CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 207568

Name: Epinephrine Injection USP, 1mg/ml

Sponsor: American Regent, Inc.

Approval Date: July 6, 2018

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 207568

CONTENTS

Reviews / Information Included in this Review

Approval Letter	**X**
Other Action Letters	**X**
Labeling	**X**
Labeling Review(s)	**X**
Medical Review(s)	
Chemistry Review(s)	**X**
Statistical Review(s)	
Microbiology Review(s)	**X**
Bioequivalence Review(s)	**X**
Other Review(s)	
Administrative & Correspondence Documents	**X**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 207568

APPROVAL LETTER

ANDA 207568

ANDA APPROVAL

Luitpold Pharmaceuticals, Inc.
6610 New Albany Road East
New Albany, OH 43054
Attention: Raenel Gibson
Regulatory Affairs Director

Dear Madam:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on June 19, 2014, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Epinephrine Injection, USP 1 mg/mL.

Reference is also made to the complete response letter issued by this office on December 18, 2015, 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 1 mg/mL, to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug (RLD), Adrenalin (epinephrine injection, USP), 1 mg/mL, of Par Sterile Products, LLC (Par).

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

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

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 1 mg/mL, under this ANDA. You have notified the Agency that Luitpold Pharmaceuticals, Inc. (Luitpold) 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 Luitpold for infringement of the '876 and '657 patents in the United States District Court for the District of New Jersey [Par Pharmaceutical, Inc., Par Sterile Products, LLC, and Endo Par Innovation Company, LLC, v. Luitpold Pharmaceuticals, Inc., Daiichi Sankyo, Inc., and Daiichi Sankyo Company, Ltd., Civil Action No. 16-02290]. You have also notified the Agency that on March 8, 2017, the court entered an

Amended Order including that "Luitpold has not infringed and is not now infringing (either directly, jointly, contributorily, by inducement, or under the doctrine of equivalents) any valid and enforceable claim of United States Patent Nos. 9,119,876 and 9,295,657."

With respect to 180-day generic drug exclusivity, we note that Luitpold was the first ANDA applicant to submit a substantially complete ANDA with a paragraph IV certification for Epinephrine Injection, USP 1 mg/mL. Therefore, with this approval, Luitpold may be eligible for 180 days of generic drug exclusivity for Epinephrine Injection, USP 1 mg/mL. 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 Luitpold 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 Luitpold'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 Luitpold begins commercial marketing of Epinephrine Injection, USP 1 mg/mL, or (b) at any time prior to the expiration of the '876 patent if Luitpold 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.

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.

Sincerely yours,

{See appended electronic signature page}

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

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[1] The Agency notes that the '876 and '657 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).

Vincent Sansone

Digitally signed by Vincent Sansone
Date: 7/06/2018 02:42:06PM
GUID: 508da7410002ba5d796f23a69ef57f39

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 207568

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

ANDA 207568

COMPLETE RESPONSE

Luitpold Pharmaceuticals, Inc.
6610 New Albany Road East
New Albany, OH 43054
Attention: Matthew Grant
Operations Manager, Regulatory Affairs

Dear Sir:

Please refer to your Abbreviated New Drug Application (ANDA) dated June 19, 2014, received June 19, 2014, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act for Epinephrine Injection USP, 1 mg/mL.

We acknowledge receipt of your amendment dated June 4, 2015.

The June 4, 2015 submission constituted a complete response to our February 23, 2015 action letter.

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

PRODUCT QUALITY

1. (b) (4)

2. (b) (4)

3.

4.

5.

BIOEQUIVALENCE

The Office of Bioequivalence has completed its review and has no further questions at this time. The bioequivalence comments provided in this communication are comprehensive as of issuance. However, these comments are subject to revision if additional concerns raised by chemistry, manufacturing and controls, microbiology, labeling, other scientific or regulatory issues or inspectional results arise in the future. Please be advised that these concerns may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

MICROBIOLOGY

1. (b) (4)

2.

LABELING

The Division of Labeling Review has no further questions/comments at this time.

Please continue to monitor available labeling resources such as 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.

FACILITY INSPECTIONS

Office of Compliance has no further questions at this time. The compliance status of each facility named in the application may be re-evaluated upon re-submission.

OTHER

A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

RESUBMISSION
MINOR
COMPLETE RESPONSE AMENDMENT
CHEMISTRY / MICROBIOLOGY

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

The drug product may not be legally marketed until you have been notified in writing that this ANDA is approved.

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1 of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the Federal Register notice announcing facility fee amounts. All finished dosage forms (FDFs) or active pharmaceutical ingredients (APIs) manufactured in a facility that has not

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In addition, we note that GDUFA requires that certain non-manufacturing sites and organizations listed in generic drug submissions comply with the self-identification requirement. The failure of any facility, site, or organization to comply with its obligation to self-identify and/or to pay fees when due may raise significant concerns about that site or organization and is a factor that may increase the likelihood of a site inspection prior to approval. FDA does not expect to give priority to completion of inspections that are required simply because facilities, sites, or organizations fail to comply with the law requiring self identification or fee payment.

Additionally, we note that the failure of any facility referenced in the application to self-identify and pay applicable fees means that FDA will not consider the GDUFA application review goal dates to apply to that application.

If you have any questions, call Edward McDonald, Regulatory Project Manager, at (240) 402-5949.

Sincerely yours,

Denise P. Toyer -S

Digitally signed by Denise P. Toyer -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=13001128 98, cn=Denise P. Toyer -S
Date: 2015.12.18 08:07:06 -05'00'

Denise P. Toyer McKan, Pharm.D.
Director, Division of Project Management
Office of Regulatory Operations
Office of Generic Drugs

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

ANDA 207568

COMPLETE RESPONSE

Luitpold Pharmaceuticals, Inc.
6610 New Albany Road East
New Albany, OH 43054
Attention: Matthew Grant
Operations Manager, Regulatory Affairs

Dear Sir:

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

PRODUCT QUALITY

Please note these deficiencies were also issued in an information request dated November 9, 2015.

1. (b) (4)

2. (b) (4)

3.

4.

5.

BIOEQUIVALENCE

The Office of Bioequivalence has completed its review and has no further questions at this time. The bioequivalence comments provided in this communication are comprehensive as of issuance. However, these comments are subject to revision if additional concerns raised by chemistry, manufacturing and controls, microbiology, labeling, other scientific or regulatory issues or inspectional results arise in the future. Please be advised that these concerns may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

MICROBIOLOGY

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1. (b) (4)

2. (b) (4)

LABELING

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Please continue to monitor available labeling resources such as 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.

FACILITY INSPECTIONS

Office of Compliance has no further questions at this time. The compliance status of each facility named in the application may be re-evaluated upon re-submission.

OTHER

A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

RESUBMISSION
MINOR
COMPLETE RESPONSE AMENDMENT
CHEMISTRY / MICROBIOLOGY

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

The drug product may not be legally marketed until you have been notified in writing that this ANDA is approved.

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1 of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the Federal Register notice announcing facility fee amounts. All finished dosage forms (FDFs) or active pharmaceutical ingredients (APIs) manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or 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.

In addition, we note that GDUFA requires that certain non-manufacturing sites and organizations listed in generic drug submissions comply with the self-identification requirement. The failure of any facility, site, or organization to comply with its obligation to self-identify and/or to pay fees when due may raise significant concerns about that site or organization and is a factor that may increase the likelihood of a site inspection prior to approval. FDA does not expect to give priority to completion of inspections that are required simply because facilities, sites, or organizations fail to comply with the law requiring self identification or fee payment.

Additionally, we note that the failure of any facility referenced in the application to self-identify and pay applicable fees means that FDA will not consider the GDUFA application review goal dates to apply to that application.

If you have any questions, call Edward McDonald, Regulatory Project Manager, at (240) 402-5949.

Sincerely yours,

Denise P. Toyer McKan, Pharm.D.
Director, Division of Project Management
Office of Regulatory Operations
Office of Generic Drugs

COMPLETE RESPONSE

ANDA 207568

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

TO: Luitpold Pharmaceuticals, Inc. TEL: 631-205-2035

ATTN: Felicia Bullock FAX: 631-205-2013

FROM: Edward McDonald FDA CONTACT PHONE: 240-402-5949

Dear Madam:

This facsimile is in reference to your abbreviated new drug application, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act.

We have completed the review and have described below our reasons for this action and, where possible, our recommendations to address these issues in the following attachments (____ pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

ANDA 207568

COMPLETE RESPONSE

Luitpold Pharmaceuticals, Inc.
Attention: Felicia Bullock
Sr. Director, Regulatory Affairs
One Luitpold Drive, PO Box 9001
Shirley, NY 11967

Dear Madam:

Please refer to your Abbreviated New Drug Application (ANDA) dated June 19, 2014 received June 19, 2014 submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act for Epinephrine Injection USP, 1mg/mL.

PRODUCT QUALITY

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies

1. (b) (4)
2.
3.

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

B. (b) (4)

BIOEQUIVALENCE

The Division of Bioequivalence III (DBIII) has completed its review and the following deficiencies have been identified:

1. In the test product, you used hydrochloric acid (HCl) and (b) (4)

   (b) (4)

2. Both RLD and test products contain HCl as the pH adjuster. Please provide HCl quantity (volume in mL) up to two significant figures (b) (4) for accurate comparison with the RLD formulation in Q1Q2 sameness determination as the basis for granting the requested waiver. Alternatively, please confirm that the HCl concentration of (b) (4) provided for your test formulation, is actually (b) (4)

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.

MICROBIOLOGY

Deficiencies:

1. (b) (4)

b. (b) (4)

c.

d.

e.

5. (b) (4)

6.

LABELING

Deficiencies:

1. **CONTAINER LABEL AND CARTON LABELING**
   a. (b) (4)

   b.

2. **PRESCRIBING INFORMATION**
   a. Submit final printed labeling.

   b. Revise the established name in the Highlights section of the insert labeling to read: (b) (4) Ensure Physician Labeling Rule (PLR) is followed in regard to drug name, only the first portion of the name, (i.e. EPINEPHRINE) should be capitalized.

   c. Include date of last revision on the package insert.

FACILITY INSPECTIONS

Office of Compliance has no further questions at this time. The compliance status of each facility named in the application may be re-evaluated upon re-submission.

OTHER

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Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

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MINOR
COMPLETE RESPONSE AMENDMENT
CHEMISTRY / BIOEQUIVALENCE / MICROBIOLOGY / LABELING

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If you have any questions, call Edward McDonald Regulatory Project Manager, at (240) 402-5949.

Sincerely yours,

For Denise P. Toyer McKan, Pharm.D.
Director, Division of Project Management
Office of Regulatory Operations
Office of Generic Drugs

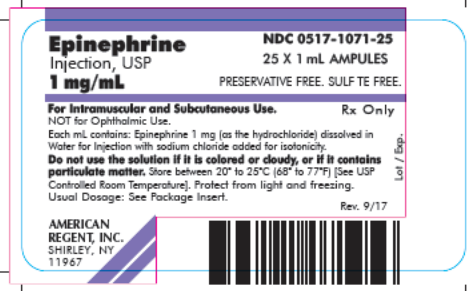
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 207568

LABELING

100%



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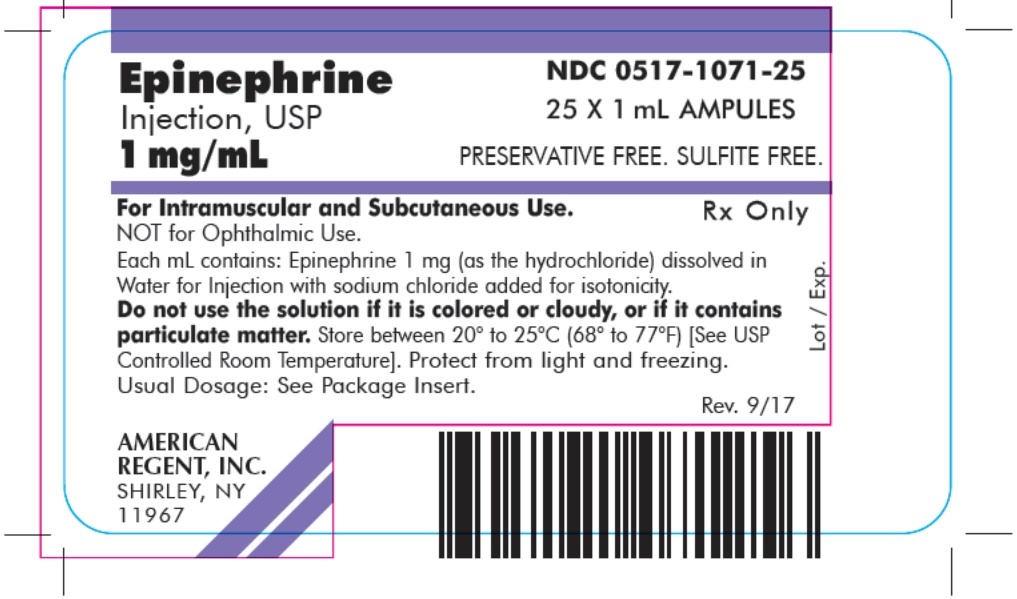


(b) (4)

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

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

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

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

Indications and Usage, Mydriasis (1)	Removed 09/2016
Dosage and Administration (2)	05/2016, 09/2016
Warnings and Precautions (5, 5.1, 5.2)	05/2016, 09/2016

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

Epinephrine injection is a non-selective alpha and beta adrenergic agonist indicated for:

- Emergency treatment of allergic reactions (Type 1), including anaphylaxis (1)

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

- Anaphylaxis:
  - *Adults and Children 30 kg (66 lbs) or more*: 0.3 to 0 5 mg (0.3 to 0.5 mL) intramuscularly or subcutaneously into anterolateral aspect of the thigh every 5 to 10 minutes as necessary (2)
  - *Children 30 kg (66 lbs) or less*: 0.01 mg/kg (0.01 mL/kg), up to 0.3 mg (0.3 mL), intramuscularly or subcutaneously into anterolateral aspect of the thigh every 5 to 10 minutes as necessary (2)

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

Injection: 1 mg/mL, 1 mL single-use ampule (3)

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

None (4)

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

- Do not inject into buttocks, digits, hands, or feet (5.1)
- 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 2)
- May aggravate angina pectoris or produce ventricular arrhythmias, particularly in patients with underlying heart disease, administer with caution when used intramuscularly or subcutaneously (5.3)
- Patients with hyperthyroidism, Parkinson's disease, diabetes, and pheochromocytoma are at greater risk of having adverse reactions when used intramuscularly or subcutaneously (5.3)

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

Common adverse reactions to systemically administered epinephrine include anxiety, apprehensiveness, restlessness, tremor, weakness, dizziness, sweating, palpitations, pallor, nausea and vomiting, headache, and respiratory difficulties. Arrhythmias, including fatal ventricular fibrillation, rapid rises in blood pressure producing cerebral hemorrhage, and angina have occurred (6)

To report SUSPECTED ADVERSE REACTIONS, contact American Regent, Inc. at 1-800-734-9236 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

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

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

Elderly patients and pregnant women may be at greater risk of developing adverse reactions when epinephrine is administered parenterally (8.1, 8.5)

See 17 for PATIENT COUNSELING INFORMATION

Revised: September 2017

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 is available as a single-use 1 mL ampule for intramuscular and subcutaneous use.

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

2 DOSAGE AND ADMINISTRATION

Inject epinephrine intramuscularly or subcutaneously into the anterolateral aspect of the thigh, through clothing if necessary. When administering to a child, to minimize the risk of injection related injury, hold the leg firmly in place and limit movement prior to and during an injection. The injection may be repeated every 5 to 10 minutes as necessary. For intramuscular administration, use a needle long enough (at least 1/2 inch to 5/8 inch) to ensure the injection is administered into the muscle. Monitor the patient clinically for the severity of the allergic reaction and potential cardiac effects of the drug, with repeat doses titrated to effect. Do not administer repeated injections at the same site, as the resulting vasoconstriction may cause tissue necrosis.

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

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

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

3 DOSAGE FORMS AND STRENGTHS

Epinephrine injection 1 mg/mL, 1 mL solution in a single-use clear glass ampule.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Incorrect Locations of Injection

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

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

Do not inject into buttock. Injection into the buttock may not provide effective treatment of anaphylaxis and has been associated with the development of 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. Epinephrine is a strong vasoconstrictor. Accidental injection into the digits, hands or feet may result in loss of blood flow to the affected area and has been associated with tissue necrosis.

5.2 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. *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 (5.1)*]. Advise patients to seek medical care if they develop signs or symptoms of infection, such as persistent redness, warmth, swelling, or tenderness, at the epinephrine injection site.

5.3 Disease Interactions

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

Patients with Heart Disease

Epinephrine should be administered with caution in patients who have heart disease, including patients with cardiac arrhythmias, coronary artery or organic heart disease, cerebrovascular disease, or hypertension. In such patients, or in patients who are on drugs that may sensitize the heart to arrhythmias, epinephrine may precipitate or aggravate angina pectoris as well as produce ventricular arrhythmias [*see Drug Interactions (7) and Adverse Reactions (6)*].

Other Patients and Diseases

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

5.4 Allergic Reactions Associated with Sulfite

This product does not contain sodium bisulfite.

6 ADVERSE REACTIONS

Common adverse reactions to systemically administered epinephrine include anxiety, apprehensiveness, restlessness, tremor, weakness, dizziness, sweating, palpitations, pallor, nausea and vomiting, headache, and respiratory difficulties. These symptoms occur in some persons receiving therapeutic doses of epinephrine, but are more likely to occur in patients with heart disease, hypertension, or hyperthyroidism [*see Warnings and Precautions (5.3)*].

Due to the lack of randomized, controlled clinical trials of epinephrine for the treatment of anaphylaxis, the true incidence of adverse reactions associated with the systemic use of epinephrine is difficult to determine. Adverse reactions reported in observational trials, case reports, and studies are listed below by body system:

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

Angina may occur in patients with coronary artery disease [see *Warnings and Precautions (5.3)*].

Arrhythmias, including fatal ventricular fibrillation, have occurred, particularly in patients with underlying organic heart disease or patients receiving drugs that sensitize the heart to arrhythmias [see *Warnings and Precautions (5.3)*].

Rapid rises in blood pressure associated with epinephrine use have produced cerebral hemorrhage, particularly in elderly patients with cardiovascular disease [*see Warnings and Precautions (5.3)*].

Respiratory: respiratory difficulties.

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

Psychiatric: anxiety, apprehensiveness, restlessness.

Gastrointestinal: nausea, vomiting.

Other:
Patients with Parkinson's disease may experience psychomotor agitation or a temporary worsening of symptoms [see *Warnings and Precautions (5.3)*].

Diabetic patients may experience transient increases in blood sugar [see *Warnings and Precautions (5.3)*].

Accidental injection into the digits, hands or feet may result in loss of blood flow to the affected area [*see Warnings and Precautions (5.1)*]. Adverse events experienced as a result of an injection into these areas include increased heart rate, local reactions including injection site pallor, coldness, hypoesthesia, and tissue loss, or injury at the injection site resulting in bruising, bleeding, discoloration, erythema, and skeletal injury.

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

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

Skin: sweating.

To report SUSPECTED ADVERSE REACTIONS, contact American Regent, Inc. at 1-800-734-9236 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

7 DRUG INTERACTIONS

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

Patients who are concomitantly receiving cardiac glycosides, digitalis, diuretics, quinidine, and other antiarrhythmics should be observed carefully for the development of cardiac arrhythmias [see *Warnings and Precautions (5.3) and Adverse Reactions (6)*].

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

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

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

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

Ergot alkaloids may reverse the pressor effects of epinephrine.

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category C.

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

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

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

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

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

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

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

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

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

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

Epinephrine overdosage can also cause transient bradycardia followed by tachycardia and these may be accompanied by potentially fatal cardiac arrhythmias. Premature ventricular contractions may appear within one minute after injection and may be followed by multifocal ventricular tachycardia (prefibrillation rhythm). Subsidence of the ventricular effects may be followed by atrial tachycardia and occasionally by atrioventricular block. Treatment of arrhythmias consists of administration of a beta-adrenergic blocking drug such as propranolol.

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

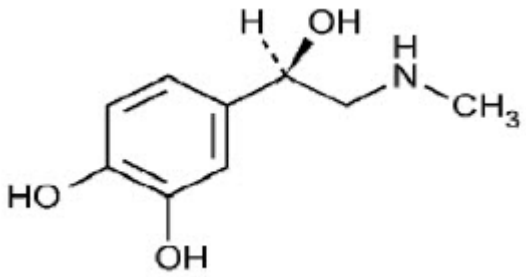
Myocardial ischemia, myocardial infarction and cardiomyopathy have been noted in the literature following overdose of epinephrine.

11 DESCRIPTION

Epinephrine Injection, USP is a clear, colorless, sterile solution containing 1 mg/mL epinephrine, packaged as 1 mL of solution in a single-use clear glass ampule. In the 1 mL ampule, each 1 mL of epinephrine injection solution contains 1 mg epinephrine, 9.0 mg sodium chloride, hydrochloric acid to adjust pH, and water for injection. The pH range is 2.2 to 5.0.

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

The chemical structure of epinephrine is:



The molecular weight of epinephrine is 183.2.

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Epinephrine acts on both alpha and beta-adrenergic receptors.

12.2 Pharmacodynamics

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

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

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

Epinephrine increases glycogenolysis, reduces glucose uptake by tissues, and inhibits insulin release in the pancreas, resulting in hyperglycemia and increased blood lactic acid [*see Warnings and Precautions (5.3)*].

Epinephrine causes mydriasis when administered parenterally.

12.3 Pharmacokinetics
When administered parenterally, 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*. Epinephrine was positive in the *Salmonella* bacterial reverse mutation assay, positive in the mouse lymphoma assay, and negative in the *in vivo* micronucleus assay. Epinephrine is an oxidative mutagen based on the *E. coli* WP2 Mutoxitest bacterial reverse mutation assay. This should not prevent the use of epinephrine under the conditions noted under *Indications and Usage (1).*

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

16 HOW SUPPLIED/STORAGE AND HANDLING
Each carton contains 25 single-use ampules containing 1 mL epinephrine injection, USP solution, 1 mg/mL in a 1 mL clear glass ampule.

NDC 0517-1071-25

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

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

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

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

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

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 (5.2)*].

AMERICAN
REGENT, INC.
SHIRLEY, NY 11967

IN1071

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 207568

LABELING REVIEWS

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	10/30/2017
ANDA Number(s)	207568
Review Number	3
Applicant Name	Luitpold Pharmaceuticals, Inc.
Established Name & Strength(s)	Epinephrine Injection, USP 1 mg/mL
Proposed Proprietary Name	NA
Submission Received Date	9/22/2017
Primary Labeling Reviewer	Oluwakemi O. Odesina
Secondary Labeling Reviewer	Theresa Liu

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 -

Justification for Major Deficiency -

*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

NA

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 (9/22/2017)

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

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"].

Reviewer Comments:

The below comments are from the labeling review C2 Addendum based on the submission dated 6/4/2015:

1. **LABELING COMMENTS**

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT

PRESCRIBING INFORMATION

Revise your insert labeling to be in accordance with the most recently approved insert labeling for the reference listed drug (RLD), ADRENALIN (epinephrine injection), NDA 204200/S-004 approved 09/12/16. Revise the information in the Structured Product Labeling (SPL) accordingly.

We note that there has been revised labeling to the reference listed drug since the comment was issued. The Applicant has noted this and submitted revised labeling. From the 9/22/2017 Cover Letter:

Reference is also made to the Easily Correctable Deficiency dated July 31, 2017 requesting revisions to the package insert to be in accordance with recently approved insert labeling for the RLD, Adrenalin, NDA 204200/S-004 approved 09/12/16.

Reference is also made to a more recent FDA approval for changes to the package insert, as a well as the container and carton labels for the RLD, Adrenalin, NDA 204200/S-007 approved 08/09/2017.

Luitpold hereby submits the following complete response to the Easily Correctable Deficiency dated July 31, 2017 which provides for changes to the container, carton, and package insert labeling to be in accordance with both recent FDA approvals for the RLD dated 09/12/2016 (S-004) and 08/09/2017 (S-007).

We find the Applicant's response to be acceptable.

2.1 CONTAINER AND CARTON LABELS

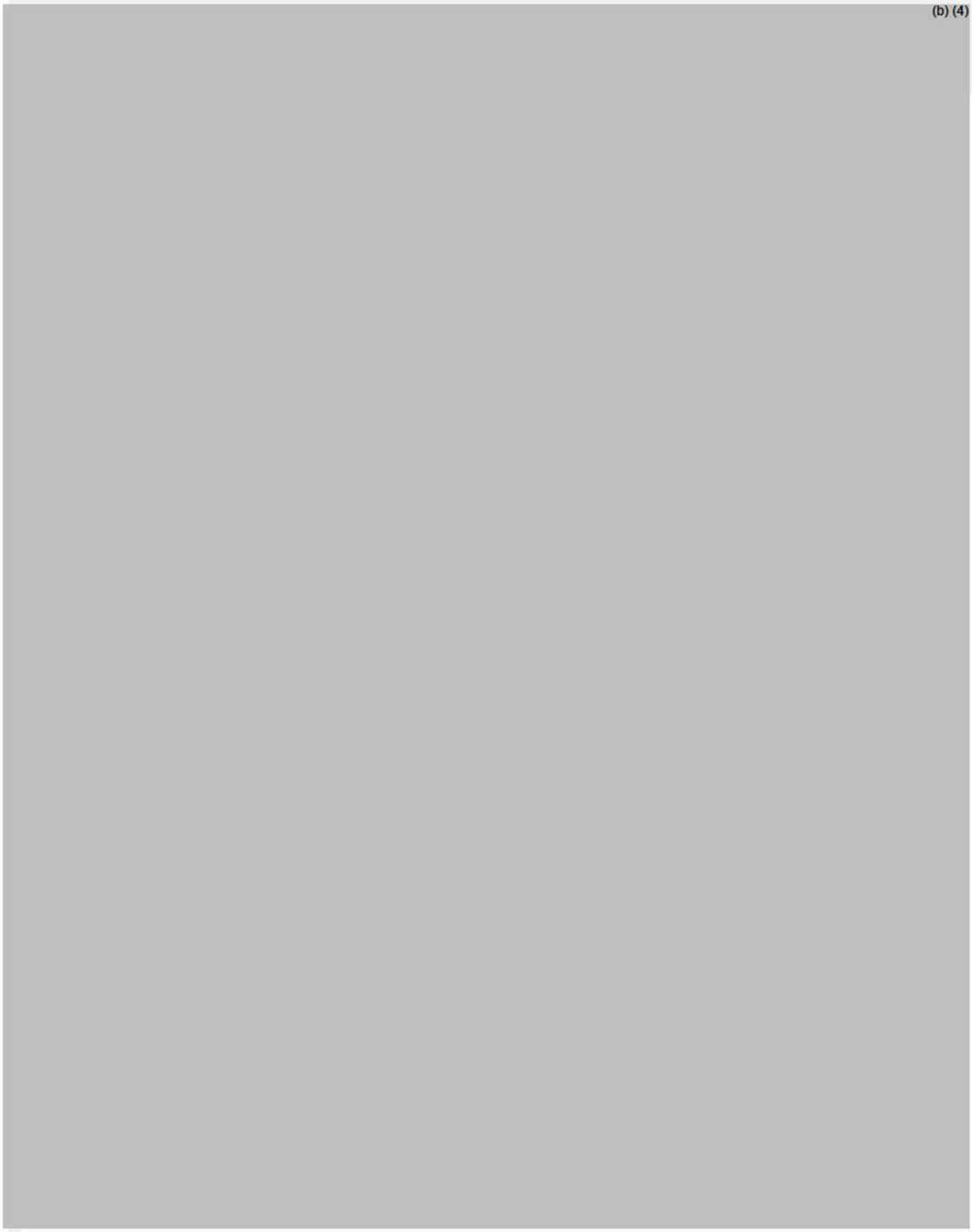
Did the firm submit container and/or carton labels that were **NOT** requested in the previous labeling review?
YES

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

Reviewer Comments:

The Applicant has submitted revised container and carton labels in accordance with the revised RLD labeling and consistent with USP and Agency thinking (see Sec 2.2).

