

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

209359Orig1s000

OTHER REVIEW(S)

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: October 31, 2019
Requesting Office or Division: Division of Cardiovascular and Renal Products (DCRP)
Application Type and Number: NDA 209359
Product Name and Strength: Epinephrine Injection, USP, 1 mg/10 mL (0.1 mg/mL)
Applicant/Sponsor Name: Hospira Inc. (Hospira)
OSE RCM #: 2019-1893-1
DMEPA Safety Evaluator: Sarah Thomas, PharmD
DMEPA Team Leader: Chi-Ming (Alice) Tu, PharmD, BCPS

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label, carton labeling, and prescribing information (PI) received on October 28, 2019 and October 30, 2019 for Epinephrine Injection, USP. The Division of Cardiovascular and Renal Products (DCRP) requested that we review the revised container label, carton labeling, and prescribing information for Epinephrine Injection, USP (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

After review of the container label, carton labeling, and prescribing information, we note that the Applicant implemented and addressed all of our recommendations. Specifically, we note the Applicant provided 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.

In regards to the expiration date format comment, Hospira responded that

^a Thomas S. Label and Labeling Review for Epinephrine Injection, USP (NDA 209359). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 OCT 1. RCM No.: 2019-1893.

Human-readable expiration dates printed on the carton labeling and container label include a non-zero day, month and year in a DDMMYYYY format for all Hospira products. For example, for a product with an expiry of Nov 1, 2019, the expiration date would appear on the carton and container as "1NOV2019". Hospira currently does not include hyphens or spaces in the expiration date. The Agency's recommendation of using a hyphen to separate expiry date will be taken under advisement, [REDACTED] (b) (4)

We find Hospira's response acceptable.

In regards to the recommendation related to the Drug Supply Chain Security Act, Hospira responded that

Hospira acknowledges awareness of the September 2018, FDA draft guidance on product identifiers required under the Drug Supply Chain Security Act. Epinephrine Injection, USP, 1 mg/10 mL is introduced in a transaction into commerce as a bundle of 10 single-dose Abboject glass syringes following assembly. As required, a 2-D data matrix barcode, containing the NDC, is affixed on the bundled package of 10 Abboject syringes (as the homogenous case) to meet the machine-readable portion requirements. In addition, the carton labeling and container label, as provided herein, meet the linear barcoding and human-readable format requirements. Hence, both machine- and human-readable formats for product identifiers will be affixed to the bundle (as the homogenous case) and imprinted on the carton labeling and container label for the proposed product, respectively.

We find Hospira's response acceptable.

Last, we note the discard statement on the label and labeling was revised from [REDACTED] (b) (4) to "Discard all unused drug." We find this revision acceptable.

We have no additional recommendations at this time.

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/s/

SARAH E THOMAS
10/31/2019 03:22:14 PM

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10/31/2019 03:45:45 PM

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

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Date of This Review:	October 1, 2019
Requesting Office or Division:	Division of Cardiovascular and Renal Products (DCRP)
Application Type and Number:	NDA 209359
Product Name and Strength:	Epinephrine Injection, USP, 1 mg/10 mL (0.1 mg/mL)
Product Type:	Combination Product (Drug-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Hospira Inc. (Hospira)
FDA Received Date:	September 5, 2019
OSE RCM #:	2019-1893
DMEPA Safety Evaluator:	Sarah Thomas, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD, BCPS

1 REASON FOR REVIEW

As part of the Class 1 Resubmission New Drug Application (NDA) review, this review evaluates the proposed container label, carton labeling, and prescribing information (PI) for Epinephrine Injection, USP 1 mg/10 mL (0.1 mg/mL) Abboject syringe for areas of vulnerability that could lead to medication errors.

2 REGULATORY HISTORY

Hospira marketed the Epinephrine Injection, USP Abboject syringe, 1 mg/10 mL, as an unapproved product beginning in 1985. On January 31, 2017, Hospira submitted a 505(b)(2) NDA for Epinephrine Injection, USP Abboject syringe, 1 mg/10 mL (0.1 mg/mL), which received tentative approval on November 29, 2017 subject to a period of patent protection for the listed drug (Epinephrine Injection by Belcher Pharmaceuticals, NDA 205029).

Hospira submitted a Class 1 Resubmission to request full approval for NDA 209359 on September 5, 2019.

3 MATERIALS REVIEWED

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

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C-N/A
ISMP Newsletters*	D-N/A
FDA Adverse Event Reporting System (FAERS)*	E-N/A
Other	F-N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

4 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

After review of the proposed container label and carton labeling, we note that only minor edits have been made by Hospira since our last review (e.g., formatting changes, updated package type term and usual dose statement, as well as updated instructions on the side panel of the carton labeling for when to discard the syringe). In addition, minor edits were made to the Prescribing Information (PI) Section 16 when compared to the labeling provided in the

November 29, 2017 tentative approval letter (e.g., the NDC table was updated to align with Pfizer's presentation of the How Supplied section). We find the edits acceptable from a medication safety perspective.

However, our review of the container label, carton labeling, and prescribing information (PI) for Epinephrine Injection, USP 1 mg/10 mL (0.1 mg/mL) Abboject syringe identified additional areas where the label and labeling may be further improved to promote the safe use of the product. Thus, we provide related recommendations below in Section 5.

5 CONCLUSION & RECOMMENDATIONS

We conclude that the proposed label and labeling for Epinephrine injection may be improved to promote the safe use of the product as described in Section 5.1 and Section 5.2.

5.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information (PI)

1. Dosage and Administration Section

- a. If available, we recommend providing storage instructions for the diluted product.

5.2 RECOMMENDATIONS FOR HOSPIRA INC. (HOSPIRA)

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

A. General Comments (Container label & Carton Labeling)

1. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use for the expiration date. We recommend that the human-readable expiration date on the drug package label include a year, month, and non-zero day. We recommend that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. We recommend that a hyphen or a space be used to separate the portions of the expiration date.^a
2. Revise the statement, (b) (4)." to the following: "Recommended dosage: see prescribing information."

^a Guidance for Industry: Product Identifiers Under the Drug Supply Chain Security Act Questions and Answers. 2018. Available from <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM621044.pdf>

3. In September 2018, FDA released draft guidance on product identifiers required under the Drug Supply Chain Security Act. The Act requires manufacturers and repackagers, respectively, to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce beginning November 27, 2017, and November 27, 2018, respectively. We recommend that you review the draft guidance to determine if the product identifier requirements apply to your product's labeling. The draft guidance is available from: <https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf>.

B. Carton Labeling

1. We note the use of the package type statement (b) (4) " on the side panel, which does not match the package type statement "Single-Dose Syringe" presented on the principal display panel (PDP) and on the container label. We recommend revising the package type statement on the side panel to read "Single-Dose Syringe" to ensure consistency in presentation across the label and labeling.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Epinephrine received on September 5, 2019 from Hospira Inc. (Hospira).

Table 2. Relevant Product Information for Epinephrine	
Initial (Tentative) Approval Date	November 29, 2017
Active Ingredient	Epinephrine
Indication	Non-selective alpha- and beta-adrenergic agonist indicated to increase mean arterial blood pressure in adult patients with hypotension associated with septic shock
Route of Administration	Intravenous
Dosage Form	Injection
Strength	1 mg/ 10 mL (0.1 mg/mL)
Dose and Frequency	Intravenous infusion rate of 0.05 mcg/kg/min to 2 mcg/kg/min, titrated to achieve desired mean arterial pressure. The dosage may be adjusted periodically, such as every 10 - 15 minutes, in increments of 0.05 mcg/kg/min to 0.2 mcg/kg/min, to achieve the desired blood pressure goal. After hemodynamic stabilization, wean incrementally over time, such as by decreasing doses of epinephrine every 30 minutes over a 12- to 24-hour period.
How Supplied	Epinephrine Injection, USP, 1 mg/10 mL (0.1 mg/mL) is a clear and colorless solution available in single-dose glass vials. Each vial is co-packaged with an injector, which together make an ABBOJECT® Syringe. It is supplied in bundles of 10 Single-dose ABBOJECT Glass Syringes.
Storage	Epinephrine is light sensitive. Protect from light until ready to use. Do not refrigerate. Protect from freezing. Store at room temperature, between 20° to 25°C (68° to 77°F). (See USP Controlled Room Temperature.) Protect from alkalis and oxidizing agents.
Container Closure	The primary container closure system for Epinephrine Injection USP Abboject™ Syringe System consists of a glass vial and a (b) (4) stopper.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On September 18, 2019, we performed a gap search for previous DMEPA reviews relevant to this current review since the May 22 and 23, 2017 searches performed for review #2017-348, using the terms, "epinephrine", NDA # "209359", and "205029" (listed drug NDA). Our search identified 6 additional previous reviews^{b,c,d,e,f,g}, and we confirmed that our previous recommendations were implemented or considered.

^b Thomas, S. Label and Labeling Review for Epinephrine (NDA 209359). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 SEP 22. RCM No.: 2017-348.

^c Thomas, S. Label and Labeling Review for Epinephrine (NDA 209359). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 NOV 6. RCM No.: 2017-348-1.

^d Thomas, S. Label and Labeling Review for Adrenalin (NDA 204200/S-009 and 204640/S-009). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 AUG 30. RCM No.: 2018-831.

^e [REDACTED] (b) (4)

^f Thomas, S. Label and Labeling Review for Adrenalin (NDA 204200/S-009 and 204640/S-009). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 OCT 24. RCM No.: 2018-831-1.

^g [REDACTED] (b) (4)

APPENDIX G. LABELS AND LABELING

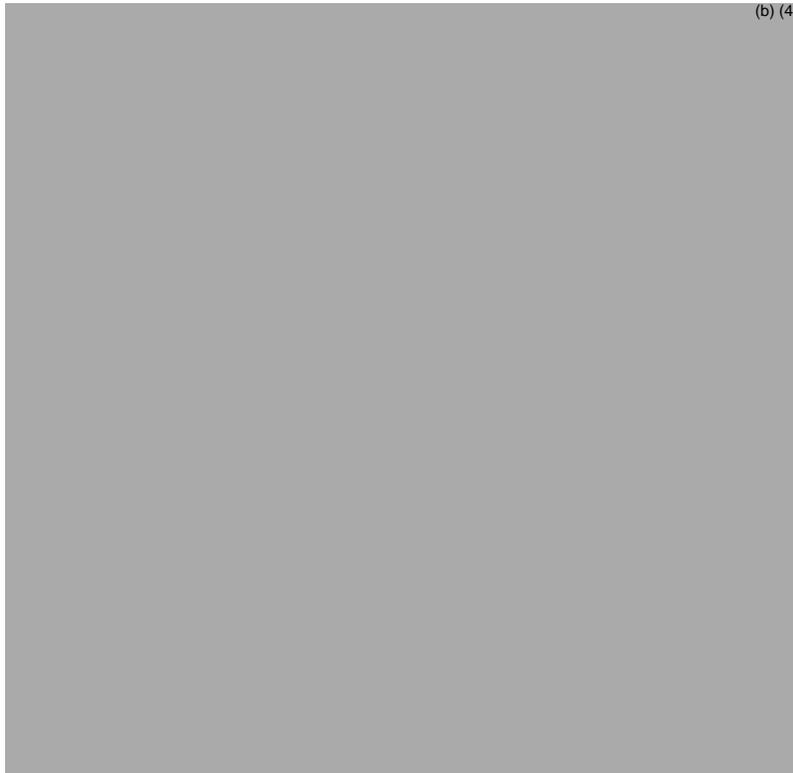
G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^h along with postmarket medication error data, we reviewed the following Epinephrine label and labeling submitted by Hospira Inc. (Hospira).

