

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

207534Orig1s000

PRODUCT QUALITY REVIEW(S)

LABELING**R Regional Information****1.14 Label/Labeling*****Immediate Container Label (Syringe, safety tab and actuator)***

(b) (4)

Reviewer's Assessment: Inadequate.

To comply with the labeling requirements for drugs 21CFR §201.10(i), which provided for exemption of information required for compliance with section 502(e)(1)(A)(ii) and (B) of the FD&C Act when the drug was packaged in a container too small or otherwise unable to accommodate a label with sufficient space, the label should at the minimum bear the proprietary and established names, lot number and expiration date, name of the manufacturer, packer, or distributor; and all the information required to appear on the label by the act and the regulations appears on the carton or on a leaflet with the package.

Case Label

Reviewer's Assessment: Adequate

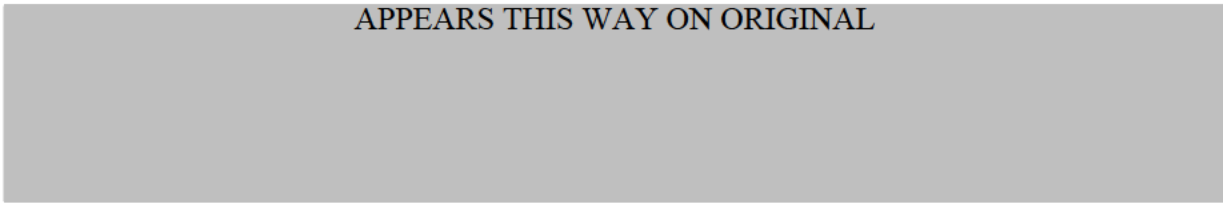
The case holds a prefilled syringe and a leaflet with instructions for use, (b) (4).

Carton Label (Single pack and Two Pack)

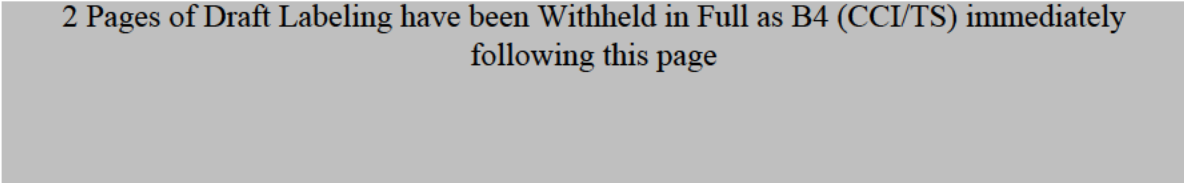
The case containing prefilled syringe and instructions for use are packaged in a carton either as a single case or two cases (b) (4). The outer carton proposed for each of the two packaging configurations must contain all required labeling information per 21 CFR 201.10(i) and other applicable provisions of the FD&C Act.

Two Pack Carton

APPEARS THIS WAY ON ORIGINAL



2 Pages of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page



Single pack Carton

(b) (4)

Reviewer's Assessment: Inadequate.

Complete drug information wasn't provided on the outer cartons (two packaging configurations proposed) per the applicable provisions of the FD&C Act and 21 CFR 201.10(i).

Names of all inactive ingredients, Quantitative ingredient information [21CFR 201.10(a), 201.100(b)(5)(iii)] and Sterility Information is required for injectables, but was not provided.

The statements indicating the Route of Administration per 21 CFR 201.100(b)(3) and “See package insert for dosage information” per 21 CFR 201.55 are missing on the outer carton.

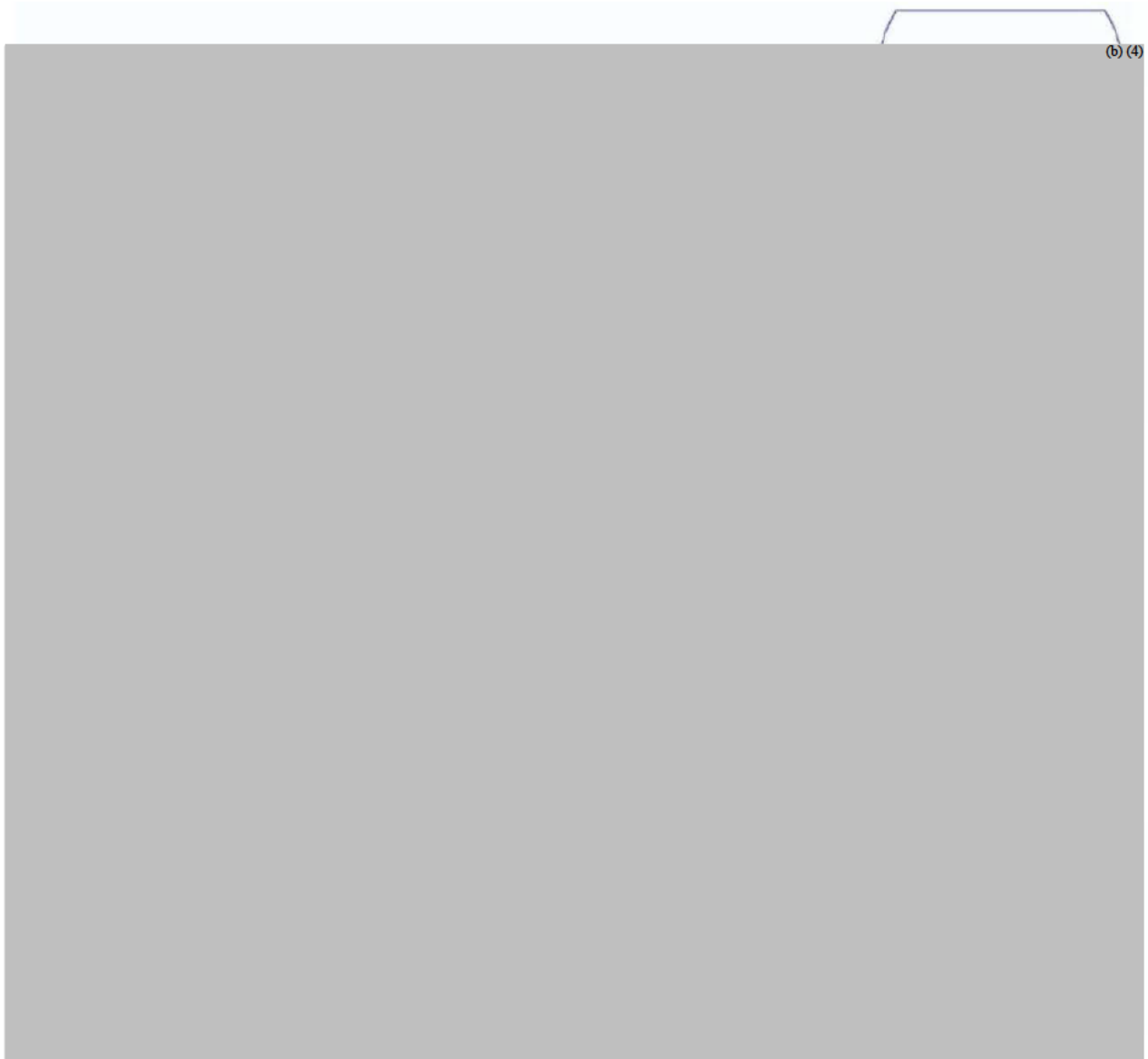
Proprietary name, established name font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2)); Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4)); Net contents (21 CFR 201.51(a)); Lot number per 21 CFR 201.18; Expiration date per 21 CFR 201.17; “Rx only” statement per 21 CFR 201.100(b)(1); Storage Conditions; NDC number (per 21 CFR 201.2); Bar Code per 21 CFR 201.25(c)(2); and Name of manufacturer/distributor were included on the carton.

Box Label

The outer box contains either six two pack units or six single pack units’ cartons.

Symjepi 2-pack, 6-pack outer:



Symjepi Single-pack, 6-pack outer:**Reviewer's Assessment: Adequate.**

Complete information was provided on the two boxes (containing either 2x6 or 1x 6 cases) per the applicable provisions of the FD&C Act and 21 CFR 201.10(i).

The required warning statements on the label, per 21 CFR 201.22(c) for sulfite-containing epinephrine for injection for use in allergic emergency situations was not provided.

Proprietary name, established name font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2)); Strength (21CFR 201.10(d)(1); 21.CFR

201.100(b)(4)); Net contents (21 CFR 201.51(a)); Lot number per 21 CFR 201.18; Expiration date per 21 CFR 201.17; “Rx only” statement per 21 CFR 201.100(b)(1); Storage Conditions; NDC number (per 21 CFR 201.2); Bar Code per 21 CFR 201.25(c)(2); and Name of manufacturer/distributor were included on the carton. Names of all inactive ingredients, Quantitative ingredient information [21CFR 201.10(a), 201.100(b)(5)(iii)] was provided. The statement “Read patient package carefully before using” (21 CFR 201.55) was given on the boxes.

Patient Instruction

(b) (4)

Reviewer’s Assessment: Acceptable from CMC perspective.

The instructions for use of the prefilled syringe for use by individual patients or by standers are reviewed by DMEPA.

Package Insert / Prescribing Information (PI) Labeling

For proposed Prescribing Information (PI) Highlights, sections 3, 11, and 16, see 14-MAR-2017, amendment 26, and module 1.14.2.3.

Reviewer’s Assessment: Adequate.

The drug product name as included in the PI is “SYMJEPI (epinephrine) Injection, (b) (4) for intramuscular or subcutaneous use” is acceptable from CMC perspective. The statement in highlights and section 3 of the PI, under DOSAGE FORMS AND STRENGTHS section

(b) (4) is adequate [21 CFR 201.57(c)(4)].

As per 21 CFR 201.57(c)(12), the DESCRIPTION section (11) of the PI includes the proposed proprietary and the established name of the drug product as well as the dosage form and route of administration. The drug contents are given as per the label, and all of the inactive ingredients are also listed in this section [see 21 CFR 201.100(b)(5)]. This section lists the therapeutic class the chemical name and structural formula.

The strength was listed adequately in the HOW SUPPLIED/STORAGE AND HANDLING section of the PI (b) (4) The Storage and Handling information given both in section 16: HOW SUPPLIED/STORAGE AND HANDLING and section 17: PATIENT COUNSELING INFORMATION is adequate from CMC perspective.

List of Deficiencies:

Labeling:

1. Provide revised text for the prefilled syringe label with Manufacturer / Distributor name included [See 21 CFR 201.10(i)].
2. Provide revised text for Carton Labels for both Single pack and Two Pack that includes Names of all inactive ingredients and Quantitative ingredient information, which is required for injectables [See 21 CFR 201.10(a), 21 CFR 201.100(b)(5)(iii)] on the outer package, when it was not possible to include such complete composition information on the primary container [See 21 CFR 201.10(i)].