(b) (4)



PREVIOUSLY SUBMITTED LABEL VS. PROPOSED LABEL

(1) (b) (4)

(b) (4)

(2) (b) (4)

(3)

(4)

(5) The statement "NOT for Ophthalmic Use" has been added.

(6) Revision date has been updated.

(b) (4)

(1)

(2),(3)

(4)

(5)

(6)

Epinephrine
Injection, USP
1 mg/mL

NDC 0517-1071-25
25 X 1 mL AMPULES
PRESERVATIVE FREE. SULFITE FREE.

For Intramuscular and Subcutaneous Use. Rx Only
NOT for Ophthalmic Use.
Each mL contains: Epinephrine 1 mg (as the hydrochloride) dissolved in Water for Injection with sodium chloride added for isotonicity.
Do not use the solution if it is colored or cloudy, or if it contains particulate matter. Store between 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature]. Protect from light and freezing.
Usual Dosage: See Package Insert.
Rev. 9/17

Lot / Exp.

AMERICAN REGENT, INC.
SHIRLEY, NY
11967

1 MG/ML AMPULE

PREVIOUSLY SUBMITTED LABEL VS. PROPOSED LABEL

(1) (b) (4)

(2)

(3)

(4) The statement "NOT for Ophthalmic Use" has been added.

(5) (b) (4)

(6) Revision date has been updated.

We find the revised proposed labels to be acceptable.

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:

We note the following from the DRUG FACTS repository:

- Epinephrine Ratio Strength Expression and USP Monograph General Chapter 7

  Presentation given at the Division meeting regarding a Working Group formed to implement compliance to (b) (4) Epin[e]phrine is the primary focus but includes Neostigmine and Isoproterenol Injections too. **..\FINAL_8.24.16_EpiRatioWG SlideDeck.pptx**

- Memo to file allowing removal of ratio expression of strength from single entity inj. Products

  Memo to file allowing ANDAs to differ from RLD with the (b) (4) (b) (4) from epinephrine, neostigmine, and isoproterenol inj. (b) (4)

- Epinephrine - DLR/OGDP meeting

  (b) (4) . It was decided that the generic labeling should be same as the RLD. See attached meeting minutes for more information. (b) (4) (b) (4)

We have evaluated the corresponding documents and note that the Applicant's proposed labeling follows USP General Chapter 7 and Agency current thinking. [See Sec. 3.2 for evaluation of proposed labeling with reference listed drug (RLD) labeling].

3. LABELING REVIEW INFORMATION AND REVIEWER ASSESSMENT

3.1 REGULATORY INFORMATION

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

If Yes, please explain in section 2.2 Additional Background Information Pertinent to the Review

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

If Yes, please explain.

Products	FDA-2017-P-3460	pramipexole, ropinirole and rotigotine	pramipexole, ropinirole and rotigotine
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.

We note that the subject ANDA is not affected.

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 enter the most recently approved ANDA labeling information as applicable.)*

NDA# /Supplement# (S-000 if original): 204200/S-007

Supplement Approval Date: 8/9/2017

Proprietary Name: ADRENALIN

Established Name: Epinephrine Injection

Description of Supplement:

We also refer to our letter dated June 28, 2017, notifying you, under Section 505(0)(4) of the FDCA, of new safety information that we believe should be included in the labeling for Adrenalin (epinephrine injection, USP) 1 mg/mL. This information pertains to the serious risk of confusion between the previous Adrenalin product that was indicated for mydriasis (ophthalmic route of administration) and the reformulated Adrenalin product that is not indicated for mydriasis.

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

☐ **MOST RECENTLY APPROVED ANDA MODEL LABELING**

ANDA#/Supplement# (S-000 if original):

Supplement Approval Date:

Proprietary Name:

Established Name:

Description of Supplement:

☐ **TEMPLATE (e.g., BPCA, PREA, Carve-out):**

☐ **OTHER (Describe):**

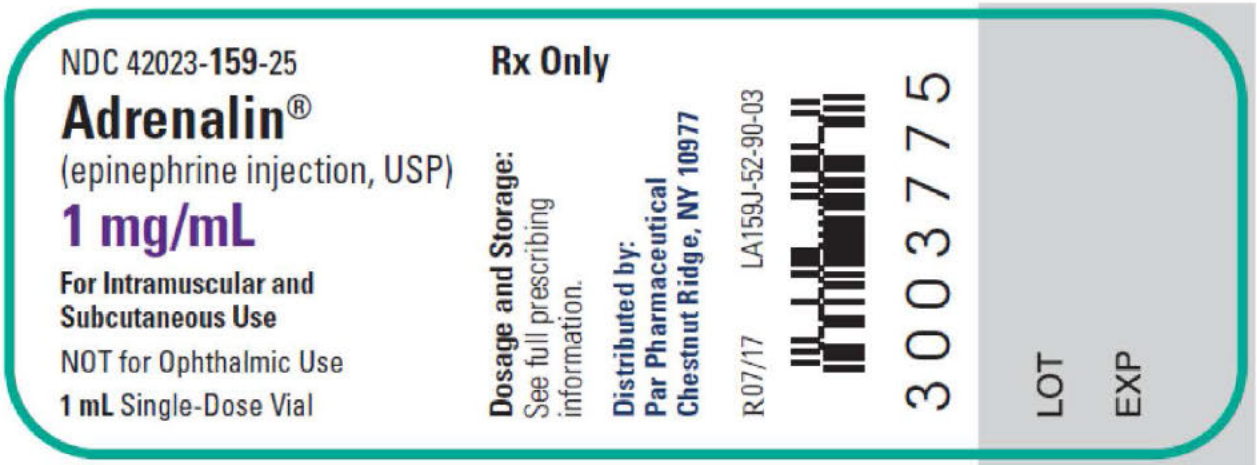
Reviewer Assessment:

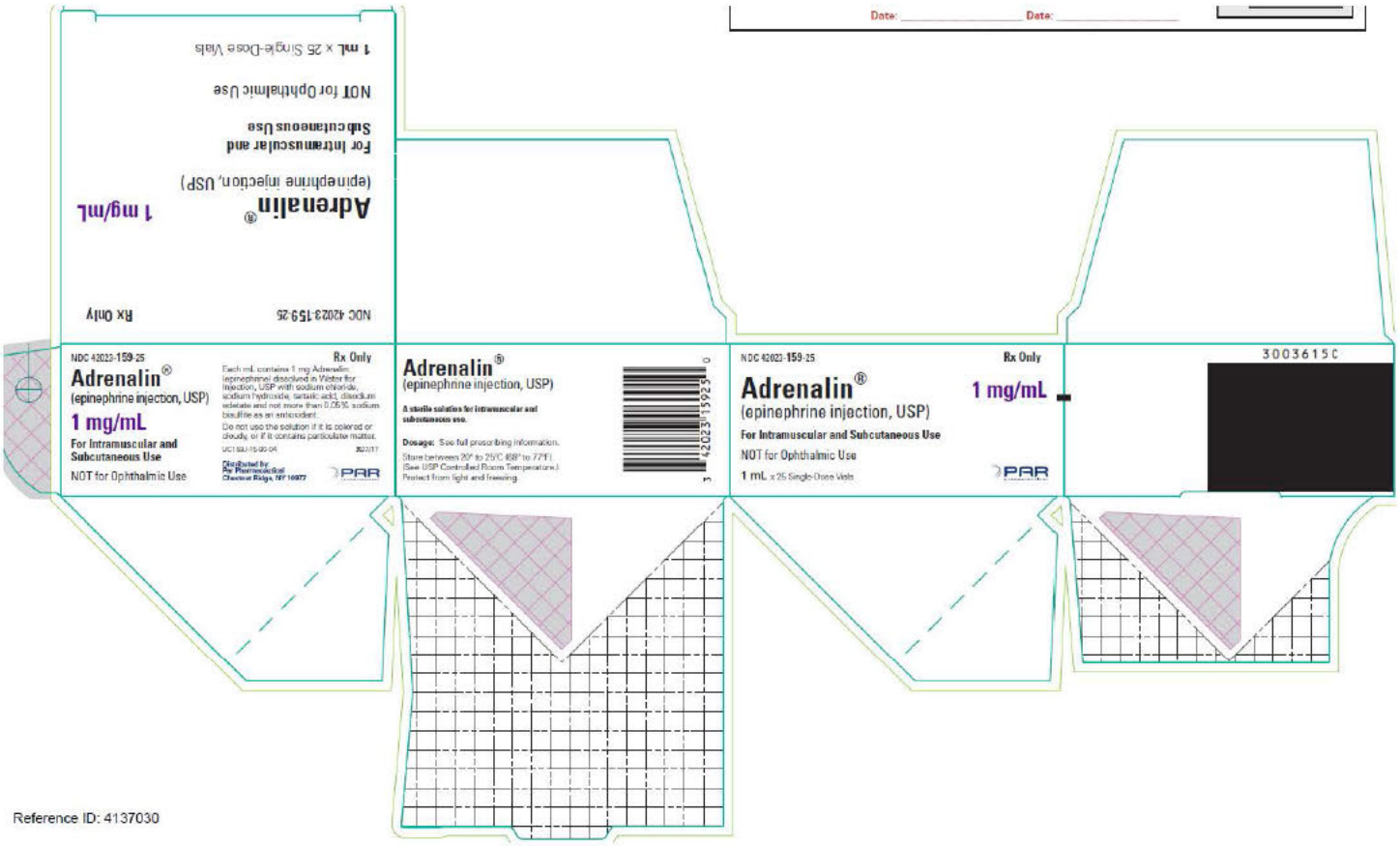
Is the Prescribing Information same as the model labeling, except for differences allowed under 21 CFR 314.94(a)(8)? **YES**
Are the specific requirements for format met under 21 CFR 201.57(new) or 201.80(old)? **YES**
Does the Model Labeling have combined insert labeling for multiple dosage forms? **NO**

Reviewer Comments:

3.3 MODEL CONTAINER LABELS

Model container/carton/blister labels [Source: DARRTS: **NDA 204200/S-007 approved : 8/9/2017]**





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

The USP was searched on 10/30/2017.

	YES or NO	Date	Monograph Title (NA if no monograph)	Packaging and Storage/Labeling Statements (NA if no monograph)
Official Monograph	YES	[redacted]	Epinephrine Injection	(b) (4) [redacted]
Pending Monograph Proposed				

Reviewer Assessment:

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

Reviewer Comments:

3.5 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 10/30/2017.

Table 3 provides Orange Book patents for the Model Labeling 204200 and ANDA patent certifications. (For applications that have no patents, N/A is entered in the patent number column)

Table 3: Impact of Model Labeling Patents on ANDA Labeling

Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact (enter "Carve-out" or "None")
9119876	Mar 13, 2035			IV	3/9/2016	None
9295657	Mar 13, 2035	U-1829	EMERGENCY TREATMENT OF ALLERGIC REACTIONS (TYPE I), INCLUDING ANAPHYLAXIS	IV	7/7/2016	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	NA	NA	NA	NA	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**

Table 5: Comparison of DESCRIPTION Section or Inactive Ingredients Subsection (OTC)		
(b) (4)	**11 DESCRIPTION** Epinephrine Injection, USP is a clear, colorless, sterile solution containing 1 mg/mL epinephrine, packaged as 1 mL of solution in a single-use clear glass ampule. In the 1 mL ampule, each 1 mL of epinephrine injection solution contains 1 mg epinephrine, 9.0 mg sodium chloride, hydrochloric acid to adjust pH, and water for injection. The pH range is 2.2 to 5.0. Epinephrine is a sympathomimetic catecholamine. The chemical name of epinephrine is: 1,2-Benzenediol, 4-[(1R)-1-hydroxy-2-(methylamino)ethyl]-, or (-)-3,4-Dihydroxy-α-[2-(methylamino)ethyl]benzyl alcohol. The chemical structure of epinephrine is: The molecular weight of epinephrine is 183.2. Epinephrine solution deteriorates rapidly on exposure to air or light, turning pink from oxidation to **adrenochrome and brown from the formation of melanin.**	**There are no changes to the inactive ingredients** (b) (4) **hich is consistent with USP and Agency guidelines as well as in accordance with the reference listed drug; we find it 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		
(b) (4)	**16 HOW SUPPLIED/STORAGE AND HANDLING** Each carton contains 25 single-use ampules containing 1 mL epinephrine injection, USP solution, 1 mg/mL in a 1 mL clear glass ampule. NDC 0517-1071-25 Store between 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature]. Epinephrine is light sensitive. Protect from light and freezing. Inspect visually for particulate matter and discoloration prior to administration. Do not use the solution if it is colored or cloudy, or if it contains particulate matter.	(b) (4)

Table 7: Manufacturer/Distributor/Packer Statements		
Previous Labeling Review	**Currently Proposed**	**Assessment**
AMERICAN REGENT, INC. SHIRLEY, NY 11967	**AMERICAN REGENT, INC. SHIRLEY, NY 11967**	**No changes, acceptable.**

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:

We note the following from the 9/17/2017 Chemistry Review:

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

(b) (4)

[redacted]

Overall Reviewer's Assessment and Signature:

CMC is inadequate

R. Murali 10/14/2015; 02/15/2017; 5/10/2017; 8/16/2017; 10/30/2017

Secondary Review Comments and Concurrence:

R. Tan, 10/24/2015; 2/22/17, 5/19/17; 8/23/17

..\RE_ Comment on Drug Product Primary Review on ANDA-207568-ORIG-1-AMEND-4 (ref# 4842957).pdf

(b) (4)

[redacted]

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	Draft	1 mg/mL Ampule	9/22/2017	Satisfactory
Blister				
Carton	Draft	25 X 1 mL Ampules per Carton	9/22/2017	Satisfactory
(Other – specify)				
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	IN1071	9/22/2017	Satisfactory
Medication Guide				
Patient Information				
SPL Data Elements		Revised: 9/2017	9/22/2017	Satisfactory

Oluwakemi Odesina

Digitally signed by Oluwakemi Odesina
Date: 10/31/2017 10:43:13AM
GUID: 5423006c00721f6b43db6c5df1f43327

Theresa Liu

Digitally signed by Theresa Liu
Date: 11/01/2017 11:09:43AM
GUID: 508da70a00028d58911de18a598cda6f

***** 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	6/15/2017 ADDENDUM 8/14/2015 (Original Review Date)
ANDA Number(s)	207568
Review Number	Addendum to C2
Applicant Name	Luitpold Pharmaceuticals, Inc.
Established Name & Strength(s)	Epinephrine Injection, USP 1 mg/mL (b) (4)
Proposed Proprietary Name	NA
Submission Received Date	6/4/2015 (Resubmission/After Action – Complete) 6/19/2014 (Original)
Labeling Reviewer	Oluwakemi O. Odesina, PharmD, BCPS
Labeling Team Leader	Theresa Liu

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

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT

PRESCRIBING INFORMATION

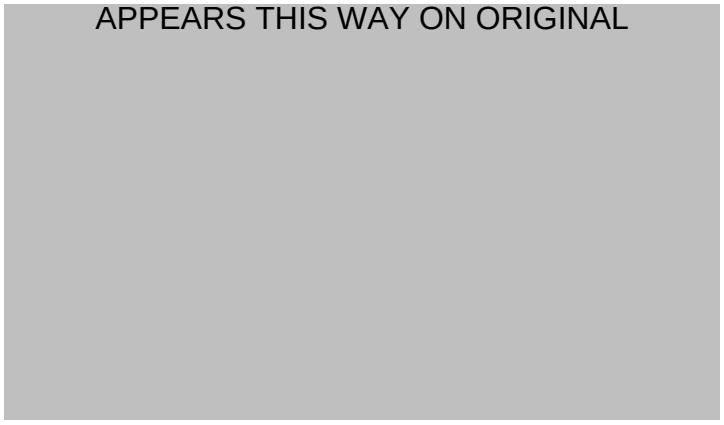
Revise your insert labeling to be in accordance with the most recently approved insert labeling for the reference listed drug (RLD), ADRENALIN (epinephrine injection), NDA 204200/S-004 approved 09/12/16. Revise the information in the Structured Product Labeling (SPL) accordingly.

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).
NA

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).



Reviewer Comments:

From Sec 1.2 Cover Letters – 06/04/2015

LABELING

To support the requested labeling changes, the following documents have been included for review:

Label	Carton	Package Insert
• PDF of FPL	• PDF of FPL	• PDF of FPL • MS Word Format • SPL Format

Deficiencies

1. **CONTAINER LABEL AND CARTON LABELING**
   a. **We recommend that you revise the container label and carton labeling to use title case in the established name.**

      The container label and carton labeling have been revised to use title case in the established name to read "Epinephrine Injection, USP."

   b. [redacted] (b) (4)

2. **PRESCRIBING INFORMATION**
   a. **Submit final printed labeling.**

      The final printed labeling have been provided in PDF, MS-Word, and XML formats.

   b. **Revise the established name in the Highlights section of the inset labeling to read:** [redacted] (b) (4) (b) (4) **Ensure Physician Labeling Rule (PLR) is followed in regard to drug name, only the first portion of the name, (i.e. EPINEPHRINE) should be capitalized.**

      The established name in the Highlights section of the insert labeling has been revised [redacted] (b) (4) (b) (4)

c. **Include date of the last revision on the package insert.**

The date of the last revision on the package insert has been updated to read "Revised: (b) (4) which appears at the end of the Highlights section.

Additional Labeling Information

(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?
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).

Reviewer Comments:

ADDENDUM – **6/15/2017 – We note that there has been an RLD update since the date of the initial review of this ANDA. This addendum accounts for these labeling updates, revisions made are highlighted in** YELLOW.

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? 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):** 204200/S-004 **Supplement Approval Date:** 9/12/2016 **Proprietary Name:** Adrenalin® (epinephrine injection, USP) **Established Name:** **Description of Supplement:** This Prior Approval supplemental new drug application proposes a change in formulation for Adrenalin® 1mL presentation to extend the shelf life of the product to 24 months, and to remove the mydriasis indication from the labeling for this product.
☐ **MOST RECENTLY APPROVED ANDA MODEL LABELING** **ANDA#/Supplement# (S-000 if original):** **Supplement Approval Date:** **Proprietary Name:** **Established Name:** **Description of Supplement:**
☐ **TEMPLATE (e.g., BPCA, PREA, Carve-out):**
☐ **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 – see comment below**
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:

We will issue the following comment to the Applicant:

"Revise your patient labeling to be in accordance with the most recently approved patient labeling for the reference listed drug (RLD), ADRENALIN (epinephrine injection), NDA 204200/S-004 approved 09/12/16. Revise the information in the Structured Product Labeling (SPL) accordingly."

3.3 MODEL CONTAINER LABELS

Model labels and carton labeling. [ANRPT 2 – 01/23/2015]


Adrenalin®
(epinephrine injection, USP)
1 mg/mL
(1:1000)
For Intramuscular, Subcutaneous, and Intraocular Use
Dilute Before Intraocular Use
1 mL 25 Single-Use Vials
NDC 42023-159-25
Rx Only
3003301
HIDDEN AREA
HIDDEN AREA
HIDDEN AREA
HIDDEN AREA


NDC 42023-159-25
Rx Only
Adrenalin®
(epinephrine injection, USP)
1 mg/mL
1:1000
1 mL Solution in a 3 mL Single-Use Vial
For Intramuscular, Subcutaneous, and Intraocular Use
Dilute Before Intraocular Use
Dosage and Storage:
See full prescribing information.
Mfg. & Dist. by:
JHP Pharmaceuticals, LLC
Rochester, MI 48307
3003299
LOT
EXP

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	8/14/2015	YES	USP Monographs: Epinephrine Injection	(b) (4)
PF				

Reviewer Comments:

3.5 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 8/14/2015.

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**
NA	NA	NA	NA	NA	NA	NA

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	NA	NA	NA	NA	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 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? **NO** Are there changes to the dosage form description(s) or package size(s) in HOW SUPPLIED? **NO** Are there changes to the manufacturing statements? **NO** If yes, then comment below in Tables 5, 6, and 7.

(b) (4)

[redacted]

Table 6: Comparison of HOW SUPPLIED Section		
Previously Labeling Review	**Currently Proposed**	**Assessment**

(b) (4)

Table 7: Manufactured by statement		
Previously Labeling Review	**Currently Proposed**	**Assessment**
AMERICAN REGENT, INC. SHIRLEY, NY 11967 IN1071	**AMERICAN REGENT, INC. SHIRLEY, NY 11967 IN1071**	**No changes, 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:

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	Final	1 mg/mL (b) (4) – 1 mL Ampule	6/4/2015	Satisfactory
Blister				
Carton	Final	25 X 1 mL Ampules per Carton	6/4/2015	Satisfactory
(Other – specify)				
Table 9 Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	**Revision Date and/or Code**	**Submission Date**	**Recommendation**
Prescribing Information	Final	Revised: June 2015	6/4/2015	Revise
Medication Guide				
Patient Information				
SPL Data Elements		Revised: 6/2015	6/4/2015	Revise

* Post-approval revision

Theresa Liu

Digitally signed by Theresa Liu
Date: 6/16/2017 01:31:01PM
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Oluwakemi Odesina

Digitally signed by Oluwakemi Odesina
Date: 6/16/2017 01:33:23PM
GUID: 5423006c00721f6b43db6c5df1f43327

APPEARS THIS WAY ON ORIGINAL

***** 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	8/14/2015
ANDA Number(s)	207568
Review Number	2
Applicant Name	Luitpold Pharmaceuticals, Inc.
Established Name & Strength(s)	Epinephrine Injection, USP 1 mg/mL (b) (4)
Proposed Proprietary Name	NA
Submission Received Date	6/4/2015 (Resubmission/After Action – Complete) 6/19/2014 (Original)
Labeling Reviewer	Oluwakemi O. Odesina, PharmD, BCPS
Labeling Team Leader	John Grace, R.Ph

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

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT

None

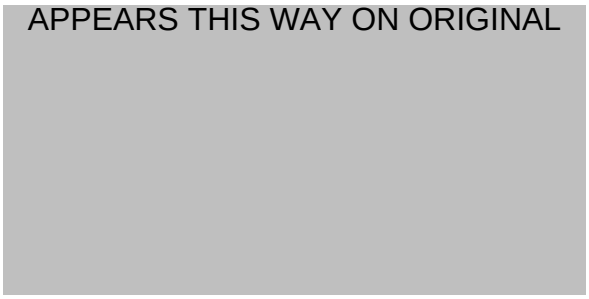
1.2 POST APPROVAL REVISIONS

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).



Reviewer Comments:

From Sec 1.2 Cover Letters – 06/04/2015

LABELING

To support the requested labeling changes, the following documents have been included for review:

Label	Carton	Package Insert
• PDF of FPL	• PDF of FPL	• PDF of FPL • MS Word Format • SPL Format

Deficiencies

1. **CONTAINER LABEL AND CARTON LABELING**
   a. **We recommend that you revise the container label and carton labeling to use title case in the established name.**

      The container label and carton labeling have been revised to use title case in the established name to read "Epinephrine Injection, USP."

   b. (b) (4)

2. **PRESCRIBING INFORMATION**
   a. **Submit final printed labeling.**

      The final printed labeling have been provided in PDF, MS-Word, and XML formats.

   b. **Revise the established name in the Highlights section of the inset labeling to read:** (b) (4) (b) (4) **Ensure Physician Labeling Rule (PLR) is followed in regard to drug name, only the first portion of the name, (i.e. EPINEPHRINE) should be capitalized.**

      The established name in the Highlights section of the insert labeling has been revised (b) (4) (b) (4)

c. **Include date of the last revision on the package insert.**

The date of the last revision on the package insert has been updated to read "Revised: (b) (4) which appears at the end of the Highlights section.

Additional Labeling Information

(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?
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).

Reviewer Comments:

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? 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):** 204200/S-000 **Supplement Approval Date:** 12/07/2012 **Proprietary Name:** Adrenalin® (epinephrine injection, USP) **Established Name:** **Description of Supplement:** NDA 204200 provides for the use of Adrenalin (epinephrine injection), 1 mg/mL for the following indications which, for administrative purposes, we have designated as follows: • NDA 204200/Original 1 – Emergency treatment of allergic reactions (Type 1), including anaphylaxis • NDA 204200/Original 2 – Induction and maintenance of mydriasis during ocular surgery The subject of this action letter is NDA 204200/Original 1 and NDA 204200/Original 2.
☐ MOST RECENTLY APPROVED ANDA MODEL LABELING **ANDA#/Supplement# (S-000 if original):** **Supplement Approval Date:** **Proprietary Name:** **Established Name:** **Description of Supplement:**
☐ TEMPLATE (e.g., BPCA, PREA, Carve-out):
☐ 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:

3.3 MODEL CONTAINER LABELS

Model labels and carton labeling. [ANRPT 2 – 01/23/2015]


Adrenalin®
(epinephrine injection, USP)
1 mg/mL
(1:1000)
For Intramuscular, Subcutaneous, and Intraocular Use
Dilute Before Intraocular Use
1 mL 25 Single-Use Vials
NDC 42023-159-25
Rx Only
3003301
HIDDEN AREA
HIDDEN AREA
HIDDEN AREA
HIDDEN AREA


NDC 42023-159-25
Rx Only
Adrenalin®
(epinephrine injection, USP)
1 mg/mL
1:1000
1 mL Solution in a 3 mL Single-Use Vial
For Intramuscular, Subcutaneous, and Intraocular Use
Dilute Before Intraocular Use
Dosage and Storage:
See full prescribing information.
Mfg. & Dist. by:
JHP Pharmaceuticals, LLC
Rochester, MI 48307
3003299
LOT
EXP

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	8/14/2015	YES	USP Monographs: Epinephrine Injection	(b) (4)
PF				

Reviewer Comments:

3.5 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 8/14/2015.