- Container label received on September 5, 2019
- Carton labeling received on September 5, 2019
- Prescribing Information (Image not shown) received on September 5, 2019

G.2 Label and Labeling Images

Container Label



^h Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

SARAH E THOMAS
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DEPARTMENT OF HEALTH & HUMAN SERVICES

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PLLR Labeling Review

Date: November 7, 2017 **Date consulted:** April 14, 2017

From: Christos Mastroyannis, M.D., Medical Officer,
Maternal Health,
Division of Pediatric and Maternal Health (DPMH)

Through: Tamara Johnson, MD, MS, Team Leader, Maternal Health,
Division of Pediatric and Maternal Health

Lynne P. Yao, MD, OND, Division Director
Division of Pediatric and Maternal Health

To: Division of Cardiovascular and Renal Products (DCRP)

Drug: Epinephrine Injection USP

Class: Agents for hypotension and shock

NDA: 209359

Applicant: Hospira Inc, a Pfizer Co (Hospira)

RLD: NDA: 205029 by Belcher Pharmaceuticals, approve July 29, 2014

Subject: Pregnancy and Lactation Labeling Rule (PLLR) Conversion

Indication(s) To increase mean arterial blood pressure in adult patients with hypotension associated with septic shock.

Materials Reviewed:

- January 31, 2017, Hospira's submission for Epinephrine Injection USP NDA 209359
- April 14, 2017, DCRP's consult request to DPMH-MHT for Epinephrine Injection USP labeling review, DARRTS Reference ID: 4084610
- July 27, 2017, Applicant's Summary of Literature Search on the Use of Epinephrine During Pregnancy, Lactation, and on the Drug's Potential Effects on Fertility, the response to Division's Information Request (IR), for a summary of available published literature and pharmacovigilance database to support the PLLR format of the Epinephrine Injection USP labeling of April 13, 2017

Consult Question: Assist with Pregnancy and Lactation Labeling Rule

INTRODUCTION

On January 31, 2017, the applicant, Hospira, submitted a New Drug Application (NDA 209359) for Epinephrine Injection USP, indicated to increase mean arterial blood pressure in hypotension associated with septic shock.

The Division of Cardiovascular and Renal Products (DCRP) consulted the Division of Pediatric and Maternal Health (DPMH) on April 14, 2017, to provide input for appropriate labeling of the pregnancy and lactation sections of Epinephrine Injection USP labeling to comply with the Pregnancy and Lactation Labeling Rule (PLLR) format.

This review provides recommended revisions and structuring of existing information related to the Pregnancy, Lactation, and Females and Males of Reproductive Potential sections in labeling in order to provide clinically relevant information for prescribing decisions and to comply with current PLLR regulatory requirements.

BACKGROUND

Regulatory History

On January 31, 2017, the applicant Hospira Inc, a Pfizer Company submitted a New Drug Application (NDA 209359) for Epinephrine Injection USP, 1 mg/10 mL (0.1 mg/mL), Single-Use, Abboject™ Syringe in accordance with Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. The referenced listed drug (RLD) for this submission is Belcher Pharmaceuticals' NDA 205029 for Epinephrine Injection USP, 1 mg/mL, approved on July 29, 2014. Both drug products have the same active moiety and deliver the same amount of drug to the patient as both products have essentially the same concentration of Epinephrine when diluted in 1000 mL of a dextrose containing solution. Furthermore, both have same route of administration, indication and method of use for this indication. Differences include,

-  (b) (4)
- Hospira's product has a slightly lower concentration of Sodium Chloride USP (8.16 mg/mL versus 9 mg/mL);
- Differences in excipients

Hospira proposes to reference the pre-clinical and clinical information included in the approved

NDA along with literature references and national and international guidelines in support of its application.

Epinephrine Drug Characteristics^{1,2}

- Epinephrine Injection is a parenteral adrenergic (sympathomimetic) agent and cardiac stimulant.
- Epinephrine belongs to the group of endogenous compounds known as catecholamines.
- Epinephrine Injection is a non-selective alpha and beta adrenergic agonist. It acts:
 - 1) directly on myocardial stimulation and increases the strength of ventricular contraction (positive inotropic action),
 - 2) increases heart rate (positive chronotropic action), and
 - 3) causes peripheral vasoconstriction.
- Epinephrine Injection has a molecular weight of 183.2 Daltons and a half-life of <5 min.

Current RLD Labeling

The current labeling for RLD Epinephrine Injection is in Physician Labeling Rule format, but has not yet complied with PLLR. It states³:

HIGHLIGHTS OF PRESCRIBING INFORMATION

USE IN SPECIFIC POPULATIONS -----

Pregnancy: Epinephrine may lead to fetal anoxia, spontaneous abortion or both.
(8.1)

FULL PRESCRIBING INFORMATION: CONTENTS

USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Labor and Delivery

8.3 Nursing Mothers

FULL PRESCRIBING INFORMATION

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 crosses the placenta. Epinephrine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus (fetal anoxia, spontaneous

¹ Epinephrine labeling BELCHER PHARMS LLC updated May 18, 2016, 11. Description and 12.2. Pharmacodynamics

² Applicant's proposed labeling. 11. Description and 12.2. Pharmacodynamics

³ Epinephrine labeling BELCHER PHARMS LLC updated May 18, 2016

abortion, or both). Epinephrine is teratogenic in rabbits, mice, and hamsters dosed during organogenesis.

Epinephrine has been shown to have teratogenic effects (including gastroschisis and embryonic lethality) when administered subcutaneous in rabbits at approximately 15 times the maximum recommended intramuscular or subcutaneous dose (on a mg/m² 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/m² 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/m² 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/m² basis at a maternal subcutaneous dose of 0.5 mg/kg/day for 4 days).

8.2 Labor and Delivery

Epinephrine usually inhibits spontaneous or oxytocin induced contractions of the pregnant human uterus and may delay the second stage of labor. Avoid epinephrine during the second stage of labor. In dosage, sufficient to reduce uterine contractions, the drug may cause a prolonged period of uterine atony with hemorrhage. Avoid epinephrine in obstetrics when maternal blood pressure exceeds 130/80 mmHg.

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.

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 the Indications and Usage.

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.

REVIEW

PREGNANCY

Animal Data

Hospira is relying on Belcher NDA 205029 for nonclinical information supporting the proposed product. Therefore, no new nonclinical studies have been performed. No new information is provided by the applicant or is in the published literature.

Review of Literature

Applicant's Review

The applicant provided a review of the literature. A literature search of LactMed, OVID MEDLINE and OVID MEDLINE(R), In-Process, BIOSIS Previews, Embase Daily Alerts, and Embase from 1946 through May 5, 2017 was conducted. Search parameters included: “epinephrine and pregnancy”, or “pregnancy outcome”, Or “pregnancy complications”, or “pregnant”, or “abortion”, or “induced abortion”, or “spontaneous abortion”, or “miscarriage”, or “embryo implantation”, or “fetal resorption”, or “embryo loss”, or “nidation”, or “birth”, or “parturition”, or “fetus”, or “embryo”, or “in utero”, or “childbirth”, or “fetal”, or “preterm”, or “birth”, or “premature birth”, or “labor and delivery”, or “developmental toxicity”, or “visceral variation”, or “skeletal variation”, or “epidemiology”, or “causality”, or “incidence of malformations”, or “birth”, or “congenital abnormalities”, or “congenital defects or deformities”, or “fetal anomalies”, or “teratogenicity”, or “prenatal exposure”, or “delayed effects”, or “structural abnormalities”, or “functional impairment”, or “growth impairment”, or “neonate”, or “neonatal”, or “newborn”, or “newly born”, or “prenatal/perinatal exposure”, or “prenatal drug exposure”, or “maternal exposure”, or “paternal exposure”, or “fetus mortality”, or “embryo mortality”, or “pharmacokinetics during pregnancy” and or “fetal exposure to drug”. Fifteen publications were presented. Of these publications, this reviewer found that only 13 were relevant, six of thirteen are further described below. However, the information from seven of these publications did not contribute any additional findings or safety concerns. These seven included case reports^{4,5} and small, non-randomized, single armed studies^{6,7} and literature reviews,⁸ also the applicant identified two additional older publications regarding anaphylaxis in pregnancy and epinephrine use for anaphylactic shock during labor^{9,10}

DPMH Review

In addition to the search of published literature performed by the applicant, DPMH also conducted a literature search in PubMed, Embase and the TERIS and ReproTox databases¹¹ for epinephrine and use in pregnancy. Two additional publications were identified showing that catecholamines, such as epinephrine, can cross the placenta. Sandler *et al.*¹² demonstrated transfer

⁴ Entman SS, Moise KJ. Anaphylaxis in pregnancy. *South Med J* 1984;77(3):402

⁵ Tsuzuki Y, Narita M, Nawa M. Management of maternal anaphylaxis in pregnancy: a case report. *Acute Med Surg* 2017;4(2):202-4.

⁶ Zuspan FP, Nelson GH, Ahlquist RP, et al. Epinephrine infusions in normal and toxemic pregnancy. *Am J Obst Gynecol* 1964;90(1):88-98

⁷ Beard RW. Response of human foetal heart and maternal circulation to adrenaline and noradrenaline. *Br Med J* 1962;1(5276):443-6.

⁸ Chaudhuri K, Gonzales J, Jesurun CA, et al. Anaphylactic shock in pregnancy: A case study and review of the literature. *Int J Obstet Anesth* 2008;17(4):350-7.

