

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

209359Orig1s000

SUMMARY REVIEW

Addendum to the Cross-Discipline Team Leader (CTDL) Review

Date	04-November-2019
From	Mohan Sapru, M.S., Ph.D.
NDA	209359
Type of Application	505(b)(2)
Applicant	Hospira Inc.
Established/Proper Name	Epinephrine Injection
Dosage forms; Strength	Parenteral; 1 mg/10 mL (0.1 mg/mL)
Route of Administration	Intravenous Infusion
Proposed Indication(s)	The proposed product is indicated to increase mean arterial blood pressure in adult patients with hypotension associated with septic shock
Recommendation	Approval

For a detailed CTDL review, please refer to the attached appendix -1 Cross-Discipline Team Leader Review (DARRTS, dated 29-November-2017). This addendum includes recent updates, including the recent labeling revisions.

1. Background

This addendum to CTDL review refers to: a) pending 505(b)(2) new drug application (NDA) 209359 (Epinephrine Injection) originally submitted on January 31, 2017, and resubmitted on September 5, 2019, and b) our tentative approval (TA) letter dated November 29, 2017.

2. Revised Label and Labeling

The applicant submitted revised container label, carton labeling, and prescribing information (PI) received on October 28, 2019 and October 30, 2019 for Epinephrine Injection. After review of the container label, carton labeling, and prescribing information (PI), we note that the applicant has implemented the Agency recommendations. Specifically, the applicant incorporated the following Agency recommendations:

- Added storage instructions for the diluted product in the Dosage and Administration Section of the full PI, as well as revised their usual dose statement to “Recommended dosage: see prescribing information.” on the container label and carton labeling.
- Revised the discard statement on the label and labeling from (b) (4) to “Discard all unused drug.”

3. Manufacturing Facilities

All the manufacturing facilities listed in this NDA continue to be acceptable

4. Financial Disclosure

As stated by the applicant in the original submission, there were no clinical studies conducted for the subject drug product in support of this application. Hence, a financial disclosure is not applicable.

5. Recommended Regulatory Action

All the reviews of this application recommended approval, and I concur with the reviewers. Based on the OPQ's Integrated Quality Review (uploaded to PANORAMA, dated 27-November-2017), an expiry period of 15 months for the proposed product, stored at controlled room temperature (20°C – 25°C; 68°F – 77°F) in the proposed commercial container closure system, is granted.

Appendix-1: Next Page

Cross-Discipline Team Leader Review

Date	29-November-2017
From	Mohan Sapru, M.S., Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA	209359
Type of Application	505(b)(2)
Applicant	Hospira Inc.
Date of Receipt	31-January-2017
PDUFA Goal Date	30-November-2017
Established/Proper Name	Epinephrine Injection, USP
Dosage forms; Strength	Parenteral; 1 mg/10 mL (0.1 mg/mL)
Route of Administration	Intravenous Infusion
Proposed Indication(s)	The proposed product is indicated to increase mean arterial blood pressure in adult patients with hypotension associated with septic shock
Recommendation	Approval

This cross-discipline team leader review is based on the primary reviews, memos and documented review input, as listed below:

Material Reviewed/Consulted	Review Team
Integrated Quality Assessment (PANORAMA, dated 27-November, 2017)	Haripada Sarker, Mariappan Chelliah, Anitha Govada, Cassandra Abellard, Poonam Delvadia, Yeissa Chabrier Rosello, Susannah Gilbert, and Mohan Sapru; OPQ
Delivery Device (Abboject™ Syringe) Inter-Center Consult Review (DARRTS, dated 21-November, 2017)	Susannah Gilbert, Jamie Kamon-Brancazio, Center for Devices and Radiological Health (CDRH)
Non-Clinical Review (DARRTS, dated 25-April, 2017)	Rama Dwivedi, and Thomas Papoian; Pharmacology and Toxicology
Statistical Review (DARRTS, dated 27-April, 2017)	Fanhui Kong; Biometrics Division
Biometrics Consult Review (DARRTS, dated 25-September, 2017)	Meiyu Shen; Biometrics Division
Division of Pediatric and Maternal Health (DPMH) Labeling Review (DARRTS, dated 08-November, 2017)	Christos Mastroyannis, Tamara Johnson; DPMH
DMEPA Labeling Review (DARRTS, dated 06-November, 2017)	Sarah Thomas, Chi-Ming (Alice) Tu; Division of Medication Error Prevention and Analysis (DMEPA)
OPDP Labeling Consult Review (DARRTS, dated 03-November, 2017)	Puja Shah, James Dvorsky; Office of Prescription Drug Promotion (OPDP)

