CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209359Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA 209359; Epinephrine Injection, USP

Integrated Quality Review

Recommendation: Approval

Drug Name/Dosage Form	Epinephrine Injection, USP
Strength	1 mg/10 mL (0.1 mg/mL)
Route of Administration	IV (Infusion)
Rx/OTC Dispensed	Rx
Applicant	Hospira Inc.
Submissions (s) Reviewed	NDA 209359, and all the submitted CMC amendments.

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Haripada Sarker	ONDP/DNDPI/NDPBI
Drug Product/Environmental Assessment (EA)	Mariappan Chelliah	ONDP/DNDPI/NDPBI
Process	Anitha Govada	OPQ/OPF/DPAI/PABI
Facility	Cassandra Abellard	OPF/DIA/IABI
Biopharmaceutics	Poonam Delvadia	ONDP/DB/BBI
Microbiology	Yeissa Chabrier Rosello	OPQ/OPF/DMA/MABII
Regulatory Business Process Manager	Grafton Adams & Dahlia Woody	OPRO DRBPMI/RBPMBI
Abboject™ Syringe	Susannah Gilbert	REGO/DMQ/OC, CDRH
Application Technical Lead	Mohan Sapru	ONDP/DNDPI/NDPBI

RELATED/SUPPORTING DOCUMENTS

Document	Application Number	Description
Type II DMF	# (b) (4)	The DMF was been previously reviewed and found adequate. It was also reviewed in the context of the current submission and found adequate.
DMF	# (b) (4)	The DMF was been previously reviewed and found adequate

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing, and controls (CMC)/quality perspective, NDA 209359 (Epinephrine Injection, USP) is recommended for approval.

B. Recommendation on Post-Marketing Commitments (PMCs), Agreements, and/or Risk Management Steps, if Applicable

Not applicable.

II. Summary of Quality Assessments

The applicant, Hospira Inc., has sought U.S. marketing approval for Epinephrine Injection USP, 1 mg/10 mL (0.1 mg/mL) in accordance with Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. For the approval of this NDA, the applicant relies on FDA's previous finding of safety and efficacy for the reference listed drug (RLD) i.e., Epinephrine Injection USP, 1 mg/mL (1:1000 ampule) from Belcher Pharms LLC (NDA 205029). The proposed product is indicated to increase mean arterial blood pressure in adult patients with hypotension associated with septic shock. However, the RLD, in addition to the above indication proposed under the current submission, is also indicated for emergency treatment of allergic reactions (Type 1), including anaphylaxis, and for induction and maintenance of mydriasis during intraocular surgery. The applicant's proposed product is essentially similar to the RLD, as it has the same active moiety and delivers the same amount of drug to the patient. The proposed product and the RLD have comparable physicochemical properties such as pH and osmolality. However, Hospira's proposed product contains excipients which are not present in the RLD. The differences in inactive ingredients between the Hospira's proposed product and the RLD have been adequately justified by the applicant and are not expected to impact disposition, safety, or efficacy of the proposed drug product. The proposed control strategies for ensuring product quality are adequate.

A. Drug Substance (Epinephrine) Quality Summary

Epinephrine USP, a white to almost white crystalline powder, has one chiral center. The active moiety is l-epinephrine while its enantiomer, d-epinephrine, is inactive. The amount of d-epinephrine is controlled by a validated chiral HPLC method. The CMC details concerning the drug substance such as structural characterization, impurity profile, manufacturing, and stability have been cross- referenced to Type II DMF (b) (4) which was been previously reviewed (review-1) by L. A Rocca, dated 02/23/2015, and found to be adequate. This DMF was also reviewed in the context of the current submission and found adequate (refer to DMF review-II by H. Sarker, dated 10/24/2017). Based on review of information provided in the NDA the specifications and acceptance criteria are set to conform to the Epinephrine USP monograph requirements, USP general requirements, and/or ICH guidelines Q3A and Q3C. Specifically, the critical quality attributes (CQAs) such as description, assay, identification, optical rotation. loss on drying, residue on ignition, levels of norepinephrine, adrenalone, residual solvents, organic impurities, epinephrine sulfonic acid, and (b) (4) are tested on release.

The limit for epinephrine sulfonic acid at (b) (4)% has been qualified based on toxicological qualification (involving the 2-week intravenous toxicity study followed by a 2-week recovery period in Sprague-Dawley rats). The limit for adrenalone at (b) (4)% is also considered qualified because the limit is more stringent than the USP monograph requirement. The limits for norepinephrine and any unspecified impurities at (b) (4)% align with the ICH Q3A guideline threshold. In summary, the proposed specification, including validations of analytical methods are acceptable. Based on adequate stability data, the applicant has assigned a retest period of (b) (4) months for the drug substance.

B. Drug Product Quality Summary

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

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

(b) (4) Hospira has justified the maximum daily intake (MDI) of sodium metabisulfite by identifying 3 products, Plenamine™ 15% Amino Acids Injection, Dopamine HCl Injection USP, and Dobutamine Hydrochloride in 5% Dextrose Injection, which have significantly higher levels of sodium metabisulfite compared to MDI of sodium metabisulfite for Hospira's product. Hospira is currently marketing Epinephrine Injection USP Abboject™ Syringe as an unapproved ("grandfathered") product. In an effort to gain approval of the product, the applicant claims to have applied quality by design (QbD) principles to reformulate the current product. However, no DOE studies were performed. (b) (4) ge. Specifically, the applicant tightened the in-process pH range to 2.7 – 3.1 with the target of pH 2.9. Additionally, minor changes have been made (b) (4) It is important to note that there (b) (4) for the commercial batches that will be marketed following the approval of this NDA. The optimal concentration of sodium metabisulfite was found to be 0.46 mg/mL and the optimal pH range was found to be (b) (4) Under these conditions, the specified and unidentified related substances also remain within the acceptance limits. (b) (4) Acceptance limits for pH testing on release is 2.3 – 3.5. The drug product specification includes testing all the identified CQAs. All the analytical methods have been adequately validated. Regarding elemental impurities, the applicant conducted risk assessment per ICH Q3D Guidance. The data show that product batches contain (b) (4)% of the permitted daily exposure for class 1, 2A, 2B, and 3 elements, and hence the lack of testing for the

elemental impurities in the drug product specification is justified. Additionally, the batch analysis data for three batches of the drug product, manufactured (b) (4), are adequate.

Manufacturing: The manufacturing process involves: (b) (4)

(b) (4)

Microbiological Aspects: The validation results for the sterility testing, and container closure integrity testing performed by microbial ingress and aerosol challenge are adequate. The validation studies conducted under worst-case scenario conditions for Abboject stoppers and sub-minimal conditions support the commercial (b) (4) process. The validation details provided for the environmental monitoring program are acceptable. The batch records confirm that validated sterilization and (b) (4) manufacturing processes has been used for the manufacture of the exhibit batches. Furthermore, the drug product release specification includes sterility (USP <71>), and bacterial endotoxins (USP <85>) testing.

