deemed the BE portion of the application to be adequate.

The purpose of this addendum is to verify if the firm's response to the CR letter raise any concerns on BE outcome. On October 28, 2016, Agency sent Complete Response (CR) letter which stated that the firm may submit discipline-specific submissions in response to the CR letter, instead of one complete CR amendment[4]. In response to the CR, the firm provided same responses to BE deficiency comments which were previously sent to the Agency on March 8, 2016. The firm's responses were already evaluated in previous BE review and deemed as adequate[1].

Therefore, the BE portion of the application remains **adequate**.

The final adequate BE letter for this ANDA can be found in the previous consult response review[5].

II. DEFICIENCY COMMENT

None

III. RECOMMENDATION

The Division of Bioequivalence III (DBIII) agrees that the information submitted by Teva Pharmaceutical demonstrates that Epinephrine Injection USP, 0.3 mg/mL and 0.15 mg/mL, pre-filled syringe with auto-injector meets the requirements of Section 21 CFR § 320.24 (b) (6). The waiver request of in vivo bioequivalence study requirements for the test product granted at this time.

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[1] GDRP ANDA-090589-ORIG-1-AMEND-6, BE review: http://panorama.fda.gov/task/view?ID=5420f1160002bc9df9be4d40027ff2e6, Suman Dandamudi, 10/19/2016.
[2] GDRP for 090589: http://panorama fda.gov/task/view?ID=5420f1160002bc9df9be4d40027ff2e6, Ke Ren, 7/8/2016.
[3] GDRP for 090589: http://panorama fda.gov/task/view?ID=5420f1160002bc9df9be4d40027ff2e6, Ke Ren, 7/7/2016.
[4] EDR, ANDA-090589, Application 090589 - Sequence 0033 - Cover Letter 28Oct2016 - Complete Response, M.1.2, 10/28/2016
[5] GDRP ANDA-090589-ORIG-1-AMEND-6, BE review: http://panorama.fda.gov/task/view?ID=5420f1160002bc9df9be4d40027ff2e6 Suman Dandamudi, A09058N006DB_CRR03082016; Date uploaded 10/19/2016

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	090589		
Drug Product Name	Epinephrine Injection USP (Auto-Injector)		
Strength(s)	0.15 mg/0.3 mL, 0.3 mg/0.3 mL		
Applicant Name	Teva Pharmaceuticals USA		
Applicant Address	425 Privet Road, Horsham, PA 19044		
Applicant's Point of Contact	Cory Wohlbach Senior Director, Regulatory Affairs, US Generics		
Contact's Telephone Number	215-293-6519		
Contact's Fax Number	215-591-8812		
Contact's Email Address	Cory.wohlbach@tevapharm.com		
Original Submission Date(s)	December 21, 2007 May 30, 2008 (Amendment), May 22, 2009 (Amendment) July 31, 2013 (in vitro), December 30, 2014 (re-formulation) and May 20, 2015 (Amendment)		
Submission Date(s) of Amendment(s) Under Review	March 18, 2016 (Post Complete Response Meeting Request)		
Reviewer	Harikrishna Devalapally, Ph. D.		
OVERALL REVIEW RESULT	**ADEQUATE**		
REVISED/NEW DRAFT GUIDANCE INCLUDED	**NO**		
COMMUNICATION	☐ **ECD** ☐ **IR** ☒ **NOT APPLICABLE**		
BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	**STUDY/TEST TYPE**	**STRENGTH**	**REVIEW RESULT**
21, 25, 26	**Waiver**	**0.3 mg/0.3 mL & 0.15 mg/0.3 mL**	**ADEQUATE**

ADDENDUM: Review of Consult Responses

I. EXECUTIVE SUMMARY

This is an addendum to a previous post complete response (CR) meeting request (MR) review[1] to include the review of a consult response from the Division of Clinical Review (DCR)[2] regarding '*whether the amount* (b) (4) *sodium tartrate should be of a safety concern when administered subcutaneously in pediatric*

[1] GDRP ANDA 090589, BE review: http://panorama.fda.gov/task/view?ID=5420f1160002bc9df9be4d40027ff2e6, Ke Ren, 5/13/2016.
[2] GDRP for 090589: http://panorama fda.gov/task/view?ID=5420f1160002bc9df9be4d40027ff2e6, Ke Ren, 7/8/2016.

population'. And also to include review of a consult response from the Office of Pharmaceutical Quality (OPQ)[3] regarding '(b) (4)

(b) (4)

DCR conducted extensive search of different FDA databases regarding the inactive ingredient, sodium tartrate dihydrate. (b) (4)

(b) (4)

The Division of Bioequivalence III (DBIII) agrees with the DCR and OPQ recommendation regarding the firm's justification.

Therefore, the DBIII deems the test products, Epinephrine Injection USP, 0.15 mg/0.3 mL (Auto Injector Jr.) and 0.3 mg/0.3 mL (Auto Injector), manufactured by Teva Pharmaceuticals to be bioequivalent to the RLD product, EpiPen® and EpiPen® Jr (epinephrine injection) Auto-Injector, 0.3 mg/0.3 mL and 0.15 mg/0.3 mL respectively, manufactured by Mylan Speclt, under 21 CFR § 320. 24 (b)(6).

The BE portion of the application remains **adequate**.

[3] GDRP for 090589: http://panorama fda.gov/task/view?ID=5420f1160002bc9df9be4d40027ff2e6, Ke Ren, 7/7/2016.

II. TABLE OF CONTENTS

III. BACKGROUND

1. Teva Pharmaceuticals submitted ANDA 090589 for its test product, Epinephrine Injection (auto-injector) 0.15 mg/0.3mL and 0.3 mg/0.3mL. The submission references NDA 019430, EpiPen® (epinephrine injection) Auto-Injector, 0.3 mg and EpiPen Jr® (epinephrine injection) Auto-Injector, 0.15 mg from Mylan Speclt.

2. In the original submission dated 12/21/2007, the firm requested the waiver of in vivo bioequivalence study requirements under 21 CFR § 320.22(b)(1) for its test products, Epinephrine Injection USP, 0.15 mg/0.3 mL (Auto Injector Jr.) and 0.3 mg/0.3 mL (Auto Injector).

3. Since, the drug product is an autoinjector, in addition to the formulation comparison, device similarity by *in vitro* comparative performance should be demonstrated for approval of this drug product. The firm has provided the comparative summary results of the performance parameters between the test and RLD devices on 5/30/2008. The original application was accepted for filing on 11/21/2008[4].

4. The OGD has requested the division of pulmonary and allergy products (DPAP)'s feedback regarding the mechanism of action (MOA) of the innovator's autoinjector compared to TEVA's proposed auto-injector[5]. On 11/13/2008, DPAP reviewed OGD's request and concluded that mechanism of action of the TEVA auto-injector product and the Epipen auto-injector product is the same[6].

5. In the CR letter dated 4/30/2009, the Agency communicated the firm that the information and data provided in the original submission dated December 21, 2007, and in the addendum dated May 30, 2008 do not support claim that the TEVA' s proposed autoinjector intended for subcutaneous delivery of epinephrine is comparable to the EpiPen Autoinjector[7].

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[4] MARGAND, IAIN, 01/02/2009, MAIL, 01/02/2009, COR-ANDAFILE-01(Filing Acknowledgment (General)), Original-1
[5] LIU, THERESA C, 10/15/2008, N/A, 10/15/2008, FRM-CONSULT-01(General Consult Request) Original-1
[6] GILBERT MCCLAIN, LYDIA I, 11/13/2008, N/A, 11/13/2008, REV-CLINICAL-03(General Review) Original-1
[7] CHUH, EUNJUNG E, 04/30/2009, MAIL, 04/30/2009, COR-ANDAACTION-09(Complete Response), Original-1
Original-1

6. Since the firm did not provide the individual data for the in vitro tests to demonstrate comparable performance between the test and RLD devices, the firm was asked to conduct suitable in vitro tests to document the performance characteristics and submit the data for evaluation[8].

7. On 04/04/2012, an inter center consultation request was submitted to CDRH for the review of the firm's submitted protocol[9]. In the amendment dated 1/20/2012, the firm has submitted the protocol for the human factors study. The CDRH has conducted the review of this protocol and provided its recommendations[10]. These recommendations were conveyed to the firm by Division of Chemistry[11].

8. In the amendment dated 12/30/2014, the firm has submitted the Human Factor Study results. On 06/25/2015, an inter-center consultation request was submitted to CDRH and OSE for the review of the firm's submitted results[12]. OSE has reviewed and provided comments on the submitted human factor study results on 2/11/2016[13].

9. On 3/20/2013, OPQ requested DCR to assess if there is a clinical concern regarding the longer needle length of Teva Pharmaceuticals' proposed generic epinephrine auto-injector, compared to the needle length of the RLD, EpiPen[14]. DCR reviewed and concluded that the slightly longer needle length of Teva's product compared to the RLD is not clinically significant, and should not be a factor in the approval of ANDA 90589 as a generic to EpiPen[15].

10. In the amendment dated 12/30/2014, the firm has submitted the re-formulated test product. The re-formulated test product is NOT qualitatively (Q1) and quantitatively (Q2) the same as RLD product. The test product contains sodium tartrate dihydrate (b) (4) (b) (4) whereas the RLD product contains no (b) (4). In addition, the firm's re-formulated test product (0.4 mg) contained considerably lower quantity of Sodium Metabisulfite than in the RLD formulation (0.5 mg). The firm has also submitted the results of in vitro bioequivalence (BE) studies comparing the test and RLD product devices. The test and RLD devices comparison data submitted for different tests were acceptable from the bioequivalence perspective[16].

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[8] DARRTS for ANDA 090589: TAMPAL, NILUFER M 03/11/2010 N/A 03/11/2010 REV-BIOEQ-01(General Review) Original-1 Archive

[9] DARRTS for ANDA 090589: DARJ, MIKE 04/04/2012 N/A 04/04/2012 FRM-CONSULT-02(Intercenter/Combination Products Consult) Original-1 Archive

[10] DARRTS for ANDA 090589: TRAN, TRANG Q 05/07/2012 N/A 05/07/2012 FRM-ADMIN-01(Memorandum to File) Original-1 Archive

[11] DARRTS for ANDA 090589: DARJ, MIKE 12/20/2012 N/A 12/20/2012 REV-QUALITY-03(General Review) Original-1 Archive

[12] DARRTS for ANDA 090589: HUANG, XIAOHUA 06/25/2015 N/A 06/25/2015 FRM-CONSULT-06(OSE Consult (Except Proprietary Name Reviews)) Original-1 Archive

[13] OWENS, LISSA C, 02/11/2016, N/A, 02/11/2016, REV-SURVEPI-24(Human Factors Review) Original-1

[14] DARJ, MIKE, 03/20/2013, N/A, 03/20/2013, FRM-CONSULT-01(General Consult Request), Original-1

[15] SEIBEL, DEBORAH J, 04/29/2013, N/A, 04/29/2013, CONSULT REV-CLINICAL-01(General Consult Review), Original-1

[16] GDRP for ANDA 090589- Bioequivalence Review-

11. On 6/25/2015 a consultation request was submitted to DCR to determine whether the amount of sodium tartrate dihydrate used in the formulation of Teva's Epinephrine Injection, 0.3 mg/0.3 mL and 0.15 mg/0.3 mL should be a safety concern when administered subcutaneously[17].

12. DCR has concluded that the firm should consider re-formulating its test product since sodium tartrate dihydrate is considered as a novel excipient for the subcutaneous route of administration and there were no approved drug products administered subcutaneously that contain sodium tartrate dihydrate as an excipient[18].

13. On February 23, 2016 the deficiency related to the inactive ingredient, sodium tartrate dihydrate was conveyed to the firm through a Complete Response Letter[19] and DBIII deemed the application to be inadequate[20].

14. The OPQ has submitted inter-center consultation request to CDRH on 6/25/2015 for the evaluation of the Teva's re-designed auto-injector device (Vibex (b) (4)[21].On 10/27/2015, CDRH has provided its response to the consultation request regarding the review of the device. The CDRH has conducted thorough review of the device and its components and listed the deficiencies to be conveyed to the firm[22]. The deficiencies related to the device were sent to the firm in the Complete Response letter dated April 20, 2016 by Office of Pharmaceutical Quality.

15. On March 8, 2016, the firm submitted a request for a Post Complete Response Meeting Request (post CR MR) with the OGD for clarification of sodium tartrate dihydrate to be considered as novel excipient for the subcutaneous route of administration[23]. Agency has accepted firm's meeting request and determined that written response would be the most appropriate to discuss the deficiencies noted in CR[24].

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http://panorama.fda.gov/PanoramaDocMgmt/document/download/090026f880ae507f , Suman Dandamudi, 7/2/2015

[17] GDRP for ANDA 090589, Clinical Consult Request: http://panorama.fda.gov/PanoramaDocMgmt/document/download/090026f880ae5418, Suman Dandamudi, 7/2/2015

[18] GDRP for ANDA 090589, Consult Response: http://panorama.fda.gov/task/view?ID=5420f1160002bcdbd808308629e66727, 9/7/2016 (reviewed on 10/29/2015)

[19] GDRP for ANDA 090589: Final Decision- http://panorama.fda.gov/task/view?ID=56e1db890065a9c90d34d6a8b5cf6e6e, Jessica Kreger, 4/20/2016.

[20] GDRP for ANDA 090589: Consult Response Review- http://panorama.fda.gov/PanoramaDocMgmt/webhooks/viewdownload?id=090026f880c1b943, Suman Dandamudi, 11/16/2015

[21] DARRTS for ANDA 090589: HUANG, XIAOHUA 06/25/2015 N/A 06/25/2015 FRM-CONSULT-02(Intercenter/Combination Products Consult) Original-1

[22] GDRP for ANDA 090589: ANDA 090589.TEVA.Epipen.CDRH Engineering Evaluation. Stervens.pdf, Date uploaded 10/27/2015. http://panorama.fda.gov/task/view?ID=5420f1160002bbfe419982883f9a1a75

[23] GDRP for 090589: 03/08/2016: Meeting/Meeting Request General Information-1

[24] GDRP for 090589: http://panorama fda.gov/task/view?ID=56e1db890065a97a851fcca9c0431840, Jessica Kreger, 3/21/2016.

16. In the CR letter, the firm has provided the justification for the use of sodium tartrate dehydrate in the test formulation that included: Toxicity Study Report DS-2014-062, Inactive Ingredient Database (IID) reference for (b) (4) in an approved product, Signifor and thus request the Agency to not consider as a novel excipient for subcutaneous route of administration.

17. Based on the information provided by the firm in their submission dated March 8, 2016, the DBIII re-evaluated the amount of sodium tartrate dihydrate in the test formulation and agrees with the firm that the amount of this ingredient is within the acceptable limits for subcutaneous administration based on the FDA's Inactive Ingredient database[25].

18. However, the listed drug product Signifor® (pasireotide diasparate) Solution is indicated for the treatment of adult patients with Cushing's disease for whom pituitary surgery is not an option or has not been curative. As per the labeling, no studies have been performed and safety and effectiveness of Signifor® have not been established in pediatric patients[26]. Whereas the current test product Epinephrine Injection USP, 0.15 mg/0.3 mL (Auto Injector Jr.) and 0.3 mg/0.3 mL (Auto Injector) has pediatric use as per the labeling[27].

19. Based on the above-mentioned information, the DBIII requested expert opinion from the DCR[28]to evaluate if the amount of sodium tartrate dihydrate used in the formulation of Teva's Epinephrine Injection, 0.3 mg/0.3 mL and 0.15 mg/0.3 mL poses a safety concern for adult and pediatric patients, when administered subcutaneously?

20. In addition to the consult request submitted to the DCR, DBIII also requested the Office of Pharmaceutical Quality (OPQ) to comment whether firm's justification (b) (4) (b) (4) is acceptable[29].

IV. REVIEW OF CONSULT RESPONSES

DCR Consult Request:

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[25] GDRP for ANDA 090589: Post CR MR Review- http://panorama.fda.gov/PanoramaDocMgmt/webhooks/viewdownload?id=090026f880cf427c, Ke Ren, 5/13/2016

[26]Drugs@FDA, http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/200677s002lbl.pdf, Last accessed 7/2/2016

[27] Drugs@FDA, http://www.accessdata fda.gov/drugsatfda_docs/label/2016/019430s061lbl.pdf, Last accessed 7/2/2016

[28] GDRP for 090589: http://panorama fda.gov/task/view?ID=5420f1160002bc9df9be4d40027ff2e6, Ke Ren, 7/8/2016.

[29] GDRP for 090589: http://panorama fda.gov/task/view?ID=5420f1160002bc9df9be4d40027ff2e6, Ke Ren, 7/7/2016.

Background

Signifor® (pasireotide diasparate) Solution, Subcutaneous Injection (NDA 200677) contains [redacted]. The MDD of pasireotide diasparate is 1.8 mg/day. [redacted] Thus the amount of sodium tartrate dihydrate in the test formulation was considered within the acceptable limits for subcutaneous administration based on the FDA's Inactive Ingredient database. However, the listed drug product Signifor® (pasireotide diasparate) Solution indicated for the treatment of adult patients with Cushing's disease for whom pituitary surgery is not an option or has not been curative. As per the labeling, no studies have been performed and safety and effectiveness of SIGNIFOR have not been established in pediatric patients. Whereas the current test product Epinephrine Injection USP, 0.15 mg/0.3 mL (Auto Injector Jr.) and 0.3 mg/0.3 mL (Auto Injector) has pediatric use as per the labeling.

Consult Comments

[redacted] *DBIII requests DCR to evaluate if the amount of sodium tartrate dihydrate used in the formulation of Teva's Epinephrine Injection, 0.3 mg/0.3 mL and 0.15 mg/0.3 mL poses a safety concern for adult patients, when administered subcutaneously?*

[redacted]

In addition to the consult request submitted to the DCR, DBIII is also requesting the Office of Pharmaceutical Quality (OPQ) to comment whether firm's justification "sodium tartrate [redacted] *is acceptable. Please note that according to the OPQ draft consult response, the firm's justification is acceptable.*

DBIII is planning to coordinate the consults responses from both groups, and if necessary, arrange a meeting between DCR, OPQ and DBIII, following the consults, to reach the final recommendations that are acceptable to all disciplines.

Consult Response[31]

The Division of Clinical Review has evaluated the firm's proposed test formulation along with database searches of Mercado and FDA's internal Inactive Ingredient Database

[30] DARRTS for NDA 200677: STEPHENS, OLEN M 10/16/2012 N/A 10/16/2012 REV-QUALITY-03(General Review) Original-1 (Type 1- New Molecular Entity) Archive

[31] GDRP for 090589: http://panorama fda.gov/task/view?ID=5776aaa60042f92d3c68f61ac1cb4cd5, Karen Feibus, 9/7/2016.

(IID) to identify approved drug products administered via the SC route that contain (b) (4) and have similar conditions of use (indication and population) to the proposed epinephrine auto-injection product.

(b) (4)

Teva's proposed epinephrine auto-injection product (b) (4) (b) (4) treatment of anaphylaxis that can be administered IM or SC. The proposed epinephrine auto-injector dose for adults and children weighing ≥30 kg (b) (4) (b) (4) and the proposed epinephrine auto-injector dose for children weighing 15 to less than 30 kg (b) (4) (b) (4)

(b) (4)

[32] GDRP for 090589: http://panorama fda.gov/task/view?ID=578d28ef0036c6f42415a8448c33752a, Nitin Patel, 7/18/2016.

(b) (4)

(b) (4)

OPQ Consult Request:

Background

The amount of sodium tartrate dihydrate in the test formulation was found to be within the acceptable limits for Intramuscular administration based on the FDA's Inactive Ingredient database (IID). However, FDA's IID does not include any information for the above stated inactive ingredient for the subcutaneous route of administration. (b) (4)

(b) (4)

[33] GDRP for 090589: http://panorama fda.gov/task/view?ID=578d28f00036c6fbfb5a80e1d2464177, Mike Darj, 8/19/2016.

(b) (4)

Consult Comments

Based on the above facts, DBIII is seeking expert opinion from the Division of Chemistry in the Office of Pharmaceutical Quality (OPQ) on the following question:

(b) (4)

Consult Response [34]**:**

(b) (4)

Reviewer's Comments:

- In the amendment dated July 31, 2013, the firm requested a waiver of *in vivo* bioequivalence study requirements under 21 CFR § 320.22(b)(1) for its **re-formulated** test products, Epinephrine Injection USP, 0.15 mg/0.3 mL (Auto Injector

[34] GDRP for 090589: http://panorama fda.gov/task/view?ID=5776a72d0042c7fbc115f020696f84cc, Mike Darj, 8/10/2016.

Jr.) and 0.3 mg/0.3 mL (Auto Injector). In the previous BE review of the amendment dated 12/30/2014, the re-formulated test product was found to be NOT qualitatively (Q1) and quantitatively (Q2) the same as RLD product. The test products contain sodium tartrate dihydrate (b) (4) whereas the RLD product contains no (b) (4)

- According to 21 CFR § 314.94 (a) (9) (iii), a drug product intended for parenteral use may differ from the RLD in the use of preservatives, buffers, or antioxidants provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety and efficacy of the proposed drug product.

- The test product is intended for both Intramuscular and subcutaneous administration. The amount of Sodium Tartrate Dihydrate in the test formulation was found to be within the acceptable limits for **Intramuscular administration** based on the FDA's Inactive Ingredient database. However, the IIG limit for this inactive ingredient for subcutaneous administration is not provided in the IIG database. Therefore, the firm submitted the toxicology study report demonstrating the safety of sodium tartrate dihydrate used in the test formulation via subcutaneous administration. (b) (4) (b) (4)

- (b) (4)

- And also DBIII requested DCR to comment (b) (4) (b) (4) (b) (4) DCR conducted extensive search of different FDA databases regarding the inactive ingredient, sodium tartrate dihydrate. (b) (4) (b) (4)

- Based on the above information, DBIII agrees with the DCR and OPQ recommendation and considers the firm's proposed test formulation to be adequate.

Notes: In the IR letter dated7/27/2016, OPQ provided minor deficiency comments related to sodium tartrate dihydrate and amount of (b) (4) HCl as below.

(b) (4)

The current BE reviewer is of the opinion that the firm has adequatley demonstrated the use of sodium tartrate (b) (4)

(b) (4)

Therefore, the test formulations are considered acceptable.

V. DEFICIENCY COMMENT

None

VI. RECOMMENDATION

The Division of Bioequivalence III (DBIII) agrees that the information submitted by Teva Pharmaceutical demonstrates that Epinephrine Injection USP, 0.3 mg/mL and 0.15 mg/mL, pre-filled syringe with auto-injector meets the requirements of Section 21 CFR § 320.24 (b) (6). The waiver request of in vivo bioequivalence study requirements for the test product granted at this time.

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[35] DARRTS for ANDA 090589: Firm's Submission dated 12/203/2014. Module 3.2.P.5.4. Batch Analysis, Certificate of Analysis- Epinephrine Injection

[36] Labeling for the RLD Product http://dailymed nlm nih.gov/dailymed/drugInfo.cfm?setid=7560c201-9246-487c-a13b-6295db04274a (Accessed on 6/22/2015)

VII. ATTACHMENTS

1. Original BE Review

original BE.pdf

2. BE Review amendment

A090589N000DB_NA12302014.doc

3. DCR Consult Request (requested on 06/25/2015)

A090589N000DB_C07012015.doc

4. DCR Consult Response (responded on 10/22/2015)

A090589N006 DCR ClinPT_sodium tartrat

5. DCR Consult Response Review

A090589N006DB_CRR12302014.doc

6. Post CR MR Review

A090589N000DB_MEETINGREQUEST030820

7. DCR Consult Request (requested on 07/0 5/ 2016)

A090589N000DB_C07052016 - DCR-Final.pc

8. DCR Consult Response (responded on 09/06/2016)

A090589N006 DCR ClinPT_Follow-up_sod

9. DCR to OPQ Consult Request (requested on 07/15/ 2016)

A090589 DCR Consult to OPQ (b) (4) a

10. OPQ Consult Response (responded on 8/19/2016)

Coomment to A090589 DCR Consult

11. OPQ Consult Request (requested on 07/05/ 2016)

A090589N000DB_C11242008 - OPQ-Final.pc

12. OPQ Consult Response (responded 08/10/2016)

Comment to Consult Request from DBE-1.d

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA:	090589
APPLICANT:	Teva Pharmaceuticals USA
DRUG PRODUCT:	Epinephrine Injection USP (Auto-Injector), 0.3 mg/0.3 mL and 0.15 mg/0.3 mL

The Division of Bioequivalence III (DBIII) has completed its review of your submission acknowledged on the cover sheet and has no further questions at this time.

The bioequivalence comments provided in this communication are comprehensive as of issuance. However, these comments are subject to revision if additional concerns raised by chemistry, manufacturing and controls, microbiology, labeling, other scientific or regulatory issues or inspectional results arise in the future. Please be advised that these concerns may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

{See appended electronic signature page}

Nilufer M. Tampal, Ph.D.
Acting Director, Division of Bioequivalence III
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

VIII. OUTCOME

ANDA: 090589

Reviewer: Devalapally, Harikrishna

Date Completed:

Verifier: ,

Date Verified:

Division: Division of Bioequivalence

Description: Epinephrine Injection USP (Auto-Injector), 0.3 mg/0.3 mL and 0.15 mg/0.3 mL

Items:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Score*	*Subtotal*
28938	3/8/2016	BIO	Consult Review (For consults to Other Office)[1]	2	2
28938	3/8/2016	Parallel	Review of the Consult Response and Formal Consult to DB [1]	2	2
28938	9/11/2016	BIOQUALITY	Quality Assessment [1-5]	4	4
				Total:	8

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	090589
Drug Product Name	Epinephrine Injection USP (Auto-Injector)
Strength(s)	0.15 mg/0.3 mL and 0.3 mg/0.3 mL
Applicant Name	Teva Pharmaceuticals USA
Address	425 Privet Road, Horsham, PA 19044
Applicant's Point of Contact	Cory Wohlbach
Contact's Telephone Number	215-293-6519
Contact's Fax Number	215-591-8812
Contact's Email Address	Cory.wohlbach@tevapharm.com
Original Submission Date(s)	December 21, 2007 May 30, 2008 (Amendment), May 22, 2009 (Amendment) July 31, 2013, December 30, 2014 and May 20, 2015 (Amendment)
Submission Date(s) of Amendment(s) Under Review	March 18, 2016 (Post Complete Response Meeting Request)
Reviewer	Suman Dandamudi, Ph.D.
Study Number (s)	N/A
Study Type (s)	N/A
Strength (s)	N/A
Clinical Site	N/A
Analytical Site	N/A
OSI STATUS	**Backlog, Year 1 and Year 2 ANDAs** ☐ **Pending** ☐ **Complete** ☒ **NOT APPLICABLE**[1] **Year 3 ANDAs** ☐ **To Be Determined by OSIS** ☐ **Pending For Cause Inspection**
OVERALL REVIEW RESULT	**ADEQUATE**
REVISED/NEW DRAFT GUIDANCE INCLUDED	**NO**
COMMUNICATION	☐**ECD** ☐ **IR** ☒ **NOT APPLICABLE**

BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	**STUDY/TEST TYPE**	**STRENGTH**	**REVIEW RESULT**
21, 25	**In Vitro Tests**	**0.3 mg/0.3 mL and 0.15 mg/0.3 mL**	**ADEQUATE**

[1]No BE study is required for this application; therefore, the OSIS inspection is not applicable.

REVIEW OF A POST-CR MEETING REQUEST

1 EXECUTIVE SUMMARY

This is review of the firm's request for a Post 'Complete Response' Meeting Request.

Teva Pharmaceuticals submitted ANDA 090589 for its test products, Epinephrine Injection USP, 0.15 mg/0.3 mL (Auto Injector Jr.) and 0.3 mg/0.3 mL (Auto Injector). The submission references NDA 019430, EpiPen® and EpiPen® Jr (epinephrine injection) Auto-Injector, 0.3 mg/0.3 mL and 0.15 mg/0.3 mL by Mylan Speclt.

In the amendment dated December 30, 2014, the firm requested a waiver of *in vivo* bioequivalence (BE) study requirements under 21 CFR § 320.22(b)(1) for its re-formulated test product, Epinephrine Injection USP, 0.15 mg/0.3 mL (Auto Injector Jr.) and 0.3 mg/0.3 mL (Auto Injector). In the BE review of this amendment, the re-formulated test product was found to be **NOT** qualitatively (Q1) and quantitatively (Q2) the same as reference product[2]. The test products contain sodium tartrate dihydrate (b) (4) whereas the reference product contains no (b) (4)

The drug product is intended for both Intramuscular and Subcutaneous administration. The amount of sodium tartrate dihydrate in the test formulation was found to be within the acceptable limits for Intramuscular administration based on the FDA's Inactive Ingredient database. However, the IIG limit for the above stated inactive ingredient for subcutaneous administration is not provided in the IIG database. Therefore, a consultation request was submitted to Division of Clinical Review (DCR) to determine whether the amount of sodium tartrate dihydrate used in the formulation of Teva's Epinephrine Injection, 0.3 mg/0.3 mL and 0.15 mg/0.3 mL should be a safety concern when administered subcutaneously[3].

DCR concluded that the firm should consider re-formulating its test product without the inactive ingredient for the following reasons[4]:

1) From the clinical perspective there is insufficient evidence to support the safety of sodium tartrate dihydrate as an inactive ingredient in proposed test product when administered subcutaneously.

2) (b) (4) (b) (4) sodium tartrate dihydrate is considered as a novel excipient for the subcutaneous route of administration.

On February 23, 2016 the deficiency related to the inactive ingredient, sodium tartrate Dihydrate was conveyed to the firm through a Complete Response Letter[5].

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[2] GDRP for ANDA 090589- Bioequivalence Review-
http://panorama.fda.gov/PanoramaDocMgmt/document/download/090026f880ae507f
[3] GDRP for ANDA 090589, Clinical Consult Request:
http://panorama.fda.gov/PanoramaDocMgmt/document/download/090026f880ae5418
[4] GDRP for ANDA 090589, Consult Response:
http://panorama.fda.gov/PanoramaDocMgmt/document/download/090026f880c04574

On March 8, 2016, the firm submitted a request for a Post Complete Response Meeting Request (post CR MR) with the OGD for clarification of sodium tartrate dihydrate to be considered as novel excipient for the subcutaneous route of administration[6].

In the current review, based on the information provided by the firm in their submission dated March 8, 2016, the Division of Bioequivalence III (DBIII) re-evaluated the amount of sodium tartrate dihydrate in the test formulation and agrees with the firm that the amount of this ingredient is within the acceptable limits for subcutaneous administration based on the FDA's Inactive Ingredient database. Thus the test formulations are now considered acceptable.

The test and RLD devices comparison data submitted for different tests are considered acceptable from the bioequivalence perspective[2].

Therefore, the DBIII deems the test products, Epinephrine Injection USP, 0.15 mg/0.3 mL (Auto Injector Jr.) and 0.3 mg/0.3 mL (Auto Injector), manufactured by Teva Pharmaceuticals to be bioequivalent to the RLD product, EpiPen® and EpiPen® Jr (epinephrine injection) Auto-Injector, 0.3 mg/0.3 mL and 0.15 mg/0.3 mL respectively, manufactured by Mylan Speclt, under 21 CFR § 320. 24 (b) (6).

The application is now **adequate.**

2 TABLE OF CONTENTS

[5] GDRP for ANDA 090589: Final Decision-
http://panorama.fda.gov/PanoramaDocMgmt/document/download/090026f880c8626e
[6] DARRTS for 090589: 03/08/2016: Meeting/Meeting Request General Information-1

3 BACKGROUND

1. Teva Pharmaceuticals submitted ANDA 090589 for its test product, Epinephrine Injection (auto-injector) 0.15 mg/0.3mL and 0.3 mg/0.3mL. The submission references NDA 019430, EpiPen® (epinephrine injection) Auto-Injector, 0.3 mg and EpiPen Jr® (epinephrine injection) Auto-Injector, 0.15 mg from Mylan Speclt.

2. In the original application, the firm requested the waiver of in vivo bioequivalence study requirements under 21 CFR § 320.22(b)(1) for its test products, Epinephrine Injection USP, 0.15 mg/0.3 mL (Auto Injector Jr.) and 0.3 mg/0.3 mL (Auto Injector). Since, the drug product is an autoinjector, in addition to the formulation comparison, device similarity by *in vitro* comparative performance should be demonstrated for approval of this drug product. The firm has provided the comparative summary results of the performance parameters between the test and RLD devices.

3. Since the firm did not provide the individual data for the in vitro tests to demonstrate comparable performance between the test and RLD devices, the firm was asked to conduct suitable in vitro tests to document the performance characteristics and submit the data for evaluation[7].

4. In the amendment dated December 30, 2014, the firm has submitted the re-formulated test product. The re-formulated test product is NOT qualitatively (Q1) and quantitatively (Q2) the same as RLD product. The test product contains sodium tartrate dihydrate (b) (4) (b) (4) whereas the RLD product contains no (b) (4). In addition, the firm's re-formulated test product (0.4 mg) contains considerably lower quantity of sodium metabisulfite than in the RLD formulation (0.5 mg)[2].

5. DBIII has submitted consultation request to DCR to determine whether the amount of Sodium Tartrate Dihydrate used in the formulation of Teva's Epinephrine Injection, 0.3 mg/0.3 mL and 0.15 mg/0.3 mL should be of a safety concern when administered subcutaneously[3].

6. The DCR has concluded that the firm should consider re-formulating test product since there is insufficient evidence to support the safety of sodium tartrate dihydrate as an inactive ingredient in proposed test product when administered subcutaneously. In addition sodium tartrate dihydrate is considered as a novel excipient for the subcutaneous route of administration (b) (4) (b) (4)

7. The firm also has submitted the results of in vitro bioequivalence (BE) studies comparing the test and RLD product devices. The test and RLD devices comparison data submitted for different tests are acceptable from the bioequivalence perspective[2].

[7] DARRTS for ANDA 090589: TAMPAL, NILUFER M 03/11/2010 N/A 03/11/2010 REV-BIOEQ-01(General Review) Original-1 Archive

8. On September 30, 2014, the firm submitted a request for a Post Complete Response Meeting Request for clarification on the consideration of sodium tartrate dihydrate as novel excipient for subcutaneous route of administration.

4 REVIEW OF SUBMISSION

Complete Response Deficiencies:

1. **From the clinical perspective, there is insufficient evidence to support the safety of Sodium Tartrate Dihydrate as an inactive ingredient in your proposed Epinephrine Auto-Injector product when administered subcutaneously.**
2. (b) (4) (b) (4) **. We consider Sodium Tartrate Dihydrate to be a novel excipient for the subcutaneous route of administration.**

Firm's Response and Question: Teva's Epinephrine injection is presented as two dosage forms, 0.15 mg for a 15 kg to 30 kg person and 0.3 mg for patients at or above 30 kg. Both dosage forms deliver 0.3 mL and contain sodium chloride, sodium metabisulfite, and sodium tartrate dihydrate as excipients (b) (4) (b) (4)

Table below shows the amounts and percentages of sodium tartrate dihydrate in each dosage form of Teva's Epinephrine injection (b) (4)

Table: Amounts and Percentages of Sodium Tartrate Dihydrate in Each Dosage Form of Teva's Epinephrine Injection

Dosage Form	Amount of Sodium Tartrate Dihydrate	(b) (4)
0.15 mg Epinephrine	0.2 mg	
0.3 mg Epinephrine	0.4 mg	

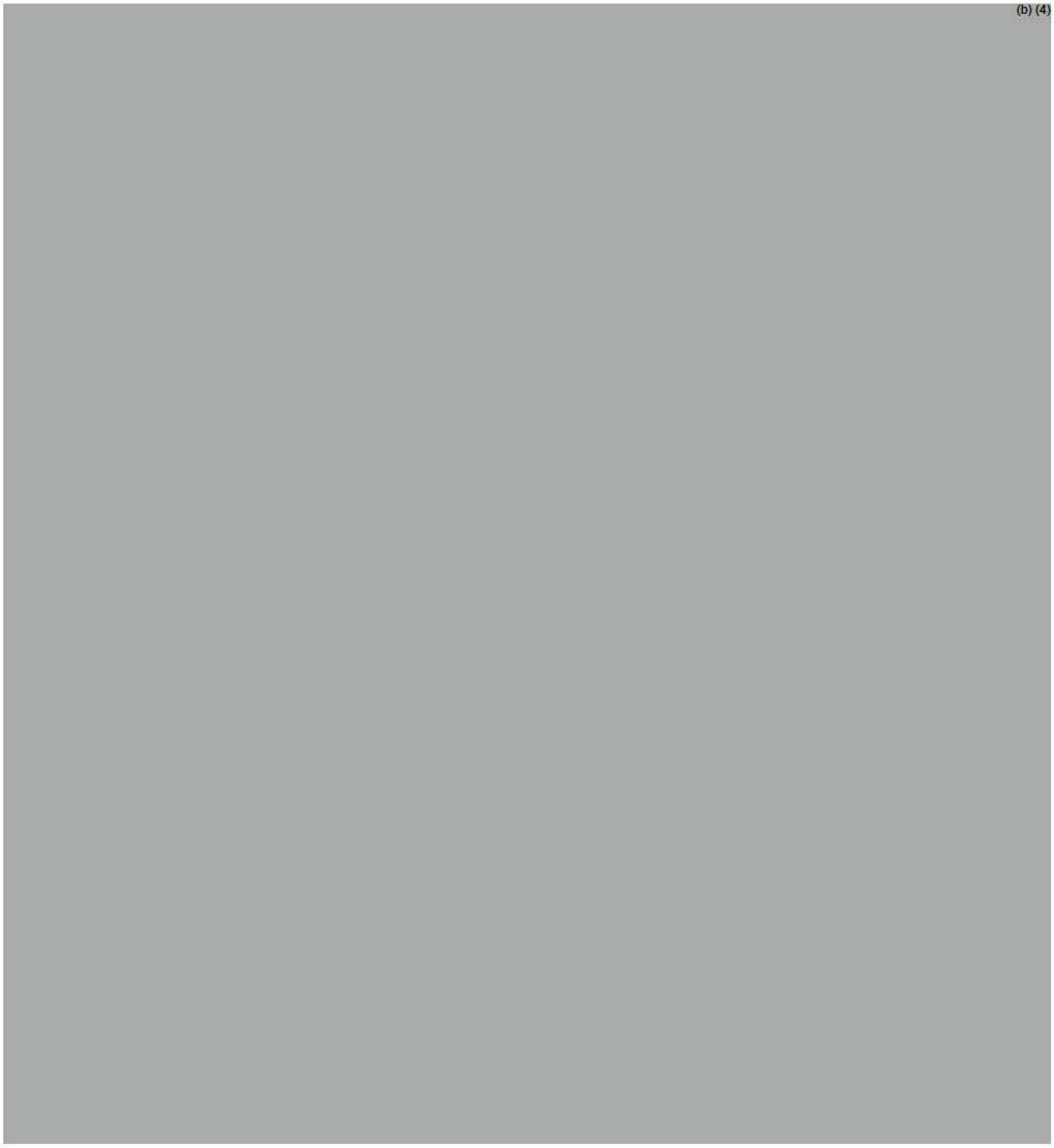
(b) (4)

(b) (4)

Toxicity

In addition, Teva had previously qualified the use of sodium tartrate dihydrate by conducting a 14-day subcutaneous qualification study (general toxicology safety study in rats) as documented in ITR Study Number 72586 (report DS-2014-062) and provided reference in Teva's December 30, 2014 Amendment (sequence 0020) within section 3.2.P.2 Pharmaceutical Development report (page 39). (b) (4)

(b) (4)



Based on the information provided above (toxicity study Report DS-2014-062, IID reference for (b) (4) ***and approved product, Signifor), does the Agency agree that sodium tartrate dihydrate, used in Teva's Epinephrine Injection USP Drug Products, is not considered a novel excipient and can be used in Teva's Epinephrine Injection USP (0.15 mg and 0.3 mg) (Auto-Injector) drug products when administered subcutaneously without any additional non-clinical or clinical studies to support Teva's pending 505(j) application?***

DBIII Response:

- The firm has re-formulated its test product to include sodium tartrate (b) (4) and reduce the concentration of Ssodium metabisulfite. In the amendment dated December 30, 2014, the firm requested a waiver of *in vivo* bioequivalence study requirements under 21 CFR § 320.22(b)(1) for its re-formulated test product, Epinephrine Injection USP, 0.15 mg/0.3 mL (Auto Injector Jr.) and 0.3 mg/0.3 mL (Auto Injector).

- In the previous BE review of this amendment[2], the re-formulated test product was found to be NOT qualitatively (Q1) and quantitatively (Q2) the same as RLD product. The test products contain sodium tartrate dihydrate (b) (4) whereas the RLD product contains no (b) (4). In addition, the firm's re-formulated test product (0.4 mg) contains considerably lower quantity of sodium metabisulfite than in the RLD formulation (0.5 mg). The firm provided following justification for the change in the formulation:

  "Teva's formulation contains a lower concentration (b) (4), sodium metabisulfite than the RLD. The concentration of sodium metabisulfite used in the Epineprhine Injection formulation is (b) (4) (b) (4) (b) (4). In addition, sodium tartrate (b) (4) is included in Teva's proposed formulation (b) (4) n (b) (4) These differences in formulation are permitted in accordance with CFR 314.94(a)(9)(iii)".

- According to 21 CFR § 314.94 (a) (9) (iii), a drug product intended for parenteral use may differ from the RLD in the use of preservatives, buffers, or antioxidants provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety and efficacy of the proposed drug product.

- In the previous BE review of this amendment, the differences in the sodium metabisulfite concentration between the test and reference products was considered to be acceptable[2].

- The test product is intended for both Intramuscular and subcutaneous administration. Since the amount of sodium tartrate dihydrate in the test formulation is within the acceptable limits for Intramuscular administration based on the FDA's Inactive Ingredient database, the above inactive ingredient in the test formulation was considered acceptable for intramuscular administration.

- However, the IIG limit for the above stated inactive ingredient for subcutaneous administration was not provided in the IIG database, at the time of submission of the amendment dated 12/30/2014, therefore the firm submitted the toxicology study report demonstrating the safety of above stated amount of sodium tartrate dihydrate in the test formulation via subcutaneous administration.

- A clinical consultation request was submitted to the Division of Clinical research (DCR) for the safety and clinical significance of the amount of sodium tartrate dihydrate in the firm's test product formulation intended for subcutaneous administration[3].

- Based on the DCR consult response, (b) (4) (b) (4)

- Regarding the 14-day repeat dose toxicity study conducted in rats, the pharm/tox reviewer in DCR found the study to be acceptable and concluded that sodium tartrate dihydrate does not pose a systemic or local risk with subcutaneous administration. However, the pharm/tox reviewer deferred to the medical officer on the clinical safety of this excipient administered subcutaneously. [4]

- DCR concluded that sodium tartrate dihydrate is considered a novel excipient for the SC route of administration, (b) (4) (b) (4)

- (b) (4)

- (b) (4)

[8] http://quantum.esu.edu/~scady/Chem495/fisher.pdf
[9] http://www.organicchem.org/oc2web/lecture/outlines/acidsbases.pdf
[10] http://www.shimadzu.com/an/hplc/support/lib/lctalk/29/29intro html
[11] IIG Database, Internal: http://intranetapps.dev.fda.gov/scripts/IIG/getiig.cfm (Last accessed on 3/23/2016)

- The amount of sodium tartrate dihydrate in the test formulation is within the acceptable limits for subcutaneous administration based on the FDA's Inactive Ingredient database.

- **Therefore, the test formulations are now considered acceptable.**

[12] DARRTS for NDA 200677: STEPHENS, OLEN M 10/16/2012 N/A 10/16/2012 REV-QUALITY-03(General Review) Original-1 (Type 1- New Molecular Entity) Archive

5 RECOMMENDATION

The Division of Bioequivalence III (DBIII) agrees that the information submitted by Teva Pharmaceutical demonstrates that Epinephrine Injection USP, 0.3 mg/mL and 0.15 mg/mL, pre-filled syringe with auto-injector meets the requirements of Section 21 CFR § 320.24 (b) (6). The DBIII recommends the waiver of bioequivalence testing be granted. Accordingly bioequivalence testing should not be undertaken.

The DBIII deems the test products, Epinephrine Injection USP, 0.15 mg/0.3 mL (Auto Injector Jr.) and 0.3 mg/0.3 mL (Auto Injector), manufactured by Teva Pharmaceuticals to be bioequivalent to the RLD product, EpiPen® and EpiPen® Jr (epinephrine injection) Auto-Injector, 0.3 mg/0.3 mL and 0.15 mg/0.3 mL respectively, manufactured by Mylan Speclt, under 21 CFR § 320. 24 (b) (6).

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 090589

APPLICANT: Teva Pharmaceuticals USA

DRUG PRODUCT: Epinephrine Injection USP (Auto-Injector), 0.3 mg/0.3 mL and 0.15 mg/0.3 mL

The Division of Bioequivalence III (DBIII) has completed the review of your request for a Post Complete Response Teleconference Meeting to discuss deficiencies noted in the Complete Response Letter dated February 23, 2016, and has the following response:

DBIII has considered the information you provided for Signifor (pasireotide diaspartate) injection and re-evaluated the amounts of sodium tartrate dihydrate in your test formulations. DBIII concludes that this inactive ingredient is not considered as a novel excipient for subcutaneous administration. Your test formulations are now considered acceptable. DBIII has no further question at this time.

The bioequivalence comments provided in this communication are comprehensive as of issuance. However, these comments are subject to revision if additional concerns raised by chemistry, manufacturing and controls, microbiology, labeling, other scientific or regulatory issues or inspectional results arise in the future. Please be advised that these concerns may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

{See appended electronic signature page}

Nilufer M. Tampal, Ph.D.
Acting Director, Division of Bioequivalence III
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

6 OUTCOME PAGE

ANDA: 090589

Completed Assignment for 204902 ID: 27196

Reviewer: Suman Dandamudi **Date Completed:**

Verifier: **Date Verified:**

Division: Division of Bioequivalence

Description: Epinephrine Injection (Auto-Injector) Post CR MR

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
27458	3/8/2016	Other (REGULAR)	Study Amendment	1	1
27458	3/24/2016	Quality Assessment	Quality	5	5
				Total:	6

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	090589		
Drug Product Name	Epinephrine Injection USP (Auto-Injector)		
Strength(s)	0.15 mg/0.3 mL, 0.3 mg/0.3 mL		
Applicant Name	Teva Pharmaceuticals USA		
Applicant Address	425 Privet Road, Horsham, PA 19044		
Applicant's Point of Contact	Cory Wohlbach Senior Director, Regulatory Affairs, US Generics		
Contact's Telephone Number	215-293-6519		
Contact's Fax Number	215-591-8812		
Contact's Email Address	Cory.wohlbach@tevapharm.com		
Original Submission Date(s)	December 21, 2007 May 30, 2008 (Amendment), May 22, 2009 (Amendment) July 31, 2013 (in vitro), December 30, 2014 (re-formulation) and May 20, 2015 (Amendment) March 08, 2016 (Post Complete Response Meeting Request) October 28, 2016 (Complete Response)		
Submission Date(s) of Amendment(s) Under Review	N/A		
First Generic	Yes		
Primary Reviewer	Suman Dandamudi, Ph. D.		
Secondary Reviewer	Ke Ren, Ph.D.		
Waiver	☐ **Granted** ☐ **Tentatively granted** ☒ **Not granted** ☐ **N/A**		
Formulation	☒ **Adequate** ☐ **Inadequate**		
Will Response to CR Result in a Reformulation?	☐ **Possibly** ☐ **No** ☒ **N/A**		
Overall Review Result	☐ **Adequate** ☒ **Inadequate**		
Revised/New Draft Guidance Generated as Part of Current Review	☐ **YES** ☒ **NO**		
DEFICIENCY CLASSIFICATION	☒ **Major** ☐ **Minor** ☐ **Not Applicable**		
BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	**STUDY/TEST TYPE**	**STRENGTH**	**REVIEW RESULT**
21, 25, 26, 38	**Waivers**	**0.3 mg/0.3 mL & 0.15 mg/0.3 mL**	**INADEQUATE**

ADDENDUM TO THE BIOEQUIVALENCE REVIEW

1 EXECUTIVE SUMMARY

This is an addendum to a previous bioequivalence (BE) addendum review[1] dated 11/21/2016.

The purpose of the current BE review addendum is to include the new draft guidance recommendations for this drug product, Epinephrine Injection (Auto-Injector)[2]. The reference listed drug (RLD) is EpiPen® (epinephrine injection) Auto-Injector, 0.3 mg and EpiPen®Jr (epinephrine injection) Auto-Injector, 0.15 mg from Mylan Speclt (NDA 019430). At the time of the previous BE review, there were no individual draft drug product bioequivalence recommendations for the current drug product.

The in vitro study results that were submitted by Teva were conducted on single lot (30 units) of test product and 3 lots (10 units of each lot) of reference product. At the time of the review of the in vitro study results, Agency did not have specific recommendations for the statistical criteria of the in vitro study data. Therefore, the BE statistical analysis was based on the 90% confidence intervals of the T/R ratios being within the limits of 80.00%-120.00% (It should be noted that the PBE analysis could not be performed, since the data from the multiple lots of the test product are needed to determine the 'between-lot variability' for PBE analysis). In addition, the firm used the test device to conduct pre-study method validations for all the in vitro studies.

As per the current draft guidance recommendation for this drug product, the following in vitro studies should be conducted for the demonstration of bioequivalence between the test and reference products:

- Delivered Volume
- Ejection Time
- Trigger Force
- Extended Needle Length
- Needle integrity post-injection

At least three batches each of the test and reference products, with no fewer than 10 units from each batch should be used in conducting the above in vitro tests. Method validation should be performed using the reference product, and the lot number(s) for the reference products used for the validation should be provided.

Therefore, based on the current bioequivalence recommendations for this drug product, the firm's in vitro studies are inadequate. The firm will be asked to re-conduct all the in

[1] GDRP for ANDA 090589: Bioequivalence Primary Review, A090589N006DB_ADD10282016.doc dated Nov 21, 2016 by Issa Nesheiwat.
http://panorama fda.gov/task/view?ID=5420f1160002bc9df9be4d40027ff2e6.

[2] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM534133.pdf

vitro studies recommended in the guidance using three batches of the test and reference products with no fewer than 10 units from each batch. The firm should also repeat all pre-study method validations related to the drug product performance using the reference product.

The BE portion application is **Inadequate**.

Note: The revised recommendation letter is attached to this addendum and this revised BE letter should supersede the previous BE letter dated 10/19/2016.

II. Draft Guidance on Epinephrine Injectable (Recommended December 2016)

Active Ingredient: Epinephrine

Dosage Form; Route: Injectable; Intramuscular, Subcutaneous

Strengths: 0.3 mg/delivery
0.15 mg/delivery

Overview:
The reference (R) product is a drug-device combination product in which the drug constituent part consists of a parenteral solution and the device constituent part consists of an auto-injector. If the proposed test (T) product meets the following criteria with respect to formulation, in vitro studies and device, FDA may waive the requirement for an in vivo bioequivalence (BE) study.

Formulation:

FDA recommends that the T formulation be qualitatively (Q1)[3] and quantitatively (Q2)[4] the same as the R formulation.

In Vitro Studies:

FDA recommends that the following in vitro studies be conducted with the T and R auto-injectors containing epinephrine.

1. Type of study: Delivered volume
   Design: The delivered volume test should be performed to determine the volume of fluid ejected out of the device.
   Equivalence based on: Population bioequivalence (PBE)[5] analysis of delivered volume.

2. Type of study: Ejection time
   Design: The ejection time test should be performed to determine the time to eject the volume of fluid out of the device.
   Equivalence based on: PBE analysis of ejection time.

3. Type of study: Trigger force

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[3] Q_1 (qualitative sameness) means that the T formulation uses the same inactive ingredient(s) as the R formulation.

[4] Q_2 (quantitative sameness) means that concentrations of the inactive ingredient(s) used in the T formulation are within ± 5% of those used in the R formulation.

[5] Refer to the product-specific recommendation for Budesonide Inhalation Suspension for relevant principles regarding population bioequivalence (PBE) analysis procedures.

Design: The trigger force test should be performed to determine the force required to activate the device.
Equivalence based on: PBE analysis of trigger force.

4. Type of study: Extended needle length
   Design: The extended needle length test should be performed to determine the needle length that extends out of the device after ejection of the volume of fluid.
   Equivalence based on: PBE analysis of extended needle length.

5. Type of study: Needle integrity post-injection
   Design: The needle integrity post-injection test should be performed to determine the integrity of the needle after injection through materials of different penetration challenge at different angles of incidence. The purpose of this test is to determine the ability of the proposed T product to trigger and penetrate when utilized at different angles of incidence and against different cloth materials, and compare these attributes to the R product. The test should include at least three materials of different penetration challenges (material attributes include, e.g., material type, density and thickness) and at least three angles of incidence. The choice of materials and angles should consider the labeling of the R product, which includes the following language: "Your auto-injector is designed to work through clothing" and "Place the orange tip against the middle of the outer thigh (upper leg) at a right angle (perpendicular) to the thigh." All choices should be adequately justified in the ANDA submission.
   Equivalence based on: Qualitative comparison between T and R devices with respect to (i) ability to trigger the injection at the angle of incidence, (ii) ability of the needle to penetrate the material, and (iii) integrity of the needle post-injection

In certain circumstances, FDA may request information and/or comparative data including, but not limited to, the following: residual volume, injection force, break force, needle cover lockout force and ability to lockout needle cover, break loose force, and extrusion force.

Additional comments:
FDA recommends that applicants conduct the above in vitro studies for both strengths of the T and R products. For each strength, use at least three batches each of the T and R products, with no fewer than 10 units from each batch. A single batch of solution can be split-filled into three equal size sub-lots of product. The three batches of the T product should be prepared from three different batches of the same critical device components. The T product should consist of the final device constituent part and final drug constituent formulation intended to be marketed. The manufacturing process for the T batches should be reflective of the manufacturing process to be utilized for the commercial batch. T and R products should be studied under the same instrumental conditions. Method validation should be performed using the R product, and the lot number(s) for the R products used for the validation should be provided. Applicants should provide all relevant standard procedures and validation data for each of the in vitro bioequivalence studies listed above.

Device:

FDA recommends sponsors consider the following characteristics of the R product in designing the T product:

- Single-use, single-dose, fixed-dose, pre-filled auto-injector device.
- External operating principles and external critical design attributes of the R product.
- Size and shape of the R product.

FDA recommends that sponsors consider the following characteristics of the T product in designing the T trainer:

- External operating principles and external critical design attributes of the T product.
- Size and shape of the T product.

Prior to product development or submission of an ANDA, FDA strongly encourages applicants to submit to OGD via controlled correspondence and/or pre-ANDA meeting request, the following:

- Working model(s) of the proposed T product and T trainer.
- Sample(s) of the R product and R trainer.
- In certain circumstances, FDA may request additional information and/or data, as appropriate.

In addition, in vitro studies should be conducted to support the functionality, accuracy, and robustness[6] of the proposed T product.

[6] Refer to the guidance for industry and FDA staff "Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products" (June 2013) for relevant principles regarding studies to support auto-injector devices.

NOTE TO REGULATORY PROJECT MANAGER (RPM): This bioequivalence letter supersedes the letter at the end of the bioequivalence review which is located in GDRP [see in GDRP for ANDA 090589 A090589B06DB_CRR03082016.doc Harikrishna Devalapally; Date uploaded 10/19/2016].

BIOEQUIVALENCE DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA:	090589
APPLICANT:	Teva Pharmaceuticals USA
DRUG PRODUCT:	Epinephrine Injection USP (Auto-Injector), 0.3 mg/0.3 mL and 0.15 mg/0.3 mL

The Division of Bioequivalence III (DBIII) has completed its review of your submission acknowledged on the cover sheet, and the following deficiencies have been identified.

In December 2016, the Agency announced the availability of a new draft guidance entitled "Draft Guidance on Epinephrine Injection." This new draft guidance provides product-specific recommendations for proposed generic drug products citing EpiPen® (epinephrine) Auto-Injector, 0.3 mg and EpiPen®Jr (epinephrine) Auto-Injector, 0.15 mg (NDA 019430) as their reference listed drug (RLD).

Specifically, the new draft guidance recommends that at least three batches each of the test and reference products should be used in all of the recommended in vitro studies. This helps ensure consistency of in vitro performance among the batches. A copy of this Draft Guidance on Epinephrine Injection is available on FDA's Drug guidance page: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM534133.pdf.

In the amendments to your application dated July 31, 2013 and December 30, 2014, you submitted in vitro study results that were conducted on a single lot (30 units) of test product and on three lots (10 units of each lot) of reference product. Please re-conduct all of the recommended in vitro studies per the current Draft Guidance on Epinephrine Injection using three batches of the test and reference products with no fewer than 10 units from each batch. Please perform population bioequivalence analysis for the following studies: Delivered Volume, Ejection Time, Trigger Force, and Extended Needle Length as per the recommendations in the draft guidance. For details regarding the in vitro studies, please refer to the Draft Guidance on Epinephrine Injection referenced above.

In addition, in the amendments to your application dated July 31, 2013 and December 30, 2014, you also used the test product to conduct pre-study method validations for all of the in vitro tests. Because the test product is not an approved drug product, it is not appropriate to use the test product for method validations involving drug product

performance. Please repeat all pre-study method validations related to the drug product performance using the reference product, per the current Draft Guidance on Epinephrine Injection.

Consistent with 21 CFR 320.24(a), the scientific recommendations reflected in the Draft Guidance on Epinephrine Injection represent FDA's determination of the most accurate, sensitive, and reproducible approach for conducting bioequivalence testing.

Sincerely yours,

{See appended electronic signature page}
Nilufer M. Tampal, Ph.D.
Director, Division of Bioequivalence III
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	090589		
Drug Product Name	Epinephrine Injection USP (Auto-Injector)		
Strength(s)	0.15 mg/0.3 mL, 0.3 mg/0.3 mL		
Applicant Name	Teva Pharmaceuticals USA		
Address	425 Privet Road, Horsham, PA 19044		
Applicant's Point of Contact	Cory Wohlbach		
Contact's Telephone Number	215-293-6519		
Contact's Fax Number	215-591-8812		
Original Submission Date(s)	December 21, 2007 May 30, 2008 (Amendment) May 22, 2009 (Amendment)		
Submission Date(s) of Amendment(s) Under Review	July 31, 2013 and December 30, 2014		
Reviewer	Suman Dandamudi, Ph.D		
OVERALL REVIEW RESULT	**INADEQUATE (PENDING DCR CONSULT RESPONSE)**		
REVISED/NEW DRAFT GUIDANCE INCLUDED	**NO**		
COMMUNICATION	**☐ECD** **☐IR** **☒NOT APPLICABLE**		
BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	**STUDY/TEST TYPE**	**STRENGTH**	**REVIEW RESULT**
21, 25	**In Vitro Tests**	**0.3 mg/0.3 mL and 0.15 mg/0.3 mL**	**ADEQUATE**

Review of a Waiver Request

1 EXECUTIVE SUMMARY

Teva Pharmaceuticals submitted its responses to the deficiency comments made by the Division of Bioequivalence (DB) in the deficiency letter dated March 29, 2010[1]. The submission references NDA 019430, EpiPen® and EpiPen® Jr (epinephrine injection) Auto-Injector, 0.3 mg/0.3 mL and 0.15 mg/0.3 mL by Mylan Speclt.

