CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207534Orig1s000

CLINICAL MICROBIOLOGY/VIROLOGY REVIEW(S)

Product Quality Microbiology Review

January 6, 2015

NDA: 207534

Drug Product Name
Proprietary: Epinephrine Injection
Non-proprietary: epinephrine injection USP (b) (4)

Review Number: 1

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
May 23, 2014	May 28, 2014	May 28, 2014	June 3, 2014
Response to IR	November 27, 2014	N/A	N/A

Submission History (for 2nd Reviews or higher) – N/A

Applicant/Sponsor Name: Adamis Pharmaceuticals Corporation
Address: 11682 El Camino Real Suite 300 San Diego, CA 92130
Representative: Dennis J. Carlo, Ph.D., President & CEO
TEL: (847)-935-0936

Name of Reviewer: Vinayak B. Pawar, Ph.D.

Conclusion: Recommend Approval

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: Original NDA

2. SUBMISSION PROVIDES FOR: New drug Application for Epinepherine injection USP (b) (4) (0.3mg Pre-filled Single Dose Syringe)

3. MANUFACTURING SITE: (b) (4)

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY: 0.3mg Pre-filled Single Dose in Syringe. A single-use, disposable, pre-filled syringe delivers a single dose of 0.3 mg (0.3 mL) of epinephrine in a sterile aqueous solution.

5. METHOD(S) OF STERILIZATION: (b) (4)

6. PHARMACOLOGICAL CATEGORY: Treatment for allergic emergencies.

B. SUPPORTING/RELATED DOCUMENTS: None.

C. REMARKS: The subject Original NDA 207534 provides for Epinephrine Injection USP (b) (4) (0.3mg Pre-filled Single Dose Syringe) indicated for the emergency treatment of allergic reactions. While epinephrine injection pre-filled syringes for the emergency treatment of severe allergic reactions (anaphylaxis) are available in other countries (including e.g. the UK), such a product is not currently approved and marketed in the US (Twinject is not currently being marketed in the US). This is an electronic submission. Submission Sections 3.2.P.3.5.2 and 3.2.P.3.3.1.2.4 were updated to 3.2.P.3.5.2.2 and 3.2.P.3.3.1.2.4.4 respectively in response to Agency's IR dated November 17, 2014.

filename: **N207534R1**

Executive Summary

I. Recommendations

A. Recommendation on Approvability – Recommend Approval.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – (b) (4) [redacted]

B. Brief Description of Microbiology Deficiencies – None.

C. Assessment of Risk Due to Microbiology Deficiencies – N/A

D. Contains Potential Precedent Decision(s) - ☐ **Yes** ☒ **No**

III. Administrative

A. Reviewer's Signature _____
Vinayak B. Pawar, Ph.D., Sr. Review Microbiologist, OPS/CDER

B. Endorsement Block _____
Stephen E. Langille, Ph.D., Sr. Review Microbiologist, OPS/CDER

C. CC Block
N/A

Product Quality Microbiology Assessment

1. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 3.2: BODY OF DATA

S DRUG SUBSTANCE - Not the subject of this review.

P DRUG PRODUCT

P.1 Description of the Composition of the Drug Product

- Description of drug product – Epinephrine Injection, USP (b) (4) (0.3mg Pre-Filled Single Dose Syringe), 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) [(b) (4) Epinephrine (b) (4)].
- Drug product composition – The composition of the dosage form is provided in Table 1 (copied from Table 3.2.P.1-1, Section 3.2.P.1.2).

Table 1. Composition of the Dosage Form

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

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

- Description of container closure system – Sterilized glass syringes (Type I) with attached needle, protected by a rigid needle shield are delivered by the supplier (b) (4) plunger stoppers are delivered (b) (4) Figure 1 (copied from Figure 1, cover letter) shows the pre-filled syringe set-up for administration of this product.

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

P.2 Pharmaceutical Development

P.2.5 Microbiological Attributes

- Container-Closure and Package integrity –
  Container closure integrity testing has been conducted using a Dye Ingress test and is used to confirm the integrity of the filled syringes. Container closure integrity test has been conducted during stability studies on the registration batches (Section 3.2.P.2.4.1.1).
  In a Dye Ingress Test, the filled syringes are immersed in a methylene blue aqueous solution. The integrity of the system is verified by applying a vacuum for 15 minutes (at least) at +/- (b) (4) mbar followed by an assessment of the presence or absence of methylene blue. The assessment is by visual inspection and spectrophotometry. The integrity is considered acceptable if the product does not show a peak at (b) (4) nm. All results conformed to the specification. Full method & validation details were provided in Section 3.2.P.8.3.