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
NA	NA	NA	NA	NA	NA	NA

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	NA	NA	NA	NA	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 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? **NO**
Are there changes to the dosage form description(s) or package size(s) in HOW SUPPLIED? **NO**
Are there changes to the manufacturing statements? **NO**
If yes, then comment below in Tables 5, 6, and 7.

Table 5: Comparison of DESCRIPTION Section		
Previous Labeling Review	**Currently Proposed**	**Assessment**
(b) (4)		

Table 6: Comparison of HOW SUPPLIED Section		
Previously Labeling Review	**Currently Proposed**	**Assessment**

Table 6: Comparison of HOW SUPPLIED Section
(b) (4)

Table 7: Manufactured by statement		
Previously Labeling Review	**Currently Proposed**	**Assessment**
AMERICAN REGENT, INC. SHIRLEY, NY 11967 IN1071	AMERICAN REGENT, INC. SHIRLEY, NY 11967 IN1071	No changes, 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:

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	Final	1 mg/mL (b) (4) – 1 mL Ampule	6/4/2015	Satisfactory
Blister				
Carton	Final	25 X 1 mL Ampules per Carton	6/4/2015	Satisfactory
(Other – specify)				
Table 9 Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	**Revision Date and/or Code**	**Submission Date**	**Recommendation**
Prescribing Information	Final	Revised: June 2015	6/4/2015	Satisfactory
Medication Guide				
Patient Information				
SPL Data Elements		Revised: 6/2015	6/4/2015	Satisfactory

* Post-approval revision

***** 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	12/10/2014
ANDA Application Number	207568
Review Cycle Number	1
Applicant Name	Luitpold Pharmaceuticals, Inc.
Established Name	Epinephrine Injection, USP
Strength(s)	1 mg/mL
Proposed Proprietary Name	NA
DARRTS Received Date	06/19/2014
Labeling Reviewer	Oluwakemi O. Odesina, PharmD, BCPS
Labeling Team Leader	John Grace, R.Ph

Review Conclusion

☐ No Comments – The Labels and Labeling are ready for

☒ 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.

LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT

1. CONTAINER LABEL AND CARTON LABELING

a. (b) (4)

b.

2. PRESCRIBING INFORMATION

a. Submit final printed labeling.

b. Revise the established name in the Highlights section of the insert labeling to read: (b) (4) Ensure Physician Labeling Rule (PLR) is followed in regard to drug name, only the first portion of the name, (i.e. EPINEPHRINE) should be capitalized.

c. Include date of last revision on the package insert.

1. MODEL LABELING FOR ANDA

Our review is based on the following model labels and labeling used for comparison to the submitted ANDA labeling.

1.1 MODEL CONTAINER LABELS FOR ANDA

In Table 1 below, check all sources for Model container labels and carton labeling (secondary packaging) that applies.

Container labels are assessed in section 2.2.

Carton labeling (outer or secondary packaging) is assessed in section 2.3.

Table 1: Review Model Labeling for Container Label and Carton Labeling (Check all sources that apply)	
Source	**Date of source document (i.e. supplement approval date, annual report date)**
☐ drugs@fda	
☐ DARRTS	
☐ DailyMed	
☒ Annual Report – ANRPT-1	02/06/2014
☐ Other	

Model labels and carton labeling. [Insert or paste images below]

FROM ANRPT-1 DARRTS SECTION 1.14.2.1

1.2 PRESCRIBING INFORMATION MODEL LABELING

The review model labels and labeling used for comparison to the submitted ANDA labeling are described in Table 2.

Prescribing information is assessed in section 2.4.

Table 2: Review Model Labeling for Prescribing Information and Patient Labeling(Check all that apply)		
☒ MOST RECENTLY APPROVED REFERENCE LISTED DRUG		
NDA : 204200	Proprietary Name: Adrenalin® (epinephrine injection, USP)	Approval date: 12/07/2012
S- 000	**Description of Supplement:** NDA 204200 provides for the use of Adrenalin (epinephrine injection), 1 mg/mL for the following indications which, for administrative purposes, we have designated as follows: • NDA 204200/Original 1 – Emergency treatment of allergic reactions (Type 1), including anaphylaxis • NDA 204200/Original 2 – Induction and maintenance of mydriasis during ocular surgery The subject of this action letter is NDA 204200/Original 1 and NDA 204200/Original 2.	
☐ BPCA or PREA TEMPLATE		
☐ OTHER (Describe):		

2. MATERIAL ANALYSIS

The results for each material reviewed in this section provide the basis for the labeling comments to the applicant (Page 2).

2.1 GENERAL

2.1.1 Established Name Assessment

We compared the established names of this ANDA, the Model Labeling and the USP to determine if the established name presented on the labeling is acceptable.

Table 3: Comparison of Established Names

Model Labeling: **Adrenalin®** (epinephrine injection, USP)
ANDA: **EPINEPHRINE** INJECTION, USP
USP: Epinephrine Injection

Reviewer Assessment:

Is the established name for ANDA acceptable? **YES**
Is the established (and proprietary name) displayed in a manner consistent 21 CFR 201.10? **YES**
Is title case used in established name? **NO --- see comment below**
Is established name on list of name pairs that use Tall Man lettering found on FDA webpage? **NO**
- If yes does labeling comply with Tall Man lettering recommendations? **NA**

Reviewer Comments: We will recommend that the Applicant revise the container label and carton labeling to use title case in the established name.

2.1.2 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 and determined how the monograph impacts the ANDA labeling with respect to packaging and storage. The results of this search are provided in Table 4.

Table 4: USP and PF Search Results

	Date Searched	Monograph? YES or NO	Labeling statements found NA if no monograph
USP	12/10/2014	YES	(b) (4)
PF	12/102014	YES	

Reviewer Assessment:

Does the ANDA labeling require revision or is clarification needed from other review disciplines based on the comparison of USP or PF label/labeling requirements? **NO**
Do required labeling statements appear on/in the ANDA labeling? **YES -- See comment below**
Are the USP packaging and storage recommendations reflected in the labels and labeling? **YES**

Reviewer Comments:

The statement **"Do not use the solution if it is colored or cloudy, or if it contains particulate matter"** appears on the (b) (4) carton label. (b) (4)

we find it acceptable as it is in accordance with the RLD.

2.2 CONTAINER LABEL

We evaluated the container labels for the inclusion of all required statements and safety considerations.

2.2.1 Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors

We used the draft Guidance for Industry titled Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors for the following assessment.

Reviewer Assessment:

Does the following information appear as the most prominent information on the Principal Display Panel?
- Proprietary name? **NA**
- Established name? **YES**
- Product strength? **YES**
- Route(s) of administration (other than oral)? **YES**
- Warnings (if any) or cautionary statements (if any)? **NA**

Does the following information appear of lesser prominence on the Principal Display Panel?
- Rx-only statement? **NO --- see comment below**
- Net quantity statement? **NO –see comment below**
- Manufacturer logo? **YES**

Are the requirements of 21 CFR 201.15 met for all required label statements? **YES**
Are the requirements of 21 CFR 201.100 met for all required label statements? **YES**

Reviewer Comments: (b) (4) [redacted]

2.2.2 Other Container Label Considerations

Reviewer Assessment:

Does this container meet the "too small" exemption found in 21 CFR 201.10(i)? **YES**
Are all abbreviations acceptable? (i.e., mg, mcg, HCl)? **YES**
Are multiple strengths differentiated by use of different color or other acceptable means? **NA**
Does the net quantity statement appear separate from and less prominent than the statement of strength (e.g., not highlighted, boxed, or bolded)? **NO** --- See comment below
Are the rules governing leading and terminal zeroes, decimals, and commas followed? **YES**
If other than oral use, is the route of administration correctly described? **YES**
Are all required warning statements that appear on Model Label properly displayed? **NA**
Is space provided to display expiration date properly? **YES**
Is bar code properly displayed per 21 CFR 201.25(c)(2)? **YES**
Is NDC properly displayed? **YES**
Is controlled substance symbol properly displayed? **NA**
Is the "Usual Dosage" on side panel and is it acceptable? **YES**
Is a product strength equivalency statement on side panel? **NA**
Are the Medication Guide Pharmacist instructions included per 208.24(d)? **NA**

Reviewer Comments: We will ask the Applicant to decrease the prominence of the net quantity statement by decreasing the font size and/or un-bold in relation to the product strength.

2.2.3 Container Label for Small Volume Parenteral Solutions:

Is container for small volume parenteral solution? **NO**
If YES go to Reviewer Assessment below, if NO go to section 2.2.4.

Reviewer Assessment:

Is the product strength expressed as total quantity per total volume followed by the concentration per milliliter (mL), as described in the USP, General Chapter <1> Injection? **NA**
If volume is less than 1 mL, is strength per fraction of a milliliter the only expression of strength?**NA**
Are inactive ingredients listed on label as required by regulations? **NA**

Reviewer Comments:

2.2.4 Container Label for Sterile Solid Injectable:

Is container for sterile solid injectable? **NO**
If YES go to Reviewer Assessment below, if NO go to section 2.2.5.

Reviewer Assessment:

Is the strength in terms of the total amount of drug per vial? **NA**
Are instructions for reconstituting the product and the resultant concentration if space permits? **NA**
Are inactive ingredients listed on label as required by regulations? **NA**

Reviewer Comments:

2.2.5 Container Label for Pharmacy Bulk Package:

Is container a Pharmacy Bulk Package? **NO**
If YES go to Reviewer Assessment below, if NO go to section 2.2.6.

Reviewer Assessment:

Is there a prominent, boxed declaration reading "Pharmacy Bulk Package – Not for Direct Infusion" on the principal display panel following the expression of strength? **NA**
Does the container label include graduation marks? **NA**
Does label contain the required information on proper aseptic technique including time frame in which the container may be used once it has been entered? **NA**
Are inactive ingredients listed on label as required by regulations? **NA**

Reviewer Comments:

2.2.6 Unit Dose Blister Labels

Is container a Unit Dose Blister Pack? **NO**
If YES go to Reviewer Assessment below, if NO go to section 2.2.7

Reviewer Assessment:

Does each blister include only one dosage unit (e.g., one tablet, one capsule)? **NA**
Do proprietary name, established name, strength, lot number, expiration date, bar code, and manufacturer appear on each blister cell? **NA**
Does the established name describe only one unit (e.g. "tablet" rather than "tablets")? **NA**

Reviewer Comments:

2.2.7 Over The Counter (OTC) Label

Is this label for an OTC product? **NO**
If YES go to Reviewer Assessment below, if NO go to section 2.2.8

Reviewer Assessment:

Is Drug Facts Labeling format acceptable per 21 CFR 201.66? **NA**
Does packaging meet the requirements for Special Packaging under the Poison Prevention Act and defined per 16 CFR 1700? **NA**
Does packaging meet the tamper-evident requirements 21 CFR 211.132? **NA**
Does "Questions?" have a toll-free number no less than size 6 pt. font per 21 CFR 201.66(c)(9) or "1-800-FDA-1088" [21 CFR 201.66 (c)(5)(vii)]? **NA**
Did firm submit a Labeling Format Information Table to evaluate the font size? **NA**

Reviewer Comments:

2.2.8 Presentation of Manufacturer/Distributor/Packer on Labeling

We compared the name and address of the manufacturer of this product to the name and address listed on the labels and labeling to determine if the labeling statements are consistent with the regulations (21 CFR 201.1). Table 5 provides a description of this comparison. [NOTE: This presentation/assessment may apply to other labeling submitted].

Table 5: Comparison of Manufacturer/Distributor/Packer Labeling Statements

Name and Address of Facility ANDA Manufactured	**From 3.2.P.3.1** **Luitpold Pharmaceuticals, Inc.** **1 Luitpold Drive** **Shirley, NY 11967** **FEI – 2410375** **Contact: Nicholas LaLima** **Phone: 631-924-4000 ext. 134** **Fax: 631-924-1731** **Email: NLaLima@luitpold.com**
Name and Address on ANDA Labels	AMERICAN REGENT, INC. SHIRLEY, NY 11967
Name and Address on ANDA Labeling	AMERICAN REGENT, INC. SHIRLEY, NY 11967

Reviewer Assessment:

Does the labeling have the required qualifiers per 21 CFR 201.1? **YES**
For Foreign manufacturers, does the labeling have the country of origin? **NA**
For Foreign manufacturers, does the labeling have a US contact/distributor? **NA**

Reviewer Comments:

We note from labeling QbR submitted by Applicant on 06/19/2014 (Sec 1.14.1.1):

9. Who distributes the drug product?

The distributor "American Regent, Inc." is listed on the labeling. In accordance with 21 CFR 201.1(g), it states "The requirement for declaration of the name of the manufacturer, packer, or distributor shall be deemed to be satisfied, in the case of a corporate person, only by the actual corporate name, except that the corporate name may be the name of a parent, subsidiary, or affiliate company where the related companies are under common ownership and control…".

To further clarify this, the names "Luitpold Pharmaceuticals, Inc." and "American Regent, Inc." can be used interchangeably because they are parent and subsidiary companies respectively and are under common ownership and control. We believe it is clear under FDA regulations that, since Luitpold Pharmaceuticals, Inc. manufactures products for American Regent, Inc. and owns it 100 percent, American Regent, Inc. can be declared on labels as the manufacturer of products manufactured by its parent company, thereby requiring no further qualification.

Ref: 21 CFR 201.1(g) Drugs; name and place of business of manufacturer, packer, or distributor.

2.2.9 Description of the Container/Closure

We evaluated the container/closure system of this product to determine if special child-resistant packaging is required based on packaging configuration. Additionally, we evaluated other aspects of the container closure that relate to the dosage form, product formulation, and product class. Below is a description of the container/closure for the ANDA product.

Reviewer Assessment:

Does the container require a child-resistant closure (CRC) as described in the Poison Prevention Act and regulations? **NO**
Describe container closure in **Reviewer Comments** text box (e.g. 30s CRC, 100s non-CRC)
If the closure is not child-resistant, does the container or carton require a labeling statement warning the product is not child-resistant? **NO**
Are the tamper evident requirements met for OTC and Controlled Substances? **NA**
Does this ophthalmic products cap color match the American Academy of Ophthalmology (AAO) packaging color-coding scheme? **NA**
For parenteral products:
Is there text on the cap/ferrule overseal of this injectable product? **NO**
If YES, does text comply with the recommendations in USP General Chapter <1>? **NA**
What is the cap and ferrule color? NA --- see comment below
NOTE: Black closure system is prohibited, except for Potassium Chloride for Injection Concentrate.

Comment: The product is supplied as an ampule.

2.2.10 Storage and Dispensing Recommendations

We compared the storage and dispensing statements that appear on the ANDA labels to the model labeling and USP to confirm the statements do not conflict and the format is consistent with USP and OGD standards (see Table 6). [NOTE: This assessment may apply to other labeling submitted]

Table 6: Model Labeling and ANDA Storage/Dispensing Recommendations	
Model Labeling	
Insert –	Store between 20°C to 25°C (68°F to 77°F). (See USP Controlled Room Temperature.) Epinephrine is light sensitive. Protect from light and freezing. Inspect visually for particulate matter and discoloration prior to administration. Do not use the solution if it is colored or cloudy, or if it contains particulate matter.
Carton –	Store between 20° to 25°C (68° to 77°F). (b) (4)
ANDA	
Insert -	**Store between 20° to 25°C (68° to 77°F)** (b) (4) **(See USP Controlled Room Temperature). Epinephrine is light sensitive. Protect from light and freezing.** **Inspect visually for particulate matter and discoloration prior to administration. Do not use the solution if it is colored or cloudy, or if it contains particulate matter.**
Carton-	**Do not use the solution if it is colored or cloudy, or if it contains particulate matter.** Store between 20° to 25°C (68° to 77°F); (b) (4) (b) (4) (See USP Controlled Room Temperature). Protect from light and freezing.
USP	
Packaging and storage—	(b) (4)
Labeling—	(b) (4)

Reviewer Assessment:

Is the storage or dispensing statement acceptable as compared to the Model Labeling? **YES** Is the storage or dispensing statement acceptable as compared to the USP? **YES** Are the storage temperature recommendations acceptable? **YES** Does the temperature statement conform to the OGD format for controlled room temperature?**YES**

Reviewer Comments:

2.2.11 Related Applications Containing the Same Active Ingredient

We evaluated the following applications that contain the same active ingredient from the same applicant to determine if the labels and labeling are adequately differentiated from one another.

Reviewer Assessment:

Are the labels and labeling of these products differentiated to avoid selection errors? **NA**

Reviewer Comments:

(b) (4)

.

2.2.12 Comparison of ANDA Inactive Ingredients that Require Special Labeling Statements to Model

We compared the list of inactive ingredients contained in this product to those contained in the Model Labeling. Specific inactive ingredients that require special warnings, precautions, or label/labeling statements are in Table 7.

NOTE: This section is for assessing required statements on container labels only for both prescription and OTC drug products. Required statements for prescribing information is assessed for Prescription drug products in Sections 2.4.2 and 2.4.3

Table 7: Inactive Ingredients contained in Model Product and ANDA that require special labeling statements

Model Labeling	ANDA
None	None

Reviewer Assessment:

Do any of the inactive ingredients need a label statement required by regulations? **NO**
If the labeling includes "Does not contain …" statements – Has this statement been verified by chemistry?
NO ---see comment below

Reviewer Comments: We note the terms "PRESERVATIVE FREE. SULFITE FREE," appears on the PDP of the carton labeling. We will defer the evaluation of acceptability of these statements to Chemistry per the MOU.

2.3 CARTON (OUTER OR SECONDARY PACKAGING) LABELING

Reviewer Assessment:

Do all required label statements and safety considerations assessed above for CONTAINER labels appear on the carton? **YES**
If container is too small or otherwise unable to accommodate a label with enough space to include all required information, is all required information present on the carton labeling? **YES**
For unit dose blister that are not child-resistant is there a statement indicating the package is not child-resistant. For example, "This package is not child-resistant. If dispensed for outpatient use, a child-resistant container should be used"? **NA**
If country of origin is not on Container, does appear on outer packaging labeling? **NA**

Reviewer Comments:

2.4 PRESCRIBING INFORMATION

Reviewer Assessment:

Are the labeling contained in the submission the same as the review model labeling? **YES**
Are the differences allowed under 21 CFR 314.94(a)(8)? **YES --- see comment below**
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:

1. We note the following differences between the proposed package insert and the RLD:

- (b) (4)
- (b) (4) The statement "This product does not contain sodium bisulfite" has been added to the proposed package insert.
- (b) (4) "This product does not contain sodium bisulfite" has been added to the proposed package insert in its place.

We find the differences to be acceptable as they are applicable to the Applicants' proposed formulation and packaging configuration.

2. We will ask the Applicant to submit final printed labeling.

3. We will ask the Applicant to make the following revisions:

- Ensure Physician Labeling Rule (PLR) is followed in regard to drug name, only the first portion of the name, (i.e. EPINEPHRINE) should be capitalized. Revise the established name in the Highlights section of the insert labeling to read: (b) (4)
- Include last revision date on the package insert

2.4.1 Patents and Exclusivities

Are there any unexpired patents or marketing exclusivities for Model Labeling? **NO**

If YES go to the table and assessments below.
If NO go to section 2.4.2.
Table 8 describes how the applicant certified to the Orange Book patent(s) for the Model Labeling and how this certification impacts the ANDA labels and labeling. For applications that have no patents N/A is entered in the patent number column.

Table 8: Impact of Model Labeling Patents on ANDA Labeling

Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	How Applicant Filed	Labeling Impact
NA	NA	NA	NA	NA	NA

Reviewer Assessment:

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

Reviewer Comments: A search of Orange Book on 12/10/2014 indicates "there are no unexpired patents for this product in the Orange Book Database."

Table 9 describes how the expiration of the Orange Book exclusivities for the Model Labeling impacts the ANDA labels and labeling. For applications that have no exclusivities N/A is entered in the Exclusivity Code column.

Table 9: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling

Exclusivity Code	Exclusivity Code Definition	Exclusivity Expiration	Labeling Impact
NA	NA	NA	NA

Reviewer Assessment:

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

Reviewer Comments: A search of Orange Book on 12/10/2014 indicates "there is no unexpired exclusivity for this product."

2.4.2 Comparison of ANDA Inactive Ingredients to Model Labeling (Topical And Oral Products Only)

Is submitted labeling for a topical or oral product? **NO**

If YES, complete tables 10a, 10b, and 10c along with assessment below.
If NO, go to section 2.4.3.
We compared the list of inactive ingredients contained in this product to those contained in the Model Labeling.

In Table 10a we compared the lists of inactive ingredients in the DESCRIPTION sections of the Model labeling and the ANDA labeling.

Table 10a: Inactive Ingredients contained in Model Product and ANDA from Description section

Model Labeling Inactive Ingredients	ANDA Inactive Ingredients
NA	NA

In Table 10b we compared the lists of inactive ingredients in the DESCRIPTION section and Components and Components statements in ANDA.

Table 10b: Comparison Inactive Ingredients contained in ANDA Description section and Components and Composition

Description Section	Components and Composition
NA	NA

We noted any specific inactive ingredients that require special warnings, precautions, or label/labeling statements are listed in Table 10c.for Model and ANDA

Table 10c Specific inactive ingredients that require special warnings, precautions

Model Labeling Inactive Ingredients	ANDA Inactive Ingredients
NA	NA

Reviewer Assessment:

Is the DESCRIPTION section of the labeling consistent with the component and composition statement contained in the ANDA? **NA**
Are the required labeling statements present in the ANDA labeling? **NA**

Reviewer Comments:

2.4.3 Comparison of ANDA Inactive Ingredients to Model Labeling (Ophthalmic, Injectable, And Otic Products Only)

Is submitted labeling for an ophthalmic, injectable, or an otic product? **YES**

If YES, complete tables 11a, 11b, and 11c along with the assessment below.
If NO go to section 2.4.4.

We compared the list of inactive ingredients and the amount of the inactive ingredient contained in this product as to those contained in the Model Labeling to determine if all components and composition are the same and if they are listed accurately in the labeling.

In Table 11a we compared the lists of inactive ingredients in the DESCRIPTION sections of the Model labeling and the ANDA labeling.

Table 11a: Inactive Ingredients contained in Model Product and ANDA from Description section

Model Labeling Inactive Ingredients	ANDA Inactive Ingredients
Adrenalin® (epinephrine injection, USP) is a clear, colorless, sterile solution containing 1 mg/mL (1:1000) epinephrine in a 3 mL clear glass vial. Each 1 mL of Adrenalin® solution contains 1 mg epinephrine, 9.0 mg sodium chloride, 1.0 mg sodium metabisulfite, hydrochloric acid to adjust pH, and water for injection. The pH range is 2.2-5.0.	(b) (4)

In Table 11b we compared the lists of inactive ingredients in the DESCRIPTION section and Components and Components statements in ANDA.

Table 11b: Comparison Inactive Ingredients contained in ANDA Description section and Components and Composition

Description Section	Components and Composition

Table 11b: Comparison Inactive Ingredients contained in ANDA Description section and Components and Composition

(b) (4)

From 3.2.P.1

3.2.P.1.2 Composition

The following table lists the components of Epinephrine Injection, USP with their amounts stated on a per unit basis.

Table 1: Composition of the Drug Product

Ingredient	Function	% Composition (w/w)	1 mg/mL
Epinephrine, USP + 10% overage	Active	(b) (4)	1 mg
Sodium Chloride, USP	(b) (4)		9 mg
Water for Injection, USP			(b) (4)
Hydrochloric acid, NF			
(b) (4			

From Carton Labeling:

Each mL contains: Epinephrine 1 mg (as the hydrochloride) dissolved in Water for Injection with sodium chloride added for isotonicity.

We noted any specific inactive ingredients that require special warnings, precautions, or label/labeling statements are listed in Table 11c.for Model and ANDA

Table 11c Specific inactive ingredients that require special warnings, precautions

Model Labeling Inactive Ingredients	ANDA Inactive Ingredients
None	None

Reviewer Assessment:

Is the DESCRIPTION section of the labeling consistent with the component and composition statement contained in the application? **YES**
Are the required labeling statements present in the ANDA labeling? **YES**
If the labeling includes "Does not contain …" statements – Has this statement been verified by chemistry? **NO --- see comment below**

Reviewer Comments: We note the terms "PRESERVATIVE FREE. SULFITE FREE," appears on the PDP of the carton labeling. We will defer the evaluation of acceptability of these statements to Chemistry per the MOU.

2.4.4 How Supplied Section

We compared the descriptions of the model product to the ANDA finished product. Product differences, such as coring configuration, are highlighted in Table 12 and will be referred to the appropriate review discipline for evaluation. Additionally, we evaluated if the text contained in the HOW SUPPLIED section is accurate based on the ANDA finished product description.

Table 12: Comparison of Model Labeling to ANDA finished product	
Model Labeling	Each carton contains 25 single-use vials containing 1 mL Adrenalin® (epinephrine injection, USP) solution 1 mg/mL (1:1000) in a 3 mL clear glass vial. NDC 42023-159-25 3 mL vial
ANDA	(b) (4)

Reviewer Assessment:

Is the description (scoring, color, and imprint) of the finished product accurate in the HOW SUPPLIED section of the insert? **NA**
Are the packaging sizes acceptable as compared to the Model Labeling? **YES**
Does the packaging configuration require the addition or deletion of labeling statements based on the comparison to Model Labeling and/or stability data? **NO**

Reviewer Comments:

2.4.5 Previous Labeling Reviews for ANDA and/or Related Correspondence

Table 13 contains a listing of previously completed OGD labeling reviews and other correspondence relating to this application from DARRTS. We reviewed this information to determine if previous labeling comments were addressed by the applicant or if there is new information that may impact the labeling.

Table 13: Completed Labeling Reviews or Other Correspondence for Application Under Review		
Search Date	**Finalized Date of DARRTS Document**	**Were Previous Comments Addressed? (Yes/No/Explain)**
12/10/2014	**NA**	**NA**

2.5 MEDICATION GUIDE

We evaluated the medication guide to ensure the text is the same as the model labeling. We also ensured the directive appears on the container and carton labeling.