In the original application, the firm requested a waiver of *in vivo* bioequivalence study requirements under 21 CFR § 320.22(b)(1) for its test products, Epinephrine Injection USP, 0.15 mg/0.3 mL (Auto Injector Jr.) and 0.3 mg/0.3 mL (Auto Injector). The formulations for each of the test products were qualitatively (Q1) and quantitatively (Q2) the same as the respective RLD products. Since, the drug product is an auto-injector, in addition to the formulation comparison, device similarity by *in vitro* comparative performance should be demonstrated for approval of this drug product. Since the firm did not provide the individual data for the in vitro tests to demonstrate comparable performance between the test and RLD devices, the firm was asked to conduct suitable in vitro tests to document the performance characteristics and submit the data for evaluation[2].

In the current amendment, the firm has submitted the re-formulated test product. The re-formulated test product is NOT qualitatively (Q1) and quantitatively (Q2) the same as RLD product. The test product contains Sodium Tartrate Dihydrate as (b) (4) whereas the RLD product contains no (b) (4). In addition, the firm's re-formulated test product (0.4 mg) contains considerably lower quantity of Sodium Metabisulfite than in the RLD formulation (0.5 mg). The acceptability of the test formulation is pending the Division of Clinical Review (DCR) consultation response.

The firm also has submitted the results of in vitro bioequivalence (BE) studies comparing the test and RLD product devices. The test and RLD devices comparison data submitted for different tests are acceptable from the bioequivalence perspective.

The OPQ has submitted inter-center consultation request to CDRH on 6/25/2015[3] for the evaluation of the Teva's re-designed auto-injector device (Vibex (b) (4). Another OPQ consult request was sent to OSE for the submitted human factor study.

The waivers of in vivo bioequivalence testing for the test products cannot be granted at this time pending the DCR consult response.

NOTE TO REGULATORY PROJECT MANAGER (RPM): Currently there is a pending clinical consult with DCR.

[1] DARRTS for ANDA 090589: SOLANA-SODEINDE, DIANA A 03/29/2010 FAX 03/29/2010 COR-ANDADE-01(Bio Incomplete Deficiencies) Original-1 Archive
[2] DARRTS for ANDA 090589: TAMPAL, NILUFER M 03/11/2010 N/A 03/11/2010 REV-BIOEQ-01(General Review) Original-1 Archive
[3] DARRTS for ANDA 090589: HUANG, XIAOHUA 06/25/2015 N/A 06/25/2015 FRM-CONSULT-02(Intercenter/Combination Products Consult) Original-1 Archive

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3 BACKGROUND

1. Teva Pharmaceuticals submitted ANDA 090589 for its test product, Epinephrine Injection (auto-injector) 0.15 mg/0.3mL and 0.3 mg/0.3mL. The submission references NDA 019430, EpiPen® (epinephrine injection) Auto-Injector, 0.3 mg and EpiPen Jr® (epinephrine injection) Auto-Injector, 0.15 mg from Mylan Speclt.

2. In the original application, the firm requested the waiver of in vivo bioequivalence study requirements under 21 CFR § 320.22(b)(1) for its test products, Epinephrine Injection USP, 0.15 mg/0.3 mL (Auto Injector Jr.) and 0.3 mg/0.3 mL (Auto Injector). Since, the drug product is an autoinjector, in addition to the formulation comparison, device similarity by *in vitro* comparative performance should be demonstrated for approval of this drug product. The firm has provided the comparative summary results of the performance parameters between the test and RLD devices.

3. Since the firm did not provide the individual data for the in vitro tests to demonstrate comparable performance between the test and RLD devices, the firm was asked to conduct suitable in vitro tests to document the performance characteristics and submit the data for evaluation[2].

4. In the current amendment, the firm has submitted the results of the comparative performance testing of the test and RLD devices.

4 SUBMISSION SUMMARY

4.1 Drug Product Information, PK/PD Information, and Relevant DB History

- See the review of the original submission, **DARRTS: TAMPAL, NILUFER M 03/11/2010 N/A 03/11/2010 REV-BIOEQ-01(General Review) Original-1 Archive.**

- Currently the DB recommendations for demonstration of bioequivalence of Epinephrine Injection (auto-injector) 0.15 mg/0.3mL and 0.3 mg/0.3mL are not listed on the FDA website for Guidance for Industry: Individual Product Bioequivalence Recommendations.

- On January 16, 2015, the innovator has submitted a citizen petition (Docket No: FDA-2015-P-0181), requesting the Agency, to refrain from approving the current application by Teva (ANDA 090589) unless a rigorous review under the established standards for proposed generic emergency use auto-injectors was performed and the Agency concludes that the proposed product is the same as the EpiPen auto-injectors. After careful consideration, the Agency has denied the above stated citizen petition (See section 4.11 for citizen petition).

4.2 Review of Current Amendment

Deficiency Comment #1: *The DB recommends in-vitro testing to demonstrate comparable performance of the device components (auto-injectors) used in your proposed test products to the reference listed drug (RLD) products, EpiPen® (epinephrine) Auto-Injector, 0.30 mg/0.3 mL and EpiPen Jr ® (epinephrine) Auto-Injector, 0.15 mg/0.3 mL. You provided summary data (means and standard deviations) for expelled volume, needle gauge, exposed needle length, force to trigger device, and spring force to inject drug for the test product. Individual data for your test products were provided only for the injection time. Comparative data for the RLD devices were not provided. Please conduct additional in vitro testing and provide comparative data for the test and reference devices under the same conditions. The performance tests may include but not be limited to the following: 1) volume of solution injected and residual content of the auto-injector, 2) dose delivery time, 3) force required to discharge actuator and force of injection, 4) exposed needle length, 5) depth of penetration, 6) needle cover test, and 7) needle integrity post injection to include testing through different clothing materials of varying thickness and different angles of incidence. Specifications such as breakloose force and extrusion force should be provided. Please provide all relevant Standard Operating Procedures (SOPs) and validation data for each test procedure conducted.*

Deficiency Comment #2: *Please submit complete electronic EXCEL spreadsheets or SAS Transport format files of individual data for each of the tests on the test device product versus the RLD products*

Firm's Response to Deficiency 1 & 2: The test reports and corresponding data, the validation report as well as the test protocols for test and RLD devices are submitted in Module 5.3.1.3. Also the excel sheets containing test data are submitted in Module 5.3.1.3.

Reviewer's Comments:

- In the amendment dated August 1, 2013, the firm has submitted the responses to the deficiency comments made by DB regarding the performance testing of the devices. The firm has conducted all the above stated performance tests and submitted the data for the evaluation [It should be noted that the DB has not conducted the review of the data submitted in this amendment].

- Subsequently, the firm has submitted another amendment on December 30, 2014. The firm has re-formulated its test product to decrease the amount of sodium metabisulfite (b) (4) and to add sodium tartrate (b) (4). In addition, the firm has also altered the device design to engage the safety guard after the delivery of the drug product. To support the above stated changes, the firm has manufactured new exhibit batches and re-conducted the performance tests comparing the test and reference product devices. The reviewer will be conducting the statistical analysis only on the data submitted on this re-formulated and re-designed test product.

4.3 Auto Injector Device Comparability

Test Product Device (b) (4)

Component	Specifications
(b) (4)	

The device is supplied (b) (4). It is a needle-based injection device (b) (4) (b) (4) and has a minimum specified needle penetration depth upon administration of (b) (4) for the adult device and (b) (4) for the pediatric device. The device is a disposable single-use autoinjector that is one piece and contains the drug product in the primary container. The AJ E device is a single-use, fixed dose device that uses pressure-assisted delivery of the drug into the target site. (b) (4)

(b) (4)

RLD Device (EpiPen Device):

The innovator has developed a Next Generation Auto-Injector (NGA) to provide automatic sharps protection after giving an injection of epinephrine. On 5/20/2009, the innovator in supplementt-48 has submitted this information on change in the device design. The NGA was designed to function in the same manner as the previously approved EpiPen devices however

provide an automatic sharps protection after the activation. Thus there was no change in the mode of activation and only the differentiating feature is the automatic deployment of a needle cover when the auto-injector is being removed from the injections site after the injection[4].

Reviewer's Comments:

- OGD has previously consulted the Division of Pulmonary and Allergy Products (DPAP) to evaluate whether the mechanism of action of test and RLD devices were identical. The DPAP has concluded that the mechanism of action of the Teva's auto-injector (AJ E) device is the same as the RLD's auto-injector device[5]. However, it should be noted that this evaluation were performed on the original devices of both test and reference products.

- In addition, at the request of OGD, the CDRH has evaluated the Teva's auto-injector device (AJE and AJE Jr) and concluded that the design verification data for the device is acceptable[6]. Again, it should be noted that this evaluation was performed on the original device of the test product.

- Since the review of the original submission, both the test (Vibex (b) (4)) and reference product devices have been re-designed. The firm has improved the device design to ensure that the user will not be presented with a device that has delivered the drug product but has not engaged the safety guard. It should be noted that the OPQ has submitted Inter-center Consultation request to CDRH on 6/25/2015[7] for the evaluation of the Teva's re-designed auto-injector device (Vibex (b) (4) In case of RLD product, as stated above currently the NGA is the only type of EpiPen and EpiPen Jr Devices that are currently available in the US market.

- Even though, both the test and RLD devices were re-designed the mechanism of operation of both the devices has remained the same as the original devices. Therefore, the reviewer considers the mode of activation of the test device (Vibex (b) (4) to be similar to the RLD device (EpiPen device). DBIII defers to OPQ for the evaluation of the acceptability of the new device design, which is currently pending the CDRH consult response and OPQ review of the consult response.

- The notable difference between the two devices is the fill volume. The EpiPen® and EpiPen® Jr auto-injectors contain **2 mL** epinephrine injection for intramuscular use. Each EpiPen and EpiPen Jr auto-injector devices deliver a single dose of 0.3 mg and 0.15 mg epinephrine in 0.3 mL of sterile solution, respectively. For stability purposes, approximately 1.7 mL remains in the auto-injector after activation and cannot be used.

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[4] DARRTS for NDA 019430: JAO, EDWIN 08/31/2009 N/A 08/31/2009 REV-QUALITY-03(General Review) Supplement-48 (Manufacturing (CMC)) Archive

[5] DARRTS for ANDA 090589: GILBERT MCCLAIN, LYDIA I 11/13/2008 N/A 11/13/2008 REV-CLINICAL-03(General Review) Original-1 Archive

[6] DARRTS for ANDA 090589: TRAN, TRANG Q 07/06/2010 N/A 07/06/2010 FRM-ADMIN-01(Memorandum to File) Original-1 Archive

[7] DARRTS for ANDA 090589: HUANG, XIAOHUA 06/25/2015 N/A 06/25/2015 FRM-CONSULT-02(Intercenter/Combination Products Consult) Original-1 Archive

However, the test product devices, Vibex (b) (4) and Vibex (b) (4) auto-injectors contain **1 mL** epinephrine injection that delivers a single dose of 0.3 mg and 0.15 mg epinephrine in 0.3 mL of sterile solution, respectively. The current reviewer is of the opinion that the difference in the fill volume is not of a concern as the delivery volume from both the test and RLD devices are same.

4.4 In Vitro Studies

Note: There is an error in the firm's submission of the individual study data in the excel format in the amendment dated 12/30/2014. The firm has re-conducted all the device comparison tests due to the changes in the test device design. However, the individual data submitted in the excel format is for the original test device. In the study report submitted for all the tests which were conducted on the redesigned test device, the firm has submitted the individual data. Based on the study report, the reviewer has created the excel file and used this data in conducting the statistical analysis. Thus, the firm will not be asked to re-submit the excel files.

4.4.1 Delivered Volume

Testing was performed on 30 Adult and Junior epinephrine devices of both the test and reference products. The delivered volume was determined gravimetrically post-device triggering into a tared test beaker.

Delivered Volume Test		
Device Model	Device Lot Number	Quantity Tested
AJE Adult	15486	30
AJE Junior	15487	30
Epi Pen Adult	0GM006	10
	0GM019	10
	0GM020	10
Epi Pen Junior	9GN828	10
	9GN766	10
	9GN788	10

Test Procedure: The delivered volume was obtained by directly shooting the auto-injector being tested (b) (4)

(b) (4)

(b) (4) The AJ E and Epi Pen devices were tested per SO (b) (4)

(b) (4)

(b) (4)

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(b) (4)

[redacted]

Reviewer's Comments:

- As per the SOP (b) (4) [redacted] he delivered volume from the injection device was measured using a [redacted] ce. The delivered volume has been evaluated on 30 devices of test and reference products. The firm submitted the individual and mean results expressed as the weight in gms.

- In addition, the firm also submitted the statistical results comparing the mean delivered volumes of the test and reference products using the following procedure:

(b) (4)

[redacted]

Based on the above results, the firm has concluded that both the test and reference product devices are statistically equivalent with respect to delivered volume.

- The firms were asked to conduct different in vitro tests for device performance comparison. However, currently the Agency does not have any recommendations for the statistical criteria of the submitted in vitro data.

- The reviewer conducted statistical analysis on the in vitro data similar to that of the Agency's recommendation for drug products for which in vitro binding studies were performed for the demonstration of bioequivalence. Per the current draft guidance on Sevelamer Carbonate[8], the test product data is considered to be similar to the reference product, when the T/R ratios are within the 90% confidence intervals of **80%- 120%.**

- Based on the reviewer's statistical analysis, the 90% confidence intervals of T/R ratios of delivered volume for adult (b) (4)) and junior (b) (4) devices are within 80%- 120%.

- (b) (4) (b) (4) The mean delivered volume of the test product is within the RLD specification (b) (4) for both the adult and junior devices.

RLD specifications in NDA 019430[9]

[8] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm089620.pdf
[9] DARRTS for NDA 019430: KIM, CHONG HO 11/04/2009 N/A 11/04/2009 REV-QUALITY-03(General Review) Supplement-49 (Manufacturing (CMC)) Archive

(b) (4)

- Thus, the test product auto-injector device is similar to the reference product auto-injector device for delivered volume.

- The Delivered Volume testing is **acceptable**.

4.4.2 Residual Fluid Volume

Testing was performed on 30 Adult and Junior epinephrine devices of both AJ E and Epi Pen Devices for residual fluid volume content.

Table 2: Test Device Identification

Residual Content Test		
Device Model	**Device Lot Number**	**Quantity Tested**
AJE Adult	15505	30
AJE Junior	15506	30
Epi Pen Adult	0GM006	10
	0GM019	10
	0GM020	10
Epi Pen Junior	9GN828	10
	9GN766	10
	9GN788	10

Test Procedure: The residual fluid volume content was determined by first triggering the auto-injector (b) (4)

(b) (4)

Study Results:

(b) (4)

Reviewer's Comments:

- As per the SOP (b) (4) the residual fluid volume was measured using a (b) (4) balance. The residual fluid volume has been evaluated on 30 devices of test and reference products.

- The total residual fluid volume left within the drug container of the test auto-injector device is considerably less than the residual fluid volume left within RLD, EpiPen devices. The RLD devices contain a pre-filled drug container filled with **2.0 mL** of fluid, and 0.3 mL is delivered when the device is triggered. However, the test devices contain a pre-filled drug container filled with only **1.0 mL** of fluid, and 0.3 mL is delivered when the device is triggered. Therefore, the residual fluid volume in test product device is not expected to be similar to the RLD device, because of the differences in filled volumes.

- Therefore, this reviewer considers the Residual Fluid Volume testing to be inappropriate for the performance comparison of test and reference devices.

4.4.3 Fluid Ejection Time

Testing was performed on 30 Adult and Junior epinephrine devices of both AJ E and EpiPen Devices for fluid ejection time. The device fluid ejection time was determined (b) (4)

(b) (4)

Ejection Time Test		
Device Model	**Device Lot Number**	**Quantity Tested**
AJE Adult	15490	30
AJE Junior	15502	30
Epi Pen Adult	0GM006	10
	0GM019	10
	0GM020	10
Epi Pen Junior	9GN828	10
	9GN765	10
	9GN788	10

Test Procedure: The ejection time was obtained by directly shooting the auto-injector being tested (b) (4)

(b) (4)

Acceptance Criteria:

[10] DARRTS for ANDA 090589: Firm's submission dated 08/01/2013. Module 5.3.1.3. Fluid Ejection Time Validation Report

- (b) (4)
-
-

Conclusion: The above results indicate that the data met the acceptance criteria. (b) (4)

(b) (4)

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(b) (4)

Reviewer's Comments:

- As per the SOP (b) (4) the fluid ejection time from the injection device was measured (b) (4) The fluid ejection time has been evaluated on 30 devices of test and reference products. The firm submitted the individual and mean results expressed as seconds.

- (b) (4)

(b) (4)

- The firm has adequately validated the methodology [redacted]. It should be noted that fluid ejection time measurements were [redacted] however the validation studies were conducted using [redacted] The reviewer is of the opinion that this [redacted] does not affect the integrity of the study data, since there is no change in the methodology.

- [redacted] The fluid ejection time (dispense time) of the test product is within the RLD specification (NMT [redacted]) for both the adult and junior devices.

- Based on the reviewer's statistical analysis, the 90% confidence intervals of T/R ratios of fluid ejection time for adult [redacted]) and junior [redacted] devices are within 80%- 120%.

- Thus, the test product auto-injector device is similar to the reference product auto-injector device for fluid ejection time.

- The fluid ejection time testing is **acceptable**.

4.4.4 Trigger Force (Force Required to Discharge Actuator)

Trigger force testing was performed on 30 Adult and Junior epinephrine devices of both AJ E and Epi Pen Devices. The trigger force was determined by positioning the "ready to discharge" device [redacted]

Test Procedure: [redacted]

(b) (4)

Conclusion: The above results indicate that the data met the acceptance criteria and the firm has adequately demonstrated the repeatability and reproducibility of the test method for measuring the trigger force. Thus method validation is acceptable.

Study Results:

Firm's Reported Statistical Results

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Reviewer's Comments:

- As per the SOP (b) (4) the trigger force of the injection device was measured. The trigger force has been evaluated on 30 devices of test and reference products. The firm submitted the individual and mean results expressed as pounds.
- (b) (4) (b) (4) The trigger force (activation force) of the test product is within the RLD[9] specification ((b) (4) for both the adult and junior devices.
- Based on the reviewer's statistical analysis, the 90% confidence intervals of T/R ratios of trigger force for adult (b) (4) and junior (b) (4)) devices are within 80%- 120%.

- Thus, the test product auto-injector device is similar to the reference product auto-injector device for trigger force.

- The trigger force testing is **acceptable**.

4.4.5 Exposed Needle Length

Testing was performed on 30 Adult and Junior epinephrine devices of both AJ E and Epi Pen Devices for exposed needle length. The device exposed needle length was measured using an optical comparator post-triggering in a fixture holding the needle guard fully retracted (i.e. maximum exposed needle length).

Exposed Needle Length Test		
Device Model	Device Lot Number	Quantity Tested
AJE Adult	15490	30
AJE Junior	15491	30
Epi Pen Adult	0GM006	10
	0GM019	10
	0GM020	10
Epi Pen Junior	9GN828	10
	9GN766	10
	9GN788	10

Test Procedure: The exposed needle length was obtained by triggering the auto-injector, (b) (4)

(b) (4)

(b) (4)

The firm has validated the methodology for the measurement of exposed needle length and submitted the report (#TR 841). The method was validated for repeatability and reproducibility. The validation results are as follows:

Crossed gage R &R: This test was conducted using three operators with each measuring the exposed needle length of 10 samples each replicating 3 times.

(b) (4)

Conclusion: The above results indicate that the data met the acceptance criteria and the firm has adequately demonstrated the repeatability and reproducibility of the test method for measuring the exposed needle length. Thus method validation is acceptable.

Study Results:

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Reviewer's Comments:

- As per the SOP (b) (4) the exposed needle length of the injection device was measured. The exposed needle length has been evaluated on 30 devices of test and reference products. The firm submitted the individual and mean results expressed as mm.

- (b) (4) (b) (4) The exposed needle length of the test product is within the RLD[99] specification (b) (4) for both the adult and junior devices.

- Based on the reviewer's statistical analysis, the 90% confidence intervals of T/R ratios of exposed needle length for adult (b) (4)) and junior (b) (4) devices are within 80%- 120%.

- Thus, the test product auto-injector device is similar to the reference product auto-injector device for exposed needle length.

- The exposed needle length testing is **acceptable**.

4.4.6 Collar Lockout Override Force

Testing was performed on 30 Adult and Junior epinephrine devices of both AJ E and Epi Pen Devices for collar lockout override force. (b) (4)

(b) (4)

Collar Lockout Override Test		
Device Model	**Device Lot Number**	**Quantity Tested**
AJE Adult	15490	30
AJE Junior	15491	30
Epi Pen Adult	0GM006	10
	0GM019	10
	0GM020	10
Epi Pen Junior	9GN828	10
	9GN766	10
	9GN788	10

Test Procedure: The collar lockout override force was obtained (b) (4)

(b) (4)

The firm has validated the methodology for the measurement of collar lockout override force and submitted the report (#TR 1313). The method was validated for repeatability and reproducibility. The validation results are as follows:

Crossed gage R &R: This test was conducted using three operators with each measuring the collar lockout override force for 3 trials of 10 samples each.

Conclusion: The above results indicate that the data met the acceptance criteria and the firm has adequately demonstrated the repeatability and reproducibility of the test method for measuring the collar lockout override force. Thus method validation is acceptable.

Study Results:

Firm's Reported Results

Reviewer's Comments:

- As per the SOP [redacted], the override force was measured. The override force has been evaluated on 30 devices of test and reference products. The firm submitted the individual and mean results expressed as pounds.

- The override force of the test auto-injector device is considerably less than the RLD, EpiPen devices. Both the test and RLD devices have the "sharp prevention feature". After the injection, when the device is removed from the injection site, the spring collar extends out covering the entire needle. The collar mechanically locks in the extended position after the device has been triggered and removed from the injection site such that the needle cannot be exposed a second time. Thus the lockout feature of the device is intended to prevent accidental needle sticks. The collar lockout force is the largest force required for the device lockout feature to fail.

- It should be noted that the test and RLD products are single-use, fixed dose devices. Even though, there are differences in the override force between the test and RLD devices, it is not of a concern since the above test only measures "sharp prevention" and not the "performance".

- [redacted] The collar override force of the test product meets the RLD specification [redacted][9] for both the adult and junior devices.

- Therefore, this reviewer considers the collar override force testing to be acceptable.

4.4.7 Depth of Penetration

Reviewer's Comments:

- The firm stated the following[12]:

  [redacted]

[12] DARRTS for ANDA 090589: Firm's Submission dated 08/01/2013. Module 1.2 Cover Letter

- The reviewer agrees with the firm's justification for not conducting the above test. The reviewer is also of the opinion that the "Exposed Needle Length Test" can be used as the performance test for "depth of penetration".

- (b) (4) (b) (4) DB has not previously recommended the "Depth of Penetration" test for the performance comparison.

4.4.8 Angled Entry and Post-Injection Needle Integrity

Testing was performed on 90 Adult and Junior epinephrine devices of both AJ E and Epi Pen Devices for angled entry and material penetration. The angled entry and material penetration capability was determined by attempting to trigger the device using a variety of angles of incidence and materials. Each device model was tested at three different angles from vertical (b) (4) and through (b) (4) cloth materials of differing penetration challenges (b) (4) (b) (4) at each angle (ten devices were tested with each cloth material at each angle per device model). Each device was inspected for proper device triggering, collar lockout post-triggering when removed from the injection site/clothing, material penetration post-triggering, and needle post-injection integrity.

Table 2: Test Material & Device Identification

Angled Entry and Material Penetration Test		
Device Model	**Device Lot Number**	**Quantity Tested**
AJE Adult	15501	90
AJE Junior	15502	90
Epi Pen Adult	0GM197	30
	0GM006	2
	0GM019	10
	0GM020	18
	0GM344	30
Epi Pen Junior	0GN278	30
	0GN280	30
	9GN788	16
	9GN828	2
	9GN766	12

Test Procedure: The angled entry and material penetration capability of the device was obtained by testing each device model at three different incidence angles, and with three different material penetration challenges at each incidence angle, resulting in nine different incidence angle and penetration material combinations. (b) (4)

(b) (4)

(b) (4)

Validation: No validation studies were conducted on this testing, since it is visual inspection test.

Reviewer's Comments:

- As per the SOP (b) (4) 3, the angular and the penetration test of the injection device was conducted. The testing was performed on 90 devices of test and reference products. For each cloth and angle pair firm recorded whether the device successfully triggered, whether there were any post-triggering needle integrity issues (i.e. deformities, damage or bending), whether the device successfully locked out when removed from the site and whether the needle penetrated the cloth and injected.

- The firm submitted the results as "Pass" or "Fail". Pass indicated that all tested representative devices (i.e. 100%) in the set of ten passed the test/inspection, whereas fail indicate that at least one tested representative device in the set often failed the test /inspection.

- Based on the firm's results, it is evident that all the test adult and junior devices triggered successfully at all combinations of angles and materials. All devices successfully locked out after triggering and being removed from the injection site. All devices successfully penetrated the test material when triggered (Please see Appendix 4.10.6 for individual device results).

- The angled entry and post-injection needle integrity testing is acceptable.

4.4.9 Specifications for Breakloose Force and Extrusion Force

Reviewer's Comments: The firm has provided the following "The syringe acceptance limit and QC release test limit for breakaway force (breakloose or initiating force) (b) (4) The syringe acceptance limit and QC release test limit for the gliding force (sustaining force) is (b) (4) These specification limits refer to the unfilled syringe. Extrusion force tests (testing both breakloose force and extrusion force) will be performed and reported with syringes filled with product throughout stability testing. It is worth noting that the liquid contents are aqueous, the syringe needle bore is relatively large, and the extrusion force should be (b) (4) The spring force of the device, which is acting upon the stopper of the prefilled syringe during delivery, is specified as greater than (b) (4) (end of delivery)".

The Office of Pharmaceutical Quality (OPQ) will be reviewing the above stated specifications.

4.5 Human Factors Study

- On 5/16/2011 through Quality Deficiency Letter, the firm was asked to conduct human factory study. The firm was also recommended to submit a protocol prior to the conductance of this test to ensure that the firm's methodology is acceptable[15].

[15] DARRTS for ANDA 090589: , CHRISTINA L 05/16/2011 FAX 05/16/2011 COR-ANDADE-07(Quality Minor Deficiencies) Original-1 Archive

- The requirement of a human factor study for the purpose of demonstration of comparability of the test and RLD devices is the recommendation that was made by Center for Devices and Radiological Health (CDRH)[16].

- The purpose of a design validation (human factors) study is to demonstrate that the device can be used by representative users under simulated use conditions without producing patterns of failures that could result in negative clinical impact to patients or injury to device users. Tasks included in the study should be those identified through completion of a risk assessment of hazards that may be associated with use-related problems and represent greater than minimal risk to users. The study should collect sufficient and appropriate data to facilitate identification and understanding of the root causes of any use failures or problems that do occur. The causes may be related to the design of the device, the device labeling (including instructions for use), and/or the training of test participants[16].

- In the amendment dated 1/20/2012, the firm has submitted the protocol for the human factors study. On 04/04/2012, an intercenter consultation request was submitted to CDRH for the review of the firm's submitted protocol[17].

- The CDRH has conducted the review of this protocol and provided its recommendations[18]. These recommendations were conveyed to the firm by Division of Chemistry[19].

- In the amendment dated 12/30/2014, the firm has submitted the Human Factor Study results. On 06/25/2015, an inter-center consultation request was submitted to CDRH and OSE for the review of the firm's submitted results[20]. Till this date the CDRH/OSE has not provided its responses to the consultation request.

- The human factory study is pending CDRH/OSE request consultation.

[16] DARRTS for ANDA 090589: , MIKE 05/16/2011 N/A 05/16/2011 REV-QUALITY-03(General Review) Original-1 Archive
[17] DARRTS for ANDA 090589: DARJ, MIKE 04/04/2012 N/A 04/04/2012 FRM-CONSULT-02(Intercenter/Combination Products Consult) Original-1 Archive
[18] DARRTS for ANDA 090589: TRAN, TRANG Q 05/07/2012 N/A 05/07/2012 FRM-ADMIN-01(Memorandum to File) Original-1 Archive
[19] DARRTS for ANDA 090589: DARJ, MIKE 12/20/2012 N/A 12/20/2012 REV-QUALITY-03(General Review) Original-1 Archive
[20] DARRTS for ANDA 090589: HUANG, XIAOHUA 06/25/2015 N/A 06/25/2015 FRM-CONSULT-06(OSE Consult (Except Proprietary Name Reviews)) Original-1 Archive

4.6 Formulation

Ingredients	Function	Test Product- Original Amount (mg) per 0.3 mL Delivered		Test Product- Re-Formulated Amount (mg) per 0.3 mL Delivered		Reference Product Amount (mg) per 0.3 mL Delivered[21]		% Difference Test vs RLD
		0.15 mg	0.3 mg	0.15 mg	0.3 mg	0.15 mg (EpiPen® Jr)	0.3 mg (EpiPen®)	
Epinephrine, USP	Active Ingredient	(b) (4)		0.15 mg*	0.3 mg*	0.15	0.3	(b) (4)
Sodium Chloride, USP/NF	(b) (4)			1.8 mg	1.8 mg	1.8	1.8	
Sodium Metabisulfite, NF				0.4 mg	0.4 mg	0.5	0.5	
Sodium Tartrate Dihydrate, NF				0.2 mg	0.4 mg	-	-	
Hydrochloric Acid, USP/NF				To adjust pH	To adjust pH	To adjust pH	To adjust pH	
Water for Injection, USP								(b) (4)

(b) (4)

[21] DARRTS for NDA 019430KIM, CHONG HO 07/28/2008 N/A 07/28/2008 REV-QUALITY-03(General Review) Supplement-40 (Manufacturing (CMC)) Archive

Reviewer's Comments:

- In the review of the original submission, the firm's test formulation was deemed to be qualitatively (Q1) and Quantitatively (Q2) the same as the RLD formulation. However, currently the firm has re-formulated its test product to include Sodium Tartrate (b) (4) and reduce the concentration of Sodium Metabisulfite.

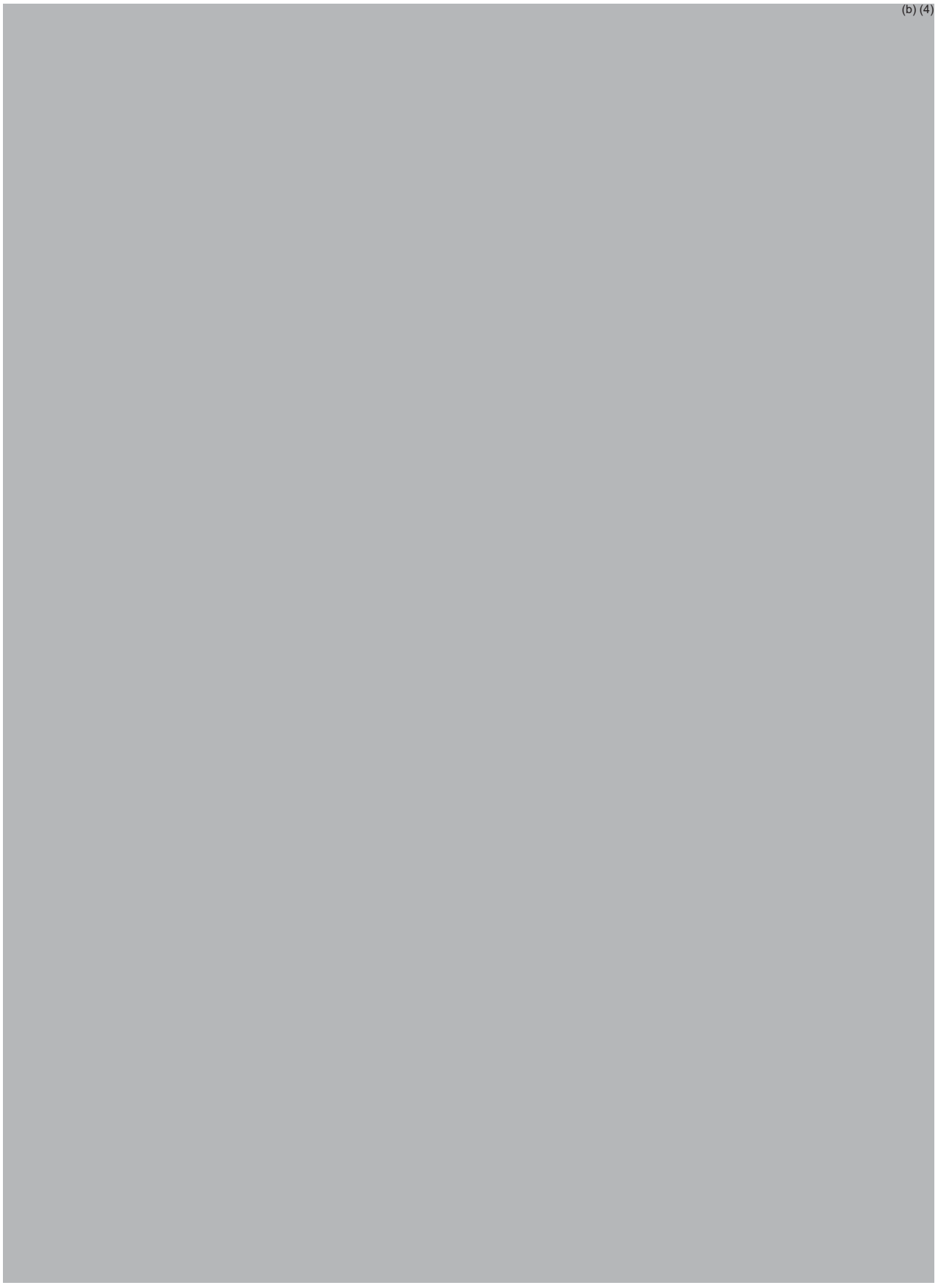
- The re-formulated test product is NOT qualitatively (Q1) and quantitatively (Q2) the same as RLD product. The test product contains Sodium Tartrate Dihydrate (b) (4) whereas the RLD product contains (b) (4). In addition, the firm's re-formulated test product (0.4 mg) contains considerably lower quantity of Sodium Metabisulfite than in the RLD formulation (0.5 mg). (b) (4) (b) (4)

  "Teva's formulation contains a lower concentration (b) (4) ***sodium metabisulfite than the RLD. The concentration of sodium metabisulfite used in the Epineprhine Injection formulation*** (b) (4) (b) (4) (b) (4) ***In addition, sodium tartrate*** (b) (4) ***is included in Teva's proposed formulation*** (b) (4) (b) (4) ***These differences in formulation are permitted in accordance with CFR 314.94(a)(9)(iii)".***

- In Module 3.2.P.2 Pharmaceutical Development Report, the firm has submitted the optimization studies that were conducted to select the amount of inactive ingredients Sodium Metabisulfite and Sodium Tartrate to be used in the test formulation.

(b) (4)

[22] DARRTS for NDA 019430: SOHN, JANE J 10/04/2011 N/A 10/04/2011 REV-NONCLINICAL-03(General Review) Supplement-51 (Manufacturing (CMC)) Archive


(b) (4)

- According to 21 CFR § 314.94 (a) (9) (iii), a drug product intended for parenteral use may differ from the RLD in the use of preservatives, buffers, or antioxidants provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety and efficacy of the proposed drug product.

- (b) (4)

- (b) (4) The pH of the Reference product, EpiPen® and EpiPen®Jr Injections ranges from 2.2- 5.0[25]. So the pH of the test product is the same as the pH of the RLD. In spite of the differences (b) (4) (Sodium Tartrate Dihydrate) between the test and RLD formulations, the pH of the test product is similar to the RLD product.

- The test product is intended for both Intramuscular and subcutaneous administration. The reviewer verified if the amount of Sodium Tartrate Dihydrate in the test formulation is within the FDA's Inactive Ingredient Guide (IIG) limits based on the MDD (b) (4) (b) (4)

Ingredient	Maximum amount/day based on MDD Amount (mg)	Maximum Level Listed in the FDA IIG Database for Approved Drug Products/Unit (Based on Route/Dosage [27]	IIG Limit Reference	Amount exceed or below the IIG limit of approved drug product/unit
Sodium Tartrate Dihydrate	(b) (4)			

(b) (4)

[23] DARRTS for NDA 019430: LAKHANI, DEEPIKA 10/25/2011 N/A 10/25/2011 REV-QUALITY-03(General Review) Supplement-51 (Manufacturing (CMC)) Archive

[24] DARRTS for ANDA 090589: Firm's Submission dated 12/203/2014. Module 3.2.P.5.4. Batch Analysis, Certificate of Analysis- Epinephrine Injection

[25] Labeling for the RLD Product http://dailymed nlm nih.gov/dailymed/drugInfo.cfm?setid=7560c201-9246-487c-a13b-6295db04274a (Accessed on 6/22/2015)

(b) (4)

(b) (4)

- The amount of Sodium Tartrate Dihydrate in the test formulation is within the acceptable limits for Intramuscular administration based on the FDA's Inactive Ingredient database. However, the IIG limit for the above stated inactive ingredient for subcutaneous administration is not provided in the IIG database. Therefore, the firm submitted the toxicology study report demonstrating the safety of above stated amount of Sodium Tartrate Dihydrate in the test formulation via subcutaneous administration.

- The DBIII has submitted a clinical consultation to the Division of Clinical research (DCR) for the safety and clinical significance of the amount of Sodium Tartrate Dihydrate in the firm's test product formulation intended for subcutaneous administration.

4.7 Deficiency Comments

None

4.8 Recommendations

The Division of Bioequivalence III (DBIII) agrees that the information submitted by Teva Pharmaceutical demonstrates that Epinephrine Injection USP, 0.3 mg/mL and 0.15 mg/mL, pre-filled syringe with auto-injector meets the requirements of Section 21 CFR § 320.24 (b) (6). The waivers of in vivo bioequivalence testing for the test products cannot be granted at this time pending the clinical consult.

4.9 Comments for Other OGD Disciplines

Discipline	Comment
Division of Clinical Review	Pending Clinical Consult

4.10 Pending Consults

OPQ has submitted Inter-center Consultation request to CDRH on 6/25/2015 for the evaluation of the Teva's re-designed auto-injector device (Vibex[(b) (4)].

OPQ has submitted Inter-center Consultation request to OSE on 6/25/2015 for the review of human factor study results[2020].

4.11 Detailed Regulatory History

Citizen Petition: FDA-2015-P-0181[29]

DEPARTMENT OF HEALTH & HUMAN SERVICES

JUN 1 5 2015

Food and Drug Administration
10903 New Hampshire Avenue
Building #51
Silver Spring, MD 20993

Frank Casty, M.D.
Mylan Specialty, L.P.
1000 Mylan Blvd.
Canonsburg, PA 15317

Re: Docket No. FDA-2015-P-0181

Dear Dr. Casty:

This letter responds to your citizen petition dated January 16, 2015 (Petition) and supplement dated April 28, 2015. In the Petition, you request that the Food and Drug Administration (FDA or the Agency) take certain actions with respect to abbreviated new drug application (ANDA) 090589, submitted by Teva Pharmaceuticals, for an epinephrine auto-injector (hereafter Teva application or product). Among other things, you ask that the Commissioner refrain from approving the Teva application unless, after conducting an appropriately rigorous review under the established standards for proposed generic emergency use auto-injectors, the Agency concludes that the proposed product is the "same as" the EpiPen auto-injector. You state that this includes the request that patients, caregivers, and other relevant user groups trained in the use of the EpiPen auto-injector who face an emergency situation be able to safely and effectively use the proposed product in accordance with the EpiPen auto-injector instructions for use, without additional physician interaction or training.

We have carefully considered the Petition and supplement. For the reasons stated below, the Petition is denied without comment on whether we will take the actions you request.

I. BACKGROUND

A. EpiPen

Mylan Specialty, L.P., holds approved new drug application (NDA) 019430 for EpiPen (epinephrine auto-injector). The product is indicated in the emergency treatment of allergic reactions (Type I) including anaphylaxis of various origins. It is available in two strengths, 0.3 milligram (mg)/delivery (0.3 mg/0.3 mL) (the EpiPen auto-injector) (yellow carrier cap and label) and 0.15 mg/delivery (0.15 mg/0.3 mL) (the EpiPen Jr auto-injector) (green carrier cap and label). EpiPen was initially approved on December 22, 1987.

[29] http://www regulations.gov/#!documentDetail;D=FDA-2015-P-0181-0009

B. Section 505(q) of the FD&C Act

Section 505(q) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) was added by section 914 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Pub. L. 110-85, 121 Stat. 823) and was amended by the Food and Drug Administration Safety and Innovation Act (FDASIA), which was signed into law on July 9, 2012 (Pub. L. 112-144, 126 Stat. 993). Section 505(q), as originally added by FDAAA, applies to certain citizen petitions and petitions for stay of Agency action that request that FDA take any form of action relating to a pending application submitted under section 505(b)(2) or (j) of the FD&C Act (21 U.S.C. 355(b)(2) or (j)) and governs the manner in which these petitions are treated. Among other things, section 505(q)(1)(F) of the FD&C Act governs the time frame for final Agency action on a petition subject to section 505(q). Under this provision, FDA must take final Agency action on a petition not later than 150 days after the date on which the petition is submitted. The 150-day period is not to be extended for any reason.

II. DISCUSSION

In the Petition, you request that FDA:

1. Refrain from approving the Teva application unless the Agency affirmatively finds that the proposed generic product is the same as the EpiPen auto-injector such that:

    a. Patients, caregivers, and other relevant user groups who were trained in the use of the EpiPen auto-injector and who face an emergency situation are able to safely and effectively use the Teva product in accordance with the instructions for the EpiPen auto-injector without additional retraining or physician interaction;

    b. No human factors or other clinical testing is required to demonstrate the Teva product's safety or effectiveness in actual use by patients or their caregivers who were trained in the use of the EpiPen auto-injector, or such that the Teva product has the same safety and effectiveness profile as the EpiPen auto-injector;

    c. The instructions for use and related aspects of the label and labeling of the Teva product do not differ from the EpiPen auto-injector label and labeling beyond differences permitted by the statute and applicable regulations, which require that a generic product generally have the same labeling as the reference listed drug (RLD);

    d. Considering the EpiPen auto-injector as a whole and its individual constituent parts, differences between the Teva product and the EpiPen auto-injector do not introduce new risks, taking into account both risks intrinsic to the Teva product and risks associated with switching from one epinephrine auto-injector to another without training or physician intervention; and

e. The Teva product is shown to be bioequivalent to the EpiPen auto-injector through appropriately designed bioequivalence testing to examine potential performance differences resulting from design differences and to assure equivalent clinical outcomes in the context of generic substitution.

2. Require Teva to provide the information necessary to make the above determinations, including specific information regarding product design and operating principles, as well as the results of comparative performance tests between the Teva product and the EpiPen auto-injector, as detailed in the Petition.

3. Require withdrawal of the ANDA and submission of an NDA under section 505(b)(2) of the FD&C Act because human factors or other clinical testing is required to demonstrate the Teva product's safety or effectiveness in actual use.

4. Not assign a therapeutic equivalence code to the Teva product indicating its therapeutic equivalence to the EpiPen auto-injector if the Teva product is approved under a 505(b)(2) NDA, unless the Agency finds that the two products are bioequivalent and can be expected to have the same clinical effect and safety profile when administered for the approved use and substituted without retraining.

5. Convene a joint meeting of the appropriate advisory committees to provide expert advice and clarity to the Agency on the complex scientific, technical, regulatory, and policy issues implicated by the data-driven evaluation of the "sameness" of the Teva proposed generic epinephrine auto-injector and the EpiPen auto-injector.

(Petition at 4-5.)

As grounds for your requests, your Petition cites previously issued Agency citizen petition responses[1] and guidances[2] that generally articulate Agency's thinking with regard to evaluating the approvability of an ANDA for a proposed generic auto-injector (Petition at 1-3, 10-13, 23-25), and states that this Petition is specific to the Teva product. You assert that application of the standards enumerated in the cited petition responses and guidances should lead FDA to not approve the Teva application, or to preclude a therapeutic equivalence rating if the product is approved under section 505(b)(2) of the FD&C Act.

You state that there are significant differences between the Teva product and the EpiPen that preclude the Teva product's approval under section 505(j) of the FD&C Act. You state that these include differences in design and operating principles, such as the manner in which the safety cap is released, preparation of the needle, and the method of injection (Petition at 9, 14-21). You assert that these differences would prevent a patient or caregiver trained on the EpiPen auto-injector from being able to use the Teva product safely and effectively in an emergency or in accordance with the EpiPen instructions for use (Petition at 14). For similar reasons, you assert that even under a 505(b)(2) approval, the product differences enumerated throughout the Petition preclude a designation of therapeutic equivalence.

As described in section I.B of this response, section 505(q)(1)(F) of the FD&C Act requires FDA to take final Agency action on the Petition within 150 days of submission. Therefore, we must take action on the Petition at this time. For the reasons explained below, we deny without comment the specific requests in your Petition regarding the approvability of any specific 505(j) application.

FDA has made no final determination on whether to approve or not approve any ANDA relying on EpiPen as the RLD. Therefore, we must determine whether it would be appropriate for us to take final Agency action on the approvability of a specific aspect of an application before taking final action on the approvability of the application as a whole. To make this determination, we believe it is appropriate to evaluate the statutory and regulatory provisions governing the content and review of 505(j) applications in connection with the statutory provision of section 505(q) of the FD&C Act governing the time frame for action on the Petition.

The FD&C Act and FDA regulations establish procedural protections for applicants in the context of application review. Section 505 of the FD&C Act and FDA's regulations at 21 CFR part 314 describe certain procedures by which the Agency reviews an NDA or ANDA and notifies an applicant if it determines that an application is approved (§ 314.105) or may not be approved (section 505(c) and (j) of the FD&C Act; §§ 314.125 and 314.127), or identifies the deficiencies in the application and the steps an applicant may take to respond to the deficiencies (§ 314.110). In addition, the statute and regulations describe a specific process through which an applicant whose application the Agency has found does not meet the requirements for approval may challenge the Agency's determination (section 505(c)(1)(B) and (d) of the FD&C Act; § 314.200). Under this process, the Agency will give the applicant notice of an opportunity for a hearing on whether the application is approvable, with a specific time frame and process, should the applicant request such a hearing (id.). These procedures ensure that applicants have an adequate opportunity to challenge a finding by the Agency that a product does not meet the requirements for approval.

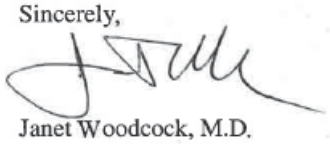
There is no evidence that in enacting section 505(q) of the FD&C Act, Congress intended to bypass the application review process or to lessen an ANDA or NDA applicant's procedural rights by requiring that the Agency make decisions that constitute final Agency action regarding the approvability of certain aspects of pending applications on a piecemeal basis outside of the

process established under the FD&C Act and FDA regulations.[3] Therefore, we do not interpret section 505(q) of the FD&C Act to require that the Agency render a final Agency decision within the statutory deadline on the approvability of a specific aspect of an application when a final decision on the approvability of any such application has not yet been made.[4] Accordingly, we are denying without comment your requests on the specific requirements for approval of an application relying on EpiPen as the RLD.

III. CONCLUSION

For the reasons described in this response, the Petition is denied.

Sincerely,



Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research

NOTE TO REGULATORY PROJECT MANAGER (RPM): Currently there is a pending clinical consult with DCR.

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA:	090589
APPLICANT:	Teva Pharmaceuticals USA
DRUG PRODUCT:	Epinephrine Injection USP (Auto-Injector), 0.3 mg/0.3 mL and 0.15 mg/0.3 mL

.

No letter is prepared at this time pending the response of the DCR consult request.

Sincerely yours,

{See appended electronic signature page}

Hoainhon Nguyen Caramenico, M.S., M.S.
Acting Director, Division of Bioequivalence III
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

5 OUTCOME PAGE

ANDA: 090589

Reviewer: Suman Dandamudi **Date Completed:**
Verifier: , **Date Verified:**
Division: Division of Bioequivalence
Description: Epinephrine Injection (Auto-Injector)

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
26150	3/8/2013	Other (REGULAR)	Study Amendment	1	1
26150	6/25/2015	Quality Assessment	Quality	5	-
			Total:	6	1

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	090589
Drug Product Name	Epinephrine Injection, USP (Auto Injector)
Strength(s)	0.15 mg/0.3 mL and 0.3 mg/0.3 mL
Applicant Name	Teva Parenteral Medicines, Inc.
Address	19 Hughes, Irvine, CA 92618
Applicant's Point of Contact	Susan O'Brien Director, Regulatory Affairs 19 Hughes, Irvine, CA 92618
Contact's Telephone Number	(949) 455-4724
Contact's Fax Number	(949) 583-7351
Original Submission Date(s)	December 21, 2007
Submission Date(s) of Amendment(s) Under Review	May 30, 2008 and May 22, 2009
Reviewer	Nilufer M. Tampal, Ph.D.
OUTCOME DECISION	**INADEQUATE**

Review of a Waiver Request

1 EXECUTIVE SUMMARY

The firm, Teva Parenteral Medicines, Inc, is requesting a waiver of *in vivo* bioequivalence study requirements under 21 CFR § 320.22(b)(1) for its test products, Epinephrine Injection USP, 0.15 mg/0.3 mL (Auto Injector Jr.) and 0.3 mg/0.3 mL (Auto Injector). The reference listed drug (RLD) products are Meridian Medical Technologies, Inc.'s EpiPen® Jr (epinephrine) Auto-Injector, 0.15 mg/0.3 mL and EpiPen® (epinephrine) Auto-Injector, 0.3 mg/0.3 mL. The formulations for each of the test products are qualitatively (Q1) and quantitatively (Q2) the same as the respective RLD products. The final acceptability of the overage of the active ingredient in the test products is deferred to the Division of Chemistry. Since, the drug product is an auto-injector, in addition to the formulation comparison, device similarity by *in vitro* comparative performance should be demonstrated for approval of this drug product. Currently, the OGD recommends that sponsors perform suitable *in vitro* tests including 1) volume of solution injected and residual content of the auto-injector, 2) dose delivery time, 3) force required to discharge actuator and force of injection, 4) exposed needle length and needle gauge, 5) depth of penetration, 6) needle cover test, and 7) needle integrity post injection to include testing through different clothing materials of varying thickness and different angles of incidence, to demonstrate comparative performance characteristics and functionality testing of the test and the reference drug products. In addition, the sponsor should provide specifications such as breakloose force and extrusion force. In the current application, the firm did not provide the *in vitro* comparison data.

The application is **incomplete**. The bio-waiver requests for the test products are **not** granted in accordance with 21CFR§ 320.22 (b) (1).

2 TABLE OF CONTENTS

3 SUBMISSION SUMMARY

3.1 Drug Product Information[1, 2]

Test Product	Epinephrine Injection USP, 0.15 mg/0.3 mL and 0.3 mg/0.3 mL
Reference Product	EpiPen® Jr (epinephrine) Auto-injector, 0.15 mg/0.3 mL and Epipen® (epinephrine) Auto-injector, 0.3 mg/0.3mL
RLD Manufacturer	Meridian Medical Technologies, Inc. (a wholly owned subsidiary of King Pharmaceuticals)
NDA No.	19-430
RLD Approval Date	December 22, 1987
Indication	A sympathomimetic catecholamine indicated in the emergency treatment of allergic reactions (anaphylaxis) to insect stings or bites, foods, drugs and other allergens as well as idiopathic or exercise-induced anaphylaxis.

The EpiPen® and EpiPen® Jr auto-injectors each contain 2 mL epinephrine solution for emergency **intramuscular** injection only. Each EpiPen® auto-injector delivers **a single dose** of 0.3 mg epinephrine from epinephrine injection, USP, 1:1000 (0.3 mL) in a sterile solution. It is intended for patients who weigh 30 kg or more (approximately 66 pounds or more). Each EpiPen® Jr auto-injector delivers **a single dose** of 0.15 mg epinephrine from epinephrine injection, USP, 1:2000 (0.3 mL) in a sterile solution. It is intended for patients who weigh 15 to 30 kg (33-66 pounds) For stability purposes, approximately 1.7 mL remains in the auto-injector after activation and cannot be used.

EpiPen® and EpiPen® Jr auto-injectors are available in individual cartons and as EpiPen® and EpiPen® Jr 2-Pak, packs that contains two EpiPen® or EpiPen® Jr auto-injectors and one EpiPen® or EpiPen® Jr auto-injector trainer devices respectively.

3.2 PK/PD Information[3]

Bioavailability	Not indicated in the drug label
Food Effect	Not indicated in the drug label
Tmax	Not indicated in the drug label
Metabolism	Not indicated in the drug label
Excretion	Not indicated in the drug label
Half-life	Not indicated in the drug label
Relevant OGD or DBE History (for details see Section 3.9, Additional Attachments)	1. A review of Orange Book (last accessed 2/12/10) shows that no generics for this drug product have been approved. (b) (4) (b) (4)

[1] Online-Orange Book (2009) http://www.fda.gov/cder/ob/default htm. Epinephrine. Last accessed: 2/12/10
[2] RLD Prescribing Information. http://www.anaphylaxis.com/files/Legacy-Physician-Insert.pdf. Last accessed: 3/1/
[3] External Database: DailyMed Current Medication Information. Search: Epinephrine (http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=8551#nlm34067-9). Last accessed: 2/16/10

	(b) (4)
Drug Specific Issues (if any)	Epinephrine is light sensitive and should be stored in the tube provided. The auto-injector should be replaced if the solution is discolored or contains a precipitate. EpiPen and EpiPen Jr should **only** be injected into the anterolateral aspect of the thigh. Large doses or accidental intravenous injection of epinephrine may result in cerebral hemorrhage due to sharp rise in blood pressure. Accidental injection into the hands or feet may result in loss of blood flow to the affected area and should be avoided.

3.3 Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	No	--
Single-dose fed	No	--
Steady-state	No	--
In vitro dissolution	No	--
Waiver requests	Yes	2
BCS Waivers	No	--
Amendment	Yes	1

3.4 Formulation

3.5 Comments Related to Formulation:

1. Qualitatively (Q_1) the test products, Epinephrine Injection USP, 0.15 mg/3 mL mg and 0.3 mg/3 mL contain the same inactive ingredients as the approved RLDs. Quantitatively (Q2) the inactive ingredients in the test products are present in the same amounts as compared with the respective RLD product strengths. (b) (4)
2. (b) (4)
3.

3.6 In Vitro Performance Comparison of Test and the RLD Devices

1. Both the test and RLD devices use a spring-loaded auto-injector, activated by applying pressure to the front end of the unit. The test device is a single-use, single injection, disposable, single piece device that contains the drug in the primary container as an integral part of the device.

[4] DAARTS, ANDA ANDA 090589, New ANDA, 12/21/07; Section 2.3.P.1.
[5] DAARTS, ANDA ANDA 090589, Resubmission /After Action-Complete, 5/23/09; Section 3.2.P.2 –Drug Product.
[6] DAARTS, ANDA ANDA 090589, Resubmission /After Action-Complete, 5/23/09; Section 3.2.P.5.4 –Batch Analyses

In the submission from 5/30/08[7], Teva provided the below summary tables for comparison of the performance parameters of their proposed actuator device versus the innovator's device. However, the means and standard deviation data alone were provided with the exception of Ejection Time test results for which the individual data for Teva's device were submitted.

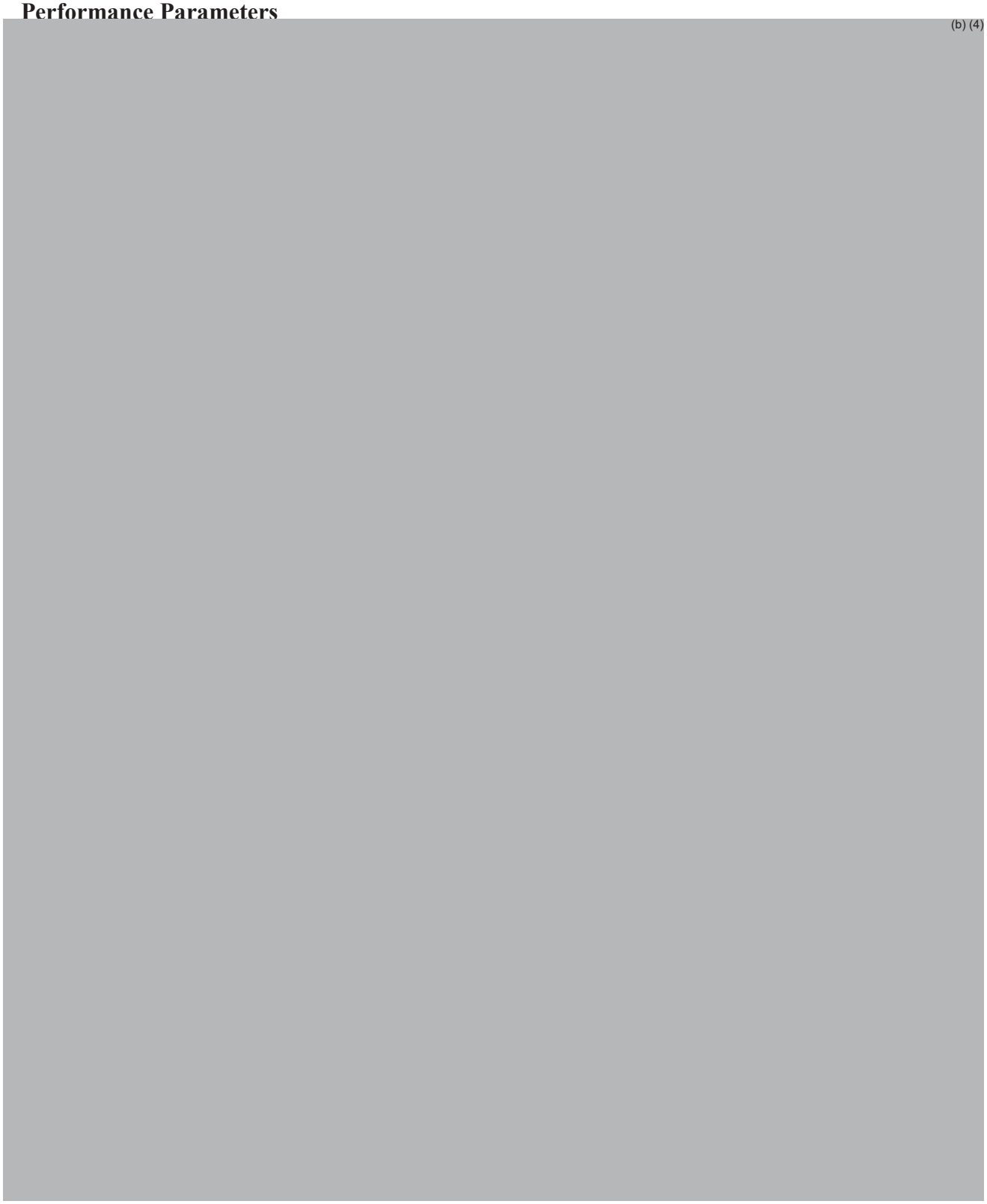
Table 1. Comparison between Teva's and EpiPen® Adult Auto-Injectors – Performance Parameters

(b) (4)

[7] DAARTS, ANDA ANDA 090589, Correspondence, 5/30/08; Module 1.2, Cover Letter

Table 2. Comparison between Teva's Junior and EpiPen ®Jr Auto-Injectors – Performance Parameters

(b) (4)



(b) (4)

The submission from 5/30/08[8] notes that studies comparing the performance parameters and function data for the proposed device and the RLD device will be provided in the MAF (Master File for Device). The performance parameters will include needle gauge, exposed needle length, injection time, expelled volume, force to retract collar, force to trigger device, and spring force in ready to fire state. The functional characteristics study will include a comparison of giving an injection with the device and sharps protection feature/process.

