

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204200Orig1s000

204200Orig2s000

CHEMISTRY REVIEW(S)

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Application: NDA 204200/000
 Submission Date: 07-MAR-2012
 Receipt Date: 07-JAN-2013

Action Goal:
 District Goal: 08-NOV-2012

Applicant: JHP PHARMS
 1 UPPER POND RD BLDG D 3RD FL
 PARSIPPANY, NJ 07054

Brand Name: ADRENALINE
 Estab. Name:
 Generic Name: ADRENALINE

Priority: 7
 Org. Code: 570

Product Number; Dosage Form; Ingredient; Strengths

001: SOLUTION, INJECTION: EPINEPHRINE (b) (4)
 (u) (u)

Application Comment: SEE ESTABLISHMENT COMMENTS BELOW (on 08-MAR-2012 by K. SHARMA () 3017961270)

FDA Contacts:	Y. LIU	Project Manager	3017961926
	Y. WANG	Review Chemist	3017961479
	A. SCHROEDER	Team Leader	3017961749

Overall Recommendation:	ACCEPTABLE	on 06-AUG-2012	by M. STOCK	(HFD-320)	3017964753
	PENDING	on 15-JUN-2012	by EES_PROD		
	WITHHOLD	on 29-MAR-2012	by EES_PROD		
	PENDING	on 20-MAR-2012	by EES_PROD		
	PENDING	on 16-MAR-2012	by EES_PROD		
	PENDING	on 16-MAR-2012	by EES_PROD		

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE OTHER TESTER
FINISHED DOSAGE OTHER TESTER

Establishment Comment: AN ALTERNATE TESTING FACILITY FOR LAL USP <85> (API AND DRUG PRODUCT), PARTICULATE MATTER USP <788> (DRUG PRODUCT), AND AME USP <51> (DRUG PRODUCT).
(on 20-MAR-2012 by K. SHARMA () 3017961270)

Profile: CONTROL TESTING LABORATORY OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	20-MAR-2012				LIUY
OC RECOMMENDATION	20-MAR-2012			ACCEPTABLE BASED ON PROFILE	STOCKM

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: (b) (4) FEI: (b) (4)
 (b) (4)

DMF No: (b) (4) AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Establishment Comment: DRUG SUBSTANCE MANUFACTURER (on 08-MAR-2012 by K. SHARMA () 3017961270)

Profile: (b) (4) OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	16-MAR-2012				LIUY
OC RECOMMENDATION	19-MAR-2012			ACCEPTABLE BASED ON PROFILE	SMITHDE

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: 1818977 FEI: 1818977
JHP PHARMACEUTICALS, LLC
870 PARKEDALE RD
ROCHESTER, MI 48307

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE OTHER TESTER
DRUG SUBSTANCE RELEASE TESTER
DRUG SUBSTANCE STABILITY TESTER
FINISHED DOSAGE LABELER
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Establishment Comment: DRUG PRODUCT MANUFACTURER, DRUG PRODUCT TESTING AND RELEASE, STABILITY TESTING OF DRUG PRODUCT. PACKAGING AND LABELING OF DRUG PRODUCT. WAREHOUSE FOR DRUG PRODUCT STORAGE. PRODUCT IS TO BE MARKETED (b) (4) (on 14-MAR-2012 by K. SHARMA () 3017961270)
Profile: STERILE-FILLED SMALL VOLUME PARENTERAL DRUGS OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	16-MAR-2012				LIUY
SUBMITTED TO DO	19-MAR-2012	10-Day Letter			SMITHDE
A ED INSPECTION TO IB PECTION ONGOING	23-MAR-2012	GMP Inspection			DOMBROWSKIR
DO RECOMMENDATION	06-AUG-2012			ACCEPTABLE	DOMBROWSKIR
EI OF FIRM 3/2012 DOWNGRADED TO VAI BASED ON FIRM'S RESPONSE AND OUTCOME OF A DISTRICT REGULATORY MEETING WITH FIRM. FIRM HAS BEEN MANUFACTURING THIS PRODUCT FOR MANY YEARS - APPLICATION ONLY RECENTLY SUBMITTED.				BASED ON FILE REVIEW	
OC RECOMMENDATION	06-AUG-2012			ACCEPTABLE	STOCKM
				DISTRICT RECOMMENDATION	

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE OTHER TESTER

Establishment Comment: DRUG SUBSTANCE AND EXCIPIENTS RESIDUAL SOLVENT TESTS (on 14-MAR-2012 by K. SHARMA () 3017961270)