Reviewer Assessment:

Does the format meet the requirements of 21 CFR 208.20? **NA**
Are the dispensing and distributions requirements of 21 CFR 208.24 met? **NA**
Has the Applicant committed to provide a sufficient number of medication guides? **NA**
Is the phonetic spelling of the proprietary or established name present? **NA**
Is the dispensing directive present on the container and carton labeling? **NA**
Is FDA 1-800-FDA-1088 phone number included? **NA**

Reviewer Comments:

2.6 OTHER PATIENT LABELING

None.

2.7 STRUCTURED PRODUCT LABELING (SPL) DATA ELEMENTS

We evaluated the SPL data elements to ensure they are consistent with the information submitted in the ANDA. Additionally, we compared the size of the model and ANDA tablet/capsule size to determine if the size of the ANDA tablet/capsule poses a safety risk or require a labeling statement (see Table 14).

Table 14: Comparison of Model and ANDA Tablet/Capsule Size	
Model Labeling	NA
ANDA Labeling	NA

Reviewer Assessment:

Are the data elements consistent with the information submitted in the ANDA? **YES**
Is the tablet/capsule size similar to the RLD? **NA**

Reviewer Comments:

APPEARS THIS WAY ON ORIGINAL

3. OVERALL ASSESSMENT OF MATERIALS REVIEWED

Tables 15 and 16 provide a summary of recommendations for each material analyzed in this review.

Table 15: Review Summary of Container Label and Carton Labeling			
	Packaging Sizes	Submission Date	Recommendation
Container ☐ Draft ☒ FPL	1 mg/mL (b) (4) – 1 mL Ampule	06/19/2014	☐ Satisfactory ☒ Revise
Blister ☐ Draft ☐ FPL			☐ Satisfactory ☐ Revise
Carton ☐ Draft ☒ FPL	25 X 1 mL Ampules per Carton	06/19/2014	☐ Satisfactory ☒ Revise
Unit Dose Carton ☐ Draft ☐ FPL			☐ Satisfactory ☐ Revise
Table 16 Review Summary of Prescribing Information and Patient Labeling			
	Revision Date and/or code	Submission Date	Recommendation
Prescribing Info ☒ Draft ☐ FPL	IN1071	06/19/2014	☒ Satisfactory ☐ Revise
Medication Guide ☐ Draft ☐ FPL			☐ Satisfactory ☐ Revise
Patient Information ☐ Draft ☐ FPL			☐ Satisfactory ☐ Revise
PPI ☐ Draft ☐ FPL			☐ Satisfactory ☐ Revise
SPL ☒	Revised: 6/2014	06/19/2014	☒ Satisfactory ☐ Revise

3.1 ANDA LABELS AND LABELING SUBMITTED

(b) (4)

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4. QUESTIONS AND COMMENTS FOR CHEMISTRY

During the course of this review, we sought clarification on the following issues to determine if a label or labeling revision is necessary.

Reviewer Assessment:

Does the response(s) received require a label and/or labeling revision? **YES**

Reviewer Comments: We note the terms "PRESERVATIVE FREE. SULFITE FREE," appears on the PDP of the carton labeling. Is this acceptable from a Chemistry standpoint?

APPEARS THIS WAY ON ORIGINAL

5. SPECIAL CONSIDERATIONS

None

6. POST APPROVAL REVISIONS

None

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 207568

CHEMISTRY REVIEWS

Potential First Generic
Recommendation:
ANDA:
☒ **Approval**
☐ **Information Request – Minor**
(_30_days for applicant to response)
☐ **Complete Response - Minor**
☐ **Complete Response – Major**

ANDA 207568

Chemistry Review #2e

Drug Name/Dosage Form	Epinephrine Injection, USP
Strength	1 mg/mL, 1 mL ampule (non-preserved)
Reviewer(s)	Raman D. Murali, Ph.D.
Applicant	Luitpold Pharmaceuticals, Inc.

SUBMISSION(S) REVIEWED	DOCUMENT DATE	Disciplines Affected
Amendment (SD#17)	4/16/2018	Drug Product
Amendment (SD#16)	12/7/2017	Drug Product
Amendment (SD#15)	9/25/2017	Drug Product
Amendment (SD#13)	06/26/2017	Drug Product/Process
Amendment (SD#12)	5/30/17	Micro
Amendment (SD#11)	04/07/2017	Drug Product/Process
Amendment (SD#9)	12/16/2016	Drug Product/Process, Micro
Amendment (SD#4)	6/4/2015	Drug Product/Process, Bioequivalence, Micro, Labeling

DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	1	Adequate (NAI)	6/1/2016	D. Skanchy
	III			4	Adequate	1/18/2017	B. Stevens

(b) (4) **Annual Report is pending review**

[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, Adequate with Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

CONSULTS:

No change, reference Quality Review #1

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

Review of Amendment dated 4/16/2018 (SD 17)

A. Chemistry Deficiencies:

(b) (4)

(b) (4)

This review template is updated on April 15, 2015

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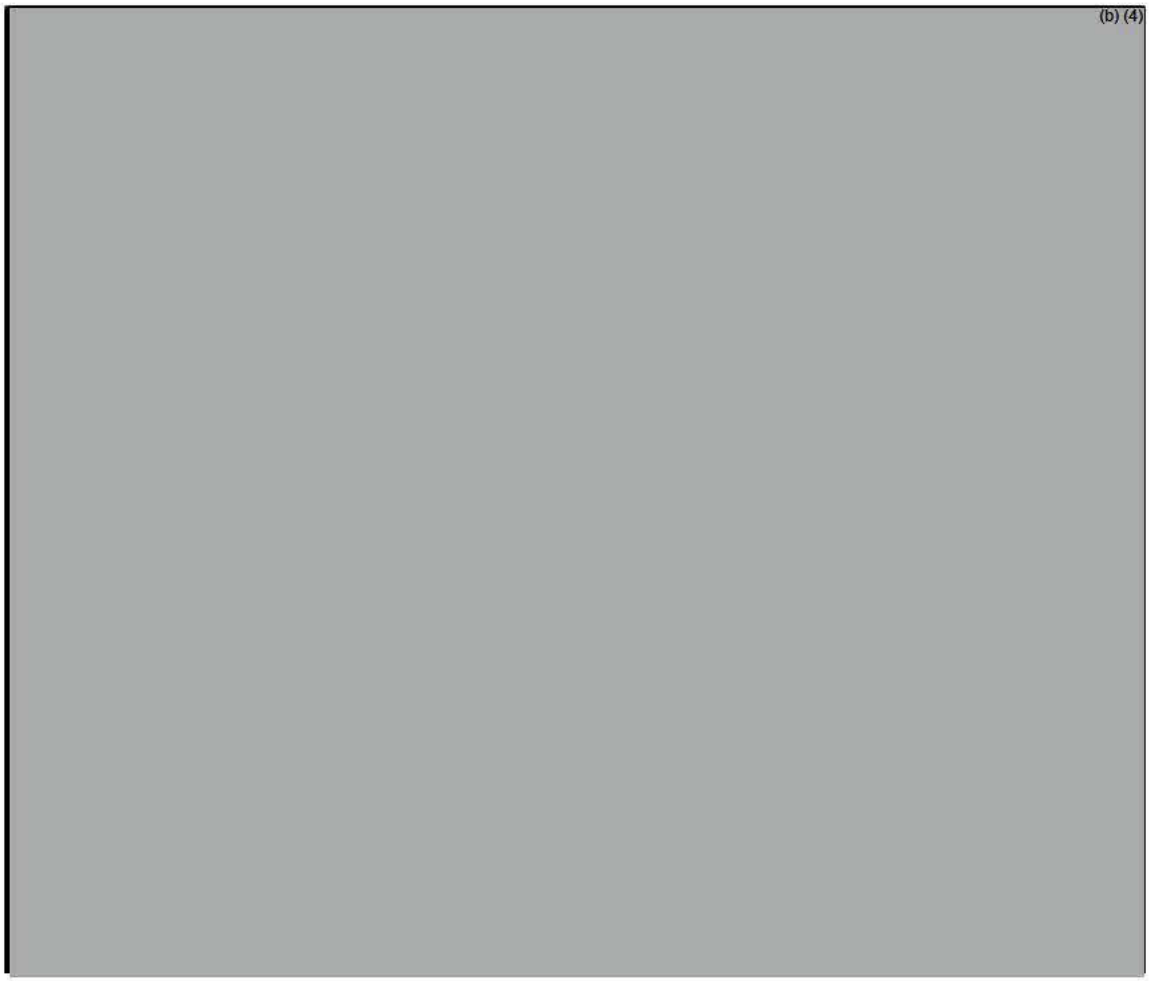
(b) (4)



Overall Reviewer's Assessment and Signature:

CMC is adequate

R. Murali 10/14/2015; 02/15/2017; 5/10/2017; 8/16/2017; 10/30/2017; 3/10/2018; 5/6/2018

Secondary Review Comments and Concurrence:

R. Tan, 10/24/2015; 2/22/17, 5/19/17; 8/23/17, 11/2/17, 3/20/18, 5/11/18

List of Deficiencies:

None

Raman Murali

Digitally signed by Raman Murali
Date: 5/24/2018 01:11:59PM
GUID: 508da701000286d1f02ed0090280bc19

Reynold Tan

Digitally signed by Reynold Tan
Date: 5/24/2018 11:19:31AM
GUID: 508da6f600027f10d05adcd85197c2aa

Recommendation:
ANDA:
☐ **Approval**
☐ **Information Request – Minor**
(_____days for applicant to response)
☒ **Complete Response - Minor**
☐ **Complete Response – Major**

ANDA 207568

Amendment Review #2

Drug Name/Dosage Form	Epinephrine Injection, USP
Strength	1 mg/mL, 1 mL ampoule (non-preserved)
Reviewer(s)	Raman D. Murali, Ph.D.
Applicant	Luitpold Pharmaceuticals, Inc.

SUBMISSION(S) REVIEWED	DOCUMENT DATE
Amendment (SD#4)	6/4/2015

DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)		1	Adequate	10/7/15	DSkanchy: DMF remains adequate after review of SD161 and SD159
	III			4			

[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, Adequate with Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

CONSULTS:

No change, reference last Quality Review #1

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

FACILITIES:

Drug Substance
(b) (4)

Drug Product			
Function	***Site Information***	***FEI/CFN#***	***Status***
Manufacturing, release testing of the excipients & release, in-process, and stability testing of drug product.	*Luitpold Pharmaceuticals, Inc. One Luitpold Drive, PO Box 9001 Shirley, NY 11967*	*2410375*	*Approve Facility; 9/21/15*

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

2.3.S DRUG SUBSTANCE

2.3.P DRUG PRODUCT

Labeling & Package CMC Related Concerns:

(b) (4)

[redacted]

Overall Reviewer's Assessment and Signature:

CMC is inadequate

R. Murali 10/14/2015

Secondary Review Comments and Concurrence:

R. Tan, 10/24/2015

List of Deficiencies To Be Communicated by Information Request or Complete Response:

(b) (4)

1. [redacted]
2. [redacted]
3. [redacted]
4. [redacted]
5. [redacted]

Not Approvable – Minor
Expedited Review
2 tier review
Total day for review: 10

ANDA 207568

Epinephrine Injection, USP 1 mg/mL, 1 mL ampoule (non-preserved)

Luitpold Pharmaceuticals, Inc.

Raman D. Murali, Ph.D.
Division of Chemistry I

Review #1

Table of Contents

Chemistry Review Data Sheet

1. ANDA #: 207568

2. REVIEW #: 1

3. REVIEW DATE: October 1, 2014

4. REVIEWER: Raman D. Murali, Ph.D.

5. PREVIOUS DOCUMENTS: N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original submission (SD#1)	6/19/2014
Patent & Exclusivity/Patent Certification (SD#2)	7/14/2014
Patent & Exclusivity/Patent Certification (SD#3)	7/22/2014

7. NAME & ADDRESS OF APPLICANT:

Name:	Luitpold Pharmaceuticals, Inc.
Address:	One Luitpold Drive, PO Box 9001 Shirley, NY 11967
Representative:	Felicia Bullock, Senior Director Phone: 631-924-4000 Fax: 631-205-2013

8. DRUG PRODUCT NAME/CODE/TYPE:

Proprietary Name: N/A
Non-Proprietary Name (USAN): Epinephrine Injection, USP

9. LEGAL BASIS FOR SUBMISSION:

The Reference Listed Drug (RLD) is Adrenalin® (Epinephrine Injection, USP) 1 mg/mL, application holder Par Sterile Products (formerly JHP Pharmaceuticals LLC), which is the subject of approved NDA 204200.

10. PHARMACOL. CATEGORY:

Emergency treatment of allergic reactions (Type 1), including anaphylaxis
Induction and maintenance of mydriasis during intraocular surgery

11. DOSAGE FORM:

Injectable

12. STRENGTH/POTENCY:

1 mg/mL

13. ROUTE OF ADMINISTRATION:

Subcutaneous, IM, Intraocular

14. Rx/OTC DISPENSED: _X_ Rx __ OTC

15a. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

☐ SPOTS product – Form Completed

☒ Not a SPOTS product

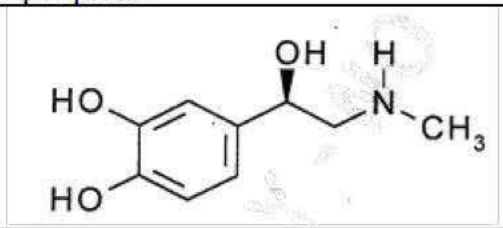
15b. NANOTECHNOLOGY PRODUCT TRACKING:

☐ 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-α-[(methylamino)methyl]benzyl alcohol 1,2-Benzenediol, 4-[1-hydroxy-2-(methylamino)ethyl]-,(R)-

	(-)-1-(3,4-Dihydroxyphenyl)-2-(methylamino)-ethanol
CAS #:	51-43-4
USAN:	Epinephrine
Molecular Structure:	
Molecular Formula:	$C_9H_{13}NO_3$
Molecular Weight:	183.2

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)		3	Adequate	6/24/2014	Reviewed by S. Bhamidipati
	III			4			

*AR dated 8/15/2014 contains administrative information only which will be reviewed in the next review cycle.

[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

18. STATUS

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Pending tertiary review		inadequate; Haijing Hu 1/2/15
EES	Pending		
Methods Validation	N/A		
Labeling	Inadequate	12/12/14	Oluwakemi Odesina
Bioequivalence	Inadequate	9/26/2014	Z. Wahaba
EA	Adequate (exclusion requested)	CR#1	R. Murali
Radiopharmaceutical	N/A		
Samples Requested	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. ☒ Yes ☐ No If no, explain reason(s) below:

20. EES INFORMATION

(b) (4)

Drug Product			
Function	***Site Information***	***FEI/CFN#***	***Status***
Manufacturing, release testing of the excipients & release, in-process, and stability testing of drug product.	*Luitpold Pharmaceuticals, Inc. One Luitpold Drive, PO Box 9001 Shirley, NY 11967*	*2410375*	*Approvable as of 1/27/15*

Chemistry Review for ANDA 207568

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

ANDA is not approvable due to Minor CMC deficiencies identified. Labeling and Microbiology reviews are pending and Bioequivalence review is deficient.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance

Epinephrine is white or off-white crystalline substance. The molecule is optically active and is not known to exhibit polymorphism. It deteriorates rapidly on exposure to air or light, turning pink from oxidation to adrenochrome and brown from the formation of melanin.

(b) (4)

(b) (4) was reviewed by S. Bhamidipati on 6/24/2014 and found to be adequate.

Drug Product

Epinephrine injection is a non-selective alpha and beta adrenergic agonist indicated for emergency treatment of allergic reactions (Type 1), including anaphylaxis induction.(b) (4) Epinephrine Injection, USP is a clear, colorless, sterile solution containing 1 mg/mL (b) (4) epinephrine in a 1 mL clear glass ampule. Each 1 mL of epinephrine injection solution contains 1 mg epinephrine, 9.0 mg sodium chloride, hydrochloric acid (b) (4) to adjust pH, and water for injection. The pH range is 2.2 to 5.0.

The drug product manufacturing process involves (b) (4)

Luitpold Pharmaceuticals, Inc. states that they have been manufacturing Epinephrine Injection, USP for over 30 years (b) (4)

[redacted] and the product has recently been placed on the drug shortage list. Since 2007, Luitpold distributed close to [redacted] units of Epinephrine Injection, USP, 1 mg/mL in the U.S.

This product is a sterile, isotonic sulfite-free formulation of epinephrine.

[redacted]

It should be noted that NDA 205029 Epinephrine Injection 1 mg/mL without the preservative [redacted] has been approved.

Each carton contains 25 ampules containing 1 mL epinephrine injection, USP solution, 1 mg/mL [redacted] in a 1 mL clear glass ampule.

NDC 0517-1071-25

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

B. Description of How the Drug Product is Intended to be Used

Dosage

Anaphylaxis:

Adults and Children 30 kg (66 lbs) or more: 0.3 to 0.5 mg (0.3 to 0.5 mL) intramuscularly or subcutaneously into anterolateral aspect of the thigh every 5 to 10 minutes as necessary (2.1)

Children 30 kg (66 lbs) or less: 0.01 mg/kg (0.01 mL/kg), up to 0.3 mg (0.3 mL), intramuscularly or subcutaneously into anterolateral aspect of the thigh every 5 to 10 minutes as necessary (2.1)

[redacted]

Maximum Daily Dose: [redacted]

[redacted]

Basis for Approvability or Not-Approval Recommendation

The ANDA is non-approvable due to major deficiencies related to drug substance release specifications, drug product manufacturing, release and stability specifications.

Bioequivalence, labeling, and microbiology reviews are deficient and manufacturing facility inspection is approvable.

Chemistry Assessment

I. Review of Common Technical Document-Quality (Ctd-Q) Module 3.2

2.3.S DRUG SUBSTANCE

2.3.S.1 General Information

What are the nomenclature, molecular structure, molecular formula, and molecular weight? ***-Same as Item 16 above***

What are the physicochemical properties including physical description, pKa, polymorphism, aqueous solubility (as function of pH), hygroscopicity, melting points, and partition coefficient?

Firm's Response:
The physicochemical properties of Epinephrine, USP are as follows:

Property	Epinephrine, USP
Physical Description	White or off-white crystalline substance, darkening on exposure to light and air
Melting range	211 – 212°C; ~ 215°C (with decomposition) when rapidly heated
pKa	8.55 (at 25°C)
Aqueous solubility (as function of pH)	Very slightly soluble in water and in alcohol, with acids, it forms salts that are readily soluble in water, (180 mg/L at 20°C)
Specific Optical Rotation	-53 to -50°, in 2% (m/V) solution
Chirality	Epinephrine has one chiral center
Photoreactivity	Known to be light sensitive
Hygroscopicity	Hygroscopic
Partition Coefficient	Octanol/Water Partition Coefficient: log Kow = -2.59
Polymorphism	No information in the public domain

Reviewer's Comment (Review #1):

The physicochemical properties information provided is inadequate.

Although several of the properties including polymorphism, particle size distribution and bulk density are not relevant. Since the drug product is a solution the firm will be asked to provide (b) (4)

(b) (4).

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ADMINISTRATIVE

A. Reviewer's Signature

B. Endorsement Block

Chemist Name/Date: R. Murali/10-27-2014
Quality Assessment Lead Name/Date: R. Tan/2-8-2015
Project Manager Name/Date: A. Yokum/2/8/15

TYPE OF LETTER: Not approvable - MINOR

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 207568

MICROBIOLOGY REVIEWS

Product Quality Microbiology Review

June 14, 2017

ANDA: 207568

Drug Product Name
Proprietary: N/A
Non-proprietary: Epinephrine Injection

Review Number: 4

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
12/16/2016	12/16/2016	N/A	N/A
4/7/2017	4/7/2017	N/A	N/A
5/30/2017	5/30/2017	N/A	N/A

Submission History (for 2nd Reviews or higher)

Submit Date(s)	Microbiology Review #	Review Date(s)
June 19, 2014	1	12/22/2014
June 4, 2015	2	11/5/2015
12/16/2016	3	2/27/2017

Applicant/Sponsor
Name: Luitpold Pharmaceutical, Inc.
Address: One Luitpold Drive, P. O. Box 9001, Shirley, NY 11967
Representative: Felicia Bullock, Sr. Director, Regulatory Affairs
Telephone: 631-205-2035
Fax: 631-205-2013

Name of Reviewer: Yuansha Chen, 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:** Original amendments

2. **SUBMISSION PROVIDES FOR:** response to the Agency's CR letter dated 12/18/2015, IR letter dated 2/28/2017 and IR letter dated 5/18/2017. (b) (4)

3. **MANUFACTURING SITE:**
Luitpold Pharmaceuticals, Inc.
1 Luitpold Drive
Shirley, NY 11967

4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/PO** (b) (4) Sterile injection, single dose; IM/subcutaneous packaged as 1mg/ml, 1ml in a 1ml ampule.

5. **METHOD(S) OF STERILIZATION:** (b) (4)

6. **PHARMACOLOGICAL CATEGORY:** Emergency treatment of allergic reactions

B. **SUPPORTING/RELATED DOCUMENTS:** Microbiology quality review 207568.doc (Not recommended) by H. Hu dated 12/22/2014. Microbiology quality reviews 207568a1.doc (dated 11/5/2015, not adequate) and A207568MR03 (dated 2/27/2017, not adequate) by Y. Chen.

C. **REMARKS:** Electronic CTD. Drug shortage.
The original submission dated 6/19/2014 (b) (4)
(b) (4)

Filename: A207568MR04.doc
Template version: OGD modified_AP_2014v6.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability -
The 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

C. Contains Potential Precedent Decision(s) - ☐ **Yes** ☒ **No**

III. Administrative

A. Reviewer's Signature _____

B. Endorsement Block
Microbiologist/Yuansha Chen, Ph.D.
Microbiology Secondary Reviewer /Neal J. Sweeney, Ph.D.

C. CC Block
cc: Field Copy

Neal Sweeney

Digitally signed by Neal Sweeney
Date: 6/14/2017 05:21:37PM
GUID: 508da70c00028f5119acd77351f33159

Yuansha Chen

Digitally signed by Yuansha Chen
Date: 6/01/2018 08:41:46AM
GUID: 545289f5000727e1136ef94794e114b8

Product Quality Microbiology Review

November 5, 2015

ANDA: 207568

Drug Product Name
Proprietary: N/A
Non-proprietary: Epinephrine Injection, USP

Review Number: 2

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
June 4, 2015	June 4, 2015	N/A	June 29, 2015

Submission History (for 2nd Reviews or higher)

Submit Date(s)	Microbiology Review #	Review Date(s)
June 19, 2014	1	12/22/2014

Applicant/Sponsor
Name: Luitpold Pharmaceutical, Inc.
Address: One Luitpold Drive, P. O. Box 9001, Shirley, NY 11967
Representative: Felicia Bullock, Sr. Director, Regulatory Affairs
Telephone: 631-205-2035
Fax: 631-205-2013

Name of Reviewer: Yuansha Chen, 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:** Original Amendment

2. **SUBMISSION PROVIDES FOR:** Response to Agency CR letter dated 2/23/2015.

3. **MANUFACTURING SITE:**
Luitpold Pharmaceuticals, Inc.
1 Luitpold Drive
Shirley, NY 11967

4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** Sterile injection, single dose; IM/subcutaneous (b) (4) packaged as 1mg/ml, 1ml in a 1ml ampule.

5. **METHOD(S) OF STERILIZATION:** (b) (4)

6. **PHARMACOLOGICAL CATEGORY:** Emergency treatment of allergic reactions

B. **SUPPORTING/RELATED DOCUMENTS:** Microbiology quality review 207568.doc (Not recommended) by H. Hu dated 12/24/2014

C. **REMARKS:** Electronic CTD. Expedited review was granted on July 29, 2014 due to drug shortage. The subject amendment is in response to the agency's complete response correspondence conveyed to the applicant on 2/23/2015.

Filename: 207568a1.doc
Template version: OGD modified_TS_2014v6.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability -

The 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. Brief Description of Microbiology Deficiencies – Please see "List of Microbiology Deficiencies and Comments" sections.

C. Contains Potential Precedent Decision(s) - ☐ **Yes** ☒ **No**

III. Administrative

A. Reviewer's Signature _____

B. Endorsement Block
Microbiologist/Yuansha Chen, Ph.D.
Microbiology Secondary Reviewer /Nandini Bhattacharya, Ph.D.

C. CC Block
cc: Field Copy

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Product Quality Microbiology Review

DEC 22 2014

ANDA: 207568

Drug Product Name
Proprietary: N/A
Non-proprietary: Epinephrine Injection, USP

Review Number: #1

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
June 19, 2014	June 19, 2014	N/A	Oct. 28, 2014

Submission History (for 2nd Reviews or higher)

Submit Date(s)	Microbiology Review #	Review Date(s)
n/a	n/a	n/a

Applicant/Sponsor
Name: Luitpold Pharmaceutical, Inc.
Address: One Luitpold Drive, P. O. Box 9001, Shirley, NY 11967
Representative: Felicia Bullock, Sr. Director, Regulatory Affairs
Telephone: 631-205-2035
Fax: 631-205-2013

Name of Reviewer: Haijing Hu

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

2. SUBMISSION PROVIDES FOR: Initial marketing of sterile drug product

3. MANUFACTURING SITE:
Luitpold Pharmaceuticals, Inc.
1 Luitpold Drive
Shirley, NY 11967

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY: Sterile injection, single dose (2.3, page 53); IM/subcutaneous (b) (4) packaged as 1mg/ml, 1ml in a 1ml ampule.

5. METHOD(S) OF STERILIZATION: (b) (4)

6. PHARMACOLOGICAL CATEGORY: Emergency treatment of allergic reactions

B. SUPPORTING/RELATED DOCUMENTS: None

C. REMARKS: Electronic CTD. Some tables are copied from the submission. Expedited review was granted on July 29, 2014 due to drug shortage.