1. Introduction

The applicant, Hospira Inc., has sought U.S. marketing approval for Epinephrine Injection USP, 1mg/10 mL (0.1 mg/mL) in accordance with Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. For

the approval of this NDA, the applicant relies on FDA's previous finding of safety and efficacy for the reference listed drug (RLD) i.e., Epinephrine Injection USP, 1 mg/mL (1:1000 ampule) from Belcher Pharms LLC (NDA 205029).

2. Background

The proposed product is indicated to increase mean arterial blood pressure in adult patients with hypotension associated with septic shock. However, the RLD, in addition to the above indication proposed under the current submission, is also indicated for emergency treatment of allergic reactions (Type 1), including anaphylaxis, and for induction and maintenance of mydriasis during intraocular surgery. The applicant's proposed product is essentially similar to the RLD, as it has the same active moiety and delivers the same amount of drug to the patient. The proposed product and the RLD have comparable physicochemical properties such as pH and osmolality. However, Hospira's proposed product contains excipients which are not present in the RLD. The differences in inactive ingredients between the Hospira's proposed product and the RLD have been adequately justified by the applicant and are not expected to impact disposition, safety, or efficacy of the proposed drug product.

3. Quality/Chemistry, Manufacturing and Controls (CMC)

Drug Substance (Epinephrine, USP): Epinephrine, a non-selective alpha and beta adrenergic agonist, has one chiral center. The active moiety is l-epinephrine while its enantiomer, d-epinephrine, is inactive. (b) (4). The DMF for the drug substance has been reviewed by CMC reviewers and found adequate. The critical quality attributes of the drug substance such as description, assay, identification, optical rotation, loss on drying, residue on ignition, levels of norepinephrine, adrenalone, residual solvents, organic impurities, epinephrine, sulfonic acid, and (b) (4) are tested on release. The limit for epinephrine sulfonic acid at (b) (4) % has been qualified based on toxicological qualification involving the 2-week intravenous toxicity study followed by a 2-week recovery period in Sprague-Dawley rats. The drug substance specification, and validations of analytical methods are adequate.

Drug Product: Epinephrine Injection, USP is a sterile aqueous solution, which is to be diluted with 5% dextrose or 5% dextrose and sodium chloride solution prior to administration. The drug product is a clear solution presented in a 10 mL clear, (b) (4) glass vial and is copackaged with Hospira's Abboject™ syringe. This is (b) (4) filled product containing no antimicrobial preservatives. All the excipients are compendial and are not of human or animal origin. Formulation differences between Hospira's proposed product and the RLD are as follows:

- (b) (4)
- Hospira's product has a slightly lower concentration of sodium chloride USP (8.16 mg/mL versus 9 mg/mL), and contains 0.46 mg/mL sodium metabisulfite (b) (4) which is absent from the RLD; and
- Hospira's product contains a buffer composed of citric acid USP (2.13 mg/mL) and sodium citrate dihydrate USP (0.41 mg/mL), which is absent from Belcher's product.