2. The OGD requested a consult for the current ANDA from the Division of Pulmonary and Allergy Products, (DPAP) HFD-570, to evaluate a) whether the mechanism of action of Teva's and the innovator's products were identical or not and (b) whether the application should be filed under the 505(j) or (505)(b)(2) pathway (DAARTS Search: ANDA 90589, Rev-Clinical-03 [General Review], 11/13/08). DPAP reviewed the information provided by Teva concerning their epinephrine auto-injector product and concluded that the mechanism of action (mechanism of release) is the same as that of the Epipen auto-injectors. (b) (4) (b) (4) Teva's exposed needle length range was slightly longer than that of Epipen Auto injector as follows:

(b) (4)

DPAP recommended that the application was fileable under 505 (j). The impact of differences in needle lengths on product performance should be evaluated during the review.

3. A consult for the current ANDA from the Center for Devices and Radiological Health (CDRH) (DAARTS Search: ANDA 090589, Rev-RPM-05 [Consult Review], 10/24/08) concluded that the information and data provided in the original submission dated December 21, 2007, and in the addendum dated May 30, 2008 do not support claim that the Teva's proposed auto-injector intended for subcutaneous delivery of epinephrine is comparable to the EpiPen Auto injector. However, the sponsor did not provide the test data to support performance claims or the clinical evaluation of the proposed auto-injector among other deficiencies.

Reviewer's Note: (b) (4)

(b) (4)

[8] , ANDA ANDA 090589, Correspondence, 5/30/08; Module 3.2.P.2.4-Container Closure

3.7 Deficiency Comments

1. The firm did not provide individual data for the *in vitro* tests to demonstrate comparable performance between the test and RLD device components. In addition to formulation comparison, the OGD recommends that sponsors perform suitable *in vitro* tests to document the following performance characteristics and provide comparison data to the reference listed drugs, EpiPen® and EpiPen Jr ® auto-injector: 1) volume of solution injected and residual content of the auto-injector, 2) dose delivery time, 3) force required to discharge actuator and force of injection, 4) exposed needle length, 5) depth of penetration, 6) needle cover test, and 7) needle integrity post injection to include testing through different clothing materials of varying thickness and different angles of incidence. Specifications such as breakloose force and extrusion force should be provided. The firm provided summary data (means and standard deviations) for expelled volume, needle gauge, exposed needle length, force to trigger device, and spring force to inject drug for the test product. Individual data for the test product were provided only for the injection time. Comparative data for the reference devices were not provided. The firm should conduct additional *in vitro* testing and provide comparative data for the test and reference devices under the same conditions. The firm should also provide all relevant SOPs and validation data for each test procedure used.

2. The firm did not submit complete electronic EXCEL spreadsheet of individual data for each of the tests on the test device product versus the RLDs products Epipen® and Epipen® Jr. for review.

3.8 Recommendations

The Division of Bioequivalence does not agree that the information submitted by Teva Parenteral Medicines, Inc., qualifies Epinephrine Injection USP, 0.15mg/0.3mL and 0.3 mg/0.3mL (auto-injectors), for a waivers of bioequivalence requirements under 21 CFR § 320.22 (b) (1). The waivers of *in vivo* bioequivalence study requirements for Epinephrine Injection USP, 0.15mg/0.3mL and 0.3 mg/0.3mL (auto-injectors) cannot be granted at this time due to deficiency comments above.

The firm should be informed of the above deficiency comments and recommendations.

3.9 Comments for Other OGD Disciplines

Discipline	Comment
Chemistry	(b) (4)

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

BIOEQUIVALENCE DEFICIENCIES

ANDA:	090-589
APPLICANT:	Teva Parenteral Medicines, Inc
DRUG PRODUCT:	Epinephrine Injection, USP (Auto Injector), 0.15 mg/0.3 mL and 0.3 mg/0.3 mL

The Division of Bioequivalence (DBE) has completed its review of your submission acknowledged on the cover sheet. The following deficiencies have been identified:

1. The DBE recommends in-vitro testing to demonstrate comparable performance of the device components (auto-injectors) used in your proposed test products to the reference listed drug (RLD) products, EpiPen® (epinephrine) Auto-Injector, 0.30 mg/0.3 mL and EpiPen Jr ® (epinephrine) Auto-Injector, 0.15 mg/0.3 mL. You provided summary data (means and standard deviations) for expelled volume, needle gauge, exposed needle length, force to trigger device, and spring force to inject drug for the test product. Individual data for your test products were provided only for the injection time. Comparative data for the RLD devices were not provided. Please conduct additional *in vitro* testing and provide comparative data for the test and reference devices under the same conditions. The performance tests may include but not be limited to the following: 1) volume of solution injected and residual content of the auto-injector, 2) dose delivery time, 3) force required to discharge actuator and force of injection, 4) exposed needle length, 5) depth of penetration, 6) needle cover test, and 7) needle integrity post injection to include testing through different clothing materials of varying thickness and different angles of incidence. Specifications such as breakloose force and extrusion force should be provided. Please provide all relevant Standard Operating Procedures (SOPs) and validation data for each test procedure conducted.

2. Please submit complete electronic EXCEL spreadsheets or SAS Transport format files of individual data for each of the tests on the test device product versus the RLD products.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence I
Office of Generic Drugs
Center for Drug Evaluation and Research

4.0 Outcome Page

ANDA: 90-589

Productivity

http://cdsogd1/bioprod

Reviewer:	Tampal, Nilufer	**Date Completed:**
Verifier:	,	**Date Verified:**
Division:	Division of Bioequivalence	
Description:	Epinephrine Injection, USP, (AutoInjector) 0.15 mg/0.3 mL and 0.3 mg/0.3 mL -Teva	

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
10393	12/21/2007	Other	Waiver Injectable	1	1
10393	12/21/2007	Other	Waiver Injectable	1	1
				Bean Total:	2

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-90589	ORIG-1	TEVA PARENTERAL MEDICINES INC	EPINEPHRINE

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

/s/

NILUFER M TAMPAL
03/10/2010

APRIL C BRADDY
03/11/2010

HOAINHON N CARAMENICO on behalf of DALE P CONNER
03/11/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 090589

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

SUPERSEDING MEMORANDUM TO REVIEW COMPLETED IN NOVEMBER 2016

Consult Requester	Lissa Owens, OMEPRM/DMEPA
Type of Consult	Evaluation of Comparative Use Human Factors Data for ANDA 090589 Teva's Epinephrine Auto-injector
Reference Listed Drug **Indication**	Mylan's EpiPen® (Epinephrine Injection, USP) 0.3 mg and EpiPen® Jr (Epinephrine Injection, USP) 0.15 mg (NDA 019430) Life-threatening allergic reactions (anaphylaxis) caused by allergens, exercise, or unknown triggers.
Dates	Document Date: 09/26/2016 Review Complete Date: 11/10/2016 Superseding Memorandum Date: 8/14/2018
Biometrics Division	DB VIII/OB/OTS/CDER
Statistical Primary Reviewer **Statistical Secondary Reviewer**	Yifan (Katie) Wang, Ph.D. Stella Grosser, Ph.D.
OMEPRM/OSE Division	DMEPA/OMEPRM/OSE/CDER
DMEPA Primary Reviewer **OMEPRM Deputy Director**	Mishale Mistry, PharmD, MPH Kellie Taylor, PharmD, MPH Lubna Merchant, PharmD, MS
Key Words	Generic Drug-Device Combination, Epinephrine, Auto-injector, Comparative Human Factors Study, Use Error Rate, Current RLD User, Adult, Teen

This memo supersedes the original consult review (dated November 10, 2016). It reflects our current thinking as to the appropriate analysis of the comparative HF data for Teva's proposed epinephrine (referred to by Teva as the AJE), auto-injector submitted in ANDA 090589.

1. BACKGROUND AND SUMMARY OF CONSULT REQUEST

Mylan's EpiPen® (Epinephrine Injection, USP) 0.3 mg and EpiPen® Jr (Epinephrine Injection, USP) 0.15 mg were approved on December 22, 1987 (NDA 019430) for the emergency treatment of life-threatening allergic reactions (anaphylaxis) caused by allergens, exercise, or unknown triggers.

Dr. Lissa Owens, OMEPRM/DMEPA, sent a consult request to review Teva's submission dated September 26, 2016, in response to the face-to-face meeting held with FDA on September 14, 2016, to determine whether Teva's comparative human factors (HF) study methodology for Epinephrine Auto-injector (ANDA 090589) is acceptable. More specifically, the OTS/OB Division of Biometrics VIII was asked to provide an evaluation of the randomization of assigning participants to devices within the HF studies, the study methodology in terms of data collection, and the additional data regarding the error rates associated with the RLD (Mylan's EpiPen®) and Teva's AJE (test product).

The statistical reviewer sent an ECD regarding the rationale of actions taken for the HF studies on October 27, 2016. Teva responded to this ECD on November 4, 2016.

2. REVIEWER'S RESPONSE TO THE CONSULT

Teva proposed that participants included in the HF studies be combined from study TR927 and study TR-1340. Both studies are simulated use studies with elimination of actual drug injections (i.e., no study drug was administered). All participants were greater than 12 years old, and used the 0.3 mg presentation of the applicable device.

Table 1 presents the subject disposition of study subjects classified as current RLD users using AJE and RLD devices in both studies, for Adult and Teen groups. Here, "Adult" refers to participants age 18 and over, and "Teen" refers to participants age 13 to 17.

Table 1: Subject Disposition of Current RLD Users

Number of Current RLD Users		AJE	RLD	Total
Study TR927	**Adult**	15	11	26
	Teen	16	10	26
Study TR1340	**Adult**	17	14	31
	Teen	14	15	29
Combined from both studies	**Adult**	32	25	57
	Teen	30	25	55
Total		**62**	**50**	**112**

Source: Reviewer's Analysis.

Table 2 presents the subject disposition of study subjects classified as non-RLD users using AJE and RLD devices in both studies, for Adult and Teen groups.

Table 2: Subject Disposition of Non-RLD Users

Number of Current RLD Users		AJE	RLD	Total
Study TR927	**Adult**	14	12	26
	Teen	19	11	30
Study TR1340	**Adult**	15	16	31
	Teen	14	16	30
Combined from both studies	**Adult**	29	28	57
	Teen	33	27	60
Total		**62**	**55**	**117**

Source: Reviewer's Analysis.

2.1 Device Use Assignment

Studies TR927 and TR1340 were designed as two-sequence crossover studies in which each participant attempted to complete two injections with one of the two devices (either the proposed product or the RLD), immediately after which the participant attempted to complete two injections with the other device. The Applicant provided details on the process for determining which device the study participants used first within the two HF studies.

The Applicant used four steps to assign users to the order of device use in the study. First, a third party company recruited participants by inviting participants to choose their preferred time slot. Second, screening answers were used to categorize participants into four user groups (current RLD adult users, current RLD teen users, non-RLD (naïve) adult users, non-RLD (naïve) teen users) until user group quotas were filled. Then, participant numbers were chronologically assigned within each user group to all participants. Finally, the device to be used first was assigned based on the assigned participant number (odd numbered participants were given AJE first and even numbered participants were given RLD first.

Strictly speaking, the assignment method is not a randomized procedure. However, it would be difficult to manipulate it to introduce a bias. Although we would generally recommend the

generation of random numbers to assign participants to which device they would use first, the approach for device use assignment in sponsor's TR927 and TR1340 studies is a reasonable approach to use in a comparative HF study and would achieve the goals of randomization..

2.2 Data Collection

An (b) (4) conducted the HF studies using the following methods: A study moderator, a video camera, and a data analyst simultaneously recorded behavioral (quantitative) and interview (qualitative) data during the study sessions, with no prompts or guidance provided to participants. The study moderator recorded data directly onto the interview guide, while the data analyst recorded data on successful or failed performance of all tasks into a spreadsheet from behind a two-way mirror. A study staff member compared the interview guide and spreadsheet to ensure both methods agreed. If there was any discrepancy, the staff member reviewed the video to resolve it.

The methodology used in data collection described in the sponsor's cover letter is appropriate for the HF studies.

2.3 Data Analysis

This section includes discussion of the applicant's statistical margin used in its analysis, our data analyses of use error for current RLD users and non-RLD users, and a graphical depiction of the difference in error rate of RLD and Test ("delta") versus RLD error rate. The Applicant defined the 5 tasks (which the applicant referred to as "steps") to be evaluated in its HF studies as follows:

1. Step 1: Remove the yellow cap (proposed product device only), or remove the device from the carrier tube (RLD device only)
2. Step 2: Pull off the blue safety release
3. Step 3: Select proper injection location (i.e., middle of the upper thigh)
4. Step 4: Use sufficient force to trigger the injection
5. Step 5: Inject entire dose – users must hold the device firmly against the skin for a minimum of 1 second to administer the entire dose

A. Margin Used in Applicant's Analysis

In its submission dated September 26, 2016, the Applicant based its choice of a 10% margin on the following reasoning (quoted from the applicant):

> "The study protocol defined success criteria as follows: 'That the AJE device use errors and close calls occur at a frequency that is no more than 10% greater than the frequency of the use errors and close calls for the RLD.

"This is calculated by subtracting the percent error rate of the AJE from the percent error rate of the RLD. For example, a positive value for delta would mean that the error rate for the AJE device occurred at a frequency less than the RLD.

"The following information is provided in order to give clarification to the FDA as to why The Sponsor believes the margin specified within the protocol is reasonable and appropriate:

1. The simulated use task of administering epinephrine represents an emergency scenario, where some errors would be expected with any device, given the context of use and performance influencing factors (time pressure, stress, distractions etc.). Indeed, errors were experienced even by the Current RLD users when using the RLD (who should, due to their experience, be the most reliable group using the RLD).

2. Therefore, such a study would not be expected to generate results of zero v zero error rates for the RLD v Generic devices. The objective of such a study would be to show that a generic device is "similar enough" to "result in a product that will perform the same as the RLD under the conditions of use described in the labeling" (ANDA Submissions – Refuse-to-Receive Standards. Guidance for Industry, May 2015). This requires a justification of what performance could be considered to be "*the same*" and what could be an indicator of a "*difference*" given that we are considering a Human Factors study with the inherent variability of human performance within the sample sizes used for validation testing.

3. The minimum number of participants for a validation study is 15 (*Section 8.1.1, Applying Human Factors and Usability Engineering to Medical Devices. Guidance for Industry and Food and Drug Administration Staff,* February 3, 2016).

"As stated in Points 1 and 2, errors would be expected to occur, and there will be some naturally expected variation in how and when they occur across and within user groups. Acknowledging that there will be some differences experienced within Human Factors studies, and allowing for only the smallest amount of variance possible (that is, 1 per 15) give a baseline expected variance of 6.7%. Therefore, for an expected nominal variance of 1 error per 15 participants between user groups or devices, any consideration of variances at or below

this level is considered unnecessary because such variances would be naturally expected.

"Two use errors per 15, gives a 13.3% variance. At and beyond this point, it is considered worth investigating the difference and the reason for the difference, since a variation of 2 within a sample of 15 *could* be a signal of one device being more susceptible to error than another.

"Therefore, a nominal 10% difference (i.e., between 6.7% and 13.3 %) provide a point below which it is considered that naturally occurring variations in error would be expected, but beyond which differences are worthy of further investigation.

"Given that the value is a percentage, it can then also be applied to larger sample sizes where more than 15 users are involved within a study / user group."

We see two primary problems with this reasoning. First, there is no explanation or justification, neither in general nor for this product, for the claim that one excess error out of 15 is expected but two indicates a possible problem. The second concern is that Teva's reasoning does not account for variability in the estimates of the error rates (the observed error rates) and in the difference of error rates between groups or products. If this study were to be replicated under the same conditions (same products, similar populations of study subjects), then even with same underlying "true" error rates, it is likely that the observed rates and the observed difference in rates in the repeat study would not be the same as the first study due to sampling variability resulting from natural human variation in task performance

Given the limitations in the applicant's reasoning, we used 90% Wald's confidence interval with Yate's continuity correction to compare use errors between the proposed product and RLD. The Wald statistic is a commonly used way to interpret data, by comparing a parameter estimate to a proposed value and scaling the difference by the standard error. The Wald statistic can be shown to have a normal distribution. The Wald statistic is often present in a squared form and this form follows a chi-square distribution. Wald confidence intervals are built on the same theoretic foundations as the Wald statistic. The Yates continuity correction is a method used to refine assumptions that binomial random variables follow the normal distribution under certain conditions. Confidence intervals are used to describe variability around a point estimate. In general, the wider a confidence interval, the more variability there might be around the point estimate, and thus less precision in the finding, while narrower confidence intervals suggest more precision in the findings. Using a confidence interval approach accounts for the inherent variability which Teva's reasoning fails to account for and gives probabilistic bounds on what we might observe in non-simulated use..

For each of the critical tasks affected by the difference in external critical design attribute for the proposed product as compared to the RLD, the between-group difference in use error rates was determined, along with a 90% confidence interval around that point estimate. The between-group difference is calculated by measuring the use error rate with the proposed product and subtracting from it the use error rate with the RLD. Thus, a between-group point estimate of a difference that is greater than zero suggests a higher error rate with the test product than with the RLD. Because Teva's HF studies were not prospectively designed to exclude a specific threshold of the upper bound, we use the 90% confidence intervals to describe the data. Because we are using a non-inferiority approach, we focused on the upper bound of the 90% confidence interval and not on the lower bound.

B. Current RLD User Error Analysis

Table 3 presents the results of reviewer's analysis of "*Step 1" Remove Cap or Tube use errors* using 90% CI of difference between Test (AJE) and RLD, for Adult and Teen current RLD users.

Table 3: Current RLD User Error Analysis for Remove Cap or Tube (Step 1)

Current User	Use Error Rate % (*n*/*N*)*		Difference in Use Error Rate (Test-RLD)	Lower 90% Confidence Bound	Upper 90% Confidence Bound
	Test (AJE)	RLD			
Adult	1.56% (1/64)	4.00% (2/50)	-2.44%	-9.44%	**4.57%**
Teen	3.33% (2/60)	0.00% (0/50)	3.33%	-2.31%	**8.98%**

*Each participant had two injections from a given device. *n* = number of errors in both injections. *N* = total number of injections.
Source: Reviewer's Analysis.

For current RLD users Adults, the upper 90% confidence bound of the difference in user error rates is 4.57% for Step 1. This analysis shows that we can rule out differences in use error rates greater than 4.57% (meaning use error rate is no more than 4.57% higher with the test product vs. RLD) with 95% confidence. for Step 1 Remove Cap or Tube.

For current RLD users Teens, the upper 90% confidence bound of the difference in user error rates is 8.98% for Step 1. This analysis shows that we can rule out differences in use error rates greater than 8.98% (meaning use error rate is no more than 8.98% higher with the test product vs. RLD) with 95% confidence for Step 1 Remove Cap or Tube.

Table 4 presents the results of reviewer's analysis of "*Step 2" Remove Blue Safety Release use errors* using 90% CI of difference between Test (AJE) and RLD, for Adult and Teen current RLD users.

Table 4: Current RLD User Error Analysis for Remove Blue Safety Release (Step 2)

Current User	Use Error Rate % (*n*/*N*)*		Difference in Use Error Rate (Test-RLD)	Lower 90% Confidence Bound	Upper 90% Confidence Bound
	Test (AJE)	RLD			
Adult	0.00% (0/64)	8.00% (4/50)	-8.00%	-16.09%	**0.09%**
Teen	5.00% (3/60)	4.00% (2/50)	1.00%	-7.33%	**9.33%**

*Each participant had two injections from a given device. *n* = number of errors in both injections. *N* = total number of injections.
Source: Reviewer's Analysis.

For current RLD users Adults, the upper 90% confidence bound of the difference in user error rates is 0.09% for Step 2. This analysis shows that we can rule out differences in use error rates greater than 0.09% (meaning use error rate is no more than 0.09% higher with the test product vs. RLD) with 95% confidence for Step 2 Remove Blue Safety Release.

For current RLD users Teens, the upper 90% confidence bound of the difference in user error rates is 9.33% for Step 2. This analysis shows that we can rule out differences in use error rates greater than 9.33% (meaning use error rate is no more than 9.33 % higher with the test product vs. RLD) with 95% confidence for Step 2 Remove Blue Safety Release.

Table 5 presents the results of the reviewer's analysis of *all steps cumulative use errors* using 90% CI of difference between Test (AJE) and RLD, for Adult and Teen current RLD users.

We note that the cumulative use error rates that the Applicant submitted are composite estimates, which estimate the rate at which users commit errors in at least one of the five administration steps, as those steps were defined in the HF studies. The high variance often seen in the cumulative use error rates is due to compounding variability in each of the subcomponents (each task that makes up the cumulative error rate), and is not necessarily driven by any differences in design of the product. In addition, all steps are given the same importance in this composite estimate, regardless of whether the step is related to any difference in design between the proposed product and the RLD.

Table 5: Current RLD User Error Analysis for All Steps Cumulative

Current User	Use Error Rate % (*n*/*N*)*		Difference in Use Error Rate (Test-RLD)	Lower 90% Confidence Bound	Upper 90% Confidence Bound
	Test (AJE)	RLD			
Adult	32.81% (21/64)	32.00% (16/50)	0.81%	-15.49%	**17.12%**
Teen	18.33% (11/60)	18.00% (9/50)	0.33%	-13.64%	**14.31%**

*Each participant had two injections from a given device. If any of the five steps has use error for a certain injection, the injection is considered as an error. *n* = total number of error injections. *N* = total number of injections.
Source: Reviewer's Analysis.

For current RLD users Adults, the upper 90% confidence bound of the difference in user error rates is 17.12% for all steps cumulative. This analysis shows that we can rule out differences in use error rates greater than 17.12 % (meaning use error rate is no more than 17.12% higher with the test product vs. RLD) with 95% confidence for all steps cumulative.

For current RLD users Teens, the upper 90% confidence bound of the difference in user error rates is 14.31% This analysis shows that we can rule out differences in use error rates greater than 14.31% (meaning use error rate is no more than 14.31% higher with the test product vs. RLD) with 95% confidence for all steps cumulative.

C. Non-RLD User Error Analysis

Teva provided use error data on non-RLD (naïve) users. Although we did not request such data to address the HF deficiency nor are these data needed to support our conclusions, we looked at the data provided. Table 6 to

Table 8 presents reviewer's additional analyses on single Step 1, Step 2 and cumulative all steps for non-RLD ("naïve") users.

Table 6: Non-RLD User Error Analysis for Remove Cap or Tube (Step 1)

Non-RLD User	Use Error Rate % (*n*/*N*)*		Difference in Use Error Rates (Test-RLD)	Lower 90% Confidence Bound	Upper 90% Confidence Bound
	Test (AJE)	RLD			
Adult	0% (0/58)	1.79% (1/56)	-1.79%	-6.45%	**2.88%**
Teen	1.52% (1/66)	1.85% (1/54)	-0.34%	-5.92%	**5.25%**

Source data: Excel sheet "Summary Tables" in additional-data-analysis.xlsx

For naïve Adult users, the upper 90% confidence bound of the difference in user error rates is 2.88% for Step 1.

For naïve Teen users, the upper 90% confidence bound of the difference in user error rates is 5.25% for Step 1.

Table 7: Non-RLD User Error Analysis for Remove Blue Safety Release (Step 2)

Non-RLD User	Use Error Rate % (*n*/*N*)*		Difference in Use Error Rates (Test-RLD)	Lower 90% Confidence Bound	Upper 90% Confidence Bound
	Test (AJE)	RLD			
Adult	10.34% (6/58)	17.86% (10/56)	-7.51%	-19.95%	**4.93%**
Teen	9.09% (6/66)	33.33% (18/54)	-24.24%	-37.98%	**-10.51%**

Source data: Excel sheet "Summary Tables" in additional-data-analysis.xlsx

For naïve Adult users, the upper 90% confidence bound of the difference in user error rates is 4.93% for Step 2.

For naïve Teen users, the upper 90% confidence bound of the difference in user error rates is -10.51% for Step 2.

Table 8: Non-RLD User Error Analysis for All Steps Cumulative

Non-RLD User	Use Error Rate % (*n*/*N*)*		Difference in Use Error Rates (Test-RLD)	Lower 90% Confidence Bound	Upper 90% Confidence Bound
	Test (AJE)	RLD			
Adult	25.86% (15/58)	51.79% (29/56)	-25.92%	-42.17%	**-9.67%**
Teen	28.79% (19/66)	68.52% (37/54)	-39.73%	-55.27%	**-24.19%**

*Each participant had two injections from a given device. If any of the five steps has use error for a certain injection, the injection is considered as an error. *n* = total number of error injections. *N* = total number of injections.
Source data: Excel sheet "Summary Tables" in additional-data-analysis.xlsx

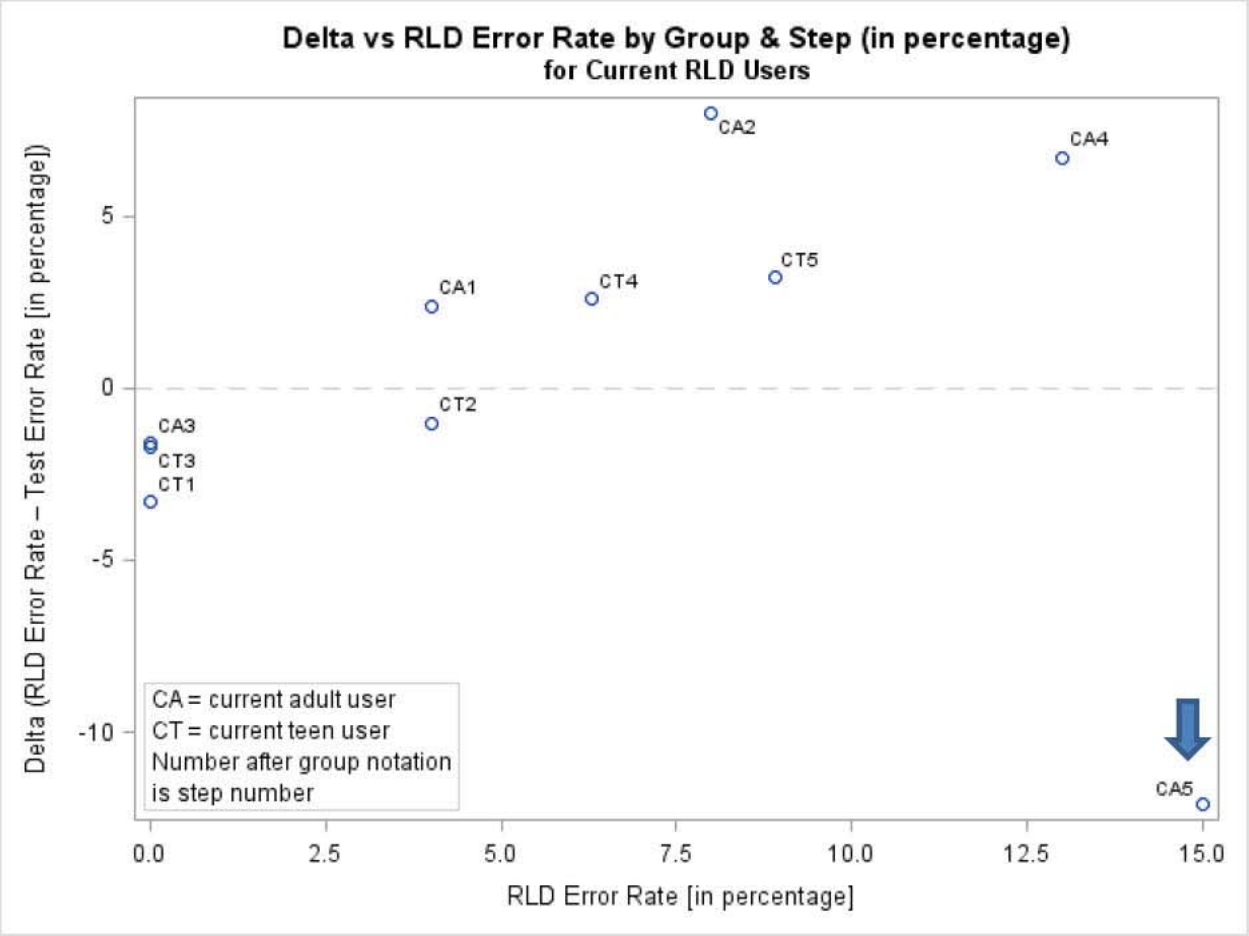
For naïve Adult users, the upper 90% confidence bound of the difference in user error rates is -9.67%% for all steps cumulative.

For naïve Teen users, the upper 90% confidence bound of the difference in user error rates is -24.19% for all steps cumulative.

D. Graph of Delta vs RLD Error Rate for Current RLD User

Below is a plot of delta, the difference in error rate of RLD and Test (Delta = RLD Error Rate – Test Error Rate), versus error rate of RLD in percentage for current RLD user by user group and step (CA = current adult user, CT = current teen user, the number after the group notation is the step number).

Figure 1: Delta vs RLD Error Rate by Group & Step for Current RLD User



Delta = RLD Error Rate – Test Error Rate (in percentage)

CA = current adult user, CT = current teen user, the number after the group notation is the step number

Source data: Single step error rates in Excel sheet "Summary Tables" in additional-data-analysis.xlsx

The graph shows a positive association between RLD error rate and delta, the difference in error rate of RLD and Test, for current RLD users. The difference increases as RLD error rate goes up. A delta greater than 0 means RLD has more errors than Test, and a delta less than 0 means Test has more errors than RLD. It is worth noting that the value of CA5, the current adult user group for Step 5, does not appear to follow this pattern of positive association, with RLD error rate being 15.0%, Test, 27.1%, and delta, -12.12%.

2.4 FDA's Comments to Teva's ECD Responses

FDA's ECD Request on October 27, 2016:

For Table 5 through Table 10 in the cover letter dated September 26, 2016, clarify or provide justification for why the total number of injections of RLD and AJE (the denominators in column 3 RLD 1st and column 5 AJE 1st) for Step 4 Trigger Injection

and Step 5 Hold in Place, are not equal to the total number of injections for the first 3 steps. For example, in Table 5, the denominator is 100 for RLD at Step 1, 2 and 3, but 94 at Step 4 and 85 at Step 5. Provide clarification or justification for why the denominator changed from 100 to 94 at Step 4, and further changed to 85 at Step 5.

Teva's Response on November 4, 2016:

Please refer to Appendix B.

FDA's Comments:

The sponsor stated the rationale of actions taken as follows. If a participant failed Step 1 (Remove Cap or Tube) and/or Step 2 (Remove Safety), then Step 4 (Trigger Injection) and Step 5 (Hold in Place) would be not assessable. The failed number of injections in Step 1 and Step 2 is subtracted from the total number of injections at Step 4 and Step 5. If a participant failed Step 4, then Step 5 would be not assessable. The failed number of injections in Step 4 is subtracted from the total number of injections at Step 5. Step 1, Step 2 and Step 3 (Correct Injection Site) are relatively independent actions. Participants who failed Step 1 can still succeed on Step 2 and/or Step 3. A failure on Step 3 does not affect actions on Step 4 and Step 5.

The rationale of actions taken is appropriate for the HF studies. The numbers in denominators (total number of injections for each step) of Table 5 through Table 10 in the cover letter dated September 26, 2016 correspond to this procedure.

REFERENCES

Draft Guidance for Industry (January 2017). Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA.

Fleiss, J. L., Levin, B., and Paik, M. C. (1981). Statistical Methods for Rates and Proportions (2nd edition). New York: Wiley-Interscience.

Clopper, C., and Pearson, S. (1934). The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika 26: 404-413.

APPENDIX A: ORIGINAL CONSULT REQUEST

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	**REQUEST FOR CONSULTATION**			
TO *(Division/Office)*: OTS/DBV			FROM: Lissa Owens, OMEPRM/DMEPA	
DATE 10/5/2016	IND NO.	ANDA NO. 090589	TYPE OF DOCUMENT Human Factors Data	DATE OF DOCUMENT 9/26/2016
NAME OF DRUG Epinephrine Autoinjector	PRIORITY CONSIDERATION		CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE 10/27/2016
NAME OF FIRM: Teva				

REASON FOR REQUEST

I. GENERAL

☐ NEW PROTOCOL	☐ PRE–NDA MEETING	☐ RESPONSE TO DEFICIENCY LETTER
☐ PROGRESS REPORT	☐ END OF PHASE II MEETING	☐ FINAL PRINTED LABELING
☐ NEW CORRESPONDENCE	☐ RESUBMISSION	☐ LABELING REVISION
☐ DRUG ADVERTISING	☐ SAFETY/EFFICACY	☐ ORIGINAL NEW CORRESPONDENCE
☐ ADVERSE REACTION REPORT	☐ PAPER NDA	☐ FORMULATIVE REVIEW
☐ MANUFACTURING CHANGE/ADDITION	☐ CONTROL SUPPLEMENT	☐ OTHER *(SPECIFY BELOW)*:
☐ MEETING PLANNED BY		

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

☐ DISSOLUTION	☐ DEFICIENCY LETTER RESPONSE
☐ BIOAVAILABILTY STUDIES	☐ PROTOCOL-BIOPHARMACEUTICS
☐ PHASE IV STUDIES	☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL	☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES	☐ SUMMARY OF ADVERSE EXPERIENCE
☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)	☐ POISON RISK ANALYSIS
☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP	

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:
In response to the face-to-face meeting held with Teva on September 14, 2016, Teva submits the requested additional information on the following:

1. Details on randomization of assigning participants to devices within the HF studies
2. Details on study methodology in terms of data collection
3. Additional data regarding the error rates associated with the RLD and the AJE.

Please review the submission to determine whether the study methodology is acceptable.

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SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

STELLA C GROSSER on behalf of YIFAN WANG
08/14/2018

STATISTICAL REVIEW AND EVALUATION
CONSULT REVIEW

Consult Requester	Lissa Owens, OMEPRM/DMEPA
Type of Consult	Evaluation of Human Factors Data for ANDA 090589 Teva's Epinephrine Auto-injector
Reference Listed Drug **Indication**	Mylan's EpiPen® (Epinephrine Injection, USP) 0.3 mg and EpiPen® Jr (Epinephrine Injection, USP) 0.15 mg (NDA 019430) Life-threatening allergic reactions (anaphylaxis) caused by allergens, exercise, or unknown triggers.
Dates	Document Date: 09/26/2016 Review Assignment Date: 10/07/2016 ECD Date: 10/27/2016 ECD Response Date: 11/04/2016
Biometrics Division **Statistical Primary Reviewer** **Statistical Secondary Reviewer**	 Yifan Wang, Ph.D., DB VIII/OB/OTS/CDER Stella Grosser, Ph.D., DB VIII/OB/OTS/CDER
Key Words	Epinephrine, Auto-injector, Human Factors Study, Randomization, Data Collection, Use Error Rate, Design Difference, Current RLD User, Adult, Teen, Rationale of Actions Taken

1. BACKGROUND AND SUMMARY OF CONSULT REQUEST

Mylan's EpiPen® (Epinephrine Injection, USP) 0.3 mg and EpiPen® Jr (Epinephrine Injection, USP) 0.15 mg were approved on December 22, 1987 (NDA 019430) for the emergency treatment of life-threatening allergic reactions (anaphylaxis) caused by allergens, exercise, or unknown triggers.

Dr. Lissa Owens, OMEPRM/DMEPA, sent a consult request to review Teva's submission on September 26, 2016, in response to the face-to-face meeting held with FDA on September 14, 2016, to determine whether Teva's human factors (HF) study methodology for Epinephrine Auto-injector (ANDA 090589) is acceptable. More specifically, the OTS/OB Division of Biometrics VIII was asked to provide an evaluation of the randomization of assigning participants to devices within the HF studies, the study methodology in terms of data collection, and the additional data regarding the error rates associated with the RLD (Mylan's EpiPen®) and Teva's AJE (test product).

The statistical reviewer sent an ECD regarding the rationale of actions taken for the HF studies on October 27, 2016. Teva responded to this ECD on November 4, 2016.

2. REVIEWER'S RESPONSE TO THE CONSULT

Participants included in the HF studies were from pooled formative study TR927 (2012) and validation study TR-720B (2014). Both are simulated studies with elimination of actual drug injections. All participants were greater than 12 years old, and used Adult Model/Version of devices. This review focuses on participants who have used EpiPen in the past ("current RLD users").

Table 1 presents the subject disposition using AJE and RLD devices in both studies, for Adult and Teen groups. Here, "Adult" refers to participants age 18 and over, and "Teen" refers to participants age 13 to 17.

Table 1: Subject Disposition of Current RLD Users

Number of Participants		**AJE**	**RLD**	**Total**
TR927	**Adult**	15	11	26
	Teen	16	10	26
TR-720B	**Adult**	17	14	31
	Teen	14	15	29
TR927 & TR-720B	**Adult**	32	25	57
	Teen	30	25	55
Total		**62**	**50**	**112**

Source: Reviewer's Analysis.

2.1 Device Use Assignment

The randomization approach the sponsor used included four steps. First, a 3rd party company recruited participants by inviting participants to choose their preferred time slot. Second, screening answers were used to categorize the user group (i.e., adult or teenager, current RLD user or non-user) until user group quotas were filled. Then, participant numbers were assigned to all participants within each user group. At last, device to be used first was assigned based on participant number, with odd numbers given AJE first and even numbers given RLD first.

Strictly speaking, the assignment method is not a randomized procedure. However, it would be difficult to manipulate it to introduce a bias. Also, in the original design, all participants were to use both devices and only the order (AJE or RLD first) was assigned.

The approach for device use assignment in sponsor's TR927 and TR720-B studies may be a reasonably random approach to use in a comparative HF study, although we would recommend the generation of random numbers to assign participants which device they would use first.

2.2 Data Collection

An (b) (4) conducted HF studies using the following methods. A study moderator, a video camera, and a data analyst simultaneously recorded behavioral and qualitative data during the study sessions, with no prompts or guidance provided to participants. The study moderator recorded data directly onto the interview guide, while the data analyst recorded data into a spreadsheet from behind a two-way mirror. A study staff member compared the interview guide and spreadsheet to ensure both methods agreed. If there was any discrepancy, the staff member reviewed the video to resolve it.

The methodology used in data collection described in the sponsor's cover letter is appropriate for the HF studies.

2.3 Additional Data Analysis

The action steps included in the HF studies are: Step 1 Remove Cap or Tube, Step 2 Remove Safety, Step 3 Correct Injection Site, Step 4 Trigger Injection, and Step 5 Hold in Place.

Table 2 presents the frequencies of cumulative use error injections among current RLD Adult and Teen users for all steps.

Table 2: All Steps Cumulative Use Error Data of Current RLD Users

		Number of Subjects	Number of Injections	Number of Successes	Number of Use Errors
Adult	**RLD**	25	50	34	16 (32.0%)
	AJE	32	64	43	21 (32.8%)
Teen	**RLD**	25	50	41	9 (18.0%)
	AJE	30	60	49	11 (18.3%)
Adult & Teen	**RLD**	50	100	75	25 (25.0%)
	AJE	62	124	92	32 (25.8%)

Source: Reviewer's Analysis.

Because of concern that the design difference of a cap versus a tube might introduce new risk of error, we examine Step 1 separately from cumulative use error rates. Table 3 presents the frequencies of use error injections among current RLD Adult and Teen users for Step 1 Remove Cap or Tube.

Table 3: Remove Cap or Tube (Step 1) Use Error Data of Current RLD Users

		Number of Subjects	Number of Injections	Number of Successes	Number of Use Errors
Adult	**RLD**	25	50	48	2 (4.0%)
	AJE	32	64	63	1 (1.6%)
Teen	**RLD**	25	50	50	0 (0.0%)
	AJE	30	60	58	2 (3.3%)
Adult & Teen	**RLD**	50	100	98	2 (2.0%)
	AJE	62	124	121	3 (2.4%)

Source: Reviewer's Analysis.

The sponsor stated that errors would be expected with any device under an emergency scenario, and that the minimum number of participants for a validation study is 15 according to FDA's Human Factors Guidance. The sponsor therefore claimed that a nominal 10% difference (between one and two possible variations, that is, between 1/15=6.7% and 2/15=13.3%) would be expected.

We do not agree the 10% margin sponsor used for a comparison of use error rate difference between RLD and AJE is adequate. It appears the margin is arbitrarily chosen.

As an exploratory analysis, we used 90% Wald's confidence interval with Yate's continuity correction to test equivalence of use errors between AJE and RLD for all steps (Table 4), and for Step 1 Removing Cap or Tube (Table 5).

Table 4 presents the equivalence results of *all steps cumulative use errors* using 90% CI of difference between Test (AJE) and RLD, for Adult and Teen current RLD users.

Table 4: Equivalence Test of Cumulative Use Errors for All Steps

Equivalence	Test (AJE)	RLD
Current User – Adult		
Number of Subjects	32	25
Number of Injections*	64	50
Use Error % (*n/N*)	32.8% (21/64)	32.0% (16/50)
Difference (Test-RLD)	0.81%	
90% Wald's CI with Yate's Continuity Correction	(-15.49%, 17.12%)	
Is the 90% within (-20%, 20%)?	Yes	
Current User - Teen		
Number of Subjects	30	25
Number of Injections*	60	50
Use Error % (*n/N*)	18.3% (11/60)	18.0% (9/50)
Difference (Test-Reference)	0.33%	
90% Wald's CI with Yate's Continuity Correction	(-13.64%, 14.31%)	
Is the 90% within (-20%, 20%)?	Yes	
Current User – Both Adult and Teen		
Number of Subjects	62	50
Number of Injections*	124	100
Use Error % (*n/N*)	25.8% (32/124)	25.0% (25/100)
Difference (Test-Reference)	0.81%	
90% Wald's CI with Yate's Continuity Correction	(-9.71%, 11.33%)	
Is the 90% within (-20%, 20%)?	Yes	

*Each participant had two injections from the given device.

Source: Reviewer's Analysis.

Table 5 presents the equivalence results of *Step 1 Remove Cap or Tube use errors* using 90% CI of difference between Test (AJE) and RLD, for Adult and Teen current RLD users.

Table 5: Equivalence Test of Use Errors for Remove Cap or Tube (Step 1)

Equivalence	Test (AJE)	RLD
Current User – Adult		
Number of Subjects	32	25
Number of Injections*	64	50
Use Error % (*n/N*)	1.6% (1/64)	4.0% (2/50)
Difference (Test-RLD)	2.44%	
90% Wald's CI with Yate's Continuity Correction	(-9.44%, 4.57%)	
Is the 90% within (-20%, 20%)?	Yes	
Current User - Teen		
Number of Subjects	30	25
Number of Injections*	60	50
Use Error % (*n/N*)	18.3% (11/60)	18.0% (9/50)
Difference (Test-Reference)	3.33%	
90% Wald's CI with Yate's Continuity Correction	(-2.31%, 8.98%)	
Is the 90% within (-20%, 20%)?	Yes	
Current User – Both Adult and Teen		
Number of Subjects	62	50
Number of Injections*	124	100
Use Error % (*n/N*)	2.4% (3/124)	2.0% (2/100)
Difference (Test-Reference)	0.42%	
90% Wald's CI with Yate's Continuity Correction	(-3.72%, 4.56%)	
Is the 90% within (-20%, 20%)?	Yes	

*Each participant had two injections from the given device.

Source: Reviewer's Analysis.

For current RLD users Adults and Teens groups, all confidence intervals are within (-20%, 20%), demonstrating the equivalence of use errors between AJE and RLD for both scenarios (*all steps cumulative* and *Step 1 Remove Cap or Tube*).

Therefore, there is no difference between AJE and RLD with regard to cumulative use error rates, and the design difference of the cap with AJE does not introduce new risk of error compared to the tube with RLD.

2.4 FDA's Comments to Teva's ECD Responses

FDA's ECD Request on October 27, 2016:

> **For Table 5 through Table 10 in the cover letter dated September 26, 2016, clarify or provide justification for why the total number of injections of RLD and AJE (the denominators in column 3 RLD 1st and column 5 AJE 1st) for Step 4 Trigger Injection and Step 5 Hold in Place, are not equal to the total number of injections for the first 3 steps. For example, in Table 5, the denominator is 100 for RLD at Step 1, 2 and 3, but 94 at Step 4 and 85 at Step 5. Provide clarification or justification for why the denominator changed from 100 to 94 at Step 4, and further changed to 85 at Step 5.**

Teva's Response on November 4, 2016:

> Please refer to Appendix B.

FDA's Comments:

> The sponsor stated the rationale of actions taken as follows. If a participant failed Step 1 (Remove Cap or Tube) and/or Step 2 (Remove Safety), then Step 4 (Trigger Injection) and Step 5 (Hold in Place) would be not assessable. The failed number of injections in Step 1 and Step 2 is subtracted from the total number of injections at Step 4 and Step 5. If a participant failed Step 4, then Step 5 would be not assessable. The failed number of injections in Step 4 is subtracted from the total number of injections at Step 5. Step 1, Step 2 and Step 3 (Correct Injection Site) are relatively independent actions. Participants who failed Step 1 can still succeed on Step 2 and/or Step 3. A failure on Step 3 does not affect actions on Step 4 and Step 5.
>
> The rationale of actions taken is appropriate for the HF studies. The numbers in denominators (total number of injections for each step) of Table 5 through Table 10 in the cover letter dated September 26, 2016 correspond to this procedure.

3. Conclusions and Recommendations

In summary, for the sponsor's submission on September 26, 2016, the approach for device use assignment in sponsor's HF studies is a reasonably random approach, the data collection methodology is appropriate for the HF studies, and the use error data demonstrates the equivalence of error rates between AJE and RLD for current RLD users. The design difference of the cap with AJE does not introduce new risk of error compared to the tube with RLD.

The sponsor's rationale of actions taken specified in their ECD responses dated November 4, 2016 is appropriate for the HF studies.

References

Guidance for Industry and Food and Drug Administration Staff (February 3, 2016). Applying Human Factors and Usability Engineering to Medical Devices.

Fleiss, J. L., Levin, B., and Paik, M. C. (1981). Statistical Methods for Rates and Proportions (2nd edition). New York: Wiley-Interscience.

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DATE 10/5/2016	IND NO.	ANDA NO. 090589	TYPE OF DOCUMENT Human Factors Data	DATE OF DOCUMENT 9/26/2016
NAME OF DRUG Epinephrine Autoinjector	PRIORITY CONSIDERATION		CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE 10/27/2016
NAME OF FIRM: Teva				

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☐ MEETING PLANNED BY		

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☐ CLINICAL	☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:
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/s/

YIFAN WANG
12/14/2016

STELLA C GROSSER
03/10/2017
Belated concurrence

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 090589

MICROBIOLOGY REVIEW(S)

Product Quality Microbiology Review

June 13, 2017

ANDA: 090589

Drug Product Name
Proprietary: N/A
Non-proprietary: Epinephrine Injection USP
Drug Product Priority Classification: N/A

Review Number: 4

Dates of Submission(s) Covered by this Review

Letter	Stamp	Consult Sent	Assigned to Reviewer
01/31/2017	01/31/2017	N/A	02/06/2017
04/04/2017	04/04/2017	N/A	06/05/2017
06/02/2017	06/02/2017	N/A	06/05/2017

Submission History (for amendments only)

Date(s) of previous submission(s)	Microbiology Review #	Date(s) of previous Micro Review(s)
12/21/2007	1	06/17/2009
05/23/2009	1	06/17/2009
09/09/2009	2	09/21/2009
12/30/2014	3	07/17/2015

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Address: 425 Privet Road, Horsham, PA 19044
Representative: Cory Wohlbach, Senior Director, US Generics Regulatory Affairs
Telephone: 215-293-6519
Fax: 215-591-8812

Name of Reviewer: Eric K. Adeeku, Ph.D.

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

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: ANDA amendment

2. SUBMISSION PROVIDES FOR: Response to the Agency's complete response letter and microbiology deficiencies. The firm also proposes the use of an (b) (4) in the 04/04/2017 gratuitous amendment.

3. MANUFACTURING SITE:

(b) (4)

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY: Sterile Injection, Intramuscular 0.15 mg/0.3 mL and 0.30 mg/0.30 mL in 1 mL pre-filled syringes, single dose.

5. METHOD(S) OF STERILIZATION: (b) (4)

6. PHARMACOLOGICAL CATEGORY: N/A

B. SUPPORTING/RELATED DOCUMENTS:

(b) (4)

(b) (4)

[redacted]

C. REMARKS:

This ANDA is an electronic application in the EDR.
Expedited review status granted by OGD on 01/08/2015.
The TAD is 10/13/2016.

Response to the Agency's 02/23/2016 complete response letter was provided 01/31/2017. Further deficiencies issued in the 05/19/2017 microbiology information request were responded to in the 06/02/2017 submission. The 04/04/2017 gratuitous amendment also provides for the use of an (b) (4) [redacted] (b) (4)

filename: A090589MR04.doc
Template version: OGD modified_AP_2014v6.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability –
This submission is **recommended** for approval on the basis of sterility assurance.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable - N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology - (b) (4)
(b) (4)

B. Brief Description of Microbiology Deficiencies -
None identified

C. Assessment of Risk Due to Microbiology Deficiencies -
No microbiology deficiencies were identified. The applicant demonstrates an adequate level of sterility assurance for the manufacturing process.

D. Contains Potential Precedent Decision(s) - ☐ **Yes** ☒ **No**

III. Administrative

A. Reviewer's Signature _____

B. Endorsement Block
Microbiologist: Eric Adeeku, Ph.D.
Microbiology Secondary Reviewer: Jesse Wells, Ph.D.

C. CC Block
cc: Field Copy

Product Quality Microbiology Assessment

The subject amendment is in response to microbiology deficiencies conveyed to the applicant in the Agency's complete response letter dated 02/23/2016. Further deficiencies issued in the 05/19/2017 microbiology information request were responded to in the 06/02/2017 submission. The original deficiencies are italicized. A 04/04/2017 gratuitous amendment (b) (4) reviewed after the review of responses to the previous deficiencies.

A. Microbiology Deficiencies:

1. *DMF (b) (4) deficient. The DMF holder has been notified.*

   Response: The 07/15/2015 amendment to DMF (b) (4) was reviewed in microbiology review (b) (4) by E. Adeeku on 02/15/2017 and found acceptable.

Acceptable

2. *(b) (4) is deficient. The DMF holder has been notified.*

   Response: The holder of (b) (4) has notified the applican (b) (4) (b) (4)

   The following deficiency was issued in the 05/19/2017 microbiology information request and responded to in the 06/02/2017 submission:

(b) (4)

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(b) (4)

Acceptable

Jesse Wells

Digitally signed by Jesse Wells
Date: 6/14/2017 12:41:08PM
GUID: 508da70b00028ea901ac6652677f7d00

Eric Adeeku

Digitally signed by Eric Adeeku
Date: 6/15/2017 09:42:48AM
GUID: 508da70b00028e3db199467cfbd47cb0

Product Quality Microbiology Review

June 17, 2015

ANDA: 090589

Drug Product Name
Proprietary: N/A
Non-proprietary: Epinephrine Injection USP
Drug Product Priority Classification: N/A

Review Number: 3

Dates of Submission(s) Covered by this Review

Letter	Stamp	Consult Sent	Assigned to Reviewer
12/30/2014	12/30/2014	N/A	04/01/2015

Submission History (for amendments only)

Date(s) of previous submission(s)	Microbiology Review #	Date(s) of previous Micro Review(s)
12/21/2007	1	06/17/2009
05/23/2009	1	06/17/2009
09/09/2009	2	09/21/2009

Applicant/Sponsor
Name: Teva Pharmaceuticals USA
Address: 425 Privet Road, Horsham, PA 19044
Representative: Rich Leone, Senior Director, US Generics Regulatory Affairs
Telephone: 215-293-6330
Fax: 215-591-8812

Name of Reviewer: Eric K. Adeeku, Ph.D.

Conclusion: The submission is **not recommended** for approval on the basis of sterility assurance.

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: Gratuitous ANDA amendment

2. SUBMISSION PROVIDES FOR: change in manufacturing/testing site, formulation and device

3. MANUFACTURING SITE:

(b) (4)

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY: Sterile Injection, Intramuscular 0.15 mg/0.3 mL and 0.30 mg/0.30 mL in 1 mL pre-filled syringes, single dose.

5. METHOD(S) OF STERILIZATION: (b) (4)

6. PHARMACOLOGICAL CATEGORY: N/A

B. SUPPORTING/RELATED DOCUMENTS:

(b) (4)

C. REMARKS:

This ANDA is an electronic application in the EDR. Expedited review status granted by OGD on 01/08/2015.

filename: 090589a2.doc
Template version: OGD modified_AP_2014v6.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability –

This submission is **not recommended** for approval on the basis of sterility assurance. Specific comments and deficiencies are provided in the "Product Quality Microbiology Assessment" and "List of Microbiology Deficiencies and Comments" sections.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable - N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology

(b) (4)

(b) (4)

B. Brief Description of Microbiology Deficiencies -

(b) (4)

C. Assessment of Risk Due to Microbiology Deficiencies -

(b) (4)

D. Contains Potential Precedent Decision(s) - ☐ Yes ☒ No

III. Administrative

A. Reviewer's Signature _____

B. Endorsement Block

Microbiologist: Eric Adeeku, Ph.D.
Microbiology Secondary Reviewer: Jesse Wells, Ph.D.

C. CC Block

cc: Field Copy

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-90589	ORIG-1	TEVA PARENTERAL MEDICINES INC	EPINEPHRINE

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/s/

ERIC K ADEEKU
09/24/2009

ELIZABETH T MCNEAL
09/24/2009
Checked for correct file and subbmission link. Both ok.

LYNNE A ENSOR
09/25/2009

Product Quality Microbiology Review

September 21, 2009

ANDA: 90-589

Drug Product Name
Proprietary: N/A
Non-proprietary: Epinephrine Injection, USP
Drug Product Priority Classification: N/A

Review Number: 2

Dates of Submission(s) Covered by this Review

Letter	Stamp	Consult Sent	Assigned to Reviewer
09/09/2009	09/09/2009	N/A	09/10/2009

Submission History (for amendments only)

Date(s) of previous submission(s)	Microbiology Review #	Date(s) of previous Micro Review(s)
12/21/2007	1	06/17/2009
05/23/2009	1	06/17/2009

Applicant/Sponsor
Name: Teva Parenteral Medicines, Inc.
Address: 19 Hughes, Irvine, CA 92618
Representative: Susan O'Brien
Telephone: 949-455-4724

Name of Reviewer: Eric K. Adeeku

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

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: Original ANDA amendment

2. SUBMISSION PROVIDES FOR: Initial marketing of the drug product

3. MANUFACTURING SITE:

(b) (4)

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY: Sterile Injection, Intramuscular 0.15 mg/0.3 mL and 0.30 mg/0.30 mL in 1 mL pre-filled syringes, single dose.

5. METHOD(S) OF STERILIZATION: (b) (4)

6. PHARMACOLOGICAL CATEGORY: N/A

B. SUPPORTING/RELATED DOCUMENTS:

(b) (4)

C. REMARKS:

This ANDA is an electronic application in the EDR. The subject amendment provides responses to the microbiology deficiencies conveyed to the applicant in the Agency's 06/03/2009 deficiency letter.

filename: 90-589a1.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability –

This submission is **recommended** for approval on the basis of sterility assurance.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable - N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology -

(b) (4)

(b) (4)

B. Brief Description of Microbiology Deficiencies –

None identified

C. Assessment of Risk Due to Microbiology Deficiencies -

No microbiology deficiencies were identified (b) (4)

(b) (4)

III. Administrative

A. Reviewer's Signature _____

B. Endorsement Block

Microbiologist: Eric Adeeku, Ph.D.
Microbiology Team Leader: Lynne Ensor, Ph.D.

C. CC Block

cc: Field Copy

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-90589	ORIG-1	TEVA PARENTERAL MEDICINES INC	EPINEPHRINE

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/s/

ERIC K ADEEKU
09/24/2009

ELIZABETH T MCNEAL
09/24/2009
Checked for correct file and subbmission link. Both ok.

LYNNE A ENSOR
09/25/2009

Product Quality Microbiology Review

June 17, 2009

ANDA: 90-589

Drug Product Name
Proprietary: N/A
Non-proprietary: Epinephrine Injection, USP
Drug Product Priority Classification: N/A

Review Number: 1

Dates of Submission(s) Covered by this Review

Letter	Stamp	Consult Sent	Assigned to Reviewer
12/21/2007	12/21/2007	N/A	03/04/2009
05/23/2009	05/26/2009	N/A	06/17/2009

Submission History (for amendments only)
N/A

Applicant/Sponsor
Name: Teva Parenteral Medicines, Inc.
Address: 19 Hughes, Irvine, CA 92618
Representative: Susan O'Brien
Telephone: 949-455-4724

Name of Reviewer: Eric K. Adeeku

Conclusion: The submission is **not recommended** for approval on the basis of sterility assurance.

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: Original ANDA

2. SUBMISSION PROVIDES FOR: Initial marketing of the drug product

3. MANUFACTURING SITE:

(b) (4)

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY: Sterile Injection, Intramuscular 0.15 mg/0.3 mL and 0.30 mg/0.30 mL in 1 mL pre-filled syringes, single dose.