Biopharmaceutics Aspects: The original submission included a request for biowaiver of *in vivo* bioavailability/bioequivalence (BA/BE) study for the proposed product under the provision of 21 CFR 320.22(b)(1)(I) and (ii). However, it was noted during filing that the proposed product does not fully satisfy the criteria for granting a waiver under 21 CFR 320.22(b)(1). Specifically, the proposed product does not fulfill the requirement of same inactive ingredients as the RLD. The applicant updated the waiver request with inclusion of reference of 21 CFR 320.24(b)(6) in addition to 21 CFR 32022(b)(1)(I) and (ii). Therefore, the biowaiver request has been evaluated under the provisions of 21 CFR 320.24(b)(6). The proposed product and the RLD have comparable physicochemical properties (pH and osmolality). The differences in inactive ingredients are adequately justified by the applicant and are not expected to impact disposition, safety, or efficacy of the proposed drug product. The request for biowaiver by the applicant for the proposed product is granted.

Abboject Vial Syringe System: Given that Epinephrine Abboject Syringe System is a combination product, CDRH reviewed the device component i.e., Abboject™ Syringe. For details about the

Abboject™ Vial Injector, the applicant cross-referenced DMF 24131, which has been previously reviewed and found adequate The Epinephrine Abboject Syringe System, which has been marketed for years in conjunction with both approved and unapproved drug products, is a legacy product that was not developed under design controls. DMF 24131 was also cross-referenced for the review of ANDAs 202495 & 202679 that have been approved in March of 2017. Epinephrine Abboject Syringe Systems referenced for these two ANDAs were also developed without design controls because they have been on the market for over 30 years, and the DMF was created retroactively to comply with Agency's cGMP draft guidance *Current Good Manufacturing Practice Requirements for Combination Products*. During the review of this NDA and DMF 24131, the similarities between the device constituents in this application and those used under ANDA 202495, and ANDA 202679 became evident. 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 QSD.11, Device Design Control Policy. Regarding the applicable 21 CFR 820 regulations and manufacturing of the finished combination product, the applicant in addition to referring to DMF 24131, provided adequate details to demonstrate that the Rocky Mount facility complies with CFR 820.20 and CFR 4. The design validation for the Abboject Syringe System has been demonstrated based on the historical safe and effective use of the combination product.

Container Closure System: The Epinephrine Injection USP Abboject™ Syringe will be packaged in a 10 mL, (b) (4) clear glass vial closed with a 10 mL (b) (4) rubber stopper. The product is administered using the Abboject vial injector. The secondary packaging consists of a carton containing Epinephrine Injection USP Abboject™ Syringe vial and an Abboject vial injector. The proposed container meets the requirements for (b) (4) glass, as detailed in USP <(b) (4)>. The proposed closures comply with USP <381> physicochemical and biological testing requirements. In addition, it has been demonstrated that the container closure system remains integral and, therefore, can maintain the sterility of the product. The product stability data also indicate suitability of the proposed container closure system for the intended use.

Expiration Date & Storage Conditions: The stability data support a shelf-life of 15 months when stored at controlled room temperature (20°C – 25°C; 68°F – 77°F). in the proposed commercial container closure system. Epinephrine is light sensitive, and instructions for storage include:

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

In addition, the stability data adequately support sterility assurance of the drug product for the duration of shelf-life.

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

III. Summary of Drug Product and Intended Use

Proprietary Name of the Drug Product	Not applicable
Non Proprietary Name of the Drug Product	Epinephrine Injection, USP
Active ingredient	Epinephrine

Route of Administration	Intravenous Infusion
Strength(s)	1 mg/10 mL (0.1 mg/mL)
Proposed Indication(s)	Epinephrine is a non-selective alpha and beta adrenergic agonist indicated to increase mean arterial blood pressure in adult patients with hypotension associated with septic shock.
Maximum Daily Dose/ Duration of Treatment	For dosage and administration: • Dilute epinephrine in dextrose solution prior to infusion by adding 10 mL (1 mg) of epinephrine from the syringe to 1,000 mL of a 5 percent dextrose containing solution. Each mL of this dilution contains 1 mcg of epinephrine. • Infuse epinephrine into a large vein. • Intravenous infusion rate of 0.05 mcg/kg/min to 2 mcg/kg/min, titrated to achieve desired mean arterial pressure. • Wean gradually. Epinephrine Injection, USP contains sodium metabisulfite which may cause mild to severe allergic reactions including anaphylaxis or asthmatic episodes in susceptible individuals. However, the presence of sodium metabisulfite in this product should not preclude its use for the treatment of hypotension associated with septic shock even if the patient is sulfite-sensitive, as the alternatives to using epinephrine in a life-threatening situation may not be satisfactory.
Alternative Methods of Administration	N/A

D. Biopharmaceutics Considerations

1. BCS Designation: The proposed drug product is an injectable solution, and the applicant has not request an official BCS designation,
2. Biowaivers/Biostudies: The applicant's biowaiver request was evaluated under 21 CFR 320.24(b)(6).
3. IVIVC: N/A.

E. Any Special Product Quality Labeling Recommendations: All labeling recommendations were accepted by the applicant, and are reflected in the most recent version of the product labeling.

F. Life Cycle Knowledge Information

(Please see the next page)

QUALITY ASSESSMENT

Final Risk Assessment-

NDA 209359 (Epinephrine Injection, USP)

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors Affecting CQA**	**Initial Risk Ranking**	**Risk Mitigation**	**Final Risk Evaluation**	**Comments**
Sterility	Formulation Container Closure Process Parameters Scale/Equipment/ Site	**H** **(High)**	(b) (4)	Acceptable	Given that the product sterility is the high risk attribute, any proposed changes in (b) (4) manufacturing process or microbiological testing-related product specification may need to be carefully evaluated.
Endotoxin Pyrogen	Formulation Container Closure Process Parameters Scale/equipment/ Site	**M** **(Moderate)**		Acceptable	Any proposed changes concerning acceptance limits for endotoxin levels will need to be evaluated based on the maximum total daily dose.
Assay (API), Stability	Formulation Container Closure Raw Materials Process Parameters Scale/Equipment/ Site	L (Low)		Acceptable	
Assay (b) (4)	Formulation Raw materials Process parameters Scale/equipment/ site				Any formulation change s especially the acceptance limits of (b) (4) may need to be carefully evaluated.
Uniformity of Dose – Fill/ deliverable Volume	Formulation Container Closure Process Parameters Scale/equipment/ site	L (Low))		Acceptable	

Final Risk Assessment (continued)

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors Affecting CQA**	**Initial Risk Ranking**	**Risk Mitigation**	**Final Risk Evaluation**	**Comments**
Osmolality	Formulation Raw materials Process parameters Scale/equipment/ site	L (Low)	(b) (4)	Acceptable	
pH (b) (4)	Formulation Container Closure Raw materials Process parameters Scale/equipment/ site	L (Low)		Acceptable	
Particulate Matter	Formulation Container Closure Process Parameters Scale/equipment/ site	**M (Moderate)**		Acceptable	
Leachable Extracts	Formulation Container Closure Raw materials Process parameters Scale/equipment/ site	L (Low)		Acceptable	There is some low risk of glass delamination on storage beyond the currently granted expiration period Therefore, during the lifecycle management of this product; the vials/product may need to be monitored for delamination and fine particles formation.
Appearance	Formulation Raw materials Process Parameters Scale/equipment/ site	L (Low)		Acceptable	

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

Application Technical Lead (ATL) Assessment and Signature:

From the chemistry, manufacturing, and controls (CMC)/quality perspective, NDA 209359 (Epinephrine Injection, USP) is recommended for approval.