Primary Labeling Reviewer Name and Date: Venkateswara R. Pavuluri, Ph. D., R. Ph.;
04-MAY-2017

Secondary Reviewer Name and Date (and Secondary Summary, as needed): Julia C. Pinto,
Ph. D.



**Venkateswara
Pavuluri**

Digitally signed by Venkateswara Pavuluri
Date: 5/12/2017 08:20:46AM
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**Julia
Pinto**

Digitally signed by Julia Pinto
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Memo to Quality Review # 2 for NDA 207534

EPINEPHRINE INJECTION, USP (b) (4)

Review of Responses to Complete Response Letter Dt. 30-JUN-2016

I. Administrative Information

Date: 18-APR-2017
Description: Response to CRL 3941301, Resubmission
NDA number: 207534
Established name: Epinephrine Injection, USP (b) (4)
Proposed proprietary name: Symjepi
Dosage form and strength: Injection; Pre-filled single dose syringe (b) (4)
(0.3 mg/0.3 ml)
Indication: Emergency treatment of allergic reactions
(Type I) including anaphylaxis

Background Information: Through the complete response (CR) letter dated June 3, 2016, sponsor was advised to conduct additional human factors and usability assessment studies that include formative evaluation and human factor validation testing and provide adequate data to support the safe and effective use of the prefilled syringe. In addition to the deficiency identified, FDA had comments regarding the reliability, sharps injury prevention failure rate, and biocompatibility tests conducted.

SUBMISSION(S) BEING REVIEWED:

Submission(s)	Document Sequence (Amendment)	Date
Meeting Request (Type A)	0018 (19)	02-SEP-2016
Response to Complete Response	0021 (22)	15-DEC-2016
Quality Information	0025 (26)	14-MAR-2017

3.2.P.1 DESCRIPTION AND COMPOSITION OF THE DRUG PRODUCT

[EPINEPHRINE INJECTION, USP (b) (4)]

3.2.P.1.1. Description of the Dosage Form

EPINEPHRINE INJECTION, USP (b) (4) is a solution for injection in a prefilled syringe. Each pre-filled syringe is intended for single-use, and delivers a single dose of (b) (4) Epinephrine (b) (4). A (b) (4) percent overage of the active substance, epinephrine base, is included in the formulation. The solution for injection is ready to use and does not require dilution or reconstitution.

3.2.P.1.2. Composition of the Dosage Form

Start of sponsor material:

Table 3.2.P.1-1 Composition of the dosage form

Component	Quantity of syringe contents (mg/ml)	Quantity per dose (mg/0.3 mL)	Function	Reference to Standard
(b) (4) (Epinephrine) Base	(b) (4)	(b) (4)	Active	USP

Sodium Chloride	(b) (4)	1.8	(b) (4)	USP
Sodium Metabisulfite		0.50		USP NF
Hydrochloric Acid	(b) (4) pH 2.2 to 5.0 ²	(b) (4) pH 2.2 to 5.0 ²	pH Modifier	USP NF
Water for Injection			(b) (4)	USP

1 - Labeled active content is 1.0mg/mL, formulation includes (b) (4)% overage
2 - pH range included in the finished product specification is 2.2 to 5.0

End of sponsor material

3.2.P.1.4. Container and Closure System

The pre-filled syringe consists of a 1 mL standard glass syringe barrel sealed at one end by a rubber plunger stopper, and at the other end fitted with a 25 G5/8" injection needle, covered by a rigid needle shield. The pre-filled syringe constitutes the primary packaged product.

The plunger rod assembly, which constitutes the secondary packaging, is subsequently fitted to the pre-filled syringe. (b) (4)

The transparent view window allows the patient or caregiver to check for drug discoloration. It also includes a needle guard that can be manually deployed after injection. Delivery of the dose is achieved by manually depressing the plunger rod. Further details on the container closure system were provided, in section 3.2.P.7.

Each pre-filled syringe of EPINEPHRINE INJECTION was proposed to be packaged into a plastic carrying case with a patient information leaflet. Individual plastic carrying cases are further assembled into two-packs which in turn are packed, along with a prescribing information leaflet into a cardboard carton.

Start of sponsor material





End of sponsor material

Reviewer Evaluation: Adequate.

(b) (4)

(b) (4)



3.2.P.2 PHARMACEUTICAL DEVELOPMENT

(b) (4)



Components in redesign

(b) (4)



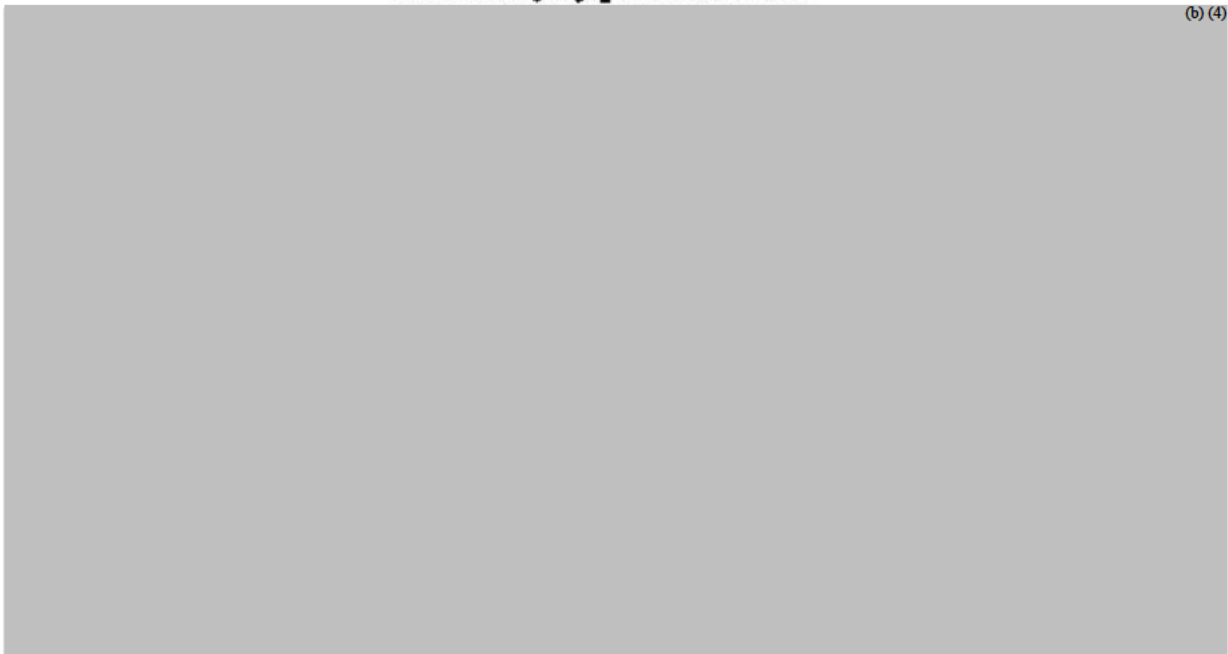
Redesign assembly sequence

(b) (4)



Revised Symjepi device labels

(b) (4)



Demonstration testing requirements and acceptance criteria

Requirement	Acceptance criteria
Device to deliver an accurate dose over a variable actuation speed	Plunger Rod to lock in the down position after actuation when subject to the return force (b) (4) ((b) (4) N max)
Users shall have the ability to determine when a full dose is delivered	Device to have: 1. Audible click at end of stroke 2. Tactile snap at end of stroke
Users shall have the ability to determine when a full dose is delivered	Device to have a positive stop at the end of stroke
Drug to remain stable to point of use	Drug to be protected from visible Light exposure while in the case. UV protection is not required.
Users cannot readily alter the dose	Device prevents inward movement of the plunger rod prior to use when held in the case
Users can check the device for drug discoloration prior to use	View window in the device with complete see through
Users to have limited view of remaining drug in the device and the (b) (4) bubble to prevent user confusion	View window to drug positioned to minimize visibility to (b) (4) bubble and remaining drug
Product to have IFU and Labeling at the point of use	Device to have front and back labels
Product to have IFU and Labeling at the point of use	Device labels to have Lot # and expiration date
Product to have IFU and Labeling at the point of use	(b) (4)
Product to have IFU and Labeling at the point of use	(b) (4)
Product to have IFU and Labeling at the point of use	IFU to be retained with the device or case
User shall be able to readily carry two devices for repeat doses	(b) (4)

End of sponsor material

Reviewer Comment: Acceptable. The minor design changes proposed to the (b) (4) (b) (4) added user instructions are intended to facilitate safe use of the device (b) (4). The design verification and validation program results support proposed target deliverable volume of 0.30 mL, with a lower limit of (b) (4) mL and an upper limit of (b) (4) mL.

3.2.P.7.1 CONTAINER CLOSURE SYSTEM

EPINEPHRINE INJECTION is primary packaged (b) (4) into a pre-filled single dose syringe consisting of a sterilized glass syringe (Type I) with attached needle, protected by a rigid needle shield and a sterilized plunger stopper. (b) (4)

The specifications and suppliers for primary packaging components are the same as in the previous submission. Supplier's certificate of conformance and technical drawing (b) (4) were included in the submission. (b) (4)

Delivery of the dose is achieved by manually depressing the plunger rod. (b) (4)

Reviewer Evaluation: Adequate. (b) (4)

Refer CDRH and Pharm. Tox. reviews for evaluation of the Biocompatibility testing, and in vitro cytotoxicity, irritation and delayed hypersensitivity test results.

Overall Conclusions: The (b) (4) corresponding design verification /validation test data generated (b) (4) support effective delivery of the target dose of epinephrine injection, i.e. 0.30 mL with a lower limit of (b) (4) mL and an upper limit of (b) (4) mL, when used as per the Instructions for Use (IFU) and directions on the case labels. Thus the NDA 207534 submitted under section 505(b)(2) of the FD&C Act, is recommended for approval from Quality (CMC) perspective.