- Preservative Effectiveness – N/A
- Justification for not having a microbial limit specification for a non-sterile drug product – N/A

ADEQUATE

REVIEWER COMMENT – The applicant's verification of container closure integrity is consistent with regulatory expectations for a pharmaceutical product.

P.3 Manufacture

P.3.1 Manufacturers: (b) (4)

P.3.3 Description of the Manufacturing Process and Process Controls

(b) (4) MANUFACTURING PROCESS

- Building and facilities (floorplan, air quality, equipment locations) – Manufacturing is conducted in building/facilities suitable for manufacture of sterile products with critical stages of manufacture conducted in an appropriately classed environment (details in Section 3.2.P.3.3.1). Location of Equipment was provided in Table 3.2.P.3.3-1.

- Overall manufacturing operation (b) (4) –
  (b) (4)
  All validation results for the (b) (4) testing comply with the acceptance criteria and are presented in Section 3.2.P.3.5. (b) (4)
  The validation results showed

acceptable control of microbiological quality (b) (4) throughout the process and are presented in Section 3.2.P.3.5. (b) (4) Figure 2 (copied from Figure 3.2.P.3.3-2) represents the epinephrine injection manufacturing flow chart.

Figure 2. Manufacturing Process Flow Chart.

(b) (4)

(b) (4) The suitability (b) (4) has been verified and is summarized in the Process Validation Section P.3.5 of this review.

- Sterilization/Depyrogenation of containers, closures, equipment and components –

(b) (4)

- Environmental monitoring –
  Environmental monitoring appropriate to the manufacture of a sterile product is conducted as described in Section 3.2.P.3.3.1. Frequency and action limits for non-viable and viable particle monitoring were provided in Tables 3.2.P.3.3-15 through 22.

P.3.5 Process Validation and/or Evaluation

(b) (4) tests were performed on the three validation batches and all results complied with the acceptance criteria. The (b) (4) results are provided in Table 2 (copied from Table 3.2.P.3.5-4, Section 3.2.P.3.5).

Table 2. (b) (4) Results (b) (4)

(b) (4)

(b) (4)

(b) (4)

Response (revised submission Section 3.2.P.3.3.1.2.4.4):

(b) (4)

This response meets the regulatory expectations for microbial retention studies (See Reviewer Comment below).

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Action in event of media fill failures was tabulated in Table 7 (copied from Table 3.2.P.3.5-18, Section 3.2.P.3.5).

Table 7. Actions in Event of Media Fill Contamination

(b) (4)

[redacted]

ADEQUATE

REVIEWER COMMENT – The applicant has met regulatory expectations for validating the process (b) (4) [redacted] in support of the (b) (4) manufacture of the subject drug product. The sponsor's response to the IR dated November 17, 2014 is acceptable and meets the regulatory expectations.

P.5 Control of Drug Product

The finished drug product appears to be fully tested in accordance with the specification (see Section 3.2.P.5.1). A sterility test and bacterial endotoxins test are carried out as part of this final testing to ensure the sterility of the final, packaged product. A threshold endotoxin concentration has been defined for the drug product in accordance with the Epinephrine Injection USP Monograph; sterility is assessed according to USP<71>.

P.5.1 Specifications

P.5.2 Analytical Procedures

- Endotoxin – The bacterial endotoxins test is included in the USP Monograph for Epinephrine Injection and is performed according to USP <85>. The specification limit chosen by the drug product manufacturer (b) (4) [redacted] is controlled to a tighter standard than required by the USP Monograph. A copy of a validation report was provided in Section 3.2.R.3.P.6 (b) (4) [redacted]
- Sterility – The sponsor states that the sterility test is performed per Ph.Eur 2.6.1 but due to harmonization it is suitable according to USP

<71>. A copy of a validation report was provided in Section 3.2.R.3.P.8.

- Microbial Limits – N/A

ADEQUATE

REVIEWER COMMENT – The applicant has met regulatory expectations with regard to the test method, acceptance criteria and verification of the suitability of use of the sterility & bacterial endotoxins tests that will be performed on the drug product prior to its release.

P.7 Container Closure System – See Review Section P.1.