Mohan Sapru, M.S., Ph.D.
Application Technical Lead (ATL)
CMC Lead for Cardiovascular and Renal Products (Actg)
ONDP/DNDPI/NDPBI

Mohan K. Sapru -S

Digitally signed by Mohan K. Sapru -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Mohan K. Sapru -S, 0.9.2342.19200300.100.1.1=2000589315
Date: 2017.11.21 12:16:05 -05'00'

BIOPHARMACEUTICS

NDA: NDA-209359-ORIG-1

Applicant Name: Hospira Inc.

Type of NDA: 505(b)(2) Division of Cardiovascular and Renal Products (DCRP)

Drug Product Name: Epinephrine Injection USP, 1 mg/10 mL (0.1 mg/mL)
ABBOJECT™ Syringe, for intravenous infusion

Dosage Form: Solution for Injection

Strength: 1 mg/10 mL (0.1 mg/mL)

Route of Administration: For Intravenous (IV) Infusion

Reference Drug/Listed Drug: NDA 205029 [EPINEPHRINE INJECTION USP, 1 mg/mL (1:1000) ampule, for intravenous, intramuscular, subcutaneous, and intraocular use; Approved on July 29, 2014]

Product Background

NDA 209359 is submitted as a 505(b)(2) application for the use of epinephrine injection USP, 1 mg/10 mL (0.1 mg/mL) to increase mean arterial blood pressure in adult patients with hypotension associated with septic shock.[1] Epinephrine is a non-selective alpha and beta adrenergic agonist. The Applicant relies for the approval of this NDA on FDA's previous finding of safety and efficacy for the reference drug Epinephrine Injection USP, 1 mg/mL (1:1000 ampule) from Belcher Pharms LLC (NDA 205029).[2] The reference drug, in addition to the above indication proposed for the current submission, is also indicated for emergency treatment of allergic reactions (Type 1), including anaphylaxis and for induction and maintenance of mydriasis during intraocular surgery.[3] For the current 505(b)(2) submission, only one indication mentioned above is proposed. The proposed product, Epinephrine Injection USP, 0.1 mg/mL is a sterile solution, which is intended for intravenous use after dilution. The product (1 mg of epinephrine in 10 mL) is diluted in 1000 mL of 5 percent dextrose solution or 5 percent dextrose and sodium chloride solution.[1] Administration in saline solution alone is not recommended. The dextrose containing fluids (b) (4). The concentration of epinephrine in diluted solution is 1 µg/mL. The proposed product Epinephrine Injection, USP, 1 mg/10 mL (0.1 mg/mL) ABBOJECT™ Syringe will be supplied as 10 individual cartons each containing the proposed product (10 cartons are shrink-wrapped

[1] Global Submit – N209359 – 0001(1) dated 01/31/2017. Module 1.14.1.3. Draft Labeling Text – Epinephrine USPI Clean - PDF. (Accessed on August 24, 2017)
[2] Global Submit – N209359 – 0001(1) dated 01/31/2017. Module 1.2. Cover Letters – (CL) Initial 505(b)(2). (Accessed on August 24, 2017)
[3] Drugs@fda – N205029 – EPINEPHRINE INJECTION USP, 1 mg/mL Drug Labeling. (Accessed on August 24, 2017)

with clear plastic film into a 10-pack bundle). The product in each carton contains 10 mL of solution consisting of 1 mg of epinephrine.[1,4]

This submission includes a request for waiver of *in vivo* bioavailability/bioequivalence (BA/BE) studies comparing the proposed test product and the reference drug, under the provision of 21 CFR 320.22(b)(1)(i) and (ii).[5] It was noted during filing[6] that the proposed product does not fully satisfy the criteria for granting a waiver of evidence of in vivo bioavailability or bioequivalence under 21 CFR 320.22(b)(1). Specifically, the proposed product does not fulfill the requirement of same inactive ingredients as the reference drug product (NDA 205029). Therefore, the biowaiver request is evaluated under 21 CFR 320.24(b)(6) and was communicated to the Applicant in the information request (IR) (Discussed in detail under the section "***Biowaiver Request***").[7] To support the biowaiver request, the Applicant also provided physicochemical properties (osmolality and pH) comparing the proposed test and reference drug products.[8] The biopharmaceutics assessment focuses on (1) the evaluation of the biowaiver request, (2) comparative physicochemical properties between the proposed product and the reference drug, and (3) responses to the biopharmaceutics information request. This evaluation can be found under the section "***Biowaiver Request***".

Review Summary

The Applicant submitted a biowaiver request under the provision of 21 CFR 320.22(b)(1) supported by comparative physiochemical properties for the approval of the proposed Epinephrine Injection USP, 1 mg/10 mL (0.1 mg/mL). As discussed in detail in the review body under the section "**Biowaiver Request**", the biopharmaceutics information submitted in support of the approval is evaluated under 21 CFR 320.24(b)(6) since the proposed product does not meet 21 CFR 320.22(b)(1)(ii) criteria. The proposed and reference drug product differs with respect to inactive ingredients qualitatively. During the review cycle, information was requested with regards to comparative physicochemical properties and justification on differences in inactive ingredients and evidences of the absence of the effect of the inactive ingredient differences on disposition, safety, and efficacy of the proposed product. The Applicant adequately responded to these requests. The proposed and reference drug product have comparable physicochemical properties (pH and osmolality). The differences in inactive ingredients are adequately justified by the Applicant and are not expected to impact disposition, safety, or efficacy of the proposed drug product. Based on the biopharmaceutics information provided in the original submission and amendment (responses to biopharmaceutics information

[4] Global Submit – N209359 – 0010(10) dated 06/28/2017. **Module 1.11.1. Quality Information Amendment – Response.** (Accessed on August 24, 2017)
[5] Global Submit – N209359 – 0001(1) dated 01/31/2017. **Module 1.12.15. Request for Waiver of In Vivo Bioavailability Studies.** (Accessed on August 24, 2017)
[6] NDA 209359 at SharePoint.FDA – **Filing Template 209359.** (Accessed on 08/24/2017)
[7] Global Submit – N209359 – 0003(3) dated 04/21/2017. **Module 1.11.1. Quality Information Amendment – Information Request.** (Accessed on August 24, 2017)
[8] Global Submit – N209349 – 0001(1) dated 01/31/2017. **Module 3.2.P.2. Pharmaceutical Development – Drug Product.** (Accessed on August 24, 2017)

request), the request for biowaiver by the Applicant for the proposed Epinephrine Injection USP, 1 mg/10 mL (0.1 mg/mL), for intravenous infusion is granted.