5. METHOD(S) OF STERILIZATION: (b) (4)

6. PHARMACOLOGICAL CATEGORY: N/A

B. SUPPORTING/RELATED DOCUMENTS:

(b) (4)

C. REMARKS:
This application is an electronic submission

(b) (4)

filename: 90-589.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability –

This submission is **not recommended** for approval on the basis of sterility assurance. Specific comments and deficiencies are provided in the 'Product Quality Microbiology Assessment'.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable - N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology

(b) (4)

(b) (4)

B. Brief Description of Microbiology Deficiencies -

(b) (4)

(b) (4)

C. Assessment of Risk Due to Microbiology Deficiencies -

(b) (4)

III. Administrative

A. Reviewer's Signature _____

B. Endorsement Block

Microbiologist: Eric Adeeku, Ph.D.
Microbiology Team Leader: Lynne Ensor, Ph.D.

C. CC Block

cc: Field Copy

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/s/

Erik Adeeku
7/1/2009 03:03:50 PM
MICROBIOLOGIST

Bonnie McNeal
7/2/2009 12:05:03 PM
MICROBIOLOGIST
Checked for correct file and submission links. All ok.

Lynne Ensor
7/6/2009 08:18:09 AM
MICROBIOLOGIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 090589

OTHER REVIEW(S)

Addendum to Clinical Consultation Review

Division of Clinical Review (DCR)
Office of Bioequivalence (OB), Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

Drug Product:	Epinephrine Injection USP (Auto-Injector), 0.15 mg/0.3 mL & 0.3 mg/0.3 mL
ANDA#/ Applicant:	ANDA 090589 / Teva Pharmaceuticals USA, Inc.
RLD #/Approval Date:	EpiPen® (0.3 mg), EpiPen Jr.® (0.15 mg), NDA 019430 / December 22, 1987
Sponsor:	Mylan Specialty LP
Clinical Primary Reviewer:	Sarah Yim, M.D. Director, Division of Clinical Review (DCR)
Tertiary Reviewer	Same
To:	Division of Bioequivalence III (DBIII)
Reason for Consult:	Does the slightly greater force needed to activate the test device compared to reference device raise any safety or efficacy concern for the test product?
Date of Submission	April 19, 2017
Date Consult Received:	October 11, 2017
Date of Completion (Original Consult Review):	November 7, 2017
Date of Completion (Addendum to Consult Review):	August 14, 2018
Deficiency Classification	☐ Major ☐ Minor **(See section 4 for Recommendation)** ☒ N/A (Review is Adequate)

ADDENDUM to Prior Review

This is an addendum to the previous clinical consultation review, dated November 7, 2017, which responded to a consult from DBIII, Office of Bioequivalence, regarding the force needed to activate the test device under Teva's ANDA 090589 as compared to the reference device (reference listed drug (RLD), EpiPen / EpiPen Jr under NDA 019430). In the November 7, 2017 clinical consultation review, DCR concluded that the slightly greater force needed to activate the test device compared to the reference device does not raise any safety or efficacy concerns

regarding the test product.[1] This addendum clarifies that the reference to safety and efficacy regarding activation force in the November 7, 2017 clinical consultation review was intended to convey our conclusion that the slightly greater activation force required for Teva's ANDA 090589 is not expected to affect the bioequivalence or therapeutic equivalence of Teva's product to the RLD, EpiPen / EpiPen Jr under NDA 019430.

[1] GDRP ANDA 090589, DCR Clinical Consultation Review, http://panorama.fda.gov/task/view?ID=599451230042d5a0ed0907431a6d15ce, Sarah Yim, 11/7/2017.

Sarah Yim

Digitally signed by Sarah Yim
Date: 8/16/2018 10:03:35AM
GUID: 50841a8900009e1fe2b0e31699e4e531

Clinical Review of Drug-Device Combination Product

Division of Clinical Review (DCR)
Office of Bioequivalence (OB), Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

ANDA / Applicant	090589 / Teva Pharmaceuticals USA, Inc.
Drug Product/Strength(s)	Epinephrine Injection USP (Auto-Injector), 0.3 mg/0.3 mL & 0.15 mg/0.3 mL
RLD/RS#/ Name / Approval Date	NDA 019430, EpiPen® (0.3 mg), EpiPen Jr.® (0.15 mg) December 22, 1987
RLD/RS Sponsor	Mylan Specialty LP
Primary Reviewer	Sarah Yim, M.D. Director Division of Clinical Review
Tertiary Reviewer	Same
Submission Date	12/02/07
Date of Review	08/14/18
GDUFA Goal Date	7/31/18
Materials Reviewed	• Division of Medication Error Prevention and Analysis (DMEPA), Office of Surveillance and Epidemiology, Human Factors Study Report Review (February 10, 2016), OSC RCM No. 2015-1409. • FDA's Draft Guidance on *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA* (January 2017). • DMEPA's Memorandum re: Review of Label and Labeling (June 11, 2018), OSC 2016-2377. • Division of Labeling Review, Review No. 8 (June 25, 2018). • DMEPA Comparative Human Factors Review, August 14, 2018, OSC RCM No. 2016-2345.

DCR Conclusion	DCR concludes that there are "other design differences" between the Teva Pharmaceuticals USA, Inc.'s (Teva) generic epinephrine injection (auto-injector), 0.15 mg and 0.3 mg and the reference listed drug (RLD), EpiPen and EpiPen Jr. The differences in the carrier tube for the RLD vs. yellow cap for Teva's product and in the blue safety release between the two products are acceptable. The comparative analyses included here, coupled with the conclusions set forth in DMEPA's Comparative Human Factors Review, support the finding that Teva's generic epinephrine injection (auto-injector) can be expected to produce the same clinical effect and safety profile as the RLD under the conditions specified in the labeling.
DCR Comparative Analyses Conclusion	☐ No Design Differences ☐ Minor Design Differences ☐ Acceptable ☐ Not acceptable Explain: ☒ Other Design Differences ☒ Acceptable ☐ Not acceptable Explain:
Deficiency Classification	☐ Major ☐ Minor **(See section 4 for Recommendation)** ☒ N/A (Review is Adequate)

1 INTRODUCTION AND BACKGROUND

1.1 Application History and Purpose of Review

ANDA 090589 was submitted to FDA on December 21, 2007, and was received for review by FDA on November 21, 2008. As a result, ANDA 090589 has a long regulatory history. Refer to DMEPA's Comparative Human Factors Review for more details on the regulatory history of ANDA 090589.[1]

The purpose of this review is to provide a clinical assessment through a comparative analysis of Teva's proposed generic epinephrine injection (auto-injector), 0.15 mg and 0.3 mg (Teva epinephrine AI) and its RLD, EpiPen and EpiPen Jr (collectively, EpiPen). This assessment

[1] DMEPA's Comparative Human Factors Review, August 14, 2018, OSC RCM No. 2016-234 (DMEPA Comparative HF Review), at 3-6.

complements DMEPA's assessment of the device user interface[2] and Teva's human factors data in DMEPA's Comparative HF Review.[3]

1.2 General Background

Drug products that are approved in ANDAs are generally considered by FDA to be therapeutically equivalent to their RLD. Like other generic drug products approved in ANDAs, generic combination products classified as therapeutically equivalent to their RLD can be expected to produce the same clinical effect and safety profile as the RLD under the conditions specified in labeling when substituted for the RLD. In assessing the therapeutic equivalence of a proposed generic combination product, FDA may consider whether the proposed generic can be substituted for the RLD without the intervention of a healthcare provider or without additional training prior to use. While FDA does not expect that the user interface for a proposed generic drug be identical to the user interface for its RLD, any identified differences between the proposed generic and its RLD should be adequately analyzed, scientifically justified, and not preclude approval under an ANDA. In certain instances, additional information and/or data may be warranted to further assess whether the differences identified in the user interface between the proposed generic product and the RLD might introduce a risk that could impact the clinical effect or safety profile of the generic combination product as compared to the RLD when the generic is substituted for the RLD.[4]

The draft Comparative Analyses and Related Comparative Use HF Studies for a Drug-Device Combination Product Submitted in an ANDA Guidance provides recommendations to applicants who plan to develop a generic drug-device combination product for FDA approval.[5] Specifically, this guidance generally focuses on assisting potential applicants regarding the analysis of the proposed user interface for the generic drug-device combination product when compared to the user interface for the RLD.

As per the draft Comparative Analyses HF Studies Guidance, FDA recommends a threshold analysis to compare the user interface of the proposed generic combination product to the user interface of its RLD (e.g., physical comparison of the delivery device constituent part, comparative task analysis, and labeling comparison).[6] The outcome of the threshold analysis may reveal differences in the design of the user interface of a proposed generic product as compared to the RLD that may impact an external critical design attribute[7] that involves administration of the product. These differences may fall into the "other design differences"

---

[2] The term "user interface" refers to all components of the combination product with which a user interacts, which includes the delivery device constituent part of the combination product and any associated controls and displays, as well as product labeling and packaging. See FDA's draft guidance on *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA* (January 2017) at 1 (Comparative Analyses HF Studies Guidance), available at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM536959.pdf.

[3] See DMEPA Comparative HF Review.

[4] See generally draft Comparative Analyses HF Studies Guidance.

[5] Id. at 1.

[6] Id. at 6-7.

[7] External critical design attributes are defined as "those features that directly affect how users perform a critical task that is necessary in order to use or administer the drug product." See id. at 5.

category.[8] The Agency will use the results of this threshold analysis in determining whether proposed design differences are acceptable for a proposed generic combination product.

2 COMPARATIVE THRESHOLD ANALYSES

2.1 Physical Comparison of the Delivery Device Constituent Part

Table 1 (below) shows photographic images of the physical characteristics of the Teva epinephrine AI and EpiPen. In addition, Figures 1 (below) provides a comparison of the external physical dimensions of the Teva epinephrine AI and EpiPen.

Table 1: Pictorial Comparison of EpiPen/EpiPen Jr and Teva Epinephrine AI

EpiPen/EpiPen Jr	Teva Epinephrine AI
(Photo source: EpiPen Instructions for Use) ***EpiPen trainer*** 	(b) (4)

[8] Id. In assessing the significance of the differences in design, the Agency considers the impact of the identified differences in the context of the overall risk profile for the product.

EpiPen/EpiPen Jr	Teva Epinephrine AI
	(b) (4)

EpiPen in carrying case

Blue safety release removed

EpiPen post-activation

(b) (4)

(b) (4)

the proposed-to-be-marketed device

Reviewer Comments:

The overall size and shape of the Teva epinephrine AI is similar to that of the RLD, EpiPen. Visually, the Teva epinephrine AI utilizes a similar color scheme as the currently approved version of the EpiPen. For example, as noted above, both products have a blue safety release on one end and an orange tip on the other end (needle end).[9]

As evident from the images above, the primary observable differences between the Teva epinephrine AI and EpiPen include:

[9] See also DMEPA Comparative HF Review at 2, for a detailed description of the similar color scheme between the proposed generic and the RLD; see also DMEPA's Memorandum re: Review of Label and Labeling completed June 11, 2018 at 2 (DMEPA Label Memo).

1) the presence of the clear carrier tube for the EpiPen and the presence of the yellow cap on Teva's epinephrine AI (and the absence of a clear carrier tube); and
2) the blue safety release.

Each of these primary observable differences is addressed below.

1) Differences in carrier tube versus yellow cap

As depicted in Table 1, there is a difference in the Teva epinephrine AI and EpiPen with respect to the yellow cap versus the carrier tube. Specifically, EpiPen comes in a carrier tube, whereas the Teva epinephrine AI does not utilize a carrier tube but instead has a protective yellow/green closure cap[10] over the needle end of the injector. In the case of EpiPen, the auto-injector must be removed from the carrier tube prior to use, while for the Teva epinephrine AI, the yellow cap must be removed prior to use. Given that this design difference in the carrier tube (EpiPen) versus the cap (Teva epinephrine AI) affects an external critical design attribute that affects the first step in administration of the proposed product as compared to administration of EpiPen, this difference is considered as an "other design difference" and is discussed in greater detail below.[11]

2) The blue safety release

As depicted in Table 1 and Figure 1, the blue safety release differs between the Teva epinephrine AI and EpiPen. Specifically, the Teva epinephrine AI blue safety release has ridges on one side and an extended clip on the other side of the safety release, whereas the EpiPen has two short legs on both sides and an elongated pin in the center. For reasons discussed in greater detail below, this difference affects an external critical design attribute and, thus, is considered as an "other design difference."

2.2 Comparative Task Analysis

As noted in the DMEPA Comparative HF Review, the main difference in the external critical design attributes associated with administering the product between the Teva epinephrine AI and EpiPen lie in the two-part first step (i.e., the step preparing the injector for administration).[12] Specifically, the differences are: (1) removing EpiPen from its carrier tube versus "twisting off" the yellow cap from the Teva epinephrine AI; and (2) removing the blue safety release from the applicable product. These design differences are discussed in more detail below.

2.3 Labeling Comparison

As noted in the DMEPA Comparative HF Review, Teva provided a side-by-side labeling comparison of the Teva epinephrine AI and EpiPen on October 18, 2016.[13] DMEPA also

[10] The higher strength product (i.e., 0.3 mg/0.3 mL) under ANDA 090589 includes a yellow cap and the lower strength product (i.e., 0.15 mg/0.3 mL) includes a green cap. For ease of reference, we use the term "yellow cap" in this review to refer to the applicable cap on either the lower strength or higher strength product. We note that, apart from the color of the cap, the auto-injector under ANDA 090589 is identical for both strengths.
[11] See Comparative Analyses HF Studies Guidance
[12] See DMEPA Comparative HF Review at 7-8.
[13] See id. at 6-7

conducted its own labeling comparison in its prior review dated February 10, 2016,[14] and in the DMEPA Labeling Memo.[15] DCR has also independently reviewed the labeling of the Teva epinephrine AI and EpiPen, including the package insert and the instructions for use (IFU). We note that the proposed labeling differences in Teva's labeling are consistent with the user interface differences discussed above. Our conclusions with respect to these labeling differences are discussed in more detail below.

3 REVIEW OF COMPARATIVE THRESHOLD ANALYSIS

Epinephrine auto-injectors are emergency-use products and, as such, would potentially be used under situations of high stress and anxiety. These auto-injectors are also unique due to the infrequency of their use. For example, in one study only 17% (41 patients) out of a cohort of 969 patients who had been prescribed an epinephrine auto-injector used their auto-injector, despite almost half the cohort (466 patients, 48%) experiencing at least one allergic reaction in the past year.[16] Only 12 patients (1%) received two doses and one patient received three doses.[17] This study illustrates why epinephrine auto-injectors generally come with trainers, and why patients/caregivers are encouraged to re-train themselves regularly. Because patients/caregivers that have been prescribed EpiPen generally do not routinely use (or may have never used) EpiPen, such patients/caregivers may have significantly different levels of familiarity with or training on EpiPen. As explained in more detail below, the identified differences in external critical design attributes between the Teva epinephrine AI and EpiPen would not be expected to affect the clinical effect and safety profile of the proposed product as compared to the RLD. In addition, patients/caregivers should be able to use the Teva epinephrine AI without additional training or intervention by a healthcare provider.

Included below is an assessment of the aforementioned differences between the Teva epinephrine AI and EpiPen in light of these considerations and our conclusions regarding these differences.

3.1 "Other Design Differences"

As previously discussed and as indicated in the DMEPA Comparative HF Review,[18] there are two differences in external critical design attributes in the user interface between the Teva epinephrine AI and EpiPen that may impact the administration of the product:

1) the Teva epinephrine AI comes with a yellow cap over the needle end, whereas the EpiPen does not have a yellow cap but comes in a carrier tube; and
2) the appearance of the blue safety release differs between the Teva epinephrine AI and EpiPen.

[14] See generally DMEPA Human Factors Study Report Review (February 10, 2016), OSC RCM No. 2015-1409 (DMEPA HF Study Report Review).
[15] See DMEPA's Memorandum re: Review of Label and Labeling (June 11, 2018), OSC 2016-2377.
[16] See generally Noimark L et al., "The use of adrenaline auto-injectors by children and teenagers." Clin Exp Aller 2012; 42:284-292.
[17] Id.
[18] See DMEPA Comparative HF Review at 7-8.

As stated above, because these differences in external critical design attributes may impact administration of the product, they fall into the "other design differences" category as the threshold comparative analysis outcome.[19] As such, additional information and/or data—such as data from a comparative use human factors study—may be needed to address whether these differences introduce a risk that might impact the clinical effect or safety profile of the Teva epinephrine AI as compared to EpiPen when the generic product is substituted for the RLD.[20]

Although Teva's product was developed prior to the publication of the Comparative Analyses HF Studies Guidance, Teva conducted comparative use human factors studies and submitted them to the Agency for review. Refer to the DMEPA Comparative HF Review for details of the history, results, and assessment of the human factors studies. DMEPA's conclusions are discussed in more detail below.

3.1.1 EpiPen Carrier Tube vs. Teva Epinephrine AI Yellow Cap

As noted above, there are differences in the auto injectors (e.g., carrier tube for EpiPen vs. yellow cap for Teva's Epinephrine AI and differences in the blue safety release). However, from a clinical perspective, these differences in external critical design attributes should not affect the clinical effect and safety profile of the proposed product as compared to the RLD for the following reasons:

1. The EpiPen carrier tube obscures the blue safety release of the EpiPen, whereas the blue safety release is clearly visible with the Teva epinephrine AI. Consequently, an EpiPen-familiar user will likely be able to identify that the Teva epinephrine AI lacks the transparent plastic carrier tube.
2. The Teva epinephrine AI provides additional visual cues to the user by including the word "twist" and a directional arrow on the yellow cap, which directs the user to twist off the yellow cap to expose the orange tip.[21]

Given the reasons above, a user would likely be able to navigate these differences, even where an EpiPen-familiar user with a strong expectation of the auto-injector being in a carrier tube receives the Teva epinephrine AI in a carton and does not open the carton prior to an emergency-use situation. Thus, despite this observable difference in the two auto-injectors (i.e., carrier tube vs. yellow cap), there are sufficient visual cues in the Teva epinephrine AI to orient an EpiPen-familiar user so that navigating this difference would likely be intuitive and not cause undue delay in an emergency-use situation. We note that these conclusions are consistent with and supported by DMEPA's conclusions regarding the results of Teva's comparative use human factors study. Refer to the DMEPA Comparative HF Review for details.

3.1.2 The Shape of the Blue Safety Release Differ Between the Products

As noted above, EpiPen has a blue safety release with an elongated pin in the center[22] and two short legs on either side of the safety release. The EpiPen IFU instructs users to pull the blue

[19] See generally draft Comparative Analyses HF Studies Guidance at 8.
[20] See generally id.
[21] As indicated in Table 1, the Teva epinephrine AI yellow cap is clearly labeled with "TWIST" and an arrow depicting the direction on the needle end of the epinephrine AI.
[22] The elongated pin is not visible when the blue safety release has not been pulled off.

safety release straight up without bending or twisting. The Teva epinephrine AI blue safety release has a short leg and ridges on one side and an extended leg on the other side of the safety release. The Teva IFU instructs users to pull off the blue safety release. Although a user may not notice this design difference until administration, the same or similar pulling off motion for the EpiPen blue safety release will also result in detachment of the Teva blue safety release, which mitigates concerns arising from differences in the design of the blue safety release. Further, while a slightly different pull angle may be optimal (because of different leg lengths and positions) for each product, the same pulling motion will result in the detachment of the blue safety release for the Teva AI as for the RLD. Therefore, from a clinical perspective, the difference in the blue safety release is not likely to affect the clinical efficacy or safety profile of the Teva AI as compared to the RLD. We note that these conclusions are consistent with and supported by DMEPA's conclusions regarding the results of Teva's comparative use human factors study. Refer to the DMEPA Comparative HF Review for details.

3.1.3 DMEPA's Evaluation of Human Factors Study Data

As reflected in the DMEPA Comparative HF Review, DMEPA has reviewed and evaluated the results of Teva's comparative use human factors studies, which assessed differences in the comparative use error rates between the Teva epinephrine AI and EpiPen for EpiPen-familiar users with respect to: (i) the step of removing the yellow cap or carrier tube; and (ii) the removal of the blue safety release. [23] In its review, DMEPA concludes that the differences identified in external critical design attributes between the Teva epinephrine AI and EpiPen (i.e., presence of the yellow cap on the Teva product and differences in the blue safety release) do not introduce a risk that might impact the clinical effect or safety profile of the Teva epinephrine AI as compared to EpiPen when the Teva epinephrine AI is substituted for EpiPen.[24] DMEPA further concludes that the Teva epinephrine AI can be substituted for EpiPen without the intervention of the healthcare provider and/or without additional training prior to use of the Teva Epinephrine AI.[25] We note that the analysis and conclusions set forth in DMEPA's Comparative HF Review are consistent with and further support the conclusions in this review.

3.2 Labeling Differences

As noted above, the proposed labeling differences in Teva's labeling are consistent with the user interface differences discussed above. Given our conclusions above that the user interface differences (i.e., differences in the carrier tube versus yellow cap and differences in the blue safety release) between the EpiPen and the Teva epinephrine AI are acceptable from a clinical perspective, DCR considers the proposed labeling differences in Teva's labeling to fall within the scope of permissible differences in labeling for a product approved under an ANDA and considers such labeling differences to be acceptable.[26] Additionally, as noted in the Division of Labeling Review's (DLR) review dated June 25, 2018, DLR has also determined that the label and labeling proposed by Teva for the Teva epinephrine AI are acceptable.[27]

[23] See DMEPA Comparative HF Review at 16-19.
[24] See id. at 21.
[25] Id. at 21.
[26] See 21 CFR 314.94(a)(8)(iv).
[27] Division of Labeling Review, Review No. 8 (June 25, 2018).

4 CONCLUSION

From a clinical perspective, the "other design differences" in the user interface (i.e., carrier tube versus yellow cap and the blue safety release) between EpiPen and the Teva epinephrine AI are acceptable. The additional comparative use human factors study data provided by Teva (and found adequate by DMEPA) further support the conclusion that the differences in external critical design attributes do not introduce a risk that might impact the clinical effect or safety profile of the Teva AI as compared to the RLD when the Teva AI is substituted for the RLD. As such, the comparative task analysis included above and the comparative use human factors study data evaluated by DMEPA support the conclusion that the Teva epinephrine AI can be substituted for EpiPen without the intervention of a health care provider and without additional training. That is, the Teva epinephrine AI is expected to produce the same clinical effect and safety profile as EpiPen under the conditions specified in the labeling.

5 RECOMMENDATION

CLINICAL COMMENTS TO BE CONVEYED BY THE RPM TO THE APPLICANT

The Clinical Discipline has completed its review of the comparative (threshold) analyses and has:

No comments at this time.

CLINICAL CONSULTATION REVIEW
Division of Clinical Review (DCR)
Office of Bioequivalence (OB), Office of Generic Drugs (OGD)
Center for Drug Evaluation & Research (CDER)

Drug Product:	Epinephrine Injection USP (Auto-Injector), 0.15 mg/0.3 mL & 0.3 mg/0.3 mL
ANDA#/Applicant:	ANDA 090589 / Teva Pharmaceuticals USA, Inc.
RLD#/Approval Date: **Sponsor:**	EpiPen® (0.3 mg), EpiPen Jr.® (0.15mg) NDA 019430 / December 22, 1987 Mylan Specialty LP
Clinical Primary Reviewer:	Sarah Yim, M.D. Director, Division of Clinical Review (DCR)
Tertiary Reviewer:	Same
To:	Division of Bioequivalence III
Reason for Consult:	Does the slightly greater force needed to activate the test device compared to reference device raise any safety or efficacy concern for the test product?
Date of Submission:	April 19, 2017
Date Consult Received:	October 11, 2017
Date of Completion:	November 7, 2017
Conclusion:	(b) (4) (b) (4) Given that EpiPen/EpiPen Jr labeling only specifies to "push firmly," it is likely that an imprecise and relatively wide range of activation forces would be observed, and that the range would include the activation force numbers observed with the test and RLD devices. Both sets of activation force numbers are well within the capability of likely users of the devices; and both sets of numbers are in the typical range of activation forces for this type of autoinjector. Therefore, DCR concludes the slightly greater force needed to activate the test device compared to the reference device does not raise any safety or efficacy concerns regarding the test product.
Deficiency Classification:	☐ Major ☐ Minor ☒ N/A (Review is Adequate)

1 Executive Summary:

DCR concludes that the slightly greater force needed to activate the test device compared to the reference device does not raise any safety or efficacy concerns regarding the test product, based on the following: 1) given that EpiPen/EpiPen Jr labeling only specifies to "push firmly," it is likely that an imprecise and relatively wide range of activation forces would be observed, and that the range would include the activation force numbers observed with the test and RLD devices; 2) average activation force values for the test products are consistent with the range considered acceptable based on the literature (b) (4) and are consistent with published results for other approved epinephrine autoinjectors (b) (4) 3) the average activation force for the test products is well within the capability of expected users of the products, even younger self-administrators (e.g., 8-12 year olds can generate (b) (4); 4) small differences in activation forces between the test and RLD would not be particularly notable to the user given that the context of use is typically infrequent emergency-use; and 5) activation force specification ranges for approved epinephrine autoinjectors reflect the lack of precision needed within a clinically acceptable range. Within that range, a difference of (b) (4) would not be a concern.

2 Regulatory Background:

The regulatory background of the RLD and ANDA is extensive and is beyond the scope of this consultation. DCR has provided previous consults for ANDA 090589 on 4/25/13 regarding the difference in needle length and on 9/6/16 and 10/29/15 regarding the level of inactive ingredient sodium tartrate dihydrate.

2.1 Orange Book Information

EpiPen and EpiPen Jr is one of three marketed brands of epinephrine autoinjectors in the Orange Book that come in the 0.3 mg and 0.15 mg strengths per delivery, and all are Reference Listed Drugs (RLD) (see Table 1 below). No generic epinephrine autoinjectors are currently approved.

Table 1: Orange Book Currently Approved Applications for Epinephrine Autoinjectors

Active ingredient	Proprietary Name	Application No. / Holder	Dosage Form	Route	Strength		
Epinephrine	EpiPen	NDA 019430 Mylan Specialty LP	Injectable	IM; SC	EQ 0.3 mg / delivery	RLD	RS
Epinephrine	EpiPen Jr	NDA 019430 Mylan Specialty LP	Injectable	IM; SC	EQ 0.15 mg / delivery	RLD	RS
Epinephrine	Adrenaclick	NDA 020800 Impax Laboratories Inc.*	Injectable	IM; SC	EQ 0.3 mg / delivery	RLD	RS
Epinephrine	Adrenaclick	NDA 020800 Impax Laboratories Inc.	Injectable	IM; SC	EQ 0.15 mg / delivery	RLD	RS
Epinephrine	Auvi-Q	NDA 201739 Kaleo Inc.	Injectable	IM; SC	EQ 0.3 mg / delivery	RLD	RS
Epinephrine	Auvi-Q	NDA 201739 Kaleo Inc.	Injectable	IM; SC	EQ 0.15 mg / delivery	RLD	RS

Source: Search on 10/22/17, website: https://www.accessdata fda.gov/scripts/cder/ob/search_product.cfm
RLD=Reference Listed Drug; RS=Reference Standard. All of the above are currently rated "BX."
*NDA 020800 also previously included Twinject 0.3 mg and 0.15 mg epinephrine autoinjectors, which have been discontinued.

2.2 Labeling

The currently approved prescribing information[1] and patient/caregiver instructions for use[2] for EpiPen and EpiPen Jr were reviewed and are notable for the following:

1) Although there is a tiered weight-based dosing recommendation that separates the target patient population of EpiPen 0.3 mg (patients greater than or equal to 30 kg/66 lbs) from EpiPen Jr 0.15 mg (patients 15 to 30 kg/33 to 66 lbs), the label is silent regarding the abilities or characteristics of the person administering/self-administering the injection.
2) The patient/caregiver instructions for use are also silent regarding the abilities or characteristics of the person administering/self-administering the injection. The instruction is to "Swing and push the auto-injector **firmly** until it 'clicks'."

The lack of specificity regarding strength requirements for using the EpiPen and EpiPen Jr, as well as the lack of specificity regarding how "firmly" one must push the auto-injector, suggests a lack of precision and implies the acceptability of activation forces within a certain range; i.e., what an average person mature enough to use one of these injectors might consider to be pushing "firmly." What this range might encompass is considered further in Section 3 below.

3 Review

General expectations for activation force range for epinephrine autoinjectors

Like the other currently approved epinephrine autoinjectors in the U.S., EpiPen is a cartridge-based autoinjector. With this type of device, after the safety cap has been removed, the injector is activated by holding the outer housing and pressing the device tip onto the tissue, allowing the outer housing to move against the inner housing. After activation, the released spring moves the cartridge and the attached needle to its end position, which then pierces through the closure and into the tissue. Application of an adequate activation force and maintaining this throughout the injection compresses subcutaneous tissue, which facilitates intramuscular delivery.[3] While subcutaneous delivery is an approved route of administration, intramuscular delivery of epinephrine is more desirable in that achieves peak concentrations faster.[4] The activation force of the typical epinephrine autoinjector is generally designed to be in the range of 5 to 10 lbs.[5] The main consideration in the decision to allow self-administration of autoinjectors with children is not the ability to generate the force needed to activate the autoinjector or control the recoil, but rather, judgment and maturity factors, and thus there are no standardized age recommendations.[4] In fact, children as young as 8 to 12 years of age can generate more than adequate forces, e.g., in the range of 38 to 43 N [redacted (b) (4)][6], depending on the shape of the grip. Therefore, junior version autoinjectors typically do not differ in activation or recoil forces compared to adult

[1] https://www.accessdata fda.gov/drugsatfda_docs/label/2017/019430s067lbl.pdf , supplement 67, approved 4/28/17
[2] https://www.accessdata fda.gov/drugsatfda_docs/label/2016/019430s061lbl.pdf , supplement 61, approved 5/18/16
[3] Frew AJ, "What are the 'ideal' features of an adrenaline (epinephrine) auto-injector in the treatment of anaphylaxis?" Allergy 2011; 66:15-24
[4] Sicherer SH, Simons FER, AAP Section on Allergy and Immunology. Epinephrine for First-aid Management of Anaphylaxis. Pediatrics. 2017; 139(3):e20164006
[5] Dennerlein JT, "Anaphylaxis Treatment: Ergonomics of Epinephrine Autoinjector Design." The American Journal of Medicine (2014) 127, S12-S16.
[6] Barbir A et al., "Designing Auto-Injectors for Children: Effect of Form Factor on the Human Factors of Efficient Drug Delivery." J Allergy and Clin Immunol February 2015, 135 (2): supplement AB210. Abstract 678.

version autoinjectors, though needle length is a unique consideration, and has been addressed in a separate DCR consult.

The results of in-vitro testing of EpiPen injectors published in the literature have generally ranged closer to [(b) (4)] 23 [(b) (4)] N ([(b) (4)][7] in one article and at an average of 23.4 N [(b) (4)][8] in another. Similar activation forces were observed with Adrenaclick and Twinject injectors, as shown in Table 2 below. Activation forces are lower with syringe-based injectors (e.g. 8-[(b) (4)])[7], but no epinephrine syringe-based injectors are approved in the U.S.

Table 2

TABLE E1. Descriptive statistics for EAIs and EAITDs

	Actual				Trainer			
Injector	**No.**	**Mean**	**SD**	**95% CI**	**No.**	**Mean**	**SD**	**95% CI**
EpiPen								
Activation	5	23.4 N	1.9	21.7-25.1	5	28.0 N	5.8	22.9-33.1
Recoil	5	42.2 N	4.0	38.7-45.7	5	13.3 N	3.2	10.5-16.1
Adrenaclick								
Activation	5	22.6 N	5.7	17.6-27.6	5	16.0 N	0.6	15.5-16.5
Recoil	5	15.4 N	4.3	11.6-19.2	5	13.1 N	1.4	11.9-14.3
Twinject								
Activation	5	27.1 N	2.6	24.8-29.4	5	16.5 N	0.9	15.7-17.3
Recoil	5	18.9 N	1.9	17.2-20.6	5	13.7 N	1.0	12.8-14.6

Source: Jacobsen et al., J Allergy Clin Immunol., 129(4):1143-5. Conversion factor: 1 N = 0.22481 lbf.

Teva proposed epinephrine autoinjector results vs. RLD

[(b) (4)]

Based on the population bioequivalence (PBE) analysis performed by the Division of Bioequivalence III (DBIII) reviewer, the 95% upper bound of trigger force for adult [(b) (4)] and junior [(b) (4)] device are greater than 0 (PBE criterion is 95% upper bound must be ≤0), which is not passing, as shown in Table 3 below.

[(b) (4)]

[7] Schwirtz A and H Seeger, "Are adrenaline autoinjectors fit for purpose? A pilot study of the mechanical and injection performance characteristics of a cartridge versus a syringe-based autoinjector." Journal of Asthma and Allergy 2010 (3):159-167

[8] Jacobsen RC et al. "Comparing activation and recoil forces generated by epinephrine autoinjectors and their training devices." J Allergy Clin Immunol 2012, 129 (4): 1143-5

However, the firm provided justification for the slightly higher average trigger/activation force for the test product, which included: 1) that a (b) (4) difference in force would not be clinically meaningful to the user, and 2) that there is variability in the RLD lots, as shown by their own activation force data on the RLD in 2015 and 2017 BE studies (see Table 4 below). They reason that if the 2015 RLD would not pass PBE compared to the 2017 RLD, then their test product would not pass either, since they developed their product to be equivalent to the 2015 RLD product. They also conclude that as both 2015 and 2017 RLD versions were approved to be marketed, that any differences between them would not be considered clinically significant.

As discussed at an FDA internal meeting between Office of Bioequivalence (OB) and Office of Research and Standards (ORS) on 6/12/17, the RLD activation force specification for both the adult and junior devices is (b) (4), and specifications for other epinephrine autoinjectors are also similarly broad (b) (4) so the variability in RLD activation force noted by the ANDA sponsor would fall well within this range and would not be unexpected. This lends further credence to the ANDA sponsor's data on the RLD.

(b) (4)

Other clinical considerations

Other considerations that impact the potential acceptability of the proposed difference in activation force pertain to the context of use. Specifically, EpiPen and EpiPen Jr are not chronically administered products, so their activation forces are not forces to which patients or caregivers would likely become very accustomed. These are emergency-use medications that are used infrequently and sporadically, so it is unlikely that a patient or caregiver would be highly attuned to a specific activation force, as long as activation does not require a very large or very small amount of effort.

4 Conclusions:

(b) (4) (b) (4). DCR concludes that the slightly greater force needed to activate the test device compared to the reference device does not raise any safety or efficacy concerns regarding the test product.

The rationale for this conclusion is based on the following:

1) Given that EpiPen/EpiPen Jr labeling only specifies to "push firmly," it is likely that an imprecise and relatively wide range of activation forces would be observed, and that the range would include the activation force numbers observed with the test and RLD devices;
2) The average activation force for the test products are well within the range considered acceptable based on the literature (e.g., 5-10 lbf), and are consistent with published results for other approved epinephrine autoinjectors (b) (4).
3) The average activation force for the test products are well within the capability of expected users of the products, even younger self-administrators (e.g., 8-12 year olds can generate (b) (4)).
4) Small differences in activation forces between the test and RLD would not be particularly notable to users given that the product is used infrequently/sporadically in emergency use situations.
5) Acceptable activation force specification ranges for approved epinephrine autoinjectors reflect the lack of precision needed within a clinically acceptable range. Within that range, a difference of (b) (4) would not be a concern.

Sarah Yim

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Date: 11/08/2017 08:04:56AM
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HUMAN FACTORS STUDY REPORT 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:	February 10, 2016
Requesting Office or Division:	Office of Pharmaceutical Quality (OPQ), Office of Lifecycle Drug Products (OLDP)
Application Type and Number:	ANDA 090589
Product Name and Strength:	Epinephrine Auto-Injector 0.15 mg/0.3mL and 0.3 mg/0.3 mL
Product Type:	Combination Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Teva Pharmaceuticals Inc.
Submission Date:	December 30, 2014
OSE RCM #:	2015-1409
DMEPA Primary Reviewer:	Lissa C. Owens, PharmD Kellie Taylor, PharmD, MPH
DMEPA Associate Director:	Lubna Merchant, PharmD, MS

1 REASON FOR REVIEW

This review evaluates the results of the human factors study that was submitted by the Applicant on December 30, 2014 under abbreviated new drug application (ANDA) 090589.[1] We were consulted by the Office of Pharmaceutical Quality (OPQ) to review the results of the human factors study.

The epinephrine auto-injector (AJE) product proposed in ANDA 090589 differs from the reference listed drug (RLD) under new drug application (NDA) 019430 (i.e., EpiPen), and our review focused on determining whether the differences would preclude substitution of the proposed AJE for the RLD because, for example, additional physician intervention or additional training would be necessary to ensure appropriate use of the AJE.[2]

2 REGULATORY HISTORY

ANDA 090589 was received for review by the Office of Generic Drugs (OGD) on November 21, 2008. On May 16, 2011, OGD issued a minor deficiency letter to the Applicant, in which OGD requested that the Applicant conduct a human factors study with respect to the AJE device in ANDA 090589 and recommended that the Applicant submit a study protocol in advance of conducting the human factors study for FDA's review and comment.[3] On January 20, 2012, the Applicant submitted a protocol for the human factors study for FDA's review and comment. The protocol was reviewed by the Center for Devices and Radiological Health (CDRH) and comments

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[1] As part of its human factors study submission, the Applicant indicated that the study was "intended to demonstrate that the AJE [i.e., auto-injector] device's performance is not different from the EpiPen®, that patients in an emergency situation can use the AJE device safely and effectively in accordance with instructions provided for the EpiPen® without the need for additional training prior to use, and that the AJE device does not introduce new use errors as compared to the EpiPen®." See ANDA 090589, Section 5.3.5.4 (December 30, 2014) (HF Study) at 71. We note that the Applicant has referred to this study as a "human factors" study, "usability" study and "validation" study throughout its submission. However, for purposes of consistency, we refer to this study as a "human factors" study throughout this review.

[2] We note that FDA has previously issued citizen petition responses on ANDAs referencing EpiPen auto-injectors and we have considered those issues as they relate to this matter. See Letter from Janet Woodcock to King Pharmaceuticals dated July 29, 2009 (Docket FDA-2009-P-0040) and Letter from Janet Woodcock to Dey Pharma, L.P. dated May 27, 2010 (Docket FDA-2009-P-0578). [3] This letter from OGD to the Applicant indicated that the purpose of this study was to "demonstrate that the device can be used by representative users under simulated use conditions without producing patterns of failures that could result in negative clinical impact to patients or injury to device users." See Letter from FDA to Teva re Quality Deficiency – Minor for ANDA 090589 (May 17, 2011) at 2.

[3] This letter from OGD to the Applicant indicated that the purpose of this study was to "demonstrate that the device can be used by representative users under simulated use conditions without producing patterns of failures that could result in negative clinical impact to patients or injury to device users." See Letter from FDA to Teva re Quality Deficiency – Minor for ANDA 090589 (May 17, 2011) at 2.

were sent to the Applicant; however, DMEPA was not consulted at that time with respect to the study protocol or more generally to review the human factors studies for ANDA products. On August 30, 2013, the Applicant submitted a human factors study report as an amendment to ANDA 090589. This human factors study report was not reviewed by FDA.[4] On December 30, 2014, the Applicant submitted another human factors study report (TR 720-B) that included data evaluating changes in the design of the AJE device proposed as part of the Applicant's December 30, 2014 amendment. Study Report TR 720-B is the subject of this review.

3 MATERIALS REVIEWED

We considered the human factors study report submitted by the Applicant on December 30, 2014, along with the design of the RLD device and the currently proposed AJE device.[5]

We note that the proposed product under ANDA 090589 has the same active ingredient, route of administration, dosage form, and strength(s) as the RLD, EpiPen. In addition, both the EpiPen product and Teva's AJE product have auto-injector devices with a blue safety release cap on one end and an orange needle end. The devices each use a green color on the auto-injector label to represent the pediatric strength and a yellow color to represent the adult strength. Both products have instructions for use listed on the carton labeling and on the device itself, and the administration for both products is a three-step process (see Appendix A, Figure 2 and 3).

However, the products differ in that the EpiPen device is contained within a carrier tube and must be removed from the tube prior to use, whereas the AJE device does not have a carrier tube, but rather has a cap that must be removed prior to use. In fact, the instructions for use for the AJE product states that a carrier tube is not provided "as seen with other products."[6] This difference between the carrier tube for the EpiPen and the cap for the AJE is a difference in a design attribute between the products as the cap/carrier tube would need to be removed in order to deliver the drug to a patient. As a result of this difference in a design attribute, the first step in administration of each product differs (see Appendix A and the Instructions for Use

[4] The study report dated March 14, 2013 was submitted by the Applicant prior to redesigning their proposed auto-injector device. See ANDA 090589, Section 5.3.5.4 (August 29, 2013). Following the Applicant's submission of this human factors study in 2013, the Applicant subsequently redesigned its proposed auto-injector device, and the Applicant determined that such changes to the device required a new validation study. As a result of these device design changes, the Applicant submitted data from a new human factor study that evaluated the redesigned auto-injector device as part of the December 30, 2014, amendment to ANDA 090589.

[5] See HF Study.

[6] HF Study at 22.

in Appendix B). Specifically, the proposed AJE product has a cap that must be "twisted," whereas the EpiPen product has no cap to be twisted, and instead has a carrier tube that must be removed. After this step, the instructions for use to administer the drug are largely identical.

As noted above, the human factors study was conducted in September 2014, and OGD's comments on the protocol in May 2011 occurred prior to DMEPA assuming the lead responsibility for reviewing human factors studies for drug-led combination products under ANDA review. Therefore, DMEPA was not consulted by OGD to provide any comment, advice or agreement to the protocol, dated December 19, 2011, for the human factors study (TR 720-B) that formed the basis for the study report submitted on December 30, 2014. However, as noted above, FDA did provide comments to the Applicant based on advice from CDRH (December 20, 2012)). Importantly, FDA communicated to the Applicant that FDA did not agree with the threshold for errors suggested by the Applicant to support approval.

The human factors study report TR 720-B includes observations of 151 subjects: current EpiPen user adults (n=31) and adolescents (n=29); EpiPen non-user adults (n=31) and adolescents (n=30), and trained EpiPen providers[7] (a mix of parents, caregivers, and school nurses n=30). In the testing sessions each user was given either the EpiPen device or the AJE device and asked to simulate an injection twice. Following the two simulated injections, the users were given the opposite auto-injector and asked again to simulate two injections.

The design of the study has several notable flaws. First, current users in TR 720-B were defined as those subjects who have been diagnosed by a physician as being at risk for severe allergic reactions, and who have been previously prescribed and regularly carry an EpiPen. It is not made clear from the study report whether these criteria reflect actual current users of the product. Considering that the failure to regularly carry an EpiPen is a known behavior among current EpiPen users, the use of this criterion to define the current EpiPen user population may be inappropriate. It is also not clear whether all members of the 'current user' group have ever administered epinephrine. Furthermore, among those subjects with experience in administering EpiPen, there is thought to be a range in the patterns of use with respect to

[7] The study report does not describe the training that this user group was given, or the proximity of the training to the observed simulated uses in this study. It is also not clear to us what actual users this user group was intended to represent as healthcare providers such as nurses have much different knowledge and skill than typical lay users such as parents and caregivers and would not normally be include within the same user group.

recency and regularity[8], which should be used to inform the selection of user groups and study design. The applicant provides no information to characterize the use characteristics of current EpiPen users to justify whether the current users included in this study accurately represent the actual current users of EpiPen, undermining the interpretability of the data.

Second, some users simulated the use of the AJE product twice before the EpiPen simulation exercise for all observations. It is unclear whether this test method would sufficiently evaluate the risks of substitution where the users of EpiPen would have used or been familiar with using that product for some period of time before switching to the AJE product, which is a safety concern, as familiarity may predispose patients accustomed to the design of EpiPen to make mistakes with the AJE product. It is unclear whether this sequencing (simulating AJE use before giving users either the AJE device or EpiPen instead of simulating EpiPen use first) may have influenced participant performance, and the Applicant does not justify this approach in the study report.

Third, the methods do not describe whether there was an interruption between the simulated use of the AJE product and the EpiPen product. In actual use, the administration of epinephrine products is episodic, and it is likely that such administrations of epinephrine would be separated by some period of time. In human factors studies, sponsors generally include a time period (hours, days, or weeks) of separation between observations to simulate the elapsed time between administrations in actual use. To some extent, the administration of AJE first for all observations may have adequately represented this episodic use, but the report does not describe when (if ever) the current EpiPen users last administered the product to provide a reasonable understanding of whether this observation might accurately reflect the transition of current EpiPen users to a new product.

Lastly, although the study collected some quantitative data comparing the use of the two products, the applicant failed to design a study to reliably estimate (i.e. with statistical significance) whether the rate of errors related to the removal of the yellow cap of the proposed AJE among users who are substituted the AJE for the RLD without additional training prior to use is not significantly greater than the rate of errors observed with removing the

[8] In previous work, the applicant did collect some of this detail for subjects for the HF Study Report TR-927 conducted in 2012. Among the current user groups in that study, about half of the subjects had never administered EpiPen, a further third had not ever used the EpiPen trainer device, about half of the subjects "always" carried EpiPen with them, and among those that had injected there were some that had injected more than once and within a year, but others that had only injected once and not recently. The demographics suggests that current users may possess varying degrees of familiarity with EpiPen based on their reported patterns of use, and therefore careful attention should be given to definition of current users in order to ensure appropriate subject and subgroup selection which is impact the interpretability of the data.

carrier tube of the RLD if those users were to continue using the RLD. Such errors with the proposed AJE product would prevent some current EpiPen users from administering epinephrine when the proposed AJE product is substituted for the RLD without additional training. The residual uncertainty about the magnitude of the difference in error rates between the proposed AJE product and the RLD, if any, is a significant deficiency introduced by the study design employed.

4 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We note that certain user errors were observed as part of the human factors study with both the AJE product and the EpiPen product, which included failure to remove the blue safety release, inappropriate injection site selection, inadequate force to correctly administer the injection, and failure to hold the device at the injection site for the duration of time required to administer a full dose. Although these failures negatively impact the use of epinephrine products for some users, it is important to note that such failures are known to occur with the currently marketed EpiPen.[9,10,11,12] We have evaluated these errors in previous reviews and made recommendations to the EpiPen NDA holder regarding the EpiPen device, container label and carton labeling to address some of these errors.[13,14,15] Although the EpiPen label and labeling has been changed in an effort to alleviate the aforementioned failures, we acknowledge that we continue to receive reports of these errors with EpiPen. Importantly,

[9] Institute for Safe Medication Practices (ISMP). Epinephrine for Anaphylaxis Volume 20, Issue 4, February 26, 2015. Pages 1- 3

[10] Institute for Safe Medication Practices (ISMP). Trainer EpiPen Used During Code. Volume 19, Issue 4, February 27, 2014. Page 1

[11] Institute for Safe Medication Practices (ISMP), Thumb Injected Despite EpiPen Redesign, Volume 15, Issue 22, November 4, 2010 at 1.

[12] Institute for Safe Medication Practices (ISMP), Medication Safety Alert, Volume 2, Issue 21, October 22, 1997 at 1.

[13] Owens, L. Label and Labeling Review for EpiPen (NDA 019430). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2012 FEB 22. 15 p. OSE RCM No.: 2011-4500.

[14] Owens, L. Label and Labeling Review for EpiPen (NDA 019430). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2014 FEB 20. 14 p. OSE RCM No.: 2013-2645 and 2013-2606.

[15] Owens, L. Label and Labeling Memo for EpiPen (NDA 019430). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2014 May 28. 6 p. OSE RCM No.: 2014-561.

certain errors observed in the human factors study for both devices stem from tasks in administering these products that are the same for both devices ("common tasks") and that involve design attributes that are the same for both devices.

While the Applicant's study would not be sufficient to permit us to conclude that the error rate associated with these common tasks is not significantly different between the two products due to the study design deficiencies discussed above, a comparative human factors study is actually not needed to reach this conclusion. We can conclude that the common task error rates would not be expected to be significantly different based on the fact that the critical design attributes associated with these tasks are the same.

In addition to the errors associated with the two products' common device design attributes, user errors were observed with respect to the first step of administration for each product (i.e., not removing the yellow cap on the AJE device and not removing the EpiPen device from its carrier tube). The difference between the first step in administration of the EpiPen, which involves removing the product from a carrier tube, and the first step in administration of the AJE, which involves removing a yellow cap for the AJE, represents a difference in a critical design attribute between the two products. Because the AJE and EpiPen products differ primarily with respect to these critical design attributes and their first step of administration, our evaluation of the human factors study focused on the use errors associated with this first step of administration.

In the study report, a current EpiPen user (b) (6) an adolescent, made an error with the AJE product in the first step of administration (i.e., removing the yellow cap) in both observations (see HF Study, Table 39). This user went on to complete correctly the remaining instructional steps for the AJE product, which are the same as the EpiPen product. However, because the user did not remove the yellow cap from the AJE product in the first step, the user would not have received the epinephrine injection under actual use conditions. Thus, the two observed errors associated with this first step of administration represent two instances of critical failures. By contrast, subject (b) (6) performed all of the tasks for the EpiPen product correctly.

In addition, the study report data describe three close calls in which test subjects (b) (6) (b) (6) attempted to inject the AJE product without twisting off the yellow cap, the step that differs from the RLD.[16] Notably, two of three of these subjects were current users of the EpiPen product and the third was trained in the use of EpiPen. Ultimately, the participants self-corrected their initial mistake and went on to perform the remaining tasks correctly for the AJE product.

[16] See HF Study at 78.

However, the observed close calls represent a noteworthy safety concern for several reasons. First, anaphylaxis is an emergent condition that can progress in severity in a short time; thus, treatment with epinephrine in a timely fashion is critical. Second, use of epinephrine is intermittent, unpredictable, and occurs under conditions of stress. Thus, in actual use, the ability of users to self-correct an initial mistake associated with administering the AJE product may be diminished due to the circumstances under which the product is used. Close-calls observed in the simulated use of the AJE product in the human factors study may manifest as errors in actual use. Finally, the close calls themselves represent a risk to users or their caregivers since the associated corrections occurred after the engagement of the safety release on AJE product, thus increasing the risk of inadvertent injection to the user's hand or to the caregiver. Such inadvertent injections are labelled for the RLD (see section 5 of the prescribing information for EpiPen) and are known to occur with epinephrine auto-injectors generally and were captured observations in this study (for the AJE product and RLD).[17] Injections in the hand or digits with epinephrine could lead to decreased blood flow to the area and would require medical intervention with vasodilators to avoid resulting in further adverse outcomes. Thus, even if users are able to self-correct their initial mistake with the AJE product, the self-corrective behavior itself may lead to an increased risk for such wrong-site injection errors in actual use.

The errors that were observed with the proposed AJE product in the human factors study are concerning. In particular, these observed errors suggest that when the AJE product is substituted for EpiPen, without any additional training provided, some users of the AJE product would be expected to fail to appropriately administer the product or experience difficulty in administering the product appropriately, thus not receiving a life-saving drug or not receiving a life-saving drug in a timely fashion in actual use. Based on our analysis, the close calls and two errors observed in the human factors study are likely caused by negative transfer based on the user's expectations of how the proposed product should be administered based on their familiarity with the use of EpiPen.

Furthermore, although the AJE product has been redesigned (b) (4) after the original ANDA submission in 2008[18], we note that the current submission includes data

[17] See HF Study at 82.

[18] See HF Study Report at p. 41. The AJE product was redesigned in 2010 based on FDA input to include changes to align with EpiPen instructions, and other design changes including safety tab redesign to ease removal, change in the removal steps for the yellow safety cap, reduction of activation force, and change in color of viewing window to match EpiPen, and the addition of the word "end" to accompany the text pointing to the needle. In 2012, the applicant redesigned the components to indicate to the user when the device had inadvertently fired and should not be reused. It is not clear from the study report whether on either occasion FDA advised or the Applicant considered

from formative studies that suggests that the design difference of the AJE product compared to the RLD can be expected to cause errors by some individuals. In 2012 Study Report TR-927 evaluated the ability of 138 subjects to administer the AJE (two tasks) or EpiPen (two tasks). Among these observations, there were 5 incidents with the AJE trials in which the users (b) (6) (b) (6) did not remove the yellow cap[19], and four of these observed errors occurred in subjects that were current or trained EpiPen users. It is also notable that among these four users, two (b) (6) were able to successfully remove the carrier tube when the simulation tasks for EpiPen were performed.[20]

We note that although the overall number of study participants that made the error and close-calls in the first step of administration is small, this observed error introduces a risk in using the product. This human factors study was not appropriately designed to reliably estimate whether the rate of error in removing the cap of the AJE product among current EpiPen users is less than, or not significantly greater than, the rate of error in removing the carrier tube if those current EpiPen users continued to use only EpiPen. The residual uncertainty about the magnitude of the difference in error rates between the proposed product and the RLD, if any, is a significant deficiency in this application.

Furthermore, our analysis concludes that such errors and close calls are directly attributable to the differences introduced in the design of the AJE product, given that the errors are likely the result of negative transfer. Importantly, these errors and close calls occurred in a critical task in a product used in an emergency situation and any failure to perform a task correctly may lead to an inability to treat anaphylaxis in a timely fashion. Thus, the observed errors are potentially life-threatening. For these reasons, we find the applicant has failed to submit adequate data to

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design modifications to the closure to provide for the use of a carrier tube to further align the AJE product design and administration to EpiPen.

[19] See Table 6 at p 568 of the HF Study Report.

[20] By contrast with the RLD tasks, there were ten occurrences in which the subjects failed to remove the carrier tube including 6 occurrences among the" current" or "trained" EpiPen user groups. Among these six occurrences, one of the current EpiPen users had also failed to remove the yellow cap on the AJE (b) (6) but the other five were observed as correctly removing the yellow cap on the AJE product. It is important to bear in mind that the design of the proposed AJE was subsequently changed following this study report. However, this qualitative finding may suggest that for certain of the current EpiPen users, the difference in design of the AJE product (i.e. the use of the yellow cap instead of a carrier tube) may avoid an existing risk of error that impacts certain users ability to correctly use the RLD and thus may not negatively impact the ability of certain users to use the epinephrine autoinjectors appropriately. However, as noted elsewhere in this review, as with study TR 720-B, study TR 927 was not designed to allow a determination of the rate of errors with this task (i.e. cap removal) are not significantly greater than the rate of errors observed with removing the carrier tube of the RLD if those users were to continue using the RLD.

support a conclusion that the proposed AJE product can be substituted for the EpiPen RLD without additional training or physician intervention before use.

5 CONCLUSION

DMEPA concludes that the study data results show that some current users of EpiPen who may be dispensed the AJE product in place of EpiPen without additional training prior to use would not be able to use the proposed AJE product appropriately. Thus, there is continued residual uncertainty regarding whether the proposed AJE can be substituted for the RLD.

The study report data identifies a new type of use error for the AJE product in the first step of administration (i.e., not twisting off the yellow cap) that is attributable to a difference in a critical design attribute in design of the AJE product when compared to the EpiPen product. In addition, the Applicant has not provided sufficient comparative data to characterize whether the rate of error in removing the cap of the AJE product among current EpiPen users is less than, or not significantly greater than, the rate of error in removing the carrier tube if those current EpiPen users continued to use only EpiPen. Furthermore, the Applicant did not identify any measure to mitigate this error. Although the data do not allow us to characterize the expected rate of occurrence of this particular error with the proposed AJE product in actual use because of limitations in the study design employed, we can reasonably conclude from the data that if the proposed AJE is approved under 505(j) (and subsequently substituted for EpiPen), FDA would expect that some current users of EpiPen would be unable to use the Applicant's proposed product appropriately based on the pattern of observed errors and close calls observed in the human factors study. It may be possible that the rate of errors observed with this task for the AJE product is within an acceptable margin so as not to be significantly worse than the rate of errors observed with the RLD task of removing the carrier tube, but the data from this human factors study are insufficient to support this conclusion. On this basis we find that the data provided by the Applicant with respect to its proposed AJE product is insufficient to show that the proposed AJE product can be substituted for the RLD without additional training or physician intervention before use of the proposed AJE. We understand that this Applicant has outstanding deficiencies that will be communicated in a Complete Response (CR) letter, and recommend that OGD communicate this deficiency to the Applicant in such CR letter. We also would be happy to work with OGD further post-CR letter to assist the Applicant with respect to submitting data that might be appropriate to address this deficiency.

APPENDIX A COMPARISON OF PRODUCTS

	EpiPen	ANDA
	(b) (4) [redacted]	**Quickly twist in the direction of "twist arrow" to remove green (or yellow) cap and to expose orange tip. Pull off blue safety release**

Step 1. Prepare epinephrine 0.3 mg (auto-injector) or epinephrine 0.15 mg (Jr. auto-injector) for injection

Quickly twist the yellow cap of the epinephrine (auto-injector) or the green cap off the epinephrine (Jr. auto-injector) in the direction of the "twist arrow" to remove it.

Grasp the auto-injector in your fist with the orange tip pointing downward. With your other hand, pull off the blue safety release.

Table 1: Comparison Between Generic Drug and Reference Listed Drug in Accord with 21 CFR 314.94(a)(4) through (6)

	Epinephrine Injection USP, 0.3 mg (Auto-Injector) Epinephrine Injection USP, 0.15 mg (Jr. Auto-Injector) Teva Pharmaceuticals USA	**EpiPen® EpiPen Jr.® Mylan Specialty L.P.**
Conditions of Use	For the emergency treatment of allergic reactions (anaphylaxis).	For the emergency treatment of allergic reactions (anaphylaxis).
Active Ingredient	Epinephrine, USP	Epinephrine, USP
Inactive Ingredients	Please see attached 1.12.12 **Formulation Comparison**	Please see attached 1.12.12 **Formulation Comparison**
Route of Administration	Intramuscular injection, subcutaneous	Intramuscular injection, subcutaneous
Dosage Form	Parenteral solution	Parenteral solution
Strengths	0.15 mg/0.3mL and 0.3 mg/0.3mL	0.15 mg/0.3mL and 0.3 mg/0.3mL
Bioequivalence	Please refer to 1.12.15 **Request for Waiver of in vivo bioavailability studies** and refer to Device Equivalence information contained in Module 5.	
Labeling	The labeling proposed for the Teva Pharmaceuticals USA drug product is the same as the labeling for the listed drug except for changes required because: (1) Teva's formulation contains a lower amount of Sodium Metabisulfite (b) (4) and an additional inactive ingredient, Sodium Tartrate Dihydrate (b) (4) This formulation difference is permitted in accord with CFR 314.94(a)(9)(iii). (2) The drugs are produced and distributed by different manufacturers. (3) Differences based on standard Teva format.	

Figure 2: (b) (4)

(b) (4)

Figure 3: EpiPen[4]

APPENDIX B. LABELS AND LABELING

B.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[21] along with postmarket medication error data, we reviewed the following Epinephrine Autoinjector labels and labeling submitted by Teva on December 30, 2014.