A. Reviewer's Signature

Electronic signatures at the end of the document

B. Endorsement Block

Reviewer Name/Date: **Venkateswara R. Pavuluri, Ph.D.; 18-APR-2017**

Secondary Reviewer Name/Date: **Julia C. Pinto, Ph.D.; 19-APR-2017**



**Venkateswara
Pavuluri**

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**Julia
Pinto**

Digitally signed by Julia Pinto
Date: 4/19/2017 12:24:17PM
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NDA-207534-ORIG-1-RESUB-12 » Manufacturing Facility Inspection

Overall Manufacturing Inspection Recommendation

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Task Summary Task Details Issues Updates **Inspection Management Form**

As of May 26, 2016 6:05 pm GMT

Edit Task | Task Actions

Assigned To

Juandria Williams

Edit Assignment

This was done on

May 23, 2016

(3 days ago)

Status

Complete

Requested by

Grace McNally

This task is waiting on

Facilities

Last Update

May 23, 2016

Submitted On

Dec 8, 2015

Reference Number

6299942

Inspection Management Form

NDA-207534-ORIG-1-RESUB-12

- (b) (4) | (b) (4) | CTL CONTROL TESTING LABORATORY | Approve
- (b) (4) | Approve Facility +
- (b) (4) | (b) (4) | (b) (4)
- (b) (4) | Approve Facility +
- (b) (4) | CTL CONTROL TESTING LABORATORY | Approve Facility +
- (b) (4) | Approve Facility +
- (b) (4)
- Approve Facility +
- ADAMIS PHARMACEUTICALS CORPORATION | 3011688328 | CTL CONTROL TESTING LABORATORY | -
- ADAMIS PHARMACEUTICALS CORPORATION | 3011688328 | DNA DEVICE KIT ASSEMBLER | Approve Facility +
- (b) (4)
- (b) (4) FACILITY PROFILE CANCELLED -
- (b) (4)
- (b) (4) FACILITY PROFILE CANCELLED -
- (b) (4)
- FACILITY PROFILE CANCELLED -

Overall Manufacturing Inspection Recommendation

- Approve
- Withhold

Cancel

Submission Manufacturing Facilities

Facility Status	Completion Date	Project Name	FEI	DUNS	Global ID	Facility Name
Approve Facility	5/23/2016	NDA-207534-ORIG-1-RESUB-12	3011688328	618661680	256689	ADAMIS PHARMACEUTICALS CORE
Cancelled						(b) (4)
Approve Facility						(b) (4)
Cancelled						(b) (4)
Approve Facility						(b) (4)
No Further Evaluation	3/11/2016	NDA-207534-ORIG-1-RESUB-12	3011688328	618661680	256689	ADAMIS PHARMACEUTICALS CORE
Cancelled						(b) (4)
Approve Facility						(b) (4)
Approve Facility						(b) (4)
Approve Facility						(b) (4)
Approve Facility						(b) (4)

Project Name	Established Name	Project Proprietary Name	Drug Strength	GD/TA Goal Date	Project OND PDUA Goal Date	Significant Findings	Facility #	Facility Name
NDA 207534-Orig1-NewNDA(1)				3/28/15		Pending		(b) (4)
NDA 207534-Orig1-NewNDA(1)				3/28/15		Pending		
NDA 207534-Orig1-NewNDA(1)				3/28/15		Pending		
NDA 207534-Orig1-NewNDA(1)				3/28/15		Pending		
NDA 207534-Orig1-NewNDA(1)				3/28/15		Pending		

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Request	Request	Request	Request	Request	Request	Request	Request
(b) (4)				Recommendation	based on extension request from Linde Ag.	Recommendation	Acceptable based on extension request (per email from Linde)
						Approve Facility	Approve Facility

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DO Recommendation	Decision	DOF Recommendation	DOF Review Date	DOF Recommendation	Comments	Office of Process and Facilities - DOF Recommendation	Reasons
based on extension request from Linda Ivy, acceptable based on extension request (per email from Linda)		Approve Facility		(b) (4)		Based on File Review	
PREVIOUS GMP E1 UNDER THE DEVICE PAC DATED (b) (4) IS CLASSIFIED NAI. P		Approve Facility				Based on File Review	
		Approve Facility				District Recommendation	
		Approve Facility				PROFILE Based on Profile	
		Approve Facility				PROFILE Based on Profile	

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SRP Remedial Action	SRP Remedial Action	Office of Management & State
Complete	1/27/2015 Approve Facility	Complete
Complete	1/27/2015 Approve Facility	Complete
Complete	11/14/2014 Approve Facility	Complete
Complete	11/14/2014 Approve Facility	Complete
Complete	11/14/2014 Approve Facility	Complete

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NDA 207534

Epinephrine Injection, USP, 1 mg/mL (b) (4)

Adamis Pharmaceuticals Corporation

Venkateswara R. Pavuluri, Ph. D., R. Ph.

**Division of New Drug Products II for
Division of Pulmonary, Allergy, and Rheumatology Products**

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Chemistry Review Data Sheet

1. **NDA 207534**

2. **REVIEW #: 2**

3. **REVIEW DATE: 30-APR-2016**

4. **REVIEWER: Venkateswara R. Pavuluri, Ph. D., R. Ph.**

5. **PREVIOUS DOCUMENTS:**

<u>Previous Documents</u>	<u>Document Date</u>
Original Submission	28-May-2014
Correspondence (C)	08-OCT-2014
Amendment (BC)	28-NOV-2014
Amendment (BC)	20-JAN-2015
Amendment (BC)	06-FEB-2015
CMC Review of NDA 207534 (1 st Review)	23-FEB-2015
Agency's Complete Response	27-MAR-2015

6. **SUBMISSION(S) BEING REVIEWED:**

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Meeting Request (Type A)	19-JUN-2015
Response to Complete Response	04-DEC-2015
Response to Request for Information	15-MAR-2016
Response to Request for Information	31-MAR-2016

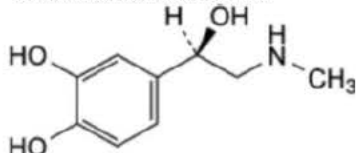
7. **NAME & ADDRESS OF APPLICANT:**

Name: Adamis Pharmaceuticals Corporation
Address: 11682 El Camino Real, Suite 300
San Diego CA 92130
Representative: Dr. Dennis J. Carlo
Telephone: (858) 412 7943

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:a) **Proprietary Name:** Symjepib) **Non-Proprietary Name (USAN):** Epinephrine Injection, USP, 1 mg/mL (b) (4)**9. LEGAL BASIS FOR SUBMISSION:** 505(b)(2)**10. PHARMACOL. CATEGORY:** Sympathomimetic**11. DOSAGE FORM:** Injection; Pre-filled single dose syringe.**12. STRENGTH/POTENCY:** 0.3mg per dose; 1 mg/mL (b) (4)**13. ROUTE OF ADMINISTRATION:** intramuscular, subcutaneous**14. Rx/OTC DISPENSED:** Rx OTC**15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):** SPOTS product – Form Completed Not a SPOTS product**16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:**Chemical Name: (-)-3,4-Dihydroxy- α -[(methylamino)methyl]benzyl alcohol (CAS)

Structural Formula:

Molecular Formula: $C_9H_{13}NO_3$

Relative Molecular Mass: 183.2 g/mol.

17. RELATED/SUPPORTING DOCUMENTS:

Chemistry Review Data Sheet

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	3	Adequate	06/24/2014	Shastri Bhamidipati
	III			7	Adequate	6/16/2008	Found syringe adequate for approved injection product
	III			7	Adequate	01/04/2008	Found the stopper adequate for approved injection product

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

ONDP:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	1/27/2015	
Pharm/Tox	Acceptable	10/27/2014	Dr. Jane J. Sohn
Biopharm	Acceptable	11/05/2014	Dr. Assadollah Noory
LNC	N/A		
Methods Validation	N/A, according to the current ONDP policy		

Chemistry Review Data Sheet

DMEPA	Trade name Acceptable HF studies – Final Report Pending		
EA	Categorical exclusion acceptable (see review)		Dr. Ying Wang
Microbiology	Acceptable	1/16/2015	Dr. Vinayak B. Pawar
CDRH (Device)	Pending responses to IR (4/21/2016, 4/25/2016)		

Note: CDRH Device review division was consulted by the clinical division (OND/DPARP) due to a concern that the newly designed device components may functionally impact the robustness of the device compared to simple pre-filled syringe.

The Chemistry Review for NDA 207534

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This class 2 resubmission of NDA 207534 is for Epinephrine Injection, USP (b) (4) as a single dose (0.3 mg / 0.3 mL) Pre-filled syringe. The prefilled syringe is fitted with (b) (4) plunger rod (b) (4) for controlling the delivered volume within acceptable range of label claim, i.e. 0.3 mL $\pm$ (b) (4) %.

The specification for (b) (4) content in the drug substance were revised to meet the Ph. Eur specification adopted by the drug substance manufacturer. A regulatory analytical method was included in resubmission for determining the extractable volume and is now part of the revised drug product specification. The data available up to six months from additional stability studies focused on deliverable volume, integrity and sterility of syringes (b) (4) (b) (4) is acceptable. Thus the NDA as resubmitted under section 505(b)(2) of the FD&C Act, is recommended for approval from Quality (CMC) perspective.

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

N/A

II. Summary of Chemistry Assessments

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

- Drug Substance:** Drug substance epinephrine is a white to off-white crystalline powder. It is very slightly soluble in water and ethanol. With acid it forms salts that are readily soluble in water. It darkens on exposure to light and air. Drug substance information was referenced in DMF (b) (4) for which (b) (4) is the holder.
- Drug Product:** EPINEPHRINE INJECTION, USP, (b) (4) is a sterile solution for injection supplied in Pre-filled single dose syringe. Each pre-filled syringe contains approximately 0.8 mL Epinephrine solution (1 mg / mL), designed for single use to deliver 0.3 mL dose by subcutaneous or intramuscular routes for self-administration by the patient or care giver. (b) (4)

Chemistry Assessment Section

(b) (4)

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

Epinephrine Injection, USP (b) (4) is indicated in the emergency treatment of allergic reactions (Type I) including anaphylaxis and is intended for immediate administration in patients who are determined to be at increased risk for anaphylaxis, including individuals with a history of anaphylactic reactions. Epinephrine pre-filled syringe is to be injected intramuscularly or subcutaneously into the anterolateral aspect of the thigh, through clothing if necessary by patients or caregivers under non-medically supervised environment. Each pre-filled syringe is a single-use injection.

C. Basis for Approvability or Not-Approval Recommendation

Epinephrine pre-filled syringe is a one-time use device and is intended to be used by patients or caregivers under non-medically supervised environment. The deliverable volume is a critical quality attribute of this drug/device combination product. The target value for the deliverable volume should be around labeling claim (0.3 mL) with limit within a narrow range of the target value. The original drug/device combination product as submitted was targeted to deliver a volume (b) (4). (b) (4) Based on these observations a complete response (CR) letter was sent to sponsor, advising to redesign the pre-filled syringe to deliver a target volume of 0.3 mL with narrow acceptance criteria. Refer to CR letter of the Agency, dated Mar 27, 2015 for additional details.