ONDP-Division of Biopharmaceutics reviewed NDA 209359 and responses to biopharmaceutics information requests. The NDA 209359 is recommended for Approval from a Biopharmaceutics perspective.

List Submissions being reviewed (Table):

SEQUENCE #	SUBMISSION(S) DATE	MODULE #	SUBMISSION DOCUMENT(S) REVIEWED
0001(1)	01/31/2017	1.12.15	Request for waiver of in vivo bioavailability studies
		3.2.P.2	Pharmaceutical Development – Drug Product
0003(3)	04/21/2017	1.11.1	Quality Information Amendment – Information Request
		1.12.15	Request for waiver of in vivo bioavailability studies
		3.2.P.2	Pharmaceutical Development – Drug Product

Highlight Key Outstanding Issues from Last Cycle: No pending issues (All biopharmaceutics information request (IRs) were addressed in review cycle and discussed in detail under the section "***Biowaiver Request***").

Concise Description Outstanding Issues Remaining: No pending issues (All biopharmaceutics information request (IRs) were addressed in review cycle and discussed in detail under the section "***Biowaiver Request***").

Bridging of Formulations

Reviewer's Assessment: (b) (4)

The Applicant submitted comparative physicochemical testing results (pH and osmolality) on test products (b) (4) *does not impact pH and osmolality properties of the product and hence any effect on safety and efficacy is not expected. Therefore from biopharmaceutics perspective, there is no need to bridge the formulations* (b) (4).

Biowaiver Request

The Applicant included a biowaiver request of *in vivo* bioavailability/bioequivalence (BA/BE) study for the proposed test product under the provision of 21 CFR 320.22(b)(1)(i) and (ii).[5] 21 CFR 320.22(b)(1)(i) and (ii) states the following:

(1) The drug product:
  (i) Is a parenteral solution intended solely for administration by injection, or an ophthalmic or otic solution; and
  (ii) Contains the same active and inactive ingredients in the same concentration as a drug product that is the subject of an approved full new drug application or abbreviated new drug application.

(b) (4)

The biowaiver request; however, is evaluated under 21 CFR 320.24(b)(6) which states "Any other approach deemed adequate by FDA to measure bioavailability or establish bioequivalence" and was communicated to the Applicant via biopharmaceutics IR.[7] In response, the Applicant updated the waiver request with inclusion of reference of 21 CFR 320.24(b)(6) in addition to 21 CFR 32022(b)(1)(i) and (ii).[10] The below review focuses on biowaiver request based on 21 CFR 320.24(b)(6).

[9] Global Submit – N209359 – 0001(1) dated 01/31/2017. **Module 1.6.3. Correspondence Regarding Meetings.** (Accessed on August 24, 2017)
[10] Global Submit – N209359 – 0003(3) dated 04/21/2017. **Module 1.12.15. Request for Waiver of In Vivo Bioavailability Studies.** (Accessed on August 24, 2017)

Table 1. Composition of the Proposed Test and Reference Drug Products (Epinephrine Injection, USP)

NDA Holder		Belcher Pharmaceuticals (NDA 205029)	Hospira, Inc.
Product		Epinephrine Injection USP, 1 mg/mL, Single-Dose Ampuls	Epinephrine Injection USP, 0.1 mg/mL, Abboject™ Single-Use Syringe
(b) (4)		*1 mg/mL (base equivalent)*	----------
Active Ingredient (Epinephrine USP)		----------	*0.1 mg/mL*
Inactive Ingredient(s)	Sodium Chloride USP	*9 mg/mL*	*8.16 mg/mL*
	Hydrochloric Acid USP	*q.s.*	*N/A*
	(b) (4)		
	Sodium Metabisulfite NF	*N/A*	*0.46 mg/mL*
	Citric Acid Anhydrous USP	*N/A*	*2.13 mg/mL*[1]
	Sodium Citrate Dihydrate USP	*N/A*	*0.41 mg/mL*[1]
Fill Volume		*1 mL*	*10 mL*
Dosage Form		Injectable	Injectable
Configuration		*1 mL fill in 2 mL clear glass ampul*	*10 mL fill in 10 mL Abboject™ clear glass syringe cartridge*
Route of Administration		Intravenous (Infusion)	Intravenous (Infusion)
Strength/Concentration for Administration to Patient		*1 mg/(b) (4) mL*	*1 mg/(b) (4) mL*
Indication(s)		To increase mean arterial blood pressure in adult patients with hypotension associated with septic shock.	To increase mean arterial blood pressure in adult patients with hypotension associated with septic shock.

[1]An additional amount may be added for pH adjustment.

Differences between Belcher's Epinephrine product and Hospira's Epinephrine product are italicized and highlighted in yellow.

To support the biowaiver request, the Applicant states the following:[5]

(1) The proposed test product delivers the same amount of drug to patient as that of the reference drug since both product have the same concentration of epinephrine when diluted in 1000mL of dextrose containing solution. Though the drug concentration in the proposed product is 1 mg/10 mL and the reference product is 1 mg/mL; however, after dilution with the same diluent (1000 mL of 5% dextrose containing solution), the epinephrine concentration in both products is similar (T – 0.9901 µg/mL and R – 0.999 µg/mL). This difference is considered insignificant since the drug is titrated to effect and

a slight difference will not impact the disposition, efficacy, or safety of the proposed drug product;

(2) The proposed test product is administered by the same route, has the same indication, and has the same method of use;

(3) The differences in excipients for the proposed product (presence of [redacted] sodium metabisulfite, and pH buffering agents citric acid anhydrous and sodium citrate dehydrate in the proposed test product) [redacted] is not expected to affect the product's disposition, safety or efficacy;

(4) Since both products are diluted prior to administration with the same diluent and to same concentration, the osmolarity of both products administered to the patients is equivalent;[8]

(5) The pH is the same for both products;[8]

Based on the above, the Applicant concluded that IV administration of the two products will result in an identical amount of drug delivered directly to the systemic circulation, and equivalent epinephrine plasma concentration profiles can be expected for the two products and no bioequivalence study is necessary.[5]