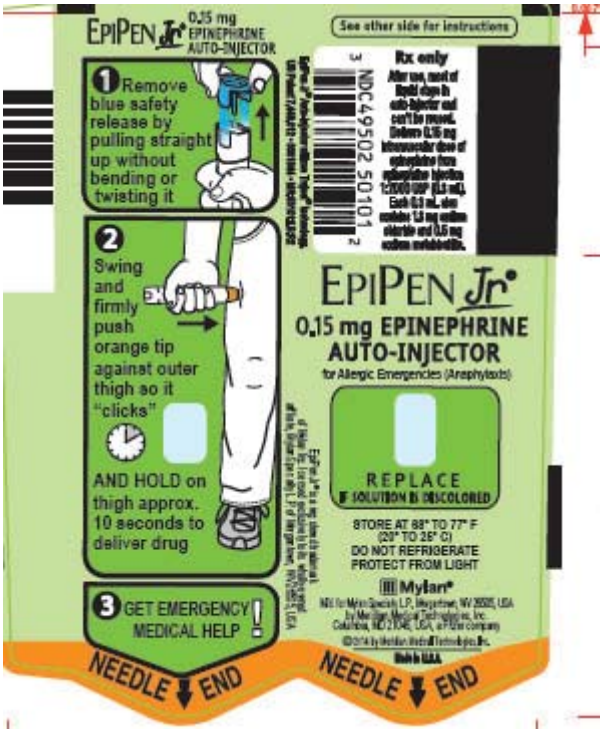
- Instructions for Use
- Labels and Labeling

B.2 Label and Labeling Images

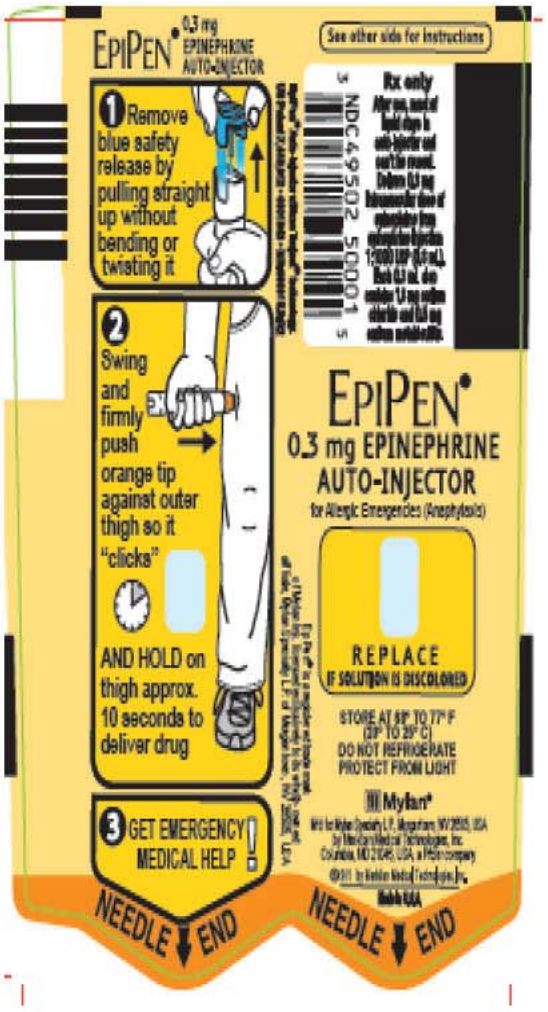
Proposed **EpiPen**

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

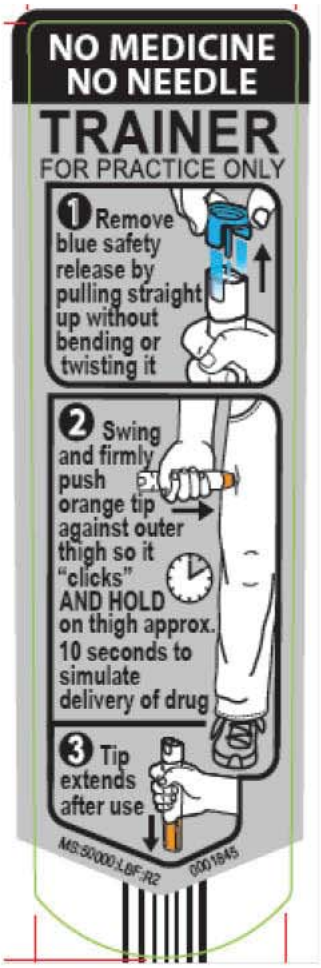
(b) (4)


EPIPEN Jr 0.15 mg EPINEPHRINE AUTO-INJECTOR
See other side for instructions
1 Remove blue safety release by pulling straight up without bending or twisting it
2 Swing and firmly push orange tip against outer thigh so it "clicks"
AND HOLD on thigh approx. 10 seconds to deliver drug
3 GET EMERGENCY MEDICAL HELP
NEEDLE END
NEEDLE END
Rx only
NDC 49502 501012
EPIPEN Jr
0.15 mg EPINEPHRINE AUTO-INJECTOR
for Allergic Emergencies (Anaphylaxis)
REPLACE IF SOLUTION IS DISCOLORED
STORE AT 68° TO 77° F (20° TO 25° C)
DO NOT REFRIGERATE
PROTECT FROM LIGHT
Mylan

(b) (4)


EPIPEN® 0.3 mg EPINEPHRINE AUTO-INJECTOR
See other side for instructions
1 Remove blue safety release by pulling straight up without bending or twisting it
2 Swing and firmly push orange tip against outer thigh so it "clicks"
AND HOLD on thigh approx. 10 seconds to deliver drug
3 GET EMERGENCY MEDICAL HELP
NEEDLE END
NEEDLE END
Rx only
NDC 49502 501 01 5
EPIPEN®
0.3 mg EPINEPHRINE
AUTO-INJECTOR
for Allergic Emergencies (Anaphylaxis)
REPLACE
IF SOLUTION IS DISCOLORED
STORE AT 68° TO 77° F
(20° TO 25° C)
DO NOT REFRIGERATE
PROTECT FROM LIGHT
Mylan®

(b) (4)



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/s/

LISSA C OWENS
02/11/2016

KELLIE A TAYLOR
02/11/2016

LUBNA A MERCHANT
02/11/2016

DIVISION OF PULMONARY, ALLERGY AND RHEUMATOLOGY PRODUCTS (DPARP)
PHARMACOLOGY/TOXICOLOGY CONSULTATION REVIEW

Date:	May 13th, 2013
To:	Office of Generic Drugs
From:	Carol M. Rivera-López, Ph.D., PharmTox Reviewer, DPARP
Through:	Marcie L. Wood, Ph.D., Acting PharmTox Supervisor, DPARP, and Lydia Gilbert-McClain, M.D., Division Deputy Director, DPARP
Subject:	ANDA 90-589 PharmTox Consultation

Application:	ANDA 90-589
Sponsor:	TEVA Pharmaceuticals USA
Drug Product:	Epinephrine Injection, USP, Auto Injector, 0.15 mg and 0.3 mg
Indication:	Allergic emergencies
Subject:	Nonclinical evaluation of the drug product specifications (b) (4) (b) (4) in Epinephrine Injection, 0.15 mg and 0.3 mg.
Date of Submission:	6/12/2009
Date of Request:	5/4/2010
Date Received:	4/9/2013

Safety Assessment

This review evaluates the safety of up to (b) (4) as an impurity in Epinephrine Injection under ANDA 90-589. The Office of Generic Drugs (OGD) requested a Pharmacology/Toxicology consultation on May 4th, 2010 to evaluate the proposed specifications ((b) (4) Epinephrine Injection 0.15 mg and 0.3 mg, under ANDA 90-589. (b) (4)

(b) (4)

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/s/

CAROL M RIVERA-LOPEZ
05/13/2013

MARCIE L WOOD
05/13/2013

LYDIA I GILBERT MCCLAIN
05/14/2013

Clinical Consultation

Epinephrine 0.15 mg/0.3 mL and 0.30 mg/0.3 mL

Drug Product:	Epinephrine Injection, USP (Auto Injector)
Drug Class:	6010100 (Bronchodilator)
Chemical Name:	Epinephrine 0.15 mg/0.30 mL and 0.30 mg/0.30 mL
ANDA:	090589
ANDA Sponsor:	Teva Parenteral Medicines, Inc.
Reference Listed Drug:	EpiPen® Jr (epinephrine) Auto-Injector, 0.15 mg/0.3 mL and EpiPen® (epinephrine) Auto-Injector, 0.3 mg/0.3 mL
NDA:	19430
RLD Sponsor:	Meridian Medical Technologies, Inc.
Reviewer:	Deborah Seibel, M.D. Medical Officer, Division of Clinical Review (DCR), Office of Generic Drugs
Secondary Reviewer:	John Peters, M.D. Director, Division of Clinical Review (DCR) Office of Generic Drugs
To:	Mike Darj, OMPT/CDER/OPS/OGD/DCI HFD-620
Reason for Consult:	On November 13, 2008 the Division of Pulmonary and Allergy Products concluded in their communication to OGD that the Teva's product should be filed under the 505(j) pathway. The reviewer indicated that the needle length of the generic is longer than the RLD's needle length and this issue should be evaluated as part of the review process. Please assess if the longer needle length of the proposed generic is a clinical concern.
Materials Reviewed:	Submissions 12/ 21/2007, 5/30/2008, 5/22/ 2009
Date of Consultation Request:	3/20/2013
Date of Completion:	4/25/2013
Conclusion:	The slightly longer needle length of Teva's product compared to the RLD is not clinically significant, and should not be a factor in the approval of ANDA 90589 as a generic to EpiPen.

1 Executive Summary:

The DCR is asked to assess if there is a clinical concern regarding the longer needle length of Teva Pharmaceuticals' proposed generic epinephrine auto-injector, compared to the needle length of the RLD, EpiPen. The generic epinephrine 0.30 mg/0.30 mL and 0.15 mg/0.3 mL autoinjectors' needles are slightly longer than the equivalent EpiPen dose. For the .3mg dose Teva's average exposed needle length is (b) (4) longer than the RLD's average; for the 0.15mg dose the difference is (b) (4). This difference in needle length is not clinically significant.

- There is precedent for accepting the difference in needle length. A different epinephrine auto-injector with a larger range of needle lengths than the Teva product was approved as a 505(b)(2) application, and has PK and clinical data to show it is equivalent to the same Epipen RLD.
- The amount by which the needle lengths differ is negligible in the setting of the much larger variability of the patients, variability of the injection sites, and variability of the conditions (e.g. through clothing) under which the emergency epinephrine injection might be given.
- The specified route of administration for both test and RLD is intramuscular. Penetration of the test by possibly (b) (4) more than the RLD could only make the injection more likely intramuscular but the injection would still be compliant with the specified route of administration.

2 Recommendation:

The slightly longer needle length of Teva's product compared to the RLD is not clinically significant, and should not be a factor in the approval of ANDA 90589 as a generic to EpiPen.

3 Clinical Consultation:

Background: In 2008 OGD consulted the Division of Pulmonary, Allergy, and Rheumatology Products asking if Teva's epinephrine auto-injectors should be filed under the 505(j) pathway. In her response to OGD's consult, Lydia I. Gilbert-McClain M.D. FCCP, Deputy Director Division of Pulmonary and Allergy Products wrote, "Needle length is an important aspect of these products and appropriate needle length is necessary to ensure adequate penetration to the intended site of administration. Whether the differences in needle length between Teva's autoinjector product and the reference product are a clinical concern should be determined as part of review considerations. In an ideal situation the needle length should match that of the reference for a generic product.[1]"

On 5/22/2009, Teva submitted documentation of the auto-injector device specifications and usability including comparisons with the RLD, Epipen. On 5/04/2010 OGD requested CDRH evaluate[2] the comparative performance parameters[3] between Teva's test product and the RLD, Epipen. The CDRH consult response[4] confirms specifications of 3 different auto-injector models,

[1] DARRTS, ANDA 90589, Gilbert-McClain, Lydia I 11/13/2008 REV-CLINICAL-03(General Review) Original-1
[2] DARRTS, ANDA 90589, CHUH, EUNJUNG E 05/04/2010 FRM-CONSULT-01(General Consult Request)
[3] Performance parameters include: expelled volume, ejection time, exposed needle length, needle guard lockout override force, activation force, safety cap removal torque, safety removal force, ram/latch pushout force, device integrity testing, device drop test, and spring relaxation
[4] DARRTS, ANDA 90589, TRAN, TRANG Q 07/06/2010 FRM-ADMIN-01(Memorandum to File) Original-1

including the auto-injector used for Teva's epinephrine product. The data related to needle specifications is included in Table 1. Interestingly, CDRH reports the minimum needle length, possibly suggesting the minimum, rather than the range is of most importance. "The needle exposure for the adult device will be (b) (4)) minimum and for the junior (pediatric) device it will be (b) (4)) minimum." These data confirm the previously noted length discrepancy between the Teva and the RLD product, but do not provide information on the clinical implications of the needle length discrepancy.

Table 1 shows the needle lengths of the currently available epinephrine auto-injectors (EAI).

(b) (4)

A similar needle length discrepancy was addressed in a different epinephrine auto-injector (EAI) by Sanofi that was approved as a 505(b)(2) application in 2010 by the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP). Sanofi's product under NDA 201739 (see Table 1), has needle lengths more similar to the Teva product that is the subject of this consult. Additionally, the Sanofi EAI has the same doses, and more importantly, the same RLD (EpiPen), as the proposed Teva EAI. In the Cross-Discipline Team Leader Review[7] of NDA 201739 Susan Limb, M.D. wrote, "In terms of device attributes [Sanofi] EAI is similar to EpiPen in terms of needle length, gauge, and injection force." Although not a requirement for the application, Sanofi conducted a single pivotal PK trial (see 9). Dr. Limb concluded, "the trial demonstrated bioequivalence (BE) between [Sanofi] EAI 0.3 mg and the reference 0.3 mg product using a scaled BE approach, which is an analytic approach that may be applied in situations of high intra- and inter-individual variability. Satisfactory review of the drug constituent and device components, in conjunction with

[5] EDR NDA 201739 CMC supplement 0069(83) 10/16/2012
[6] DARRTS NDA 20800 Kim, Chong Ho 12/23/2002 REV-QUALITY-03(General Review) Original-1
[7] DARRTS, NDA 201739, Limb, Susan L 7/8/2011 REV-CLINICAL-03(General Review) Original-1 Cross-Discipline Team Leader Review

the Agency's prior findings of efficacy and safety for epinephrine in the proposed indication, form the basis of the Approval recommendation for [Sanofi] EAI.[8]"

Thus, in the case of Sanofi's EAI, it was not the needle lengths differing from Epipen, but the wide interpatient and intrapatient variability that necessitated a less stringent analytical approach to assess bioequivalence of the Sanofi EAI to Epipen.[9]

The relevance of needle length to the PK of the delivered dose was also noted by the ONDQA/Biopharmaceutics reviewer. The review recommended that positive results of the clinical bioavailability of the 0.3 mg strength of Sanofi's EAI compared with the 0.3mg strength of EpiPen would support both the 0.3 mg and 0.15 mg dose levels. "The needle's length for the 0.3mg and 0.15mg doses are not similar (b) (4)). However, this also holds true for the two approved strengths of EpiPen, suggesting the lack of clinical relevance of needle dimensions similarities between strengths in this particular case.[10]"

Another epinephrine auto-injector Twinject (and Adrenaclick, authorized generic) is approved under NDA 020800. Both the 0.3 mg and 0.15 mg versions of these products have identical needle lengths. Although other products have shorter needle lengths for the lower dose presentation, Twinject's lower dose is delivered with the same needle as the higher dose, suggesting a minimal needle length difference is not a significant factor in appropriate dose delivery. (b) (4)

(b) (4)

The recommended intramuscular route of administration of the RLD is intramuscular. If the Teva EAI needle were shorter than the RLD it is conceivable that the epinephrine injection given by the shorter needle would be subcutaneous rather than intramuscular. However, Teva's needle penetrates (b) (4) than the RLD Epipen (refer to Table 1). (b) (4)

(b) (4)

A similar difference in depth of injection could also occur from choice of injection sites. Although it is recommended that the injection be given in the lateral thigh, each patient is different with different skin thickness and different amounts of subcutaneous tissue, not only between patients but

[8] DARRTS, NDA 201739, Limb, Susan L 7/8/2011 REV-CLINICAL-03(General Review) Original-1 Cross-Discipline Team Leader Review
[9] DARRTS, ANDA 201739, Porter, Brian 6/24/2011 REV-CLINICAL-03(General Review) Original-1
[10] DARRTS, NDA 201739 Suarez, Sandra 5/27/2011 REV-QUALITY-03(General Review) Original-1
[11] DARRTS NDA 20800 Starke, Peter R 8/08/2012 REV-CLINICAL-03(General Review)

also on the same patient at different points on the same lateral thigh. The authors of a study on epidermal thickness measurements at multiple body sites commented "what was most striking in our results was not that there was some variability *between* body sites, but that there was so much variation within a particular site." [12] The injection depth can vary further if the injection is given through clothing, as recommended in the Epipen label.[13] In an emergency situation, it is likely that the choice of injection site on the lateral thigh would be less important than the ease of access and the speed at which the injection could be given.

An (b) (4) difference in needle length between the Teva test product and the RLD Epipen is not clinically significant. (b) (4) (b) (4). The Teva difference in needle length is negligible in the setting of a much larger variability between patients and also between injection sites in the same patient. If other factors are acceptable, the difference in needle length should not deter recommendation of the Teva epinephrine auto-injector(s) for approval as a generic to the EpiPen(s).

4 Regulatory Background:

1. EpiPen epinephrine auto-injector (0.3 mg and 0.15 mg) was approved under NDA 19430 on December 22, 1987. Particulars of the application are not available in electronic format.

2. Twinject (0.3 mg and 0.15 mg), a different type of product containing with both an auto-injector dose and a manual pre-filled syringe dose, was approved May 30, 2003 (NDA 20800). Further, by licensing agreement, Adrenaclick was approved as a generic to Twinject, under Twinject's NDA.

   (b) (4) (b) (4) However, the clinical component of the application was deemed acceptable to allow approval. The clinical section of the initial NDA submission consisted of published references addressing PK, PD, toxicology, and clinical efficacy of epinephrine in the treatment of anaphylaxis, as well as a brief review of these articles. This information was supported by a (simulated) non-invasive study of the time required to administer the second of the two doses contained in the drug product. Particulars of the original application or early submissions and reviews are not available in electronic format.

3. The Sanofi Auvi-Q epinephrine auto-injector (0.3 mg and 0.15 mg) was approved as a 505(b)(2) application in August 10, 2012 (NDA 201739). Approval was based on the Agency's prior findings of efficacy and safety for epinephrine, satisfactory review of the drug constituent and device components, and on the results of a single clinical study that demonstrated bioequivalence between the Sanofi auto-injector and the reference EpiPen in healthy adult subjects.

[12] Robertson, K and Rees, J. Variation in Epidermal Morphology in Human Skin at Different Body Sites as Measured by Reflectance Confocal Microscopy, Acta Derm Venereol 2010; 90: 368–373
[13] EpiPen /EpiPen Jr [package insert]. Napa, CA: Dey; September 2008.
[14] DARRTS, NDA 020800 SULLIVAN, EUGENE J 1/17/2003 REV-CLINICAL-03(General Review) Original-1

4. Teva proposes an epinephrine auto-injector in the same doses (0.3 mg and 0.15 mg) as the above, previously approved products. Because of additional similarities to the EpiPen, Division of Pulmonary, Allergy, and Rheumatology Products (responsible for review of the three other epinephrine auto-injectors) determined the Teva product should be filed under the 505(j) pathway,[15] as ANDA 90589.

4.1 DARRTS Listings for This Product:

Table 2 shows the applications for epinephrine auto-injectors that are listed in DARRTS.

Table 2: DARRTS Listings for Epinephrine auto-injectors

Application Number	Product Name	Submitter	Current Status	Status Date	Indication/Subject/Issue
					(b) (4)
NDA-201739	Auvi-Q (epinephrine) Auto-Injector	SANOFI AVENTIS US LLC	Approved	08/10/2012	Emergency Treatment of Allergic Reactions (Type 1)
					(b) (4)
NDA-020800	TWINJECT	AMEDRA PHARMACEUTICALS LLC	Approved	05/30/2003	ADRENERGIC-USED IN EMERGENCY TREATMENT OF ALLERGEN INDUCED ANAPHYLAXIS AND BRONCHASPASM
					(b) (4)

4.2 Current Guidances/Draft Guidances:

None.

[15] DARRTS, ANDA 90589, Gilbert-McClain, Lydia I 11/13/2008 REV-CLINICAL-03(General Review) Original-1

4.3 Orange Book:

A review of Orange Book[16] shows that no generics for this drug product have been approved. Approved epinephrine auto-injectors are listed below in Table 3.

Table 3: Approved Epinephrine auto-injectors Listed in the Orange Book

Appl No	TE Code	RLD	Dosage Form; Route	Strength	Proprietary Name	Applicant
N020800	BX	Yes	INJECTABLE; IM-SC	EQ 0.15MG/DELIVERY	ADRENACLICK	AMEDRA PHARMS
N020800	BX	Yes	INJECTABLE; IM-SC	EQ 0.15MG/DELIVERY	TWINJECT 0.15	AMEDRA PHARMS
N020800	BX	Yes	INJECTABLE; IM-SC	EQ 0.3MG/DELIVERY	ADRENACLICK	AMEDRA PHARMS
N020800	BX	Yes	INJECTABLE; IM-SC	EQ 0.3MG/DELIVERY	TWINJECT 0.3	AMEDRA PHARMS
N201739	BX	Yes	INJECTABLE; IM-SC	EQ 0.15MG/DELIVERY	AUVI-Q	SANOFI AVENTIS US
N201739	BX	No	INJECTABLE; IM-SC	EQ 0.3MG/DELIVERY	AUVI-Q	SANOFI AVENTIS US
N019430	BX	Yes	INJECTABLE; INTRAMUSCULAR	0.15MG/DELIVERY	EPIPEN JR.	MERIDIAN MEDCL TECHN
N019430	BX	Yes	INJECTABLE; INTRAMUSCULAR	0.3MG/DELIVERY	EPIPEN	MERIDIAN MEDCL TECHN

Reviewer's comment: *Note that none of these products are AB rated due to the fact that all entered under a 505(b)(2) pathway as NDAs and none of the sponsors chose to request AB rating. Thus, none of the currently available products are considered interchangeable.*

[16] Online-Orange Book http://www.fda.gov/cder/ob/default.htm. Epinephrine

4.4 Formulations:

5 Label:

The current product label for Epipen and Epipen Jr was approved on 8/20/2012. There is not a black box warning.

5.1 Indications:

A sympathomimetic catecholamine indicated in the emergency treatment of allergic reactions (anaphylaxis) to insect stings or bites, foods, drugs and other allergens as well as idiopathic or exercise-induced anaphylaxis.

5.2 Usual dosage:[18]

The EpiPen® and EpiPen® Jr auto-injectors each contain 2 mL epinephrine solution for emergency intramuscular injection only.

- Each EpiPen® auto-injector delivers a single dose of 0.3 mg epinephrine from epinephrine injection, USP, 1:1000 (0.3 mL) in a sterile solution. It is intended for patients who weigh 30 kg or more (approximately 66 pounds or more).
- Each EpiPen® Jr auto-injector delivers a single dose of 0.15 mg epinephrine from epinephrine injection, USP, 1:2000 (0.3 mL) in a sterile solution. It is intended for patients who weigh 15 to 30 kg (33-66 pounds)
- For stability purposes, approximately 1.7 mL remains in the auto-injector after activation and cannot be used.

5.3 Initial dosage:

One injection of the fixed dose of epinephrine delivered from EpiPen (0.3 mg IM) or EpiPen Jr (0.15 mg IM) into the anterolateral aspect of the thigh, through clothing if necessary. [19]

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[17] DARRTS ANDA 90589 DARJ, MIKE 4/30/2009 REV-QUALITY-03(General Review) Original-1 Archive
[18] RLD Prescribing Information. http://www.anaphylaxis.com/files/Legacy-Physician-Insert.pdf.
[19] EpiPen /EpiPen Jr [package insert]. Napa, CA: Dey; September 2008.

5.4 Maximum dose:

With severe persistent anaphylaxis, repeat injections with an additional EpiPen Auto-Injector may be necessary. More than 2 sequential doses should only be administered under direct medical supervision.

5.5 Contraindications:

There are no absolute contraindications to the use of epinephrine in a life-threatening situation.

5.6 Significant Warnings and Precautions:

- Epinephrine auto-injectors should only be injected into the anterolateral aspect of the thigh.
- Accidental injection into the digits, hands, or feet may result in loss of blood flow to the affected area and should be avoided.
- Tissue necrosis may develop if extravasation occurs.
- Arrhythmias, including fatal ventricular fibrillation, have been reported in patients with underlying cardiac disease or certain drugs.

5.7 Adverse Reactions:

The most commonly reported adverse reactions reported include:

- Cardiovascular: anginal pain; cardiac arrhythmias; excessive rise in blood pressure; palpitations
- CNS: Apprehensiveness; dizziness; restlessness; cerebral hemorrhage; hemiplegia; headache
- Dermatologic: pallor, sweating
- GI: nausea, vomiting
- Local: repeated local injections can result in necrosis at sites of injection from vascular constriction.

5.8 Drug Interactions:

- Cardiac glycosides or diuretics: possible cardiac arrhythmias
- Tricyclic antidepressants, monoamine oxidase inhibitors, levothyroxine sodium, certain antihistamines, (chlorpheniramine, tripelennamine and diphenhydramine): can potentiate epinephrine effects
- Beta-adrenergic blocking drugs (propranolol): antagonize cardiostimulating and bronchodilating effects of epinephrine.
- Alpha-adrenergic blocking drugs (phentoloamine): antagonize vasoconstricting and hypertensive effects of epinephrine
- Ergot alkaloids: reverse the pressor effects of epinephrine.

5.9 Pregnancy Category: C

5.10 Off-Label Uses:

Epinephrine injection can be effective for:[20]

- hemostasis in the management of acute lower GI bleeding

[20] Drug Facts and Comparisons: http://online factsandcomparisons.com

- treatment of overdoses of tricyclic antidepressant (and other sodium channel blockers), calcium channel blockers, and beta-blockers
- emergency treatment of symptomatic bradycardia or hypotension

5.11 Pharmacokinetics:

The drug becomes fixed in the tissues and is rapidly inactivated by enzymatic transformation in the liver and other tissues to metanephrine or normetanephrine, either of which is subsequently conjugated and excreted in the urine in the form of sulfates and glucuronides.

5.12 Mechanism of Action:

Epinephrine imitates all actions of the sympathetic nervous system except those on the arteries of the face and sweat glands. The most prominent actions of epinephrine are on the beta receptors of the heart, vascular and other smooth muscle.
Epinephrine produces a rapid rise in blood pressure through direct stimulation of cardiac muscle, increasing strength of ventricular contraction and of heart rate, and by constriction of the arterioles in the skin, mucosa, and splanchnic areas of the circulation.

6 Discussion:

Teva proposes a generic to the EpiPen and EpiPen Jr. The Teva product has needle lengths that are (b) (4) the needles of the RLD, EpiPen and EpiPen Jr. The differences are small, (b) (4) for the 0.3mg dose, and (b) (4) for the 0.15mg dose. A Sanofi epinephrine auto-injector, approved as a 505(b)(2) application, has the same doses and RLD as the proposed Teva product. The Sanofi product also has needle lengths that differ from the RLD, but a PK study demonstrated bioequivalence to the RLD using an analytic approach that may be applied in situations of high intra- and inter-patient variability. This variability, a function of the patients not of the drug, is applicable to Teva's epinephrine auto-injector, as well as to Sanofi's product and to the RLD.

The emergency use of epinephrine for treatment of anaphylaxis is quicker and more convenient with use of a pre-filled auto-injector, such as the EpiPen. In an emergency situation, the necessary depth of an injection is subject to wide patient variability, as well as to the possible necessity of injection through clothing. The (b) (4) needle length of the Teva products is negligible in the setting of such wide variability.

7 Conclusions and Recommendations:

The Teva epinephrine auto-injector(s) uses the same route of administration as the RLD, in the same population with wide inter and intra patient variability. The difference in needle lengths of the Teva product is not clinically significant; the issue of needle length should not negatively impact a decision to approve Teva's epinephrine auto-injector as a generic to Epipen.

8 References:

1. DARRTS NDA 201739, Limb, Susan L 7/8/2011 REV-CLINICAL-03(General Review) Original-1 Cross-Discipline Team Leader Review
2. DARRTS NDA 201739, Porter, Brian 6/24/2011 REV-CLINICAL-03(General Review) Original-1
3. DARRTS NDA 201739 Suarez, Sandra 5/27/2011 REV-QUALITY-03(General Review) Original-1
4. DARRTS NDA 20800 Kim, Chong Ho 12/23/2002 REV-QUALITY-03(General Review) Original-1
5. DARRTS NDA 020800 SULLIVAN, EUGENE J 1/17/2003 REV-CLINICAL-03(General Review) Original-1
6. DARRTS ANDA 90589, CHUH, EUNJUNG E 05/04/2010 FRM-CONSULT-01(General Consult Request)
7. DARRTS ANDA 90589 DARJ, MIKE 4/30/2009 REV-QUALITY-03(General Review) Original-1 Archive
8. DARRTS ANDA 90589, Gilbert-McClain, Lydia I 11/13/2008 REV-CLINICAL-03(General Review) Original-1
9. DARRTS ANDA 90589, TRAN, TRANG Q 07/06/2010 FRM-ADMIN-01(Memorandum to File) Original-1
10. Drug Facts and Comparisons: http://online.factsandcomparisons.com
11. EDR NDA 201739 CMC supplement 0069(83) 10/16/2012
12. EpiPen /EpiPen Jr [package insert]. Napa, CA: Dey; September 2008.
13. EpiPen /EpiPen Jr Prescribing Information. http://www.anaphylaxis.com/files/Legacy-Physician-Insert.pdf
14. Online-Orange Book http://www.fda.gov/cder/ob/default.htm. Epinephrine
15. Robertson, K and Rees, J. Variation in Epidermal Morphology in Human Skin at Different Body Sites as Measured by Reflectance Confocal Microscopy, Acta Derm Venereol 2010; 90: 368–373
16. Simons et al. Epinephrine absorption in adults: intramuscular versus subcutaneous injection. J Allergy Clin Immunol. 2001. Nov; 108(5):871-3).

9 Appendix: A brief summary of Study INT0802 for NDA 201739

NDA 201739 is for Sanofi's Auvi-Q epinephrine auto-injectors with needle lengths different than the RLD auto-injectors (Epipen) to which it was compared. Bioequivalence was demonstrated in Study INT0802, a randomized, single-blind, two-treatment, three-period, three-sequence study of bioavailability of two formulations/delivery devices for epinephrine in healthy human volunteers.

The primary objective was to document bioavailability following a single injection of 0.3 mg epinephrine USP 1:1000 administered using Sanofi's EAI and EpiPen under fasting conditions.

The target sample size of 66 subjects was calculated to provide 80% power to establish bioequivalence, using variance estimates derived from the medical literature.[21]

Study subjects (66 healthy male and female young to middle-aged adults aged 18-45 years) were randomized 1:1:1 to each of 3 treatment sequences of three treatment periods with a single dose each of epinephrine 0.3 mg administered via either Sanofi's EAI (Test Drug = T) or EpiPen (Reference Drug = R). Serial PK blood sampling was done in each treatment period at pre-dose and throughout the first 6 hours post-dose at 5, 10, 15, 20, 30, 40, and 50 minutes and 1, 1.25, 1.5, 2, 3, 4, and 6 hours.

Results: As the primary measure of bioavailability, plasma epinephrine concentration was quantified for each treatment period. A total of 71 subjects were included in the PK data set. The plasma-time concentration curves (mean and standard deviation) of the treatments largely overlapped, with slightly higher epinephrine bioavailability conferred by Sanofi's EAI after 30 minutes post-dose.

A descriptive analysis of the main pharmacokinetic parameters reflective of this overlap is shown in the following table. Comparison of these mean values demonstrates that epinephrine administered via Sanofi's EAI has greater bioavailability and a longer half-life that that of the RLD, although Cmax was slightly lower for Sanofi's EAI compared to EpiPen.

Comparative PK parameters: Sanofi Epinephrine auto-injector 0.3 mg vs EpiPen 0.3mg

Treatment		C_{max}	T_{max}	$T_{1/2}$	$AUC_{(0-t)}$	$AUC_{(inf)}$	$AUC_{(0-Rtmax)}$
EAI	N	67	67	59	67	59	49
	Mean	0.486	0.330	1.656	0.536	0.724	0.139
EpiPen	N	135	135	131	135	131	52
	Mean	0.520	0.170	1.139	0.466	0.583	0.119

An analysis of these data for bioequivalence via a mixed-effects linear model analysis using the Haidar method (2008) indicated that bioequivalence was established for both observed and change from baseline values in Cmax, AUC(0-t), AUC(inf), and AUC(0-Rtmax). Therefore, overall it can be concluded that the exposure of the two products is equivalent.

[21] Simons et al. Epinephrine absorption in adults: intramuscular versus subcutaneous injection. J Allergy Clin Immunol. 2001. Nov; 108(5):871-3).

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/s/

DEBORAH J SEIBEL
04/29/2013

JOHN R PETERS
04/29/2013

DIVISION OF PULMONARY AND ALLERGY PRODUCTS
MEDICAL OFFICER CONSULTATION

Date:	November 12th, 2008
To:	Susan E. Pellock, Office of Generic Drugs (OGD)
From:	Lydia I. Gilbert-McClain M.D. FCCP, Deputy Director Division of Pulmonary and Allergy Products, HFD-570
Through:	Badrul A. Chowdhury, M.D., Ph.D., Director Division of Pulmonary and Allergy Products, HFD-570
Subject:	ANDA 090589

General Information

Request from: Susan E. Pellock
Through: Gary J Buehler, Director, and Office of Generic Drugs
Date of Request: October 16th, 2008

Materials Reviewed: Consult request dated 6/20/2008 to DACCADP-HFD 170

Background

TEVA is developing two epinephrine auto-injector products one adult and one junior to mirror the currently marketed Epipen adult and Epipen Junior products for the treatment of anaphylaxis. In terms of composition, the product contains the same dose/strength of epinephrine, with similar expelled volume per injection and similar characteristics of the device. The OGD is requesting the division's feedback regarding the mechanism of action (MOA) of the innovator's auto-injector compared to TEVA's proposed auto-injector. (b) (4)

(b) (4)

(b) (4) Because of this experience, the OGD would like us to comment on the following

(a) whether the mechanism of action of TEVA's product and the Innovator product are identical or not

(b) Whether this application should be filed in OGD under the 505(j) pathway, or if it should be filed under (505)(b)(2)

Division Response

We have reviewed the information provided by TEVA concerning their epinephrine auto-injector product and have concluded that the mechanism of action (mechanism of release) is the same as that of Epipen auto-injector. TEVA provided the following information comparing the functional characteristics.

Comparison between TEVA's Auto-injector and the EpiPen Auto-injector

(b) (4)

The needle gauge of both the TEVA adult and junior auto-injector and the Epipen adult and junior auto-injector is the same (b) (4) The TEVA exposed needle length range is slightly longer than that of Epipen Auto injector as follows:

TEVA adult auto-injector (b) (4)
TEVA Junior auto-injector

From the division standpoint, we do not view this difference in needle length as a factor that would preclude a 505(j) pathway. However, of note, needle length is an important aspect of these products and appropriate needle length is necessary to ensure adequate penetration to the intended site of administration. Whether the differences in needle length between TEVA's auto-injector product and the reference product are a clinical concern should be determined as part of the review. In an ideal situation the needle length should match that of the reference for a generic product.

In conclusion, we agree that (a) the mechanism of action of the TEVA auto-injector product and the Epipen auto-injector product is the same and that (b) this product should be filed under the 505(j) pathway.

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Lydia McClain
11/13/2008 01:54:01 PM
MEDICAL OFFICER

Badrul Chowdhury
11/13/2008 02:27:20 PM
MEDICAL OFFICER
I concur

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 090589

PROPRIETARY NAME REVIEW(S)

PROPRIETARY NAME 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:	March 22, 2017
Application Type and Number:	ANDA 090589
Product Name and Strength:	Rescuject (epinephrine injection, USP) 0.3 mg Rescuject jr. (epinephrine injection, USP) 0.15 mg
Total Product Strength:	0.3 mg/0.3 mL and 0.15 mg/0.3 mL
Product Type:	Single ingredient drug-device combination product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Teva Pharmaceuticals
Panorama #:	2017-13596940 and 2017-13608708
DMEPA Primary Reviewer:	Lissa C. Owens, PharmD
DMEPA Team Leader (Acting):	Sarah K. Vee, PharmD
DMEPA Deputy Director (Acting):	Danielle Harris, PharmD, BCPS

1 INTRODUCTION

This review evaluates the proposed proprietary names [redacted] for ANDA 090589. The proposed proprietary name was submitted by Teva Pharmaceuticals for evaluation on March 8, 2017. The Applicant submitted an external name study, conducted by OptiBrand Rx, Inc., for this product.

1.1 PRODUCT INFORMATION

The following product information is provided in the March 8, 2017 proprietary name submission.

- Intended Pronunciation: [redacted]
- Active Ingredient: Epinephrine
- Indication of Use: Emergency treatment of allergic reactions (Type I) including anaphylaxis
- Route of Administration: Intramuscularly or subcutaneously into the anterolateral aspect of the thigh
- Dosage Form: injection
- Strength: 0.3 mg/0.3 mL and 0.15 mg/0.3 mL
- Dose and Frequency: Single-use injection
- How Supplied: a pack that contains two Auto-Injectors and one Auto-Injector trainer device. They also include a W-clip to clip two auto-injectors together.
- Storage: Store at 20° to 25°C (68° to 77°F);excursions permitted to 15° to 30°C (59° to 86°F). Protect from light

2 DISCUSSION

During the initial steps of the proprietary name review process, the Office of Prescription Drug Promotion (OPDP) did not recommend the use of the proposed proprietary names [redacted] because it would misbrand the proposed product. OPDP provided the following statement:

OPDP objects to the proposed proprietary names [redacted] *The proposed indication for these epinephrine products is for the emergency treatment of allergic reactions, including anaphylaxis. According to the products' draft product labeling, they are intended for immediate administration as emergency supportive therapy only and are not substitutes for immediate medical care. The proposed trade names, however, would misleadingly imply that* [redacted] *and* [redacted] *alone, can completely save or deliver a patient from the dangers of allergic reactions, including anaphylaxis, when such is not the case and is further articulated in the draft labeling accompanying the submission. Additionally, the active ingredient in* [redacted] *and*

(b) (4) is epinephrine, which is a common substance for which the limitations are readily recognized when (b) (4) and (b) (4) are listed by their established names [21 CFR 201.10(c)(3)]. (b) (4) (b) (4)

Please note that the Federal Food, Drug, and Cosmetic Act (FD&C Act) provides that labeling or advertising can misbrand a product if misleading representations are made (See 21 U.S.C. 321(n)). The FD&C Act also provides that a drug is misbranded if its labeling is false or misleading in any particular (21 U.S.C. 352(a)). A proprietary name, which appears in labeling, could result in such misbranding if it is false or misleading, such as by making misrepresentations with respect to safety or efficacy.

DMEPA also concurs with this finding and will not perform a safety assessment of the proposed proprietary names.

3 CONCLUSIONS AND RECOMMENDATIONS

The proposed proprietary names, (b) (4) are unacceptable as they would misbrand the proposed products. The Applicant will be notified of FDA's decision to object to the names via letter.

3.1 COMMENTS TO THE APPLICANT

We have completed our review of the proposed proprietary names, (b) (4) and have concluded that these names are unacceptable for the following reason:

The proposed proprietary names (b) (4) (b) (4)

The proposed indication for these epinephrine products is for the emergency treatment of allergic reactions, including anaphylaxis. According to the products' draft product labeling, they are intended for immediate administration as emergency supportive therapy only and are not substitutes for immediate medical care. The proposed trade names, however, would misleadingly imply that (b) (4) (b) (4) (b) (4). Additionally, the active ingredient in (b) (4) is epinephrine, which is a common substance for which the limitations are readily recognized when (b) (4) are listed by their established names [21 CFR 201.10(c)(3)]. (b) (4) (b) (4)

Please note that the Federal Food, Drug, and Cosmetic Act (FD&C Act) provides that labeling or advertising can misbrand a product if misleading representations are made (See 21 U.S.C. 321(n)). The FD&C Act also provides that a drug is misbranded if its labeling is false or misleading in any particular (21 U.S.C. 352(a)). A proprietary name, which appears in labeling, could result in such misbranding if it is false or misleading, such as by making misrepresentations with respect to safety or efficacy.

If you require additional information on developing proprietary names for drugs, proposing alternative proprietary names for consideration, or requesting reconsideration of our Name decision, we refer you to the draft Guidance for Industry, Best Practices in Developing Proprietary Names for Drugs, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM398997.pdf

Also See the Guidance for Industry, Contents of a Complete Submission for the Evaluation of Proprietary Names, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf and "PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012".

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/s/

LISSA C OWENS
03/22/2017

SARAH K VEE
03/23/2017

DANIELLE M HARRIS
03/23/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 090589

ADMINISTRATIVE and CORRESPONDENCE DOCUMENT(S)

Approval Type: ☒ **FULL APPROVAL** ☐ **TENTATIVE APPROVAL** ☐ **SUPPLEMENTAL APPROVAL (NEW STRENGTH)**

RPM: Jessica Kreger Team Leader:

☐ **PI** ☐ **PII** ☐ **PIII** ☒ **PIV** (*eligible for 180 day exclusivity* ☐ **Yes** ☒ **No**) ☐ **MOU** ☒ **RX or** ☐ **OTC**

ANDA #: 090589 Applicant: Teva Pharmaceuticals USA, Inc.
Established Product Name: Epinephrine Injection USP, 0.3 mg (Auto-Injector) and Epinephrine Injection USP, 0.15 mg (Auto-Injector)

Basis of Submission (RLD): N19-430/EPIPEN AND EPIPEN JR/Mylan Specialty L.P.
Basis Of Submission Discontinued? Yes ☐ No ☒
If yes, has FR published indicating the Agency determined the product was not withdrawn for reasons of safety or effectiveness?
Yes ☐ FR Notice dated _____; Document Citation _____; FR _____(Example: 78 FR 67365)
No ☐ Consult completed but not yet published in FR

(Is ANDA based on an approved Suitability Petition? ☐ Yes ☒ No, if yes, use SP language in template)

Does the ANDA contain REMS? ☐ Yes ☒ No *(If YES, initiate approval action 6 weeks prior to target action date)*

Regulatory Project Manager Evaluation: **Date: 6/29/2018**

☒ Date (Received) Acceptable for Filing -- Date **11/21/2008**

☒ Date last Complete Response (CR) letter was issued -- Date **2/23/2016**

☐ Previously reviewed and tentatively approved (if applicable) --- Date _____

YES	NO		
☒	☐	All submissions have been reviewed and relevant disciplines are adequate and finalized in the platform (Date or N/A)	
		Date of Acceptable Bioequivalence **11/22/2017** • Date of BE Guidance (if any) **12/2016** Date of Acceptable Labeling **6/26/2018** • Date of last RLD labeling update **4/28/2017** Date of Acceptable Quality **8/15/2018** • DMF No(s). **005822** Date(s) Acceptable **8/10/2018** • No outstanding DMF review amendments ☐ • Date of Acceptable Overall Manufacturing Inspection **5/15/2018**	If applicable: Date of Acceptable Microbiology **6/15/2017** Date of Acceptable Clinical Review **N/A** Date of Acceptable Dissolution **N/A** Date of Acceptable REMS **N/A**
☒	☐	**MMA:** All amendments submitted to the Agency on or after December 5, 2016 contain (1) a patent certification or section viii statement, (2) a recertification, or (3) a verification statement per 21 CFR 314.96(d). 6/22/2018 – present, 5/30/2018 – present, 3/8/2018 – present, 3/2/2018 – present, 3/1/2018 – submitted in 3/8/2018 amendment, 2/28/2018 – present, 1/29/2018 – present, 1/26/2018 – present, 1/11/2018 – present, 12/1/2017 – present, 10/6/2017 – present, 7/28/2017 – present, 7/12/2017 – present, 7/12/2017 – present, 6/23/2017 – present, 6/2/2017 – present, 6/2/2017 – present, 5/22/2017 – present, 5/4/2017 – present, 4/19/2017 – present, 4/4/2017 – present, 4/4/2017 – present, 3/31/2017 – present, 3/27/2017 – present, 3/8/2017 – submitted in 7/5/2018 amendment, 1/31/2017 – present, 12/27/2016 – present = MMA for 12/7/2016, 12/7/2016 – found in 12/27/2017 cover letter	
☐	☒	Are consults pending for any discipline?	
☒	☐	OSIS Clinical Endpoint and Bioequivalence Site Inspections are acceptable	
☒	☐	Is there a pending legal or regulatory issue (refer to Policy Alert Tracker)? If YES → OGD Policy Lead confirmed ANDA may proceed ☒; Memo uploaded (if applicable) ☒	
☒	☐	Has there been an amendment providing for a major change in formulation or new strength since filing? If YES→Verify a second filing review was completed (if applicable) and that all disciplines completed new reviews ☒	
☒	☐	Is ANDA a Priority Approval (First generic, drug shortage, PEPFAR, other OGD Communications priorities)? If YES → Email OGD Communications Staff or Division liaison 30 to 60 days prior to approval, Date emailed _____	

Review Discipline/Division and RPM TL Endorsements		
☒	☐	Applicable review discipline/division endorsements completed
☒	☐	RPM Team Leader endorsement completed
Additional Notes (if applicable)		

ANDA APPROVAL ROUTING SUMMARY ENDORSEMENTS AND FINAL DECISION

1. Division of Legal and Regulatory Support Endorsement

Date: 7/27/2018
Name: RTP

Patent/Exclusivity Certification:
☐ **PI** ☐ **PII** ☐ **PIII** ☒ **PIV** ☐ **section viii**
If Paragraph IV Certification- did applicant:
Notify patent holder/NDA holder: Yes ☒ No ☐
Was applicant sued w/in 45 days: Yes ☐ No ☒
Has case been settled: Yes ☐ No ☒
Applicant addressed all listed exclusivities Yes ☒ No ☐

Do the patent and exclusivity certifications align? Yes ☒ No ☐
Have there been any revisions to the use code since the original submission? Yes ☒ No ☐

RLD = **Epipen and EpiPen Jr.** NDA# **19430** ☒ **RX or** ☐ **OTC**
Date Checked in Orange Book#: **7/27/2018**

Type of Letter:
☒ APPROVAL
☐ TENTATIVE APPROVAL
☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH)

LETTER RECOMMENDED FOR DRUGS@FDA Yes ☒ No ☐

Forfeiture Information
Is a forfeiture memo needed for the first applicant: Yes ☐ No ☐
Unknown at this time
If yes, the date forfeiture memo was completed
Date _____ ANDA # _____

180 Day Exclusivity Information
Is applicant eligible for 180 day exclusivity Yes ☒ No ☐
☒ Sole
☐ Shared
ANDA Exclusivity for each strength: Yes ☒ No ☐
Which strength(s) eligible 0.15 mg and 0.3 mg

Comments: BOS= EpiPen and EpiPen Jr, NDA 19430. ANDA 90589 submitted on 12/21/2007 with no relevant patents statement. ANDA ack for filing on 11/21/2008 (LO Date 12/11/2008) for Epinephrine Injection USP, 0.15 mg/0.3 mL and 0.3 mg/0.3 mL auto-injectors. Initially, Teva inadvertently received a PIV acknowledgement letter stating their application contained a PIV certification. On or about December 16, 2008, the error was caught, subsequently on January 2, 2009, a corrected standard acknowledged letter was issued. Acknowledgement for filing date remain unchanged, 11/21/2008. The information and data provided in the original submission dated December 21, 2007, and in the addendum dated May 30, 2008 do not support claims that TEVA' s proposed autoinjector intended for subcutaneous delivery of epinephrine is comparable to the EpiPen Autoinjector. Upon submission of supporting documents, the received date was moved to November 21, 2008. Our records do not reflect that a refuse to receive letter was issued to Teva.
Patent amendment rec'd on 7/20/2009: Teva submitted a PIV certification to the first of five patents listed in OB, the '012 patent (patent issuance date 11/11/2008, patent received date 7/17/2009 (CDER stamp date), patent expiry date 09/11/2025). [30 months from the date a substantially complete application was received, 11/21/2008 + 30 months =Tentative approval date: 05/21/2011]
Patent amendment rec'd on 8/25/2009: In accordance with 21 CFR 314.95(e), Teva provides the (b) (4) delivery receipts to document receipt of notice to Verus Pharmaceuticals, San Diego, CA, signed and delivered on July 21, 2009; King Pharmaceutical, Bristol, TN signed and delivered on July 21, 2009; to Meridian Medical Technologies, Columbia, MD signed

and delivered on July 21, 2009. Copy of notice letter was also provided. Clearance to send the notice by (b) (4) was given to Teva by Ms. Saundra Middleton, OGD, FDA.

Patent amendment rec'd on 9/4/2009: On August 31, 2009, suit filed by King Pharmaceuticals, Inc. and Meridian Medical Technologies, Inc., against Teva Parenteral Medicines, Inc. and Teva Pharmaceuticals USA, Inc. with respect to the '012 patent in the United District Court for the District of Delaware (civil action no 1:09-cv-00652). A copy of compliant was provided. Note, the patent was not listed at the time of Teva's original submission, therefore the '012 patent does not give rise to a statutory 30-month stay of approval of this ANDA.

Patent amendment rec'd on 11/2/2010: PIV certification with respect to the '432 patent (patent issuance dated 9/14/2010, patent receive date 9/15/2010, later-listed patent, patent expiry date 09/11/2025).

Patent amendment rec'd on 11/16/2010: In accordance with 21 CFR 314.95(e), Teva provides the (b) (4) delivery receipts to document receipt of notice to King Pharmaceutical, Bristol, TN signed and delivered on November 2, 2010; to Meridian Medical Technologies in Columbia, MD signed and delivered on November 2, 2010. Copy of notice letter indicates that notice letter was also sent to Verus Pharmaceutical; however, no documentation receipt of notice to Verus Pharmaceuticals was submitted to the Agency.

Patent amendment rec'd on 11/4/2011: Teva informs the Agency that civil action no. 1:09-cv-00652 was amended on November 11, 2010 to include the '432 patent. The amended complaint was filed in the United States District Court for the District of Delaware, within the statutory 45-day period.

Patent amendment rec'd on 12/21/2011: Teva submitted a PIV certification with respect to the '035 patent (patent issuance dated 11/25/2011, patent receive date 11/23/2011, later-listed patent, patent expiry date 09/11/2025).

Patent amendment rec'd on 1/17/2014: Documentation of receipt of notice to Meridian Medical Technologies, Inc. in Columbia, MD signed and delivered on December 22, 2011; to King Pharmaceuticals, Inc. in Bristol, TN signed and delivered on December 22, 2011; and Pfizer Inc in New York, NY signed and delivered on December 22, 2011. On May 1, 2012, Joint Stipulation of Dismissal was entered related to civil action 1:09-cv-00652. All claims and counterclaims asserted in the civil action regarding the '012 and '432 patents were dismissed without prejudice. A copy of the May 1, 2012 Joint Stipulation of Dismissal was provided.

Reformulation and patent amendment rec'd on 12/30/2014: Teva submits a PIV certification to the newly listed '827 patent (patent issuance date 10/28/2014, patent receive date 10/30/2014, later listed patent, patent expiry date 09/11/2025). Furthermore, Teva recertifies to patents '012, '432 and '035 due to a reformulation of the drug product to decrease the amount of sodium metbisulfite (b) (4), add sodium tartrate (b) (4) in accordance with CFR 314.94(a)(9)(iii); and change the device to improve the design to ensure users will not be presented with a device that has delivered the drug product but has not engaged the safety guard. Additionally, to support these changes, new exhibit batches for epinephrine injection USP, 0.15 mg and 0.3 mg were manufactured and submitted. Copies of "first" round of notices along with notice letter to the respective NDA holder and patent owner dated July 21, 2009 were submitted.

Patent amendment rec'd on 03/20/2015: Documentation of receipt of notice to Mylan Specialty L.P., in Basking Ridge, NJ signed and delivered on January 5, 2015; Meridian Medical Technologies, Inc, in Columbia, MD signed and delivered on January 2, 2015; King Pharmaceuticals, Inc., in Bristol, TN signed and delivered on December 31, 2014; Pfizer Inc., in New York, NY signed and delivered on December 31, 2014, and by Mylan Inc., in Canonsburg, PA signed and delivered on December 31, 2014. In accordance with 21 CFR 314.95(f), the first day of the 45-day period provided for in Section 505(j)(4)(B)(iii) of the Act was January 6, 2015, the first day after receipt of the notice. Therefore, the 45-day period ended on February 19, 2015. Teva informs that no suit was filed within the noted 45-day period for any of the patents.

Patent amendment rec'd on 6/23/2017: Teva submitted a PIV certification with respect to the '010 patent (patent issuance date 3/7/2017, patent receive date 5/12/2017, late-listed patent, patent expiry date 09/11/2025)

Patent amendment rec'd on 7/12/2017: Documentation of receipt of notice to Mylan Specialty L.P., in Morgantown, WV signed and delivered on June 26, 2017; Meridian Medical Technologies, Inc, in Columbia, MD signed and delivered on June 26, 2017 and Pfizer Inc., in New York, NY signed and delivered on June 26, 2017.

This ANDA is eligible for immediate Full Approval. Teva provided PIV certifications to all unexpired patents, which were also considered later listed for this ANDA. Teva's original suit and litigation was dismissed without prejudice on May 1, 2012. Teva submitted a reformulation on December 30, 2014 (after the dismissal order was entered) for which Teva recertifies and renotifies to all listed patents at the time of the amendment. On March 20, 2015, Teva informed the Agency they were not sued with the statutory 45-day window.

Teva was the first applicant to file a PIV certification for these drug products on 7/20/2009, a date, after the '012 patent was listed in the OB for EpiPen and EpiPen Jr. To retain eligibility for 180-day exclusivity this ANDA must have been TA'd within 30 months of ANDA submission, on May 21, 2011. This ANDA was not tentatively approved or approved within this time. Therefore, this ANDA will be approved with punt language regarding eligibility for 180-day exclusivity.

180 Day Exclusivity Status/Landscape: see above, Teva is the first filer for both EpiPen and EpiPen JR
Citizen Petitions Impact: see memo for [redacted] (b) (4) new drug application (NDA) 019430 for EpiPen (epinephrine injection), 0.3 mg and EpiPen Jr (epinephrine injection), 0.15 mg. On January 16, 2015, Mylan submitted a citizen petition and a citizen petition supplement dated April 28, 2015 requesting the Agency to take certain actions with respect to Teva's ANDA 090589 for epinephrine auto-injector citing EpiPen as its reference listed drug (RLD). On June 15, 2015, FDA denied Mylan's EpiPen Petition without comment on the merits, as FDA had not made a final determination on whether to approve an application referencing EpiPen. A final determination has been made, please see memo for further details. Additionally, see memo for CP FDA-2017-P-3352- requesting FDA amend the sulfite warning requirement in 21 C.F.R. 201.22 for sulfite-containing epinephrine for injection for use in emergency situations, to remove misleading information and acknowledge the current availability of approved epinephrine products that do not contain sulfite.
First Legally Approvable Date: n/a; all the listed patents are considered later listed for this ANDA and litigation did not create a statutory stay of approval. Therefore, this ANDA would have been eligible for Full Approval as soon as it was scientifically adequate.
If Tentative Approval, anticipated full approval date: n/a

2. Final Decision

Date: 8/16/2018
Name: sgk

ANDA received on **11/21/2008** for the **0.15 mg and 0.3 mg** strengths
RTR'd? Yes ☐ No ☒ If yes, RTR'd on Enter date
Priority Status? Yes ☒ No ☐ If yes, prioritization factor is **First generic/drug shortage**
Basis of Submission (RLD)

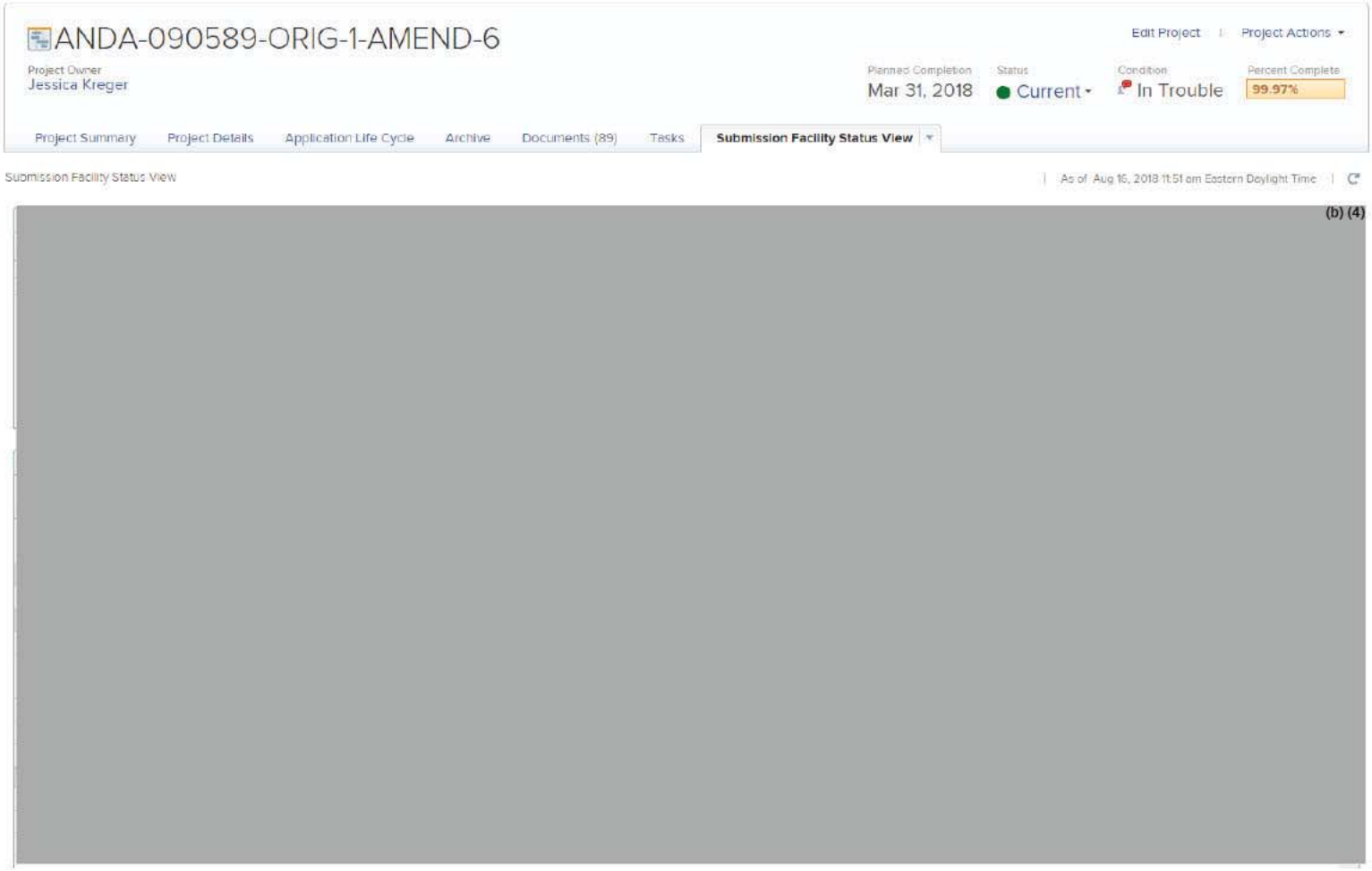
Drug Name	**EpiPen and EpiPen Jr. Auto-Injectors**
NDA #	**019430**
Applicant Name	**Mylan Specialty LP**

☒ Verified the following:

1. Completion of the following endorsement tasks, if applicable:
   a. Division of Legal and Regulatory Support Endorsement
   b. Paragraph IV Evaluation
   c. REMS Endorsement
   d. Quality Endorsement
   e. Bioequivalence Endorsement
   f. Clinical-Bioequivalence Endorsement
   g. Labeling Endorsement
   h. RPM Team Leader Endorsement
2. All applicable endorsement tasks are completed in the platform within 30 days of potential approval.
3. No updates to patents and/or exclusivities in Orange Book since the Division of Legal and Regulatory Support Endorsement
4. No Reference Listed Drug updates at Drugs@FDA since the Labeling Endorsement
5. No issues listed on the current version of the Policy alert list since the RPM Team Leader Endorsement
6. No new alerts in the Submission Facility Status View since the Quality Endorsement
7. Overall Inspection Recommendation of Approve of the current project (see screenshot below)
8. No new DMF amendments since Quality Endorsement
9. No amendments received since the RPM Team Leader Endorsement

This ANDA is ready for **FULL** APPROVAL.