⁹ Gallagher JS. Anaphylaxis in pregnancy. *Obstet Gynecol* 1988;71(3 Pt 2):491-93

¹⁰ Gei AF, Pacheco LD, Vanhook JW, et al. The use of continuous infusion of epinephrine for anaphylactic shock during labor. *Am Coll Obstet Gynecol* 2003;102(6):1132-5.

¹¹ TERIS and ReproTox databases, Truven Health Analytics, Micromedex Solutions, 2016.

¹² Sandier M, Ruthven CRF, Contractor SF, Wood C, Booth R J, and Pinkerton JHM: Transmission of noradrenaline across the human placenta, *Nature*, 1963, 197:598.

of labeled norepinephrine (NE) from mother to fetus in rats. Morgan *et al.*¹³ using in vitro perfused human placenta, also demonstrated maternal to fetal catecholamine (CAT) transfer.

GG Briggs and RK Freeman¹⁴ in *Drugs in Pregnancy and Lactation* report that human teratogenicity has not been suspected. Both Briggs and the Reprotox database refer to the Collaborative Perinatal Project where 508 mother-child pairs were exposed to epinephrine any time during pregnancy.¹⁵ One hundred eighty-nine mother-child pairs had 1st trimester exposure to epinephrine. An association was identified between 1st trimester exposure to epinephrine and major and minor malformations and with inguinal hernia after any time use. Findings were confounded by the potentially serious maternal status for which epinephrine was administered. Briggs also reports a surveillance study of Michigan Medicaid recipients involving 229,101 completed pregnancies from 1985 till 1992. Thirty-five newborns were identified who were exposed to epinephrine of unspecified route and dose during the first trimester. No major birth defects were observed (1.5 expected).

Schatz *et al.*¹⁶ report on 259 pregnant asthmatic patients who used inhaled beta sympathomimetics including mostly metaproterenol, and (less commonly used isoetharine, epinephrine and albuterol). One hundred eighty used these agents during the 1st trimester. The authors reported no increase in congenital anomalies or adverse perinatal outcomes. The applicant does not report any published studies on the epinephrine use during pregnancy and adverse developmental outcomes. Different case reports in the literature refer to that epinephrine may pose a risk to the placental-fetal circulation during pregnancy. Epinephrine may cause uterine vasoconstriction, with resultant hypoxic damage to the fetus.^{17,18} Epinephrine administration may potentially potentiate the vasoconstrictive effects of preeclampsia to the uterine vessels and thus has led to the recommendation in the epinephrine labeling to avoid epinephrine in obstetrics when maternal blood pressure exceeds 130/80 mmHg. This event constitutes a theoretical risk. Placental transfer of epinephrine to the fetus may influence the fetal glucose levels by causing fetal hepatic glycogenolysis. The administration of epinephrine during active labor may cause decreased uterine activity, decrease in uterine tone, and increase inequality in the length of the interval between uterine contractions.^{19,20,21}

¹³ Morgan CD, Sandler M, Panigel M: Placental transfer of catecholamines in vitro and in vivo, *Am J Obstet Gynecol*, 1972. 112:1068.

¹⁴ Briggs GG and Freeman RK, *Drugs in Pregnancy and Lactation*, Wolters Kluwer, Philadelphia, PA. 2015

¹⁵ Heinonen OP, Slone D, Shapiro S. *Birth Defects and Drugs in Pregnancy*. Littleton, Publishing Sciences Group, 1977, pp 345-56, 439, 477, 492

¹⁶ Schatz M, Zeiger RS, Harden KM, Hoffman CP, Forsythe AB, Chilingar LM, Preece RP, Benenson AS, Sperling WL, Saunders BS, Kagnoff MC: The safety of inhaled (beta)-agonist bronchodilators during pregnancy. *J Allergy Clin Immunol* 1988;82:686-95

¹⁷ Chaudhuri K, Gonzales J, Jesurun CA, et al. Anaphylactic shock in pregnancy: A case study and review of the literature. *Int J Obstet Anesth* 2008;17(4):350-7.

¹⁸ Zuspan FP, Whaley WH, Nelson GH, et al. Placental transfer of epinephrine. I. Maternal-fetal metabolic alterations of glucose and nonesterified fatty acids. *Am J Obstet Gynecol* 1966;95(2):284-9.

¹⁹ Kaiser IH. The effect of epinephrine and norepinephrine on the contractions of the human uterus in labor. *Surg Gynecol Obstet* 1950;90(6):649-54.

²⁰ Garrett WJ. The effects of adrenaline and noradrenaline on the intact non-pregnant human uterus: With a note on the effects of these hormones in early pregnancy. *J Obstet Gynaecol* 1955;876-83.

²¹ Pose SV, Cibils LA, Zuspan FP. Effect of 1-epinephrine infusion on uterine contractility and cardiovascular system. *Am J Obst Gynecol* 1962;84(3):297-306

Reviewer comment

Placental transfer of epinephrine to the fetus may influence the fetal glucose levels by causing fetal hepatic glycogenolysis: reduces glucose uptake by tissues, and inhibits insulin release in the pancreas, resulting in hyperglycemia and increased blood lactic acid. The clinical importance of it would be only during prolonged administration. This reviewer, based on the lack of reports in the published literature and the short drug half-life, considers that it is not clear, if one or two maternal doses could cause glycogenolysis that may have any impact to the fetus

Summary

Nonclinical data demonstrate that epinephrine at high doses and with prolonged exposure during organogenesis is teratogenic in rabbits, mice, and hamsters. Based on the mechanism of action, epinephrine may cause acceleration of fetal heart rate, uterine vasoconstriction, and fetal anoxia. Review of the limited published literature on human use during pregnancy did not show a clear association between epinephrine use during the 1st trimester and adverse developmental outcomes. Therefore, the information is not sufficient to determine a drug-associated risk for major birth defects or miscarriage. There are risks to the mother and fetus associated with hypotension associated with septic shock. Treatment should not be delayed for a life-threatening condition due to potential risks from epinephrine use.

LACTATION

Animal Data

No information exists with use of epinephrine and its presence in animal milk. Animal data indicate that intraarterial epinephrine can decrease serum oxytocin and inhibit milk production.^{22,23}

Review of Literature

The applicant provided a literature search of LactMed, OVID MEDLINE and OVID MEDLINE(R), In-Process, BIOSIS Previews, Embase Daily Alerts, and Embase from 1946 through May 5, 2017. Search parameters included: epinephrine and breast-feeding, breast secretion, lactation, milk, exposure through breast milk, drug excretion in milk, alteration in lactation and milk supply. No publications were identified by either the applicant or by this reviewer upon search of the literature for information on lactation or breastfeeding in patients treated with epinephrine. There are no reports in *Medication's and Mother's Milk* by Thomas Hale, LactMed, or *Drugs in Pregnancy* by GG Briggs and RK Freeman. Lactation studies have not been conducted to assess the presence of epinephrine in human milk, the effects on the breastfed infant, or the effects on milk production. Because of short half-life and poor oral bioavailability (swallowed epinephrine is metabolized fast by catechol-o-methyltransferase in the wall of the gastrointestinal tract and by monoamine oxidase in the gastrointestinal tract wall and in the liver)^{24,25}, theoretically, a breastfed infant would experience very low exposure to epinephrine.

²² Gorewit RC, Aromando MC. Mechanisms involved in the adrenalin-induced blockade of milk ejection in dairy cattle. *Proc Soc Exp Biol Med.* 1985;180:340-7

²³ Song SL, Crowley WR, Grosvenor CE. Evidence for involvement of an adrenal catecholamine in the beta-adrenergic inhibition of oxytocin release in lactating rats. *Brain Res.* 1988;457:303-9.

²⁴ Simons KJ¹, Simons FE. Epinephrine and its use in anaphylaxis: current issues. *Curr Opin Allergy Clin Immunol.* 2010 Aug;10(4):354-61

²⁵ Breuer C, Wachall B, Gerbeth K, Abdel-Tawab M, Fuhr U. Pharmacokinetics and pharmacodynamics of moist inhalation epinephrine using a mobile inhaler. *Eur J Clin Pharmacol* (2013) 69:1303–1310

Summary

It is not known if epinephrine is present in the breast milk. There is no data to inform of any effects on milk production or effects on the breastfed infant. Epinephrine characteristics (low molecular weight, short half-life, and poor oral bioavailability) make it likely that the breastfed infant would experience a very low exposure to epinephrine. However, physicochemical characteristics alone are not sufficient to determine the transfer of a drug into breastmilk.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Animal data

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.

Review of Literature

The applicant provided a literature search of LactMed, OVID MEDLINE and OVID MEDLINE(R), In-Process, BIOSIS Previews, Embase Daily Alerts, and Embase from 1946 through May 5, 2017. Search parameters included: epinephrine and fertility, reproduction, reproduction process, fecundity, fecundability, placentation, sperm, testis, ovary, infertility, anovulation, primary ovarian insufficiency, subfertility, sterility, luteal insufficiency.

Levin *et al.*²⁶ conducted a small single-armed study to evaluate the effect of epinephrine on testosterone production in 10 healthy male volunteers. The authors found an epinephrine infusion significantly diminished the production rate of testosterone. Garrett WJ²⁷ administered adrenaline to 12 subjects during endometrial non-secretory phase of non-pregnant uterus. In these 12 uteruses, the smaller doses of epinephrine had little or no effect on uterine activity, but stimulation of spontaneous activity was seen with larger doses.

Reviewer comment

The clinical significance of the decreased testosterone on male fertility in the Levin publication is unknown. The authors did not evaluate the impact of the decreased testosterone to the fertility potential of these normal men. In the clinical setting of “hypotension associated with septic shock”, the indication of this drug, the study finding is not clinically important.

Summary

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

²⁶ Levin J, Lloyd CW, Lobotsky J, et al. The effect of epinephrine on testosterone production. Acta Endocrinol 1967;55:184-92.

²⁷ Garrett WJ. The effects of adrenaline and noradrenaline on the intact non-pregnant human uterus: With a note on the effects of these hormones in early pregnancy. J Obstet Gynecol 1955;876-83.

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. Subsection 8.3 will be omitted from labeling because there is nothing to be reported.

CONCLUSIONS

Epinephrine labeling has been updated to comply with the PLLR. The limited published data on epinephrine use are not sufficient to inform of any drug-associated risk of adverse pregnancy- and lactation-related outcomes.