The above-specified excipient differences are necessary to optimize the impurity profile of the product. Hospira has justified the maximum daily intake (MDI) of sodium metabisulfite by identifying 3 products, Plenaminate™ 15% Amino Acids Injection, Dopamine HCl Injection USP, and Dobutamine Hydrochloride in 5% Dextrose Injection, which have significantly higher levels of sodium metabisulfite compared to MDI of sodium metabisulfite for Hospira's product. Hospira is currently marketing Epinephrine Injection USP Abboject™ Syringe as an unapproved ("grandfathered") product. (b) (4)

Acceptance limits for pH testing on release is 2.3 – 3.5. The drug product specification includes testing all the identified critical quality attributes. All the analytical methods have been adequately validated. Regarding elemental impurities, the applicant conducted risk assessment per ICH Q3D Guidance. The data show that product batches contain < (b) (4) % of the permitted daily exposure for class 1, 2A, 2B, and 3 elements, and hence the lack of testing for the elemental impurities in the drug product specification is justified. The batch analysis data for three batches of the drug product, manufactured (b) (4), are adequate.

Product Manufacturing: The manufacturing process involves: (b) (4)
(b) (4) The proposed control strategy that includes environmental controls, and in-process controls and specifications are adequate to ensure product quality on a consistent basis.

Biopharmaceutics: This NDA submission included a request for biowaiver of *in vivo* bioavailability/bioequivalence (BA/BE) study for the proposed product under the provision of 21 CFR 320.22(b)(1)(I) and (ii). However, it was noted during filing that the proposed product does not fully satisfy the criteria for granting a waiver under 21 CFR 320.22(b)(1). Specifically, the proposed product does not fulfill the requirement of same inactive ingredients as the RLD. The applicant updated the waiver request with inclusion of reference of 21 CFR 320.24(b)(6) in addition to 21 CFR 320.22(b)(1)(I) and (ii). Therefore, the biowaiver request has been evaluated under the provisions of 21 CFR 320.24(b)(6). The proposed product and the RLD have comparable physicochemical properties. The differences in inactive ingredients are adequately justified by the applicant and are not expected to impact disposition, safety, or efficacy of the proposed drug product. The request for biowaiver by the applicant for the proposed product is granted.

Abboject Vial Syringe System: Given that Epinephrine Abboject Syringe System is a combination product, CDRH reviewed the device component i.e., Abboject™ Syringe. The Epinephrine Abboject Syringe System, which has been marketed for years in conjunction with both approved and unapproved drug products is a legacy product that was not developed under design controls. DMF 24131 for Abboject Syringe Systems has been submitted retroactively to comply with Agency's cGMP draft guidance Current Good Manufacturing Practice Requirements for Combination Products. The retrospective design and development activities for the Abboject products have been performed per QSD.11, Device Design Control Policy. Regarding the applicable 21 CFR 820 regulations and manufacturing of the finished combination product, the applicant in addition to referring to DMF 24131, provided adequate details to demonstrate that the Rocky Mount facility complies with CFR 820.20 and CFR 4. In addition, the design validation for the Abboject Syringe System has been demonstrated based on the historical safe and effective use of the combination product.

Microbiological Aspects: The validation results for the sterility testing, and container closure integrity testing are adequate. The validation studies conducted under worst-case scenario conditions for Abboject stoppers and sub-minimal conditions support the commercial (b) (4) process. The validation details provided for the environmental monitoring program are acceptable. The batch records confirm that validated sterilization and (b) (4) manufacturing processes has been used for the manufacture of the

exhibit batches. Furthermore, the drug product release specification includes sterility (USP <71>), and bacterial endotoxins (USP <85>) testing

Assessment of Manufacturing Facilities: The office of Process and Facilities has recommended overall approval for all the currently listed manufacturing facilities concerning this NDA.

Container Closure System and Product Stability: The Epinephrine Injection USP Abboject™ Syringe will be packaged in a 10 mL, (b) (4) clear glass vial closed with a 10 mL (b) (4) rubber stopper. The product is administered using the Abboject vial injector. The secondary packaging consists of a carton containing Epinephrine Injection USP Abboject™ Syringe vial and an Abboject vial injector. The proposed container meets the requirements for (b) (4) glass, as detailed in USP (b) (4) >. The proposed closures comply with USP <381> physicochemical and biological testing requirements. In addition, it has been demonstrated that the container closure system remains integral and, therefore, can maintain the sterility of the product. Using the proposed container closure system, the product stability data support a shelf-life of 15 months at controlled room temperature, including the sterility assurance of the drug product for the duration of shelf-life.

