CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 207568

Name: Epinephrine Injection, 1 mg/mL

Sponsor: American Regent, Inc

Approval Date: June 06, 2018

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA207568Orig1s000

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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

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				

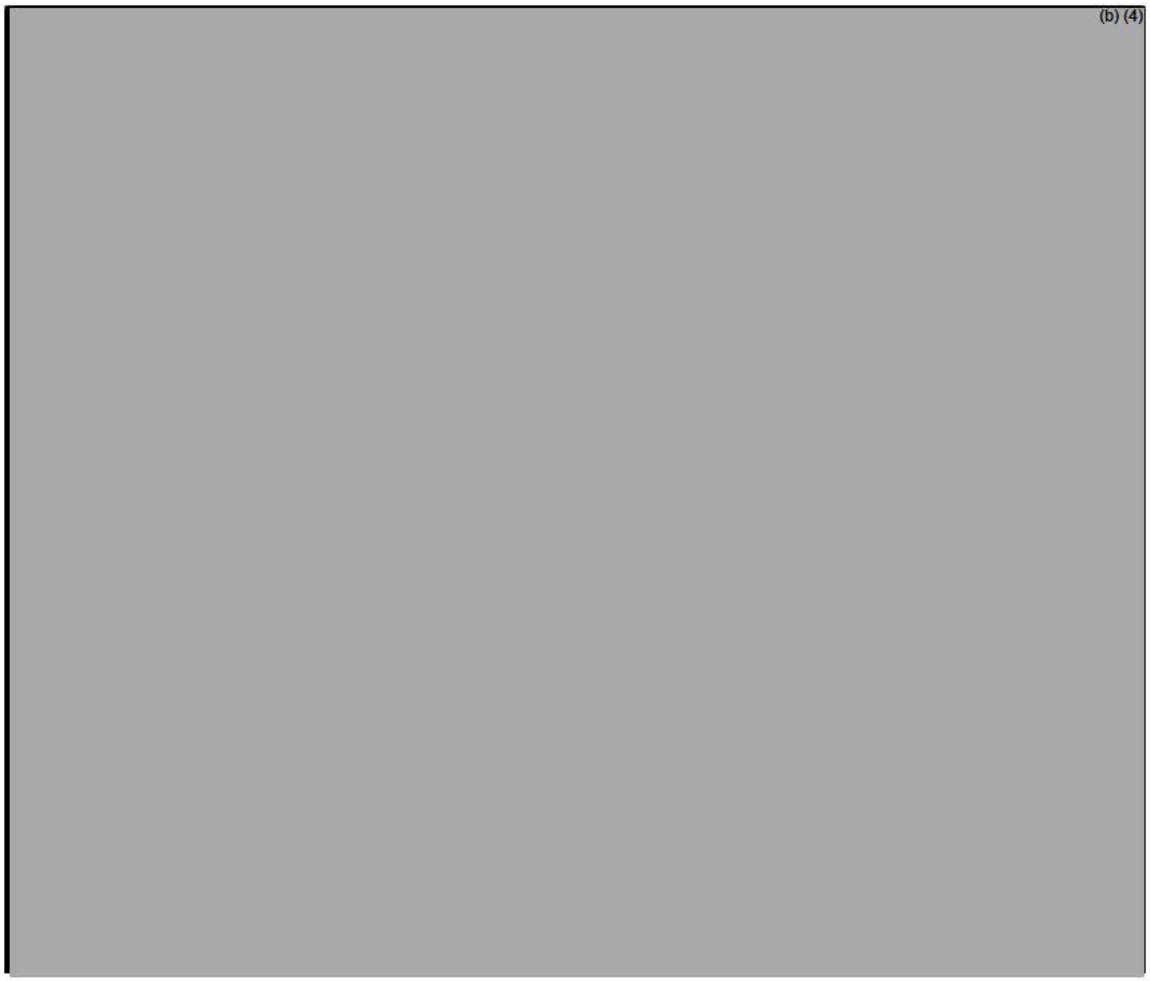
Review of Amendment dated 4/16/2018 (SD 17)

A. Chemistry Deficiencies:

1. **If you haven't already submitted adequate information to comply with the USP <232/233> requirements or ICH Q3D recommendations regarding elemental impurities, please provide adequate information to comply. If you have already provided this information, please reference the specific date you submitted and location for such information. Please acknowledge that a statement of compliance regarding USP <232> or ICH Q3D will be included in all certificates of analysis over the life of the drug product.**

In compliance with ICH Q3D and USP <232/233> elemental impurities, Luitpold commits to screening the first three production batches of Epinephrine Injection, USP for elemental impurities, and commits that a statement of compliance regarding USP <232> (or the current USP monograph for elemental impurities) will be included in all certificates of analysis over the life of the drug product.
A risk assessment summary was provided in Luitpold's response to FDA Information Request on December 07, 2017 in section 3.2.P.2. The certificate of analysis for test results performed by Eurofins Lancaster is provided in section 3.2.P.5.4.

(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*

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

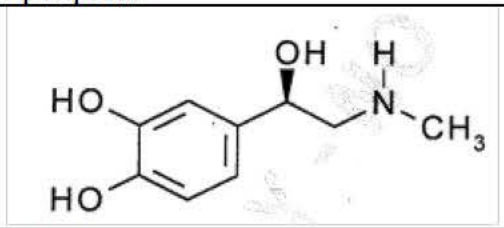
15b. NANOTECHNOLOGY PRODUCT TRACKING:

☐ 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*

Executive Summary Section

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 (1:1000) 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 and/or sodium hydroxide 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 (1:1000) in a 1 mL clear glass ampule.

NDC 0517-1071-25

Store between 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) (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)

Intraocular surgery: Dilute 1 mL with 100 to 1000 mL of an ophthalmic irrigation fluid, for ophthalmic irrigation or intracameral injection (2.2)

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).

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

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