The Pregnancy and Lactation subsections of Epinephrine Injection USP labeling were structured to be consistent with the PLLR as follows:

- **Pregnancy, Subsection 8.1**
The “Pregnancy” subsection of Epinephrine Injection USP labeling was formatted in the PLLR format to include: “Risk Summary”, “Clinical Considerations” and “Data” headings.
- **Lactation, Subsection 8.2**
The “Lactation” subsection of Epinephrine Injection USP labeling was formatted in the PLLR format to include the “Risk Summary” heading.
- **Females and Males of Reproductive Potential, Subsection 8.3**
Females and Males of Reproductive Potential subsection is omitted because there is nothing to be reported. There is no data to be found on Epinephrine Injection USP and its effects on fertility. Contraception and pregnancy testing are not recommended.

RECOMMENDATIONS

The below include DPMH recommendations on subsections 8.1 and 8.2 of Epinephrine Injection USP labeling for compliance with the PLLR. DPMH refers to the final NDA action for final labeling.

PRESCRIBING INFORMATION

HIGHLIGHTS OF PRESCRIBING INFORMATION

USE IN SPECIFIC POPULATIONS

- Pregnancy: May cause fetal harm (8.1)

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Limited published data on epinephrine use in pregnant women are not sufficient to determine a drug-associated risk for major birth defects or miscarriage. However, there are risks to the mother and fetus associated with epinephrine use during labor or delivery, and risks due to untreated hypotension associated with septic shock (*see Clinical Considerations*). In animal reproduction studies, epinephrine demonstrated adverse developmental effects (including delayed skeletal ossification, gastroschisis and embryonic lethality) when administered to pregnant rabbits, mice, and hamsters during organogenesis at doses approximately 15 times, 3 times and 2 times the maximum recommended daily intramuscular or subcutaneous dose, respectively (*see Data*).

All pregnancies have a background risk of birth defects, loss, or other adverse outcomes. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

Hypotension associated with septic shock is a medical emergency in pregnancy which can be fatal if left untreated. 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.

Labor or Delivery

Epinephrine usually inhibits spontaneous or oxytocin induced contractions of the pregnant human uterus and may delay the second stage of labor. Avoid epinephrine during the second stage of labor. In dosage sufficient to reduce uterine contractions, the drug may cause a prolonged period of uterine atony with hemorrhage. Avoid epinephrine in obstetrics when maternal blood pressure exceeds 130/80 mmHg.

Although epinephrine may improve maternal hypotension associated with septic shock, it may result in uterine vasoconstriction, decreased uterine blood flow, and fetal anoxia.

Data

Animal Data

In a study in pregnant rabbits administered 1.2 mg/kg/day epinephrine (approximately 15 times the maximum recommended intramuscular or subcutaneous dose on a mg/m² basis) subcutaneously during organogenesis (on days 3 to 5, 6 to 7 or 7 to 9 of gestation), epinephrine caused teratogenic effects (including gastroschisis). Animals treated on days 6 to 7 had decreased number of implantations.

In a teratology study, pregnant mice were subcutaneously administered epinephrine (0.1 to 10 mg/kg/day) on Gestation Days 6 to 15. Teratogenic effects, embryonic lethality, and delays in skeletal ossification were observed at approximately 3 times the maximum recommended intramuscular or subcutaneous dose (on a mg/m² 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/m² basis at a subcutaneous maternal dose of 0.5 mg/kg/day for 10 days).

Subcutaneous administration of epinephrine to pregnant hamsters at a dose of 0.5 mg/kg/day (approximately 2 times the maximum recommended intramuscular or subcutaneous dose on a mg/m² basis) on Gestation Days 7 to 10 resulted in delayed skeletal ossification and a reduction in litter size.

8.2 Lactation

Risk Summary

There is no information regarding the presence of epinephrine in human milk, or the effects of epinephrine on the breastfed infant or on milk production. However, due to its poor oral bioavailability and short half-life, epinephrine exposure is expected to be very low in the breastfed infant. The lack of clinical data during lactation precludes a clear determination of the risk of epinephrine to a breastfed infant. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for epinephrine and any potential adverse effects on the breastfed child from epinephrine or from the underlying maternal condition.

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/s/

CHRISTOS MASTROYANNIS
11/08/2017

TAMARA N JOHNSON
11/08/2017

LYNNE P YAO
11/08/2017

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

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

Date of This Memorandum: November 6, 2017
Requesting Office or Division: Division of Cardiovascular and Renal Products (DCRP)
Application Type and Number: NDA 209359
Product Name and Strength: Epinephrine Injection, USP, 1 mg/10 mL (0.1 mg/mL)
Applicant/Sponsor Name: Hospira Inc. (Hospira)
Submission Date: October 31, 2017
OSE RCM #: 2017-348-1
DMEPA Safety Evaluator: Sarah Thomas, PharmD
DMEPA Team Leader: Chi-Ming (Alice) Tu, PharmD, BCPS

1 PURPOSE OF MEMO

The Division of Cardiovascular and Renal Products (DCRP) requested that we review the revised container label and carton labeling for Epinephrine Injection, USP (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

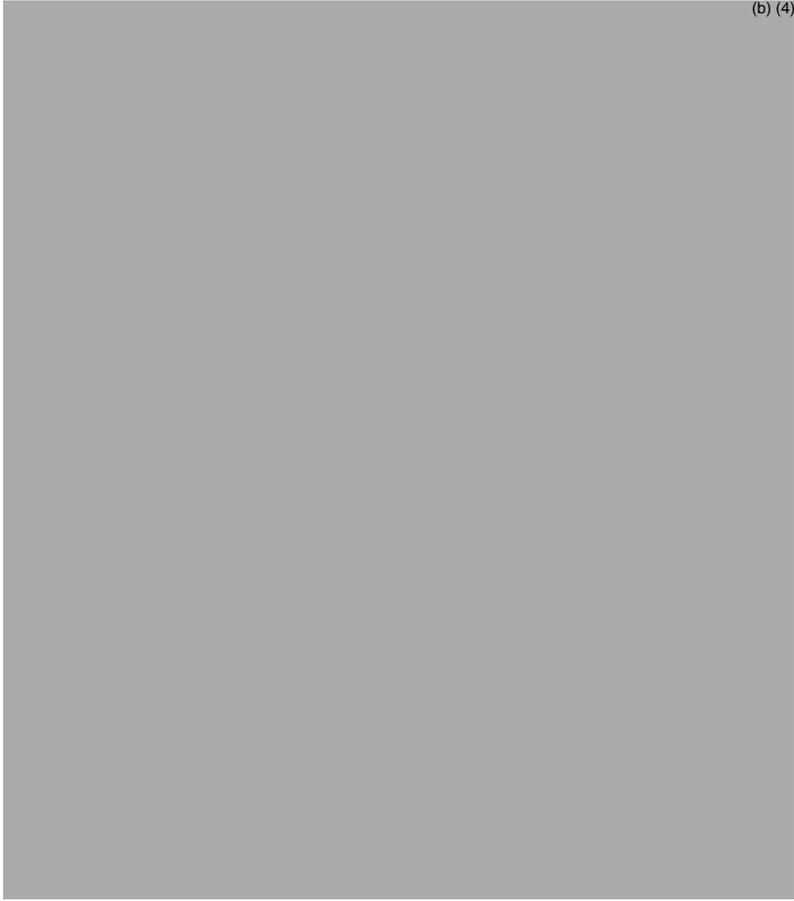
2 CONCLUSION

The revised container label and carton labeling for Epinephrine Injection, USP are acceptable from a medication error perspective. We have no further recommendations at this time.

^a Thomas S. Label and Labeling Review for Epinephrine Injection, USP (NDA 209359). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 SEP 22. RCM No.: 2017-348.

APPENDIX A. LABEL AND LABELING SUBMITTED ON OCTOBER 31, 2017

Container label



(b) (4)

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/s/

SARAH E THOMAS
11/06/2017

CHI-MING TU
11/06/2017

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: October 3, 2017

To: Quynh M. Nguyen, Pharm.D., RAC, Regulatory Project Manager
Division of Cardiovascular and Renal Products (DCaRP)

Michael Monteleone, Associate Director for Labeling, DCaRP

From: Puja Shah, Pharm.D., RAC, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: James Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for EPINHERPHRINE INJECTION USP,
1 mg/10mL (0.1mg/mL)
ABBOJECT™ Syringe, for intravenous infusion

NDA: 209359

In response to DCaRP's consult request dated March 27, 2017, OPDP has reviewed the proposed product labeling (PI) and carton and container labeling for the original NDA submission for Epinephrine Injection with ABBOJECT™ Syringe.

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DCaRP on September 20, 2017, and are provided below.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on January 31, 2017, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Puja Shah at (240) 402-5040 Puja.Shah@fda.hhs.gov.

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/s/

PUJA J SHAH
10/03/2017

LABEL AND LABELING REVIEW

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

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

Date of This Review:	September 22, 2017
Requesting Office or Division:	Division of Cardiovascular and Renal Products (DCRP)
Application Type and Number:	NDA 209359
Product Name and Strength:	Epinephrine Injection, USP, 1 mg/10 mL (0.1 mg/mL)
Product Type:	Combination Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Hospira Inc. (Hospira)
Submission Date:	July 27, 2017 and July 28, 2017
OSE RCM #:	2017-348
DMEPA Primary Reviewer:	Sarah Thomas, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD, BCPS
DMEPA Associated Director for Human Factors:	Quynh Nhu Nguyen, MS
DMEPA Deputy Director (Acting):	Danielle Harris, PharmD, BCPS

1 REASON FOR REVIEW

As part of the New Drug Application (NDA) review, this review evaluates the proposed container label, carton labeling, and prescribing information (PI) for Epinephrine Injection, USP 1 mg/10 mL (0.1 mg/mL) Abboject syringe for risk of medication error.

1.1 REGULATORY HISTORY

Hospira has marketed the Epinephrine Injection, USP Abboject syringe, 1 mg/10 mL, as an unapproved product since 1985.

On January 31, 2017, Hospira submitted a 505(b)(2) NDA for Epinephrine Injection, USP Abboject syringe, 1 mg/10 mL (0.1 mg/mL). The listed drug is the Epinephrine Injection USP, 1 mg/1 mL, packaged in ampules from Belcher Pharmaceuticals, LLC.

2 MATERIALS REVIEWED

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

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information (PI)	A
Previous DMEPA Reviews	B
Human Factors Study	C-N/A
ISMP Newsletters	D
FDA Adverse Event Reporting System (FAERS)*	E
Other- Information Requests	F
Label and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Based on our review of the materials submitted, we identified areas where the labels and labeling may be improved to promote the safe use of the product. We provide recommendations in Section 4 below.

Additionally, we note the inconsistencies for the package type term on the:

- Proposed container label is “Single-dose”,
- Proposed carton labeling is “^{(b) (4)} Syringe” on the principal display panel, and “Single-dose ^{(b) (4)}” on the side panel, and

- Proposed PI does not contain any package type term.