Though the Applicant's justification stated above in support of biowaiver seems adequate, the information is not complete for the review of biowaiver request and the following biopharmaceutics IR was sent to the Applicant:

a. It is acknowledged that osmolality (Pg # 34 under the section "Excipients") and pH (Table 41, exhibit batch # 66454SB [redacted]) information are submitted in the document titled "Drug Product" [0001(1) dated 01/31/2017;Module 3.2.P.2.; Drug Product). Clarify, if the osmolality value of 290mOsm/kg represents the final optimized formulation [redacted] and exhibit batch # 66454SB [redacted]

Applicant's Response[11] and Reviewer's Evaluation: *In response, the Applicant provided osmolality measurements for both the proposed test product [redacted] (3 batches) and [redacted] (1 batch) as well as the reference product (Table 2). The Applicant clarified that previously reported osmolality value for 290mOsm/kg represented the formulation [redacted]. The osmolality value for the batch 66-454-SB [redacted] is 287 mOsm/kg and is comparable to that of the reference drug product. The Applicant also stated that [redacted] does not affect the osmolality as values are very similar (Table 2).* ***The Applicant's response is adequate.***

[11] Global Submit – N209359 – 0003(3) dated 04/21/2017. Module 1.11.1. Information Request Response. (Accessed on August 25, 2017)

Table 2. Osmolality of Epinephrine Injection USP (Proposed test – Hospira, and Reference product - Belcher)[11,12]

Hospira Proposed Drug Product		RLD Belcher Product	
Exhibit Batch Number	Osmolality (mOsm/kg)	RLD Lot Number	Osmolality (mOsm/kg)
66-454-SB (b) (4)	287	15199	285
48-332-SB	290	16163	284
48-333-SB	289		
48-334-SB	290		

b. It is stated in the "Request for waiver of in vivo bioavailability studies" [0001(1) dated 01/31/2017; Module 1.12.15; pg # 4] that "since both products are diluted prior to administration with the same diluents and to essentially the same concentration, the osmolarity of both products administered to the patient remains equivalent. Further, the final pH of the diluted solution is the same for both products". The comparative pH and osmolality values on the diluted proposed and reference product could not be located. Provide comparative physicochemical properties (pH and osmolality) of your proposed product (b) (4) and the reference product after dilution with dextrose and if any difference is observed justify its impact on safety and efficacy of the proposed product.

Applicant's Response[11,12] and Reviewer's Evaluation: *In response, the Applicant provided pH and osmolality determinations for both the proposed drug product* (b) (4), *final formulation) and the reference drug product after dilution with 5% dextrose and 5% dextrose in saline (0.9% NaCl) as per the reference product package insert (Table 3). The Applicant concludes that osmolality of the diluted products are same and the difference of 0.5 pH units observed between the diluted proposed and reference drug product is insignificant and is not expected to have impact on safety and efficacy of the proposed product since the USP pH specification for the 5% dextrose injection is as wide as 3.2-6.5. Further, according to the Applicant, any pH difference in the two drug products would be irrelevant since the ionized state of the active ingredient is the same under the physiologic conditions encountered after administering the drug. In response to the drug product IR dated 07/12/2017 with respect to tightening of drug product (undiluted) pH specification from 2.2 - 5 (in accordance to USP 40-NF 35 S1 drug product monograph) to* (b) (4) *the Applicant proposed specification of* (b) (4) *with justification.[13] The newly proposed pH specification is tighter than the USP monograph requirements and provides better control strategy. Considering this and above,* ***the Applicant's response is adequate.***

[12] Global Submit – N209359 – 0003(3) dated 04/21/2017. **Module 3.2.P.2. Pharmaceutical Develpoment Report – Drug Product.** (Accessed on August 25, 2017)

[13] Global Submit – N209359 – 0012(12) dated 07/28/2017. **Module 1.11.1. Response to 12-July-2017 Information Request to NDA 209359 from US FDA.** (Accessed on September 01, 2017)

Table 3. Osmolality and pH of the Proposed Test [redacted] and Reference Drug Product After Dilution with 5% Dextrose Containing Solution (5% Dextrose or 5% Dextrose in Saline)[12]

Diluent	Osmolality (mOsm/kg)		pH	
	Proposed Product (Batch 66-454-SB [redacted])	Belcher RLD (lot 16163)	Proposed Product (Batch 66-454-SB [redacted])	Belcher RLD (lot 16163)
5% Dextrose	265	263	4.0	4.5
5% Dextrose and 0.9% Sodium Chloride	554	557	4.0	4.4

c. Provide justification that the differences in inactive ingredients between your proposed and the reference product do not impact disposition and efficacy of epinephrine in your proposed product.

Applicant's Response[11] and Reviewer's Evaluation: *In response, the Applicant stated the following:*

i. Sodium metabisulfite (0.46 mg/mL) is added in the formulation [redacted]

ii. Small amounts of citrate acid anhydrous (2.13 mg/mL) and sodium citrate dihydrate (0.41 mg/mL) are included as buffering agents [redacted]

iii. The concentration of sodium chloride (8.16 mg/mL) is slightly lower in the proposed test product in comparison to that of the reference product (9 mg/mL) [redacted]

iv. Inclusion of small amounts of sodium metabisulfite, citric acid, and sodium citrate in the formulation is permitted as per 21 CFR 314.94 (a)(9)(iii) for inactive ingredient changes permitted in drug products intended for parenteral use, as the changes are in [redacted] and in a pH buffer.

v. The concentration of sodium metabisulfite used [redacted] in commercially available epinephrine products are [redacted] mg/mL (EpiPen®) and [redacted] mg/mL (Adrenalin®) respectively for intramasuclar (IM) and subcutaneous (SC) administration. The Applicant based on comprehensive literature search did not find any report of potential effect of sodium metasbisulfite on the pharmacokinetics (PK) and/or efficacy of epinephrine.

vi. Based on the literature reference provided, according to the Applicant, comparing the amount of citric acid produced daily in human body, the amount of citric acid and

sodium citrate present in the proposed product are unlikely to affect the PK or efficacy of epinephrine. Specifically, citric acid, an essential endogenous intermediate produced in human cells, is present mainly as citrates. It is reported that the human body produces approximately 2 kg of citric acid daily. Citric acid is also present in a variety of foods. Further, the Applicant states that since the proposed product is intended for IV infusion after being diluted 100 times, the concentration of citric acid and sodium citrate in the diluted solution is 0.0213 mg/mL and 0.0041 mg/mL respectively. Based on the calculated concentrations and assuming a maximum infusion volume of 5000 mL for a day, the estimated daily dose for citric acid and sodium citrate would be approximately 107 mg (0.0213 mg/mL x 5000 mL = 106.5mg) and 21 mg (0.0041 mg/mL x 5000 mL = 20.5 mg), respectively which is very less than the amount produced in human body.

vii. The levels of the excipients in the proposed drug product, with and without dilution, are within the permitted limits listed in the FDA Inactive Ingredient Guide for the IV infusion route of administration.