(b) (4)

A regulatory analytical method for determining the extractable volume was proposed and is now part of the drug product specification. Comparative data provided for

Chemistry Assessment Section

justifying the use of alternate method for determining the extractable volume at (b) (4) the drug product manufacturing site is acceptable. Validation and performance data (Average deliverable volume, standard deviation, and minimum and maximum volume delivered) from the device (b) (4) are provided. A regulatory method for determining the content of the final drug product, in addition to the alternate method used during manufacturing prior to device assembly.

The drug substance specification and test procedures were revised in this resubmission to i) update the limits for content of (b) (4) meeting the limits as specified by the manufacturer (b) (4) and current ICH Q3A guideline. ii) include the test for residual solvent (b) (4) and iii) update the appearance and solubility acceptance criteria. The revised specification for the drug substance is deemed adequate to support the quality of the drug product. Thus the responses to the three questions in Agency's complete response letter and additional information request are deemed adequate from CMC perspective.

Based on the information provided on the performance of pre-filled syringe (b) (4) the Epinephrine Injection drug /device combination is suitable to deliver the targeted volume with acceptance criteria of $0.3 \text{ mL} \pm \frac{(b)(4)}{(4)}\%$. This NDA is recommended for "APPROVAL" from a CMC perspective. All deficiencies noted in the CR letter of the Agency were adequately addressed in the resubmission.

Chemistry Assessment Section

III. Administrative**A. Reviewer's Signature**

(See appended electronic signature page)

Venkateswara R. Pavuluri, PhD, R. Ph.

B. Endorsement Block

(See appended electronic signature page)

Chemist Name / Date: Venkateswara R. Pavuluri, PhD, R. Ph.; 04-MAY-2016

Chemistry Team Leader Name/ Date: Craig M. Bertha, PhD;

Chemistry Branch Chief: Julia C. Pinto, PhD;

Project Manager Name / Date

C. CC Block

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Chemistry Assessment Section

R REGIONAL INFORMATION**R1 Executed Batch Records**

The executed manufacturing records for the filling and visual inspection of the registration batches and the assembling of plunger rod device assembly were provided in the submission.

R2 Comparability Protocols

N/A

R3 Methods Validation Package

N/A

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1**A. Labeling & Package Insert**

See the attachment for the corrections proposed for section 3, 11 and 16 of the PI.

B. Environmental Assessment Or Claim Of Categorical Exclusion

No additional information was included in the resubmission on Environmental impact. Refer to original NDA CMC review by Dr. Ying Wang, PhD, for details.

III. List Of Deficiencies To Be Communicated

No additional deficiencies were identified from the CMC perspective at the time of this review. A deficiency identified earlier was communicated to the sponsor and received an acceptable response as mentions in the above review.

Chemistry Assessment Section

**Venkateswara R. Pavuluri
-A (Affiliate)**

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0.9.2342.19200300.100.1.1=0011799946, cn=Venkateswara R.
Pavuluri -A (Affiliate)
Date: 2016.05.04 20:24:00 -04'00'

I concur.

**Craig M.
Bertha -S**

Digitally signed by Craig M. Bertha -S
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ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=1300103470,
cn=Craig M. Bertha -S
Date: 2016.05.05 05:34:41 -04'00'



NDA 207534

Symjepi (Epinephrine)

Adamis

Ying Wang, PhD

Review Chemist

**Office of New Drug Quality Assessment
Division of New Drug Quality Assessment III
Branch VIII**

**CMC REVIEW OF NDA 207534
For the Division of Pulmonary, Allergy and Rheumatology Products**

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CMC Review Data Sheet

CMC Review Data Sheet

1. NDA 207534
2. REVIEW #: 1
3. REVIEW DATE: 18-Feb-2015
4. REVIEWER: Ying Wang, PhD
5. PREVIOUS DOCUMENTS:N/A
6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original Submission	5/28/2014
Correspondence (C)	
Amendment (BC)	10/08/2014
Amendment (BC)	11/28/2014
Amendment (BC)	1/20/2015
Amendment (BC)	2/06/2015

7. NAME & ADDRESS OF APPLICANT:

Name: Admis Pharmaceuticals Inc.
Address: 116821 Camino Real, Suite 300, San Diego, CA
92130, USA
Representative: Dennis J. Carlo
Telephone: 858-412-7943

8. DRUG PRODUCT NAME/CODE/TYPE:

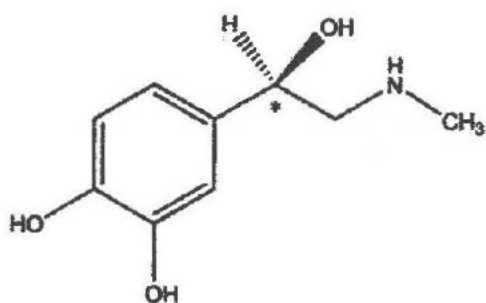
- a) Proprietary Name: Symjepi
- b) Non-Proprietary Name: Epinephrine
- c) Code Name/# (ONDQA only): N/A
- d) Chem. Type/Submission Priority (ONDQA only):
 - Chem. Type: 5
 - Submission Priority: Standard

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

CMC Review Data Sheet

10. PHARMACOL. CATEGORY: Sympathomimetic
11. DOSAGE FORM: Injection
12. STRENGTH/POTENCY: 0.3 mg/0.3 mL
13. ROUTE OF ADMINISTRATION: IM, SC
14. Rx/OTC DISPENSED: Rx OTC
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
 SPOTS product – Form Completed
 Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
 1,2-Benzenediol, 4-[1-hydroxy-2-(methylamino)ethyl]-, (R) (USP)
 (-)-3,4-Dihydroxy- α -[(methylamino)methyl]benzyl alcohol (CAS)
 R-1-(3,4-dihydroxyphenyl)-2-methylaminoethanol (BP)



Molecular Formula

$C_9H_{13}NO_3$

Relative Molecular Mass

183.20



CMC Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	3	Adequate	06/24/2014	Shastri Bhamidipati
	III			7	Adequate	6/16/2008	Found (b) (4) adequate for approved injection product
	III			7	Adequate	01/04/2008	Found (b) (4) adequate for approved injection product

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)



CMC Review Data Sheet

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	1/27/2015	
Pharm/Tox	Acceptable	10/22/2014	Dr. Jane J. Sohn
Biopharm	Acceptable	11/05/2014	Dr. Assadollah Noory
LNC	N/A		
Methods Validation	N/A, according to the current ONDQA policy		
DMEPA	Pending		
EA	Categorical exclusion acceptable (see review)		Ying Wang
Microbiology	Acceptable	1/6/2015	Dr. Vinayak B. Pawar



Executive Summary Section

The CMC Review for NDA 207534

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA is recommended for a complete response from Chemistry, Manufacturing, and Control (CMC) perspective.

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

N/A

II. Summary of CMC Assessments

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

(1) Drug Substance

Drug substance epinephrine is a white to off-white crystalline powder. It darkens on exposure to light and air. It is very slightly soluble in water and ethanol. With acid it forms salts that are readily soluble in water. Drug substance information is referenced in DMF ^{(b) (4)} for which ^{(b) (4)} is the holder. ^{(b) (4)}

Specification proposed in this NDA for drug substance is looser than the specification from the supplier and doesn't meet current ICH Q3A guideline. The specification from the supplier is adequate.

(2) Drug Product

EPINEPHRINE INJECTION, USP ^{(b) (4)} (0.3mg Pre-Filled Single Dose Syringe) is a solution for injection in a prefilled syringe. The sterile solution is a clear, colorless solution. Each pre-filled syringe contains approximately 0.8 mL Epinephrine solution for injection. EPINEPHRINE INJECTION is designed to be self-administered by the patient or caregiver, to deliver a 0.3 mL dose by subcutaneous or intramuscular injection. Each pre-filled syringe is intended for single-use, and delivers a single dose of 0.3 mL [0.3 mg of Epinephrine ^{(b) (4)}].

See risk assessment table below.



Executive Summary Section

DP attribute/ CQA	Factors that can impact the CQA ¹	O ²	S ^{4,3}	D ⁴	FMECA RPN #	Comment & considerations
Sterility ⁴						
Endotoxins ⁴						
Deliverable Volume	- Device is not properly designed to deliver the desired dose - Variability of the pre-filled single use syringe	5	4	4	80	The device as submitted was designed to deliver wrong target volume
Assay (API)	- Loss of API due to degradation - Incorrect formulation	4	3	4	48	(b) (4)
Assay (b) (4)	(b) (4)	3	2	4	24	(b) (4)
Purity (API-related)	- Purity of input API - Increase in API-related impurities due to degradation (b) (4)	3	3	4	36	(b) (4)
Uniformity of dose	- Incorrect fill - Variability of the single use device - Leakage of formulation - API assay variability (see above)	3	5	3	45	(b) (4)
Osmolality	Incorrect formulation	1	2	5	10	(b) (4)

¹ Based on underlying assumption that patients use the device as intended (human factors beyond scope of CMC evaluation).

² O = Probability of Occurrence; S = Severity of Effect; D = Detectability

³ Severity of effect can only be estimated; input from clinical or pharmacology/toxicology team would be necessary for more accurate assessment of clinical impact of failures of product CQAs.

⁴ To be evaluated by the microbiology team (as per microbiology pilot).



CMC REVIEW OF NDA 207534



Executive Summary Section

							(b) (4)
pH	- Incorrect pH adjustment - Incorrect formulation	1	2	3			
Particulate matter	- Particulates in formulation components - Particulates in or from CCS components - Particulates from manufacturing process	2	3	3			
Leachables	- CCS components incompatible with formulation - Incorrect pH or formulation	2	2	4			
Appearance	- API degradation (b) (4) - Interaction of formulation components - Leachables from CCS components - Presence of particulate matter	2	2	3			

Executive Summary Section

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

Epinephrine Injection, USP (b)(4) is indicated in the emergency treatment of allergic reactions (Type I) including anaphylaxis and is intended for immediate administration in patients who are determined to be at increased risk for anaphylaxis, including individuals with a history of anaphylactic reactions.

Epinephrine (b)(4) is to be injected intramuscularly or subcutaneously into the anterolateral aspect of the thigh, through clothing if necessary by patients or caregivers under non-medically supervised environment. Each pre-filled syringe is a single-use injection.

C. Basis for Approvability or Not-Approval Recommendation

Epinephrine pre-filled syringe is a one-time use device and is intended to be used by patients or caregivers under non-medically supervised environment. The deliverable volume is a critical quality attribute of this drug/device combination product. The target value for the deliverable volume should be around labeling claim (0.3 mL) with limit within a narrow range of the target value. Apparently the applicant misunderstood the requirement and developed the syringe to deliver the volume (b)(4) in the original submission. The original proposed acceptance criterion of (b)(4) mL for the "deliverable volume" is completely unacceptable and unprecedented. This (b)(4) (b)(4) is a serious safety issue. The drug/device combination product as it is submitted in the application would cause the active drug to be delivered to the patients outside the (b)(4)% of the labeling claim value.