4. Non-Clinical Pharmacology/Toxicology

The Pharmacology and Toxicology review evaluated the safety concerning the use of sodium metabisulfite, (b) (4), in the proposed formulation. In 1982, sodium and potassium metabisulfite were classified “generally recognized as safe” (GRAS) by the FDA. However, by October 1986, FDA had received reports of adverse reactions following ingestion of sulfites as preservatives. Reevaluation of the GRAS status concluded that there was no evidence that sulfite agents are a hazard “for the majority of the population.” However, “for the fraction of the public that is sulfite sensitive,” evidence was available to suspect that these agents were a “hazard of unpredictable severity to such individuals when they are exposed to sulfite agents in some foods at levels that are now current and in the manner now practiced.” Based on evaluation of published results, and the use of sodium metabisulfite in approved products, the Pharmacology and Toxicology review concluded that the level of sodium metabisulfite in Hospira’s proposed epinephrine drug product is lower than the previously approved DOPA hydrochloride (NDA 18132) and is reasonably safe for human use from toxicology perspective.

5. Clinical Pharmacology

N/A

6. Statistical-Evaluation:

Based on statistical analyses and evaluation of the 12-month long term stability data from 3 batches of the drug product (b) (4), the product is expected to remain within specifications through 15 months with appropriate control of pH per product specification.

7. Safety

N/A

8. Advisory Committee Meeting

N/A

9. Pediatrics

N/A

10. Other Relevant Regulatory Issues

N/A

11. Labeling

All labeling recommendations made by the division have been accepted by the applicant, and are reflected in the most recent version of the product labeling. Epinephrine is light sensitive, and instructions for storage include:

- Protect from light until ready to use.
- Do not refrigerate. Protect from freezing.
- Protect from alkalis and oxidizing agents.

The product labeling has been updated to comply with the PLLR. Based on DPMH's labeling review (DARRTS, dated 08-November, 2017), the limited published data on epinephrine use are not sufficient to inform of any drug-associated risk of adverse pregnancy- and lactation-related outcomes. Specifically, there is limited human and animal information regarding epinephrine's effects on fertility in females and males of reproductive potential. Hypotension associated with septic shock is a medical emergency in pregnancy which can be fatal if left untreated. However, delaying treatment in pregnant women with hypotension associated with septic shock may increase the risk of maternal and fetal morbidity and mortality. Life-sustaining therapy for the pregnant woman should not be withheld due to potential concerns regarding the effects of epinephrine on the fetus. Therefore, contraception and pregnancy testing during treatment with epinephrine are not indicated. Based on OPQ's Integrated Quality Assessment (PANORAMA, dated 27-November, 2017), and DMEPA's labeling review (DARRTS, dated 06-November, 2017), the revised container label and carton labeling for Epinephrine Injection, USP are acceptable.

12. Recommendations/Risk Benefit Assessment

• Recommended Regulatory Action

All the reviews of this application recommended approval, and I concur with the reviewers. Based on the OPQ's Integrated Quality Review (uploaded to PANORAMA, dated 27-November, 2017) including statistical analyses of stability date, an expiry period of 15 months for the proposed product stored at controlled room temperature (20°C – 25°C; 68°F – 77°F). in the proposed commercial container closure system is granted.

• Risk Benefit Assessment

The current NDA is a 505(b)(2) application and relies on FDA's previous finding of safety and efficacy for the reference listed drug (RLD) i.e., Epinephrine Injection USP, 1 mg/mL (NDA 205029). The applicant's proposed product is essentially similar to the RLD, as it has the same active moiety and delivers the same amount of drug to the patient. Hence, the risk-benefit ratio with the proposed product is expected to be similar to that for currently marketed RLD.

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/s/

MOHAN K SAPRU
11/05/2019 11:26:03 AM

NORMAN L STOCKBRIDGE
11/05/2019 11:39:06 AM

I concur with the attached CDTL review.