****INCLUDE SNIP OF SUBMISSION FACILITY STATUS VIEW AT THE TIME OF APPROVAL****



Facility Screenshot (by RPM):

REFERENCES / ASSOCIATED DOCUMENTS

4000-LPS-041 Processing Approval and Tentative Approval of an Original ANDA

REVISION HISTORY

Version	Effective date	Name	Role	Summary of changes
01	10/1/2014	Heather Strandberg	Author	New Form
02	10/03/2017	Kevin Denny	Reviser	• Update form to reflect revisions to SOP 4000-LPS-041 Processing Approval and Tentative Approval of an Original ANDA, Version 04 • Remove content adequately captured in the platform • Update information captured in the Division of Legal and Regulatory Support Endorsement section • Other minor administrative corrections to format and content
03	1/24/18	Kevin Denny	Reviser	• Update Final Decision section

ANDA 090589

DISCIPLINE REVIEW LETTER

Teva Pharmaceuticals USA
425 Privet Road
Horsham, PA 19044

Attention: Cory Wohlbach
Senior Director, US Generics

Dear Cory Wohlbach:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on December 21, 2007, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Epinephrine Injection USP, 0.3 mg (Auto-Injector) and Epinephrine Injection USP, 0.15 mg (Auto-Injector).

Reference is also made to any amendments submitted prior to the issuance of this letter.

We have concluded the Labeling review of this ANDA based on your submissions dated October 28, 2016, March 8, 2017 and June 2, 2017 and have identified the following initial deficiencies:

1. GENERAL COMMENTS
    a. Please ensure that your final container label, carton labeling and SPL (STRUCTURED PRODUCT LABELING) appropriately reflect your proposed product without the proprietary name. We note that these label/labeling with proprietary name are currently found in your ANDA as final label/labeling.

    b. On the container label and carton labeling, the illustration for step 2 does not clearly depict the injection site (e.g., the entire leg, including the foot). Revise the illustration to further clarify the proper injection site.

2. CONTAINER LABEL
    a. For the 0.15 mg strength:
    In the section that starts with the statement “After use most of liquid stays in auto-injector and can’t be reused...”, second sentence, remove the ratio expression (1:2000) and revise the strength statement so that it reads “Delivers 0.15 mg intramuscular dose of epinephrine from epinephrine injection USP, 0.15 mg/0.3 mL.”.

b. For the 0.3 mg strength:
In the section that starts with the statement "After use most of liquid stays in auto-injector and can't be reused.", second sentence, remove the ratio expression (1:1000) and revise the strength statement so that it reads "Delivers 0.3 mg intramuscular dose of epinephrine from epinephrine injection USP, 0.3 mg/ 0.3 mL.".

3. CARTON LABELING
   a. On the principal display panel (PDP), remove "xx mg each" following "For Allergic Emergencies (Anaphylaxis)". Refer to RLD labeling.
   b. On the PDP, remove "For intramuscular use" and "For one time use." statements to be same as the RLD labeling.
   c. On the side panel, remove the ratio expression of strength (1:2000 and 1:1000) and revise the strength statement to "xx mg/xx mL" format. Refer to Container Label comments.

4. PATIENT INFORMATION and INSTRUCTIONS FOR USE
   In the title section under PATIENT INFORMATION and under INSTRUCTIONS FOR USE, remove the parenthesis to read "one dose of 0.3 mg epinephrine USP, 0.3 mg/0.3 mL" for the 0.3 mg auto-injector and "one dose of 0.15 mg epinephrine USP, 0.15 mg /0.3 mL" for the 0.15 mg auto-injector. Make the same revision in the applicable section at the end of the INSTRUCTIONS FOR USE.

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

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

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

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

If you would like to respond to these initial deficiencies before the end of this review-cycle, we request a complete written response to this discipline review letter no later than July 6, 2018. We will not process or review a partial response. Facsimile or e-mail responses will also not be accepted. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

DISCIPLINE REVIEW LETTER
LABELING

If you do not submit a complete written response by July 6, 2018, these initial deficiencies may be incorporated in a complete response letter.

Please note that we are providing these preliminary thoughts on possible deficiencies to you before a complete review of your entire application. As contemplated in the Generic Drug User Fee Amendments of 2017 (GDUFA II) Commitment Letter[1], these possible deficiencies do not reflect a complete review of your application and should not be construed as such. In addition, these possible deficiencies do not necessarily reflect input from supervisory levels. You should be aware that these deficiencies may be modified as we complete our review of your entire application.

If you respond to these issues during this review cycle, depending on the timing of your response, we may not be able to consider your response before taking action on your application.

The Electronic Common Technical Document (eCTD) is CDER's standard format for electronic regulatory submissions. Beginning May 5, 2017, ANDAs must be submitted in eCTD format and beginning May 5, 2018, drug master files must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: www.fda.gov/ectd.

If you have any questions, please contact Carrie Lemley, Labeling Project Manager, at Carrie.Lemley@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Carrie Lemley, PMP
Labeling Project Manager
Division of Labeling
Office of Generic Drugs

[1] GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2018-2022 (available at: https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM525234.pdf).

Carrie Lemley

Digitally signed by Carrie Lemley
Date: 6/21/2018 10:17:17AM
GUID: 508da70600028af201b2e3b0a74990bf

MEMORANDUM

REVIEW OF LABEL AND LABELING

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)

Date of This Memorandum:	June 11, 2018
Requesting Office or Division:	Office of Generic Drugs (OGD)/ Office of Regulatory Operations (ORO)/Division of Labeling Review (DLR)
Application Type and Number:	ANDA 090589
Product Name and Strength:	Epinephrine injection, USP 0.3 mg/0.3 mL and 0.15 mg/0.3 mL
Applicant/Sponsor Name:	Teva Pharmaceuticals, Inc.
FDA Received Date:	October 28, 2016
OSE RCM #:	2016-2377
DMEPA Associate Director:	Mishale Mistry, PharmD, MPH

1 PURPOSE OF MEMORANDUM

In a Request for Consultation, dated October 13, 2016, the Division of Labeling Review (DLR)/Office of Regulatory Operations (ORO) in the Office of Generic Drugs (OGD) requested that we review the container labels, carton labeling, and DLR's proposed labeling comments to issue to the applicant for ANDA 090589 (Appendix A) to determine if the proposed labels and labeling were acceptable from a medication error perspective and whether further differentiation was needed between the two proposed strengths. Further, DLR provided additional comments to us via email on November 15, 2016, which requested, among other things, that we review the illustration in step 2 of the proposed label.

2 DISCUSSION

We reviewed the labels and labeling, and we generally agree with the proposed labeling comments included in DLR's original consult dated October 13, 2016. However, with respect to further differentiating the adult and pediatric strengths, as discussed below, we do not think that further differentiation is necessary for the safe use of the product.

In its original consult, DLR specifically requests feedback regarding the adequacy of differentiation between the adult and pediatric strengths in container labels and carton labeling. DLR requested consideration of whether it was necessary to include statements such

as “Adult dose” and “Pediatric dose,” or “Adult Auto Injector” and “Pediatric Auto Injector,” after the established name on the carton labeling. Alternatively, DLR requests consideration of whether weight requirements on the carton labeling would be necessary to further differentiate the adult and pediatric strengths.

We note that the two strengths are differentiated by color in the proposed carton labeling for ANDA 090589 (i.e., green for 0.15 mg/0.3 mL strength product and yellow for the 0.3 mg/0.3 mL strength product), which aligns with the colors used by the RLD to differentiate the EpiPen and EpiPen Jr. strengths. However, we note that the proposed product will not include the term ‘Jr.’ with respect to the 0.15 mg/0.3 mL strength, whereas the RLD uses the proprietary name “EpiPen Jr.” for this strength. Although we agree that the inclusion of patient weight information on the carton labeling for each strength (e.g., “FOR ALLERGIC EMERGENCIES in patients weighing over 66 lbs” for the 0.3 mg/0.3 mL strength and “FOR ALLERGIC EMERGENCIES in patients weighing 33 lbs to 66 lbs” for the 0.15 mg/0.3 mL strength[1]) would further differentiate the two strengths, we note this information is not included in the RLD labeling. We do not think that this information is necessary for the safe use of the product, particularly because the Applicant proposes to differentiate the two strengths using the same carton and container coloring scheme as the RLD. As a result, we do not think that the proposed labels and labeling for ANDA 090589 require additional labeling statements to further differentiate the two strengths from a safety perspective.

In addition, upon review of the illustration on the container label and carton labeling demonstrating the location to inject, we note that the illustration does not distinctly indicate the outer thigh. We agree with DLR in that the proposed picture may not clearly depict the location of the injection site and may cause confusion. The illustration should clearly depict the injection site. One example is by depicting the full leg, including the foot, similar to the illustration provided in the RLD labels and labeling. We recommend that the Applicant revise the illustration to further clarify the proper injection site.

3 CONCLUSION

We note that the proposed labels and labeling should be clarified with respect to the depiction of the injection site. The illustration in Step 2 of the proposed product does not clearly indicate the outer thigh. We recommend that the illustration clearly depict the injection site (e.g. the entire leg, including the foot) to avoid confusion. Therefore, we agree with DLR that the applicant should revise the illustration to address this concern.

[1] We note that the carton labeling for Auvi-Q (epinephrine injection, USP) 0.3 mg, 0.15 mg, and 0.1 mg, Auto-Injector under new drug application (NDA) 201739 includes similar patient weight information. See Approved Labeling for NDA 201739/S-008, 009 (Nov. 17, 2017).

APPENDIX A. DIVISION OF LABELING REVIEW CONSULT

Initial Recommendations by OGD/DLR

Epinephrine
ANDA Consult a...

http://darrts.fda.gov:9602/darrts/ViewDocument?documentId=090140af80409221&showAsPdf=true

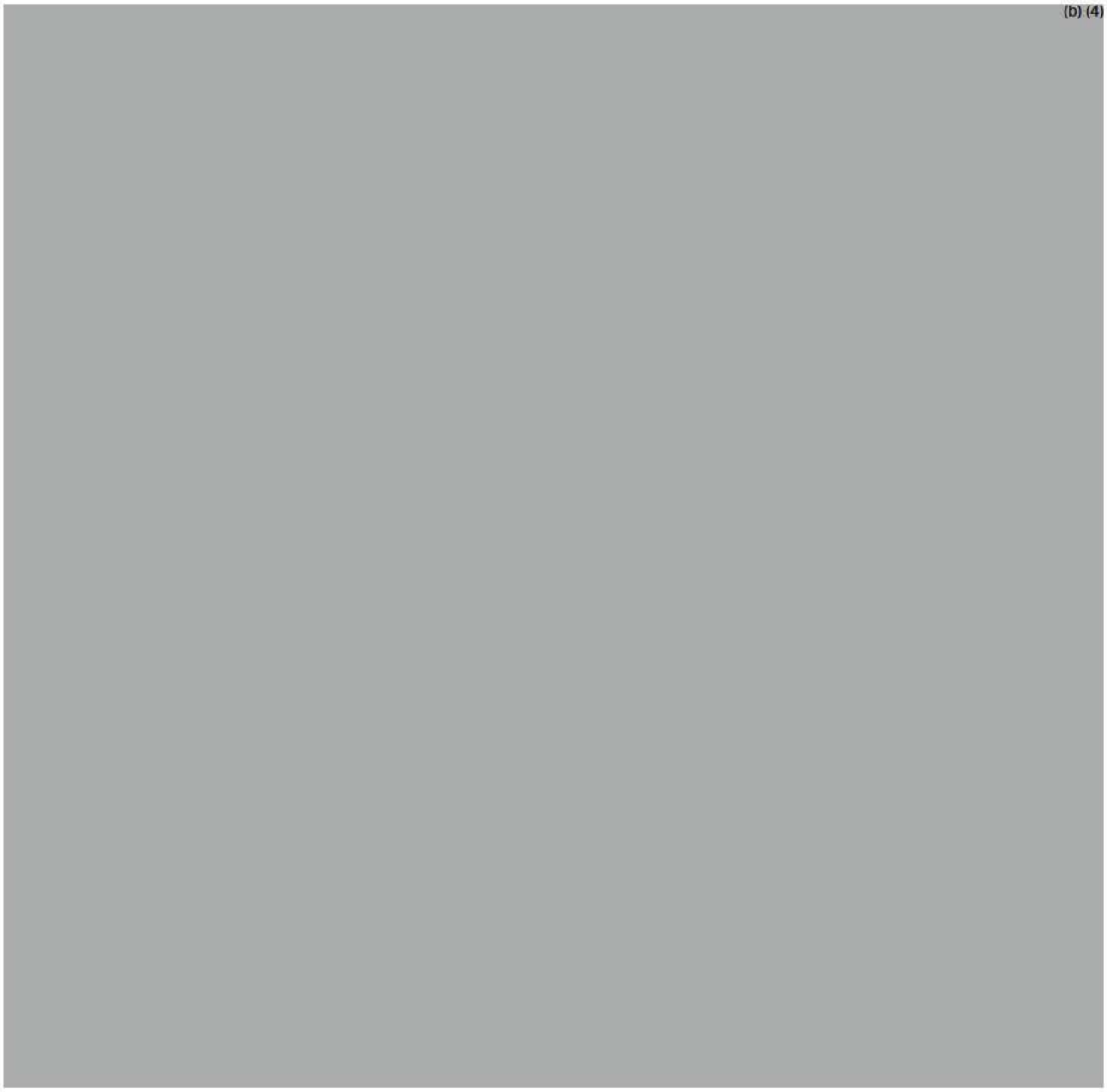
OGD/DLR provided the following updated comments regarding the original 10/13/2016 consult from OGD/DLR based on the revised labels and labeling submitted by the Applicant on October 28, 2016, after OGD/DLR sent the original consult:

1. Please note that applicant provided labeling amendment on 10/28/2016. We would like to inform you that the applicant provided revised labeling to be in accordance with recently revised RLD labeling NDA 019430/s-061 approved May 18, 2016. We find that the revision is consistent with the RLD labeling update. Although the applicant did not yet receive the deficiency comments that were sent to you with the consult request on 10/11/2016, their labeling amendment addresses those comments also.
2. Please note that the applicant provided further product differentiation by revising the carton color from white to green (0.15 mg/0.3 mL strength) and to yellow (0.3 mg/0.3 mL strength). However, as requested in our consult to you, further written differentiation may be needed in place of "Jr" designated for the lower strength in the RLD labeling.
3. We note that the picture of the leg in the container and carton labeling does not include a foot. This is not a change from the previously proposed labeling, however upon further review of the illustration, we note that the proposed picture may not clearly depict the location of the injection site versus the illustration provided in the RLD labeling. We would appreciate your comment on the applicant's proposed illustration.

APPENDIX B. IMAGES OF LABEL AND LABELING RECEIVED ON OCTOBER 28, 2016

Container labels

(b) (4)



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

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

/s/

MISHALE P MISTRY
06/11/2018

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

ANDA 090589

INFORMATION REQUEST

Teva Pharmaceuticals USA, Inc.
Attention: Cory Wohlbach
425 Privet Road
Horsham, PA 19044

Dear Sir:

Please refer to your Abbreviated New Drug Application (ANDA) dated December 21, 2007, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act) for Epinephrine Injection USP, 0.15 mg and 0.3 mg.

We are reviewing the Quality section of your submission and have the following comments and information requests. We request a prompt written response, no later than June 14, 2018, in order to continue our evaluation of your ANDA.

1. (b) (4)

2.

3.

4. (b) (4)

5.

6.

7.

Send your submission through the Electronic Submission Gateway http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/default.htm. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

INFORMATION REQUEST
QUALITY/Drug Product

If you have any questions, please contact Jennifer Nguyen, Regulatory Business Process Manager, at (240) 402-8729.

Sincerely,

{See appended electronic signature page}

Jennifer Nguyen
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Jennifer Nguyen

Digitally signed by Jennifer Nguyen
Date: 5/14/2018 01:42:51PM
GUID: 5293935b0000d4f769fa5b7ff58fbb74

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

ANDA 090589

INFORMATION REQUEST

Teva Pharmaceuticals USA, Inc.
Attention: Cory Wohlbach
425 Privet Road
Horsham, PA 19044

Dear Sir:

Please refer to your Abbreviated New Drug Application (ANDA) dated December 21, 2007, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act) for Epinephrine Injection USP, 0.15 mg and 0.3 mg.

We are reviewing the Quality section of your submission and have the following comments and information requests. We request a prompt written response, no later than February 28, 2018, in order to continue our evaluation of your ANDA.

A. Deficiencies

1. (b) (4)

2.

3.

(b) (4)

4.

5.

6.

7.

8.

B.

1.

Send your submission through the Electronic Submission Gateway http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/default.htm. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

INFORMATION REQUEST
QUALITY/Drug Product

If you have any questions, please contact Jennifer Nguyen, Regulatory Business Process Manager, at (240) 402-8729.

Sincerely,

{See appended electronic signature page}

Jennifer Nguyen
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Jennifer Nguyen

Digitally signed by Jennifer Nguyen
Date: 1/31/2018 08:58:48AM
GUID: 5293935b0000d4f769fa5b7ff58fbb74

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

ANDA 090589

INFORMATION REQUEST

Teva Pharmaceuticals USA, Inc.
Attention: Cory Wohlbach
425 Privet Road
Horsham, PA 19044

Dear Sir:

Please refer to your Abbreviated New Drug Application (ANDA) dated December 21, 2007, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act) for Epinephrine Injection USP, 0.15 mg and 0.3 mg.

We are reviewing the Quality section of your submission and have the following comments and information requests. We request a prompt written response, no later than January 29, 2018 in order to continue our evaluation of your ANDA.

Send your submission through the Electronic Submission Gateway http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/default.htm. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

INFORMATION REQUEST
QUALITY/CDRH

If you have any questions, please contact Jennifer Nguyen, Regulatory Business Process Manager, at (240) 402-8729.

Sincerely,

{See appended electronic signature page}

Jennifer Nguyen
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Jennifer Nguyen

Digitally signed by Jennifer Nguyen
Date: 1/26/2018 11:51:29AM
GUID: 5293935b0000d4f769fa5b7ff58fbb74

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

ANDA 090589

INFORMATION REQUEST

Teva Pharmaceuticals USA, Inc.
Attention: Cory Wohlbach
425 Privet Road
Horsham, PA 19044

Dear Sir:

Please refer to your Abbreviated New Drug Application (ANDA) dated December 21, 2007, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act) for Epinephrine Injection USP, 0.15 mg and 0.3 mg.

We are reviewing the Quality section of your submission and have the following comments and information requests. We request a prompt written response, no later than January 11, 2018 in order to continue our evaluation of your ANDA.

(b) (4)

[redacted]

Send your submission through the Electronic Submission Gateway http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/default.htm. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

INFORMATION REQUEST
QUALITY/CDRH

If you have any questions, please contact Jennifer Nguyen, Regulatory Business Process Manager, at (240) 402-8729.

Sincerely,

{See appended electronic signature page}

Jennifer Nguyen
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Jennifer Nguyen

Digitally signed by Jennifer Nguyen
Date: 1/09/2018 02:19:22PM
GUID: 5293935b0000d4f769fa5b7ff58fbb74

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADM NISTRATION	REQUEST FOR CONSULTATION

TO *(Division/Office)*:	FROM:
Sarah Yim, M.D. Division of Clinical Review Office of Bioequivalence Office of Generic Drugs	Harikrishna Devalapally, Ph.D. Through Nilufer M. Tampal, Ph.D. Director, Division of Bioequivalence III (DBIII) Office of Bioequivalence Office of Generic Drugs

DATE	IND NO.	ANDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
September 25, 2017	N/A	090589	Bioequivalence Review	April 19, 2017

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Epinephrine Injection USP (Auto-Injector) 0.15 mg/0.3 mL & 0.3 mg/0.3 mL	High	Bronchodilator	November 30, 2017

NAME OF FIRM: Teva Pharmaceuticals USA, Inc.

REASON FOR REQUEST

I. GENERAL

☐ NEW PROTOCOL	☐ PRE--NDA MEETING	☐ RESPONSE TO DEFICIENCY LETTER
☐ PROGRESS REPORT	☐ END OF PHASE II MEETING	☐ FINAL PRINTED LABELING
☐ NEW CORRESPONDENCE	☐ RESUBMISSION	☐ LABELING REVISION
☐ DRUG ADVERTISING	☒ SAFETY/EFFICACY	☐ ORIGINAL NEW CORRESPONDENCE
☐ ADVERSE REACTION REPORT	☐ PAPER NDA	☐ FORMULATIVE REVIEW
☐ MANUFACTURING CHANGE/ADDITION	☐ CONTROL SUPPLEMENT	☐ OTHER *(SPECIFY BELOW)*:
☐ MEETING PLANNED BY		

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

☐ DISSOLUTION	☐ DEFICIENCY LETTER RESPONSE
☐ BIOAVAILABILTY STUDIES	☐ PROTOCOL-BIOPHARMACEUTICS
☐ PHASE IV STUDIES	☒ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL	☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES	☐ SUMMARY OF ADVERSE EXPERIENCE
☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)	☐ POISON RISK ANALYSIS
☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP	

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Background:

DBIII is reviewing the generic application submitted by Teva Pharmaceuticals USA, Inc. for Epinephrine Injection USP (Auto-Injector), 0.15 mg/0.3 mL, 0.3 mg/0.3 mL (ANDA 090589) referencing EpiPen® (epinephrine) Injection (Auto-Injector), for intramuscular and subcutaneous use. There are no approved generics and pending applications referencing this RLD.

In the original submission dated 12/21/2007, the firm requested the waiver of *in vivo* bioequivalence (BE) study requirements under 21 CFR § 320.22(b)(1) for its test product, Epinephrine Injection USP, 0.15 mg/0.3 mL (Auto Injector Jr.) and 0.3 mg/0.3 mL (Auto Injector). Since the drug product is an autoinjector, in addition to the formulation comparison, the firm was asked to demonstrate device similarity by *in vitro* comparative performance tests for approval of this drug product[1]. The firm has provided the comparative summary results of the performance parameters between the test and RLD devices on 5/30/2008. In 2014, the firm reformulated its test product and submitted the component and composition of the re-formulated test product in the amendment dated 12/30/2014,. The firm has also submitted the results of *in vitro* BE studies comparing the reformulated test product lot and RLD product lots. The *in vitro* study results that were submitted by Teva were conducted on single lot (30 units) of test product and 3 lots (10 units of each lot) of reference product. At the time of the review of the *in vitro* study results, Agency did not have specific recommendations for the statistical criteria of the *in vitro* study data. Therefore, the BE statistical analysis was based on the 90% confidence intervals of the T/R ratios being within the limits of 80.00%-120.00% (since the data from the multiple lots of the test product are needed to determine the 'between-lot variability' for PBE analysis, the reviewer did not perform PBE analysis at that time)[2]. The test and RLD devices comparison data submitted for different tests were deemed acceptable from the bioequivalence perspective prior to the posting of the product-specific guidance on Epinephrine Injection (Auto-Injector)[3].

In December 2016, the Agency drafted new product-specific guidance on Epinephrine Injection[4]. As per the current draft guidance recommendation for this drug product, the following *in vitro* studies should be conducted for the demonstration of bioequivalence between the test and reference products:

- Delivered Volume
- Ejection Time
- Trigger Force
- Extended Needle Length
- Needle integrity post-injection

At least three batches each of the test and reference products, with no fewer than 10 units from each batch should be used in conducting the above in vitro tests. Therefore, based on the current bioequivalence recommendations for this drug product, the firm's *in vitro* studies were deemed inadequate. The firm was asked to re-conduct *in vitro* tests to document the performance characteristics and submit the data for evaluation through information request[5]. In response to the information request,

[1] DARRTS for ANDA 090589: TAMPAL, NILUFER M 03/11/2010 N/A 03/11/2010 REV-BIOEQ-01(General Review) Original-1 Archive

[2] GDRP for ANDA 090589- Bioequivalence Review- http://panorama fda.gov/PanoramaDocMgmt/document/download/090026f880ae507f , Suman Dandamudi, 7/2/2015

[3] GDRP for ANDA 090589- Bioequivalence Review- http://panorama fda.gov/PanoramaDocMgmt/document/download/090026f880ae507f , Suman Dandamudi, 7/2/2015

[4] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM534133.pdf, Recommended December 2016

[5] GDRP ANDA-090589-ORIG-1-AMEND-6, BE review: http://panorama.fda.gov/task/view?ID=5420f1160002bc9df9be4d40027ff2e6, Suman Dandamudi, A09058N006DB_ADD12302014; Date uploaded 1/25/2017

the firm conducted studies as per the guidance and submitted the results of the comparative performance testing of the test and RLD devices in the amendment dated April 19th, 2017. The in vitro equivalence tests were conducted using three lots of the test and RLD products with 20 units from each lot of both strengths. Delivered volume and extended needle length passed PBE analysis. However, PBE analysis results of ejection time and trigger force (activation force) data shows that the test device is not statistically equivalent to the reference device.

Since both ejection time and trigger force data failed to meet PBE analysis criteria, DBIII requested a meeting with the management of the Office of Bioequivalence (OB) and Office of Research and Standards (ORS) to discuss whether to accept or ask the firm to repeat these two in vitro studies[6].

(b) (4)

(b) (4) The fluid ejection time (dispense time) of the test product is within the RLD specification (NMT (b) (4)) for both the adult and junior devices. The difference in ejection time between the test and reference devices is approximately (b) (4). As the mean fluid ejection time differences are small and also shorter ejection time of test product will not have impact on clinical outcome, meeting attendees recommended ejection time study to be acceptable from BE perspective.

Issue:

(b) (4)

It should be noted that the trigger force (activation force) of the test product is within the RLD specification (b) (4) for both the adult and junior devices. The firm provided the following justification for considering the trigger force to be acceptable inspite of the observed differences between the test and reference products: *Irrespective of statistic equivalence, when used as intended, a* (b) (4) *difference in activation force will be imperceptible to the user. The test device distributions fall well within the historical reference device distribution. From the user perspective, a small difference in activation force does not prevent use of the product and therefore the test and reference product are considered equivalent.*

(b) (4)

[6] GDRP, ANDA-090589-ORIGI-1-AMEND-6, Meeting minutes review, http://panorama fda.gov/task/view?ID=5420f1160002bc9df9be4d40027ff2e6, Suman Dandamudi, 9/15/2017

(b) (4)

It should be noted that the DBIII had a meeting with the management of OB and ORS to discuss in vitro study results submitted by the firm specifically Ejection Time and Trigger Force studies. In this meeting dated 06/12/2017, attendees concluded that the clinical significance of the observed statistical difference in trigger force should be further evaluated by a medical officer.

Consult Request:

Based on the above-mentioned information, the Division of Bioequivalence III (DBIII) is seeking expert opinion from the Division of Clinical Review (DCR) in the Office of Bioequivalence (OB) on the following:

> Does the slightly greater force needed to activate the test device compared to reference device raise any safety or efficacy concern for the test product?

Attachment:
In Vitro BE Study Report

PD-RPT-0142_
PD-PLN-0015_€Teva™

Thank you for your consideration. Please address comments/questions to nilufer.tampal@fda.hhs.gov

SIGNATURE OF REQUESTER Harikrishna Devalapally, Ph.D.	METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

[7] GDRP, ANDA-090589-ORIGI-1-AMEND-6, http://panorama.fda.gov/task/view?ID=5420f1160002bc9df9be4d40027ff2e6, A090589DB_NA04192017.doc, Uploaded by Suman Dandamudi on 09/15/2017

ANDA 090589

INFORMATION REQUEST

Teva Pharmaceuticals USA, Inc.
Attention: Cory Wohlbach (Cory.Wohlbach@tevapharm.com)
Director, Regulatory Affairs
425 Privet Road
Horsham, PA 19044

Dear Sir:

Please refer to your Abbreviated New Drug Application (ANDA) dated December 21, 2007, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act for Epinephrine Injection USP, 0.15 mg and 0.30 mg.

We are reviewing the Quality sections of your submission and have the following comments and information requests. We request a prompt written response, no later than **October 06, 2017**, in order to continue our evaluation of your ANDA.

A. Chemistry Deficiencies:

1. (b) (4)
2.
3.
4.

5. (b) (4)

6.

7.

8.

B. Device Comment:

1. (b) (4)

C. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Please acknowledge your awareness that USP <231> will be obsolete and replaced by USP <232/233> as of January 1, 2018. We expect you to comply with USP <232/233> as of January 1, 2018.

Please send your submission through the Electronic Submission Gateway http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/default.htm. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

INFORMATION REQUEST
QUALITY

If you have any questions, please contact Ankara "Nikki" Yokum, Regulatory Business Process Manager at (240) 402-8838 or Ankara.Yokum@fda.hhs.gov.

Sincerely,

Ankara "Nikki" Yokum, PharmD
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Ankara (Nikki) Yokum

Digitally signed by Ankara (Nikki) Yokum
Date: 9/06/2017 03:43:51PM
GUID: 52fbf0da000298b6e0a1d3ba6e6cee85

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

ANDA 090589

INFORMATION REQUEST

Teva Pharmaceuticals USA, Inc.
Attention: Cory Wohlbach
425 Privet Road
Horsham, PA 19044

Dear Sir:

Please refer to your Abbreviated New Drug Application (ANDA) dated December 21, 2007, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act for Epinephrine Injection USP, 0.15 mg and 0.30 mg.

We are reviewing the Quality sections of your submission and have the following comments and information requests. We request a prompt written response, no later than **July 14, 2017**, in order to continue our evaluation of your ANDA.

After review of your justification for the sample size of the reliability protocol we have the following information requests:

1. (b) (4)
2.
3.
4.

If you do not submit a complete response by July 14, 2017, the review will be closed and the listed deficiencies will be incorporated in a COMPLETE RESPONSE correspondence.

All items listed on this Information Request shall be addressed in its entirety, any partial or incomplete response will not be reviewed and the same deficiency list will be issued to you again as part of the Complete Response Letter issued by OGD. Please note that a commitment to address an item in the future is not considered satisfying the Information Request.

Please send your submission through the Electronic Submission Gateway http://www fda.gov/ForIndustry/ElectronicSubmissionsGateway/default htm. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

INFORMATION REQUEST
QUALITY

If you have any questions, please contact Jennifer Nguyen, Regulatory Business Process Manager at (240) 402-8729.

Sincerely,

{See appended electronic signature page}

Jennifer H. Nguyen, PharmD
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Jennifer Nguyen

Digitally signed by Jennifer Nguyen
Date: 7/10/2017 07:49:06PM
GUID: 5293935b0000d4f769fa5b7ff58fbb74

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

ANDA 090589

INFORMATION REQUEST

Teva Pharmaceuticals USA, Inc.
Attention: Cory Wohlbach
425 Privet Road
Horsham, PA 19044

Dear Sir:

Please refer to your Abbreviated New Drug Application (ANDA) dated December 21, 2007, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act for Epinephrine Injection USP, 0.15 mg and 0.30 mg.

We are reviewing the Quality sections of your submission and have the following comments and information requests. We request a prompt written response, no later than **July 12, 2017**, in order to continue our evaluation of your ANDA.

As a follow up to the Information Request letter sent on March 22, 2017 and response received on March 27, 2017, please provide the following information:

1. Who is the owner of the design history file and what is the location?
2. Summarize the Procedures/SOP for Process/Design Change for a validated product.
3. Provide a description of the applicant organizational structure.

If you do not submit a complete response by July 12, 2017, the review will be closed and the listed deficiencies will be incorporated in a COMPLETE RESPONSE correspondence.

All items listed on this Information Request shall be addressed in its entirety, any partial or incomplete response will not be reviewed and the same deficiency list will be issued to you again as part of the Complete Response Letter issued by OGD. Please note that a commitment to address an item in the future is not considered satisfying the Information Request.

Please send your submission through the Electronic Submission Gateway http://www fda.gov/ForIndustry/ElectronicSubmissionsGateway/default htm. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

INFORMATION REQUEST
QUALITY

If you have any questions, please contact Jennifer Nguyen, Regulatory Business Process Manager at (240) 402-8729.

Sincerely,

{See appended electronic signature page}

Jennifer H. Nguyen, PharmD
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Jennifer
Nguyen

Digitally signed by Jennifer Nguyen
Date: 7/07/2017 04:03:20PM
GUID: 5293935b0000d4f769fa5b7ff58fbb74

Internal Meeting Minutes

Date: June 12, 2017
Time: 1:00 PM – 2:00 PM
Meeting Location: Bldg. 75, Room 5500

Drug Product: Epinephrine Injection USP (Auto-Injector), 0.15 mg/0.3 mL, 0.3 mg/0.3 mL

RLD: EpiPen® (epinephrine) Injection (Auto-Injector), 0.15 mg/0.3 mL and 0.3 mg/0.3 mL (NDA 019430 by Mylan Speclt, Approved on December 22, 1987)

Attendees:
Office of Bioequivalence (OB)
Dale Conner, Pharm. D., Director, OB
Nilufer Tampal, Ph.D., Director, Division of Bioequivalence (DB) III
Ke Ren, Ph.D., Associate Director, DBIII
Suman Dandamudi, Ph.D., Acting Team Leader, DBIII
Harikrishna Devalapally, Ph.D., Reviewer, DBIII (*Presenter*)
Issa Nesheiwat, Pharm. D., Project Manager, DBIII (Meeting Recorder)

Office of Regulatory Science (ORS)
Xiaohui Jiang, Ph.D., Chemist, ORS
Lanyan Fang, Ph.D., Acting Team Leader, DQMM
Markham Luke, MD., Supervisory Medical Officer, DTP
Liang Zhao, MD., Supervisory Pharmacologist, DQMM
Myong-Jin Kim, MD., Supervisory Interdisciplinary, DQMM
Denise Conti, Ph. D., Visiting Associate, DTP
Meng Hu, Ph.D., Staff Fellow, DQMM
Kimberly Witzmann, MD., Medical Officer, DTP

Purpose:

The Division of Bioequivalence III (DBIII) requested a meeting with the management of the Office of Bioequivalence (OB) and Office of Research and Standards (ORS) to discuss in vitro study results submitted by the firm specifically Ejection Time and Trigger Force studies.

Background:

DBIII is reviewing the generic application submitted by Teva Pharmaceuticals USA, Inc. for Epinephrine Injection USP (Auto-Injector), 0.15 mg/0.3 mL, 0.3 mg/0.3 mL (ANDA 090589) referencing EpiPen® (epinephrine) Injection (Auto-Injector), for intramuscular and subcutaneous use. EpiPen® Injection (Auto-Injector) contains epinephrine, a non-selective alpha and beta-adrenergic receptor agonist, indicated in the emergency treatment of allergic reactions (Type I) including anaphylaxis. To date, FDA has approved 4 epinephrine auto-injectors: EpiPen®, Twinject®, Adrenaclick®, and Auvi-Q®. Twinject® is no longer marketed. Auvi-Q® was voluntarily recalled by the manufacturer in October 2015. EpiPen® is being marketed and has the large majority of market share at this time. The application holder of Adrenaclick has chosen to market Adrenaclick without a trade name, i.e., as an 'authorized generic' to Adrenaclick. As of 9/25/2017, based on the Orange Book and DARRTS database search there are no approved generics and pending applications referencing this RLD.

In the original submission dated 12/21/2007, the firm requested the waiver of *in vivo* bioequivalence (BE) study requirements under 21 CFR § 320.22(b)(1) for its test product, Epinephrine Injection USP, 0.15 mg/0.3 mL (Auto Injector (b) (4)) and 0.3 mg/0.3 mL (Auto Injector). The original application was accepted for filing on 11/21/2008[1]. Since, the drug product is an autoinjector, in addition to the formulation comparison, device similarity by *in vitro* comparative performance should be demonstrated for approval of this drug product. The firm has provided the comparative summary results of the performance parameters between the test and RLD devices on 5/30/2008. In 2014, the firm reformulated its test product and submitted the component and composition of the reformulated product in the amendment dated 12/30/2014. The re-formulated test product was found to be not qualitatively (Q1) and quantitatively (Q2) the same as reference product. The test product contains sodium tartrate dihydrate (b) (4) (b) (4). The firm has re-submitted the results of *in vitro* BE studies comparing the reformulated test lot with RLD product. The studies were conducted on single lot (30 units) of test product and 3 lots (10 units of each lot) of reference product.[2, 3] At the time of the review of the *in vitro* study results, Agency did not have specific recommendations for the statistical criteria of the *in vitro* study data. Therefore, the BE statistical analysis was based on the 90% confidence intervals of the T/R ratios being within the limits of 80.00%-120.00% (since the data from the multiple

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[1] DARRTS for ANDA 090589: MARGAND, IAIN, 01/02/2009, MAIL, 01/02/2009, COR-ANDAFILE-01(Filing Acknowledgment (General)), Original-1

[2] GDRP for ANDA 090589- Bioequivalence Review- http://panorama.fda.gov/PanoramaDocMgmt/document/download/090026f880ae507f , Suman Dandamudi, 7/2/2015

[3] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM534133.pdf, Recommended December 2016

lots of the test product are needed to determine the 'between-lot variability' for PBE analysis, the PBE analysis did not perform at that time).[4] In December 2016, the Agency posted new product-specific guidance on Epinephrine Injection. As per the current draft guidance recommendation for this drug product, the following *in vitro* studies should be conducted for the demonstration of bioequivalence between the test and reference products:

- Delivered Volume
- Ejection Time
- Trigger Force
- Extended Needle Length
- Needle integrity post-injection

At least three batches each of the test and reference products, with no fewer than 10 units from each batch should be used in conducting the above in vitro tests. Method validation should be performed using the reference product, and the lot number(s) for the reference products used for the validation should be provided. Therefore, based on the current bioequivalence recommendations for this drug product, the firm was asked to conduct *in vitro* tests to document the performance characteristics and submit the data for evaluation through information request[5]. In response to the information request, the firm submitted the results of the comparative performance testing of the test and RLD devices in the amendment dated April 19th, 2017. PBE analysis results of ejection time and trigger force data showed that the test device is not statistically equivalent to the reference device.

Question:

The discussion of the meeting focused on the following key questions:

- (b) (4)
-

Study Details:

The *in vitro* studies which require PBE analysis only were presented for discussion in the meeting. The firm used 3 lots of 20 units each (total 60) of adult and junior devices of test and reference products.

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[4] GDRP for ANDA 090589- Bioequivalence Review- http://panorama.fda.gov/PanoramaDocMgmt/document/download/090026f880ae507f , Suman Dandamudi, 7/2/2015

[5] GDRP ANDA-090589-ORIG-1-AMEND-6, BE review: http://panorama.fda.gov/task/view?ID=5420f1160002bc9df9be4d40027ff2e6, Suman Dandamudi, A09058N006DB_ADD12302014; Date uploaded 1/25/2017

Delivered Volume:

Testing was performed on 20 Adult and Junior epinephrine devices of three lots of both the test and reference products. (b) (4)

(b) (4)

The mean delivered volume from the test and reference product adult and junior devices are comparable. (b) (4)

(b) (4) Thus, the test product auto-injector device is similar to the reference product auto-injector device for delivered volume.

Extended Needle Length:

Testing was performed on 20 Adult and Junior epinephrine devices of three lots of both AJ E and EpiPen Devices for exposed needle length. (b) (4)

(b) (4)

(b) (4)

(b) (4). Thus, the test product auto-injector device is similar to the reference product auto-injector device for exposed needle length.

Ejection Time:

Testing was performed on 20 Adult and Junior epinephrine devices of three lots of both AJ E and EpiPen Devices for fluid ejection time. (b) (4)

(b) (4)

(b) (4)

(b) (4) The fluid ejection time (dispense time) of the test product is within the RLD specification (NMT (b) (4)) for both the adult and junior devices. The 95% upper bound of ejection time for adult (b) (4)) and junior (b) (4) device are greater than 0 (PBE criterion is 95% upper bound must be ≤0). Thus, the test product auto-injector device is **statistically not equivalent** to the reference product auto-injector device for fluid ejection time. Please also note that mean T/R ratios of fluid ejection time for adult and junior devices are not within (b) (4).

Trigger Force:

Trigger force testing was performed on 20 Adult and Junior epinephrine devices each of three lots of both AJ E and EpiPen Devices. (b) (4)

(b) (4)

[redacted]

[redacted]. The trigger force (activation force) of the test product is within the RLD specification [redacted] for both the adult and junior devices. Based on the PBE statistical analysis, the 95% upper bound of trigger force for adult [redacted] and junior [redacted] device are greater than 0 (PBE criterion is 95% upper bound must be ≤0). Therefore, the test product auto-injector device is **statistically not equivalent** to the reference product auto-injector device for trigger force. Please also note that the mean T/R ratios of trigger force for adult and junior devices are not within [redacted].

Review of the basis for the current recommendations:

The discussion was focused mainly on two *in vitro* studies (ejection time and trigger force) which failed PBE analysis.

[redacted] The fluid ejection time (dispense time) of the test product is within the RLD specification (NMT [redacted])[6] for both the adult and junior devices. The difference in ejection time between the test and reference devices is approximately [redacted] only. Since the ejection time for the test device was slightly faster than for the reference device in the tested populations, the firm has provided the following justification: *The data for ejection time are considered, [redacted]) for the test product vs [redacted]) for reference product, the differences while statistically significant in these populations are not of clinical significance for the use of the product. Prompt administration of epinephrine for pre-hospital self-management of anaphylaxis is of utmost importance to achieve successful outcomes. This fact has been supported with numerous clinical experiences and literature articles. From the data presented in this report, the test product ejection time is marginally shorter than the reference product. Given the fact that rapid treatment with epinephrine is a key component to successful patient outcomes, this extremely small difference [redacted] resulting in shorter ejection time, will not be clinically meaningful.*

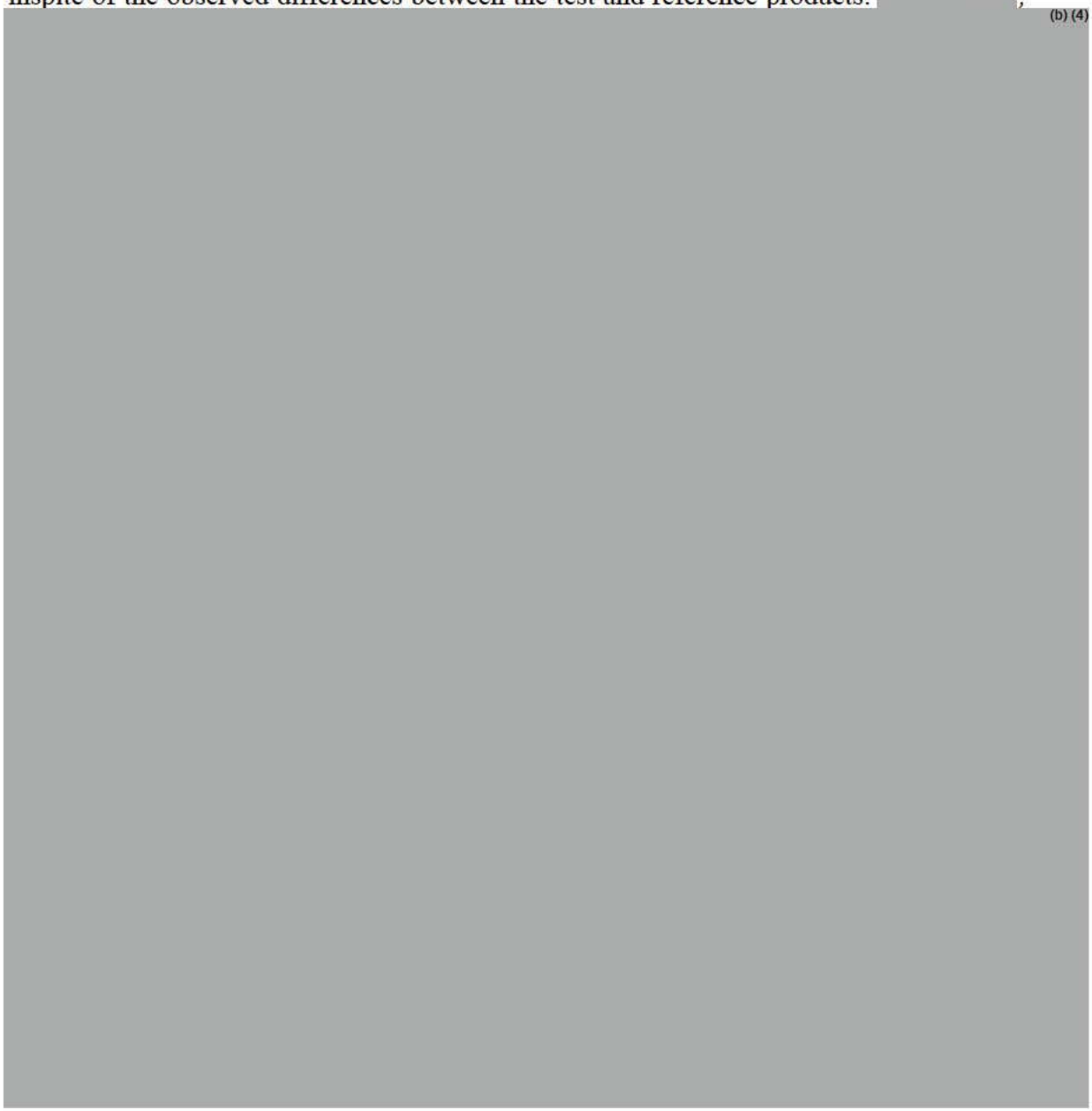
[redacted]

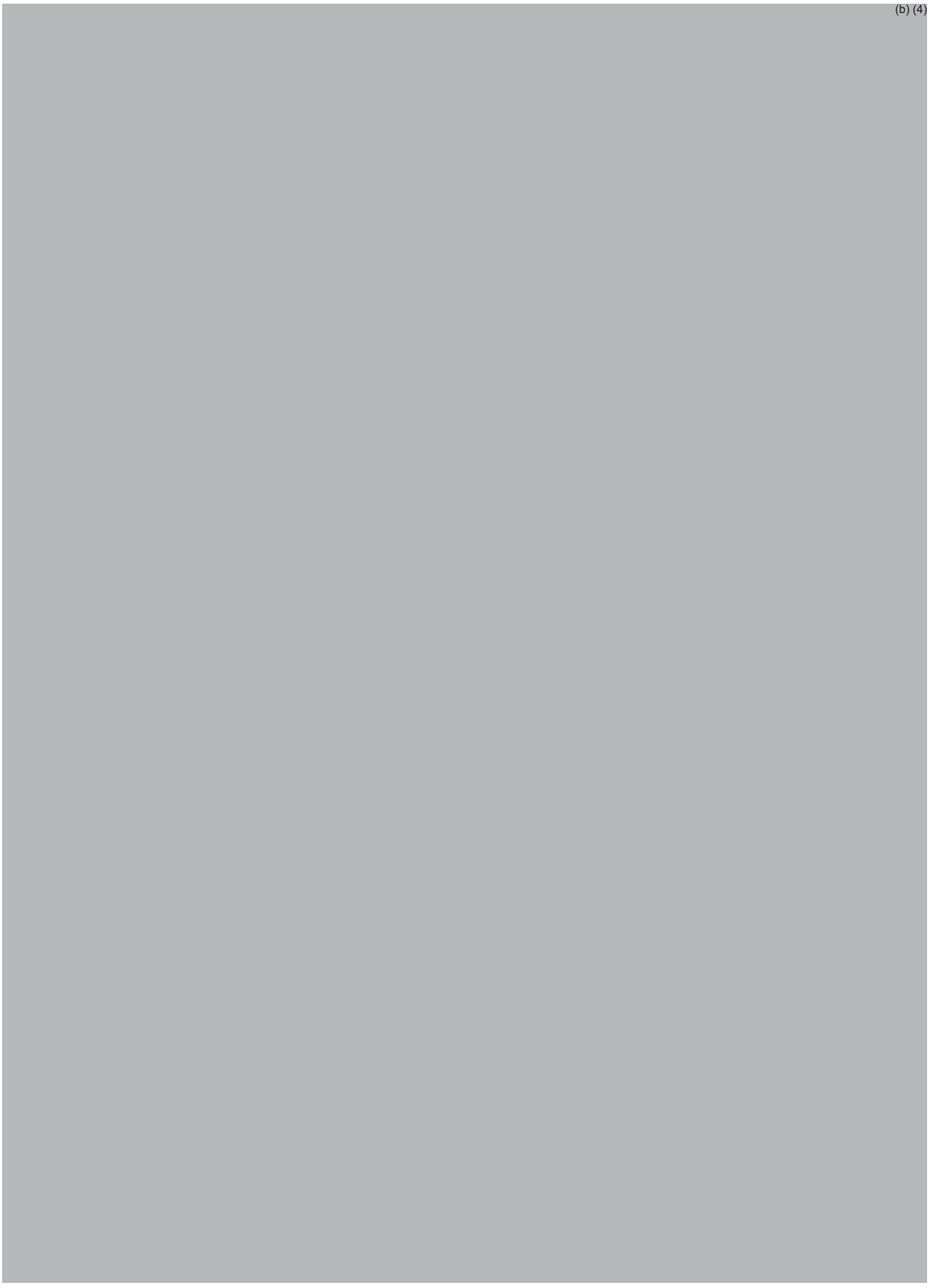
trigger force (activation force) of the test product is within the RLD specification [redacted] for both the adult and junior devices. Since the trigger force for the test device is greater than the reference device, the firm has justified as follows: *Irrespective of statistic equivalence, when used as intended, [redacted] in activation force will be imperceptible to the user. The test device distributions fall well within the historical reference device distribution. From the user perspective, a small difference in activation*

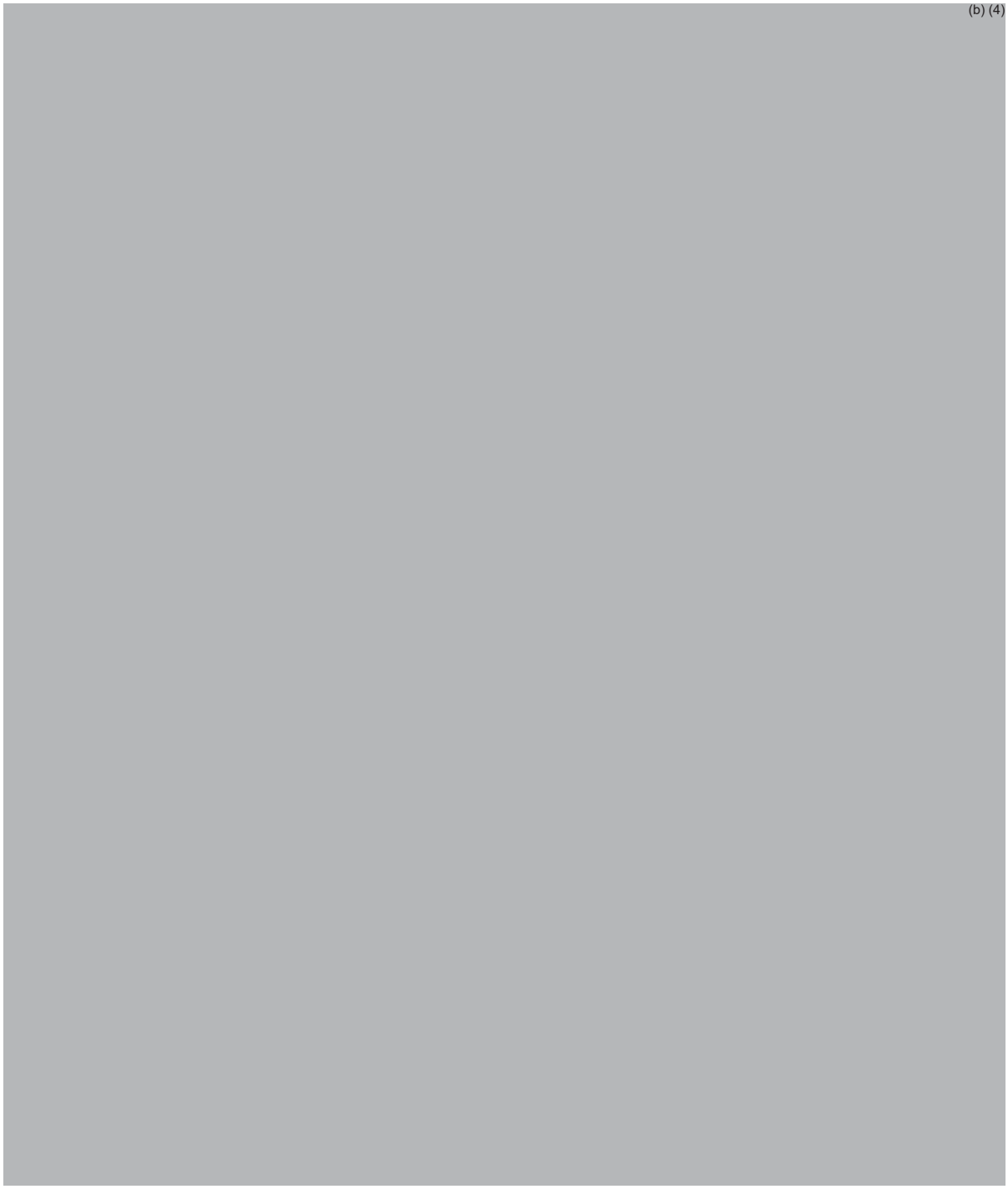
[6]DARRTS for NDA 019430: KIM, CHONG HO 11/04/2009 N/A 11/04/2009 REV-QUALITY-03(General Review) Supplement-49 (Manufacturing (CMC)) Archive

force does not prevent use of the product and therefore the test and reference product are considered equivalent.

As per the firm's study report, the activation force test data demonstrated the test and reference product activation forces were not similar enough to meet PBE criterion. The firm provided the following justification for considering the trigger force to be acceptable inspite of the observed differences between the test and reference products: (b) (4)




(b) (4)



Since the trigger force of the test devices greater than the reference devices but within the RLD specification range, Dr. Dale Conner also suggested to collect additional information regarding *justification of specifications* of the RLD batch release and trigger force data of the RLD release batches to show if any of the RLD batches had trigger force greater than the trigger force of the test devices in the current study. Further, Dr. Kimberly Witzmann recommended sending clinical consult to evaluate the impact of the observed statistical difference in the trigger force on safety and efficacy of the test product.

There are two auto-injector products containing epinephrine that have been the subject of an NDA. The Agency approved Adrenaclick® auto-injector (NDA 20-800) as a 505(b)(2) application on Nov 25, 2009, with the reference drug being EpiPen®. Stability specifications for these drug products are (b) (4) and NMT (b) (4) for trigger force and ejection time, respectively[7].

Auvi-Q® auto-injector was approved on Aug 10, 2012 referencing EpiPen®. Batch release and stability specifications for trigger force and ejection time for this product are (b) (4) and NMT (b) (4), respectively[8, 9]. Reviewer provided below data for information purpose only

Based on the above information, it is not necessary to recommend the firm to repeat ejection time study. Meeting attendees concluded that the *Ejection time study is* acceptable from BE perspective. However, the clinical significance of the statistical difference in the trigger force between the test and reference product needed further evaluation by a medical officer.

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[7] EDR, NDA 20800, Application 020800 - Sequence 0055 - Stability Report-0.15mg- Lot G130903Z-Ver-01, M.3.2.P.8.3, 7/27/2016

[8] DARRTS, NDA 201739, RAMSEY, ANGELA H, 11/23/2010, N/A, 11/23/2010, FRM-CONSULT-08(Clinical Inspections Request), Original-1 (Type 5- New Formulation or New Manufacturer)

[9] EDR, NDA 201739, Application 201739 - Sequence 0158 - MAF 1570 - Main Body, Page 200, M.3.2.P.7, 5/19/2017

Action Item:

DBIII will send the consult request to DCR on the safety of the test device with respect to slightly greater trigger force required compared to reference device.

Slides Presented in the Meeting for Discussion

Epinephrine Autoinjector_A0...

Drafted by Issa Nesheiwat 7/19/2017
Revised by Harikrishna Devalapally 8/16/2017
Revised by Suman Dandamudi 9/7/2017
Reviewed by Ke Ren 9/21/2017
Reviewed by Nilufer Tampal 9/22/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

ANDA 090589

INFORMATION REQUEST

Teva Pharmaceuticals USA, Inc.
Attention: Cory Wohlbach
425 Privet Road
Horsham, PA 19044

Dear Sir:

Please refer to your Abbreviated New Drug Application (ANDA) dated December 21, 2007, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act for Epinephrine Injection USP, 0.15 mg and 0.30 mg.

We are reviewing the Quality sections of your submission and have the following comments and information requests. We request a prompt written response, no later than **June 19, 2017**, in order to continue our evaluation of your ANDA.

1.

2.

(b) (4)

If you do not submit a complete response by June 19, 2017, the review will be closed and the listed deficiencies will be incorporated in a COMPLETE RESPONSE correspondence.