Filename: 207568.doc
Template version: OGD modified_TS_2014v6.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability -

The 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)

[redacted]

B. Brief Description of Microbiology Deficiencies – Please see the Deficiencies Section at the end of the review memo.

C. Contains Potential Precedent Decision(s) - ☐ Yes ☒ No

III. Product Quality Microbiology Risk Assessment

A. Initial Product Quality Microbiology Risk Assessment

CQA	Risk Factor	Prob. of Occ. (O)	Modifier for O[3, 4, 5]	Severity of Effect (S)	Detect. (D)	Risk Priority Number[6] (RPN)	Additional Review Emphasis based on Risk (in addition to normal review process)
Ster.	Terminal Overkill Cycle F_0 ≥12	6		5	5	150	CCI at max cycle; flexible container port sterilization
Endo		4		4	4	64	

1 = A Closed Aseptic Process is one that has no exposed manipulations other than filling and stoppering after the components are sterilized. (e.g., RABS, isolator, closed drying and filling process for a powder)
2 = An Open Aseptic Process is one that has one or more steps with potential to contaminate the drug product after the component sterilizing. (e.g., sterile drug substance/excipient, interaction of operators with sterile product path, traditional Class 100 filling area).
3 = Anti-Microbial Formulation (e.g., meets USP <51>), modifies O (-1) [less emphasis on in process hold
times]
4 = Post-Constitution/-Dilution Hold Times in Labeling, modifies O (+1) [emphasize Labeling instructions for administration, dosing, storage conditions, and specified diluents. Microbial challenge

studies supporting label recon/dilution/storage instructions if >4 hr RT or >24 hr refrig.]
5 = Components derived from animal sources, modifies O (+1) [emphasize Component bioburden, TSE/BSE-free documentation (TS and AP), viral inactivation studies (AP), bioburden reduction processes.]
6 = RPN = O(after modification when applicable)×S×D
RPN <50 = Low Risk; RPN 50-120 = Moderate Risk; RPN >120 = High Risk

B. Final Risk Assessment - The safety risk associated with the microbiology deficiencies is considered moderate.

IV. Administrative

A. Reviewer's Signature _____

B. Endorsement Block

Microbiologist/Haijing Hu, Ph.D.
Microbiology Team Leader (Acting) /John Arigo, Ph.D.
Microbiology Division Director (Acting)/Lynne Ensor, Ph.D.

C. CC Block

cc: Field Copy

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 207568

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	207568		
Drug Product Name	Epinephrine Injection, USP		
Strength(s)	1 mg/mL (non-preserved)		
Applicant Name	Luitpold Pharmaceuticals, Inc.		
Address	One Luitpold Drive, PO Box 9001, Shirley, NY 11967		
Applicant's Point of Contact	Felicia Bullock, Sr. Director, Regulatory Affairs		
Contact's Telephone Number	631-205-2035 (4000)		
Contact's Fax Number	631-205-2013		
Original Submission Date(s)	06/19/2014		
Submission Date(s) of Amendment(s) Under Review	06/04/2015		
Reviewer	Harikrishna Devalapally, Ph. D.		
OVERALL REVIEW RESULT	**ADEQUATE**		
COMMUNICATION	☐ **ECD** ☐ **IR** ☒ **NOT APPLICABLE**		
WAIVER REQUEST RESULT	**ADEQUATE**		
REVISED/NEW DRAFT GUIDANCE INCLUDED	N/A		
BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	**STUDY/TEST TYPE**	**STRENGTH**	**REVIEW RESULT**
4	**WAIVER**	**1 mg/mL**	**ADEQUATE**

Review of an Amendment

1 EXECUTIVE SUMMARY

Luitpold Pharmaceuticals, Inc. submitted its responses to the deficiency comments made by the Division of Bioequivalence III (DBIII) in the Complete Response letter dated February 23, 2015[1]. The submission references NDA 204200, Adrenalin® (epinephrine hydrochloride) Injection, EQ 1 mg base/mL, manufactured by Par Sterile Products (formerly JHP Pharmaceuticals LLC).

In the original application, the firm submitted a waiver request of *in vivo* bioequivalence study requirements for the test product Epinephrine Injection, USP 1 mg/mL (non-preserved, 1 mL ampule) per 21 CFR § 320.22 (b)(1). (b) (4) In addition, the firm was also asked to provide HCl quantity (volume in mL) up to two significant figures (b) (4) for more accurate comparison with the RLD formulation.

In the current amendment dated 06/04/2015, the firm submitted revised components and composition statement and formulation master batch record for the test product. (b) (4)

Based on the information submitted in current submission, the firm's test product is not Q1 and Q2 the same as the RLD product. The reference product contains sodium metabisulfite as antioxidant whereas the test product contains no antioxidant agent. Per 21 CFR § 314.94 (a) (9) (iii), the differences in "antioxidant agent" is permitted for injectable. The firm provided sufficient data in the original submission to support that the difference in active ingredient does not affect the safety and efficacy of the test drug products.

Therefore, the DBIII deems the test product, Epinephrine Injection, USP 1 mg/mL, manufactured by Luitpold Pharmaceuticals, Inc. to be bioequivalent to the RLD product, Adrenalin® (epinephrine hydrochloride), EQ 1 mg base/mL, manufactured by Par Sterile Products (formerly JHP Pharmaceuticals LLC), under 21 CFR § 320. 24 (b) (6).

The application is **adequate** with no deficiencies.

---

[1]DARRTS for ANDA 207568: BENSON, JASON A 02/23/2015 DUPLICATE 02/23/2015 COR-ANDAACTION-09(Complete Response) Original-1 (Unknown) Archive

[2] DARRTS for ANDA 207568: WAHBA, ZAKARIA Z 9/26/2014 N/A 9/26/2014 REV-BIOEQ-21(Primary Review) Original-1 (Unknown) Archive

2 TABLE OF CONTENTS

3 REVIEW OF CURRENT SUBMISSION

Deficiency Comment #1: *In the test product, you used hydrochloric acid (HCl)* (b) (4)

(b) (4)

Firm's Response: (b) (4)

Although not specifically requested by the Agency, the drug product labeling has also been revised to (b) (4) Refer to the labeling section of this

A. Composition of the Test Product Epinephrine Injection, USP 1 mg/mL

Ingredient	Function	% Composition (w/w)	Amount per mL
Epinephrine, USP	Active	(b) (4)	
Sodium Chloride, USP	(b) (4)		
Water for Injection, USP			
Hydrochloric acid, NF			
(b) (4)			

B. Master Batch Record

(b) (4)

Reviewer's Comments: The firm has revised its test product formulation (b) (4) . The firm's response to Deficiency #1 is **acceptable**.

Deficiency Comment #2: *Both RLD and test products contain HCl as the pH adjuster. Please provide HCl quantity (volume in mL) up to two significant figures* (b) (4) (b) (4) *) for accurate comparison with the RLD formulation in Q1Q2 sameness determination as the basis for granting the requested waiver. Alternatively, please confirm that the HCl concentration of* (b) (4) *provided for your test formulation, is actually* (b) (4)

Firm's Response: (b) (4) This table has been revised and is provided in section 3.2.P.1

(b) (4)

Q.S.: quantity sufficient
N/A: not applicable

Reviewer's Comments: The firm's response to Deficiency #2 is **adequate.**

- Both the test and RLD products contain HCl as pH adjuster. The volume of HCl in RLD formulation is expressed in two significant digits. Therefore, in the current amendment, as per the Agency's request, the firm provided HCl quantity (volume in mL) up to two significant figures (b) (4) for accurate comparison with the RLD formulation.

- The test product contains concentrated HCl (b) (4) while the RLD formulation contains (b) (4) HCl as pH adjuster.

Conversion of amount of concentrated HCl in test product equivalent to amount for (b) (4) HCl:

(b) (4)

- The amount of HCl in test product is slightly less than the amount in reference product.

RLD Formulation[4]

(Not to be released under FOIA)

LABEL CLAIM -- UNIT FORMULA			
EACH 1.0 ML CONTAINS	LABEL CLAIM	EXCESS USED	UNIT FORMULA
EPINEPHRINE USP SODIUM BISULFITE SODIUM CHLORIDE HYDROCHLORIC ACID (b) (4) WATER FOR INJECTION USP/EP (b) (4)	(b) (4)		

(b) (4)

[3] DARRTS for ANDA 207568: Firm's Submission date 06/19/2014. Module 3.2.P.4.1. Supplier-COA-Hydrochloric Acid

[4] DARRTS for NDA 204200: Firm's submission dated 01/23/2015. Module 3.2.P.3.3. mbr-adrenalin-1 mL-2002211-rev003, page No: 6

[5] DARRTS for NDA 204200: 3.2 P.4.1. Specifications Dated 01/23/2015

Comparison of Test and RLD Formulations

(b) (4)

- The reviewer checked the other in-house applications received for Epinephrine Injection with regards to the amount of Hydrochloric Acid in the test formulations. It is noticed that in the other applications, the amount of the Hydrochloric Acid is not specified and just stated as "Q.S. to pH Adjustment". Thus the differences in the amount of HCl between the test and reference formulations were not calculated for the Q1/Q2 determination.

Amount of HCl in Different Epinephrine Drug Products

ANDA	Test	RLD
(b) (4)		
090589[7] Epinephrine Injection (Auto-injector)		(b) (4)
(b) (4)		

- (b) (4) and reference (b) (4) formulations, the pH value of the both the test product (3.3) is similar to the reference[10] (3.9) product.

(b) (4)

[7] GDRP for ANDA 090589: http://panorama.fda.gov/PanoramaDocMgmt/document/download/090026f880ae507f

(b) (4)

DARRTS for ANDA 207568: Firm's Submission date 06/19/2014, Module 3.2.P.5.4, Batch Analysis, Certificate of analysis

[10] DARRTS for NDA 204200: Firm's Submission dated 10/31/2014, Module 3.2.P.5.4. Batch Analysis, Certificate of analysis

- Based on the above information, the reviewer considers the differences in the HCl concentration between the test and reference products to be acceptable.

- 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 review of the original submission, the test formulation not containing the anti-oxidant, sodium metabisulfite is deemed to be adequate[2]. The stability studies from the commercial batches indicated that these differences have no impact on the stability of the proposed drug product.

- Therefore, the DBIII deems the test product, Epinephrine Injection, 1 mg/mL, bioequivalent to the reference product, Adrenalin® (epinephrine hydrochloride), EQ. 1 mg /mL, under 21 CFR § 320.24 (b) (6).

4 DEFICIENCY COMMENTS

None

5 RECOMMENDATIONS

1. The Division of Bioequivalence III (DBIII) **agrees** that the information submitted by Luitpold Pharmaceuticals, Inc. demonstrates that it's Epinephrine Injection, USP 1 mg/mL (non-preserved, 1 mL ampule), 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.

2. The DBIII deems the test product, Epinephrine Injection, USP 1 mg/mL (non-preserved, 1 mL ampule), manufactured by Luitpold Pharmaceuticals, Inc. to be bioequivalent to the reference product, Adrenalin® (epinephrine hydrochloride), EQ. 1 mg base/mL, manufactured by Par Sterile Products (formerly JHP Pharmaceuticals LLC).

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA:	207568
APPLICANT:	Luitpold Pharmaceuticals, Inc.
DRUG PRODUCT:	Epinephrine Injection, USP EQ 1 mg/mL

The Division of Bioequivalence III (DBIII) has completed its review of your submissions 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}

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

6 OUTCOME PAGE

Reviewer: Devalapally, Harikrishna **Date Completed:**
Verifier: **Date Verified:**
Division: Division of Bioequivalence
Description: Epinephrine Injection, USP 1 mg/mL

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
26320	6/4/2015	Other (REGULAR)	Study Amendment	1	1
26320	7/28/2015	Quality Assessment	Quality	5	-
				Total:	1

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	207568		
Drug Product Name	Epinephrine Injection, USP		
Strength(s)[1]	1 mg/mL (non-preserved)		
Applicant Name	Luitpold Pharmaceuticals, Inc.		
Address	One Luitpold Drive, PO Box 9001, Shirley, NY 11967		
Applicant's Point of Contact	Felicia Bullock, Sr. Director, Regulatory Affairs		
Contact's Telephone Number	631-205-2035 (4000)		
Contact's Fax Number	631-205-2013		
Original Submission Date(s)[2]	06/19/2014		
Submission Date(s) of Amendment(s) Under Review	N/A		
Reviewer	Harikrishna Devalapally, Ph. D.		
OVERALL REVIEW RESULT	**INADEQUATE**		
WAIVER REQUEST RESULT	**INADEQUATE**		
REVISED/NEW DRAFT GUIDANCE INCLUDED	**N/A**[3]		
BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	**STUDY/TEST TYPE**	**STRENGTH**	**REVIEW RESULT**
1	**WAIVER**	**1 mg/mL**	**INADEQUATE**

[1] The drug product is available as 1 mg fill in a 1 mL glass ampule.
[2] ANDA 207568 EDR 1, dated 06/19/2014
[3] http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm081292.htm

1 EXECUTIVE SUMMARY

This application was granted expedited review[4] on July 29, 2014 as this drug is currently listed under Drug Shortage list of the Agency.

Luitpold Pharmaceuticals, Inc., submitted this application to request a waiver of *in vivo* bioequivalence (BE) study requirements under Section *21 Code of Federal Regulations (CFR) §320.22(b)(1)* for its test product, Epinephrine Injection, USP 1 mg/mL (non-preserved, 1 mL ampule). The reference-listed drug (RLD) is ADRENALIN® (epinephrine hydrochloride), EQ 1 mg Base/mL, manufactured by Par Sterile Products (formerly JHP Pharmaceuticals LLC) and approved on December 07, 2012 under NDA 204200[5].

(b) (4)

In addition, the firm is requested to provide HCl quantity (volume in mL) up to two significant figures for accurate comparison (b) (4) for more accurate comparison with the RLD formulation in quanlitative (Q1) and quantitative (Q2) sameness determination.

The proposed test drug product, Epinephrine Injection, USP 1 mg/mL will be available as 1 mg fill in 1 mL glass ampule for single-use. It is intended for intramuscular (IM), subcutaneous (SC) (b) (4) administration[8].

Based on the information provided, the waiver request for *in vivo* BE study requirements for Epinephrine Injection, USP 1 mg/mL may not be granted, based on criteria set forth in 21 CFR §320.22 (b)(1)[9].

The application is **inadequate** with deficiencies cited in the deficiency section of the review.

[4] DARRTS: ANDA #207568, FRM-ADMIN-28 (Expedited Review Determination), Final Date: 07/29/2014.
[5] Online Orange Book, http://www.accessdata fda.gov/scripts/cder/ob/docs/tempai.cfm, Search word: Epinephrine. Last accessed: 09/02/14
[6] DARRTS: ANDA #207568 REV-RPM-03(Filing Review) Submit Date: 07/29/2014
[7] DARRTS: EDR NDA 204200, 2.3 P 1. Quality Overall Summary, Page 4.
[8] ANDA 207568, EDR 3.2.P.1, dated 06/19/2014
[9] http://www.accessdata fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=320.22

2 TABLE OF CONTENTS

3 SUBMISSION SUMMARY

3.1 Drug Product Information[10]

Test Product	Epinephrine Injection, 1 mg/mL
Reference Product	ADRENALIN® (epinephrine hydrochloride), EQ 1 mg Base/mL
RLD Manufacturer	Par Sterile Products (formerly JHP Pharmaceuticals LLC)
NDA No.	204200
RLD Approval Date	December 07, 2012
Indication[11]	Epinephrine is the adrenergic drug of choice for the emergency treatment of acute hypersensitivity (anaphylactoid reactions to drugs, animal serums, insect stings, and other allergens). Induction and maintenance of mydriasis during intraocular surgery.

3.2 PK/PD Information[9]

Bioavailability	The extent of human systemic exposure at the labeled intraocular dose has not been evaluated, however, significant systemic concentrations or plasma exposure of epinephrine are not expected when administered intraocularly.
Food Effect	N/A
Tmax	Following I.V. injection, epinephrine disappears rapidly from the blood stream. Subcutaneous, intraocular or I M. administered epinephrine has a rapid onset and short duration of action. Subcutaneous administration during asthmatic attacks may produce bronchodilation within 5 to 10 minutes, and maximal effects may occur within 20 minutes.
Metabolism	The drug becomes fixed in the tissues and is rapidly inactivated chiefly by enzymic transformation to metanephrine or normetanephrine, either of which is subsequently conjugated and excreted in the urine in the form of sulfates and glucuronides. Either sequence results in the formation of 3-methoxy-4-hydroxy-mandelic acid (vanillylmandelic acid, VMA) which is also detectable in the urine.
Excretion	The tissues with the highest contribution to removal of circulating exogenous epinephrine are the liver (32%), kidneys (25%), skeletal muscle (20%), and mesenteric organs (12%).
Half-life	Terminal elimination half <5 min.
Drug Specific Issues (if any)	**WARNING** • Do not inject into buttocks, digits, hands, or feet. • May aggravate angina pectoris or produce ventricular arrhythmias, particularly in patients with underlying heart disease, administer with caution when used intramuscularly or subcutaneously. • Patients with hyperthyroidism, Parkinson's disease, diabetes, and pheochromocytoma are at greater risk of having adverse reactions when used intramuscularly or subcutaneously. • Presence of sulfite in this product should not deter use for

[10] Online Orange Book, Search word: Epinephrine. Last accessed: 09/02/14.
[11] Drugs@FDA, Search word: Epinephrine, Check ADRINALIN NDA 204200, Label approved on 12/07/2012.

	anaphylaxis.

3.3 OGD Recommendations for Drug Product

Number of studies recommended:	N/A-Waiver Request
Analytes to measure (in plasma/serum/blood):	N/A-Waiver request
Bioequivalence based on:	According to 21 CFR §320.22 (b)(1), a waiver of the requirement for the submission of evidence measuring in vivo bioavailability or demonstrating bioequivalence may be granted to a parenteral solution administered by injection that contains the same active and inactive ingredients in the same concentration as a drug product that is the subject of an approved full new drug application or abbreviated new drug application.
Waiver request of in-vivo testing:	YES
Source of most recent recommendations:	N/A
Summary of OGD or DB History	There are no approved ANDAs[12] (referencing NDA 204200) and controlled correspondence documents[13] for Epinephrine Injection, USP 1 mg/mL.

3.4 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	1
BCS Waivers	No	--
Clinical Endpoints	No	--
Failed Studies	No	--
Amendments	No	--

3.5 Formulation

Location in appendix	Section 3.11.1, Page 7
If a tablet, is the RLD scored?	N/A
If a tablet, is the test product biobatch scored	N/A
Is the formulation acceptable?	**FORMULATION NOT ACCEPTABLE**
If not acceptable, why?	N/A

[12] DARRTS, Search epinephrine, injection. Last accessed 09/02/14.
[13] Internal Control document database. Search epinephrine. Last accessed 09/02/14.

3.6 Waiver Request(s)

Strengths for which waivers are requested	1 mg/mL
Proportional to strength tested in vivo?	N/A
Is dissolution acceptable?	N/A
Waivers granted?	**NOT GRANTED**
If not then why?	N/A

3.7 Deficiency Comments

1. (b) (4)
2.

3.8 Recommendation

The DBIII deems that the test product, Epinephrine Injection, USP 1 mg/mL (non-preserved, 1 mL ampule), manufactured by Luitpold Pharmaceuticals Inc., (b) (4) the RLD, Adrenalin® (epinephrine injection) EQ1 mg base/mL (1:1000) due to the deficiencies cited above.

3.9 Comments for Other OGD Disciplines

Discipline	Comment
OPQ	(b) (4)

3.10 Pending Consults (Clinical, Statistical, Science Staff, Chemistry etc.)

Discipline	Comment
None	None

3.11 APPENDIX

3.11.1 Formulation Data

- Epinephrine Injection, USP 1 mg/mL is a sterile, clear, colorless, (b) (4) solution containing 1 mg/mL Epinephrine Injection, USP in Water for Injection with Sodium Chloride added for isotonicity and pH adjusted with Hydrochloric Acid (b) (4)
- Epinephrine Injection, USP 1 mg/mL drug product will be supplied in a 1 mL ampule in trays of 25.
- It is administered by IM, SC (b) (4)

  Anaphylaxis:
  Adults and Children 30 kg (66 lbs) or more: 0.3 to 0.5 mg (0.3 to 0.5 mL) intramuscularly or subcutaneously into anterolateral aspect of the thigh every 5 to 10 minutes as necessary.
  Children 30 kg (66 lbs) or less: 0.01 mg/kg (0.01 mL/kg), up to 0.3 mg (0.3 mL), intramuscularly or subcutaneously into anterolateral aspect of the thigh every 5 to 10 minutes as necessary.

(b) (4)

A. Formulation Composition for the Test Drug Product, Epinephrine Injection, USP 1 mg/mL[14]

Ingredient	Function	% Composition (w/w)	1 mg/mL
Epinephrine, USP (b) (4)	Active	(b) (4)	
Sodium Chloride, USP			
Water for Injection, USP			
Hydrochloric acid, NF			
(b) (4)			

(b) (4)

[14] EDR 207568, Module 2.3 P.1, QOS, Page 23

B. Formulation Composition for the Reference Listed Drug (RLD), Epinephrine Injection, USP 1 mg/mL[15]

(Not to be released under FOIA)

Ingredient	Function	Unit formula
Epinephrine (+ 14% overage)	(b) (4)	
Sodium Chloride		
Sodium Metabisulfite		
(b) (4) Hydrochloric acid		
Water for Injection		

(b) (4)

C. Epinephrine Injection, USP 1 mg/mL Formulation Comparison to the RLD[17]:

(Not to be released under FOIA)

(b) (4)

Is there an overage of the active pharmaceutical ingredient (API)?	Yes
If the answer is yes, has the appropriate chemistry division been notified?	(b) (4)

[15] EDR NDA 204200, 2.3 P.1. Quality Overall Summary, Page 4.
[16] EDR NDA 204200, 3.2 R.1. Executed Batch Record, Page 38.
[17] EDR 207568, Module 2.3 P.1. Quality Overall Summary, Page 24.

If it is necessary to reformulate to reduce the overage, will bioequivalence be impacted?	N/A
Are the amounts of all inactive ingredients based on Maximum Daily Dose (MDD) within IIG (per unit) limits?	Yes
If no, are they all above/within IIG (per day) limits?	--
If no, are additional data or Pharm/Tox consult necessary?	--
Are all color additives and elemental iron within limits specified by CFR (if applicable) or less than 0.1% of the total unit weight (w/w)?	N/A
Are all strengths of the test product proportionally similar per the BA/BE guidance criteria?	--
Are all strengths of the RLD product dose-proportional?	--
Are all strengths of the test formulation acceptable	--

3.12 Reviewer's Comments:

- In Orange Book, the RLD is listed as Epinephrine Hydrochloride whereas the RLD labeling described the drug product as Adrenalin® (epinephrine injection) EQ 1 mg base/mL (1:1000)[8, 9]. Each 1 mL of Adrenalin® solution contains 1 mg epinephrine, 9.0 mg sodium chloride, 1.0 mg sodium metabisulfite, hydrochloric acid to adjust pH, and water for injection. The pH range is 2.2-5.0.

- The proposed test drug product, Epinephrine Injection, USP 1 mg/mL is a single use vial containing 1 mg/mL of epinephrine as solution. It is intended for IM, SC (b) (4) dosing. Epinephrine Injection, USP 1 mg/mL (b) (4)

- (b) (4)

- The test drug product, Epinephrine Injection, USP 1 mg/mL contains the same active ingredient in the same dosage form as the reference product, ADRINALIN® (epinephrine hydrochloride) 1 mg/mL, except the omission of antioxidant, sodium metabisulfite (Sulfite-containing epinephrine has the potential to cause severe corneal edema and its use should be avoided, especially during ophthalmic surgery. Therefore, non-preserved, bisulfite-free epinephrine is ideal for use in patients with histories of anaphylaxis to sulfite preservatives as well as for ophthalmological use where bisulfite-free epinephrine is preferred. Due to the nature of the preservative-free formulation, the

[18] EDR NDA 204200, 03/07/2012, Module 2.3.P.2.2.3 QOS, Page 15.
[19] EDR ANDA 207568, 06/19/2014, Module 3.2.P.2.3.2 Pharmaceutical Development, Page 10.
[20] http://www.uspnf.com/uspnf/pub/index?usp=37&nf=32&s=1&officialOn=August 1, 2014.

proposed recommended storage condition for test product is 20°C to 25°C and shielded from light) (b) (4), which is not an exception excipients in accordance with 21 CFR 314.94(a)(9)(iii))[21]. Difference in antioxidant between the test and RLD products is permissible provided that the firm provides adequate justification as stated in 21 CFR 314.94(a)(9)(iii)). On the other hand, difference in pH adjuster is not permissible (Please see additional comments below).

- The formulation of the test product is the same as the RLD except sodium metabisulfite (is presented in RLD as antioxidant) (b) (4). In accordance to 21 CFR §314.94(a)(9)(iii), "*Generally, a drug product intended for parenteral use shall contain the same inactive ingredients and in the same concentration as the reference listed drug identified by the applicant under paragraph (a)(3) of this section. However, an applicant may seek approval of a drug product that differs from the reference listed drug in preservative, buffer, or antioxidant 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.*" Therefore, omitting the antioxidant, sodium metabisulfite is considered acceptable. (b) (4) Yet, the above differences between Luitpold's' proposed formulation and the RLD may present concerns with respect to therapeutic equivalence and the stability of the product. Therefore, the differences between Luitpold's proposed formulation and the RLD are considered **not acceptable**. (b) (4)

- In the test product, the firm used HCl (b) (4)

  (b) (4)

- RLD and test products contain HCl as pH adjuster. The firm is requested to provide HCl quantity (volume in mL) up to two significant figures for accurate comparison (b) (4)

[21] EDR ANDA 207568, 06/19/2014, Module 2.3 Quality Overall Summary, page 25

(b) (4) for accurate comparison with the RLD formulation in quanlitative (Q1) and quantitative (Q2) sameness determination.

- The finished test product Epinephrine Injection, USP 1 mg/mL solution has a pH of 3.0-3.6[22] (Batch pH 3.3). Per USP monograph for Epinephrine Injection17, the reference product's pH is between 2.2 and 5.0 (Batch pH 4.0). The pH range of the test product is noted to be within the pH specification of the RLD product as per USP.

3.13 Overall Reviewer Comments

1. The test product is intended for IM, SC (b) (4) administration.

2. The route of administration, dosage form, and strength of the test product are the same as those of the RLD product.

3. The pH range of test product is between 3.0 and 3.6, which falls within the pH specification range of the RLD product.

4. The test product and the RLD (b) (4).

5. Inactive ingredients (Hydrochloric acid, Sodium chloride, WFI) are in the same concentrations except the sodium metabisulfite (presented in RLD as antioxidant) (b) (4) .

   In order to assure that the test product is qualitatively and quantitatively the same as the reference listed drug product, the firm is requested to update its components and composition statement for this drug product (b) (4)

6. RLD and test products contain HCl as pH adjuster. The firm is requested to provide HCl quantity (volume in mL) up to two significant figures (b) (4)

7. Per 21 CFR § 320.22 (b)(1), the waiver request for the test product, Epinephrine Injection USP, 1 mg/mL is **not granted**.

3.14 Detailed Regulatory History (If Applicable):

None

[22] EDR ANDA 207568, 06/19/2014, Module 2 3, Page 41.