Cross-Discipline Team Leader Review

Date	29-November-2017
From	Mohan Sapru, M.S., Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA	209359
Type of Application	505(b)(2)
Applicant	Hospira Inc.
Date of Receipt	31-January-2017
PDUFA Goal Date	30-November-2017
Established/Proper Name	Epinephrine Injection, USP
Dosage forms; Strength	Parenteral; 1 mg/10 mL (0.1 mg/mL)
Route of Administration	Intravenous Infusion
Proposed Indication(s)	The proposed product is indicated to increase mean arterial blood pressure in adult patients with hypotension associated with septic shock
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- Hospira's product uses epinephrine USP (base); Belcher's product contains epinephrine hydrochloride;
- Hospira's product has a slightly lower concentration of sodium chloride USP (8.16 mg/mL versus 9 mg/mL), and contains 0.46 mg/mL sodium metabisulfite (b) (4), which is absent from the RLD; and
- Hospira's product contains a buffer composed of citric acid USP (2.13 mg/mL) and sodium citrate dihydrate USP (0.41 mg/mL), which is absent from Belcher's product.

(b) (4)
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5. Clinical Pharmacology

N/A

6. Statistical-Evaluation:

Based on statistical analyses and evaluation of the 12-month long term stability data from 3 batches of the drug product (b) (4), the product is expected to remain within specifications through 15 months with appropriate control of pH per product specification.

7. Safety

N/A

8. Advisory Committee Meeting

N/A

9. Pediatrics

N/A

10. Other Relevant Regulatory Issues

N/A

11. Labeling

All labeling recommendations made by the division have been accepted by the applicant, and are reflected in the most recent version of the product labeling. Epinephrine is light sensitive, and instructions for storage include:

- Protect from light until ready to use.
- Do not refrigerate. Protect from freezing.
- Protect from alkalis and oxidizing agents.

The product labeling has been updated to comply with the PLLR. Based on DPMH's labeling review (DARRTS, dated 08-November, 2017), the limited published data on epinephrine use are not sufficient to inform of any drug-associated risk of adverse pregnancy- and lactation-related outcomes. Specifically, there is limited human and animal information regarding epinephrine's effects on fertility in females and males of reproductive potential. Hypotension associated with septic shock is a medical emergency in pregnancy which can be fatal if left untreated. However, delaying treatment in pregnant women with hypotension associated with septic shock may increase the risk of maternal and fetal morbidity and mortality. Life-sustaining therapy for the pregnant woman should not be withheld due to potential concerns regarding the effects of epinephrine on the fetus. Therefore, contraception and pregnancy testing during treatment with epinephrine are not indicated. Based on OPQ's Integrated Quality Assessment (PANORAMA, dated 27-November, 2017), and DMEPA's labeling review (DARRTS, dated 06-November, 2017), the revised container label and carton labeling for Epinephrine Injection, USP are acceptable.

12. Recommendations/Risk Benefit Assessment

• Recommended Regulatory Action

All the reviews of this application recommended approval, and I concur with the reviewers. Based on the OPQ's Integrated Quality Review (uploaded to PANORAMA, dated 27-November, 2017) including statistical analyses of stability date, an expiry period of 15 months for the proposed product stored at controlled room temperature (20°C – 25°C; 68°F – 77°F). in the proposed commercial container closure system is granted.

• Risk Benefit Assessment

The current NDA is a 505(b)(2) application and relies on FDA's previous finding of safety and efficacy for the reference listed drug (RLD) i.e., Epinephrine Injection USP, 1 mg/mL (NDA 205029). The applicant's proposed product is essentially similar to the RLD, as it has the same active moiety and delivers the same amount of drug to the patient. Hence, the risk-benefit ratio with the proposed product is expected to be similar to that for currently marketed RLD.

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/s/

MOHAN K SAPRU
11/29/2017

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/s/

NORMAN L STOCKBRIDGE
11/29/2017