This is a safety issue and therefore an approvability issue. This issue has been communicated with the applicant multiple times during the review cycle. The Agency has communicated clearly with the applicant that the device needs to be redesigned to accurately deliver the labeling claim amount of the drug to the patients. In the latest amendment (dated 2/6/2015) submitted by the applicant there is no information regarding the redesigned device. There is no development or validation report for the redesigned device. There is no new batch data with the redesigned device. The applicant only submitted a revised acceptance criterion for the "mean deliverable volume" without any supporting data.

There is no analytical method description for the extractable volume which is part of the drug product specification.

The proposed specification in the NDA for the drug substance is looser than the specification from the drug substance supplier and doesn't meet current ICH guideline.



Executive Summary Section

Due to the deficiencies noted above, the identity, strength, quality, purity, and potency of the drug product cannot be adequately assured per CFR 314.50(ii)(a). Therefore, this NDA is recommended for "COMPLETE RESPONSE" from a CMC perspective.

See deficiency list at the end of this review.

III. Administrative

A. Reviewer's Signature:

(See appended electronic signature page)

Ying Wang, PhD

B. Endorsement Block:

(See appended electronic signature page)

Julia Pinto, PhD, Branch Chief, Branch VIII, ONDQA

C. CC Block: entered electronically in DFS

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CMC Assessment Section

Evaluation:

It is noted that one of the unidentified impurities at RRT (b) (4) has levels (b) (4) at 18 month time point. As discussed in Section P.5.6 per ICH the threshold for identification and qualification for this drug product is (b) (4). So this impurity needs to be identified and qualified. This issue has been discussed at Section P.5.6 and information request has been sent to the applicant. The applicant has proposed to identify and qualify any impurity that is (b) (4) ICH limit for all future batches. This approach is acceptable.

It is also noted that there is no required photo stability data in the application. However, this drug is well known to be light sensitive. A secondary opaque plastic case is provided to protect the syringe from the light. The language of light sensitivity and protection from the light is also included in the storage condition of the labeling. From risk perspective it is minimum risk without the photo stability data.

18 month expiry is proposed and granted when the syringes are stored at room temperature 77°F (25°C) in the plastic case provided.

A APPENDICES**A.1 Facilities and Equipment (biotech only)**

N/A

A.2 Adventitious Agents Safety Evaluation

N/A

A.3 Novel Excipients

N/A

R REGIONAL INFORMATION**R1 Executed Batch Records**

Executed batch records are provided in the submission.

R2 Comparability Protocols

N/A

R3 Methods Validation Package

N/A

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1**A. Environmental Assessment Or Claim Of Categorical Exclusion**

In accordance with 21 CFR 25.31, Adamis certifies that the proposed drug that is the subject of this 505(b)(2) New Drug Application (NDA) qualifies for a categorical



CMC Assessment Section

exclusion from the requirement to prepare an Environmental Assessment or an Environmental Impact Statement under 21 CFR 25.31. To our knowledge, no extraordinary circumstances exist that would warrant the preparation of an Environmental Assessment because the action of this drug product that is the subject of this New Drug Application will not increase the use of any active moiety.

Evaluation: Adequate

III. List Of Deficiencies to be Communicated

1. The deliverable volume of the drug product is a critical quality attribute for this drug for its intended use and use environment. The drug/device combination product as submitted in the applicant is not capable of delivering the labeling claim amount of the drug. This will not ensure the identity, strength, quality, purity, and potency of the drug product per CFR 314.50(ii)(a).

You need to redesign the pre-filled syringe to deliver the target volume at labeling claim. In your future submission you need to provide the following:

- i) Detailed device information with the original design and redesign comparison
- ii) Detailed validation report with the redesigned device performance data. It should include but not limited to; sample size, average deliverable volume, standard deviation, minimum and maximum volume delivered, etc.
- iii) Detailed validation batch (with the intended drug product solution) data with the redesigned device

You need to propose an acceptance criterion for the “deliverable volume” with reasonable lower and upper limits that is comparable to the limits of other approved drug products in this class. Please note the proposed acceptance criterion for “mean deliverable volume” with limit in the footnote (as in your amendment dated Feb 6, 2015) is not appropriate or adequate.

2. The volume determination as described in USP <1> is not specifically defined for which type of the volume. The (b) (4) is irrelevant regarding the analytical methods for the extractable volume. For this pre-filled syringe to be used by the patients. You need to provide detailed analytical methods and adequate validation report for the extractable volume of the drug product.
3. Your proposed drug substance specification (Table 3.2.S.4.1-1) in the NDA is looser than that used by the drug substance supplier ((b) (4) referenced in DMF (b) (4)). Specifically,
 - i) The proposed acceptance criterion for impurity (b) (4) is (b) (4)% in your NDA submission. The (b) (4) acceptance criterion for this impurity is (b) (4)%.
 - ii) There is residual solvent (b) (4) limit of (b) (4) ppm in the (b) (4) specification. However, this limit is not in the drug substance specification proposed in the NDA.



CMC Assessment Section

Revise your specification to match the specification of the drug substance supplier (b) (4). Accordingly you also need to provide an appropriate analytical method and adequate validation report for impurity (b) (4). Please note a limit test for any impurity is not acceptable. Alternately, provide justification to support your proposed specification (or lack of such specification). Please note merely following USP monograph is not sufficient justification for any impurity limit. ICH Q3A guideline also needs to be followed. Any potential residual solvent in the drug substance needs to be specifically listed and limit be set in the specification. Statement of (b) (4) is not sufficient.



CMC Assessment Section

Ying Wang -S

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Date: 2015.02.23 10:35:25 -05'00'

Julia C. Pinto -A

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ou=FDA, ou=People, cn=Julia C. Pinto -A,
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**MEMORANDUM: DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC
HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: 14-DEC-2014

TO: N207534 File

FROM: Craig M. Bertha, Ph.D.
Acting CMC Lead
ONDQA, Division II, Branch VIII

SUBJECT: Consult review from CDRH for the pre-filled syringe for
the epinephrine injection NDA 207534



SUMMARY:

Upon the advice of Jacqueline Ryan, MD of the CDRH Office of Compliance, a consult review was requested of the CDRH Office of Device Evaluation for the syringe part of the pre-filled syringe injection of NDA 207534. The consult review dated December 12, 2014 was forwarded to CDER. The consult has provided a list of 16 recommendations and these have been carefully evaluated. Question 1 requests information about the needle portion of the syringe, but this information has been provided in the referenced DMF ^{(b) (4)} from the syringe manufacturer. The second question requests drug delivery data for the syringe but this information has already been provided in the application as a result of typical performance tests. The CMC reviewer is evaluating data as part of her review. The glass syringe and ^{(b) (4)} needle is used in conjunction with a plunger that is connected to an elastomeric rubber plunger. Questions 4-7 address the biocompatibility of this component, but it is important to note that this elastomer material has been used as part of the container closure system from other approved injection drug products according to the CMC reviewer. Therefore, it is not necessary to seek more information from the sponsor or elastomer DMF ^{(b) (4)} holder about this component and its composition. Question 8 from the consult deals with microbiology related issues, but these are to be covered specifically by the microbiology reviewer of this application so no information request for this information is necessary unless the microbiologist concurs that this information is needed during his evaluation. Question 9 deals with the testing of the device for particulates, but this test is covered by the general testing in the specification of the drug product for particulates as per the USP recommendations of chapter <788>. Question 10 addresses the potential for leachables in the drug product formulation from the elastomeric component of the device. This is to be addressed directly by the CMC reviewer. Question 11-15 addresses issues pertaining to sterilization. These aspects will be considered by the microbiology reviewer. Finally, the final question 16 addresses the shelf-life of the product, which will be evaluated by the CMC reviewer in conjunction with the stability and other related data provided in module 3 of the NDA. The consult review from CDRH has provided a thorough overall evaluation of all the device-related aspects that should be considered during the review of the drug product. These issues have and will be addressed by the CMC and microbiology reviewers during their respective evaluation of the NDA.

RECOMMENDATION: NAI – At this time it is not considered necessary to send any comments to the applicant or the DMF holders for the device components until such time as deemed necessary following the evaluation of the application by the CMC and microbiology reviewers.

Craig M. Bertha -5

Thank you for Craig M. Bertha's
signature. I will be sure to
include it in the final version of
the document. I will be sure to
include it in the final version of
the document. I will be sure to
include it in the final version of
the document.

Craig M. Bertha, Ph.D.
Acting CMC Lead, ONDQA

cc:

OND/DPARP/CJackson
ONDQA/DIV 3/CBertha/17-DEC-2014
ONDQA/DIV 3/JPinto
ONDQA/DIV 3/EDuffy
ONDQA/DIV 3/YWang
OPS/NDMS/VPawar
OPS/NDMS/BRiley

BIOPHARMACEUTICS REVIEW
Office of New Drug Quality

Application No.:	NDA 207-534	Reviewer: Assadollah Noory, PhD
Submission Dates:	May 23, 2014,	
Division:	Division of Pulmonary, Allergy and Rheumatology Products	Team Leader: Tapash Ghosh, PhD
Applicant:	Adamis Pharmaceuticals	Acting Supervisor: Paul Seo, PhD
Established Name:	Epinephrine Injection, USP	Type of Submission: Original New Drug Application – 505(b)(2)
Indication:	(b) (4)	
Dosage form/ strengths	Solution for Injection/ 0.3 mg in 0.3 mL pre-filled syringe	
Route of Administration	IM or SC injection	

Background:

The proposed drug product is a sterile solution for injection intended to be administered via the intramuscular (IM) or subcutaneous (SC) route of administration. The proposed drug product is a single use syringe containing 0.8 mL epinephrine solution that can only deliver 0.3 mg in 0.3 mL upon injection. The reference listed drug (RLD) is EpiPen®. The Applicant requested a waiver of the requirement to provide evidence of in-vivo bioavailability for both route of administration (IM, SC) of the proposed drug product.

Formulation Composition:

The following table contains the formulation composition for this product.

Table 3.2.P.1-1 Composition of the dosage form

Component	Quantity of syringe contents (mg/mL)	Quantity per dose (mg/0.3 mL)	Function	Reference to Standard
(b) (4) Epinephrine Base	(b) (4)	(b) (4)	Active	USP
Sodium Chloride		1.8	(b) (4)	USP
Sodium Metabisulfite		0.50		USP NF
Hydrochloric Acid	(b) (4) pH 2.2 to 5.0 ²	(b) (4) pH 2.2 to 5.0 ²	pH Modifier	USP NF
Water for Injection			(b) (4)	USP

1 - Labeled active content is 1.0mg/mL, formulation includes (b) (4)% overage
2 - pH range included in the finished product specification is 2.2 to 5.0

The applicant also provided a comparative formulation composition against RLD, shown below.