3.15 Consult Reviews

None

3.16 Additional Attachments

None

3.17 Outcome Page

Completed Assignment for 207568 ID: 23916

Reviewer: Devalapally, Harikrishna **Date Completed:09/03/2014**
Verifier: , **Date Verified:**
Division: Division of Bioequivalence
Description: Q1/Q2 Epinephrine Injection, USP 1 mg/mL

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
23916	6/19/2014	Other (REGULAR)	Waiver Injectable	1	1
				Total:	1

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	207568		
Drug Product Name	Epinephrine Injection, USP		
Strength(s)[1]	1 mg/mL (non-preserved)		
Applicant Name	Luitpold Pharmaceuticals, Inc.		
Address	One Luitpold Drive, PO Box 9001, Shirley, NY 11967		
Applicant's Point of Contact	Felicia Bullock, Sr. Director, Regulatory Affairs		
Contact's Telephone Number	631-205-2035 (4000)		
Contact's Fax Number	631-205-2013		
Original Submission Date(s)[2]	06/19/2014		
Submission Date(s) of Amendment(s) Under Review	N/A		
Reviewer	Harikrishna Devalapally, Ph. D.		
OVERALL REVIEW RESULT	**INADEQUATE**		
WAIVER REQUEST RESULT	**INADEQUATE**		
REVISED/NEW DRAFT GUIDANCE INCLUDED	**N/A**[3]		
BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	**STUDY/TEST TYPE**	**STRENGTH**	**REVIEW RESULT**
1	**WAIVER**	**1 mg/mL**	**INADEQUATE**

[1] The drug product is available as 1 mg fill in a 1 mL glass ampule.
[2] ANDA 207568 EDR 1, dated 06/19/2014
[3] http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm081292.htm

1 EXECUTIVE SUMMARY

This application was granted expedited review[4] on July 29, 2014 as this drug is currently listed under Drug Shortage list of the Agency.

Luitpold Pharmaceuticals, Inc., submitted this application to request a waiver of *in vivo* bioequivalence (BE) study requirements under Section *21 Code of Federal Regulations (CFR) §320.22(b)(1)* for its test product, Epinephrine Injection, USP 1 mg/mL (non-preserved, 1 mL ampule). The reference-listed drug (RLD) is ADRENALIN® (epinephrine hydrochloride), EQ 1 mg Base/mL, manufactured by Par Sterile Products (formerly JHP Pharmaceuticals LLC) and approved on December 07, 2012 under NDA 204200[5].

On 07/29/2014, ANDA #207568 was accepted for filling[6], despite the firm's test formulation not being qualitatively the same as the RLD product. Specifically, the RLD product uses hydrochloric acid (HCl) as pH adjuster in its formulation[7], but the test drug product uses hydrochloric acid (HCl) (b) (4) In order to assure that the test product is qualitatively and quantitatively the same as the reference listed drug product, the firm is requested to update its components and composition statement for this drug produc (b) (4)

In addition, the firm is requested to provide HCl quantity (volume in mL) up to two significant figures for accurate comparison (b) (4) for more accurate comparison with the RLD formulation in qualitative (Q1) and quantitative (Q2) sameness determination.

The proposed test drug product, Epinephrine Injection, USP 1 mg/mL will be available as 1 mg fill in 1 mL glass ampule for single-use. It is intended for intramuscular (IM), subcutaneous (SC) (b) (4) administration[8].

Based on the information provided, the waiver request for *in vivo* BE study requirements for Epinephrine Injection, USP 1 mg/mL may not be granted, based on criteria set forth in 21 CFR §320.22 (b)(1)[9].

The application is **inadequate** with deficiencies cited in the deficiency section of the review.

---

[4] DARRTS: ANDA #207568, FRM-ADMIN-28 (Expedited Review Determination), Final Date: 07/29/2014.
[5] Online Orange Book, http://www.accessdata.fda.gov/scripts/cder/ob/docs/tempai.cfm, Search word: Epinephrine. Last accessed: 09/02/14
[6] DARRTS: ANDA #207568 REV-RPM-03(Filing Review) Submit Date: 07/29/2014
[7] DARRTS: EDR NDA 204200, 2.3 P.1. Quality Overall Summary, Page 4.
[8] ANDA 207568, EDR 3.2.P.1, dated 06/19/2014
[9] http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=320.22

2 TABLE OF CONTENTS

3 SUBMISSION SUMMARY

3.1 Drug Product Information[10]

Test Product	Epinephrine Injection, 1 mg/mL
Reference Product	ADRENALIN® (epinephrine hydrochloride), EQ 1 mg Base/mL
RLD Manufacturer	Par Sterile Products (formerly JHP Pharmaceuticals LLC)
NDA No.	204200
RLD Approval Date	December 07, 2012
Indication[11]	Epinephrine is the adrenergic drug of choice for the emergency treatment of acute hypersensitivity (anaphylactoid reactions to drugs, animal serums, insect stings, and other allergens). Induction and maintenance of mydriasis during intraocular surgery.

3.2 PK/PD Information[9]

Bioavailability	The extent of human systemic exposure at the labeled intraocular dose has not been evaluated, however, significant systemic concentrations or plasma exposure of epinephrine are not expected when administered intraocularly.
Food Effect	N/A
Tmax	Following I.V. injection, epinephrine disappears rapidly from the blood stream. Subcutaneous, intraocular or I.M. administered epinephrine has a rapid onset and short duration of action. Subcutaneous administration during asthmatic attacks may produce bronchodilation within 5 to 10 minutes, and maximal effects may occur within 20 minutes.
Metabolism	The drug becomes fixed in the tissues and is rapidly inactivated chiefly by enzymic transformation to metanephrine or normetanephrine, either of which is subsequently conjugated and excreted in the urine in the form of sulfates and glucuronides. Either sequence results in the formation of 3-methoxy-4-hydroxy-mandelic acid (vanillylmandelic acid, VMA) which is also detectable in the urine.
Excretion	The tissues with the highest contribution to removal of circulating exogenous epinephrine are the liver (32%), kidneys (25%), skeletal muscle (20%), and mesenteric organs (12%).
Half-life	Terminal elimination half <5 min.
Drug Specific Issues (if any)	**WARNING** • Do not inject into buttocks, digits, hands, or feet. • May aggravate angina pectoris or produce ventricular arrhythmias, particularly in patients with underlying heart disease, administer with caution when used intramuscularly or subcutaneously. • Patients with hyperthyroidism, Parkinson's disease, diabetes, and pheochromocytoma are at greater risk of having adverse reactions when used intramuscularly or subcutaneously. • Presence of sulfite in this product should not deter use for

[10] Online Orange Book, Search word: Epinephrine. Last accessed: 09/02/14.
[11] Drugs@FDA, Search word: Epinephrine, Check ADRINALIN NDA 204200, Label approved on 12/07/2012.

	anaphylaxis.

3.3 OGD Recommendations for Drug Product

Number of studies recommended:	N/A-Waiver Request
Analytes to measure (in plasma/serum/blood):	N/A-Waiver request
Bioequivalence based on:	According to 21 CFR §320.22 (b)(1), a waiver of the requirement for the submission of evidence measuring in vivo bioavailability or demonstrating bioequivalence may be granted to a parenteral solution administered by injection that contains the same active and inactive ingredients in the same concentration as a drug product that is the subject of an approved full new drug application or abbreviated new drug application.
Waiver request of in-vivo testing:	YES
Source of most recent recommendations:	N/A
Summary of OGD or DB History	There are no approved ANDAs[12] (referencing NDA 204200) and controlled correspondence documents[13] for Epinephrine Injection, USP 1 mg/mL.

3.4 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	1
BCS Waivers	No	--
Clinical Endpoints	No	--
Failed Studies	No	--
Amendments	No	--

3.5 Formulation

Location in appendix	Section 3.11.1, Page 7
If a tablet, is the RLD scored?	N/A
If a tablet, is the test product biobatch scored	N/A
Is the formulation acceptable?	**FORMULATION NOT ACCEPTABLE**
If not acceptable, why?	N/A

[12] DARRTS, Search epinephrine, injection. Last accessed 09/02/14.
[13] Internal Control document database. Search epinephrine. Last accessed 09/02/14.

3.6 Waiver Request(s)

Strengths for which waivers are requested	1 mg/mL
Proportional to strength tested in vivo?	N/A
Is dissolution acceptable?	N/A
Waivers granted?	**NOT GRANTED**
If not then why?	N/A

3.7 Deficiency Comments

1. In the test product, the firm used HCl [redacted] (b) (4)

   In order to assure that the test product is qualitatively and quantitatively the same as the reference listed drug product, the firm is requested to update its components and composition statement for this drug product [redacted] (b) (4)

2. RLD and test products contain HCl as pH adjuster. The firm is requested to provide HCl quantity (volume in mL) up to two significant figures [redacted] (b) (4) for accurate comparison with the RLD formulation in qualitative (Q1) and quantitative (Q2) sameness determination.

3.8 Recommendation

The DBIII deems that the test product, Epinephrine Injection, USP 1 mg/mL (non-preserved, 1 mL ampule), manufactured by Luitpold Pharmaceuticals Inc., is not Q1/Q2 the same as the RLD, Adrenalin® (epinephrine injection) EQ1 mg base/mL (1:1000) due to the deficiencies cited above.

3.9 Comments for Other OGD Disciplines

Discipline	Comment
OPQ	[redacted] (b) (4)

3.10 Pending Consults (Clinical, Statistical, Science Staff, Chemistry etc.)

Discipline	Comment
None	None

3.11 APPENDIX

3.11.1 Formulation Data

- Epinephrine Injection, USP 1 mg/mL is a sterile, clear, colorless, [redacted] solution containing 1 mg/mL Epinephrine Injection, USP in Water for Injection with Sodium Chloride added for isotonicity and pH adjusted with Hydrochloric Acid [redacted].

- Epinephrine Injection, USP 1 mg/mL drug product will be supplied in a 1 mL ampule in trays of 25.

- It is administered by IM, SC [redacted]

  Anaphylaxis:
  Adults and Children 30 kg (66 lbs) or more: 0.3 to 0.5 mg (0.3 to 0.5 mL) intramuscularly or subcutaneously into anterolateral aspect of the thigh every 5 to 10 minutes as necessary.
  Children 30 kg (66 lbs) or less: 0.01 mg/kg (0.01 mL/kg), up to 0.3 mg (0.3 mL), intramuscularly or subcutaneously into anterolateral aspect of the thigh every 5 to 10 minutes as necessary.

[redacted]

A. Formulation Composition for the Test Drug Product, Epinephrine Injection, USP 1 mg/mL[14]

Ingredient	Function	% Composition (w/w)	1 mg/mL
Epinephrine, USP [redacted]	Active	[redacted]	[redacted]
Sodium Chloride, USP	[redacted]		
Water for Injection, USP			
Hydrochloric acid, NF			
[redacted]			

[14] EDR 207568, Module 2.3 P.1, QOS, Page 23

B. Formulation Composition for the Reference Listed Drug (RLD), Epinephrine Injection, USP 1 mg/mL[15]

(Not to be released under FOIA)

Ingredient	Function	Unit formula
Epinephrine (b) (4)	Active	(b) (4)
Sodium Chloride	(b) (4	
Sodium Metabisulfite		
(b) (4) Hydrochloric acid		
Water for Injection		
(b) (4)		

C. Epinephrine Injection, USP 1 mg/mL Formulation Comparison to the RLD[17]:

(Not to be released under FOIA)

(b) (4)

Is there an overage of the active pharmaceutical ingredient (API)?	Yes
If the answer is yes, has the appropriate chemistry division been notified?	(b) (4)

[15] EDR NDA 204200, 2.3 P.1. Quality Overall Summary, Page 4.
[16] EDR NDA 204200, 3.2 R.1. Executed Batch Record, Page 38.
[17] EDR 207568, Module 2.3 P.1. Quality Overall Summary, Page 24.

If it is necessary to reformulate to reduce the overage, will bioequivalence be impacted?	N/A
Are the amounts of all inactive ingredients based on Maximum Daily Dose (MDD) within IIG (per unit) limits?	Yes
If no, are they all above/within IIG (per day) limits?	--
If no, are additional data or Pharm/Tox consult necessary?	--
Are all color additives and elemental iron within limits specified by CFR (if applicable) or less than 0.1% of the total unit weight (w/w)?	N/A
Are all strengths of the test product proportionally similar per the BA/BE guidance criteria?	--
Are all strengths of the RLD product dose-proportional?	--
Are all strengths of the test formulation acceptable	--

3.12 Reviewer's Comments:

- In Orange Book, the RLD is listed as Epinephrine Hydrochloride whereas the RLD labeling described the drug product as Adrenalin® (epinephrine injection) EQ 1 mg base/mL (1:1000)[8, 9]. Each 1 mL of Adrenalin® solution contains 1 mg epinephrine, 9.0 mg sodium chloride, 1.0 mg sodium metabisulfite, hydrochloric acid to adjust pH, and water for injection. The pH range is 2.2-5.0.

- The proposed test drug product, Epinephrine Injection, USP 1 mg/mL is a single use vial containing 1 mg/mL of epinephrine as solution. It is intended for IM, SC (b) (4)

- (b) (4)

- The test drug product, Epinephrine Injection, USP 1 mg/mL contains the same active ingredient in the same dosage form as the reference product, ADRINALIN® (epinephrine hydrochloride) 1 mg/mL, except the omission of antioxidant, sodium metabisulfite (Sulfite-containing epinephrine has the potential to cause severe corneal edema and its use should be avoided, especially during ophthalmic surgery. Therefore, non-preserved, bisulfite-free epinephrine is ideal for use in patients with histories of anaphylaxis to sulfite preservatives as well as for ophthalmological use where bisulfite-free epinephrine is preferred. Due to the nature of the preservative-free formulation, the

[18] EDR NDA 204200, 03/07/2012, Module 2.3.P.2.2.3 QOS, Page 15.
[19] EDR ANDA 207568, 06/19/2014, Module 3.2.P.2.3.2 Pharmaceutical Development, Page 10.
[20] http://www.uspnf.com/uspnf/pub/index?usp=37&nf=32&s=1&officialOn=August 1, 2014.

proposed recommended storage condition for test product is 20°C to 25°C and shielded from light) (b) (4) which is not an exception excipients in accordance with 21 CFR 314.94(a)(9)(iii)) . Difference in antioxidant between the test and RLD products is permissible provided that the firm provides adequate justification as stated in 21 CFR 314.94(a)(9)(iii)). (b) (4)

- The formulation of the test product is the same as the RLD except sodium metabisulfite (is presented in RLD as antioxidant) (b) (4) In accordance to 21 CFR §314.94(a)(9)(iii), "*Generally, a drug product intended for parenteral use shall contain the same inactive ingredients and in the same concentration as the reference listed drug identified by the applicant under paragraph (a)(3) of this section. However, an applicant may seek approval of a drug product that differs from the reference listed drug in preservative, buffer, or antioxidant 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.*" (b) (4) Therefore, the differences between Luitpold's proposed formulation and the RLD are considered **not acceptable**. (b) (4)

- (b) (4)

(b) (4)

- RLD and test products contain HCl as pH adjuster. The firm is requested to provide HCl quantity (volume in mL) up to two significant figures for accurate comparison (i.e., (b) (4) for accurate comparison with the RLD formulation in qualitative (Q1) and quantitative (Q2) sameness determination.

[21] EDR ANDA 207568, 06/19/2014, Module 2.3 Quality Overall Summary, page 25

- The finished test product Epinephrine Injection, USP 1 mg/mL solution has a pH of 3.0-3.6[22] (Batch pH 3.3). Per USP monograph for Epinephrine Injection17, the reference product's pH is between 2.2 and 5.0 (Batch pH 4.0). The pH range of the test product is noted to be within the pH specification of the RLD product as per USP.

3.13 Overall Reviewer Comments

1. The test product is intended for IM, SC [redacted] (b) (4)

2. The route of administration, dosage form, and strength of the test product are the same as those of the RLD product.

3. The pH range of test product is between 3.0 and 3.6, which falls within the pH specification range of the RLD product.

4. The test product and the RLD contain [redacted] (b) (4) respectively of overage of API.

5. Inactive ingredients (Hydrochloric acid, Sodium chloride, WFI) are in the same concentrations except the sodium metabisulfite (presented in RLD as antioxidant) [redacted] (b) (4)

   In order to assure that the test product is qualitatively and quantitatively the same as the reference listed drug product, the firm is requested to update its components and composition statement for this drug product [redacted] (b) (4)

6. RLD and test products contain HCl as pH adjuster. The firm is requested to provide HCl quantity (volume in mL) up to two significant figures [redacted] (b) (4)) for accurate comparison with the RLD formulation in qualitative (Q1) and quantitative (Q2) sameness determination..

7. Per 21 CFR § 320.22 (b)(1), the waiver request for the test product, Epinephrine Injection USP, 1 mg/mL is **not granted**.

3.14 Detailed Regulatory History (If Applicable):

None

[22] EDR ANDA 207568, 06/19/2014, Module 2.3, Page 41.

3.15 Consult Reviews

None

3.16 Additional Attachments

None

BIOEQUIVALENCE DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA:	207568
APPLICANT:	Luitpold Pharmaceuticals, Inc.
DRUG PRODUCT:	Epinephrine Injection, USP 1 mg/mL

The Division of Bioequivalence III (DBIII) has completed its review and the following deficiencies have been identified:

1. In the test product, you used hydrochloric acid (HCl) (b) (4)

   (b) (4)

2. Both RLD and test products contain HCl as the pH adjuster. Please provide HCl quantity (volume in mL) up to two significant figures (b) (4) for accurate comparison with the RLD formulation in Q1Q2 sameness determination as the basis for granting the requested waiver. Alternatively, please confirm that the HCl concentration of (b) (4), provided for your test formulation, is actually (b) (4)

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}

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

3.17 Outcome Page

Completed Assignment for 207568 ID: 23916

Reviewer: Devalapally, Harikrishna **Date Completed:09/03/2014**
Verifier: , **Date Verified:**
Division: Division of Bioequivalence
Description: Q1/Q2 Epinephrine Injection, USP 1 mg/mL

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
23916	6/19/2014	Other (REGULAR)	Waiver Injectable	1	1
				Total:	1

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

/s/

ZAKARIA Z WAHBA
09/26/2014
Signed for Hari Devalapally

CHRISTINA H LEE
09/26/2014

HOAINHON N CARAMENICO
09/26/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 207568

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

OPQ QUALITY ENDORSEMENT CHECKLIST (See Reference Guide for details):

ANDA# 207568 - Epinephrine Solution

Function	Performed By (Initial and Date)	Check appropriate box
Is the final review signed and archived in the current IT platform?	EA – 6/28/18	☒ Yes ☐ No
DMF adequate and review up to date?	EA – 6/28/18	☒ Yes ☐ No *(see comments)
Are consults complete and adequate?	EA – 6/28/18	☐ Yes *(see comments) ☐ No ☒ N/A
Are all facility inspections acceptable?	EA – 6/28/18	☒ Yes ☐ No
Is microbiology recommendation adequate for sterile products?	EA – 6/28/18	☒ Yes ☐ No ☐ N/A
Final recommended dissolution method/specification acknowledged by Firm?	DD, BC or designee	☐ Yes ☐ No ☒ N/A
Are there comparability protocols provided? If yes, how many?	DD, BC, or designee	☐ Yes How many:_____ ☒ No
If USP monograph exists, do the specifications conform to the current USP?	DD, BC or designee	☒ Yes ☐ No *(see comments) ☐ N/A
Is the application compliant with USP <232/233> requirements or ICH Q3D (regarding elemental impurities)?	DD, BC or designee	☒ Yes ☐ No *(see comments) ☐ N/A

Comments

Division	Name	Date
Division of Liquid-Based Products (DLBP)	Reynold Tan	6/28/18

Reynold Tan

Digitally signed by Reynold Tan
Date: 6/28/2018 03:07:44PM
GUID: 508da6f600027f10d05adcd85197c2aa

Erin Andrews

Digitally signed by Erin Andrews
Date: 6/28/2018 03:38:47PM
GUID: 52e7d3790000f03cf7ec38aacca759ed

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

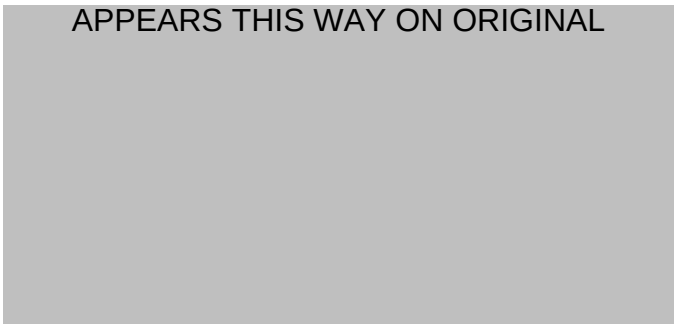
Sent: 03/23/2018 02:27:14 PM
To: rgibson@luitpold.com
CC: ERIN.ANDREWS@FDA.HHS.GOV
BCC:
Subject: ANDA - 207568 - INFORMATION REQUEST

Dear Raenel Gibson
Please see attached, time sensitive, correspondence in reference to ANDA 207568.
NOTE: Upon receipt of this email please send confirmation to Erin Andrews via email at erin.andrews@fda.hhs.gov.
Thank you

DO NOT RESPOND TO THIS EMAIL ADDRESS – IT IS A SEND-ONLY ACCOUNT. For questions, please contact the Regulatory Project Manager assigned to your application.

Please find the attached documents below:

207568 ANDA_ChemIR.pdf



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

ANDA 207568

INFORMATION REQUEST

Luitpold Pharmaceuticals, Inc.
Attention: Raenel Gibson
6610 New Albany Road East
New Albany, OH 43054
rgibson@luitpold.com

Dear Sir or Madam:

Please refer to your Abbreviated New Drug Application (ANDA) dated June 19, 2014, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act) for Epinephrine Injection, USP, 1 mg/mL.

We are reviewing the Quality section of your submission and have the following comments and information requests. We request a prompt written response, no later than April 24, 2018 in order to continue our evaluation of your ANDA.

List of the deficiencies:

A. Chemistry Deficiencies:

(b) (4)

Send your submission through the Electronic Submission Gateway http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/default.htm. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

INFORMATION REQUEST
QUALITY

If you have any questions, please contact me at 240-402-8578.

Sincerely,

{See appended electronic signature page}

Erin Andrews, PharmD
LCDR, U.S. Public Health Service
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Sent: 11/07/2017 05:18:40 PM
To: rgibson@luitpold.com
CC: erin.andrews@fda.hhs.gov
BCC:
Subject: ANDA INFORMATION REQUEST 207568

Dear Raenel Gibson:

Please see attached, time sensitive, correspondence in reference to ANDA 207568.

NOTE: Upon receipt of this email please send confirmation to Erin Andrews via email at erin.andrews@fda.hhs.gov

Thank you.

Please find the attached documents below:

207568 ANDA_ChemIR_11617_12617.pdf
http://panorama.fda.gov/document/download?ID=5a00a9ae005b6cfbc3e12c20d3b16e87

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

ANDA 207568

INFORMATION REQUEST

Luitpold Pharmaceuticals, Inc.
Attention: Raenel Gibson
6610 New Albany Road East
New Albany, OH 43054
rgibson@luitpold.com

Dear Sir or Madam:

Please refer to your Abbreviated New Drug Application (ANDA) dated June 19, 2014, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act) for Epinephrine Injection, USP, 1 mg/mL.

We are reviewing the Quality section of your submission and have the following comments and information requests. We request a prompt written response, no later than December 7, 2017 in order to continue our evaluation of your ANDA.

List of the deficiencies:

A. Chemistry Deficiencies:

1. (b) (4)

2.

3.

If you do not submit a complete response by December 7, 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.

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 me at 240-402-8578.

Sincerely,

Erin Andrews, PharmD
LCDR, U.S. Public Health Service
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Erin Andrews

Digitally signed by Erin Andrews
Date: 11/07/2017 05:15:46PM
GUID: 52e7d3790000f03cf7ec38aacca759ed

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Sent: 08/25/2017 03:38:57 PM
To: rgibson@luitpold.com
CC: erin.andrews@fda.hhs.gov
BCC:
Subject: INFORMATION REQUEST ANDA 207568

Dear Raenel Gibson:

Please see attached, time sensitive, correspondence in reference to ANDA 207568.
NOTE: Upon receipt of this email please send confirmation to Erin Andrews via email at erin.andrews@fda.hhs.gov.

Thank you

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

ANDA 207568

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Attention: Raenel Gibson
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Dear Sir or Madam:

Please refer to your Abbreviated New Drug Application (ANDA) dated June 19, 2014, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act) for Epinephrine Injection, USP, 1 mg/mL.

We are reviewing the Quality section of your submission and have the following comments and information requests. We request a prompt written response, no later than September 25, 2017 in order to continue our evaluation of your ANDA.

List of the deficiencies:

A. Chemistry Deficiencies:

1. (b) (4)

2.

If you do not submit a complete response by September 25, 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.

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 me at 240-402-8578.

Sincerely,

Erin Andrews, PharmD
LT, U.S. Public Health Service
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Erin Andrews

Digitally signed by Erin Andrews
Date: 8/25/2017 03:33:57PM
GUID: 52e7d3790000f03cf7ec38aacca759ed

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Sent: 07/31/2017 10:31:52 AM
To: rgibson@luitpold.com
CC: Carol.Lee@fda.hhs.gov
BCC: edward.mcdonald1@fda.hhs.gov
Subject: ANDA 207568 EASILY CORRECTABLE DEFICIENCY

Dear Ms. Gibson,

Please find attached Easily Correctable Labeling Deficiencies for your pending ANDA 207568.

Provide a complete response to these deficiencies as soon as possible but no later than August 14, 2017. We will not process or review a partial response. Facsimile or e-mail responses will 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:

EASILY CORRECTABLE DEFICIENCY
LABELING
REFERENCE # 16653296

If you do not submit a complete response by August 14, 2017, the review may be closed and the listed deficiencies may be incorporated in a COMPLETE RESPONSE correspondence. For more information, please refer to the guidance for industry, ANDA Submissions – Amendments and Easily Correctable Deficiencies Under GDUFA, available on FDA's website.

If you have questions regarding these deficiencies or would like acknowledgement of receipt of your amendment upon submission, please contact the Labeling Project Manager, Carol Lee, at Carol.Lee@fda.hhs.gov.