We communicated these inconsistencies in an email to CMC on June 22, 2017. We deferred to CMC for the determination of the correct packaging type term, and we recommended the correct package type term be consistently applied to the container labels, carton labeling, and PI.

We note Section 16 of the proposed PI describes a “Unit of Sale” that is “NDC 0409-4933-01 Bundle of 10” but no 10-count carton labeling was submitted for review. We sent an information request (IR) on June 23, 2017 to clarify if the “NDC 0409-4933-01 Bundle of 10” is packaged in a carton (see Appendix F). Hospira responded on June 28, 2017 that the “NDC 0409-4933-01 Bundle of 10” is not packaged in a carton, but rather is shrink-wrapped with clear plastic film into a 10-pack bundle. A print-on-demand sticker will be applied to the front side of each bundle and will include the product name, strength, NDC number, recommended storage condition and orientation. Additionally, since each bundle is wrapped in clear plastic, the individual carton labeling is visible through the plastic. We note this same packaging configuration and similar print-on-demand sticker is also employed on the unapproved drug labeling for Epinephrine Injection, USP “Unit of Sale” with “NDC 0409-4901-18 Bundle of 10” , and we did not identify any medication safety concerns related to this from Hospira’s medication error and complaint submission on June 16, 2017. As such, we do not have concerns with bundled packaging configuration at this time.

We note that Hospira did not submit a comprehensive use-related risk analysis to support the review of this combination product; therefore, we sent an IR to Hospira on June 2, 2017 (see Appendix F). Hospira’s June 16, 2017 response explained that in an effort to bring the marketed and unapproved Epinephrine product into approved status in accordance with FDA’s unapproved product initiative, the currently marketed product was remediated (e.g., changes made to formulation composition, intended indication, and container closure (b) (4) rubber stopper). Per Hospira’s IR response, the dosage form, route of administration, configuration, co-packaged injector device, and user interface remain the same between the two products, with a difference in the formulation composition, intended indication, and container closure (b) (4) stopper material (please see Table 1 below).

Table 1. Comparison of the Currently Marketed and the Proposed Epinephrine Injection USP, 1mg/10mL Abboject™ Syringe

Product	Currently Marketed Epinephrine Injection USP, 1 mg/10 mL, Abboject™ Single-Use Syringe	Proposed Epinephrine Injection USP, 1 mg/10mL, Abboject™ Single-Use Syringe
Dosage Form	Injectable	Injectable
Strength	1 mg/ 10mL	1 mg/ 10mL
Configuration	10 mL fill in 10 mL Abboject™ clear glass syringe cartridge	10 mL fill in 10 mL Abboject™ clear glass syringe cartridge
Indication(s)¹	(1) treatment of acute hypersensitivity (anaphylactoid reactions to drugs, animal serums and other allergens), (2) treatment of acute asthmatic attacks to relieve bronchospasm not controlled by inhalation or subcutaneous administration of other solutions of the drug and (3) treatment and prophylaxis of cardiac arrest and attacks of transitory atrioventricular (A-V) heart block with syncopal seizures (Stokes-Adams Syndrome).	To increase mean arterial blood pressure in adult patients with hypotension associated with septic shock.
Route of Administration	Intravenous (Infusion)	Intravenous (Infusion)
Drug Constituent - Formulation Composition		
Formulation Component	Quantity per mL	Quantity per mL
Epinephrine ¹	0.1 (b) (4)	0.10 mg
Sodium Metabisulfite	0.46 mg	0.46 mg
Sodium Chloride	8.16 mg	8.16 mg
Citric Acid, Anhydrous ¹	2.00 mg	2.13 mg
Sodium Citrate, Dihydrate ¹	0.60 mg	0.41 mg
Citric Acid, Anhydrous	q.s.	q.s.
Sodium Citrate, Dihydrate	q.s.	q.s.
(b) (4)		
Device Constituents - Container Closure and Injector		
Device Constituents	Description	Description
Container	Vial, Straight Wall, USP Glass, 10 mL (b) (4)	Vial, Straight Wall, USP Glass, 10 mL (b) (4)
Closure (Elastomeric)	Stopper, Plunger, Blue Rubber,	Stopper, Plunger, Gray Rubber,
Product	Currently Marketed Epinephrine Injection USP, 1 mg/10 mL, Abboject™ Single-Use Syringe	Proposed Epinephrine Injection USP, 1 mg/10mL, Abboject™ Single-Use Syringe
Stopper ¹	(b) (4)	(b) (4)
Cap	Cap, 10 mL Vial, (b) (4)	Cap, 10 mL Vial (b) (4)
Vial Injector	Vial Injector, 10 mL, (b) (4) with a 20-G Needle and the LIFESHIELD Needle Shield and Male Luer Lock Adapter, Radiation Grade	Vial Injector, 10 mL, (b) (4) with a 20-G Needle and the (b) (4) and Male Luer Lock Adapter, Radiation Grade

¹: Key differences between the currently marketed and the proposed Epinephrine Injection Abboject™.

Based on their Risk Management Report (see Appendix F), Hospira determined that all residual risks identified in their use related risk analysis have been mitigated to an acceptable level and the benefits of the use of the product outweigh the residual risks. As such, Hospira determined that the overall residual risk was acceptable, and a human factors validation study was not

necessary. Hospira further stated that Epinephrine Injection, USP Abboject syringe is a legacy product that has been marketed for over 30 years.

We acknowledge that Epinephrine Injection, USP Abboject syringe has been marketed and used by health care providers for over 30 years, and we are not aware of any post-market use-related issues based on our routine post-marketing surveillance that haven't already been addressed by Hospira. Additionally, we anticipate that the intended user population (i.e., healthcare providers) is familiar with the use and manipulation of the Abboject device and other similar pre-filled syringe device designs. However, we note that the proposed labeling recommends dilution of the product prior to intravenous use for the proposed indication, which differs from the unapproved labeling for the Epinephrine Injection, USP Abboject syringe. Thus, we requested Hospira to provide additional justification that the Abboject syringe could be used safely taking into consideration the dilution step. In their response, Hospira notes that the Agency recently approved two ANDAs utilizing the Abboject syringe (ANDAs 202495 and 202679 for sodium bicarbonate products) that also may be diluted prior to intravenous use. Hospira notes that the delivery device constituent parts of the approved sodium bicarbonate Abboject products are identical to the proposed product.

Hospira also provided a side-by-side comparison between the Sodium Bicarbonate Injection Abboject syringe and the proposed Epinephrine Injection, USP Abboject syringe. The side-by-side comparison found that the same dosage form, route of administration, configuration, and device components exist for both the Sodium Bicarbonate Injection Abboject syringe and the proposed Epinephrine Injection, USP Abboject syringe, with differences in the rubber (b) (4) used for the product stoppers/plungers. Hospira reports that this difference does not have any impact on the stopper functionality, and has no meaningful impact on the user interface. In addition, Hospira reports that the overall product displays are similar between the two products with the product name and strength adequately differentiated, the use tasks and steps are identical when the Abboject Sodium Bicarbonate syringe is diluted, and both products have the same step-by-step instructions on the back display panel of the carton labeling, including identical steps, text, and figures/images. We note the intended users and use environments are the same for both products. Also, our FAERS search for Sodium Bicarbonate Injection Abboject products and routine post-market surveillance did not identify any errors associated with difficulty in diluting the Abboject syringe before intravenous administration (see Appendix E). We find this comparison acceptable to support safe use of the Abboject device constituent by the intended users in the intended use environments even when dilution of the product is required. Thus, we determined that Hospira has comprehensively evaluated the risks associated with using this product and adequately mitigated any residual risk to an acceptable level.

Based on the aforementioned reasons, the fact that the Epinephrine and Sodium Bicarbonate Abboject syringes have been used in typical clinical settings for over 30 years, and the healthcare provider's familiarity with the products, we find the proposed Epinephrine Injection, USP Abboject Syringe acceptable and agree that a human factors validation study is not needed at this time.

4 CONCLUSION & RECOMMENDATIONS

We conclude that the proposed label and labeling for Epinephrine injection may be improved to promote the safe use of the product as described in Section 4.1 and Section 4.2.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information (PI)

1. In Sections 3 and 16 of the full PI, provide identification characteristics for the injection dosage form (e.g., color of the epinephrine solution, etc.).

4.2 RECOMMENDATIONS FOR HOSPIRA

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

A. Container Label and Carton Labeling

1. We note the absence of a lot number and expiration date on the proposed container label and carton labeling. The lot number is required per 21 CFR 201.10(i). USP requires the label of an official drug product to bear an expiration date. Therefore, we also strongly recommend including the product's expiration date on the container labels.^a
 - i. Revise the container label to include the lot number per 21 CFR 201.10(i), and to bear the expiration date per USP.
 - ii. Ensure the lot number and expiration date are presented on the carton labeling in accordance with 21 CFR 201.10(i) and 21 CFR 201.17, and ensure that they are clearly differentiated from one another.^a

B. Container Label

1. If space allows, add "Discard Unused Portion" after the package type term statement.^b

C. Carton Labeling

1. We note the usual dose statement on the side panel of the carton labeling reads, "(b) (4)." We recommend revising the usual dose statement to read, "(b) (4) dosage: See prescribing information."
2. If space allows, add the additional storage information provided in Section 16 of the full PI (e.g., "Do not refrigerate. Protect from freezing.") to the carton labeling after the statement "...[See USP Controlled Room Temperature.]"

^a Institute for Safe Medication Practices. Safety briefs: Lot number, not expiration date. ISMP Med Saf Alert A cute Care. 2014;19(23):1-4.

^b Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use. 2015. Available from <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM468228.pdf>

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Epinephrine Injection that Hospira submitted on July 27, 2017, and the listed drug (LD).