The Applicant's above responses to the IR are adequate and support the conclusion that the differences in inactive ingredients will not affect the PK and efficacy of the proposed product. Further, the Applicant submitted detailed justification on the safety aspect of sodium metabisulfite[14] as advised by FDA given the possible risk of allergic hypersensitivity or anaphylactic reactions that are known to occur with sulfites in a letter dated Nov 21, 2016 during IND period[15]. The sodium metabisulfite safety justification report is found adequate by the Office of New Drugs (OND).[16] ***The Applicant's response is adequate.***

It was also noted during the review that the Applicant presents in Table 1 that epinephrine is present as hydrochloride salt in the reference drug product; whereas, in the proposed product, epinephrine is not present as a salt. However, based on the information in drug labeling, submission, drug product quality review, and drug master file (# (b) (4)) for the reference product, it also contains epinephrine and not epinephrine hydrochloride. Also, both the proposed and reference drug product is epinephrine injection USP product that contains epinephrine USP which is not a salt.

[14] Global Submit – N209359 – 0001(1) dated 01/31/2017. **Module 3.2.P.2. Pharmaceutical Development Safety Justification for Amount of Sodium Metabisulfite in Epinephrine Injection.** (Accessed on August 25, 2017)
[15] Global Submit – N209359 – 0001(1) dated 01/31/2017. **Module 1.6.3. Advice Information Request – Nov 21, 2016.** (Accessed on August 25, 2017)
[16] DARRTS – N209359 – REV-NONCLINICAL-21(Primary Review) dated 04/25/2017 by Dwivedi, Rama S. (Accessed on August 25, 2017).

Reviewer's Assessment: ***Adequate***

The proposed and reference drug product have comparable physicochemical properties (pH and osmolality). The differences in inactive ingredients are adequately justified by the Applicant and are not expected to impact disposition, safety, or efficacy of the proposed drug product. The request for biowaiver by the Applicant for the proposed Epinephrine Injection USP, 1 mg/10 mL (0.1 mg/mL), for intravenous infusion is granted.

R Regional Information

Comparability Protocols

Reviewer's Assessment: *Not Applicable.*

Post-Approval Commitments

Reviewer's Assessment: *None.*

Lifecycle Management Considerations

None.

List of Deficiencies

Deficiencies – None. All deficiencies or the IRs were addressed during the review cycle and are described in detail in the main body of the review under section "***Biowaiver Request***".

ONDP-Division of Biopharmaceutics reviewed NDA 209359 and responses to biopharmaceutics information requests. The NDA 209359 is recommended for Approval from a Biopharmaceutics perspective.

Primary Biopharmaceutics Reviewer Name and Date
Poonam Delvadia, Ph.D. (Branch 3\DB\ONDP\OPQ), September 1, 2017

Secondary Reviewer Name and Date (and Secondary Summary, as needed)
Kimberly Raines, Ph.D., Acting Branch Chief (Branch 3\DB\ONDP\OPQ), September 1, 2017

Poonam Delvadia

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Kimberly Raines

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MICROBIOLOGY

Product Background: -

NDA: 209359

Drug Product Name / Strength: Epinephrine Injection, USP/ 1 mg/10 ml (0.1 mg/ml)

Route of Administration: Intravenous injection

Applicant Name: Hospira Inc., a Pfizer company, 275 N. Field Dr., Lake Forest, IL 60045

Manufacturing Site: Hospira Inc., Highway 301 North, Rocky Mount, NC 27801

Method of Sterilization: (b) (4)

Review Summary: Recommended for Approval

List Submissions being reviewed: 1/31/2017, 5/25/2017, 6/16/2017 & 9/8/2017

Highlight Key Outstanding Issues from Last Cycle: N/A

Concise Description Outstanding Issues Remaining: Container closure integrity testing, environmental monitoring, holding periods, sterilization validation, endotoxin testing and post-dilution studies.

Supporting/Related Documents: N/A

Remarks Section: This is an eCTD submission. The review includes the responses to an information request sent on 8/13/2017. Some of the tables and diagrams in this review are adapted from the original submission.

S. Drug Substance

The drug substance is not provided as sterile; therefore, a microbiology review of the drug substance is not conducted.

P.1 Description of the Composition of the Drug Product

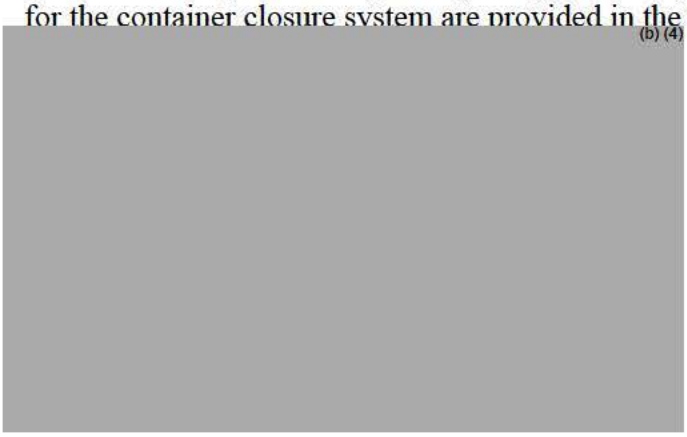
Drug product is a sterile aqueous solution presented in 10 ml clear vials (b) (4) glass vial and co-packaged with Hospira' s Abboject™ syringe. The drug product is intended for dilution with 5% dextrose or 5% dextrose and sodium chloride solution prior to administration.

Drug product composition:

Ingredient	Content mg/ml
Epinephrine	0.10
Sodium metabisulfate	0.46
Sodium chloride	8.16
Citric acid	2.13
Sodium citrate	0.41

(b) (4)

Description of the container closure system:
The drug product is supplied as 0.1mg/ml in the Abbject 10 ml glass vial and co-packaged with the sterile Abboject Vial Injector (see figure below). The descriptions and supplier information for the container closure system are provided in the table below.



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		
Cap	Cap, 10 mL Vial, (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		Hospira, Inc. Global Park Free Zone 1Km Noreste Del Centro Commercial Real Cariri La Aurora, Heredia Costa Rica

Acceptable

Reviewer's Assessment: The firm provided an adequate description of the drug product composition and of the container closure system, designed to maintain the drug product sterility. The drug product is a combination product, the Abboject vial is co-packaged with the Abboject Vial Injector. For the purpose of this review, the Abboject vial is considered the drug product and the Abboject Vial Injector is considered the device. Review of the relevant information for the sterility assurance of the Abboject Vial Injector device was performed by CDRH (John Stansberry, CDRH/ODE/DAGID/INCB, confirmed with ATL-Mohan Sapru on 7/31/2017). Therefore, this review does not evaluate any sterility assurance information associated with the Abboject Vial Injector.

P.2.5 Microbiological Attributes

Container/Closure and Package Integrity
(P.2.5 Microbiological Attributes)

"The 10 mL Abboject vial is comprised of a vial, yellow cap with a tortuous path, and a stopper inside the vial." The applicant performed container closure integrity of the 10 ml vial using two methods, aerosol challenge and microbial ingress. The aerosol challenge was performed to show the ability of the vial's cap to maintain sterility of the fluid path. The cap is designed (b) (4) The results for aerosol challenge and the microbial ingress tests are reviewed below.