Sincerely,

Division of Labeling Review

Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

EASILY CORRECTABLE DEFICIENCY

ANDA 207568

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

APPLICANT: Luitpold Pharmaceuticals, Inc. TEL: 614-289-6268

ATTN: Raenel Gibson EMAIL: rgibson@luitpold.com

FROM: Carol Lee FDA CONTACT EMAIL: Carol.Lee@fda.hhs.gov

Dear Ms. Gibson:

This communication is in reference to your abbreviated new drug application (ANDA) dated June 19, 2014, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Epinephrine Injection, USP 1 mg/mL (b) (4)

The deficiencies presented below represent *EASILY CORRECTABLE DEFICIENCIES* identified during the review and the current review cycle will remain open. You should provide a complete response to these deficiencies within ten (10) U.S. business days.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

EASILY CORRECTABLE DEFICIENCY
LABELING
REFERENCE # 16653296

If you do not submit a complete response within ten (10) U.S. business days, the review will be closed and the listed deficiencies will be incorporated in the next COMPLETE RESPONSE. Please provide your response after that complete response communication is received along with your response to any other issued comments.

If you are unable to submit a complete response within ten (10) U.S. business days, please contact the Labeling Project Manager immediately so a complete response may be issued if appropriate.

Please submit official archival copies of your response to the ANDA, facsimile or e-mail responses will not be accepted. A partial response to this communication will not be processed as an amendment and will not start a review.

We have completed our review and have the following comments:

LABELING:

PRESCRIBING INFORMATION

Revise your insert labeling to be in accordance with the most recently approved insert labeling for the reference listed drug (RLD), ADRENALIN (epinephrine injection), NDA 204200/S-004 approved 09/12/16. Revise the information in the Structured Product Labeling (SPL) accordingly.

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

If you have questions regarding these deficiencies or would like acknowledgement of receipt of your amendment upon submission, please contact the Labeling Project Manager, Carol Lee, at Carol.Lee@fda.hhs.gov.

Sincerely,

Carol Lee, Pharm.D.
Labeling Project Manager
Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research

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

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Sent: 05/25/2017 09:01:27 AM
To: rgibson@luitpold.com
CC: erin.andrews@fda.hhs.gov
BCC:
Subject: INFORMATION REQUEST ANDA 207568

Dear Raenel Gibson:

Please see attached, time sensitive, correspondence in reference to ANDA 207568.

NOTE: Upon receipt of this email please send confirmation to Erin Andrews via email at erin.andrews@fda.hhs.gov

Thank you

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

ANDA 207568

INFORMATION REQUEST

Luitpold Pharmaceuticals, Inc.
Attention: Raenel Gibson
6610 New Albany Road East
New Albany, OH 43054
rgibson@luitpold.com

Dear Sir or Madam:

Please refer to your Abbreviated New Drug Application (ANDA) dated June 19, 2014, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act) for Epinephrine Injection, USP, 1 mg/mL.

We are reviewing the Quality section of your submission and have the following comments and information requests. We request a prompt written response, no later than June 26, 2017 in order to continue our evaluation of your ANDA.

List of the deficiencies:

A. Chemistry Deficiencies:

1. (b) (4)
2.
3.
4.

If you do not submit a complete response by June 26, 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.

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 me at 240-402-8578.

Sincerely,

Erin Andrews, PharmD
LT, U.S. Public Health Service
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Sent: 05/18/2017 01:49:46 PM
To: rgibson@luitpold.com
CC: erin.andrews@fda.hhs.gov
BCC:
Subject: INFORMATION REQUEST ANDA 207568

Dear Raenel Gibson:

Please see attached, time sensitive, correspondence in reference to ANDA 207568.

NOTE: Upon receipt of this email please send confirmation to Erin Andrews via email at erin.andrews@fda.hhs.gov

Thank you.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

ANDA 207568

INFORMATION REQUEST

Luitpold Pharmaceuticals, Inc.
Attention: Raenel Gibson
6610 New Albany Road East
New Albany, OH 43054
rgibson@luitpold.com

Dear Sir or Madam:

Please refer to your Abbreviated New Drug Application (ANDA) dated June 19, 2014, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act) for Epinephrine Injection, USP, 1 mg/mL.

We are reviewing the Quality section of your submission and have the following comments and information requests. We request a prompt written response, no later than May 30, 2017 in order to continue our evaluation of your ANDA.

List of the deficiencies:

A. Microbiology Deficiencies:

1. (b) (4)
2.
3.

4 (b) (4)

If you do not submit a complete response by May 30, 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.

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 me at 240-402-8578.

Sincerely,

Erin Andrews, PharmD
LT, U.S. Public Health Service
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Sent: 02/28/2017 09:07:28 AM
To: rgibson@luitpold.com
CC: erin.andrews@fda.hhs.gov
BCC:
Subject: INFORMATION REQUEST ANDA 207568

Dear Raenel Gibson:

Please see attached, time sensitive, correspondence in reference to ANDA 207568.

NOTE: Upon receipt of this email please send confirmation to Erin Andrews via email at erin.andrews@fda.hhs.gov

Thank you.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

ANDA 207568

INFORMATION REQUEST

Luitpold Pharmaceuticals, Inc.
Attention: Raenel Gibson
6610 New Albany Road East
New Albany, OH 43054
rgibson@luitpold.com

Dear Sir or Madam:

Please refer to your Abbreviated New Drug Application (ANDA) dated June 19, 2014, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act) for Epinephrine Injection, USP, 1 mg/mL.

We are reviewing the Quality section of your submission and have the following comments and information requests. We request a prompt written response, no later than March 30, 2017 in order to continue our evaluation of your ANDA.

List of the deficiencies:

A. Chemistry Deficiencies:

1. (b) (4)

2.

If you do not submit a complete response by March 30, 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.

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 me at 240-402-8578.

Sincerely,

Erin Andrews, PharmD
LT, U.S. Public Health Service
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Sent: 01/05/2017 05:00:42 PM
To: mgrant@luitpold.com
CC:
BCC: edward.mcdonald1@fda.hhs.gov
Subject: MMA verification, ANDA 207568

Good afternoon,

This is in reference to your abbreviated new drug application (ANDA) 207568 for Epinephrine Injection USP, 1 mg/mL. Your amendment dated December 16, 2016 was submitted to the Agency on or after December 5, 2016, the effective date of the final rule on Abbreviated New Drug Applications and 505(b)(2) Applications; Final Rule, 81 FR 69580 (Oct. 6, 2016). This rule revised 21 CFR 314.96(d), which concerns amendments to unapproved ANDAs. In part, the rule now requires an amendment to an unapproved ANDA to contain an appropriate patent certification or section viii statement described in 21 CFR 314.94(a)(12), or a recertification for a previously submitted paragraph IV certification, if approval is sought for changes described in any of the following types of amendments:

(i) To add a new indication or other condition of use;
(ii) To add a new strength;
(iii) To make other than minor changes in product formulation; or
(iv) To change the physical form or crystalline structure of the active ingredient.

If an amendment to an unapproved ANDA does not contain a patent certification or section viii statement, or a recertification, the applicant must verify that the proposed change described in the amendment is not one of the types of amendments described above.

Your amendment is deficient under 21 CFR 314.96(d). It currently does not contain (1) a patent certification or section viii statement, (2) a recertification, or (3) a verification statement. As appropriate, please submit a patent certification or section viii statement, a recertification, or a verification statement (referencing your amendment dated December 16, 2016).

For future reference, to comply with the requirement of 21 CFR 314.96(d), we recommend that a patent certification or section viii statement, or recertification be referenced in the cover letter of an amendment to an unapproved ANDA and included in module 1.3 of such unapproved ANDA. Similarly, we recommend that a verification statement be included in the cover letter of an amendment to an unapproved ANDA. For inquiries related to this requirement please contact the Patent and Exclusivity Team at CDER-OGDPET@fda.hhs.gov.

Complete Response Letter Checklists

Complete Response Letter (**not cGMP**)

Yes	No	If any statement is checked NO, STOP and DO NOT issue letter
☒	☐	All relevant discipline reviews are complete and finalized in DARRTS
☒	☐	DMF first cycle review(s) complete
☒	☐	DMF Deficiency letter(s) issued to DMF holder(s) prior to ANDA CR issuance OR DMF is adequate
☒	☐	Status of the DMF(s) cited in the Product Quality and Microbiology (if applicable) sections is/are current →if needed, update DMF deficiencies to reflect current status per DMF Status and ANDA CR Chart
☒	☐	All amendments have been addressed (reviewed or deferred per IQP 4025.02)
☒	☐	There are no pending consults
☐	☐	Received clearance from REMS Coordinator (if applicable)
☒	☐	ANDA is not on hold for "other" reasons (e.g. safety, tamper resistance, abuse deterrent)
☒	☐	Chemistry (Product Quality) deficiencies have been accurately added to CR letter OR Chemistry is adequate
☒	☐	Bioequivalence deficiencies have been accurately added to the CR letter OR Bioequivalence is adequate
☐	☐	Dissolution deficiencies have been accurately added to the CR letter OR Dissolution is adequate
☒	☐	Microbiology deficiencies have been accurately added to the CR letter OR Microbiology is adequate (if applicable)
☐	☐	Clinical deficiencies have been accurately added to the CR letter OR Clinical is adequate (if applicable)
☒	☐	Labeling deficiencies have been accurately added to the CR letter OR Labeling is adequate
☒	☐	EES is acceptable or withheld (if withheld EES provided approval of selected CR template language) OR RPM received concurrence from Team Leader that ANDA is a priority and CR letter should be issued
☒	☐	OSI is not pending/is not required OR RPM received concurrence from Team Leader that ANDA is a priority and CR letter should be issued

RE: ANDA 207568

OPF Facilities Questions

Follow up. Start by Monday, December 14, 2015. Due by Monday, December 14, 2015.

Sent: Sun 12/13/2015 3:17 PM

To: McDonald, Edward G (CDER); OPF Facilities Questions

Yes, the overall recommendation is still effective.

Thanks,

Rose

From: McDonald, Edward G (CDER)
Sent: Friday, December 11, 2015 1:02 PM
To: OPF Facilities Questions
Subject: ANDA 207568

Hello OPF,

ANDA 207568 (epinephirine inj) is a drug shortage product that is ready for a CR. I would like to confirm the overall manufacturing status is still adequate. Please let me know, thanks.

-Ed

Respectfully,

Edward McDonald, PharmD, BCPS
Regulatory Project Manager
CDER/FDA/OGD
10903 New Hampshire Avenue
White Oak Building 75
Silver Spring, MD 20993

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

ANDA 207568

Luitpold Pharmaceuticals, Inc.
Attention: Felicia Bullock
One Luitpold Drive, PO Box 9001
Shirley, NY 11967

Dear Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is also made to the electronic mail dated July 11, 2014 and telephone communication dated July 22, 2014 and your correspondences dated July 14, 2014 and July 22, 2014.

In accordance with your request for expedited review under MaPP 5240.3, the Office of Generic Drugs has granted expedited review to this ANDA.

NAME OF DRUG: Epinephrine Injection USP, 1mg/mL

DATE OF APPLICATION: June 19, 2014

DATE (RECEIVED) ACCEPTABLE FOR FILING: June 19, 2014

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Heather Strandberg
Regulatory Project Manager
240-402-9096

Sincerely yours,

{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

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

/s/

SHANNON L HILL
07/29/2014
Signing for Wm Peter Rickman

ANDA FILING CHECKLIST

(Pre June 20, 2014)

ANDA:	207568
APPLICANT:	Luitpold Pharmaceuticals, Inc.
RELATED APPLICATION(S):	~RELATEDAPPLICATIONS~
DRUG NAME:	**Epinephrine**
DOSAGE FORM:	Injection, 1 mg/mL
LETTER DATE:	6/19/2014
RECEIVED DATE:	6/19/2014
Type II DMF #:	(b) (4)
Therapeutic Code:	6010100 (Bronchodilator)
Archival Copy:	Gateway

BASIS OF SUBMISSION:

NDA/ANDA:	**NDA 0204200**
FIRM:	**PAR Sterile Products LLC**
RLD:	**Adrenalin**
On Cards:	Yes

APPLICATION PROPERTIES

P-IV	☐ Yes ☐ No
EXPEDITED REVIEW REQUEST	☒ Yes
MaPP 5240.1 or 5240.3 or GDUFA	☐ Approved ☐ Denied
FIRST GENERIC Received	☐ Yes ☒ No
Market Availability	☐ Rx ☐ OTC
PEPFAR	☐ Yes ☒ No
PET	☐ Yes ☐ No
Product Type	☐ Small Molecule Drug
USP Drug Product (at time of filing review)	☒ Yes ☐ No

**Document Room Note: for New Strength amendments and supplements, if specific reviewer(s) have already been assigned for the original, please assign to those reviewer(s) instead of the default random team(s).

Review Team:

RPM:	**Denise McKan** ☒ **Activity**	Div. of Bioequivalence:	**Team 1** ☒ **Activity**
CHEM Team:	**DC1 Team 11** ☒ **FYI**	Dissolution Review:	~DissoTeam~ ☐ **FYI**
CHEM PQRPM:	**Lee, Danbi** ☒ **FYI**	Division of Clinical Review:	☐ **Activity**
CHEM Team Leader:	Bita Mirzai-Azarm ☐ **No Assignment Needed in DARRTS**	DMF Review Team Leader:	Dave Skanchy ☒ **FYI**
Labeling Team:	**Ann Vu** ☒ **Activity**	Micro Review:	**Micro Team 1** ☒ **Activity**
SPECIAL INSTRUCTIONS FOR DOCUMENT ROOM (applicable only for a response to a refuse to receive):			

Regulatory Reviewer: Ogochukwu Umejei Date: 07/08/14	Recommendation: ☒ **FILE** ☐ **REFUSE to RECEIVE**

1. Edit Application Property Type in DARRTS
2. Edit Submission Patent Records
   ☐ Yes
3. Edit Contacts Database with Bioequivalence Recordation where applicable
   ☐ Yes
4. EER (internal notation: RSB to submit at time of filing)
   ☒ Yes
5. GDUFA Obligations Met (Filing Fee, Type II DMF Fee, and Facility Fee)
   ☒ Yes- (internal notation-if not met contact: cder-om-collection@fda.hhs.gov)
6. DMF Complete Assessment
   ☒ Yes

ADDITIONAL COMMENTS REGARDING THE ANDA:

1. It appears the Title in the Patent Certification module is incongruent within the body of the certification. Please amend either the title or citation so that they are congruent. *DONE* 7/23/14

Telephone convo with Felicia Bullock on 7/22/2014 around 10:47am

Paragraph I Certification

In accordance with the Federal Food, Drug and Cosmetic Act, as amended, September 24, 1984, Patent Certification is hereby provided for the drug product, which is the subject of this ANDA.

Luitpold Pharmaceuticals, Inc. hereby certifies that, in our opinion and to the best of our knowledge, no unexpired patents exist for Adrenalin® (Epinephrine Injection, USP), NDA 204200, Applicant holder, Par Sterile Products (formerly JHP Pharmaceuticals LLC). This certification is made in accordance with Section 505(j)(2)(A)(vii)(I) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.94(a)(12)(i)(A)(1).

ANDA 207568

Umejei, Ogochukwu

Sent: Fri 7/11/2014 10:59 AM

To: 'fbullock@luitpold.com'

Dear Felicia Bullock,

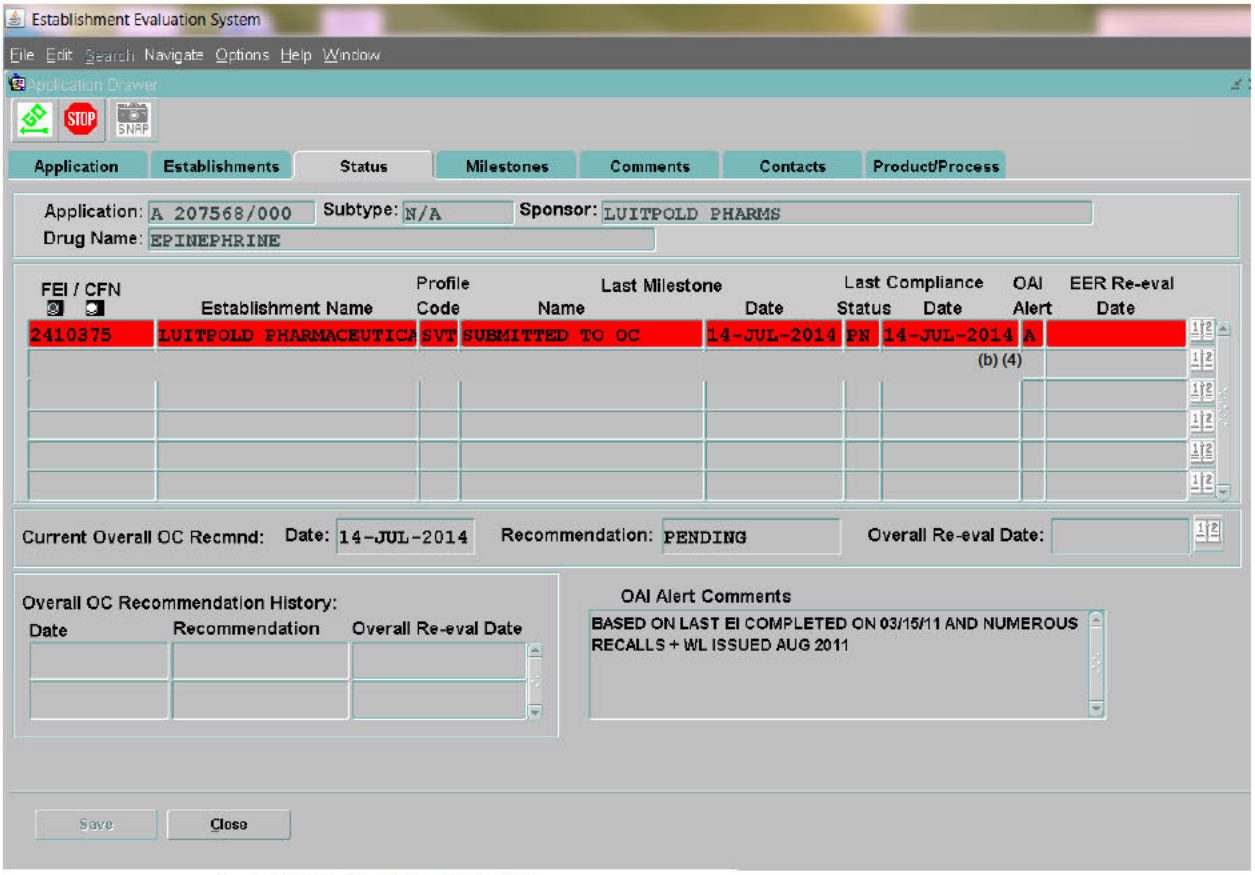
This electronic mail is in reference to your abbreviated new drug application pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for **Epinephrine Injection, USP 1mg/mL.**

SPECIAL INSTRUCTIONS: Please provide a complete response to all of the items identified below within 10 business days from the date of this communication. If the complete response is not received within 10 days, the application will be deemed incomplete and will be refused for filing. Your response should contain a point-by-point reply to each of the identified comment(s) with corresponding hyperlink(s), where applicable, to the body of data within the ANDA. You should notify me via email or telephone when you have submitted your response. Your cover letter should clearly indicate Quality - Response to Information Request.

1. It appears the title in the Patent Certification is incongruent within the body of the certification. Please amend either the title or citation so that they are congruent.

Thank you,

Ogochukwu Umejei, PharmD
Regulatory Support
FDA/CDER/Office of Generic Drugs
Silver Spring, MD 20993
(P) 240-402-8807



User Fee Validation Checklist for ANDA or PAS

Facilities

FEI	Facility Name	Type (API, FDF, Both)	PIN (FY)	UFO Status	Receipt Date
(b) (4)					
2410375	Luitpold Pharmaceuticals, Inc.	FDF (D)	8304226 (13) 8001816 (14)	Met	2/1/13 9/20/13

List the application numbers for backlog applications owned by the applicant:

Backlog

"Not Met" Application(s)
N/A

List known affiliate information and user fee obligation status:

Affiliates

Facility Name	FEI	Type (API, FDF, Both)
N/A	N/A	N/A

VALIDATION RESULTS

Reviewer Name:	Overall Status of User Fee Obligation:
Qianyi Zhang	☒ Met ☐ Not Met ☐ Unknown

Comment:

Signature (Required unless signed electronically): Qianyi Zhang -S — Date:

CORRESPONDENCE

Type: ☐ COR-USERFEE-06 (User Fee Obligation Not Met) ☐ COR-ANDAACK-06 (No User Fee Received) ☐ COR-ANDAACK-03 (User Fees Received)
☐ COR-USERFEE-01 (User Fee General Correspondence) ☐ COR-ANDAACK-05 (No User Fees Received) ☐ COR-ANDAACK-04 (User Fee Received)
☐ FRM-CHECKLIST-10 (User Fees Validation Request) ☒ FRM-CHECKLIST-11 (User Fees Validation Results) ☐ FRM-ADMNL-68 (User Fee Acceptability Memo)

Comment:

Prepared By: Olivia G. Kelly -S — Date:

GDUFA DMF COMPLETENESS ASSESSMENT CHECKLIST

For evaluation of initial COMPLETENESS for review of a Type II Drug Master File which has paid the required GDUFA DMF fee.

(b) (4)

Primary Reviewer: Keduo Qian	Review Recommendation for Initial Completeness Assessment:
Date: 08/15/2013	☒ COMPLETE ☐ INCOMPLETE

1. Has the GDUFA fee been paid? Enter date paid: 08/13/2013 Fee ID: 8000806

☒ Yes ☐ No

2. Is the DMF active?

☒ Yes ☐ No

If no, DMF is INCOMPLETE per policy. Issue Incomplete Letter to DMF holder.

3. Has the DMF been reviewed, after November 30, 2007, for chemistry, manufacturing and controls (CMC) by FDA in the context of a review of a prior application?

☒ Yes ☐ No

If "yes," the DMF is COMPLETE per policy.
If "no," review DMF with checklist.

ADDITIONAL COMMENTS REGARDING THE DMF:

MODULE 1: ADMINISTRATIVE

			COMMENT(S)
1.1	1.1.2	**Signed and Completed Application Form (356h)** (Rx / OTC Status) **Rx** (original signature) **Electronic, Fillable Copy** (if a signed, scanned copy is provided) **Rx** Refer to the links provided for the newly revised form 356h and updated instructions. http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM321897.pdf http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/ucm082348.pdf **PLACE ESTABLISHMENT CONTACT INFORMATION IN SECTION 29: MANUFACTURING STEPS AND/OR TYPE OF TESTING***	
		Form FDA 3794 (PDF) GDUFA **Select**	
1.2	*	**Cover Letter YES** **Is the drug product subject to REMS requirements?** ☐ Yes ☐ No	
	1.2.1	**Form FDA 3674 (PDF)** 42 U.S.C. 282(j)(5)(B) **A** **Electronic, Fillable Copy** (if a signed, scanned copy is provided) **Select**	
*	*	**Table of Contents** (paper submission only) **N/A**	
1.3	1.3.1	**Contact/Sponsor/Applicant Information** **1.3.1.2 U.S. Agent Appointment Letter** 21 CFR §314.50(a)(5) **N/A** If the applicant identifies a U.S. Agent on the 356h, a U.S. Agent Appointment letter should be provided.	
	1.3.2	**Field Copy Certification** 21CFR §314.94(d)(5) **Select** (Original Signature)	
	1.3.3	**Debarment Certification** Generic Drug Enforcement Act (GDEA)/ Other: (no qualifying statement) FD&C Act §306(k), §306(a) and (b) (21 U.S.C. 335a(k), 335(a) and (b)) 1. Debarment Certification (original signature) **YES** 2. List of Convictions statement (original signature) **Select**	
	1.3.4	**Financial Certifications** 21 CFR §54 | 21 CFR §54.2(e) | 21 CFR §314.94(13) Bioavailability/Bioequivalence Financial Certification (Form FDA 3454) **N/A** Disclosure Statement (Form FDA 3455) **Select**	
	1.3.5	**Patent and exclusivity** **1.3.5.1 Patent Information** 21 CFR §314.94(a)(12) | FD&C Act 505(j)(2)(A)(vii) Patents listed for the RLD in the Electronic Orange Book Approved Drug Products with Therapeutic Equivalence Evaluations **1.3.5.2 Patent Certification** 21 CFR §314.94(a)(12)(i)(A)(1) through (4) or §314.94(a)(12)(iii) 1. Patent number(s) **N/A** 2. Paragraph: (Check all certifications that apply) MOU☐ PI☒ PII☐ PIII☐ PIV☐ Statement of Notification (21 CFR §314.95 | 505(j)(2)(B))☐ 3. Expiration of Patent(s): a. Pediatric exclusivity submitted? **Select** b. Expiration of Pediatric Exclusivity? **1.3.5.3 Exclusivity Claim** Exclusivity Statement: State marketing intentions? **Select**	

Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

FDA Home › Drug Databases › Orange Book

Start Over | Back to Search Page

Application Number Search Results from "OB_Rx" table for query on "204200."

Displaying records 1 to 1 of 1

Download data

Appl No	TE Code	RLD	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
N204200		Yes	EPINEPHRINE	INJECTABLE; INTRAMUSCULAR, INTRAOCULAR, SUBCUTANEOUS	1MG/ML	ADRENALIN	PAR STERILE PRODUCTS

Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

FDA Home · Drug Databases · Orange Book

Patent and Exclusivity Search Results from query on Appl No 204200 Product 001 in the OB_Rx list.

Patent Data

There are no unexpired patents for this product in the Orange Book Database.

Exclusivity Data

There is no unexpired exclusivity for this product.