Table 2. Relevant Product Information for Epinephrine Injection and the Listed Drug		
Product Name	Epinephrine Injection (Proposed)	Epinephrine Injection (NDA 205029)
Initial Approval Date	N/A	7/29/2014
Active Ingredient	Epinephrine	Epinephrine
Indication	Non-selective alpha and beta adrenergic agonist indicated to increase mean arterial blood pressure in adult patients with hypotension associated with septic shock	Non-selective alpha and beta adrenergic agonist indicated: <ul style="list-style-type: none"> • To increase mean arterial blood pressure in adult patients with hypotension associated with septic shock • For emergency treatment of allergic reactions (Type 1), including anaphylaxis • For induction and maintenance of mydriasis during intraocular surgery.
Route of Administration	Intravenous	Intravenous, intramuscular, subcutaneous, and intraocular use
Dosage Form	Injection	Injection
Strength	1 mg/ 10 mL (0.1 mg/mL)	1 mg/1 mL (1:1000)
Dose and Frequency	Intravenous infusion rate of 0.05 mcg/kg/min to 2 mcg/kg/min, titrated to achieve desired mean arterial pressure. The dosage may be adjusted periodically, such as every 10 - 15 minutes, in increments of 0.05 mcg/kg/min to 0.2 mcg/kg/min, to achieve the desired blood pressure goal. Continuous epinephrine infusion is generally required over several hours or days until the patient's hemodynamic	Hypotension associated with septic shock: -Intravenous infusion rate of 0.05 mcg/kg/min to 2 mcg/kg/min, titrated to achieve desired mean arterial pressure. Wean gradually. Anaphylaxis: -Adults and Children 30 kg (66 lbs) or more: 0.3 to 0.5 mg (0.3 to 0.5 mL) intramuscularly or

	<p>status improves. The duration of perfusion or total cumulative dose cannot be predicted. After hemodynamic stabilization, wean incrementally over time, such as by decreasing doses of epinephrine every 30 minutes over a 12- to 24-hour period.</p>	<p>subcutaneously into anterolateral aspect of the thigh every 5 to 10 minutes as necessary.</p> <p><i>-Children 30 kg (66 lbs) or less:</i> 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.</p> <p>Intraocular surgery: -Dilute 1 mL with 100 to 1000 mL of an ophthalmic irrigation fluid, for ophthalmic irrigation or intracameral injection.</p>
How Supplied	Epinephrine Injection, USP, 1 mg/10 mL (0.1 mg/mL) ABBOJECT™ Syringe is supplied in a bundle of 10 syringes	Epinephrine Injection USP, 1 mg/1 mL (1:1000), 2 mL single-use clear glass ampule supplied in a box of 10 single-use ampules
Storage	Epinephrine is light sensitive. Protect from light until ready to use. Do not refrigerate. Protect from freezing. Store at room temperature, between 20° to 25°C (68° to 77°F). (See USP Controlled Room Temperature.) Protect from alkalis and oxidizing agents.	Epinephrine is light sensitive. Protect from light until ready to use. Do not refrigerate. Protect from freezing. Store at room temperature, between 20° to 25°C (68° to 77°F). (See USP Controlled Room Temperature.) Protect from alkalis and oxidizing agents.
Container Closure	The primary container closure system for Epinephrine Injection USP Abboject™ Syringe System consists of a glass vial and a (b) (4) stopper.	The primary packaging is (b) (4) (USP) 2 ml clear colorless glass ampules with score-break. The ampules have an adhesive label and are packed, with a leaflet, in lithographed cardboard-boxes. The cardboard-box contains 10 ampoules of Epinephrine USP 1:1000, 1 mg/ml preservative free and sulphite free.

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On May 22 and 23, 2017, we searched the L:drive and AIMS respectively using the terms, “epinephrine” to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified one previous post-marketing review^c, and we confirmed that our previous recommendations were implemented or considered.

^c Pamer, C. Label and Labeling Review for Epinephrine (American Regent, Hospira, International Medical Systems, McKesson, JHP, West-Ward). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2011 OCT 12. RCM No.: 2010-1226 and 2010-1559.

APPENDIX D. ISMP NEWSLETTERS

D.1 Methods

On May 22, 2017, we searched the Institute for Safe Medication Practices (ISMP) newsletters using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newsletter(s)	Searched the Acute Care, Community, and Nursing Newsletters.
Search Strategy and Terms	Match Exact Word or Phrase: epinephrine

D.2 Results

Our search retrieved 165 newsletters, and we evaluated only those newsletters published in the last ten years (between the years 2007 to 2017). Three of the newsletters published from 2014 to 2015 describe medication error cases potentially related to Hospira's Epinephrine Injection label and labeling.^{d,e,f}

1. The first newsletter described a stocking error involving Hospira's intracardiac epinephrine stocked in place of the intended IV epinephrine syringes. Several practitioners from different hospitals reported unintentionally ordering and stocking prefilled epinephrine 1 mg/10 mL syringes for intracardiac injection rather than the intended IV syringe formulation.

Hospira confirmed in their June 16, 2017 response to our June 2, 2017 IR that the intracardiac epinephrine is being discontinued.

2. The second newsletter described instances of confusion between real epinephrine syringe products and the corresponding demo replica. The demo replica is available for demonstration and training of healthcare professionals and does not contain the actual medication it is simulating. The distilled water in the demo syringe is not sterile and so administration to a patient could result in infection. ISMP contacted and informed the medical supplies company and Hospira of this issue. Of note, the name on the demo syringe is intentionally misspelled from its actual medication syringe counterpart to provide differentiation (e.g., "EPINEPHRN" on demo syringe versus "Epinephrine" on actual medication syringe).

^d Institute of Safe Medication Practices. Intracardiac EPINEPHrine stocked in error in place of IV EPINEPHrine syringes. ISMP Med Saf Alert Acute Care. 2015;20(17):6.

^e Institute of Safe Medication Practices. Mistaken identity: Will the real EPINEPHrine please step forward. ISMP Med Saf Alert Nurse Advise-ERR. 2014;12(2):4.

^f Institute of Safe Medication Practices. Farewell to ratio expressions on single entity drug labels. ISMP Med Saf Alert Community/Ambulatory Care. 2015;14(12):5.

DMEPA is not aware of any other similar case since this case described in the 2014 newsletter.

3. The third newsletter reports that the United States Pharmacopeia (USP) and The National Formulary (NF) will no longer allow the use of the ratio expression on single entity drug products. For example, the ratio expression 1:1,000 for epinephrine injection is to be replaced by 1 mg/mL. All changes to manufacturer product strength expressions were to be completed by May 1, 2016. The proposed label and labeling for NDA 209359 already utilizes 1 mg/mL and no ratio expression.

APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

E.1 Methods

On August 22, 2017, we searched FAERS using the criteria in the table below and identified 70 cases. We searched the narratives for the term “Abboject,” in order to limit our search to Sodium Bicarbonate Abboject product cases. Of note, only 1 case dealt with the Sodium Bicarbonate Abboject products. We then reviewed this case to determine whether or not the case described errors involving dilution of the Sodium Bicarbonate Abboject products. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter.⁸ The single case did not describe an error involving dilution of the Sodium Bicarbonate Abboject products, but rather involved an Sodium Bicarbonate Abboject injection breaking during a code and cutting a nurse’s hand while the medication was being pushed. From the narrative, it is “unknown if the syringe was handled roughly or damaged by staff prior to attempted use.”

Criteria Used to Search FAERS	
Initial FDA Receive Dates:	Date-Initial FDA Rcvd. Date From: 20170301
Product Name:	---
Product Active Ingredient (PAI):	SODIUM BICARBONATE
Event:	SMQ <i>Medication errors</i> (Narrow)
Country (Derived):	---

E.2 Results

Our search identified 70 cases, of which none described errors relevant for this review.

E.4 Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. FDA’s Office of Surveillance and Epidemiology codes adverse events and medication errors to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at: <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm>.

⁸ The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website <http://www.nccmerp.org/pdf/taxo2001-07-31.pdf>.

APPENDIX F. INFORMATION REQUESTS

IR for medication errors/complaints, comprehensive use-related risk analysis (URRA), and human factors (HF) validation study dated June 2, 2017, and Hospira's response dated June 16, 2017

<\\cdsesub1\evsprod\nda209359\0008\m1\us\info-request.pdf>

<\\cdsesub1\evsprod\nda209359\0008\m1\us\rresponse.pdf>

<\\cdsesub1\evsprod\nda209359\0008\m1\us\currently-marketed-pi.pdf>

We determined that Hospira's response for medication errors/complaints and their mitigation is acceptable. Our review of Hospira's response for URRA and HF is in Section 3 above.

IR to clarify "Unit of Sale" dated June 23, 2017, and Hospira's response dated June 28, 2017

<\\cdsesub1\evsprod\nda209359\0010\m1\us\info-request.pdf>

<\\cdsesub1\evsprod\nda209359\0010\m1\us\rresponse.pdf>

IR on dilution requirement and side by side comparison of user interface dated August 4, 2017, and Hospira's response dated August 11, 2017

<\\cdsesub1\evsprod\nda209359\0013\m1\us\info-req.pdf>

<\\cdsesub1\evsprod\nda209359\0013\m1\us\rresponse.pdf>

Risk Management Report

<\\cdsesub1\evsprod\nda209359\0004\m1\us\info-request-response-attach2.pdf>

APPENDIX G. LABEL AND LABELING

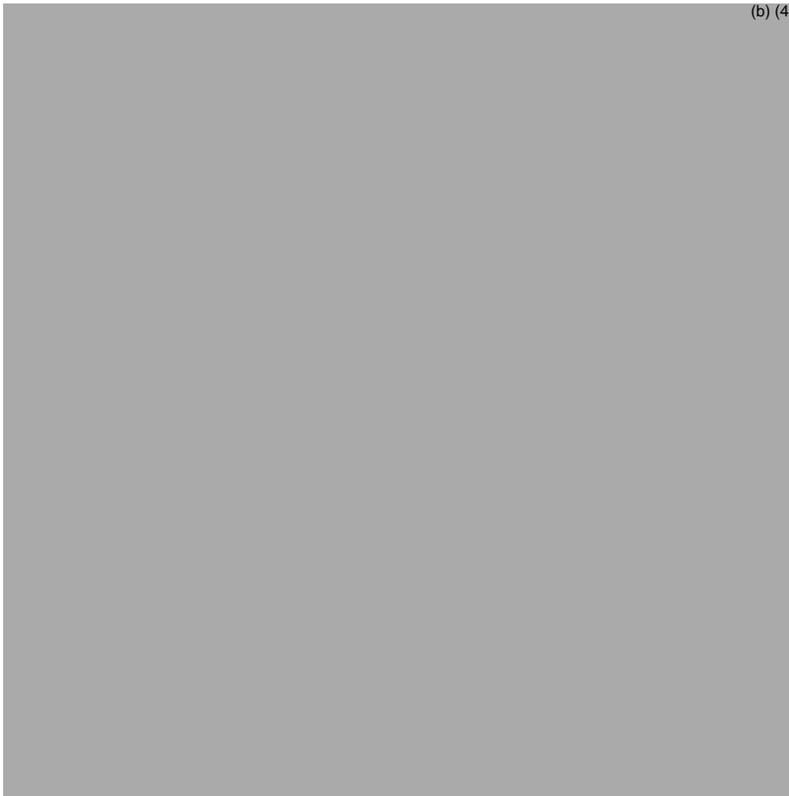
G.1 List of Label and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^h along with postmarket medication error data, we reviewed the following Epinephrine Injection label and labeling submitted by Hospira.