Profile: CONTROL TESTING LABORATORY OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	16-MAR-2012				LIUY
OC RECOMMENDATION	19-MAR-2012			ACCEPTABLE BASED ON PROFILE	SMITHDE

CMC Review Amendment

NDA: 204200

Drug Name: Adrenalin (Epinephrine)

Applicant: JHP Pharmaceuticals LLC

Reviewer: Ying Wang, PhD

Date: Nov. 13, 2012

Submissions covered in this review: Amendment dated Oct 15, 2012 and Nov. 9, 2012

Previous Review: CMC Review of NDA 204200 dated August 10, 2012

Summary:

The original NDA had major deficiencies in drug product quality and the original CMC review (dated Aug. 10, 2012) recommended a complete response. Discussions between the Agency and the applicant have continued and multiple amendments have been submitted to address the deficiencies since then. The latest amendments have adequately addressed the issues regarding the specification for the drug product and the analytical method validations. At the Agency's recommendation the applicant has also agreed to a commitment to conduct a post market study to investigate the cause(s) of the major impurity [REDACTED] (b) (4).

Conclusion:

This NDA as amended is adequate and is recommended for approval from CMC perspective.

The proposed expiry of 15 months when stored at controlled room temperature (20 – 25°C; 68 – 77°F) is granted.

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/s/

YING WANG
11/15/2012

PRASAD PERI
11/15/2012
I concur

To: NDA 204-200 Adrenalin® (epinephrine) Injection - Document File
From: Rapti D. Madurawe, Branch Chief, Branch V, ONDQA
Through: Terrance Ocheltree, Division Director, Division II, ONDQA
Date: 06-September-2012
Re: PDUFA Goal Date Extension

Quality Review #1 dated August 14, 2012 (*see DARRTS*) recommended a complete response (CR) action for NDA 204-200. The primary reason for the CR recommendation was the failure to assure adequate drug product quality (b) (4)

Specifically, the proposed acceptance criterion of NMT (b) (4)
for total impurities of the drug product (b) (4)

In addition, there are some adequacy concerns regarding three analytical methods.

On August 17, 2012, JHP Pharmaceuticals submitted to the NDA the 9-month and 12-month stability updates for the three registration stability batches. (b) (4)

The Agency held a teleconference with JHP Pharmaceuticals on Aug 31, 2012, to discuss the updated stability data and the drug product specification. Prior to the teleconference, JHP submitted additional supportive stability data from other (historic) drug product batches.

During the teleconference JHP confirmed (b) (4)

Subsequently, on September 6, 2012, the Agency received a new proposal from JHP for drug product specifications with additional justification for the revised acceptance criteria.

The new information provided after Quality Review #1 indicates further evaluation (b) (4) is warranted and ONDQA would need to reassess the manufacturing process controls, analytical methods, stability data, specifications and proposed shelf-life. Therefore, ONDQA recommends the PDUFA goal date of NDA 204-200 be extended.

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/s/

RAPTI D MADURAWA
09/07/2012

TERRANCE W OCHELTREE
09/07/2012



NDA 204200

Adrenalin (Epinephrine)

JHP Pharmaceuticals LLC

**Ying Wang, PhD
Xiaobin Shen, PhD**

Review Chemist

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

**CMC REVIEW OF NDA 204200
For the Ophthalmic and Anti-Infective Products Division and
Pulmonary, Allergy and Rheumatology Products Division**

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CMC Review Data Sheet

1. NDA 204200
2. REVIEW #: 1
3. REVIEW DATE: 10-August-2012
4. REVIEWER: Ying Wang, PhD
Xiaobin Shen, PhD
5. PREVIOUS DOCUMENTS: N/A
6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original Submission	3/7/2012
Correspondence (C)	
Amendment (BC)	6/19/2012
Amendment (BC)	7/20/2012
Amendment (BC)	8/2/2012

7. NAME & ADDRESS OF APPLICANT:

Name: JHP Pharmaceutical, LLC
Address: One Upper Pond Road, Building D, 3rd Floor,
Parsippany, NJ 07054
Representative: Steve Richardson
Telephone: 973-658-3561

8. DRUG PRODUCT NAME/CODE/TYPE:

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

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

CMC Review Data Sheet

10. PHARMACOL. CATEGORY: Sympathomimetic catecholamine

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 1 mg/mL

13. ROUTE OF ADMINISTRATION: IM, SC, IO

14. Rx/OTC DISPENSED: Rx OTC

15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#)