Comparison of Epinephrine Injection and EpiPen® Dose Compositions

Component	Epinephrine Injection Quantity per dose (mg/0.3 mL)	EpiPen® Quantity per dose (mg/0.3 mL)
Epinephrine (b) (4) Base	0.3	0.3
Sodium Chloride	1.8	1.8
Sodium Metabisulfite	0.5	0.5
Hydrochloric Acid	(b) (4) pH 2.2 to 5.0 ²	(b) (4) pH 2.2 to 5.0
Water for Injection	(b) (4)	

1 – Source: EpiPen® (epinephrine), Prescribing Information, NDA 019430 (revised August 2012);

2 – pH range in the finished product specification is proposed to be 2.2 to 5.0

Reviewer's Comment: Based on the similarity of the formulation composition and the route of administration, no difference in physico-chemical and pharmacokinetic characteristics is expected between the proposed product and the RLD. Therefore, a biowaiver is granted for this product.

Recommendation:

Based on the information provided by the applicant, a waiver of conducting an *in-vivo* bioavailability study for the proposed drug product, EPINEPHRINE INJECTION, USP (b) (4) for IM and SC administration is granted from biopharmaceutics perspective.

The Office of New Drug Quality completed the review of Biopharmaceutics portion of this NDA and recommends that NDA 207-534 be approved.

Signature 11/05/14

Assadollah Noory, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality

Signature 11/5/14

Tapash Ghosh, Ph.D.
Team Leader
Office of New Drug Quality

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DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=1300006250, cn=Assadollah Noory -S
Date: 2014.11.05 10:51:08 -05'00'

Tapash K.
Ghosh -S

Digitally signed by Tapash K. Ghosh -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=1300148262,
cn=Tapash K. Ghosh -S
Date: 2014.11.05 11:35:39 -05'00'



ONDQA Biopharmaceutics IQA and Filing Review

NDA SUBMISSION INFORMATION

NDA Number	207534
Submission Date:	5/23/14
Product name/generic name of the API and dosage form and strength	Epinephrine Injection, USP, (b)(4) (0.3 mg pre-filled single dose syringe)
Applicant Name	ADAMIS
Clinical Division	DPARP
Type of Submission	505(b)(2)
Biopharmaceutics Reviewer	Assadollah Noory, Ph.D.
Biopharmaceutics Team Leader	Tapash Ghosh, Ph.D.

BIOPHARMACEUTICS FILING CONCLUSIONS AND RECOMMENDATIONS

Is the Product Quality Section of the application fileable from a Biopharmaceutics perspective? Yes ☒ No ☐ Biopharmaceutics Filing Issues: 1.

Are there potential Biopharmaceutics review issues to be forwarded to the Applicant with the 74-Day letter? Yes ☐ No ☒ Biopharmaceutics Comments for 74-Day Letter: 1.

ONDQA Biopharmaceutics IQA and Filing Review Worksheet

Initial Quality-Biopharmaceutics Assessment

Biopharmaceutics Synopsis, Critical Issues or Complexities
Submission: Pursuant to 21 §CFR 314.50, Adamis Pharmaceuticals Corporation is submitting herein a 505(b)(2) new drug application for EPINEPHRINE INJECTION, USP, (b)(4) (0.3mg Pre-filled Single Dose Syringe) indicated for the emergency treatment of allergic reactions (Type I) including anaphylaxis.
Introduction: Epinephrine Injection is indicated in the emergency treatment of allergic reactions (Type I) including anaphylaxis to stinging insects (e.g., order Hymenoptera, which include bees, wasps, hornets, yellow jackets and fire ants) and biting insects (e.g., triatoma, mosquitos), allergen immunotherapy, foods, drugs, diagnostic testing substances (e.g., radiocontrast media) and other allergens, as well as idiopathic anaphylaxis or exerciseinduced anaphylaxis. Epinephrine Injection is intended for immediate administration in patients, who are determined to be at increased risk for anaphylaxis, including individuals with a history of anaphylactic reactions. The Sponsor is requesting a biowaiver for their product. The reference listed drug is EpiPen®.
Product Description:

ONDQA Biopharmaceutics IQA and Filing Review Worksheet

EPINEPHRINE INJECTION (Figure 1) is a single-use, disposable, pre-filled syringe that delivers a single dose of 0.3 mg (0.3 mL) of epinephrine in a sterile aqueous solution. EPINEPHRINE INJECTION has been developed based on the USP monograph for Epinephrine Injection and on information available on existing commercial products, including the proposed reference listed drug, EpiPen.

Figure 1: EPINEPHRINE INJECTION, USP (b) (4) product



EPINEPHRINE INJECTION has been designed to provide an intuitive, safe and simple to use device for the emergency treatment of severe allergic reactions (anaphylaxis).

The following table shows a side by side comparison of the formulation composition.

Comparison of Epinephrine Injection and EpiPen® Dose Compositions

Component	Epinephrine Injection Quantity per dose (mg/0.3 mL)	EpiPen® Quantity per dose (mg/0.3 mL)
Epinephrine (b) (4) Base	0.3	0.3
Sodium Chloride	1.8	1.8
Sodium Metabisulfite	0.5	0.5
Hydrochloric Acid	(b) (4) pH 2.2 to 5.0 ²	(b) (4) pH 2.2 to 5.0
Water for Injection		(b) (4)

1 – Source: EpiPen® (epinephrine), Prescribing Information, NDA 019430 (revised August 2012);
2 – pH range in the finished product specification is proposed to be 2.2 to 5.0

Review Objectives:

The objective of this review is to determine whether this application is fillable.

Issues Identified:

No issues have been identified in this filing review.

Filing Recommendation:

ONDQA-biopharmaceutics recommends the filing of NDA 207-534.

ONDQA Biopharmaceutics IQA and Filing Review Worksheet

Biopharmaceutics Filing Review Checklist

Depending on the drug product and type of submission, some of the following parameters are necessary to initiate the Biopharmaceutics review (e.g., The NDA submission should be complete enough to review but may have minor deficiencies that can be addressed during the review cycle).

A. BIOPHARMACEUTICS FILING PARAMETERS				
	Parameter	Yes	No	Comment
1.	Does the application contain dissolution data?		X	
2.	Is the dissolution test part of the drug product specifications?		X	
3.	Does the application contain the dissolution method development report including data supporting the discriminating ability?		X	
4.	Is there a validation package for the analytical method and dissolution methodology?		X	
5.	Does the application include a biowaiver request?	X		
6.	Are there adequate in vitro and/or in vivo data supporting the bridging of formulations throughout the drug product's development?			NA
7.	Are there any formulation and/or manufacturing changes implemented to the clinical formulation? If yes, Are data supporting the bridging between the clinical and commercial drug products and/or manufacturing sites?			NA
8.	Is the proposed drug product a modified release dosage form (e.g., controlled release, delayed release)?		X	
9.	Does the application include an IVIVC model?		X	
10.	Does the application include information/data on the in vitro alcohol dose-dumping potential of the proposed drug product?		X	
11.	Is there enough information to assess the extended release designation claim?		X	

ONDQA Biopharmaceutics IQA and Filing Review Worksheet

12.	Is there any <i>in vivo</i> BA or BE study in the submission?		X	
13.	Is the Biopharmaceutics team responsible of reviewing the <i>in vivo</i> BA or BE studies? <u>If yes.</u> • Does the application contain the complete BA/BE data? • Are the PK files in the correct format? • Is an inspection request needed for the BE study(ies)?			NA
14.	Is there any design space proposed using <i>in vitro</i> release as a response variable?		X	
15.	Is the control strategy related to <i>in vitro</i> drug release?			NA
B. BIOPHARMACEUTICS FILING CONCLUSION AND COMMENTS				
	Parameter	Yes	No	Comment
16.	IS THE PRODUCT QUALITY AND BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?	X		
17.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide filing comments to be sent to the Applicant.			NA
18.	Are there any potential review issues identified?		X	
19.	Are there any comments to be sent to the Applicant as part of the 74-Day letter?	X		
20.	Are there any internal comments for the other disciplines?		X	

{See appended electronic signature page}

Assadollah Noory, Ph.D.
Senior Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Date

{See appended electronic signature page}

Tapash Ghosh, Ph.D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

Date

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/s/

ASSADOLLAH NOORY
06/23/2014

TAPASH K GHOSH
06/24/2014

Initial Manufacturing (CGMP/Facilities) Assessment (IMA) and Filing Review for Pre- Marketing Applications (Original)

- I. Review Cover Sheet
- II. Application Detail
- III. Filing Checklist
- IV. Manufacturing Summary
- V. Overall Conclusions and Recommendations

I. Review Cover Sheet

1. OMPQ Reviewer: Linda Ng, Ph.D.
2. NDA/BLA Number: NDA 207534
Submission Date: May 23, 2014
21st C. Review Goal Date: January 23, 2015
PDUFA Goal Date: March 23, 2015

3. PRODUCT PROPERTIES:

Trade or Proprietary Name:	None submitted
Established or Non-Proprietary Name (USAN) and strength:	Epinephrine Injection
Dosage Form:	Pre-filled single dose glass syringe for injection

4. SUBMISSION PROPERTIES:

Review Priority :	PRIORITY
Applicant Name:	Adamis Pharmaceutical Corporation
Responsible Organization (OND Division):	DPARP

II. Application Detail

1. INDICATION: For emergency treatment of type I allergic reactions including anaphylaxis to stinging insects and biting insects, allergen immunotherapy, foods, drugs, diagnostic testing substances and other allergens, as well as idiopathic anaphylaxis or exercise-induced anaphylaxis.
2. ROUTE OF ADMINISTRATION: Intramuscular or subcutaneous injections (IM or SC)
3. STRENGTH/POTENCY: 0.3 mg/0.3 mL
4. Rx/OTC DISPENSED: x Rx OTC
5. ELECTRONIC SUBMISSION (yes/no)? Yes
6. PRIORITY CONSIDERATIONS:

	Parameter	Yes	No	Unk	Comment
1.	NME / PDUFA V		X		
2.	Breakthrough Therapy Designation		X		
3.	Orphan Drug Designation		X		
4.	Unapproved New Drug		X		
5.	Medically Necessary Determination		X		
6.	Potential Shortage Issues [either alleviating or non-approval may cause a shortage]		X		
7.	Rolling Submission		X		
8.	Drug/device combination product with consult	X			pre-filled single dose glass syringe for injection
9.	Complex manufacturing		X		
10.	Other (e.g., expedited for an unlisted reason)		X		

OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review
For Pre-Marking Applications

III. FILING CHECKLIST

The following parameters are necessary in order to initiate a full review (i.e., the application is complete enough to start review but may have deficiencies). On **initial** review of the NDA application:

A. COMPLETENESS OF FACILITY INFORMATION				
	Parameter	Yes	No	Comment
11.	Is all site information complete (e.g., contact information, responsibilities, address)?	X		
12.	Do all sites indicate they are ready to be inspected (on 356h)?	X		Except for the DS facility (DMF (b)(4))
13.	Is a single comprehensive list of all involved facilities available in one location in the application?		X	The drug substance info is listed in the section 3.2.S.2.1.1.1
14.	For testing labs, is complete information provided regarding which specific test is performed at each facility and what stage of manufacturing?	X		
15.	Additional notes (non-filing issue)	X		
	1. Are all sites registered or have FEI #?			
	2. Do comments in EES indicate a request to participate on inspection(s)?		X	
	3. Is this first application by the applicant?		X	

*If any information regarding the facilities is missing/omitted, communicate to OPS/ONDQA regarding missing information and copy EESQuestions. Notify OMPQ management if problems are not resolved within 3 days and it can be a *potential* filing issue.

OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review
For Pre-Marking Applications

B. DRUG SUBSTANCE (DS) / DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
16.	Have any Comparability Protocols been requested?		X	

IMA CONCLUSION				
	Parameter	Yes	No	Comment
17.	Does this application fit one of the EES Product Specific Categories?		X	
18.	Have EERs been cross referenced against the 356h and product specific profile for accuracy and completion? Have all EERs been updated with final PAI recommendation?	X		The ONDQA PM followed up with the sponsor for clarification. (b) (4) Adamis Pharm Co is responsible for paper review of drug product release (b) (4) should be entered in EES. Three EES entries have been updated with PAI AP recommendation; one is on 10 day request.
19.	From a CGMP/facilities perspective, is the application fileable? If the NDA is not fileable from a product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.	X		

IV. Manufacturing Summary: Critical Issues and Complexities

Does the submission contain any of the following elements?			
Nanotechnology ☐	RTRT Proposal ☐	PAT ☐	Drug/Device Combo X ☐
PET ☐	Design Space ☐	Continuous Mfg ☐	Naturally derived API ☐
Other (explain):			

Manufacturing Highlights

1. Drug Substance

	Parameter	Yes	No	Comment
	Is manufacturing process considered complex (e.g., unusual unit operations, innovative manufacturing technology, unusual control strategy)?		X	

Include process flow chart/diagram (see eCTD Section 2.3.S.1)

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V. Overall Conclusions and Recommendations

Is the application fileable? (yes/no, Yes to questions 11-12) Yes
Based on Section IV, is a KTM warranted for any PAI? (yes/no). If yes, please identify the sites in the above chart. No. The facility ^{(b)(4)} should be entered in EES with profile ^{(b)(4)} . Both drug substance and drug product manufacturing facilities entered to date are found acceptable based on profile.
Are there comments/issues to be included in the 74 day letter, including appropriate identification of facilities? (yes/no) No
Comments for 74 Day Letter
1.
2.
3.

REVIEW AND APPROVAL (DARRTS)

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/s/

LINDA L NG
08/13/2014

MAHESH R RAMANADHAM
08/13/2014



ONDQA Biopharmaceutics IQA and Filing Review

NDA SUBMISSION INFORMATION

NDA Number	207534
Submission Date:	5/23/14
Product name/generic name of the API and dosage form and strength	Epinephrine Injection, USP (b) (4) (0.3 mg pre-filled single dose syringe)
Applicant Name	ADAMIS
Clinical Division	DPARP
Type of Submission	505(b)(2)
Biopharmaceutics Reviewer	Assadollah Noory, Ph.D.
Biopharmaceutics Team Leader	Tapash Ghosh, Ph.D.

BIOPHARMACEUTICS FILING CONCLUSIONS AND RECOMMENDATIONS

Is the Product Quality Section of the application fileable from a Biopharmaceutics perspective? Yes ☒ No ☐
Biopharmaceutics Filing Issues:
1.

Are there potential Biopharmaceutics review issues to be forwarded to the Applicant with the 74-Day letter? Yes ☐ No ☒
Biopharmaceutics Comments for 74-Day Letter:
1.

Initial Quality-Biopharmaceutics Assessment

Biopharmaceutics Synopsis, Critical Issues or Complexities

Submission:

Pursuant to 21 §CFR 314.50, Adamis Pharmaceuticals Corporation is submitting herein a 505(b)(2) new drug application for EPINEPHRINE INJECTION, USP (b)(4) (0.3mg Pre-filled Single Dose Syringe) indicated for the emergency treatment of allergic reactions (Type I) including anaphylaxis.

Introduction:

Epinephrine Injection is indicated in the emergency treatment of allergic reactions (Type I) including anaphylaxis to stinging insects (e.g., order Hymenoptera, which include bees, wasps, hornets, yellow jackets and fire ants) and biting insects (e.g., triatoma, mosquitos), allergen immunotherapy, foods, drugs, diagnostic testing substances (e.g., radiocontrast media) and other allergens, as well as idiopathic anaphylaxis or exerciseinduced anaphylaxis. Epinephrine Injection is intended for immediate administration in patients, who are determined to be at increased risk for anaphylaxis, including individuals with a history of anaphylactic reactions.

The Sponsor is requesting a biowaiver for their product. The reference listed drug is EpiPen®.

Product Description:

ONDQA Biopharmaceutics IQA and Filing Review Worksheet

EPINEPHRINE INJECTION (Figure 1) is a single-use, disposable, pre-filled syringe that delivers a single dose of 0.3 mg (0.3 mL) of epinephrine in a sterile aqueous solution. EPINEPHRINE INJECTION has been developed based on the USP monograph for Epinephrine Injection and on information available on existing commercial products, including the proposed reference listed drug, EpiPen.

Figure 1: EPINEPHRINE INJECTION, USP (b) (4) product



EPINEPHRINE INJECTION has been designed to provide an intuitive, safe and simple to use device for the emergency treatment of severe allergic reactions (anaphylaxis).

The following table shows a side by side comparison of the formulation composition.

Comparison of Epinephrine Injection and EpiPen® Dose Compositions

Component	Epinephrine Injection Quantity per dose (mg/0.3 mL)	EpiPen® Quantity per dose (mg/0.3 mL)
Epinephrine (Adrenaline) Base	0.3	0.3
Sodium Chloride	1.8	1.8
Sodium Metabisulfite	0.5	0.5
Hydrochloric Acid	(b) (4) pH 2.2 to 5.0 ²	(b) (4) pH 2.2 to 5.0
Water for Injection		(b) (4)

1 – Source: EpiPen® (epinephrine), Prescribing Information, NDA 019430 (revised August 2012);
2 – pH range in the finished product specification is proposed to be 2.2 to 5.0

Review Objectives:

The objective of this review is to determine whether this application is fillable.

Issues Identified:

No issues have been identified in this filing review.

Filing Recommendation:

ONDQA-biopharmaceutics recommends the filing of NDA 207-534

ONDQA Biopharmaceutics IQA and Filing Review Worksheet

Biopharmaceutics Filing Review Checklist

Depending on the drug product and type of submission, some of the following parameters are necessary to initiate the Biopharmaceutics review (e.g., The NDA submission should be complete enough to review but may have minor deficiencies that can be addressed during the review cycle).

A. BIOPHARMACEUTICS FILING PARAMETERS				
	Parameter	Yes	No	Comment
1.	Does the application contain dissolution data?		X	
2.	Is the dissolution test part of the drug product specifications?		X	
3.	Does the application contain the dissolution method development report including data supporting the discriminating ability?		X	
4.	Is there a validation package for the analytical method and dissolution methodology?		X	
5.	Does the application include a biowaiver request?	X		
6.	Are there adequate in vitro and/or in vivo data supporting the bridging of formulations throughout the drug product's development?			NA
7.	Are there any formulation and/or manufacturing changes implemented to the clinical formulation? If yes. Are data supporting the bridging between the clinical and commercial drug products and/or manufacturing sites?			NA
8.	Is the proposed drug product a modified release dosage form (e.g., controlled release, delayed release).		X	
9.	Does the application include an IVIVC model?		X	
10.	Does the application include information/data on the in vitro alcohol dose-dumping potential of the proposed drug product?		X	
11.	Is there enough information to assess the extended release designation claim?		X	

ONDQA Biopharmaceutics IQA and Filing Review Worksheet

12.	Is there any <i>in vivo</i> BA or BE study in the submission?		X	
13.	Is the Biopharmaceutics team responsible of reviewing the <i>in vivo</i> BA or BE studies? <u>If yes.</u> • Does the application contain the complete BA/BE data? • Are the PK files in the correct format? • Is an inspection request needed for the BE study(ies)?			NA
14.	Is there any design space proposed using <i>in vitro</i> release as a response variable?		X	
15.	Is the control strategy related to <i>in vitro</i> drug release?			NA
B. BIOPHARMACEUTICS FILING CONCLUSION AND COMMENTS				
	Parameter	Yes	No	Comment
16.	IS THE PRODUCT QUALITY AND BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?	X		
17.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide filing comments to be sent to the Applicant.			NA
18.	Are there any potential review issues identified?		X	
19.	Are there any comments to be sent to the Applicant as part of the 74-Day letter?	X		
20.	Are there any internal comments for the other disciplines?		X	

{See appended electronic signature page}

Assadollah Noory, Ph.D.
 Senior Biopharmaceutics Reviewer
 Office of New Drug Quality Assessment

Date

{See appended electronic signature page}

Tapash Ghosh, Ph.D.
 Biopharmaceutics Team Leader
 Office of New Drug Quality Assessment

Date

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/s/

ASSADOLLAH NOORY
06/23/2014

TAPASH K GHOSH
06/24/2014

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

IQA and Filing Review Cover Sheet

1. NEW DRUG APPLICATION NUMBER: N207534

2. DATES AND GOALS:

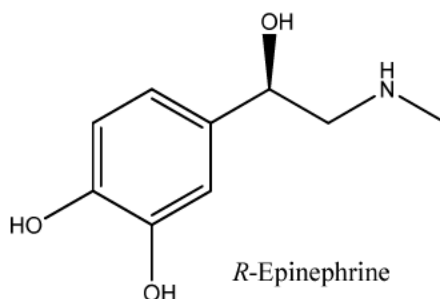
Letter Date: 23-MAY-2014	Submission Received Date : 28-MAY-2014
PDUFA Goal Date: 28-NOV-2014 (as per DARRTS)	

3. PRODUCT PROPERTIES:

Trade or Proprietary Name:	N/A
Established or Non-Proprietary Name (USAN):	Epinephrine
Dosage Form:	Injection
Route of Administration	Intramuscular or subcutaneous injections (IM or SC)
Strength/Potency	0.3 mg/0.3 mL
Rx/OTC Dispensed:	Rx <u>X</u> OTC

4. INDICATION: For emergency treatment of type I allergic reactions including anaphylaxis to stinging insects and biting insects, allergen immunotherapy, foods, drugs, diagnostic testing substances and other allergens, as well as idiopathic anaphylaxis or exercise-induced anaphylaxis.