- Container label submitted on July 28, 2017
- Carton labeling submitted on July 28, 2017
- Prescribing Information (Image not shown), submitted on July 27, 2017

G.2 Label and Labeling Images

Container Label



^h Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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

/s/

SARAH E THOMAS
09/22/2017

CHI-MING TU
09/22/2017

QUYNHNHU T NGUYEN
09/25/2017

DANIELLE M HARRIS
09/26/2017

ICCR QUALITY SYSTEM REVIEW

Date: June 19, 2017

To: ICCR Lead-Center Contact, Office, Location, E-mail:
Cassandra Abbelard, CDER/OPQ/DIA/IABII,
Cassandra.Abellard@fda.hhs.gov
Derek Smith, CDER/OPQ/OPF/DIA/IABII, WO51 RM3171,
Derek.Smith@fda.hhs.gov

CC: Office of Combination Product at: combination@fda.gov
Regulatory Business Program Manager (RBPM)/Regulatory
Program Manager (RPM): Name, Office, E-Mail:
Grafton Adams, CDER/OPQ/OPRO/DRB, WO75 Rm4609,
Grafton.Adams@fda.hhs.gov
CDER/OPQ/OPF: Juandria.Williams@fda.hhs.gov

Through: Jamie Kamon-Brancazio, REGO/DMQ/OC, CDRH, WO 66, Rm
3427, E-mail: Jamie.Kamon-Brancazio@fda.hhs.gov

From: Susannah Gilbert, REGO/DMQ/OC, CDRH, WO 66, Rm 3431, E-
mail: Susannah.Gilbert@fda.hhs.gov

Applicant/Licensure: Hospira Inc. a Pfizer Company
275 North Field Drive,
Lake Forest, IL, 60045
FEI: 3004591926

Submission (Type & Number): NDA 209359

Combination Product Name: Epinephrine Injection USP Abboject™ Syringe

Combination Product Intended Use: To increase mean arterial blood pressure in adult patients with
hypotension associated with septic shock.

Device Constituent (Type): Syringe

ICCR Number: ICCR17000251

ICCR Instruction (ICCR Form): Assess for need for facility inspection from a device perspective.
The DP facility has interesting compliance history and unsure
previous device coverage so there is potential for a PAI need.

Pre-Approval Facility Inspection: No

Documentation Review (Status): Complete, Information – Adequate
IR Response Adequate

CDRH/OC Recommendation: Approvable

The Office of Compliance at CDRH received a consult from CDER requesting the identification of the device manufacturing sites for NDA209359 which will require a device inspection.

PRODUCT DESCRIPTION

NDA 209359 consists of an Epinephrine Injection, USP, in the form of a solution that is administered via IV infusion in 1mg/10ml (0.1mg/ml) strengths. Epinephrine Injection USP Abboject™ Syringe is available as a sterile aqueous solution, which is intended for dilution with 5% dextrose or 5% dextrose and sodium chloride solution prior to administration.

The drug product is a clear solution, free from visible particulates, presented in a **10 mL clear, (b) (4) glass vial and is co-packaged with Hospira's Abboject™ syringe.** The pH range is 2.2 to 5.0. This is (b) (4) filled product containing no antimicrobial preservatives.

Primary Container Closure: The Epinephrine Injection USP Abboject Syringe Vial consists of a glass vial and (b) (4) stopper. Packaging includes a (b) (4) cap that is not considered primary packaging as it does not directly contact the drug product.

The vial is intended to be used with the Abboject™ Vial Injector. Supporting information for the injector can be found in Hospira, Inc. DMF (b) (4)

The following table is a list of the various container closer components, their descriptions, product numbers, and where they are manufactured prior to being assembled at the Rocky Mount, NC Hospira facility:

Table 1. Components of Epinephrine Injection USP Abboject™ Syringe System

Primary Packaging Component	Description	Hospira Commodity No.	Supplier Name and Address
Container	Vial, Straight Wall, USP (b) (4) Glass, 10 mL	(b) (4)	(b) (4)
Closure	Stopper, Plunger, Gray Rubber, (b) (4) (b) (4) 10 mL	(b) (4)	(b) (4)
Cap	Cap, 10 mL Vial (b) (4)	(b) (4)	Hospira, Inc. Global Park Free Zone 1Km Noreste Del Centro Commercial Real Cariri La Aurora, Heredia Costa Rica
Vial Injector	Vial Injector, 10 mL, (b) (4) with a 20-G Needle and the (b) (4) Needle Shield and Male Luer Lock Adapter, Radiation Grade	(b) (4)	Hospira, Inc. Global Park Free Zone 1Km Noreste Del Centro Commercial Real Cariri La Aurora, Heredia Costa Rica

Section 3.2.P.2 of NDA209359 states the Epinephrine Injection Abboject™ syringe product has been manufactured unapproved for over 30 years. Similarly Section 2.2 of DMF24131 states that

the Abboject Vial Syringe System has been marketed by Hospira for over 25 years in conjunction with both approved and unapproved drug products.

DMF24131 was also used in the review of ANDAs 202495 & 202679 for similar Abboject vial and injector products that were approved in March of 2017. Just as with NDA209359, both these two ANDAs were developed without design controls because they have been on the market for over 30 years, and the DMF was created retroactively to comply with FDA requirements.

The following image is an example of the Abboject Vial Syringe System taken from DFM24131 (please note the vial pictured is for 50ml, while a 10ml vial is reviewed for this submission.:



During the review of DMF24131, ANDA202495, and ANDA202679 the similarities between the products in this submission and the previously approved systems became evident. With the exception of the closer (i.e. the stopper and plunger), the product numbers of the components provided in the table above are identical to those provided in the previously approved ANDAs.

The review memo for approval of ANDAs 202494 and 202679 (entitled Hospira - ANDAs 202494 - 202495 - 202679 - ICC1500253 Response Review Memo.pdf) was reviewed to confirm that these components, the facilities, and manufacturing processes are the same.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance (OC)
Division of Manufacturing and Quality (DMQ)

REGULATORY HISTORY

The following facilities were identified as being involved in the manufacturing and/or development of the finished combination product in NDA209359:

1. Hospira Inc.
375 North Field Drive
Lake Forest IL, 60045
FEI: 3004591926

Performs: stability testing of commercial product, storage of the design history file, record for design controls, records for CAPAs, and records for purchasing controls

This is the location of the applicant headquarters. Although this location is not where combination product is assembled, nor where the final device constituent or drug product is manufactured, an inspection history of this facility is included since this is the applicant location.

Inspection Date	Classification	Comments
3/25 - 4/13 2015	VAI	CDER Good Clinical Practice Assessment Branch initiated inspection for Pre-Approval/Monitor/ contract research organizations (CRO) inspection; focused on clinical research studies
		483 observations for inadequate monitoring of study and inability to provide name and address of the CRO and a list of the obligations transferred to the CRO.
11/25-12/11 2014	NAI	Surveillance GMP inspection
9/3-9/9 2013	NAI	Surveillance GMP inspection for injectable drug products and infusions devices

Inspection Recommendation:

An inspection is not required because:

- The facility is not responsible for major activities related to the manufacturing and development of the final combination product or the device constituent part;

2. Hospira, Inc.
Highway 301 North
Rocky Mount, NC, 27801
FEI: 1021343

Performs: Manufacturing of drug product, manufacture of the injector: (b) (4) & assembly, (b) (4), packaging of drug product with the injector, maintaining records for the design controls, CAPAs, and purchasing controls

Inspection Date	Classification	Comments
5/23 - 5/26 2016	NAI	Pre-approval inspection for ANDAs that are combination injectable drug/device products. Inspection covered: compliance programs, drug manufacturing, and

DEPARTMENT OF HEALTH & HUMAN SERVICES
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 Food and Drug Administration
 Center for Devices and Radiological Health
 Office of Compliance (OC)
 Division of Manufacturing and Quality (DMQ)

		medical device manufacturing
9/14 - 9/24 2015	VAI	Drug Work Plan inspection for compliance program for pre-approval, and drug manufacturing; follow-up to (b) (4) to verify CAPAs
		483 observations issued (b) (4)
6/3 - 6/13 2014	NAI	Inspection of sterile pharmaceutical/medical device manufacturer. Inspection covered: quality, production, lab controls, facilities / equipment, and materials.
		CAPAs from the 2/12-3/1 2013 inspection including CAPAs, current procedures, facility/equipment, and actual practices were reviewed and adequately addressed.
9/30-11/15 2013	OAI	Medical device inspection only. As discussed in 2015 EIR, observations from this inspection included:
		<ul style="list-style-type: none"> • (b) (4) • • • • • • • •

Inspection Recommendation:

An inspection is not required because:

- An analysis of the firm’s recent inspectional history showed that during the most recent inspection the firm was in compliance with applicable device quality system requirements.
- A recent pre-approval inspection of this facility was conducted for ANDAs approving similar drug products, and was classified as NAI.

3. Hospira Inc.
 La Aurora de Heredia
 1 Km Noreste Del Centro
 Real Cariari, Global Park de Entrada

Costa Rica

FEI: 3002999813

Performs: Manufacture of the injector: (b) (4) and assembly, maintain records for design control, CAPAs, and purchasing controls.

Inspection Date	Classification	Comments
3/6-3/9 2017	NAI	Routine surveillance Level II QSIT inspection requested by CDRH.
2/23-2/25 2015	NAI	Medical device inspection. Compliance Level III follow-up to (b) (4).
		All prior deficiencies (from a 2012 OAI inspection) were reported to be corrected.

Inspection Recommendation:

An inspection is not required because:

- An analysis of the firm's recent inspectional history showed that the facility was in compliance with medical device quality system regulations and the inspections were classified as NAI.

4. (b) (4)
 FEI: (b) (4)
 Performs: (b) (4)

Inspection Date	Classification	Comments
(b) (4)	NAI	Abbreviated, routine GMP inspection.
		No 483 issued with citations, however observations discussed with management
	NAI	Medical Device Level I (abbreviated) inspection; enforcement of MDR regulation. Covered complaint handling, CAPAs, and production and process controls. Topics discussed at previous inspection discussion addressed.
		No 483 issued with citations; verbal observations discussed related to training record documentation, process record review, process record documentation of product handling, adequate complaint and CAPA investigations.
NAI	Postmarket inspection (b) (4) (b) (4) covered: records related to the PMA, complaints, CAPAs, and MDR procedures	
	No 483 issued, verbal observations discussed	

Inspection Recommendation:

An inspection is not required because:

- The recent inspections of the facility reported that the facility was in compliance with medical device regulations and were classified as NAI.