SPOTS product – Form Completed

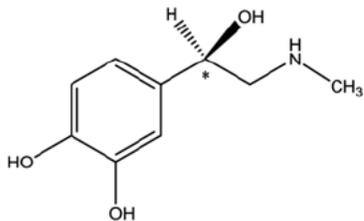
Not a SPOTS product

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**

C₉H₁₃NO₃

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)	Epinephrine drug substance	3	Adequate	Jan. 2012	
	III	(b) (4)	(b) (4)	4	N/A		See container closure review in NDA
	III	(b) (4)	(b) (4)	3	Adequate	June 23, 2011	NDA 201739
	III	(b) (4)	(b) (4)	3	Adequate	Dec. 15, 2008	Reviewed by Steven Donald from microbiology

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:

N/A

CMC Review Data Sheet

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	Aug. 6, 2012	
Pharm/Tox	Acceptable	June 1, 2012	Jane Sohn, Ph.D.
Biopharm	Acceptable	Aug 13, 2012	Kareen Rivere, Ph.D.
LNC	N/A		
Methods Validation	Not recommended currently but may be reevaluated later	Aug 14, 2012	
DMETS	N/A		
EA	Categorical exclusion acceptable (see NDA review)		Ying Wang, Ph.D.
Microbiology	Acceptable	August 7, 2012	Erika Pfeiler, Ph.D.

The CMC Review for NDA 204200

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA is recommended for COMPLETE RESPONSE from the 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

Epinephrine is white to nearly white, odorless, microcrystalline powder or granules, gradually darkening on exposure to light and air. (b) (4)
(b) (4) Epinephrine is hydrophilic, sparingly soluble in water, dependent on solution pH, and is insoluble in most organic solvents. It is soluble in mineral acids and alkali hydroxide solutions.

Drug substance information is referenced in DMF (b) (4) for which (b) (4) is the holder. See the DMF status table earlier in this review.

(2) Drug Product

The drug product, Adrenalin[®] (epinephrine injection, USP, 1:1000), is a sterile injectable solution and is packaged in (b) (4) vials (1 mg/mL). (b) (4)
The drug product is manufactured by JHP Pharmaceuticals, LLC. The storage condition for the drug product is 20°C to 25°C (68°F to 77°F). Protect from light and freezing.

(b) (4)

Executive Summary Section

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

This drug has the following two indications: **Hypersensitivity Reactions (Anaphylaxis)** and for the **Induction of Mydriasis in Cataract Surgery**

Hypersensitivity Reactions: Anaphylaxis

The recommended initial intramuscular injection into the anterolateral aspect of the thigh using a needle long enough (at least 1/2" to 5/8") to ensure the injection is administered into the muscle. The injection may be administered every 5 to 10 minutes as necessary. For treatment of a hypersensitivity reaction caused by drugs that were administered IM, epinephrine may be administered at the site of injection to minimize further absorption.

(b) (4)

(b) (4)

Continuous hemodynamic monitoring is essential, and the dose level should be titrated according to response to treatment and side effects.

(b) (4)

Ophthalmic Use: Induction of Mydriasis in Cataract Surgery

ADRENALIN[®] 1 MG/ML. Use only the Adrenalin[®] 1 mL (b) (4) for ophthalmic use. Adults and Pediatric: In order to maintain mydriasis, Adrenalin[®] may be added to the irrigation fluid at very low doses (1:100,000 to 1:1,000,000 [10 mcg to 1 mcg/mL]). In adults, Adrenalin[®] may also be injected intraocularly as a bolus dose in 0.1 mL at a dilution of 1:100,000 to 1:400,000 (10 mcg to 2.5 mcg/mL).

C. Basis for Approvability or Not-Approval Recommendation

The major drug product degradants

(b) (4)

The proposed acceptance

Executive Summary Section

criterion for total impurities is NMT [REDACTED]

(b) (4)

This is unprecedented for a FDA approved drug product.

Some of the analytical methods [REDACTED] (b) (4) cannot accurately measure the actual level of impurities through the whole reporting range and the level of quantification limits for the methods are far above the ICH reporting threshold (0.1%). The analytical method for sodium bisulfite (antioxidant) can not accurately measure the sodium bisulfite level within the range proposed in the specification. These methods are not acceptable.