Aerosol challenge:
The container closure system used for the studies is the same as proposed for production. Thirty media filled vials, as proposed for commercial production (with stopper and yellow cap) were subjected to the aerosol challenge with a minimum $1x10^3$ CFU/liter of air of *Staphylococcus sp* for 30 minutes. The vials were placed into the aerosol chamber and exposed to the aerosolized organism suspension, followed by 2 in Hg vacuum for 2 minutes. The controls used consisted of 2 negative controls, 2 growth promotion controls (PC2), 2 positive controls (PC1-cap removed prior to aerosol exposure) and 3 positive controls consisting of 3 closed petri plates with sterile filter paper inside (PC3). The test vials and the positive controls, PC1 and PC3, were placed in the chamber. After exposure, the outer surface of the vials was disinfected and the contents of each vial was aseptically ejected using an Abboject Injector into an empty sterile stoppered vial and the exposed filter paper was removed from the petri plates and placed in a 50 ml of Butterfiled's Buffer 1% Tween 80 and enumerated. All samples were incubated at 30-35ºC for 3 days. The vials were then visually inspected for growth and the PC3 control was enumerated. The acceptance criteria were not provided.

Results:
The test vials and the negative control showed no microbial growth; the positive control and growth promotion vials showed growth.

Microbial ingress:
The container closure system used for the studies is the same as proposed for production (Abboject 10 ml glass vials with stopper and yellow cap). Thirty media filled vials, without the cap, were immersed in a *S. marcescens* solution ($\geq 1x10^6$ CFU/ml). Prior to immersion the microbial solution was "pipetted into the space between the stopper and vial of each sample until the space was filled." The positive controls consisted of 4 vials pierced through the stopper with a 21 G needle; 4 vials were used as negative controls and 2 for growth promotion. The test and positive control vials were submerged in the microbial solution for 24 hours at room temperature; two negative control vials were kept at room temperature and the 2 were subjected to ≥7 in of Hg for 10 minutes. The outer surface of the vials was disinfected and the vials were incubated at 30-35ºC for 7 days. The vials were then visually inspected for growth. The acceptance criteria were not provided.

Results:

The test vials and the negative control showed no microbial growth; the positive control and growth promotion vials showed growth.

Information Request:
The following information request was sent on 8/13/2017:

The information and testing results for the integrity of the container closure system, by aerosol challenge and microbial ingress, are acknowledged. However, the acceptance criteria used for the aerosol challenge and microbial ingress studies cannot be located. Provide this information.

Information Request Response:
The following information request response was received on 9/8/2017:

The firm provided the acceptance criteria for the aerosol challenge and microbial ingress test. These are described below.

Acceptance criteria for the aerosol challenge:
-The yellow cap with tortuous path on the 10 ml Abbject vial must maintain sterility of the fluid pathway in response to the aerosol challenge by demonstrating absence of the challenge organism (*Staphylococcus sp.)* in the test samples.
-Positive controls and growth promotion samples must show growth; negative controls must show no growth. The growth promotion inoculum must be < (b) (4) CFU per sample.
-The average challenge concentration of *Staphylococcus sp.* In the aerosol challenge must be a minimum of 1x (b) (4) CFU/L of aerosol.

Acceptance criteria for microbial ingress:
-The container closure system must maintain sterility of the contents in response to the immersion challenge by showing absence of the challenge organism (*S. marcescens*) in the test samples.
-Positive controls and growth promotion samples must show growth; negative controls must show no growth. The growth promotion inoculum must be < (b) (4) CFU per sample.
-The *S. marcescens* suspension must be a minimum of 1x (b) (4) CFU/ml.

Acceptable

Reviewer's Assessment: The container closure integrity testing performed by microbial ingress and aerosol challenge are deemed adequate.

Antimicrobial Effectiveness Testing
Not applicable. The drug product is not preserved and indicated to be used as single-use.

P.3 Manufacture

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LABELING

R Regional Information

1.14 Labeling

Immediate Container Label

The revised container label is provided under section 1.14.11 of eCTD seq. 0012, dated 28-Jul-2017.

(b) (4)

Reviewer's Assessment: Adequate

During the review cycle, the Sponsor made the following change to the container label:

- *Replaced* (b) (4) *with 'Single-dose'.*

Please note that the container label has vertical graduation mark. Given that all content of the vial is diluted prior to infusion, graduation mark is not required for this drug product. However, according the Sarah Thomas, DMEPA reviewer, this product has been on the market as an unapproved product since 1985. Therefore, in order to minimize the risk of unintended clinical consequences, she recommends retaining the graduation mark (email dated 6-Sep-2017). This reviewer concurs with her suggestion.

In summary, the revised container label meets the labeling requirements.

Carton Labeling

The vial containing the drug product and the Abbject syringe are co-packaged in the following carton. Additionally, the cartons are shrink-wrapped in packs of 10 and a print-on-demand sticker is applied to the front side of each bundle. The revised carton label is provided under section 1.14.11 of eCTD seq. 0012, dated 28-Jul-2017. The print-on-demand sticker for the bundle configuration is provided under section 1.11.1 of eCTD seq. 0010, 28-Jun-2017.