View a list of all patent use codes
View a list of all exclusivity codes

Return to Electronic Orange Book Home Page

1.4	1.4.2	**Statement of right of references** 21 CFR §314.50(g)(1) DMF Written Statement of authorization for reference (copy of LoA received from DMF holders) 1. Type II DMF authorization letter(s) or synthesis for Active Pharmaceutical Ingredient **YES** 2. Type II DMF# (b) (4) 3. Type III DMF authorization letter(s) for container closure **Select** 4. Type III or IV DMF authorization letter(s) for sterile product sterilization process **Select**	
1.12	1.12.4	**Request for Comments and Advice** – Proprietary name requested **Select** If Yes, did the firm provide the request as a separate electronic amendment labeled "Proprietary Name Request" at initial time of filing 1. Yes **Select** 2. No – contact the firm to submit the request as a separate electronic amendment	
	1.12.11	**Basis for Submission** 21 CFR §314.94(a)(3) NDA#: NDA 0204200 Ref Listed Drug: Adrenalin Firm: Par Sterile Products LLC **ANDA suitability petition required?** 21 CFR §10.20 | 21 CFR §10.30 | 21 CFR §314.93 **N/A** If Yes, provide petition number and copy of approved petition (21 CFR §314.94(a)(3)(iii)) **ANDA Citizen's Petition required?** 21 CFR §10.25(a) | 21 CFR §10.30 | 21 CFR §314.122 **N/A** If Yes, provide petition number and copy of petition	
	1.12.12	**Comparison between Generic Drug and RLD** 505(j)(2)(A) | 21 CFR §314.94(a)(4) to (6) 1. Conditions of Use **SAME AS RLD** 2. Active Ingredients **SAME AS RLD** 3. Inactive Ingredients (21 CFR §314.94(a)(9)(ii)) **JUSTIFIED** 4. Route of Administration **SAME AS RLD** 5. Dosage Form **SAME AS RLD** 6. Strength **SAME AS RLD**	
	1.12.14	**Environmental Impact Analysis Statement** 21 CFR §25.15(d) Environmental Assessment (EA) (21 CFR §25.20) **Select** Environmental Impact Statement (EIS) (21 CFR 25.22) **Select** Claim of Categorical Exclusion (21 CFR §25.30 or 21 CFR §25.31) **YES**	
	1.12.15	**Request for Waiver** 21 CFR 320.22 | 320.24(b)(6) Request for Waiver of In-Vivo BA/BE Study(ies) **Select**	
1.14	1.14.1	**Draft Labeling** (Multi Copies N/A for E-Submissions) 21 CFR 314.94(a)(8)(ii) **1.14.1.1 Draft carton and container labels** 4 copies of draft for paper submission only (each strength and container) **Select** **1.14.1.2 Annotated draft labeling text** 21 CFR §314.94(a)(8)(iv) Side by side labeling comparison of container(s) and carton(s) for each strength with all differences visually highlighted and annotated **Select** **1.14.1.3 Draft labeling text** 1 package insert (content of labeling) in PDF and WORD format, and SPL submitted electronically **YES** **1.14.1.4 Labeling Comprehension Studies** Refer to Pharmacy Bulk Package Sterility Assurance Table (for PBP's only) See link below for table:	

		http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM352612.pdf	
	1.14.3	**Listed Drug Labeling** **1.14.3.1 Annotated comparison with listed drug** 21 CFR §314.94(a)(8)(iv) 1 side by side labeling (package and patient insert) comparison with all differences visually highlighted and annotated **YES** **1.14.3.3 Labeling text for reference listed drug** RLD package insert, 1 RLD container label, and if applicable, 1 RLD outer container label **Select**	

MODULE 2: CTD SUMMARIES

		COMMENT(S)
2.3	**Quality Overall Summary (QOS)** **E-Submission: PDF YES** **Word Processed, e.g., MS Word YES** Additional information regarding QbR may be found at the following link: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/ucm120971.htm **Question based Review (QbR) Select** **2.3.S Drug Substance (Active Pharmaceutical Ingredient) Select** 2.3.S.1 General Information 2.3.S.2 Manufacture 2.3.S.3 Characterization 2.3.S.4 Control of Drug Substance 2.3.S.5 Reference Standards or Materials 2.3.S.6 Container Closure System 2.3.S.7 Stability **2.3.P Drug Product Select** 2.3.P.1 Description and Composition of the Drug Product 2.3.P.2 Pharmaceutical Development 2.3.P.2.1 Components of the Drug Product 2.3.P.2.1.1 Drug Substance 2.3.P.2.1.2 Excipients 2.3.P.2.2 Drug Product **Oral Solids**: Immediate Release or Modified Release (Matrix Technology or Compressed Film Coated Components) tablet scoring data per Draft *Guidance for Industry, Tablet Scoring: Nomenclature, Labeling and Data for Evaluation* (if applicable) 2.3.P.2.3 Manufacturing Process Development 2.3.P.2.4 Container Closure System 2.3.P.3 Manufacture 2.3.P.4 Control of Excipients 2.3.P.5 Control of Drug Product 2.3.P.6 Reference Standards or Materials 2.3.P.7 Container Closure System 2.3.P.8 Stability	

		COMMENT(S)
2.7	**Clinical Summary (Bioequivalence)** Model BE Data Summary Tables http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM120957.pdf ** In addition to the standard tables, see the link above for tables specifically designed for in-vitro binding studies ** http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM364105.pdf **E-Submission: PDF Select** **Word Processed: e.g., MS Word Select** **2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods** **2.7.1.1 Background and Overview** Table 1. Submission Summary **Select** Table 4. Bioanalytical Method Validation **Select** Table 6. Formulation Data **Select** Table 10. Study Information **Select** Table 11. Product Information **Select** Table 17. Comparative Physiochemical Data of Ophthalmic Solution Products **Select** **2.7.1.2 Summary of Results of Individual Studies** Table 5. Summary of In Vitro Dissolution**Select** (include complete comparative In Vitro Dissolution Data (individual) with Certificate of Analysis [CoA] for Test and Reference products including: potency, assay, content uniformity, date of manufacture and lot number) Table 9. Reanalysis of Study Samples **Select** Table 12. Dropout Information **Select** Table 13. Protocol Deviation **Select** Table 14. Summary of Standard Curve and QC Data for Bioequivalence Sample Analysis **Select** **2.7.1.3 Comparison and Analyses of Results Across Studies** Table 2. Summary of Bioavailability (BA) Studies **Select** Table 3. Statistical Summary of the Comparative BA Data: 1. Unscaled Average – Table A 2. Reference-scaled Average BE Studies – Tables A **and** B BE Studies **Select** Table 16. Composition of Meal Used in Fed Bioequivalence Study **Select** **2.7.1.4 Appendix** Table 15. SOPs Dealing with Bioanalytical Repeats of Study Samples **Select** **2.7.4 Summary of Clinical Safety** **2.7.4.1.3 Demographic and Other Characteristics of Study Population** Table 7. Demographic Profile of Subjects Completing the Bioequivalence Study **Select** **2.7.4.2.1.1 Common Adverse Events** Table 8. Incidence of Adverse Events in Individual Studies **Select**	No Studies

MODULE 3: QUALITY

3.2.S DRUG SUBSTANCE (Active Pharmaceutical Ingredient)

COMMENT(S)

3.2.S.1

General Information Select
(Do not refer to DMF)
3.2.S.1.1 Nomenclature
3.2.S.1.2 Structure
3.2.S.1.3 General Properties

3.2.S.2

Manufacturer
Drug Substance (Active Pharmaceutical Ingredient)
Must correlate to the establishment information submitted in annex to Form FDA 356h

1. Name and Full Address(es) of the Facility(ies) **Select**
2. Contact name, phone and fax numbers, email address **Select**
3. U.S. Agent's Name (if applicable) **Select**
4. Specify function or responsibility **Select**
5. Type II DMF number for API **Select**
6. CFN, FEI, or DUNS number (if available) **Select**

3.2.S.3

Characterization Select
Provide the following in tabular format as follows:

IUPAC Chemical Name	Code #	Chemical Structure	Process/ Degradation Impurity	Source/ Mechanism

http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM380338.pdf

Control of Drug Substance (Active Pharmaceutical Ingredient)

3.2.S.4

3.2.S.4.1

Specification
Testing specifications and data from drug substance manufacturer(s) **Select**

3.2.S.4.2

Analytical Procedures Select

3.2.S.4.3

Validation of Analytical Procedures
(API that is USP or reference made to DMF, **MUST** provide verification of USP or DMF procedures) **Select**

1. Spectra and chromatograms for **reference standards** and **test samples Select**
2. Samples-Statement of Availability and Identification (21 CFR §314.50(e)(1))
   a. Drug Substance **Select**
   b. API lot numbers

3.2.S.4 Control of Drug Substance [Epinephrine, USP, [redacted](b) (4)

Samples

Samples of the drug substance Epinephrine, USP are available for collection by the Agency at Luitpold Pharmaceuticals, Inc. manufacturing facility, located at One Luitpold Drive, P.O. Box 9001, Shirley, New York 11967.

Sufficient quantities will be provided to the Agency to perform all tests in triplicate. In addition, samples of the reference standard will also be provided.

Drug Substance

The drug substance, Epinephrine, USP is manufactured by [redacted](b) (4) A sufficient sample of the drug substance will be provided to the Agency upon request.

Availability and Lot Number

A sample of Epinephrine, USP, Luitpold receiving number (RR#) 1010087 has been reserved for FDA sampling and is available at the Agency's convenience. This is the same lot that was used to manufacture the exhibit batch 3067, Epinephrine Injection, USP 1 mg/mL.

3.2.S.4.4

Batch Analysis

1. COAs specifications and test results from drug substance manufacturer(s) **YES**
2. Drug Product manufacturer's Certificates of analysis **YES**

3.2.S.4.5

Justification of Specification Select
Provide data in tabular format:

Chemical Name	Code#	MDD	IT	QT	TDI of Impurity	Proposed AC for Unspecified	Proposed AC for Specified	Justification if AC>QT for

								Impurities	Impurities	Specified Impurities

http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM380338.pdf

3.2.S.5	**Reference Standards or Materials** (Do NOT refer to DMF) **Select**
3.2.S.6	**Container Closure Systems Select**
3.2.S.7	**Stability** 1. Retest date or expiration date of API **Select**

	3.2.P DRUG PRODUCT	COMMENT(S)
3.2.P.1	**Description and Composition of the Drug Product** 1. Unit composition with indication of the function of the inactive ingredient(s) **YES** 2. Inactive ingredients and amounts are appropriate per IIG (per/dose justification) (provide justification in a tabular format) **Select** 3. Conversion from % to mg/dose values for inactive ingredients (if applicable) **Select** 4. Elemental iron: provide daily elemental iron calculation or statement of adherence to 21 CFR 73.1200 (calculation of elemental iron intake based on **maximum daily dose (MDD)** of the drug product is preferred if this section is applicable) **Select** 5. Injections: If the reference listed drug is packaged with a drug specific diluent, then the diluent must be Q1/Q2 and must be provided in the package configuration **YES**	Ok per 314.94(a)(9)iii Pg. 133

From RLD NDA 204200

3.2.P.1 Description and Composition

Adrenalin® currently marketed by JHP Pharmaceuticals, LLC (JHP) is the same Adrenalin® initially manufactured and marketed by Parke-Davis around the turn of the Twentieth Century (pre-1938 drug). The drug product has been commercially available for over 100 years, with a formulation similar to the current formulation described below.

JHP at Rochester, MI manufactures the drug product, Adrenalin® (epinephrine injection, USP) 1 mg/mL in 1 mL and 30 mL containers.

a) Description

Name	Adrenalin® (epinephrine injection, USP)
Strength	1 mg/mL (1:1000)
Dosage Form	Injection
Route of Administration	Intramuscular, subcutaneous or intravenous
Description	Clear, colorless to light yellow solution

b) Composition

The composition of Epinephrine Injection, USP is provided in the tables below.

Quantitative Composition for 1 mL vial

Ingredient	Grade	Function	Batch Quantity	Unit Formula
Epinephrine	USP	Active		(b) (4)
Sodium Chloride	USP	(b) (4)		
Sodium Metabisulfite	NF			
(b) (4) Hydrochloric Acid	USP			
Water for Injection	USP			

Proposed Formulation

Table 1: Composition of the Drug Product

Ingredient	Function	% Composition (w/w)	1 mg/mL
Epinephrine, USP (b) (4)	Active		(b) (4)
Sodium Chloride, USP	(b) (4)		
Water for Injection, USP			
Hydrochloric acid, NF			
(b) (4)			

3.2.P.2.3 Drug Product [Epinephrine Injection, USP 1 mg/mL]

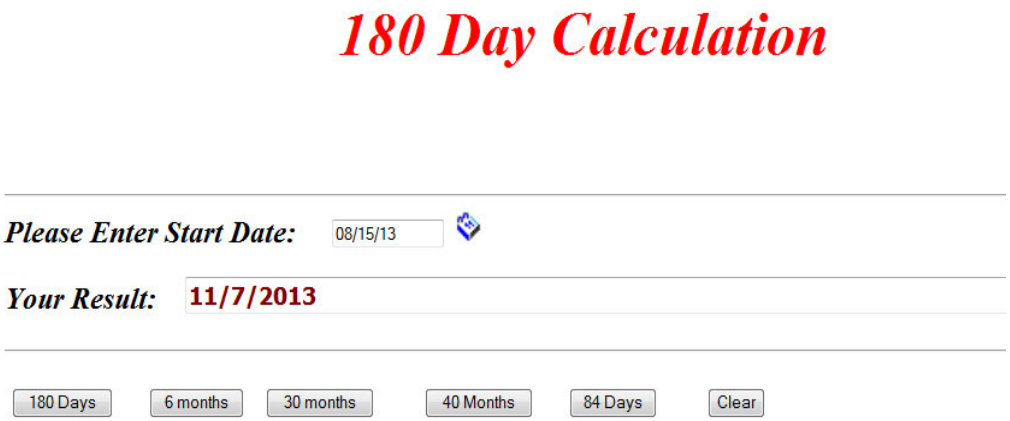
3.2.P.2.3.1 Formulation Development [Epinephrine Injection, USP 1 mg/mL]

(b) (4)

3.2.P.2		**Pharmaceutical Development** 1. Pharmaceutical Development Report **Select** 2. Microbial Attributes a. Container/Closure Integrity Testing Report for Sterile Products b. Antimicrobial Effectiveness Testing for Multi-dose Sterile Products	
Manufacture			
3.2.P.3	3.2.P.3.1	**Drug Product Manufacturer(s)** Must correlate to the establishment information submitted in annex to Form 356h for the finished dosage manufacturer and all outside contract testing laboratories. 1. Name and Full Address(es) of the Facility(ies) **Select** 2. Contact name, phone and fax numbers, email address **Select** 3. U.S. Agent's name (if applicable) **Select** 4. Specify function or responsibility **Select** 5. cGMP Certification from **Applicant Select** 6. CFN, FEI, or DUNS numbers (if available) **Select**	
	3.2.P.3.2	**Batch Formula Select**	
	3.2.P.3.3	**Description of Manufacturing Process and Process Controls** 1. Description of the Manufacturing Process and (for aseptic fill products) Facility **Select** 2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified **Select** 3. Master Packaging Records for intended marketing container(s) **Select** 4. If sterile product **YES** 5. Reprocessing Statement (cite 21 CFR 211.115) from **Applicant YES**	
	3.2.P.3.4	**Controls of Critical Steps and Intermediates**	
	3.2.P.3.5	**Process Validation and/or Evaluation** 1. Terminally Sterilized Product **YES** • Validation of production terminal sterilization process • Validation of depyrogenation of all product containers and closures • Validation of container-closure package integrity **3.2.P.2.4 Manufacturing Process Development [Epinephrine Injection, USP 1 mg/mL]** (b) (4) [redacted] 2. Aseptically Filled Product **N/A** • Validation (bacterial retention studies) of sterilizing grade filter(s) • Validation of the sterilization of sterile bulk drug or product contact equipment, components, containers, and closures • Validation of depyrogenation of product containers and closures • Validation of aseptic filling process/line/room (media fills/process simulations) • Validation of container-closure package integrity	
Controls of Excipients (Inactive Ingredients)			
3.2.P.4	*	Source of Inactive Ingredients Identified **Select**	
	3.2.P.4.1	**Specifications** 1. Testing specifications (including identification and characterization) **YES** 2. Supplier's COA (specifications and test results) **YES**	
	3.2.P.4.2	**Analytical Procedures Select**	
	3.2.P.4.3	**Validation of Analytical Procedures Select**	
	3.2.P.4.4	**Justification of Specifications** (except Applicant COA, other documents as applicable)	

		1. Applicant COA **Select** 2. Residual Solvents Statement(s) from manufacturer(s) **Select** 3. Bovine spongiform encephalopathy (BSE) **Select** 4. Transmissible spongiform encephalopathy (TS) **Select** 5. Melamine Certifications **Select**	
		Controls of Drug Product	
3.2.P.5	3.2.P.5.1	**Specification(s) Select**	
	3.2.P.5.2	**Analytical Procedures Select**	
	3.2.P.5.3	**Validation of Analytical Procedures** (if using USP procedure, must provide verification of USP procedure) **Select** Samples-Statement of Availability and Identification (21 CFR §314.50(e)(1)) 1. Finished Dosage Form **YES** 2. Lot numbers and strength of Drug Products **3.2.P.5.3.2 Samples** Sufficient quantities will be provided to the Agency to perform all tests in triplicate. In addition, samples of the reference standard will also be provided. The official company contact is Ms. Felicia Bullock, Senior Director, Regulatory Affairs, email fbullock@luitpold.com or by telephone number (b) (6) **3.2.P.5.3.3 Availability and Lot Number** A sample of Epinephrine Injection, USP 1 mg/mL Exhibit Batch lot number 3067 in 1 mL ampoule has been reserved for FDA sampling and is available at the Agency's convenience.	
	3.2.P.5.4	**Batch Analysis** Certificates of Analysis for Finished Dosage Form **YES**	
	3.2.P.5.5	**Characterization of Impurities Select** Provide in tabular format as below: IUPAC Chemical Name | Code # | Chemical Structure | Degradation Impurity | Source/ Mechanism http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM380338.pdf	
	3.2.P.5.6	**Justification of Specifications Select**	
3.2.P.7		**Container Closure System** 1. Summary of Container/Closure System (if new resin, provide data) **YES** 2. Components Specification and Test Data **Select** 3. Packaging Configurations and Sizes **Yes** 4. Container/Closure Testing (recommended additional testing for all plastic) a. Solid Orals: water permeation, light transmission **Select** b. Liquids: leachables, extractables, light transmission **Select** 5. Source of supply and suppliers address **Select**	
		Stability	
3.2.P.8	3.2.P.8.1	**Stability Summary and Conclusion (Finished Dosage Form)** 1. Stability Protocol Submitted **Select** 2. Expiration Dating Period for Marketed Packaging 3. Expiration Dating Period for Bulk packaging (if applicable)	
	3.2.P.8.2	**Post-Approval Stability Protocol and Stability Commitment** 1. Post-Approval Protocol and Commitment from **Applicant Select**	
	3.2.P.8.3	**Stability Data** 1. Accelerated stability data a. four (4) time points, 0,1,2,3 **YES** **—OR—** b. Refer to the Final Guidance for Industry *ANDAs: Stability Testing Drug Substances and Products*, dated June 2013 **Select** c. For liquid and semi-solid products, upright and inverted/horizontal storage orientation **Select** 2. Batch numbers on stability records the same as the test batch **YES**	

		3. Date accelerated stability study initiated **Select** 4. Date accelerated stability sample removed from stability chamber for each testing time point **Select**	



3.2.R REGIONAL INFORMATION 21 CFR §314.50(d)(1)(ii)(b)

			COMMENT(S)
REGIONAL INFORMATION (DRUG SUBSTANCE)			
3.2.R.S Drug Substance	3.2.R.1.S	**Executed Batch Records for drug substance (if available) Select**	
	3.2.R.2.S	**Comparability Protocols Select**	
	3.2.R.3.S	**Methods Validation Package (Required for Non-USP drugs) Select** Methods Validation Package (3 copies for paper and N/A for E-Submissions)	

REGIONAL INFORMATION (DRUG PRODUCT)			
3.2.R.P Drug Product	3.2.R.1.P	**1. Executed Batch Records** Copy of Executed Batch Record with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures) Batch Reconciliation and Label Reconciliation **YES** a. Theoretical Yield b. Actual Yield c. Packaged Yield **Table 6 Batch Reconciliation** (b) (4) [redacted] Bulk Package Reconciliation for all bulk packaging considered a commercial container is required if bulk packaging is used to achieve the minimum package requirement. Provide the following information in their respective sections: a. Bulk Package Label (1.14.1) **Select** b. Bulk Package Stability (3.2.P.8) **Select** 1. If bulk is to be shipped, provide accelerated stability data at 0,3,6 months **Select** 2. If bulk is only warehoused for repackaging, provide RT stability data at 0,3,6 months **Select** c. Bulk Package Container and Closure information (3.2.P.7) **Select** **2. Information on Components Select** Name(s) and Address(es) of the Active Pharmaceutical Ingredient (API), inactive ingredient(s), and containers and closures in **tabular format**.	
	3.2.R.2.P	**Comparability Protocols Select**	
	3.2.R.3.P	**Methods Validation Package Select** Methods Validation Package (3 copies for paper and N/A for E-Submissions) (Required for Non-USP drugs)	

MODULE 5: CLINICAL STUDY REPORTS

			COMMENT(S)
5.2		**Tabular Listing of Clinical Studies Select**	
5.3	5.3.1	**Bioavailability/Bioequivalence** 1. **Formulation data same?** a. Comparison of all Strengths (proportionality of multiple strengths) **Select** b. Parenterals, Ophthalmics, Otics and Topicals (21 CFR 314.94 (a)(9)(iii)-(v)) 2. **Lot Numbers and strength of Products used in BE Study(ies)** 3. **Study Type: IN-VIVO PK STUDY(IES)** (Continue with the appropriate study type box below)	
	*	**See Module 2.7 Clinical Summary for placement of BA/BE Summary for tables 9 – 16.** **The study data that support the BA/BE summary tables should be provided in the corresponding sections below:** **5.3.1.2 Comparative BA/BE Study Reports** **5.3.1.3 In Vitro-In Vivo Correlation Study Reports (exception: all dissolution data should be placed in 2.7)** **5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies** **Case Report Forms** should be placed under the study to which they pertain, and appropriate tagged. Refer to The eCTD Backbone File Specification for Study Tagging http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf	
5.4		**Literature References**	
		Possible Study Types:	
Study Type		**IN-VIVO BE STUDY(IES) with PK ENDPOINTS** (i.e., fasting/fed/sprinkle) 1. Study(ies) meets BE criteria (90% CI of 80-125, Cmax , AUC) **Select** *Injection* 2. In-Vitro Dissolution **Select**	
Study Type		**IN-VIVO BE STUDY with CLINICAL ENDPOINTS** Division of Clinical Review Consult Complete ☐ Yes ☐ No	
Study Type		**IN-VITRO BE STUDY(IES)** (i.e., in vitro binding assays) **Select** 1. Study(ies) meets BE criteria (90% CI of 80-125) **Select** 2. In-Vitro Dissolution **Select**	
Study Type		**NASALLY ADMINISTERED DRUG PRODUCTS** Refer to the attached links for Nasal Product BE Tables: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM209446.pdf AND http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM271017.pdf Division of Bioequivalence Consult Complete ☐ Yes ☐ No	
Study Type		**IN-VIVO BE STUDY(IES) with PD ENDPOINTS** (e.g., topical corticosteroid vasoconstrictor studies) Division of Bioequivalence Consult Complete ☐ Yes ☐ No	
Study Type		**TRANSDERMAL DELIVERY SYSTEMS** Division of Clinical Review Consult Complete ☐ Yes ☐ No	

Effective as of June 20, 2014

For More Information on Submission of an ANDA in Electronic Common Technical Document (eCTD) Format please go to:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm
For a Comprehensive Table of Contents Headings and Hierarchy please go to: http://www.fda.gov/cder/regulatory/ersr/5640CTOC-v1.2.pdf
Draft Guidance for Industry ANDA Submissions – Content and Format of Abbreviated New Drug Applications:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM400630.pdf

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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/

OGOCHUKWU UMEJEI
07/29/2014

SHANNON L HILL
07/29/2014
Signing for Iain Margand

OFFICE OF GENERIC DRUGS EXPEDITED REVIEW REQUESTED

ANDA#/SUPPLEMENT#: 207568
DRUG: Epinephrine Injection USP, 1 mg/mL

APPLICANT: Luitpold Pharmaceuticals, Inc
DATE OF SUBMISSION: 6/19/2014

The Office of Generic Drugs may grant expedited review status to either an Original or Supplemental abbreviated new drug application for the following reasons (MaPP 5240.1,MaPP 5240.3 & GDUFA). At least one of the criteria must be met to receive Expedited Review Status:

1. ☐ **PUBLIC HEALTH NEED**. Events that affect the availability of a drug for which there is no alternative

2. ☐ **EXTRAORDINARY HARDSHIP ON THE APPLICANT.**

   a) Catastrophic events such as explosion, fire storms damage.

   b) Events that could not have been reasonably foreseen and for which the applicant could not plan. Examples include:

      - ♦ Abrupt discontinuation of supply of active ingredient, packaging material, or container closure; and
      - ♦ Relocation of a facility or change in an existing facility because of a catastrophic event(see item 2.a)

3. **AGENCY NEED.**
   a) ☐ Matters regarding the government's drug purchase program, upon request from the appropriate FDA office.
   b) ☐ Federal or state legal/regulatory actions, including mandated formation changes or labeling changes if it is in the Agency's best interest.
   c) ☐ Expiration-date extension or packaging change when the drug product is the subject of a government contract award.
   d) ☐ Request for approval of a strength that was previously tentatively approved (To be used in those cases where l80-day generic drug exclusivity prevented full approval of all strengths).
   e) ☒ MaPP 5240.3 conditions.

4. ☐ **GDUFA.** Year one and year two cohort PIV 180-day eligibility (First Generic)

RECOMMENDATIONS:

DISCIPLINE	STATUS	SIGNATURE/DATE
Team Project Manager (PM must Endorse)	Grant☐ Deny☐	
Chemistry Team Leader (sign as needed)	Grant☐ Deny☐	
Micro Team Leader (sign as needed)	Grant☐ Deny☐	
Labeling Team Leader (sign as needed)	Grant☐ Deny☐	
Chem. Div./Deputy Director (DO must Endorse)	Grant☐ Deny☐	
Office Director/Deputy Director (email concurrence) (Original ANDAs)	Grant☒ Deny☐	7/21/2014

RETURN TO PROJECT MANAGER CHEMISTRY TEAM: SELECT TEAM # 11

ENTER FORM INTO DAARTS DATE 07/21/2014

Paste Email Copy Below:

RE: ANDA 207568 Drug Shortage

Chun, Nam

Sent: Mon 7/21/2014 11:20 AM
To: Umejei, Ogochukwu

Good morning Ogochukwu,

Epinephrine Injection is currently listed on the CDER Drug Shortage list and should be expedited.

Thanks,

Nam (Esther) Chun

From: Umejei, Ogochukwu
Sent: Monday, July 21, 2014 11:10 AM
To: Chun, Nam
Subject: FW: ANDA 207568 Drug Shortage

Hello Esther,

I am reviewing ANDA 207568, Epinephrine Injection, 1 mg/ml. Please confirm if this product is currently on the drug shortage list.

Thank you,

Ogochukwu Umejei, PharmD
Regulatory Support
FDA/CDER/Office of Generic Drugs
Silver Spring, MD 20993
(P) 240-402-8807

Silver Spring, MD 20993
(P) 240-402-8807

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

/s/

OGOCHUKWU UMEJEI
07/29/2014

SHANNON L HILL
07/29/2014
Signing for Iain Margand