DOCUMENTATION and MANUFACTURING REVIEW

During review of the application NDA209359, the following deficiencies were identified in reference to applicable 21 CFR 820 regulations and manufacturing of the finished combination product. These deficiencies were communicated to the firm and the following responses were received:

1. Your firm appears to have inadequately addressed the requirement for 21 CFR 820.20, management responsibility. Please provide a summary of how your management has established responsibility to ensure that the combination product is manufactured in compliance with all applicable CGMP requirements (see 21 CFR Part 4). Also, provide a description of the functions and responsibility of each facility involved in the manufacturing of the combination product.

Firm's Response:

Information on how the Rocky Mount facility complies with CFR 820.20 and CFR 4 is provided in *DMF 24131, section 1.11.1 Quality Information*, which is appended for ease of review. Please note that this information was recently reviewed and found acceptable by the Agency as demonstrated by the March 2017 approvals provided in Response 9b.

A description of the functions and responsibilities of each facility involved in the manufacturing of the combination product is provided in [Table 10](#). Please note that this information was also recently reviewed for other 10 mL Abboject presentations and found acceptable by the Agency as demonstrated by the March 2017 approvals provided in Response 9b.

Table 10. Combination Product Manufacturing Locations

Activity	Facility
(b) (4)	

Deficiency 9B:

Provide validation testing data that establishes, by objective evidence, that the combination product meets its device specifications and conforms to the user needs and intended uses. It is important to ensure that the combination device (drug and device component) has been verified and validated.

Firm's Response to 9b:

The Epinephrine Abboject Syringe System is a combination product that has been on-market for over 30 years and thus is a legacy product that was not developed under design controls. However, Hospira created a retrospective DHF consistent with the recommendations provided in the Agency's cGMP draft guidance *Current Good Manufacturing Practice Requirements for Combination Products*. On page 19, the guidance states the following:

“It is appropriate to leverage existing data in developing a design history file for a combination product that may not have been developed under design controls. For example, existing specifications may become part of the required design output documentation. Similarly, testing performed prior to distribution of the combination product may be included as documentation of design verification and validation. The combination product manufacturer is responsible for assembling available information and assessing what, if any, additional information and evidence may be needed, such as additional testing or documentation of the design control activities, to address all aspects of design control that are needed to support the manufacture of the product as currently marketed, ensure its safety and effectiveness, and support any future changes to that product.”

To build the retrospective DHF, a review of the product was completed, including a comprehensive retrospective analysis of in-process and release testing, historical test data, specifications, a detailed complaint review and a risk assessment. Data is available to demonstrate clinical safety and efficacy of the device constituent and whether any potential risks manifested during clinical use. Information from the DHF was provided in DMF 24131 for the Abboject combination product in September 2015. The Agency recently reviewed DMF 24131 for 2 ANDA applications (ANDAs [202-495](#) and [202-679](#)) for similar 10 mL Abboject products that were also developed without design controls and have been on the market for over 30 years. Both applications were approved in March, 2017. These approval letters are appended. As part of these approvals, the Agency reviewed the Abboject Design History File during the Prior Approval Inspection at the Rocky Mount manufacturing facility in May 2015. No 483 observations were received.

Additionally, an evaluation of U.S. post-market sales and product complaints of all 10ml Abboject products was performed for the time period of May 1, 2015 to March 31, 2017. Table 6 contains the list of all marketed 10 mL Abboject

products. During this time frame, the total US sales were reported as (b) (4) individual units sold; with 20 complaints that relate to the device constituent. Therefore, the complaint rate per unit sales equates to (b) (4) % or (b) (4) complaints (b) (4) units sold. This includes complaints such as: broken or damaged components, leaks, difficulty to activate, difficulty to assemble, difficulty to manipulate, and missing components. The extremely low complaint rate demonstrates the safe and effective use of the product in a clinical setting. The design validation for the device constituent of the product documents the historical safe and effective use of the product. Design verification of the Abboject Syringe System is summarized in *DMF 24131, Section 3.2.R.1 Performance Evaluation*.

Table 6. List of 10mL Abboject Products

(A)NDA	Product Description	NDC	Strength	Presentation	Fill Size
202-495	8.4% Sodium Bicarbonate Injection, USP	0409-4900-34	84 mg/mL (10 mEq/10 mL)	10 mL	10 mL
202-679	4.2% Sodium Bicarbonate Injection, USP	0409-5534-34	42 mg/ml (5 mEq/10 mL)	10 mL	10 mL
21-117	10% Calcium Chloride Injection, USP	0409-4928-34	100 mg/10 mL (1.4 mEq/mL)	10 mL	10 mL
21-146	Atropine Sulfate Injection, USP	0409-4911-34	1 mg/10 mL (0.1 mg/mL)	10 mL	10 mL
209-359	Epinephrine Injection, USP,	0409-4921-34	1 mg/10 mL (0.1 mg/mL)	10 mL	10 mL

- It is not clear to us how the requirements for 21 CFR 820.30 have been addressed, and how the design control process was utilized in development of the combination product under review. Provide a description of your design control procedures; include information about design and development planning, design input, design output, design review, design verification, design validation, design transfer, design changes, and design history. Please include how requirements for these design control procedures are fulfilled. Explain how you utilized the design control process to develop the combination product under review.

Firm's Response:

The retrospective design and development activities for the Abboject products manufactured at the Rocky Mount facility were performed at Hospira's Lake Forest location per OSD.11. Device Design Control Policy. (b) (4)



Additional information on how the requirements for CFR 820.30 and CFR 4 are met is provided in [DMF 24131, section 1.11.1 Quality Information](#), which is appended for ease of review. Please note that this information was recently reviewed and found acceptable by the Agency as demonstrated by the March 2017 approvals provided in [Response 9b](#).

3. Your firm appears to have inadequately addressed the requirement for 21 CFR 820.50, purchasing controls. Please provide a summary of the procedure(s) for purchasing controls. The summary should:
 - a. Describe your supplier evaluation process and describe how it will determine type and extent of control you will exercise over suppliers.
 - b. Define how you maintain records of acceptable suppliers and how you address the purchasing data approval process.
 - c. Explain how you will balance purchasing assessment and receiving acceptance to ensure that products and services are acceptable for their intended use. In addition, explain how the procedure(s) will ensure that changes made by contractors/suppliers will not affect the final combination product. Provide a description of how you apply the purchasing controls to the suppliers/contractors used in the manufacturing of the combination product. (e.g., through supplier agreement).

Firm's Response:



Additional information on how the requirements for CFR 820.50 and CFR 4 are met is provided in [DMF 24131, section 1.11.1 Quality Information](#), which is appended for ease of review. Please note that this information was recently reviewed and found acceptable by the Agency as demonstrated by the March 2017 approvals provided in [Response 9b](#).

4. Your firm appears to have inadequately addressed the requirement for 21 CFR 820.100, corrective and preventive actions. Please summarize the procedure(s) for your Corrective and Preventive Action (CAPA) System. The CAPA system should require:
 - a. Identification of sources of quality data and analysis of these data to identify existing and potential causes of nonconforming practices and products;
 - b. Investigation of nonconformities and their causes;
 - c. Identification and implementation of actions needed to correct and prevent recurrence of nonconformities; and
 - d. Verification or validation of the actions taken.

Firm's Response:



Additional information on how the requirements for CFR 820.100 and CFR 4 are met is provided in [DMF 24131, section 1.11.1 Quality Information](#), which is appended for ease of review. Please note that this information was recently reviewed and found acceptable by the Agency as demonstrated by the March 2017 approvals provided in [Response 9b](#).

5. Your firm has included establishment information of the various facilities used for the manufacturing, packaging, and control of Epinephrine Injection USP Abboject™ Syringe. However, it is unclear which of these locations are involved with final manufacturing of the device constituent parts, the final product assembly, and the sterilization. Therefore, please specify the facilities where these activities occur.

Firm's Response:

Please see [Table 10](#) as included in the [Response to Query 12](#) for the requested information.

Documentation and Manufacturing Review Recommendation:

- **Deficiencies originally conveyed to the applicant were adequately addressed.**
- **The firm provided sufficient evidence to show compliance with Medical Device Quality System Regulations.**
- **No additional information is required for the documentation review.**
- **No additional or outstanding deficiencies exist.**

During the review of application NDA209359 and DMF24131, the similarities between the device constituents in this application and those in ANDA202495, and ANDA202679 (approved in March 2017) became evident. The review memo for approval of ANDAs 202494 and 202679 (entitled Hospira - ANDAs 202494 - 202495 - 202679 - ICC1500253 Response Review Memo.pdf) was reviewed to confirm that these components, the facilities, and manufacturing processes are the same.

The information provided by the firm in their response to the May 2017 Information Request (IR) revealed that the same information was provided for review of ANDAs 202495 and 202679 which were subsequently approved in March of 2017. Review of the aforementioned memo documenting the medical device constituents of the combination products in ANDA202495 and ANDA202679 further demonstrated that this information has been previously reviewed and did not raise safety concerns. The specified memo concluded that the information pertaining to the applicable 21 CFR part 820 regulations for the combination products adequately demonstrated compliance, and solely recommended that further facility pre-approval and follow-up inspections be conducted prior to approval. These inspections were conducted, and the ANDA applications both received approval in March of 2017.

Based on the similarities of the information provided in this application NDA209359 and ANDAs 202495 and 202679, the review of the same information pertaining to the device constituents and the corresponding manufacturing activities, and the approval of the two ANDAs, we find this provided information adequate for the review and acceptance of application NDA209359.

RECOMMENDATION

The application for Epinephrine Injection USP Abboject™ Syringe, NDA209359 is approvable from the perspective of the applicable Quality System Requirements.

- (1) The documentation review of the application for compliance with the Quality System Requirements showed no deficiencies.
- (2) There were no facility inspections for compliance with applicable Quality System Requirements needed for approvability determination.

OC Decision:

- Approvable (Recommend approval to CDER)
- Withhold (Issue Device Quality System Deficiencies to CDER or Recommend Inspections)
- Not Approvable

Susannah Gilbert -S
2017.06.19 15:36:33
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Reviewer:

Branch Chief or Lead CSO:

Jamie Kamon-
branzazio -A

Dig tally signed by Jamie Kamon-branzazio -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA,
ou=People, o=0.2342.1820030010011-2001508505,
cn=Jamie Kamon-branzazio -A
Date: 2017.06.20 21:05:23 -04:00

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/s/

GRAFTON G ADAMS
11/21/2017