All items listed on this Information Request shall be addressed in its entirety, any partial or incomplete response will not be reviewed and the same deficiency list will be issued to you again as part of the Complete Response Letter issued by OGD. Please note that a commitment to address an item in the future is not considered satisfying the Information Request.

Please send your submission through the Electronic Submission Gateway http://www fda.gov/ForIndustry/ElectronicSubmissionsGateway/default htm. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

INFORMATION REQUEST
QUALITY/MICROBIOLOGY

If you have any questions, please contact Jennifer Nguyen, Regulatory Business Process Manager at (240) 402-8729.

Sincerely,

{See appended electronic signature page}

Jennifer H. Nguyen, PharmD
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Jennifer Nguyen

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

ANDA 090589

INFORMATION REQUEST

Teva Pharmaceuticals USA, Inc.
Attention: Cory Wohlbach
425 Privet Road
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Dear Sir:

Please refer to your Abbreviated New Drug Application (ANDA) dated December 21, 2007, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act for Epinephrine Injection USP, 0.15 mg and 0.30 mg.

We are reviewing the Quality sections of your submission and have the following comments and information requests. We request a prompt written response, no later than **May 5, 2017**, in order to continue our evaluation of your ANDA.

(b) (4)

If you do not submit a complete response by May 5, 2017, the review will be closed and the listed deficiencies will be incorporated in a COMPLETE RESPONSE correspondence.

All items listed on this Information Request shall be addressed in its entirety, any partial or incomplete response will not be reviewed and the same deficiency list will be issued to you again as part of the Complete Response Letter issued by OGD. Please note that a commitment to address an item in the future is not considered satisfying the Information Request.

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INFORMATION REQUEST
QUALITY

If you have any questions, please contact Jennifer Nguyen, Regulatory Business Process Manager at (240) 402-8729.

Sincerely,

{See appended electronic signature page}

Jennifer H. Nguyen, PharmD
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Jennifer Nguyen

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

ANDA 090589

INFORMATION REQUEST

Teva Pharmaceuticals USA, Inc.
Attention: Cory Wohlbach
425 Privet Road
Horsham, PA 19044

Dear Sir:

Please refer to your Abbreviated New Drug Application (ANDA) dated December 21, 2007, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act for Epinephrine Injection USP, 0.15 mg and 0.30 mg.

We are reviewing the Quality sections of your submission and have the following comments and information requests. We request a prompt written response, no later than **May 2, 2017**, in order to continue our evaluation of your ANDA.

(b) (4)

If you do not submit a complete response by May 2, 2017, the review will be closed and the listed deficiencies will be incorporated in a COMPLETE RESPONSE correspondence.

All items listed on this Information Request shall be addressed in its entirety, any partial or incomplete response will not be reviewed and the same deficiency list will be issued to you again as part of the Complete Response Letter issued by OGD. Please note that a commitment to address an item in the future is not considered satisfying the Information Request.

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INFORMATION REQUEST
QUALITY

If you have any questions, please contact Jennifer Nguyen, Regulatory Business Process Manager at (240) 402-8729.

Sincerely,

{See appended electronic signature page}

Jennifer H. Nguyen, PharmD
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Jennifer Nguyen

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

ANDA 090589

PROPRIETARY NAME REQUEST
UNACCEPTABLE

Teva Pharmaceuticals USA, Inc.
425 Privet Road
Horsham, PA 19044

ATTENTION: Cory Wohlbach
Senior Director, Regulatory Affairs, US Generics

Dear Mr. Wohlbach:

Please refer to your Abbreviated New Drug Application (ANDA) dated and received December 21, 2007, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act for Epinephrine Injection, 0.15 mg/0.3 mL and 0.3 mg/0.3 mL.

We also refer to your correspondence, dated and received March 8, 2017, requesting review of your proposed proprietary name, (b) (4).

We have completed our review of this proposed proprietary name and have concluded that this name is unacceptable for the following reasons:

The proposed proprietary names (b) (4) and (b) (4) (b) (4)

The proposed indication for these epinephrine products is for the emergency treatment of allergic reactions, including anaphylaxis. According to the products' draft product labeling, they are intended for immediate administration as emergency supportive therapy only and are not substitutes for immediate medical care. (b) (4) (b) (4)

Please note that the Federal Food, Drug, and Cosmetic Act (FD&C Act) provides that labeling or advertising can misbrand a product if misleading representations are made (See 21 U.S.C. 321(n)). The FD&C Act also provides that a drug is misbranded if its labeling is false or misleading in any particular (21 U.S.C. 352(a)). A proprietary name, which appears in labeling, could result in such misbranding if it is false or misleading, such as by making misrepresentations with respect to safety or efficacy.

We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, we recommend that you submit a new request for a proposed proprietary name review.

If you require additional information on developing proprietary names for drugs, proposing alternative proprietary names for consideration, or requesting reconsideration of our decision, we refer you to the following:

- Draft Guidance for Industry Best Practices in Developing Proprietary Names for Drugs, (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM398997.pdf)
- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Michael Sinks, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-2684. For any other information regarding this application, contact Jessica Kreger, Regulatory Project Manager, in the Office of Generic Drugs at (240) 402-3957.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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

/s/

DANIELLE M HARRIS on behalf of TODD D BRIDGES
03/24/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

ANDA 090589

INFORMATION REQUEST

Teva Pharmaceuticals USA, Inc.
Attention: Cory Wohlbach (Cory.Wohlbach@tevapharm.com)
425 Privet Road
Horsham, PA 19044

Dear Sir:

Please refer to your Abbreviated New Drug Application (ANDA) dated December 21, 2007, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act for Epinephrine Injection USP, 0.15 mg and 0.30 mg.

We are reviewing the Quality sections of your submission and have the following comments and information requests. We request a prompt written response, no later than **March 27, 2017**, in order to continue our evaluation of your ANDA.

Management Responsibility (21 CFR 820.20)

Your firm has inadequately addressed the requirement for 21 CFR 820.20, management responsibility.

Please provide a summary of how your firm's management has established responsibility to assure that the combination product is manufactured in compliance with all applicable CGMP requirements (see 21 CFR Part 4). Also, provide a description of the functions and responsibility of each facility involved in the manufacturing of the combination product and its constituent parts.

Design Control, General (21 CFR 820.30)

Although you provided, some design information, your firm has inadequately addressed the requirement for 21 CFR 820.30, design control.

Please explain how you utilized the design control process to develop the combination product under review and provide a description of your design control procedures. The procedures description must include how requirements for design and development planning, design input, design output, design review, design verification, design validation, design transfer, design changes, and design history file are fulfilled. Provide a copy or a summary of the plan used to design the combination product. Explain how you utilized the design control process to develop the combination product under review.

When answering, please address identified design control deficiencies that were addressed in previous information requests for this application.

Purchasing Controls (21 CFR 820.50)

Your firm has inadequately addressed the requirement for 21 CFR 820.50, purchasing controls.

Please provide a summary of the procedure(s) for purchasing controls. The summary should:

a. Describe your supplier evaluation process and describe how it will determine type and extent of control you will exercise over suppliers.
b. Define how you maintain records of acceptable suppliers and how you address the purchasing data approval process.
c. Explain how you will balance purchasing assessment and receiving acceptance to ensure that products and services are acceptable for their intended use.

Please explain how the procedure(s) will ensure that changes made by contractors/suppliers will not affect the final combination product. Provide a description of how you apply the purchasing controls to the suppliers/contractors used in the manufacturing of the combination product. (e.g., through supplier agreement).

Corrective and Preventive Action (21 CFR 820.100)

Your firm has inadequately addressed the requirement for 21 CFR 820.100, corrective and preventive actions.

Please summarize the procedure(s) for your Corrective and Preventive Action (CAPA) System. The CAPA system should require:

a. Identification of sources of quality data and analysis of these data to identify existing and potential causes of nonconforming practices and products;
b. Investigation of nonconformities and their causes;
c. Identification and implementation of actions needed to correct and prevent recurrence of nonconformities; and
d. Verification or validation of the actions taken.

Installation (21 CFR 820.170) and Servicing (21 CFR 820.200)

If installation and service requirements apply based on the type of device constituent part included in your combination product, the following information should be provided:

Installation. If applicable for the combination product, please provide a summary of how your firm has established installation, inspection instructions, and test procedures for the installation of the combination product.

Servicing. Where servicing is a specified requirement for the combination product, please provide a summary of how your firm has established and maintained instructions and procedures for performing and verifying that servicing of the combination product meets the specified requirements.

If you do not submit a complete response by March 27, 2017, the review will be closed and the listed deficiencies will be incorporated in a COMPLETE RESPONSE correspondence.

All items listed on this Information Request shall be addressed in its entirety, any partial or incomplete response will not be reviewed and the same deficiency list will be issued to you again as part of the Complete Response Letter issued by OGD. Please note that a commitment to address an item in the future is not considered satisfying the Information Request.

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INFORMATION REQUEST
QUALITY

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Sincerely,

{See appended electronic signature page}

Jennifer H. Nguyen, PharmD
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Jennifer Nguyen

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

ANDA 090589

INFORMATION REQUEST

Teva Pharmaceuticals USA, Inc.
Attention: Cory Wohlbach (Cory.Wohlbach@tevapharm.com)
425 Privet Road
Horsham, PA 19044

Dear Sir:

Please refer to your Abbreviated New Drug Application (ANDA) dated December 21, 2007, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act for Epinephrine Injection USP, 0.15 mg and 0.30 mg.

We are reviewing the Quality sections of your submission and have the following comments and information requests. We request a prompt written response, no later than **February 24, 2017**, in order to continue our evaluation of your ANDA.

1. (b) (4)

2. (b) (4)

If you do not submit a complete response by February 24, 2017, the review will be closed and the listed deficiencies will be incorporated in a COMPLETE RESPONSE correspondence.

All items listed on this Information Request shall be addressed in its entirety, any partial or incomplete response will not be reviewed and the same deficiency list will be issued to you again as part of the Complete Response Letter issued by OGD. Please note that a commitment to address an item in the future is not considered satisfying the Information Request.

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Jennifer H. Nguyen, PharmD
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Jennifer
Nguyen

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

ANDA 090589

FACE TO FACE MEETING MINUTES

Teva Pharmaceuticals USA, Inc.
425 Privet Road
Horsham, PA 19044
Attention: Cory Wohlbach
Director, US Generics Regulatory Affairs

Dear Sir:

Please refer to your Abbreviated New Drug Application (ANDA) submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act for Epinephrine Injection USP, 0.15 mg/0.3 mL and 0.3 mg/0.3 mL (Auto-Injectors).

We also refer to the teleconference between representatives of your firm and the FDA on September 14, 2016. The purpose of the requested teleconference meeting was to further discuss Response #2 in the Product Quality section of FDA's Meeting Request Granted Written Response letter dated April 20, 2016.

A copy of the official minutes of the face to face meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

The Electronic Common Technical Document (eCTD) is CDER's standard format for electronic regulatory submissions. Beginning May 5, 2017 ANDA and Master Files must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: www.fda.gov/ectd.

If you have any questions, call Jessica Kreger, Regulatory Project Manager at (240) 402-3957.

Sincerely,

{See appended electronic signature page}

Jessica Kreger, PharmD, PMP
Regulatory Project Manager
Division of Project Management
Office of Generic Drugs
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Post Complete Response Face to Face Meeting
Meeting Category:	End of Review
Meeting Date and Time:	September 14, 2016 from 1:00 PM – 2:00 PM
Meeting Location:	White Oak Building #71; Room #1208/1210
Application Number:	090589
Product Name:	Epinephrine Injection USP, 0.15 mg/0.3 mL and 0.3 mg/0.3 mL (Auto-Injectors)
Applicant Name:	Teva Pharmaceuticals USA, Inc.
Meeting Recorder:	Lakeeta Carr

FDA ATTENDEES

John Peters, Deputy Director, OGD
Edward "Ted" Sherwood, Director, CDER/OGD/ORO/IO
CAPT Carol Holquist, Acting Deputy Director, CDER/OGD/ORO/IO
CAPT Aaron Sigler, Deputy Director, CDER/OGD/ORO/DPM
CDR Lakeeta Carr, Regulatory Project Manager, CDER/OGD/ORO/DPM
Scott Janiczak, Regulatory Project Manager, CDER/OGD/ORO/DPM
Sarah Kurtz, Acting Supervisor, CDER/OGD/ORO/DLR
Kellie Taylor, Director, CDER/OSE/OMEPRM
Lubna Merchant, Deputy Director, CDER/OSE/DMEPA
Mishale Mistry, Team Leader, CDER/OSE/DMEPA
Lissa Pringle-Owens, Reviewer, CDER/OSE/DMEPA
Mike Darj, DP Secondary Reviewer, CDER/OPQ/OLDP/DIRPII/IRBIV
Song (Sonni) Kim or Jennifer Nguyen, CDER/OPQ/OPRO/DRBPMI/RBPMBI
Maryll Toufanian, Deputy Director, CDER/OGD/OGDP
James Myers, Regulatory Counsel, CDER/OGD/OGDP/DLRS
Thomas Gwise, Deputy Division Director, OMPT/CDER/OTS/OB/DBV
Stella Grosser, Statistical Reviewer, OMPT/CDER/OTS/OB/DBVIII
Kim Witzmann, CDER/OGD/ORS/DTP
Denise Conti, Reviewer, CDER/OGD/ORS/DTP
Markham C. Luke, CDER/OGD/ORS/DTP
CDR Alan Stevens, Branch Chief, CDRH/ODE/DAGID/GHDB
Mark Ritter, Acting Deputy Director, CDER/OGD/OB/DCR

Denise Toyer-Mckan, Director, CDER/OGD/ORO/DPM
CDR Tina Nhu, Team Lead, CDER/OGD/ORO/DPM
Esther Chuh, Primary Reviewer, CDER/OGD/ORO/DLR
Hyon Kim, Labeling Project Manager, CDER/OGD/ORO/DLR
Ruby Wu, Acting Director, CDER/OGD/ORO/DLR
Lillie Golson, Acting Deputy Director, CDER/OGD/ORO/DLR
Malik Imam, Acting Supervisor, CDER/OGD/ORO/DLR
Kemi Odesina, Acting Supervisor, CDER/OGD/ORO/DLR
Thuyanh (Ann) Vu, Acting Team Lead, CDER/OGD/ORO/DLR
Quynh Nguyen, MS, Associate Director for Human Factors, CDER/OSE/DMEPA
Todd Bridges, Director, CDER/OSE/DMEPA
Irene Chan, Deputy Director, CDER/OSE/DMEPA
Sean Bradley, Chief Project Manager, CDER/OSE/PMS
Nichelle Rashid, Team Leader, CDER/OSE/PMS
Michael Sinks, Project Manager, CDER/OSE/PMS
Xiaohua Huang, DP primary reviewer, CDER/OPQ/OLDP/DIRPII/IRBIV
Bing Wu, Branch Chief, CDER/OPQ/OLDP/DIRPII/IRBIV
Robert (Bob) Gaines, Director, CDER/OPQ/OPRO/DRBPMII
Jesse Wells, Secondary Reviewer, CDER/OPQ/OPF/DMA/MABI
Andrew Leboeuf, Regulatory Counsel, CDER/OGD/OGDP/DPD
Honggang Wang, Pharm/Tox Reviewer, CDER/OGD/OB/DCR
Robert Dorsam, Team Leader, CDER/OGD/OB/DCR
Karen Feibus, Clinical Consult Reviewer, CDER/OGD/OB/DCR
Lolita Lopez, Clinical Consult Team Leader, CDER/OGD/OB/DCR
Daiva Shetty, Acting Deputy Director, CDER/OGD/OB/DCR
Casey Hadsall, Project Manager, Pharm/Tox Team, CDER/OGD/OB/DCR
Tiffany Hoang, Project Manager, Pharm/Tox Team, CDER/OGD/OB/DCR
Margarita Tossa, Project Manager Team Leader, CDER/OGD/OB/DCR

APPLICANT ATTENDEES

Scott Tomsky, Vice President Regulatory Affairs
Cory Wohlbach, Senior Director Regulatory Affairs
Don Lewis, Associate Director Regulatory Affairs
Rosario Lobrutto, R&D Site Head, Project Leader
Vijay Joguparthi, R&D Associate Director
Paul Shelley, Senior Quality Engineer
Richard Simcock, Human Factors Scientist

(b) (4)

(b) (4)

A. BACKGROUND

Purpose of meeting:

To further discuss FDA's Response #2 in the Product Quality section of FDA's Meeting Request Granted Written Response letter from April 20, 2016.

Expected outcome for the meeting:

At this meeting, the Sponsor (Teva) and the Agency intend to discuss FDA's Response #2 in the Product Quality section of FDA's Meeting Request Granted Written Response letter from April 20, 2016 and Teva's follow-up questions.

B. DISCUSSION

Question #1

USER GROUP CRITERIA

Agency's points to consider

Please describe the criteria used to define the "Adult User" groups and "Teen User" groups, respectively, in formative study TR927 and validation study TR-720B. We are interested in understanding whether the same or similar criteria were used to define these user groups in the studies. We are also interested in understanding whether each of these user groups from the two studies adequately represents current users of EpiPen in terms of demographics and user experience. To help establish that your user population reasonably represents the current users of EpiPen, you could consider providing information to characterize the use patterns and other pertinent characteristics of current EpiPen users. For example, you may consider providing information regarding whether the subjects in the pooled analysis user groups have ever administered EpiPen, and, if so, how frequently and recently they had experience in administering EpiPen.

Applicant's response

The recruiting criteria for all user groups for both studies were identical in terms of their previous experience with the RLD (i.e., have RLD prescription, have a current, valid RLD device, and may have prior training), as well as their ages and genders.

The relevant demographic criteria for the RLD owners and trained providers show that these participants represented a wide range of experience, as would be typical in the real user

population, including the following factors: experience with anaphylaxis, training to use the RLD, and how recently and frequently, if ever, they had used the RLD. Given these recruiting criteria and demographics, the user groups defined in each study were identical and therefore justifies pooling of the participant data and results from the 2012 and 2014 studies. Additionally, the study protocol methodologies were identical and the device design and labeling were comparable for both studies (there were no changes to the AJE device cap), further supporting the pooling of the study data.

a. Applicant's Clarifying Questions

Does FDA agree that the criteria described by Teva, which was used to define the "Adult User" and "Teen User" groups in formative study TR927 and validation study TR-720B, is the same or similar in both groups?

FDA Response

We agree that the selection criteria for study TR927 is substantially similar to the selection criteria of study TR-720B.

b. Applicant's Clarifying Question

Does FDA agree that the user population for Teva's studies reasonably represents the current users of EpiPen?

FDA Response

Based on the information provided in your IR response, we agree that the adult and adolescent populations appear to reasonably represent those of the current users of EpiPen. We note, however, that your adolescent population does not include patients younger than 13 years.

Question #2

METHODOLOGY OF STUDIES

Agency's points to consider

Consider summarizing the methodology used in formative study TR927 and validation study TR-720B. To understand the extent to which data from these studies address the deficiencies identified in our complete response letter, we recommend you provide justification for why your test method(s) sufficiently evaluated the risks of substitution inherent when existing users of EpiPen, familiar with the operating principals of EpiPen for some period of time, are switched to your AJE product. In particular, we recommend providing clarification or justification, as appropriate, for the following items:

- *Simulation conditions*: Please describe the study conditions for validation study TR-720B and formative study TR927. Given that epinephrine injection is intended to treat emergent anaphylaxis, we encourage you to describe in your study the methods used to simulate this condition of emergency use and justify the representativeness of the study conditions employed with respect to the actual use of epinephrine injection.

Applicant's response

The simulated use study environment for both the 2012 and 2014 studies were identical. The study environment simulated a home or other non-clinical environment. There was variation in lighting, noise, and distraction conditions, as well as conditions of the hands (wet vs. dry), to simulate conditions of use of an epinephrine injection. The study facilitator repeatedly informed the study participants that this medical condition is serious and potentially fatal; therefore, the participant needed to act in a realistic manner as immediately as possible. These methodologies used to simulate an emergency setting in a non-clinical environment represent the current state-of-the-art methods; the science of this simulation has not evolved since conducting these studies in such a way that would invalidate them.

a. Applicant's Clarifying Questions

Does FDA agree that the methodology used in Teva's formative study TR927 and validation study TR-720B, to simulate the condition of emergency use, is sufficient in justifying the representativeness of the study conditions employed with respect to the actual use of epinephrine injection?

FDA Response
FDA agrees that the conditions you describe in the cover letter and study report are appropriate for these human factors studies.

Question #3

Agency's points to consider

Simulation sequencing: it appears that in validation study TR-720B, the current users simulated use of your AJE product before demonstrating use of either EpiPen or the AJE product (for a second time). Please clarify or provide justification as to why the use of the AJE product first adequately simulates the expected use of your proposed product (i.e., under conditions in which the AJE product would be substituted for EpiPen to current users of EpiPen or used by EpiPen non-users).

Applicant's response

In both studies, the study protocols were the same in terms of device presentation and tasks. The participants did not receive any training, and the study facilitator did not demonstrate how to use either device. The study participants conducted two simulated injections with the first device and

then conducted two simulated injections with the second device, all during a single usability session. The order of device usage was counterbalanced in an alternating manner, so that half of the participants interacted with the AJE device first and the RLD second, while the other half interacted with the RLD first and AJE second. The tasks for both devices were presented in exactly the same manner. This study design eliminated any potential ordering/learning effects.

Applicant's clarifying question

Does FDA agree that alternating device usage in two separate groups (i.e., Group 1: AJE 1st/RLD 2nd; Group 2: RLD 1st/AJE 2nd) adequately simulates the expected use of Teva's product?

FDA Response

We do not agree that this study design adequately simulated the expected use of Teva's product for patients. The current labeling for the RLD limits the self-administration of epinephrine injections to a maximum of two injections per episode of anaphylaxis, and your study design simulated the sequential and un-interrupted administration of 4 injections.

Question #4

Agency's points to consider

Task simulation: your study report for TR-720B does not describe whether there was an interruption between the simulated use of the AJE product and the EpiPen product. Please clarify whether there was an interruption between the simulated use of the products in either formative study TR927 or validation study TR-720B, and, if so, the applicable period of interruption. In actual use, the administration of epinephrine products may be episodic, and it is likely that the administration of two different epinephrine products to treat two different episodes of anaphylaxis would be separated by some period of time. In comparative human factors studies, we would generally see protocols that include a time period (hours, days, or weeks) of separation between observations to simulate the elapsed time between administrations in actual use.

Applicant's response

The study protocols evaluated the risks of substitution by taking into account device use sequence (as discussed above in "Task simulation") and the delay between uses. In both studies, the participants completed 2 simulated injections with the first device and then completed 2 simulated injections with the second device, all during a single usability testing session. There was no structured time delay between the simulated injections during the usability testing because, with epinephrine injections, it is possible that the patient experiencing anaphylaxis may require multiple injections within a short time span (within minutes)1. There was no structured interruption between the different devices during the usability testing because the counterbalancing of the device orders was intended to account for the ordering/learning effects. The participants did not receive any training during the study, so we were not attempting to

assess training decay. The usability testing covered all potential real-life use cases for device use order and interruption between them:

- The study participant simulated injections with the RLD first, and then simulated injections with the AJE, both during the same usability testing session.

- An RLD experienced user interacted with the RLD first (either by being trained to use it or actually delivering an injection in real-life between 1 month and 10 years prior to the usability study). This participant then participated in the usability study and simulated injections with the AJE device.

- The study participant simulated injections with the AJE first, and then simulated injections with the RLD, both during the same usability testing.

Additionally, a structured interruption of 1 week, as is often built into human factors testing, would not accurately represent the real-life, episodic use of epinephrine injectors. Such episodic use would be impossible to accurately represent in a human factors study, hence the studies included participants who had used the RLD in the past to represent real-world interruption between uses.

Applicant's clarifying question

Although there was no structured interruption between the different devices during the usability testing, does FDA agree that Teva's usability testing (as noted above) cover all potential real-life use cases?

FDA Response

In your study design, the first two observations for each device injection (AJE1, AJE2 and RLD1, RLD2) adequately simulate real-life use cases as these observations most closely resemble the intended use scenario where a user is faced with an episode of anaphylaxis and, without further training or preparation, required to administer the drug. In these instances, the data collected for the first two observations for the Teva product (AJE1, AJE2) may be used to represent those use cases where a patient is administering Teva's generic product, and the data collected for the first two observations for the RLD product (RLD1, RLD2) may be used to represent those use cases where a patient is administering the RLD. Comparing these data may help answer the question of whether the risk for error for your proposed AJE is not any worse than the risk of error associated with the RLD if users continue to use the RLD.

Please describe the way that patients were assigned to Use Case A or Use Case B for each study, as this will be an important consideration for the data analysis.

The data collected in the subsequent two observations (i.e., AJE 3, AJE 4, RLD 3, RLD 4) are not reflective of expected use for the reasons we describe in our response to Question 3. Without the inclusion of a time interval to reasonably simulate the time that might elapse between

episodes of anaphylaxis, we have concern that the data collected could be biased by the preceding administrations.

Question #5

USE ERRORS

Agency's points to consider

Your original submission did not show that the difference in the design of your proposed device would not be expected to introduce a new risk. To assess whether the difference in design with respect to removing the yellow closure cap introduces a new risk, one approach we suggest you consider is to evaluate the comparative rate of error related to removing the yellow cap as compared to the rate of error associated with removing the EpiPen from the carrier tube if current RLD users continue to use only the RLD. Importantly, if you undertake such an assessment, we recommend that you should consider whether the data reasonably reflect the conditions under which patients will use your proposed product (i.e., the study conditions adequately simulate emergency use of your product) following substitution for the RLD (i.e., without physician intervention or further training).

Applicant's response

Only 13 of the 289 participants in the 2012 and 2014 studies made an error when removing the cap (AJE device) and/or removing the device from the carrier tube (RLD). Of these 13 participants, 3 participants made errors on both devices, 5 participants made an error on the AJE device but not the RLD, and 5 participants made an error on the RLD but not the AJE. The Agency has expressed concern about participants who made errors on the AJE device but not the RLD, who potentially exhibit some negative transfer between the devices. However, the evidence shows that any possible negative transfer was exactly balanced by improved performance on the AJE, making the small net number of participants who made errors equivalent for the two devices. Given the identical (error free) performance of the other 276 out of 289 participants, the chances are extremely small that the similarity of patterning is due to chance.

Additionally, to answer the FDA's specific questions about the data, we analyzed the use error data for the step of removing the cap (AJE device) and removing the device from the carrier tube (RLD) according to the following factors:

- The device upon which the error was committed.
- The user group of the participants who committed errors.
- Whether the device was used first or second.

- Whether or not the participant had recent experience using or receiving training on the RLD.

Comparing all errors, there was no pattern of error specific to any user group. The participants' previous experience with the RLD did not have any impact on whether or not they made errors during cap/carrier tube removal with the AJE device compared to the RLD device. The order in which the devices were presented also made no difference. Overall, the total number of errors on this step was comparable between the AJE and the RLD devices.

a. **Applicant's clarifying questions**

Does FDA agree that the difference in design between the devices used in Teva's product, as compared to the devices used in the RLD product, is not expected to introduce a new risk?

FDA Response

No, we do not agree.

Based on the information presented in your cover letter and as noted above in our responses to question 3 and 4, we recommend that you focus your quantitative analysis on the data collected from the treatment groups for observations RLD1, RLD2, and AJE1, AJE2.

We plan to review your findings to help assess whether your design difference is acceptable. We recommend that you focus your analysis on demonstrating that the error rate for your AJE statistically are not worse than that of the observed rate for the use of the RLD with respect to a) overall use and b) removal of the cap or the carrier tube, as appropriate, for the relevant device.

In order to achieve adequate power, it may be appropriate based on the information you have presented in this meeting request, to pool data from study TR720-B and study TR927. We would expect that your quantitative analysis would continue to treat the groups of nonuser adult, current user adults, nonuser teens, current user teens as distinct user populations as you have done in TR-720B and TR927, or provide justification on why the user groups are not distinct.

You may analyze the healthcare provider use if desired, but we find the TR927 and TR-720B data sufficient to establish that healthcare providers are able to use your AJE product.

b. **Applicant's clarifying questions**

What does the Agency deem as acceptable differences in key design performance parameters such that the Sponsor's device falls within the threshold for sameness relative to the RLD's device?

FDA Response

See our response immediately above to Q1 of this question.

Also, we remind you that our review will consider the overall device difference introduced by your proposed product in the context of applicable ANDA regulations, including those pertaining to permissible labeling differences. Moreover, we note that the product proposed under your ANDA will need to meet all applicable legal and regulatory requirements relevant to ANDAs before being in a position to be approved and that FDA's review of your application, including information related to your proposed device, remains ongoing.

c. **Applicant's clarifying questions**

Taking the Agency's response no. 2 into account, what study design features should be considered when evaluating comparative rate of error in an alternative approach?

FDA Response

An alternative approach may be to design and conduct prospectively a comparative use study to show that your AJE product may be substituted for use at the pharmacy level with its RLD.

If you proceed to conduct a prospective evaluation, the comparative use human factors study should be designed to provide sufficient data to confirm that the use error rate that is impacted by the differing external critical design attribute of your AJE is not worse than the corresponding use error rate for the RLD when used by patients and caregivers in representative use scenarios and use environments consistent with the labeled conditions of use. The use scenarios in your TR720-B and TR927 studies for Group 2 may be a reasonable approach to incorporate within a comparative human factors study, although we would recommend the inclusion of a structured time interruption to ensure independent evaluation of the two products if using a paired design (cross-over). A parallel arm design would obviate the need for a waiting period.

You should include a statistical plan for your study, and you may consider a noninferiority (NI) study design. FDA recommends that patient and caregiver (if applicable) end-users of the RLD be considered for inclusion in the comparative use human factors study. The primary endpoint for a comparative use human factors study in the context of a drug-device combination product will be the rates of errors observed when removing the cap/carrier tube and the overall use of the presentations of the proposed generic drug-device combination product and the RLD. We advise you consider the findings from your previous human factors study work in the design of a comparative study, and to propose and discuss study designs with us before you initiate studies.

C. ISSUES REQUIRING FURTHER DISCUSSION

FDA and applicant will agree on any proposed/additional studies before applicant embarks on further studies.

D. PERTINENT DISCUSSTION & ACTION ITEMS

Action Item/Description	Owner	Due Date
1. Send Labeling Easily Correctable Deficiency - FDA will inform Teva if the labeling comments will introduce additional Human Factors assessment needs that had not otherwise been communicated in the F2F meeting	FDA	Not Applicable (See post meeting clarification below with regards to ECD.)
2. Teva would provide further analysis of HF data based on the response provided during the meetings. (For example, assignments on randomization trial, background supporting information/justification of margins.)	Teva	September 23, 2016 (Submission arrived September 26, 2016)
3. If additional HF studies are needed/proposed, Teva will discuss the format/protocols with FDA prior to initiating studies.	FDA	TBD (if applicable)

E. POST MEETING CLARIFICATION

With regards to Action Item D-1 (above): Upon further review by the Division of Labeling Review (DLR), it was determined that an ECD was not forthcoming and that the only comment from DLR was for the applicant to ensure that its labeling is in agreement with the most recent RLD labeling update.

F. ATTACHMENTS AND HANDOUTS

(b) (4)

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Jessica Kreger

Digitally signed by Jessica Kreger
Date: 10/06/2016 02 24 56PM
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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*:
Xiaohua Huang, Ph.D., Chemistry Reviewer
Mike Darj, Ph.D., Chemistry Team Leader
Division of Chemistry
Office of Pharmaceutical Quality

FROM (*Name, Office/Division, and Phone Number of Requestor)*:
Mark Ritter, MD
Acting Deputy Director
Division of Clinical Review (DCR)
Office of Bioequivalence (OB)/Office of Generic Drugs

DATE	IND NO.	ANDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
July 15, 2016	N/A	090586	Post-CR Meeting Request	03/08/2016

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Epinephrine Injection USP (Auto-Injector) 0.15 mg/0.3 mL and 0.3 mg/0.3 mL	High	Bronchodilator	08/01/2016

NAME OF FIRM: Teva Pharmaceuticals USA, Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☒ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY _____
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER: documenting chemistry basis for the Firm's justification of the safety of subcutaneous drug administration based on bridging between (b) (4) : (b) (4) sodium tartrate dihydrate in the proposed aqueous solution

II. BIOMETRICS

- ☐ TYPE A OR B NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER _____
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER _____

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS / SPECIAL INSTRUCTIONS:

(b) (4)

Background:
Teva proposes to market a generic Epinephrine autoinjector product 0.3 mg/0.3 mL and 0.15 mg/0.3 mL under ANDA 090589; the Reference Listed Drug (RLD) product is EpiPen® Auto-Injector, 0.3 mg/0.3mL and EpiPen® Jr Auto-Injector, 0.15 mg/0.3

mL, manufactured by Mylan Specialty (NDA 019430, approved 12/22/1987). These products are intended for both intramuscular (IM) and subcutaneous (SC) administration. The test (proposed generic) formulation contains **sodium tartrate dihydrate (STD)**, (b) (4) not found in the RLD or in any products administered via **SC route** making it a novel excipient via SC route. During the ANDA review cycle, the Division of Bioequivalence III (DBIII) asked DCR to determine whether the amount of STD in the proposed product is a safety concern when administered subcutaneously.

Based on a thorough review (attached), DCR concluded that the amount of STD in the proposed epinephrine auto-injector product is acceptable for IM injection. However, for SC use, the clinical team found that the potential for adverse local effects, such as redness, irritation, scarring, and skin depression, was unknown. The DCR review from October 2015 is attached to this consult request. OGD issued a Complete Response (CR) on 02/23/2016 and listed this safety concern as a deficiency.

A090589 DCR_ClinPT review

On 03/08/2016, Teva submitted a Post Complete Response (CR) Teleconference Meeting Request. In their meeting request cover letter, Teva responded to FDA's assertions that STD is a novel excipient for the SC route of administration and that the ANDA contained insufficient evidence to support the safety of STD when administered SC (b) (4)

(b) (4)

(b) (4)

DCR Questions to OPQ:

1) Do you agree with the ANDA 090589 applicant's justification that in the proposed epinephrine (ANDA 090589) (b) (4)
(b) (4)

2)

3)

4)

Please contact Karen Feibus, MD (karen.feibus@fda.hhs.gov), Medical Officer, DCR or Nitin Patel (nitin.patel@fda.hhs.gov) , if you have any questions. Thank you.

Please provide an electronic copy of the review to Nitin Patel (nitin.patel@fda.hhs.gov) in the Division of Clinical Review (OGD). Thank you.

SIGNATURE OF REQUESTOR Nitin K. Patel	METHOD OF DELIVERY (Check all that apply) ☒ PANORAMA ☒ EMAIL ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

06/18/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	**REQUEST FOR CONSULTATION**

TO *(Division/Office)*:	FROM:
Daiva Shetty, MD Acting Director, Division of Clinical Review Office of Bioequivalence Office of Generic Drugs	Harikrishna Devalapally, Ph.D. Through Nilufer M. Tampal, Ph.D. Acting Director, Division of Bioequivalence III Office of Bioequivalence Office of Generic Drugs

DATE	IND NO.	ANDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
July 5, 2016	N/A	090589	Bioequivalence Review	November 24, 2008

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Epinephrine Injection USP (Auto-Injector) 0.15 mg/0.3 mL and 0.3 mg/0.3 mL	**High**	Bronchodilator	August 15, 2016

NAME OF FIRM: Teva Pharmaceuticals USA, Inc.

REASON FOR REQUEST

I. GENERAL

☐ NEW PROTOCOL	☐ PRE--NDA MEETING	☐ RESPONSE TO DEFICIENCY LETTER
☐ PROGRESS REPORT	☐ END OF PHASE II MEETING	☐ FINAL PRINTED LABELING
☐ NEW CORRESPONDENCE	☐ RESUBMISSION	☐ LABELING REVISION
☐ DRUG ADVERTISING	☒ **SAFETY/EFFICACY**	☐ ORIGINAL NEW CORRESPONDENCE
☐ ADVERSE REACTION REPORT	☐ PAPER NDA	☐ FORMULATIVE REVIEW
☐ MANUFACTURING CHANGE/ADDITION	☐ CONTROL SUPPLEMENT	☐ OTHER *(SPECIFY BELOW)*:
☐ MEETING PLANNED BY		

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

☐ DISSOLUTION	☐ DEFICIENCY LETTER RESPONSE
☐ BIOAVAILABILTY STUDIES	☐ PROTOCOL-BIOPHARMACEUTICS
☐ PHASE IV STUDIES	☒ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL	☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES	☐ SUMMARY OF ADVERSE EXPERIENCE
☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)	☐ POISON RISK ANALYSIS
☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP	

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Introduction:

Epinephrine Injection is indicated in the emergency treatment of allergic reactions (anaphylaxis) to insect stings or bites, foods, drugs and other allergens as well as idiopathic or exercise-induced anaphylaxis.

Teva Pharmaceuticals requested a waiver of in vivo bioequivalence (BE) testing for its test products, Epinephrine Injection USP, 0.15 mg/0.3 mL (Auto Injector Jr.) and 0.3 mg/0.3 mL (Auto Injector). The Reference Listed Drug (RLD) product is EpiPen® (epinephrine injection) Auto-Injector, 0.3 mg/0.3mL and EpiPen® Jr (epinephrine injection) Auto-Injector, 0.15 mg/0.3 mL, manufactured by Mylan Speclt (NDA 019430, approved on Dec 22, 1987). The RLD has the therapeutic equivalence code of "BX" in the Electronic Orange Book.

The drug product is intended for both Intramuscular and Subcutaneous administration. The formulation of the test product is NOT qualitatively (Q1) and quantitatively (Q2) the same as reference product. The test product contains sodium tartrate dihydrate as (b) (4) whereas the reference product contains no (b) (4)[1].

Formulations Comparison between the Test Product and Reformulated Reference Product

Ingredients	Function	Test Product- Re-Formulated Amount (mg) per 0.3 mL Delivered		Reference Product Amount (mg) per 0.3 mL Delivered[2]	
		0.15 mg	0.3 mg	0.15 mg (EpiPen® Jr)	0.3 mg (EpiPen®)
Epinephrine, USP	Active Ingredient	0.15 mg	0.3 mg	0.15	0.3
Sodium Chloride, USP/NF	(b) (4)	1.8 mg	1.8 mg	1.8	1.8
Sodium Metabisulfite, NF		0.4 mg	0.4 mg	0.5	0.5
Sodium Tartrate Dihydrate, NF		0.2 mg	0.4 mg	-	-
Hydrochloric Acid, USP/NF		To adjust pH	To adjust pH	To adjust pH	To adjust pH
Water for Injection, USP		Q.S.	Q.S.	Q.S.	Q.S.

The amount of sodium tartrate dihydrate in the test formulation was found to be within the acceptable limits for Intramuscular administration based on the FDA's Inactive Ingredient database (IID). However, FDA's IID does not include any information for the above stated inactive ingredient for subcutaneous route of administration. Therefore, on 6/25/2015, the Division of Bioequivalence III (DBIII) submitted a consultation request to the Division of Clinical Review (DCR) to determine whether the amount of sodium tartrate dihydrate used in the formulation of Teva's Epinephrine Injection, 0.3 mg/0.3 mL and 0 15 mg/0.3 mL posed a safety concern when administered subcutaneously[3]. Since a limit for the above

[1] GDRP, ANDA 090859, http://panorama.fda.gov/PanoramaDocMgmt/webhooks/viewdownload?id=090026f880ae507f, Suman Dandamudi, 7/2/2015

[2] DARRTS for NDA 019430: KIM, CHONG HO 07/28/2008 N/A 07/28/2008 REV-QUALITY-03(General Review) Supplement-40 (Manufacturing (CMC)) Archive

stated inactive ingredient for subcutaneous administration was not provided in the IID, in the amendment dated 12/30/2014, the firm submitted the toxicology study report to support the safety of above stated amount of sodium tartrate dihydrate in the test formulation via subcutaneous administration.

DCR concluded that the firm should consider re-formulating its test product without sodium tartrate dihydrate for the following reasons[4]:

(b) (4)

On February 23, 2016 the deficiency related to the inactive ingredient, sodium tartrate Dihydrate was conveyed to the firm through a Complete Response Letter[5]. The firm was asked to re-formulate the test product without Sodium Tartrate Dihydrate. If the firm chose to pursue the proposed formulation, the firm was advised to provide safety information to support the local dermal safety of the proposed test formulation at the injection site for the entire population the product is labeled for, i.e., adults and children as young as two years of age. This safety assessment should include local/dermal adverse reactions such as irritation, scarring, skin depression etc. at the injection site following subcutaneous administration.

On March 8, 2016, the firm submitted a request for a Post Complete Response Meeting Request (post CR MR) with the OGD for clarification of sodium tartrate dihydrate to be considered as novel excipient for the subcutaneous route of administration[6]. The BE reviewer evaluated the firm's responses and agrees with firm's justification[7].

Issue:

(b) (4)

[3] GDRP for ANDA 090589, Clinical Consult Request: http://panorama.fda.gov/PanoramaDocMgmt/document/download/090026f880ae5418, Suman Dandamudi, 7/2/2015
[4] GDRP for ANDA 090589, Consult Response: http://panorama.fda.gov/PanoramaDocMgmt/webhooks/viewdownload?id=090026f880c04574, Karen Feibus, 10/29/2015
[5] GDRP for ANDA 090589: Final Decision- http://panorama.fda.gov/document/view?ID=577174980126098d4364c58e4da09ed9, Lakeeta Karr, 6/27/2016
[6] DARRTS for 090589: 03/08/2016: Meeting/Meeting Request General Information-1
[7] GDRP for ANDA 090589 A090589N000DB_Meetingrequest03082016final.doc; date uploaded 5/13/2016
[8] http://quantum.esu.edu/~scady/Chem495/fisher.pdf
[9] http://www.organicchem.org/oc2web/lecture/outlines/acidsbases.pdf
[10] http://www.shimadzu.com/an/hplc/support/lib/lctalk/29/29intro html

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[12] GDRP ANDA090589- GI-1-Meeting-31 A090589N000DB_MEETINGREQUEST0308216.doc; date uploaded 3/29/2016

[13]Drugs@FDA, http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/200677s002lbl.pdf, Last accessed

(b) (4)

DBIII is planning to coordinate the consults responses from both groups, and if necessary, arrange a meeting between DCR, OPQ and DBIII, following the consults, to reach the final recommendations that are acceptable to all disciplines.

Attachments:

1) Attachment #1: Firm's Justification[16]

CLARIFICATION SOUGHT ON BIOEQUI\

2) Attachment #2: Consult Request Review to OPQ

A090589N000DB_C11 242008 - OPQ.doc

Thank you for your consideration. Please address comments/questions to nilufer.tampal@fda.hhs.gov

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
Harikrishna Devalapally, Ph.D.	☐ MAIL ☐ HAND

7/2/2016

[14] Drugs@FDA, http://www.accessdata fda.gov/drugsatfda_docs/label/2016/019430s061lbl.pdf, Last accessed 7/2/2016

[15] http://panorama.fda.gov/document/view?ID=577eb803006739f6754bf73caa26db14 Last accessed July 8, 2016.

[16] EDR, ANDA 90859, Application 090589 - Sequence 0026 - Cover Letter 08Mar2016 - Teleconference Meeting Request, Date 3/8/2016

SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	**REQUEST FOR CONSULTATION**

TO *(Division/Office)*:	FROM:
Division of Chemistry Office of Pharmaceutical Quality	Harikrishna Devalapally, Ph.D. Through Nilufer M. Tampal, Ph.D. Acting Director, Division of Bioequivalence III Office of Bioequivalence Office of Generic Drugs

DATE	IND NO.	ANDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
July 5, 2016	N/A	090589	Bioequivalence Review	November 24, 2008

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Epinephrine Injection USP (Auto-Injector) 0.15 mg/0.3 mL and 0.3 mg/0.3 mL	**High**	Bronchodilator	July 15, 2016

NAME OF FIRM: Teva Pharmaceuticals USA, Inc.

REASON FOR REQUEST

I. GENERAL

☐ NEW PROTOCOL	☐ PRE--NDA MEETING	☐ RESPONSE TO DEFICIENCY LETTER
☐ PROGRESS REPORT	☐ END OF PHASE II MEETING	☐ FINAL PRINTED LABELING
☐ NEW CORRESPONDENCE	☐ RESUBMISSION	☐ LABELING REVISION
☐ DRUG ADVERTISING	☒ SAFETY/EFFICACY	☐ ORIGINAL NEW CORRESPONDENCE
☐ ADVERSE REACTION REPORT	☐ PAPER NDA	☐ FORMULATIVE REVIEW
☐ MANUFACTURING CHANGE/ADDITION	☐ CONTROL SUPPLEMENT	☐ OTHER *(SPECIFY BELOW)*:
☐ MEETING PLANNED BY		

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

☐ DISSOLUTION	☐ DEFICIENCY LETTER RESPONSE
☐ BIOAVAILABILTY STUDIES	☐ PROTOCOL-BIOPHARMACEUTICS
☐ PHASE IV STUDIES	☒ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL	☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES	☐ SUMMARY OF ADVERSE EXPERIENCE
☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)	☐ POISON RISK ANALYSIS
☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP	

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Introduction:

Epinephrine Injection is indicated in the emergency treatment of allergic reactions (anaphylaxis) to insect stings or bites, foods, drugs and other allergens as well as idiopathic or exercise-induced anaphylaxis.

Teva Pharmaceuticals USA, requests a waiver of *in vivo* bioequivalence (BE) testing for its Epinephrine Injection, Auto-Injector, 0.15 mg/0.3 mL and 0.3 mg/0.3 mL. The Reference Listed Drug (RLD) product is EpiPen® (epinephrine injection) Auto-Injector, 0.3 mg/0.3mL and EpiPen® Jr (epinephrine injection) Auto-Injector, 0.15 mg/0.3 mL, manufactured by Mylan Speclt (NDA 019430, approved on Dec 22, 1987). The RLD has the therapeutic equivalence code of "BX" in the Electronic Orange Book.

The drug product is intended for both Intramuscular and Subcutaneous administration. The formulation of the test product is NOT qualitatively (Q1) and quantitatively (Q2) the same as reference product. The test product contains sodium tartrate dihydrate as (b) (4) whereas the reference product contains no (b) (4) [1].

Formulations Comparison between the Test Product and Reformulated Reference Product

Ingredients	Function	Test Product- Re-Formulated Amount (mg) per 0.3 mL Delivered		Reference Product Amount (mg) per 0.3 mL Delivered[2]	
		0.15 mg	0.3 mg	0.15 mg (EpiPen® Jr)	0.3 mg (EpiPen®)
Epinephrine, USP	Active Ingredient	0.15 mg	0.3 mg	0.15	0.3
Sodium Chloride, USP/NF	(b) (4)	1.8 mg	1.8 mg	1.8	1.8
Sodium Metabisulfite, NF		0.4 mg	0.4 mg	0.5	0.5
Sodium Tartrate Dihydrate, NF		0.2 mg	0.4 mg	-	-
Hydrochloric Acid, USP/NF		To adjust pH	To adjust pH	To adjust pH	To adjust pH
Water for Injection, USP		Q.S.	Q.S.	Q.S.	Q.S.

The amount of sodium tartrate dihydrate in the test formulation was found to be within the acceptable limits for Intramuscular administration based on the FDA's Inactive Ingredient database (IID). However, FDA's IID does not include any information for for the above stated inactive ingredient for the subcutaneous route of administration. Therefore, on 6/25/2015, the Division of Bioequivalence III (DBIII) submitted a consultation request to the Division of Clinical Review (DCR) to determine whether the amount of sodium tartrate dihydrate used in the formulation of Teva's Epinephrine Injection, 0.3 mg/0.3 mL and 0.15 mg/0.3 mL posed a safety concern when administered subcutaneously[3]. Since a limit

[1] GDRP, ANDA 090859, http://panorama.fda.gov/PanoramaDocMgmt/webhooks/viewdownload?id=090026f880ae507f, Suman Dandamudi, 7/2/2015

[2] DARRTS for NDA 019430: KIM, CHONG HO 07/28/2008 N/A 07/28/2008 REV-QUALITY-03(General Review) Supplement-40 (Manufacturing (CMC)) Archive

[3] GDRP for ANDA 090589, Clinical Consult Request:

for the above stated inactive ingredient for subcutaneous administration was not provided in the IID in the amendment dated 12/30/2014, the firm submitted the toxicology study report to support the safety of above stated amount of sodium tartrate dihydrate in the test formulation via subcutaneous administration.

DCR concluded that the firm should consider re-formulating its test product without sodium tartrate dihydrate for the following reasons[4]:

(b) (4)

On February 23, 2016 the deficiency related to the inactive ingredient, sodium tartrate dihydrate was conveyed to the firm through a Complete Response Letter[5].

On March 8, 2016, the firm submitted a request for a Post Complete Response Meeting Request (post CR MR) with the OGD for clarification of sodium tartrate dihydrate to be considered as novel excipient for the subcutaneous route of administration[6].

Issue:

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http://panorama.fda.gov/PanoramaDocMgmt/document/download/090026f880ae5418, Suman Dandamudi, 7/2/2015

[4] GDRP for ANDA 090589, Consult Response: http://panorama.fda.gov/PanoramaDocMgmt/webhooks/viewdownload?id=090026f880c04574, Karen Feibus, 10/29/2015

[5] GDRP for ANDA 090589: Final Decision- http://panorama.fda.gov/document/view?ID=577174980126098d4364c58e4da09ed9, Lakeeta Karr, 6/27/2016

[6] DARRTS for 090589: 03/08/2016: Meeting/Meeting Request General Information-1

[7] http://quantum.esu.edu/~scady/Chem495/fisher.pdf

[8] http://www.organicchem.org/oc2web/lecture/outlines/acidsbases.pdf

[9] http://www.shimadzu.com/an/hplc/support/lib/lctalk/29/29intro.html

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(b) (4)

Based on the information provided by the firm in their submission dated March 8, 2016, the Division of Bioequivalence III (DBIII) agrees with the firm that the amount of sodium tartrate dihydrate is within the acceptable limits for subcutaneous administration based on the FDA's Inactive Ingredient database[11].

Consult Request:

Based on the above facts, DBIII is seeking expert opinion from the Division of Chemistry in the Office of Pharmaceutical Quality (OPQ) on the following question:

Does the firm's justification that sodium tartrate (b) (4) (b) (4)

In addition to the consult request submitted to the OPQ, DBIII is also requesting the DCR to comment if the presence of such amount of (b) (4) should be safety concerns when administrated subcutaneously in pediatric population.

[11] GDRP for ANDA 090589: Post CR MR Review- http://panorama.fda.gov/PanoramaDocMgmt/webhooks/viewdownload?id=090026f880cf427c, Ke Ren, 5/13/2016

DBIII is planning to coordinate the consults responses from both groups, and if necessary, arrange a meeting between DCR, OPQ and DBIII, following the consults, to reach the final recommendations that are acceptable to all disciplines.

Attachments:

1) Attachment #1: Firm's Justification[12]

CLARIFICATION SOUGHT ON BIOEQUI\

2) Attachment #2: Consult Request Review to DCR

A090589N000DB_C07 052016 - DCR.doc

Thank you for your consideration. Please address comments/questions to nilufer.tampal@fda.hhs.gov

SIGNATURE OF REQUESTER Harikrishna Devalapally, Ph.D.	METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

[12] EDR, ANDA 90859, Application 090589 - Sequence 0026 - Cover Letter 08Mar2016 - Teleconference Meeting Request, Date 3/8/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

MEMORANDUM

Food and Drug Administration
Center for Devices and
Radiological Health
Office of Device Evaluation
White Oak Building 66
10903 New Hampshire Avenue
Silver Spring, MD 20993

Date: October 23, 2015

From: Alan Stevens, Reliability Engineering
OMPT/CDRH/ODE/DAGRID/GHDB

To: Xiaohua Huang, Staff Fellow
OMPT/CDER/OPQ/OLDP/DIRPII/IRBIV

Subject: CDRH Consult for ANDA 90589, ICC1500320, Autoinjector for delivery of epinephrine and trainer device

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1. Purpose of Memo

CDER has requested that CDRH provide a review of an autoinjector for delivery of epinephrine under ANDA 90589.

The ANDA contains three separate device constituent parts:

- Epinephrine Injection USP, 0.3 mg (Auto-Injector)
- Epinephrine Injection USP, 0.15mg (b) (4) Auto-Injector
- Epinephrine Injection, USP (Auto-Injector Trainer)

CDRH's safety and effectiveness evaluation will consider the design related aspects of drug delivery and training devices separately.

Review of usability and drug / device interaction (both in-use and in storage) are deferred to the appropriate review divisions in CDER.

2. Review Documents and LOA References

Review Documents

- ANDA 90589, Sequence #20
- Device Master File - MAF (b) (4), Amendment 15, (drug delivery auto-injectors)
    - Section 1 – 7 ((b) (4) (b) (4). These sections / device were not considered in the evaluation of ANDA 90589)
    - Appendices 1 – 31
- Device Master File – MAF (b) (4) (auto-injector trainer)

The letters of authorization, permitting FDA to cross-reference the master files, are located in ANDA 90589 Seq#20, Section 1.4.

3. CDRH Review Team

The CDRH review team included the following individuals:

Reviewer	Discipline
CDR Alan Stevens	Engineering
Sarah Mollo, Ph.D.	Biocompatibility

4. Introduction

The ANDA 90589, Sequence #20 contains three device constituents related to the injection of epinephrine:

- Epinephrine Injection USP, 0.3 mg (Auto-Injector)
- Epinephrine Injection USP, 0.15mg ((b)(4) Auto-Injector)
- Epinephrine Injection, USP (Auto-Injector Trainer)

Each Epinephrine Injection USP, 0.3 mg (Auto-Injector) delivers **a single dose** of 0.3 mg epinephrine injection, USP, 1: 1000, (0.3 mL) in a sterile solution.

Each Epinephrine Injection USP, 0.15 mg (Auto-Injector Jr.) delivers **a single dose** of 0.15 mg epinephrine injection, USP, 1: 2000, (0.3 mL) in a sterile solution.

Per the clinical pharmacology section of the proposed USPI, epinephrine is the drug of choice for the emergency treatment of severe allergic reaction (Type I) to insect stings or bites, foods, drugs, and other allergens.

It can also be used in the treatment of anaphylaxis of unknown cause (idiopathic anaphylaxis) or exercise-induced anaphylaxis. When given intramuscularly or subcutaneously it has a rapid onset and short duration of action. Epinephrine acts on both alpha and beta adrenergic receptors. 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 that helps alleviate bronchospasm, wheezing and dyspnea that may occur during anaphylaxis. Epinephrine also alleviates pruritus, urticaria, and angioedema and may be effective in relieving gastrointestinal and genitourinary symptoms associated with anaphylaxis because of its relaxer effects on the smooth muscle of the stomach, intestine, uterus, and urinary bladder.

Table 1 - Indications for Use

Product	Indications for Use
Epinephrine Injection USP, 0.3 mg (**Auto-Injector)** Epinephrine Injection USP, 0.15mg (b) (4) **Auto-Injector**	Epinephrine Injection USP, 0.3 mg (Auto-Injector) and Epinephrine Injection USP, 0.15 mg (Auto-Injector Jr.) are indicated in the emergency treatment of allergic reactions (Type I) including anaphylaxis to stinging insects (e.g., order Hymenoptera, which include bees, wasps, hornets, yellow jackets and fire ants) and biting insects (e.g. triatoma, mosquitos), allergen immunotherapy, foods, drugs, diagnostic testing substances (e.g., radiocontrast media) and other allergens, as well as idiopathic anaphylaxis or exercise-induced anaphylaxis. Epinephrine Injection USP, 0.3 mg (Auto-Injector) and Epinephrine Injection USP, 0.15 mg (Auto-Injector Jr.) are intended for immediate administration in patients, who are determined to be at increased risk for anaphylaxis, including individuals with a history of anaphylactic reactions. Selection of the appropriate dosage strength is determined according to patient body weight (see **DOSAGE AND ADMINISTRATION** section). Such reactions may occur within minutes after exposure and consist of flushing, apprehension, syncope, tachycardia, thready or unobtainable pulse associated with a fall in blood pressure, convulsions, vomiting, diarrhea and abdominal cramps, involuntary voiding, wheezing, dyspnea due to laryngeal spasm, pruritus, rashes, urticaria or angioedema. Epinephrine Injection USP, 0.3 mg (Auto-Injector) and Epinephrine Injection USP, 0.15 mg (Auto-Injector Jr.) are intended for immediate self-administration as emergency supportive therapy only and are not a substitute for immediate medical care.
Epinephrine Injection, USP (**Auto-Injector Trainer)***	For the purpose of practicing use of the epinephrine autoinjector.

*This statement is inferred from a review of the labeling.

Dosage and Administration of Epinephrine Autoinjector
The following information is copied from the draft USPI in ANDA 90589. Important language, as it relates to CDRH's device performance evaluation, is emphasized in **bold** font.

Epinephrine Injection USP, 0.3 mg (Auto-Injector) or Epinephrine Injection USP, 0.15 mg (Auto-Injector Jr.) prescribers should ensure that the patient or caregiver understands the indications and use of this product. A health care provider should review the patient instructions and operation of the Epinephrine Injection USP, 0.3 mg (Auto-Injector) or Epinephrine Injection USP, 0.15 mg (Auto-Injector Jr.), in detail, with the patient or caregiver. Inject Epinephrine Injection USP, 0.3 mg (Auto-Injector) or Epinephrine Injection USP, 0.15 mg (Auto-Injector Jr.) intramuscularly or subcutaneously into the anterolateral aspect of the thigh, **through clothing if necessary**. See detailed Directions for Use on the accompanying Patient Instructions.

Selection of the appropriate dosage strength is determined according to patient body weight. Epinephrine Injection USP, 0.3 mg (Auto-Injector) delivers 0.3 mg epinephrine injection (0.3 mL, 1:1000) and is intended for patients who weigh 30 kg or more (approximately 66 pounds or more). Epinephrine Injection USP, 0.15 mg (Auto-Injector Jr.) delivers 0.15 mg epinephrine injection (0.3 mL, 1:2000) and is intended for patients who weigh 15 to 30 kg (33 - 66 pounds). Each Epinephrine Injection USP, 0.3 mg (Auto-Injector) or Epinephrine Injection USP, 0.15 mg (Auto-Injector Jr.) contains a single dose of epinephrine.

Since the doses of epinephrine delivered from Epinephrine Injection USP, 0.3 mg (Auto-Injector) or Epinephrine Injection USP, 0.15 mg (Auto-Injector Jr.) are fixed, consider using other forms of injectable epinephrine if doses lower than 0.15 mg are deemed necessary. The prescriber should carefully assess each patient to determine the most appropriate dose of epinephrine, recognizing the life-threatening nature of the reactions for which this drug is indicated. With severe persistent anaphylaxis, repeat injections with an additional Epinephrine Injection USP, 0.3 mg (Auto-Injector) or Epinephrine Injection USP, 0.15 mg (Auto-Injector Jr.) may be necessary.