5. DRUG SUBSTANCE STRUCTURAL FORMULAE:



6. NAME OF APPLICANT (as indicated on Form 356h): Adamis
Pharmaceuticals Corporation

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

7. SUBMISSION PROPERTIES:

Review Priority:	Priority (as per DARRTS)
Submission Classification (Chemical Classification Code):	Based on draft MaPP 7500.3, Type 5: New Formulation or New Manufacturer, Same or New Indication
Application Type:	505(b)(2)
Breakthrough Therapy	Yes No <u>X</u>
Responsible Organization (Clinical Division):	DPARP

8. CONSULTS:

CONSULT	YES	NO	COMMENTS: (list date of request if already sent)
Biometrics			The application provides stability data for 3 full scale batches for 18 months with 25°C/60%RH storage. Some trends are noted in the stability data: (b) (4) It is recommended that, although the drug is not an NME, the reviewer consider the principles outlined in ICH Q1E when evaluating the applicant's proposed expiration dating period and stability data. A consult to the biometric team may be requested as deemed necessary by the reviewer.
Clinical Pharmacology		X	
Establishment Evaluation Request (EER)	X		The ONDQA PM was informed of the arrival of the application on 30-MAY-2014; The submission of the EER to Office of Compliance is pending.
Pharmacology/Toxicology		X	It is unlikely that a consult to the pharmacology/toxicology group will be necessary with regard to drug related impurities, based on this preliminary review. However, the reviewer may need to consult the pharm./tox. group regarding the biological reactivity results for some of the CCS components (b) (4)

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

Overall Filing Conclusions and Recommendations

CMC:

Is the Product Quality Section of the application fileable from a CMC perspective? Yes ☒ No ☐
CMC Filing Issues: N/A

Are there potential CMC review issues to be forwarded to the Applicant with the 74-Day letter? Yes ☐ No ☒
CMC Comments for 74-Day Letter (assuming filing):

Biopharmaceutics:

Is the Product Quality Section of the application fileable from a Biopharmaceutics perspective? Yes ☒ No ☐
Biopharmaceutics Filing Issues: There is no biopharmaceutics information in the application, thus a biopharmaceutics filing review/IQA is not necessary.

Are there potential Biopharmaceutics review issues to be forwarded to the Applicant with the 74-Day letter? Yes ☐ No ☒
Biopharmaceutics Comments for 74-Day Letter: N/A

Microbiology:

Is the Product Quality Section of the application fileable from a Microbiology perspective? Yes ☐ No ☐
Microbiology Filing Issues: The CDER OPS IO MICRO mailbox was sent a notification of the application.

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

Summary of Initial Quality Assessment

Does the submission contain any of the following elements?			
Nanotechnology	QbD Elements	PET	Other, please explain
No	No	No	N/A

Is a team review recommended?	Yes	No	X
Suggested expertise for team:			

Summary of Critical Issues and Complexities:
• [Redacted] (b) (4) • There is very limited information in the application regarding drug product leachables. How much more information will be needed will likely depend on whether or not the elastomeric material of the CCS has been approved for use in other injection drug products. • [Redacted] (b) (4) The applicant should be encouraged to qualify an alternate source of the drug substance for this drug product, considering that this is a medically necessary drug for treatment of life-threatening allergic reactions.

INITIAL QUALITY ASSESSMENT

This application from Adamis Pharmaceuticals Corporation is for an epinephrine injection in a pre-filled syringe (not an auto-injector). The drug is to be administered IM or SC for allergic reactions and anaphylaxis. The epinephrine drug substance is obtained [Redacted] (b) (4) and a letter of authorization is included in the NDA to allow our review of BI's DMF [Redacted] (b) (4) for the CMC information supporting the drug substance. Note that this source of drug substance is the same as that used by other manufacturers of approved epinephrine injection drug products. The most recent review of DMF [Redacted] (b) (4) determined that the file was adequate for support of the use in injection drug products, however, since that time there have been additional amendments submitted that have not been reviewed.

The sterile drug product is a pre-filled single dose syringe containing a 1 mg/mL solution of epinephrine designed to deliver 0.3 mg or 0.3 mL. The syringe has a glass barrel and the attached needle will be protected by a rigid needle shield. [Redacted] (b) (4)
 [Redacted] The application

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

includes 18 months of 25°C/60%RH long term stability data (in addition to 6 months 40°C/75%RH data) for three full scale ((b) (4) syringes) batches (EP0001, EP0002, and EP0003).

Start of Applicant Material

(b) (4)

End of Applicant Material

Below is a risk-assessment based on the critical quality attributes (CQAs) of the drug product to help focus the reviewer on potential quality issues.

APPEARS THIS WAY ON ORIGINAL

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

DP attribute/ CQA	Factors that can impact the CQA ¹	O ²	S ^{4,3}	D ⁴	FMECA RPN #	Comment & considerations
Sterility ⁴						
Endotoxins ⁴						
Assay (API)	- Loss of API due to degradation - Incorrect formulation	2	3	4	24	(b) (4)
Assay (b) (4)	(b) (4)	3	3	4	36	
Purity (API-related)	- Purity of input API - Increase in API-related impurities due to degradation (b) (4)	3	3	4	36	
Uniformity of dose	- Incorrect fill - Leakage of formulation - API assay variability (see above)	2	5	2	20	

¹ Based on underlying assumption that patients use the device as intended (human factors beyond scope of CMC evaluation).

² O = Probability of Occurrence; S = Severity of Effect; D = Detectability

³ Severity of effect can only be estimated; input from clinical or pharmacology/toxicology team would be necessary for more accurate assessment of clinical impact of failures of product CQAs.

⁴ To be evaluated by the microbiology team (as per microbiology pilot).

⁵ Dose is 0.3 mL

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

(b) (4)

Osmolality	Incorrect formulation	1	2	5	10
pH	- Incorrect pH adjustment - Incorrect formulation	1	2	3	6
Particulate matter	- Particulates in formulation components - Particulates in or from CCS components - Particulates from manufacturing process	2	3	3	18
Leachables	- CCS components incompatible with formulation - Incorrect pH or formulation	2	2	4	16
Appearance	- API degradation (b) (4)	2	2	3	12

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

	• Interaction of formulation components • Leachables from CCS components • Presence of particulate matter					• The specification acceptance criterion complies with the USP monograph for epinephrine injection (injection is not pinkish and it contains no precipitate) • Patient instructions indicate that the content of the syringe should be periodically examined and that it “should be clear. If the solution is discolored (pinkish or brown color), cloudy, or contains particles, replace the unit.”

APPEARS THIS WAY ON ORIGINAL

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

FILING REVIEW CHECKLIST

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	X		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X		For those sections examined to complete this IQA review.
3.	Are all the pages in the CMC section legible?	X		For the pages that were examined for this IQA review.
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?		X	See details outlined above regarding leachables.

B. FACILITIES*				
* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a <i>potential</i> filing issue or a <i>potential</i> review issue.				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?		X	See Form 356h for drug product related facilities. The drug substance manufacturing site was not listed on this form, but was included in the S section of the application.
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? This question is not applicable for synthesized API.			NA

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	Parameter	Yes	No	Comment
7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)		X	See above; Also reference BI's DMF (b) (4)
8.	Are drug product manufacturing sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		

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	Parameter	Yes	No	Comment
9.	Are additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X		For those sites listed on the Form 356h

C. ENVIRONMENTAL ASSESMENT

	Parameter	Yes	No	Comment
11.	Has an environmental assessment or claim of categorical exclusion been provided?	X		A categorical exclusion is requested as per 21 CFR 25.31.

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D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	Yes	No	Comment
12.	Does the section contain a description of the DS manufacturing process?			Reference is made to BI's DMF (b) (4)
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?			Reference is made to BI's DMF (b) (4)
14.	Does the section contain information regarding the characterization of the DS?			Reference is made to BI's DMF (b) (4)
15.	Does the section contain controls for the DS?			Reference is made to BI's DMF (b) (4)
16.	Has stability data and analysis been provided for the drug substance?			Reference is made to BI's DMF (b) (4)
17.	Does the application contain Quality by Design (QbD) information regarding the DS?			Reference is made to BI's DMF (b) (4)
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?			Reference is made to BI's DMF (b) (4)

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E. DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		Note that the manufacture of the formulation and filling of the syringes (with fitted needle and shield) is done ^{(b) (4)} 
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X		
21.	Is there a batch production record and a proposed master batch record?		X	Three executed batch records are provided for the primary stability batches.
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?		X	See P.2 where formulation development is addressed in general; whether there is adequate linkage is a clinical/clinical pharmacology consideration, not a CMC consideration.
23.	Have any biowaivers been requested?		X	
24.	Does the section contain description of to-be-marketed container/closure system and presentations?	X		The final device was used to prepare the primary stability batches of drug product.
25.	Does the section contain controls of the final drug product?	X		
26.	Has stability data and analysis been provided to support the requested expiration date?	X		No statistical analysis of the stability data has been presented in the application, however the applicant is proposing a provisional shelf life of 18 months. Considering the trends observed on stability, the reviewer may request a biometrics consult.
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		X	
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	

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F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
29.	Is there a methods validation package?	X		

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product	X		See P.3.3

H. MASTER FILES (DMF/MAF)				
	Parameter	Yes	No	Comment
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X		

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)	2	[REDACTED]	(b) (4)	25-FEB-2014	Found adequate to support injection drug product 15-JUL-2013; amendments submitted subsequently
	3			05-MAY-2014	Not reviewed
	3			07-APR-2014	Not reviewed

I. LABELING				
	Parameter	Yes	No	Comment
32.	Has the draft package insert been provided?	X		
33.	Have the immediate container and carton labels been provided?	X		

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This document will be sequentially signed in DARRTS by all of the following who authored or reviewed this assessment:

See appended electronic signature page!

Craig M. Bertha, PhD
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Eric Duffy, PhD
Acting Branch Chief/Division Director
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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CRAIG M BERTHA
06/20/2014

ERIC P DUFFY
06/23/2014