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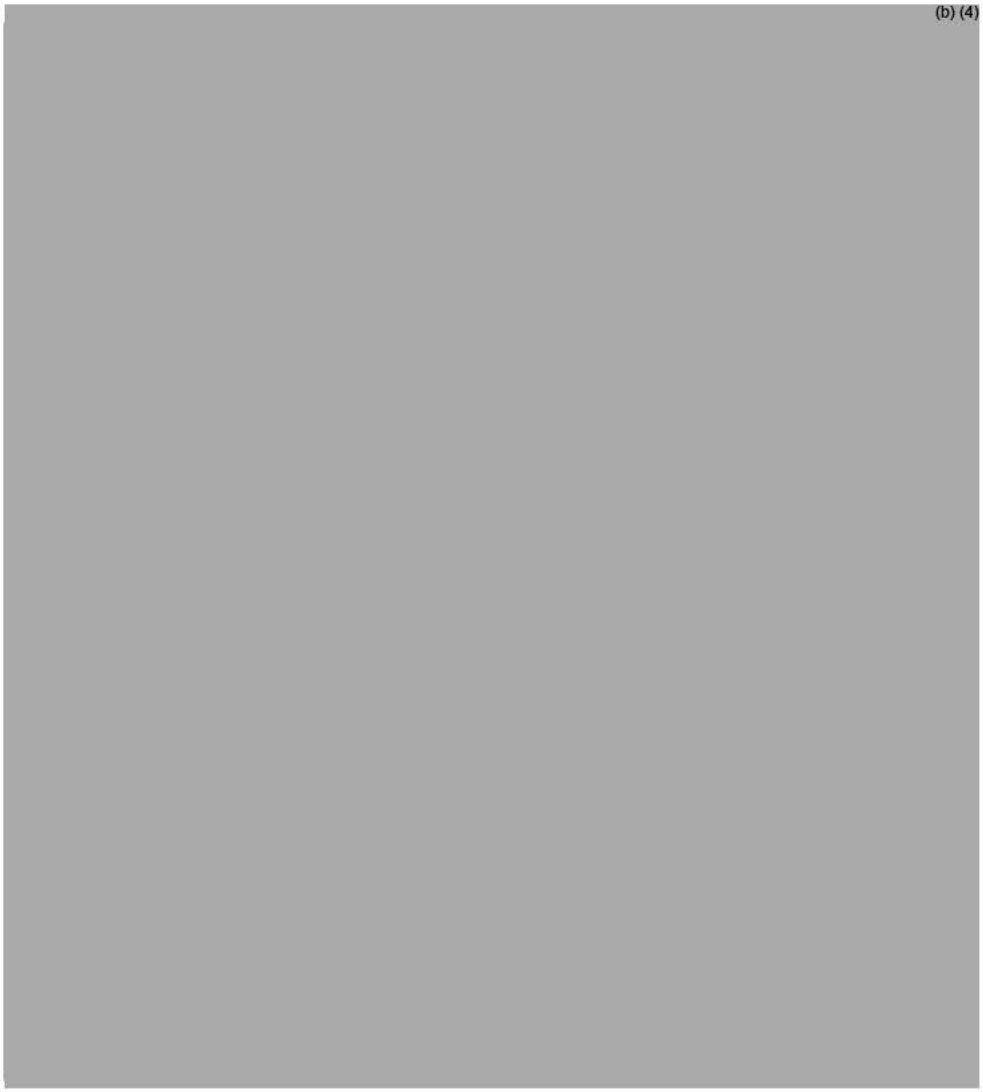
Figure 2.



Reviewer's Assessment: Adequate

The Sponsor made the following edits during the review cycle:

- Listed the excipients in alphabetical order
- Revised the excipient amounts to match what is provided under section 3.2.P.1
- Replaced [redacted] (b) (4)' with 'Single-dose unit'.
- Edited the storage condition from 20 to 25°C (68 to 77°F) to 20°C to 25°C (68°F to 77°F)

Additionally, we asked the Sponsor to justify the usage of the terms [redacted] (b) (4)' and [redacted] (b) (4) Abboject™' that were printed in the primary display panel of the initial version. However, the Sponsor opted to remove these two trade dresses. In a response to information request under eCTD seq. 0016, dated 22-Sep-2017, the Sponsor asserted that the removal of the trade dress

(b) (4)' from the labeling is not likely to cause any medication error. DMEPA has no objection to removing this trade dress.

The Sponsor also makes the following statement: *'ABBOJECT' is the registered trademark for the device system of this combination product, the usage of the trade dress of 'ABBOJECT' in the carton labeling is considered justified.* This reviewer agrees with the Sponsor. Therefore, the use of the trademark name 'ABBOJECT' is justified.

To the best of this reviewer's knowledge, the term (b) (4) Syringe' printed just below ABBOJECT on the primary display panel is not a regulatory term. However, the Agency has approved at least three NDAs that have the same Abboject syringe (see table below). Therefore, based on the prior use history of the unapproved product and the approved ANDAs, this is acceptable to this reviewer.

Previously approved products that are co-packaged with Abboject syringes

Application #	Drug	eCTDSeq, date	Action Date	Link
ANDA 202495	Sodium Bicarbonate, 8.4%	0008, 02/05/2016	03/06/2017	Carton, container
ANDA 202679	Sodium Bicarbonate, 4.2%	0008, 01/22/2016	03/07/2017	Carton, container
ANDA 202494	Sodium Bicarbonate, 7.5%	0007, 02/12/2015	03/06/2017	Carton, container

In summary, the revised container meets the labeling requirement.

List of Deficiencies: *None*

Primary Reviewer: Mariappan Chelliah (see below for date)

Secondary Reviewer: Wendy Wilson-Lee (see below for date)

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Wendy Wilson- Lee

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Chemistry Assessment Section

Initial Risk Assessment: NDA 209359 (Epinephrine Injection, USP)

Product Attribute/ CQA	Factors Affecting CQA	Probability (O)	Severity of Effect (S)	Detectability (D)	FMECA RPN Number*	Comment
Sterility	Formulation Container Closure Process Parameters Scale/Equipment/ Site	4	5	5	**100**	Potential failure mode: i.e., non-sterile units, and control strategy for assuring product sterility will need to be closely examined.
Endotoxin Pyrogen	Formulation Container Closure Process Parameters Scale/equipment/ Site	2	4	4	**32**	Potential failure mode i.e., excessive endotoxin levels, and sterility testing validation will be closely examined.
Assay (API), Stability	Formulation Container Closure Raw Materials Process Parameters Scale/Equipment/ Site	3	2	1	**6**	Evaluation of API stability will address concerns regarding the potential failure modes such as degradation, and impurity formation.
Assay (b) (4)	Formulation Raw materials Process parameters Scale/equipment/ site	3	2	3	**18**	The product involves the use of (b) (4) Potential failure mode i.e., decrease in potency will be closely examined.
Uniformity of Dose – Fill/deliverable Volume	Formulation Container Closure Process Parameters Scale/equipment/ site	2	2	2	**8**	Potential failure mode i.e., insufficient dose will be evaluated.
Osmolality	Formulation Raw materials Process parameters Scale/equipment/ site	2	3	2	**12**	Osmolality testing and acceptance limits need to be closely examined to address potential failure modes i.e., irritation; edema.
pH (b) (4)	Formulation Container Closure Raw materials Process parameters Scale/equipment/ site	3	4	1	**12**	(b) (4)

Chemistry Assessment Section

Product Attribute/ CQA	Factors Affecting CQA	Probability (O)	Severity of Effect (S)	Detectability (D)	FMECA RPN Number*	Comment
Particulate Matter	Formulation Container Closure Raw materials Process parameters Scale/equipment/ site	3	5	3	**45**	Given the failure mode i.e., bioavailability, the particulate matter testing will need to be carefully evaluated.
Leachable Extractables	Formulation Container Closure Raw materials Process parameters Scale/equipment/ site	2	4	3	**24**	Potential failure mode i.e., generation of impurities due to extractables and leachables has been addressed in the pharmaceutical development section.
Appearance	Formulation Raw materials Process Parameters Scale/equipment/ site	3	3	1	**9**	Potential failure modes i.e., degradation, and contamination are addressed by product specification.

* RPN ≤ 25: Low risk

* RPN > 25 and ≤ 60: Moderate Risk;

* RPN > 60: High Risk

Mohan K. Sapru -S

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