P.8 Stability

P.8.1 Stability Summary and Conclusion

All results for sterility and bacterial endotoxins which are a critical test for parenteral products [Validation batches EP0001, EP0002 & Ep0003], stored at long term conditions (25°C/60%RH) and accelerated conditions (40°C/75%RH) are within the proposed specification, with no apparent trends emerging.

P.8.2 Post-Approval Stability Protocol and Stability Commitment

Adamis Pharmaceuticals commits to conducting three additional stability studies on three additional full scale validation batches. The studies are planned to include testing after 15 months of long term storage and will be conducted as per the stability study protocols provided in Section 3.2.P.8.1. Furthermore, at least one production scale batch per year will be incorporated into a routine program of on-going stability testing. Testing will be conducted (b) (4) Adamis Pharmaceuticals will report results of the stability studies as they become available (e.g. in the periodic annual reports) or as specified by the Agency.

Adamis Pharmaceuticals will withdraw from the market any lots which are found to fall outside the approved specifications for this drug product. If the deviation is a single occurrence that does not affect the safety and efficacy of this drug product, immediate discussions will commence with the Agency and justification for the continued distribution of the batch will be provided.

One production batch will be incorporated into routine testing:

- Container Closure Integrity – performed at 12 & 24 month storage.
- Endotoxin – performed initially and at each storage point.
- Microbial Limits – N/A

P.8.3 Stability Data – As discussed in Review Section P.8.1, Stability data was provided for Primary Stability Batches EP0001, EP0002 and EP0003 and

the Sterility, Bacterial Endotoxins and Container Closure Integrity Test results were within required specifications.

ADEQUATE

REVIEWER COMMENT – The applicant meets the regulatory expectations with regard to the design of the stability program to support the drug product's microbiological quality throughout its shelf life.

2. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 1

A. PACKAGE INSERT

ADEQUATE

REVIEWER COMMENT – The applicant meets the regulatory expectations with regard to the information provided in the product labeling as it relates to product quality microbiology issues. Further discussion if any, will occur at the proposed labeling meetings.

3. LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENTS: None.

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/s/

VINAYAK B PAWAR
01/16/2015

STEPHEN E LANGILLE
01/16/2015

PRODUCT QUALITY MICROBIOLOGY FILING CHECKLIST

NDA Number: 207534 **Applicant:** Adamis Pharmaceuticals Corporation **Letter Date:** May 23, 2014

Drug Name: Epinephrine Injection USP (b) (4) (0.3 mg) **NDA Type:** Original **Stamp Date:** May 28, 2014

The following are necessary to initiate a review of the NDA application:

	Content Parameter	Yes	No	Comments
1	Is the product quality microbiology information described in the NDA and organized in a manner to allow substantive review to begin? Is it legible, indexed, and/or paginated adequately?	X		
2	Has the applicant submitted an overall description of the manufacturing processes and microbiological controls used in the manufacture of the drug product?	X		Section 3.2.P.3.3, Flow Chart Figure 3.2.P.3.3-2.
3	Has the applicant submitted protocols and results of validation studies concerning microbiological control processes used in the manufacture of the drug product?	X		Section 3.2.P.3.5.3 - 3.2.P.3.5.7
4	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?		X	
5	Has the applicant submitted preservative effectiveness studies (if applicable) and container-closure integrity studies?	X		CCI Validations provided in Section : 3.2.P.8.3.
6	Has the applicant submitted microbiological specifications for the drug product and a description of the test methods?	X		Section 3.2.P.5.1
7	Has the applicant submitted the results of analytical method verification studies?	X		Sterility and Bacterial endotoxins Validation Reports Section 3.2.R.3.P.6 & 8
8	Has the applicant submitted all special/critical studies/data requested during pre-submission meetings and/or discussions?			N/A
9	If sterile, are extended post-constitution and/or post-dilution hold times in the draft labeling supported by microbiological data?			N/A- Single dose injection.
10	Is this NDA fileable? If not, then describe why.	X		

Additional Comments: The drug product is a 505(b)(2) new drug application for Epinephrine Injection USP (b) (4) (0.3mg Pre-filled Single Dose Syringe).

Vinayak B. Pawar, Ph.D., Senior Review Microbiologist, OPS/NDMS **Date**

Bryan S. Riley, Ph.D., Acting Team Leader, OPS/NDMS **Date**

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

/s/

VINAYAK B PAWAR
07/15/2014

BRYAN S RILEY
07/15/2014
I concur.