Patients should be instructed to periodically visually inspect the epinephrine solution for particulate matter and discoloration. If the solution contains particulate matter or develops a pinkish color or becomes darker than slightly yellow, the patient should immediately contact their physician for a replacement, since these changes indicate that the effectiveness of the drug product may be decreased.

How Supplied
Epinephrine Injection USP, 0.3 mg (Auto-Injectors) (epinephrine injections, USP, 1:1000, 0.3 mL) are available in individual cartons, NDC 0703-9350-21, and as Epinephrine Injection USP, 0.3 mg (Auto-Injector) 2-Pack, NDC 0703-9350-20, a pack that contains two Epinephrine Injection USP, 0.3 mg (Auto-Injectors) (epinephrine injections, USP, 1:1000, 0.3 mL) and one Epinephrine Injection, USP (Auto-Injector) trainer device.

Epinephrine Injection USP, 0.15 mg (Auto-Injectors Jr.) (epinephrine injections, USP, 1:2000, 0.3 mL) are available in individual cartons, NDC 0703-9400-21, and as Epinephrine Injection USP, 0.15 mg (Auto-Injector Jr.) 2-Pack, NDC 0703-9400-20, a pack that contains two Epinephrine Injection USP, 0.15 mg (Auto-Injectors Jr.) (epinephrine injections, USP, 1:2000, 0.3 mL) and one Epinephrine Injection, USP (Auto-Injector) trainer device.

Store at 25°C (77°F); excursions permitted to 15°C-30°C (59°F-86°F) (See USP Controlled Room Temperature). Contains no latex. Protect from light.

5. Review of Epinephrine Auto-Injectors

Description
The (b) (4) Auto-Injector is an automated drug delivery device for the administration of Teva Pharmaceuticals' epinephrine from standard pre-filled syringes. It is a single-use, disposable, (b) (4) drug delivery device, designed to administer no less than 0.3 mL from the 1.0 mL pre-filled sterile syringe during one injection. (b) (4)
(b) (4)
(b) (4) The device may be used by patients, caregivers, or health professionals for the delivery of epinephrine medication. (b) (4)
(b) (4)

The (b) (4) Auto-Injector is designed specifically for Teva Pharmaceuticals for intramuscular or subcutaneous delivery of epinephrine to treat severe allergic reactions, which may lead to anaphylactic shock.

Both adult and junior versions/models will be available. Users who weigh 15 to 30 kg (33 – 66 pounds) are instructed to use the green Epinephrine Jr. Auto-Injector: the amount of injected drug will be 0.15 mg

of epinephrine in a 0.3 mL aqueous solution. Users who weigh 30 kg or more (approximately 66 pounds or more) are instructed to use the yellow Epinephrine Auto-Injector: the amount of injected drug will be 0.3 mg of epinephrine in a 0.3 mL aqueous solution.

Model	Short Description
Adult model	Delivery of a 0.3 mg dose of epinephrine for patients who weigh 30 kg or more (approximately 66 pounds or more).
Junior model	Delivery of a 0.15 mg dose used for patients who weigh 15 to 30 kg (33 – 66 pounds).

(b) (4)

(b) (4)

The following usage information is copied from the draft Patient Instructions for Use (found in ANDA 90589, Section 1.14.2.3/.

(b) (4)

[redacted]

(b) (4)

Differences between Auto-Injector and Jr Auto-Injector

The two versions of Epinephrine Auto-Injector are differentiated primarily on the dose of epinephrine supplied, (e.g., 0.15mg vs. 0.30 mg). The following table itemizes all differences between the two presentations.

The information is found in the Material Specification Sheets in ANDA 90589, Section 3.2.P.5.1

- 0.3mg Auto-Injector Material Specification Sheet – 1000692, dated December 23, 2014
- 0.15mg Auto-Injector Material Specification Sheet – 1000691, dated December 23, 2014

Table 2 - Differences between Adult and (b) (4) Auto-Injectors

Characteristic	0.3 mg ADULT Auto-Injector	0.15 mg (b) (4) Auto-Injector
Device Color Scheme and Component Identification	The device will be orange needle guard with a blue safety, **yellow** safety cap, **yellow** trigger, and **yellow** label.	The device will be orange needle guard with a blue safety, **green** safety cap, **green** trigger, and **green** label.

CDRH REVIEWER DISCUSSION

The consulting reviewer was unable to locate a complete comparison of design and performance specifications for the two epinephrine combination product presentations included in ANDA 90589.

Design Controls

To evaluate the design of the adult and junior versions of the epinephrine auto-injectors, the consulting reviewer is expecting to find the following types of design control documents (per 21 CFR 820) within the ANDA 90589 application:

- Design Inputs in the form of device requirements, including:
    - Functional
    - Physical
    - Appearance
    - Reliability
    - Safety

- Risk Analysis information which characterizes and evaluates the risks to the user or patient. The anlaysis should consider expected use, reasonably foreseeable mis-use, and potential system failure states. Such an analysis should clearly describe system hazards, mitigations implemented to reduce the risk of those hazards, effectiveness of the mitigation, as well as conclusions of the acceptability of system risks within the final finished combination product.

The applicant has referenced a device master file, MAF (b) (4) supplied by (b) (4) The consulting reviewer expects the master file to contain the following design control documents (per 21 CFR 820.30):

- Design Outputs – This includes documentation explaining how (b) (4) has designed the devices to meet the design input requirements supplied by the combination product developer, Teva Pharmaceuticals.

- Design Verification and Validation Evidence – evidence will take the form of traceability documents, bench test reports, diagrams, bill of materials, etc.

Design Requirements, Specifications, Verification and Validation Assessment

The CDRH consulting reviewer has evaluated the ANDA 90589 documentation, and located the following specification-related information:

- Specifications (Section 3.2.P.5.1)
- Justification of Specifications (Section 3.2.P.5.6)
- Device – (b) (4)
- Device –
- Device –
- Device –

The specification document in Section 3.2.P.5.1 provides the following device constituent specification for the autoinjectors:

Table 3 - ANDA 90859 Release Specifications - Epinephrine Auto-Injector

Test	Specification
Device color scheme and component identification	Adult: The device will be orange needle guard with a blue safety, yellow safety cap, yellow trigger, and yellow label Junior: The device will be orange needle guard with a blue safety, green safety cap, green trigger, and

	green label
Viewing Window	(b) (4) windows shall not be obstructed. Drug product shall be visible through both windows
	(b) (4)
Solution description when viewed through viewing windows	(b) (4)
Label	Free from peeling, discoloration and bleeding of ink and any other physical characteristics specific to the label (compared to the attachments)
Breakaway Force (Break Force)	(b) (4) lb-force
Trigger Force	NMT (b) (4) force
Delivery volume, mL	NLT 0.3 mL

CDRH REVIEWER DISCUSSION

The release specifications do not appear to incorporate essential performance characteristics for the needle component. These include the following characteristics:

- **Needle injection depth**
- **Injection initiation at correct needle depth**
- **Injection completion prior to needle retraction**
- **Needle fracture / bending stress**
- **Needle bevel**
- **Injection pathway patency**
- **Physical stability of needle / syringe connection**

ANDA 90589, Section 3.2.P.7 contains four specification documents for the autoinjectors.
These specification documents identify dimensional, color, and shape specifications.

(b) (4)

CDRH REVIEWER DISCUSSION

The statement "For Reference Only", is not understood by the CDRH consulting reviewer.

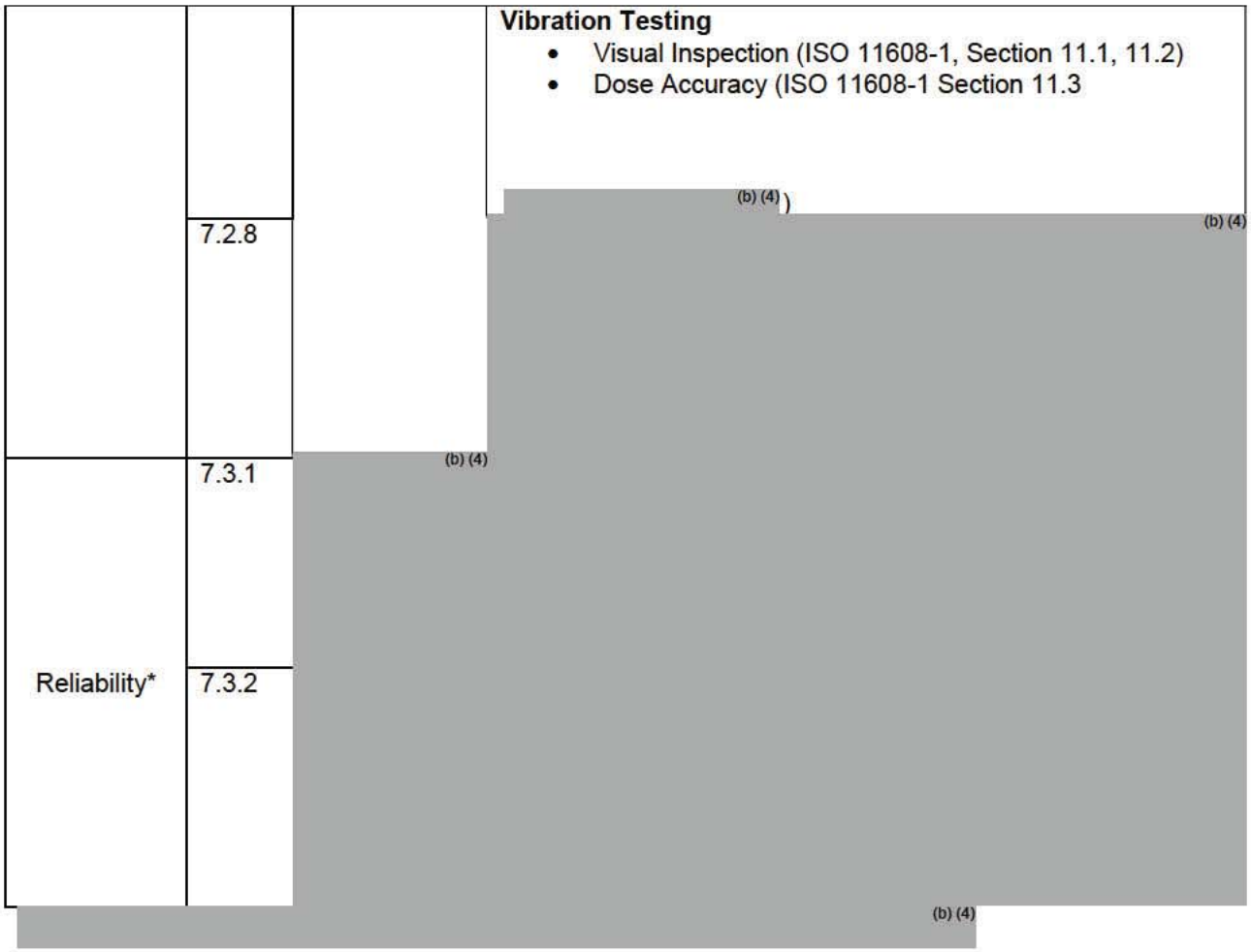
Master File Requirements Specification Documentation

(b) (4)

The CDRH reviewer is identifying the requirements specifications from the Master File Holder PRD document that relate to the specifications set forth by Teva in ANDA 90589, Section 3.2.P.5.1 or that the reviewer believes are essential the functionality of the device.

Table 5 - MAF (b) (4) Specifications

Category	Req ID	Requirement	Specification
Functionality	7.2.1	Accuracy	The device will expel no less than 0.3 mL when loaded with a customer supplied pre-filled syringe, nominally filled with 1.0 mL of drug product, and with a stopper position range as specified in feature number 7.6.3 of this document. (b) (4)
	7.2.2 7.2.3	Injection Depth*	Adult Device – Needle Insertion Depth to be (b) (4) Junior Device – Needle Insertion Depth to b
	7.2.4 7.2.5 7.2.6 7.2.7	Reliability Testing*	ISO 11608-1 Requirements **Cool, Standard, and Warm Atmosphere** • Visual Inspection (ISO 11608-1, Section 11.1, 11.2) • Dose Accuracy (ISO 11608-1 Section 11.3 (b) (4) **Free Fall Test** • Visual Inspection (ISO 11608-1, Section 11.1, 11.2) • Dose Accuracy (ISO 11608-1 Section 11.3 (b) (4) **Dry Heat and Cold Storage** • Visual Inspection (ISO 11608-1, Section 11.1, 11.2) • Dose Accuracy (ISO 11608-1 Section 11.3 (b) (4)



CDRH REVIEWER DISCUSSION

1. **The Master File product requirements document does not reference any Teva-supplied requirements. The PRD actually states in some case that requirements satisfaction is dependent on the specific syringe being loaded into the auto-injector (see Accuracy as one example).**

2. **Further, while the verification of the master file holder-specified requirements can be verified, the validation of these requirements for an epinephrine rescue-medication injector need to be supplied by the ANDA holder.**

3. **Reliability specifications are inadequately defined. The applicant references a standard, which includes some precondition tests followed by a visual and functionality assessment. However, it is unclear how these tests provide assurance that the ANDA 90589 autoinjector will reliably inject epinephrine when required by the patient. The CDRH consulting reviewer does not believe that reliability specification, and related test reports, set forth by the Master File Holder are acceptable for a rescue medication.**

4. **For verification and reliability testing provided by the Master File Holder, it is unclear that the samples tested, including the syringe, needle, test fluid, etc. are the same as the final combination product presented in ANDA 90589.**

5. (b) (4)

6.

7.

8. **A lot of the verification studies required 95% confidence with 95% conformance. The applicant states that their internal protocols (b) (4) specify a sample size of 30 to achieve the specified statistics. However, we would expect the specified statistics to require a sample size of 59. The applicant should justify the statistic used to support a sample size of 30. More importantly, the CDRH reviewer believes that the 95% / 95% statistics used is inadequate for this application given the risk associated with device malfunction. The applicant should provide data for 99% reliability with 95% confidence interval.**

9. **Shipping studies could not be located.**

Device Risk Analysis

The application (ANDA 90589 and MAF (b) (4)) does not appear to contain a risk analysis for the device design.

For drug delivery devices, CDRH believes that the potential hazards generally fall within the following categories:

Table 6 - Drug Delivery Device Hazards

Drug Delivery Device Hazards	Hazard Definitions
Delivery Error	Intended medication selected and delivery attempted, but failure to deliver within the right time, dose, volume, patient, or anatomical or physiologic site specifications. This can include over delivery, under delivery or delay in delivery situations.
Incorrect Therapy	Failure to select or deliver the intended medication because

	the wrong substance was selected for delivery.
Biological/Chemical Contamination	Unintended contact with biological or chemical substance, or unintended patient or provider physiologic response to intended biological or chemical substance.
Traumatic Injury	Burns, cuts, abrasions, air embolisms, electric shock, etc.

The CDRH review will focus primarily on Delivery Error hazards. The Incorrect Therapy hazards are also important, but the causes are generally related to combination product misuse or drug degradation issues, which are being reviewed by CDER.

Delivery Error Hazards being reviewed by CDRH are considered to include the following potential causes:

Table 7 - Delivery Error Hazards

Device Hazard	Potential Cause
Delivery Error	Device fluid path occlusion
	Failure to inject / incomplete injection
	Unexpected separation of components
	Excessive drug delivery
	Component failure
	Inadequate container dimensions
	Inadequate / Insufficient device activation
	Device aging, shipping, storage and / or use conditions result in device malfunction prior to expiry
	Injection initiates prior to needle reaching the correct tissue depth of penetration.
	Premature retraction of needle before injection ends
	Needle fracture (e.g., injection through clothing, skin tissue)
	Needle unable to penetrate to correct depth of penetration (clothing, skin, etc)

The applicant might identify additional causes. It is expected that the manufacturer will conduct their own analysis of causes, failure mechanisms, and event sequences leading to the delivery error event.

6. Review of Auto-Injector Training Device

Description

ANDA 90589 does not provide a specific description of the epinephrine autoinjector trainer (the trainer) device. The ANDA does contain labeling and drawings, which infer some information on the trainer.

The draft trainer labeling from ANDA 90589 provides a comparison of the trainer to the epinephrine autoinjector products.

Table 8 - Comparison Table from draft Trainer Labeling, ANDA 90589

(b) (4)

[redacted]

Device Requirements, Specifications, Verification and Validation

ANDA 90589 includes one specification document describing the training device requirements:

- ANDA 90589 Specifications (Section 3.2.P.5.1)

Table 9 - Trainer Release Specifications

Test	Specification
Trainer color scheme and component identification	Blue safety clip, grey cap, white label. (b) (4) [redacted]
Label	Free from peeling, discoloration and bleeding of ink and any other physical characteristics specific to the label (compared to the attachments)

Device Master File Supplied Specifications (MAF (b) (4))

Specifications for the trainer are located with device master file, MAF (b) (4), appendix 1.

(b) (4)

The specification document includes a list of required features or requirements. Some of these requirements are obvious and do not require a complete review, such as req #1 – The trainer will not be designed to be capable of expelling fluid or inserting a needle. The following table identifies the requirements which the CDRH reviewer considers important for the premarket review.

The primary focus of the CDRH review will be to assure that the engineering specifications for the trainer device are equivalent to the epinephrine auto-injectors in order to assure that the training experience is adequately representative of actual injection.

Table 11 - Comparison of Trainer & Epinephrine Auto-Injector Specifications

Trainer Requirement #	Trainer Specification	Comparison to Epinephrine Auto-Injector Products
3	The trainer will have a flip off trainer activation tab on the end of the device distal to where the needle would be. The force needed to remove it will be (b) (4) (b) (4).	Identical
5	The trainer size will be no smaller than (b) (4) (b) (4)	Identical
6	The trainer safety cap will have a torque removal force not to exceed (b) (4). The safety cap will have a cam feature to facilitate removal by turning. The word "twist" will be printed on a visible surface to correspond to directions within the instructions for use.	Identical
8	The trainer simulated injection trigger force to be a maximum of (b) (4). The trigger force is defined as the force required to release the trigger from the latch to initiate device injection simulation. Note: This applies only after the initial break force has been exceeded, allowing the needle guard to retract.	(b) (4)
10	The trainer will have an audible and / or tactile end of shot indicator.	Equivalent

29	(b) (4)
30	

CDRH REVIEWER DISCUSSION

1. (b) (4)
2.
3.

4. **The CDRH Reviewer was unable to locate information to verify the Trainer Requirement #10 – Visual and/or Tactile end-of-shot confirmation. Further, the Trainer Patient Labeling states that the Trainer does not have the "red" window-after injection to confirm the injection process is complete. It appears that the Trainer Requirement #10 has not been satisfied. The CDRH reviewer believes it is important to train users properly on the injection confirmation process.**

Device Risk Analysis
Neither ANDA 90589 nor MAF (b) (4) contain a risk analysis for the trainer device.

The CDRH reviewer has identified two potential risks for the Trainer. Most of the Trainer risks are likely to be associated with the fidelity of the training experience to the actual use of the epinephrine auto-injector.

1. How has Teva assured that the trainer device is not mistaken for the actual epinephrine device during manufacturing operations and in-use or vice versa?
2. Can the performance of the trainer degrade beyond to the point where it is no longer valid for training purposes?
3. Is the use of the Trainer equivalent to the Epinephrine AutoInjector?

CDRH REVIEWER DISCUSSION
The CDRH reviewer believes that issue #2 and #3 are adequately addressed by the equivalence of the performance specifications, notwithstanding the deficiencies associated with those specifications.

Issue #1 is not addressed by the design specifications, and therefore will be supplied as a separate information request to the ANDA holder.

Therefore, the CDRH consulting reviewer does not believe it is necessary to request an explicit risk analysis for the trainer device.

4. Device Deficiencies

The following section contains information requests for the ANDA holder followed by information requests for the device master file holder.

Information Requests for the ANDA HOLDER

1. The release specifications for the epinephrine autoinjectors and the trainer device do not appear adequately complete. The release specifications for the epinephrine auto-injectors do not include essential performance requirements, such as needle dimensions, needle injection depth, needle resistance to bending or breakage, injection does not initiate until the needle reaches intended injection depth, injection completion prior to needle retraction, needle bevel attributes, drug injection pathway patency, physical stability of needle / syringe junction, visual / audible indicator for end of injection, etc. Similarly, the trainer device release specifications do not include essential performance attributes, such as break force, trigger force, injection confirmation, etc. Provide a revised release specification to assure that the release specifications include the essential performance specifications for epinephrine injection with each auto-injector presentation and the trainer device.

2. The ANDA describes two epinephrine combination product presentations (e.g., 0.3mg and 0.15mg). However, the Agency was unable to locate a complete comparison of design and performance specifications for the two epinephrine combination product presentations included in ANDA 90589. Provide a complete comparison of the differences between the two product presentations.

3. The ANDA does not provide a design control document that identifies the design requirements for the device constituent parts of the combination product. The combination product developer is responsible for specifying the design and performance of the device constituent parts of combination product and assuring that those requirements are verified and validated. If you choose to rely on third party contract manufacturers or designers, it is expected that you, as the combination product developer, will communicate design requirements to those suppliers and assure that they have been completely and comprehensively implemented. . The ANDA submission should contain sufficient details regarding design controls that the Agency can be confident that you, as the ANDA sponsor, have developed product requirements and assured their verification and validation. Provide the design requirements document for the epinephrine

auto-injector combination product and provide evidence validating that the design specifications developed by the master file holder have met your design requirements.

4. The labeling states that injection may occur through clothing. Review of the ANDA does not identify any design requirements for the injector, needle, or assembled combination product to specify adequately reliable injection through clothing. In addition to having explicit requirements for injection through clothing, the requirements document should specify adequately valid requirements for the needle to assure that the needle will not bend, break or separate from the syringe during injection through clothing. Additionally, FDA was unable to locate any performance data to verify and validate that the combination product will reliably inject epinephrine to the target injection site when injected through clothing. Clothing attributes might include material type, density, thickness, etc. Provide evidence that the combination product will reliably inject epinephrine to the target injection when the injection occurs through clothing. The evidence should include design requirements and performance data with adequately challenging conditions (e.g., sample size, clothing types, injection angles, transversely applied stress (transverse to injection angle), etc.).

5. The ANDA does not include a device hazards analysis confirming that reasonably foreseeable delivery error hazards have been identified and mitigated. To assure the safety and effectiveness of the delivery system, we need to review documentation demonstrating that potential causes, failure mechanisms, and / or events that could result in failure to deliver epinephrine to the intended injection site have been identified and mitigated. We have identified some potential hazards that need to be addressed, which include:

    - Device fluid path occlusion
    - Failure to inject or incomplete injection
    - Unexpected separation of components
    - Excessive drug delivery
    - Component failure
    - Inadequate container dimensions
    - Inadequate or Insufficient device activation
    - Device aging, shipping, storage and / or use conditions resulting in device malfunction prior to expiry
    - Injection initiates prior to needle reaching the intended injection site.
    - Premature retraction of needle before injection is completed.
    - Needle bend or fracture (e.g., injection through clothing, skin tissue)
    - Needle unable to penetrate to correct depth of penetration (clothing, skin, etc)

    Your own analyses may have identified additional device hazards. Please provide a hazard analysis (e.g. fault tree analysis) identifying the potential causes of the device hazards we have identified from our review and any additional system hazards you may have identified. For each identified cause, provide the following:

    a. Describe the control method or mitigation for each identified cause.

    b. For each cause, provide an explanation justifying the adequacy of the control to mitigate the respective system hazard.

c. Provide evidence verifying the control method or mitigations adequately address the respective cause / hazard under conditions of use that are reasonably challenging.

6. The intended use of your product involves the delivery of medication to treat a potentially life threatening condition within use environments that may offer limited opportunity for alternative treatments. As such, the Agency believes that it is essential for your product to perform reliably. The ANDA does not include adequate documentation to verify that the combination product will reliably inject epinephrine throughout the expiry period. Product reliability should be supported by explicit reliability specifications, hazard analysis, and performance data. Therefore, we are requesting your commitment to establish reliability requirements for the combination product and complete testing which verifies combination product reliability.

   Provide the following:

   a. Establish reliability requirements for your combination product. It is recommended that reliability be directly specified as R(t) = x%, where t = time and x% = probability of meeting essential performance requirements. These requirements should be objective and relate to the ability of a population of devices to meet essential performance requirements after pre-conditioning to elements outlined within c, below. The reliability requirements should be verified with a high degree of statistical confidence.

   b. Provide rationale and justification supporting the clinical acceptability of the established reliability requirements.

   c. Provide protocols and data to verify the reliability requirements specified have been met.

   d. Final assembled combination products that are assessed within the reliability test should be preconditioned to worst-case reasonably foreseeable conditions. The Agency has conceived the following recommended preconditioning activities, however you should provide rationale supporting the final precondition elements chosen, and the order in which the products are conditioned. Your assessment of the preconditioning parameters should be based on your own failure analyses (e.g., fault tree analysis) in order to assure that the scope of preconditions and their boundary values are adequately correct and complete. It is noted that preconditioning requirements in international standards, such as ISO 11608-1, that are typically used for evaluation of auto-injectors, might be considered inadequate to verify and validate high reliability needed for an epinephrine auto-injector. Therefore, all preconditioning and test methodologies should be validated per your hazard analysis and reliability requirements.

      i. Shipping
      ii. Aging
      iii. Storage orientation and conditions
      iv. Vibration
      v. Shock (e.g., resistance to random impacts, such as being dropped)

   e. Devices assessed within the reliability analysis should be activated under worst-case reasonably foreseeable conditions. The Agency has conceived the following recommended circumstances of activation; however you should provide rationale supporting the final circumstances of activation chosen.

i. Activation orientation
ii. Environmental temperature
iii. Injection site conditions (clothing type, skin type, etc.)

f. Provide a revised post-approval commitment protocol to include evaluation of the reliability performance specifications for each auto-injector presentation.

7. Batch Analysis records provided in Section 3.2.P.5.4 describe delivery volume testing. However, the referenced method (SOP (b) (4)) does not appear to describe testing to verify specifications for delivery volume. (see section 3.2.P.5.4 COA references). Please update the batch analysis records with the reference to the auto-injector delivery volume verification data, and provide the record of the testing.

8. There are various requirements for shelf life, storage, expiry, etc. for the device constituent parts and the final combination product found within the ANDA and device master file. The Agency is unable to verify from the documentation provided that the various shelf life dates for device constituents and the final combination product have been evaluated to assure that the shelf life of a constituent part will not be reached prior to the combination product expiry. Provide information to assure that no device constituent part will reach its shelf life prior to the combination product expiry.

9. Given the sameness in design of the epinephrine autoinjectors and trainer devices, it is important to assure that the products are not mislabeled or otherwise mistaken during the manufacturing of the products. Provide information to assure that the risks associated with mixing the epinephrine autoinjectors and the training device has been adequately mitigated during manufacturing of the combination products.

10. The autoinjector package component specifications (Section 3.2.P.7) include dimensional specifications for the autoinjector package, which includes the statement “For Reference Only”. This statement is not understood in the context of the specification. Clarify the statement “For Reference Only” and clarify the dimensional specifications for the autoinjector components.

11. Please be advised that the Agency has communicated deficiencies regarding content found within MAF (b) (4) and MAF (b) (4) directly to the master file holder(s). The Agency in unable to provide details of these deficiencies to you as the documentation is not contained directly within the ANDA. Approval of the ANDA depends on resolution of the deficiencies communicated to the master file holder. Please work with the master file holder to resolve these concerns and provide responses to MAF-(b) (4) record. Alternatively, and if appropriate, you may provide responses to these questions and supporting documentation to the ANDA record.

Information Requests for the Master File HOLDER

1. We have completed a review of device master file, MAF (b) (4) to evaluate the device constituent parts under ANDA 90589 for injection of epinephrine. We were unable to locate information to validate the completeness and correctness of design requirements and specifications for the auto-injector components to meet the intended use required under ANDA 90589. Additionally, the acceptable reliability and confidence intervals should be included within specifications and justified for the intended use. It is noted from our review that the design specifications do not appear to be complete because there is missing reference to injecting through clothing, at various angles, assuring injection does not initiate until the needle reaches its target depth, Provide evidence which validates that the design specifications of the two auto-injector presentations are

correct and complete in the context of the intended use of the ANDA submission which your master file is intended to support.

2. The Agency is unable to determine that the design specifications provided have been completely verified because the information in the traceability matrix (b) (4) either did not appear to be provided in MAF (b) (4), or the test report provided did not appear to match with the test report recorded in the traceability matrix. For example, (b) (4) (b) (4) (b) (4) Provide an updated design verification traceability matrix with the correct test report numbers, or other evidence, correctly identified and reference its location in MAF (b) (4). Provide any referenced design verification data that is not already be included in MAF (b) (4).

3. After reviewing the design verification test reports, (b) (4) (b) (4) (b) (4) Provide updated design

4. The Agency does not believe that level of reliability achieved in the presented design verification data is adequate. Many of the design verification studies were presented at 95% reliability with a 95% confidence interval. Given that the intended use of the combination product ANDA submission which your master file is intended to support, we do not agree that 95% reliability is adequately safe. Further, the accelerated aging studies and preconditioning studies are considered inadequate. For example:

   a. (b) (4)

   b.

   c.

   d.

ii. (b) (4)

iii.

In conclusion, design verification is considered inadequate because:

- the delivered volume does not appear to meet specifications;
- the reliability specification is considered inadequate for the intended use; and,
- the reliability data is not considered adequate because the studies are not adequately representative of foreseeable in-use conditions and the studies not conclusive for a complete product reliability assessment because they were conducted independtly

Your assessment of the preconditioning parameters should be based on your own failure analyses (e.g., fault tree analysis) in order to assure that the scope of preconditions and their boundary values are adequately correct and complete. It is noted that preconditioning requirements in international standards, such as ISO 11608-1, that are typically used for evaluation of auto-injectors, might be considered inadequate to verify and validate high reliability needed for an epinephrine auto-injector. Provide updated design verification data that demonstrates adequate product reliability throughout the expiry period under foreseeable use conditions.

5. The device master file, MAF (b) (4), contains the epinephrine trainer device. A comparison of the design specifications for the device in MAF (b) (4) and MAF (b) (4) shows that the trigger force specifications are different for the epinephrine injector vs. the training device (b) (4) (b) (4). It is expected that the performance of the trainer device should equivalent to the epinephrine auto-injector. Modify the trigger force specification to be identical to the epinephrine autoinjector specification and verify that the provided trainer trigger force verification data remain adequate.

6. The MAF (b) (4) design requirements for the trainer specify that the trainer have a visual or tacile end of shot indicator. The Agency is unable to confirm that this requirement has been satisfied. Provide evidence to MAF (b) (4) to verify that the requirement for end of shot indicator has been met.

7. You have identified the "Vibex (b) (4) Adult, Junior, and Trainer Devices" as the Test Article in the biocompatibility test reports. Based on this device identification, it is unclear which device type was actually tested and how the testing provided represents the worst case for all three device types. (b) (4) (b) (4) (b) (4) Please clarify which devices were tested. If the devices are not extracted and tested separately, please provide a justification as to why the testing provided represents the worst case conditions of use.

8. [redacted] (b) (4) Please clarify which specific device components are being tested. Additionally, please provide a comparison chart of the components, including the chemical composition of component materials, of the patient contacting components between all three devices.

9. You have provided a list of materials in Appendix 24 in the [redacted] (b) (4) Device and Trainer Biocompatibility Test Report, section 6.3 Materials (p 517); however, it is unclear if this includes any process aids or process additives. Please clarify if the materials identified represent all materials used in the patient/user contacting components of the subject device, including additives and processing agents ([redacted] (b) (4), [redacted] (b) (4)

5. Conclusions

If CDER agrees with the device deficiencies supplied, it is recommended that they be communicated to the ANDA holder and Master File holder, respectively.

If there are questions regarding the information contained in this review or the identified deficiencies, please contact the CDRH consulting reviewer, Alan Stevens, at 301-796-6294 or alan.stevens@fda.hhs.gov.

Digital Signature Concurrence Table	
Reviewer Sign-Off	Alan M. Stevens -S Digitally signed by Alan M. Stevens -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300189211, cn=Alan M. Stevens -S Date: 2015.10.23 16:38:37 -04'00'
Team Lead	Ryan J. Mcgowan -S Ryan J. Mcgowan -S 2015.10.23 16:40:15 -04'00'
Supervisor	Richard C. Chapman -S 2015.10.23 16:50:22 -04'00'

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Lesley-Anne Furlong, M.D,
Acting Director
Division of Clinical Review
Office of Bioequivalence
Office of Generic Drugs

FROM:
Suman Dandamudi, Ph.D.
Through
Hoainhon Nguyen Caramenico, M.S., M.S.,
Acting Director
Division of Bioequivalence III
Office of Bioequivalence
Office of Generic Drugs

DATE	IND NO.	ANDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
06/25/2015		090589	Bioequivalence Review	12/30/2014 and 5/20/2015

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Epinephrine Injection, Auto-Injector		Bronchodilator	09/01/2015 (TAD: 10/21/15)

NAME OF FIRM: Teva Pharmaceuticals USA

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☒ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☒ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

Introduction:
Teva Pharmaceuticals USA, requests a waiver of *in vivo* bioequivalence (BE) testing for its Epinephrine Injection, Auto-Injector, 0.15 mg/0.3 mL and 0.3 mg/0.3 mL. The Reference Listed Drug (RLD) product is EpiPen® (epinephrine injection) Auto-Injector, 0.3 mg/0.3mL and EpiPen® Jr (epinephrine injection) Auto-Injector, 0.15 mg/0.3 mL, manufactured by Mylan Speclt (NDA 019430, approved on Dec 22, 1987). The RLD has the therapeutic equivalence code of "BX" in the Electronic Orange Book.

The test product is NOT qualitatively (Q1) and quantitatively (Q2) the same as RLD product. The test product contains Sodium Tartrate Dihydrate (b) (4) whereas the RLD product contains (b) (4). The IIG limit for the above stated inactive ingredient via Subcutaneous administration is not provided in the IIG database.

Issue:
The test product is intended for both Intramuscular and Subcutaneous administration. The reviewer verified if the amount of Sodium Tartrate Dihydrate used in the test formulation is within the FDA's Inactive Ingredient Guide (IIG) limits based on the MDD of (b) (4).

(b) (4)

The amount of Sodium Tartrate Dihydrate in the test formulation is within the acceptable limits for Intramuscular administration based on the FDA's Inactive Ingredient database. However, the IIG limit for the above stated inactive ingredient for Subcutaneous administration is not provided in the IIG database. Therefore, the firm submitted the toxicology study report[4] demonstrating the safety of Sodium Tartrate Dihydrate used in the test formulation via Subcutaneous administration.

DBIII requests a clinical consult to determine whether the amount of Sodium Tartrate Dihydrate used in the formulation of Teva's Epinephrine Injection, 0.3 mg/0.3 mL and 0.15 mg/0.3 mL should be of a safety concern when administered Subcutaneously.

Section I: Background

In the review of the original submission, the firm's test formulation was deemed to be qualitatively (Q1) and Quantitatively (Q2) the same as the RLD formulation[5]. However, currently the firm has re-formulated

[1] As per the RLD labeling, more than two sequential doses should not be administered without physician
[2] IIG Database, Internal: http://intranetappslb-dev fda.gov/scripts/IIG/ (Last accessed on 6/20/2015)

(b) (4)

[4] DARRTS for ANDA 090589: Firm's Submission dated 5/20/2015. Module 3.2.P.1. Toxicity Study (Sodium Tartrate)
[5] DARRTS for ANDA 090589: TAMPAL, NILUFER M 03/11/2010 N/A 03/11/2010 REV-BIOEQ-01(General Review) Original-1 Archive

its test product to include Sodium Tartrate (b) (4) and reduce the concentration of Sodium Metabisulfite[6]. The test product is NOT qualitatively (Q1) and quantitatively (Q2) the same as RLD product. The test product contains Sodium Tartrate Dihydrate as (b) (4) whereas the RLD product contains no (b) (4).

Ingredients	Function	Test Product- Re-Formulated Amount (mg) per 0.3 mL Delivered		Reference Product Amount (mg) per 0.3 mL Delivered[7]	
		0.15 mg	0.3 mg	0.15 mg (EpiPen® Jr)	0.3 mg (EpiPen®)
Epinephrine, USP	Active Ingredient	0.15 mg*	0.3 mg*	0.15	0.3
Sodium Chloride, USP/NF	(b) (4)	1.8 mg	1.8 mg	1.8	1.8
Sodium Metabisulfite, NF		0.4 mg	0.4 mg	0.5	0.5
Sodium Tartrate Dihydrate, NF		0.2 mg	0.4 mg	-	-
Hydrochloric Acid, USP/NF		To adjust pH	To adjust pH	To adjust pH	To adjust pH
Water for Injection, USP		Q.S.	Q.S.	Q.S.	Q.S.

According to 21 CFR § 314.94 (a) (9) (iii), a drug product intended for parenteral use may differ from the RLD in the use of preservatives, buffers, or antioxidants provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety and efficacy of the proposed drug product.

The amount of Sodium Tartrate Dihydrate in the test formulation is within the acceptable limits for Intramuscular administration based on the FDA's Inactive Ingredient database. However, the IIG limit for the above stated inactive ingredient for Subcutaneous administration is not provided in the IIG database. Therefore, the firm submitted the toxicology study report[6] demonstrating the safety of above stated amount of Sodium Tartrate Dihydrate in the test formulation via Subcutaneous administration.

Section II: OGD History of this Drug Product

Currently there are no approved generic products for Epinephrine Injection, Auto-Injector listed in the Orange Book.

(b) (4)

Currently the DB recommendations for demonstration of bioequivalence of Epinephrine Injection (auto-

[6] DARRTS for ANDA 090589: Firm's Submission dated 12/30/2014. Module 3.2.P.1.Description and Composition of the Drug Product

[7] DARRTS for NDA 019430: KIM, CHONG HO 07/28/2008 N/A 07/28/2008 REV-QUALITY-03(General Review) Supplement-40 (Manufacturing (CMC)) Archive

injector) 0.15 mg/0.3mL and 0.3 mg/0.3mL are not listed on the FDA website for Guidance for Industry: Individual Product Bioequivalence Recommendations.

Since the drug product has a device component (Auto-Injector), in addition to the formulation comparison, the DB asks for suitable in-vitro tests to document comparative performance characteristics of the devices used in the test and reference drug products.

Section III: Drug Product Information

Test Product	Epinephrine Injection USP, 0.15 mg/0.3 mL and 0.3 mg/0.3 mL
Reference Product	EpiPen® Jr (epinephrine) Auto-injector, 0.15 mg/0.3 mL and Epipen® (epinephrine) Auto-injector, 0.3 mg/0.3mL
RLD Manufacturer	Mylan Speclt
NDA No.	019430
RLD Approval Date	December 22, 1987
Indication	A sympathomimetic catecholamine indicated in the emergency treatment of allergic reactions (anaphylaxis) to insect stings or bites, foods, drugs and other allergens as well as idiopathic or exercise-induced anaphylaxis.

Section IV: Conclusion

Considering that the inactive ingredient, Sodium Tartrate Dihydrate (b) (4) in the formulation of Teva's Epinephrine Injection, 0.3 mg/0.3 mL and 0.15 mg/0.3 mL is not listed in the CDER's Inactive Ingredient Guidance (IIG) for Approved Drug Products. The DBIII asks if the presence of such amount of Sodium Tartrate Dihydrate (b) (4) should be of a safety concern when administered Subcutaneously.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

ANDA: 90589 **APPLICANT: Teva Parenteral Medicines, Inc.**

DRUG PRODUCT: Epinephrine Injection USP, Autoinjector 0.15mg/0.3mL and 0.3mg/0.3mL

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

Please conduct a design validation (human factors) study. We recommend that you submit a draft of the test protocol before you implement it for our review and feedback to ensure that your methods will be acceptable.

The purpose of a design validation (human factors) study is to demonstrate that the device can be used by representative users under simulated use conditions without producing patterns of failures that could result in negative clinical impact to patients or injury to device users. Tasks included in the study should be those identified through completion of a risk assessment of hazards that may be associated with use-related problems and represent greater than minimal risk to users. The study should collect sufficient and appropriate data to facilitate identification and understanding of the root causes of any use failures or problems that do occur. The causes may be related to the design of the device, the device labeling (including instructions for use), and/or the training of test participants. The test report should present a summary of your test results, data analysis, and conclusions regarding safe and effective use and including whether any modifications are indicated; if they are, these modifications should be described and if significant, the modifications should also be validated.

Your validation study protocol should include the items listed below.

Devices and Labeling Used and Training

For design validation, the devices used in your testing should represent the final design, which includes instructions for use, or any other labeling materials.

The training you provide to your test participants should approximate the training that your actual end users will receive. Please describe the training you plan to provide in your validation study and how it corresponds to realistic training levels.

Your participants should assess the clarity of the instructions for use and you should assess the extent to which the instructions support safe and effective use of your device. If any of the other labeling (e.g., packaging, inserts) is critical to use, include them in your validation testing as well. You may include these assessments in your validation testing or conduct them in a separate study.

If you decide to include the assessment of clarity of instructions for use and training as part of the validation study, the Agency expects that the results demonstrating effectiveness of your training and instructions for use are analyzed separately from the results of use performance.

User Tasks and Use-Related Risks Analysis

FDA expects to see a clear description of how you determined which user tasks would be included in the testing and how many trials each participant would complete. In order to adequately assess user performance and safety, the tasks selected for testing should be derived from the results of a comprehensive assessment of use-related hazards and risks that consider all

functions of the device. The tasks should be prioritized to reflect the relative magnitude and severity of the potential impact of inadequate task performance on the safety of the device and the user.

Please provide a use-related risks analysis, describe and provide a rationale for the tasks you include in your testing and their relative priority. Please also describe all activities in which your test participants will engage during the test.

Use Environment and Conditions

You should conduct your validation testing in an environment that includes or simulates all key aspects of the real-world environments in which you anticipate your device would be used.

Identification of potentially challenging use conditions should be derived through analyses of use hazards prior to conducting validation testing and aspects of use that can be reasonably anticipated, such as use with gloves or wet fingers, dim lighting, noisy situations, etc., should be included in your testing. Please evaluate use of your device under whatever conditions you identify as potentially occurring and hazardous.

Please describe the testing environment and realism of the simulated use in sufficient detail for us and justify how they were appropriate for validation testing.

Study Participants

FDA expects you to test a minimum of 15 participants from each major user group for validation of device use. Your test participants should be representative of your intended end-user populations, as described in your indications for use statement. If users with distinctly different characteristics (e.g., age ranges, skill sets, or experience levels, level of disabilities/impairments) will use your device, you should include 15 from each distinct group.

Regardless of the number of groups you test, please provide a rationale that these groups are representative the overall population of users for your device. Note that study participants should not be your own employees, or those that have been exposed to the products prior to the testing.

Data Collection

Any data collected and analyzed in a validation study should be described in terms of how it supports the safety case claim that your device can be used safely and effectively by the indicated users. FDA expects you to collect both empirical and qualitative data in a design validation study.

Empirical Data – Your test participants should be given an opportunity to use the device independently and in as realistic a manner as possible, without guidance, coaching, praise or critique from the test facilitator/moderator. Some data, such as successful or failed performance of key tasks or time taken to perform tasks – if time is a safety-critical criterion – should be measured directly rather than soliciting participant opinions. Observing participant behavior during the test is also important, in order to assess participants' adherence to protocol and proper technique and especially to assess and understand the nature of any errors or problems that occur.

Qualitative Data – The Agency expects you to ask open-ended questions of participants at the end of a usability validation, such as, "Did you have any difficulty using this device? [If so] can you tell me about that?" The questions should explore performance of each critical task involved in

the use of the device and any problems encountered. Note that since the labeling and instructions for use are considered part of the user interface for your device, the questions should cover those components as well.

Your analysis of performance and subjective data should be directed toward understanding user performance and particularly task failures. The analysis should determine the nature of failures, the causes of failures, and the clinical impact. Every test participant who experiences a "failure" (does something that would have led to harm under actual conditions of use), should be interviewed about that failure to determine the cause of the failure from the perspective of the participant.

Please describe and provide a rationale for including each type of data you collect.

Please provide a proposed protocol for the Agency to review prior to conducting the study.

B. In addition to responding to the deficiency presented above, please note and acknowledge the following comment in your response:

1. The labeling, bioequivalence and CMC portions of your application have been found to be deficient. Your responses to the deficiencies should be sent to each division under separate covers.

2. A satisfactory cGMP compliance evaluation for the firms referenced in the ANDA is required for approval. The Division of Manufacturing and Product Quality currently recommends that we withhold approval.

Sincerely yours,

{See appended electronic signature page}

Paul Schwartz, Ph.D.
Acting Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

BITA MIRZAI AZARM
05/16/2011

REVIEW OF PROFESSIONAL LABELING #2
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 090589 Date of Submission: 12 OCT 2010

Applicant's Name: Teva Pharmaceuticals

Established Name: Epinephrine Injection USP, **0.15 mg**/0.3 mL (JR Auto Injector) and **0.3 mg**/0.3 mL (Adult-auto injector)

Labeling Comments:

1. C**ONTAINER**-

   a. Is the (b) (4) noticeably different than the orange barrel that appears in the window prior to use, such that the orange color can not be confused with being a (b) (4) color?

   b. How does the (b) (4) appear in the window viewer? In diagram 4, please use an arrow to indicate the location of the (b) (4) I almost missed seeing the (b) (4) in the diagram. It would be better to locate the text in the area where the (b) (4) is going to appear. Please provide an auto injector with your draft label placed on it. Please use the reference for guidance.

   c. Upon further review, please revise Auto-Injector (b) (4) to read (b) (4) Auto- injector). This is so that (b) (4) will not be missed when looking at the name of the injections and this is also in keeping with the naming for the innovator products reading Epi-Pen Jr. Auto- Injector for the 0.15 mg product. Please revise on all labels and labeling.

2. **CARTON -** "Open immediately" stands alone on the carton. Please add "… immediately- To complete Teva's Epinephrine Injection USP Auto- Injectors for Anaphylatic Support- FREE MEMBERSHIP- Details inside.

3. **PROFESSIONAL INSERT-** See comment regarding naming.

4. **PATIENT INSTRUCTIONS** -

   a. Rather than "contain no latex" revise to read "contains no natural rubber latex" where that statement appears in the labeling.

   b. The storage statement reads … protect from light. What part of your injector will protect the product from light? The innovatory encloses the auto-injector in to an amber sleeve outer carrying case?

   c. Complete the sentence " See other side for Directions for Use and for Teva's Epinephrine auto-injector

   d. We note the following does not appear in the reference product: "Do not remove the yellow or green safety cap until ready to use" and should be deleted.

   e. Add "for Teva's Epinephrine Injections USP Auto- Injector for Anaphylatic Support- to SEE OTHER SIDE FOR "DIRECTIONS FOR USE" AND TEVA'S….. as seen in the referenced product.

   f. Steps 1, 2, 3, and 4 should be rotated so that the panels are visible in a vertical position and as the patient holds the product container.

g. DIRECTIONS FOR USE- your proposed section is missing some billets. First billet… you will have to say "a carrying case is NOT provided as seen with other products". Move "Do not use if solution is discolored up so that it follows Do not remove blue safety release…. The two sentences with the yellow or green cap statement were not seen in the referenced product.

h. TO USE AUTO INJECTOR- Please revisit this section.

This section does not read the same as the innovator. It was difficult to follow and to ensure that the sequence of steps match the innovator. This section may present confusion for customers that have used the innovator's product. Thus your proposed section, as written, will require new learning and teaching for the previous customers and physicians. The innovator label instructs "pop off the yellow cap from the outer sleeve first then the safety clip on the device. (b) (4).

(b) (4)

5. **TRAINER LEAFLET -**

a. The innovator has the following sentence in two locations and you have use the statement in only one location. Please add "The Trainer does NOT contain any medication and does NOT have a needle".

b. Add specific location the following seeing your auto-injector is designed different than the reference- Never put thumb, other fingers, or hand over orange tip (below gray safety cap).

c. We do not think your sentence added to the trainer labeling is necessary. Please delete the following sentence: (b) (4).

d. (b) (4) Please revisit the operational aspect of your container for difference. We refer you to our comments above under TO USE AUTO INJECTOR.

e. Under CAUTION section- revise to read as the reference listed drug. Do not add your own text. Example: "drug product" should read medication and Ok should read okay. In addition, the question that asks about pressure needed for the trainer device yours say moderate while the reference product says strong.

f. Title- Place the comma behind USP rather than in front of USP.

Revise your labels and labeling, as instructed above, and submit DRAFT (or final print if prefer) electronically.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling and the latest approved labeling for the reference listed drug (or your last submission) with all differences annotated and explained.

{See appended electronic signature page}

_____

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

JOHN F GRACE
02/02/2011
for Wm Peter Rickman

ANDA: 090589

APPLICANT: Teva Parenteral Medicines, Inc

DRUG PRODUCT: Epinephrine Injection, USP (Auto Injector), 0.15 mg/0.3 mL and 0.3 mg/0.3 mL.

The Division of Bioequivalence (DBE) has completed its review of your submissions acknowledged on the cover sheet. The following deficiencies have been identified:

1. The DBE recommends in-vitro testing to demonstrate comparable performance of the device components (auto-injectors) used in your proposed test product to the reference listed drug (RLD) products, EpiPen® (epinephrine) Auto-Injector, 0.30 mg/0.3 mL and EpiPen Jr ® (epinephrine) Auto-Injector, 0.15 mg/0.3 mL. You provided summary data (means and standard deviations) for expelled volume, needle gauge, exposed needle length, force to trigger device, and spring force to inject drug for the test product. Individual data for your test products were provided only for the injection time. Comparative data for the RLD devices were not provided. Please conduct additional in-vitro testing and provide comparative data for the test and reference devices under the same conditions. The performance tests may include but not limited to the following:
   a) Volume of solution injected and residual content of the auto-injector,
   b) Dose delivery time,
   c) Force required to discharge actuator and force of injection,
   d) Exposed needle length,
   e) Depth of penetration,
   f) Needle cover test, and
   g) Needle integrity post injection to include testing through different clothing materials of varying thickness and different angles of incidence.

   Specifications such as breakloose force and extrusion force should be provided. Please provide all relevant Standard Operating Procedures (SOPs) and validation data for each test procedure conducted.

2. Please submit complete electronic EXCEL spreadsheets or SAS Transport format files of individual data for each of the tests on the test device product versus the RLD products.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence I
Office of Generic Drugs
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-90589	ORIG-1	TEVA PARENTERAL MEDICINES INC	EPINEPHRINE

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/s/

DALE P CONNER
03/29/2010

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 90589 APPLICANT: Teva Parenteral Medicines, Inc.

DRUG PRODUCT: Epinephrine Injection USP, Autoinjector 0.15mg/0.3mL and 0.3mg/0.3mL

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. (b) (4)

2.

3.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comment in your response:

1. Please provide all available long term stability data.
2. (b) (4)
3. Your responses to Deficiencies 12 and 13 will be sent to the Division of Anesthesiology, General Hospital, Infection Control and Dental Devices General Hospital Device Branch of CDRH for evaluation.

Sincerely yours,

{See appended electronic signature page}

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-90589	ORIG-1	TEVA PARENTERAL MEDICINES INC	EPINEPHRINE

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/s/

BING CAI
03/02/2010

LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENTS:

ANDA: 90-589 APPLICANT: Teva Parenteral Medicines, Inc.

DRUG PRODUCT: Epinephrine Injection, USP

Microbiology Deficiencies:

1. (b) (4)
2.
3.
4.
5.

Please clearly identify your amendment to this facsimile as "RESPONSE TO MICROBIOLOGY DEFICIENCIES". The "RESPONSE TO MICROBIOLOGY DEFICIENCIES" should also be noted in your cover page/letter.

Sincerely yours,

{See appended electronic signature page}

Lynne A. Ensor, Ph.D.
Microbiology Team Leader
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

Lynne Ensor
7/6/2009 08:18:37 AM

REVIEW OF PROFESSIONAL LABELING #1
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 90-589 Dates of Submission: 21 DEC 2007 and 24 NOV 2008

Applicant's Name: Teva Pharmaceuticals.

Established Name: Epinephrine Injection USP, Auto-Injector 0.15 mg/0.3 mL Jr and 0.3 mg/0.3 mL

Labeling Deficiencies:

1. C**ONTAINER**-

   a. We were able to make only limited comments because the innovators labels you submitted lack resolution. Please resubmit.

   b. The layout of the label is not acceptable. It will cause a customer to have to turn the container in three different directions. Please realign the text so that it will flow with easy in one direction.

   c. There is an USP monograph for this product. The established name should appear on all labels and labeling expressed as "Epinephrine Injection USP, 0.15 mg (Auto Injector (b) (4)" or "Epinephrine Injection USP, 0.3 mg (Auto Injector)" in conjunction to the trade name (if there is one) on the principal display panel. You may also elect to retain "Epinephrine Auto-Injector" but add the established name (Epinephrine Injection USP). Please ensure that the route of administration is also displayed on the main panel "For IM Use" or "intramuscular Use". Note; also relocate the comma it should appear after USP rather than after injection.

   d. It is important that the tip color, safety clip, and label are the same colors as the innovator's product for both the pediatric and adult versions. This will lessen confusion for the consumer who is use to the looking at the innovators product. Currently you have a (b) (4) tip and (b) (4) safety clip while the innovator has a black tip and gray safety clip. Please (b) (4) color for your product so that it is the same as the reference listed drug. Correct your labeled diagrams and text to be consistent to the changes you make. Please explain whether the exposed needle extends beyond or protrudes beyond the container rim once the cap is removed. Please submit samples to the labeling branch.

   e. Revise "Window blocked if unit used"…" to read "A ___ window..." or restate the sentence exactly like the innovator has it. In addition, the text should be placed around the window as seen with the RLD.

   f. Diagram 4- Please explain where that portion of the label is positioned? Will it be tuck under or run on top of the extended barrel?

   g. Diagram 3 - Will the customer hear a click? If so, please state that as does the innovator. You state "…fire and hold...". . Please explain the firing mechanism. Will the patient have to push something to operate the tube? The diagram is too crowded. Please use the same picture of the thigh with cloths as seen with the innovator's label. It appears that your product can not go through clothing. Please revise and or verify. Also, a usability test may be required.

   h. Diagram 2- Was not seen in the innovator's labeling. Please delete. In addition, you should cite the color of the caps as does the innovator. We are concerned that the twist and pull method may cause a slight time delay in an emergency. Quick retrieval and safety are the goals.

   i. Diagram 1- Will the number be printed on the actual cap. Also, give the color. Please consider the innovators naming system for consistency. Cap 1 and Cap 2 are confusing. It is important that your caps

are label and colored the same as the reference listed drug for consistency across this product line.

j. Relocate "replace if solution is discolored" so that it appears below the window area.

k. .Trainer Device- Please submit for review. To prevent potential for confusion with the auto-injector containing active drug product and the training device, increase the font size of “Training Device for” .

l. Please include all inactive ingredients found in your component/composition statement on your labels.

m. The innovator places the auto-injector in an outer case that protects the needle and injector for safety reasons and from light. How will the customer safely and securely take the used syringe to the emergency room visit as instructed in the labeling? Please comment on what you are providing to do the same.

n. The route of administration is not clearly stated on the label and is included only to refer how much epinephrine is delivered. Include the route of administration as a stand alone statement outside the text (i.e. for intramuscular use only) per 21 CFR 201.100(b)(3).

o. Include a “For One Time Use” statement so that the user is clear there is only one dose per injection.

p. Epinephrine is most often used in emergent situations that preclude the removal of clothing. The EpiPen and EpiPen Jr labels and labeling depict the device being injected into a person who is fully clothed; the Anapen pictures do not convey this same message and instead it appears that the Anapen device is pressed directly upon the skin. Revise the pictures to reflect that Anapen may be injected through clothing.

q. We note that the label directions on the trainer device are positioned horizontally instead of vertically like the Anapen/Anapen Jr devices. Revise the orientation of the labels so that it is consistent with the actual device. Also, ensure that the directions are oriented so that the user will find it easy to read while holding the auto-injector.

r. Identify the needle end clearly by changing the color from (b) (4) to orange or red and include an information label that reads “Needle End” on the label and to the protective tube.

s. Bold the “10 seconds” statement so that this instruction is more visible to users.

t. Place an instruction to “pull off to use” on the safety release to increase the likelihood that users will quickly understand what needs to be removed to use the auto-injector.

u. Add Made in ____

2. CARTON - We are unable to complete comments on this section at this time. Please resubmit clearer innovators labeling.

a. Include the following statements "open immediately…" and we refer you to the RLD labeling for guidance.
b. A picture of the contents should be placed on the cartons as seen with the listed drug product.

3. PROFESSIONAL INSERT-

a. WARNINGS- The product is light sensitive and the innovator products a tube to store the product. Please do the same. This will also help with transporting the product to the emergency room visit as instructed in the labeling.

b. HOW SUPPLIED- The innovator provides individual carrying cases (tube sleeves) that provides built-in needle protection after use. The also provide a clip for the 2 pack. Please provide similar cases. Please explain how are you proposing to protect the build in needle?

4. **PATIENT INSTRUCTIONS** -Please use the innovators patient insert to ensure that your leaflet reads the same. Important information is missing from your labeling. Just to name a few areas - Add- Examine content, Support center enrollment form, four billets should follow immediately after Directions for use,

   a. DIRECTIONS FOR USE - Please revisit this entire section it is not similar or the same as the reference listed drug. Important information was omitted just to mention a few: Indicate lot number and expiration date position as seen on the reference product. The outer package information must be revisited. In addition color of caps must also be changed. Diagram should look like the innovators.. Example number 4 photo aims towards the buttocks.

   b. WARNINGS: - revisit cap colors.

   c. Expiration Reminder Program- Provide a phone number in addition to the web in case a customer has not access to the web. Must include the center for anaphylactic support information.

   d. Please combine the patient instructions sheet for both products rather than providing separate instructions sheets

5. **TRAINER LEAFLET -** This section is missing from your submission. However, we have included a few general comments.

   a. Add "Directions for use" just below the title. Just after the table add "Practice Instructions". Re-label needle cap and safety cap based on comments under CONTAINER above. You provide 5 steps while the RLD site 9. Please revisit this section. We refer you the RLD labeling. Please ensure that you cite the color of the trainer.

   b. Under "Resetting the trainer" and the last portion of this leaflet you are not consistent with stating the color of the needle cap and safety cap. You also state moderate pressure needed versus strong for the RLD. Is your needle stable if the pressure is strong because need must also travel through fabric.

Revise your labels and labeling, as instructed above, and submit final (or draft) printed electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – ANDA.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://www.fda.gov/cder/cdernew/listserv.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling and the latest approved labeling for the reference listed drug (or your last submission) with all differences annotated and explained.

{See appended electronic signature page}

_____

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

John Grace
6/4/2009 10:35:50 AM
for Wm Peter Rickman