Due to the deficiencies noted above, the identity, strength, quality, purity, and potency of the drug product can not 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:

Ying Wang, PhD

Xiaobin Shen, PhD

B. Endorsement Block:

Prasad Peri, PhD, Branch Chief, Branch VIII, ONDQA

C. CC Block: entered electronically in DFS

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/s/

PRASAD PERI

08/14/2012

CMC recommends CR at the current time due to the high level of total impurities

**MEMORANDUM: DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

REVIEW DATE: 02-MAY-2012

TO: NDA 204200

FROM: Prasad Peri, Ph.D.,
Branch Chief
ONDQA, Division III, Branch VIII



THROUGH: Eric Duffy, Ph.D.
Director
ONDQA, Division III

SUBJECT: Comment to Applicant regarding impurities in Epinephrine Drug Product

BACKGROUND: JHP Pharma submitted an NDA for epinephrine injection with two clinical indications: Anaphylaxis indication within DPARP and Mydriasis indication within DTOP. (b) (4)

Additional information on the drug products is available in Initial Quality Assessment review done by Dr. Balajee Shanmugham and entered into DARRTS on 04-12-2012.

This memo is placed into DARRTS to provide initial feedback to the applicant regarding the unacceptably high levels of impurities in the proposed drug products.

The formulation is provided below.

(b) (4)

Quantitative Composition			Batch Quantity	Unit Formula
Ingredient	Grade	Function	(b) (4)	(b) (4)
Epinephrine	USP	Active	(b) (4)	(b) (4)
Sodium Chloride	USP	Tonicity adjustor		
Sodium Metabisulfite	NF	Antioxidant		
(b) (4) Hydrochloric Acid	USP	(b) (4)		1.0 mg
Water for Injection	USP			(b) (4)

(b) (4)

Attached are the proposed drug product specifications.

Drug Product Specification

Test	Specification	Specification
	Release	Stability
Description		
Assay		
Individual Unidentified Impurity		
Total Impurities*		
Identification		
pH		
Sodium Bisulfite		
Total Acidity		
Color & Clarity		
Sterility		
Particulate Matter		
Bacterial Endotoxin		
AME		

* Total Impurities

The level of Total Impurities is approximately [redacted] (b) (4)

Discussions within branches V and VIII led to a conclusion that the applicant should be informed as early as possible that the proposed levels of impurities are unacceptably high from a ONDQA perspective and the applicant should initiate a process [redacted] (b) (4)

Conclusion

The following comment is requested to be sent to the applicant.

Based on the preliminary assessment of the drug product specifications, (b) (4)
[redacted]
[redacted] ONDQA recommends that these
criteria (b) (4) meet the current standards of approved
drug products. In addition, provide adequate mass balance information (b) (4)
[redacted] at release and on stability. For
additional information we refer you to the ICH guidance for industry, “Q3B (R2)
Impurities in New Drug Products,” available at
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073389.pdf>

Prasad Peri, Ph.D.
Branch Chief, Branch VIII

cc:
ONDQA/DIV 3/Branch VIII/PPeri/02-MAY-2012

ONDQA/DIV 3/Branch VIII/EDuffy_____

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/s/

PRASAD PERI
05/02/2012

ERIC P DUFFY
05/02/2012

PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

NDA Number	204-200
Submission Date	March 7, 2012
Product name, generic name of the active	Adrenalin® Injection (epinephrine injection, USP)
Dosage form and strength	Solution/ 1 mg per mL
Routes of Administration	(b) (4) IM, SC, and IO
Indication	Treatment of severe allergic reactions (anaphylaxis) (b) (4) IM, and SC routes) and maintenance of mydriasis in cataract surgery (IO administration)
Applicant	JHP Pharmaceuticals, LLC
Clinical Division	DPARP and DTOP
Type of Submission	505(b)(2) New Drug Application
Biopharmaceutics Reviewer	Kareen Riviere, Ph.D.
Acting Biopharmaceutics Lead	Angelica Dorantes, Ph.D.

The following parameters for the ONDQA's Product Quality-Biopharmaceutics filing checklist are necessary in order to initiate a full biopharmaceutics review (i.e., complete enough to review but may have deficiencies).

ONDQA-BIOPHARMACEUTICS				
<u>A. INITIAL OVERVIEW OF THE NDA APPLICATION FOR FILING</u>				
	Parameter	Yes	No	Comment
1.	Does the application contain dissolution data?		x	Not applicable
2.	Is the dissolution test part of the DP specifications?		x	Not applicable
3.	Does the application contain the dissolution method development report?		x	Not applicable
4.	Is there a validation package for the analytical method and dissolution methodology?		x	Not applicable
5.	Does the application include a biowaiver request?	x		The Applicant requests a waiver of in vivo bioequivalence studies under 21 CFR §320.22(d)(2) for the IM and SC routes only.
6.	Is there information provided to support the biowaiver request?	x		See Appendix
7.	Does the application include an IVIVC model?		x	Not applicable
8.	Is information such as BCS classification mentioned, and supportive data provided?		x	
9.	Is information on mixing the product with foods or liquids included?		x	Not applicable

PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

10.	Is there any <i>in vivo</i> BA or BE information in the submission?	x		The Applicant submitted pharmacokinetic data from published literature (b) (4). This data will be reviewed by the Clinical Pharmacology Team.
-----	---	---	--	---

B. FILING CONCLUSION				
	Parameter	Yes	No	Comment
11.	IS THE BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?	x		
12.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide filing comments to be sent to the Applicant.	-	-	Not Applicable
13.	Are there any potential review issues?			1. The proposed drug product's mode of delivery (manual injection) for the IM and SC routes differs from that of the RLD (auto injector) and may impact the bioavailability of epinephrine. (b) (4)
14.	Reviewer Comments (to be conveyed to the Applicant): None			

{See appended electronic signature page}

Kareen Riviere, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

April 13, 2012
Date

{See appended electronic signature page}

Sandra Suarez Sharp, Ph.D.
Secondary Signature
Office of New Drug Quality Assessment

April 13, 2012
Date

PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

APPENDIX

Biopharmaceutics Information:

This submission includes a BA/BE waiver request for the proposed product (Adrenalin® (b) (4)) for the IM and SC routes of administration. To support the biowaiver request, the Applicant provided a quantitative and qualitative comparison of the formulation, strengths, and needle dimensions for the proposed product and the reference product (EpiPen® Auto-injector) as shown on the tables below.

Comparison of Formulations:

Ingredient	Adrenalin® (b) (4) (mg/mL)	(b) (4) EpiPen® Auto-injector (mg/mL)
Epinephrine	1:1000	1:1000
Sodium Metabisulfite	1	(b) (4)
Sodium Chloride	9	(b) (4)
Hydrochloric Acid		
Water for Injection		

Side-by Side Comparison of RLD vs Proposed Product:

Parameters	RLD - EpiPen® Meridian Medical Technology	Proposed 505(b)(2) NDA JHP Pharmaceuticals, LLC
Drug Name:	EpiPen® (epinephrine injection)	Adrenalin® (epinephrine injection)
Conditions of Use	Treatment of anaphylaxis	Treatment of anaphylaxis
Dosage Form	Injection	Injection
Route of Administration	Intramuscular Subcutaneous	Intramuscular Subcutaneous
Strengths	0.3 mg/0.3 mL (1:1000)	1 mg/mL (1:1000)
Presentations	2 mL solution per Auto-Injector	1 mL (b) (4)
Mode of Delivery (needle dimension)	1/2" to 5/8"	1/2" to 5/8"

The acceptability of the waiver for the IM and SC routes of administration will be the focus of the Biopharmaceutics review. From an initial assessment of the submission, there are two potential review issues:

1. The proposed drug product's mode of delivery differs from that of the RLD and may impact the bioavailability of epinephrine.

(b) (4)

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/s/

KAREEN RIVIERE
04/13/2012

SANDRA SUAREZ
04/13/2012

Initial Quality Assessment Branch V
Pre-Marketing Assessment Division II

OND Division: Division of Transplant and Ophthalmology Products and
Division of Pulmonary, Allergy and Rheumatology
Products

NDA: 204200

Applicant: JHP Pharmaceuticals, LLC

Stamp Date : 7 March, 2012

Proposed Trademark: Adrenalin

Established Name: Epinephrine injection, USP

Dosage Form: Injection

Route of Administration: IM, SC, (b) (4) IO

Strength: 1 mg/mL

Indication: Treatment of severe acute anaphylactic reaction (DPARP)
and maintenance of mydriasis in cataract surgery.
(DTOP)

Reviewer : Milton Sloan (drug substance) & Ying Wang (drug
product)

CMC Lead : Bala Shanmugam

Prdt Quality Microbiologist: Erica Pfeiler

	YES	NO
Acceptable for filing:	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Comments for 74-Day Letter:	<input checked="" type="checkbox"/>	<input type="checkbox"/>

Summary and Critical Issues

Summary

Epinephrine, also referred to as adrenaline is a catecholamine and is the native hormone released by the adrenal medulla. The NDA under review is classified as Type 7, a category for drugs already marketed, but without an approved NDA. This 505 (b) (2) NDA refers to the Referenced Listed Drug (RLD), EpiPen®, marketed under NDA 19-430 which also utilizes the same API, epinephrine. As mentioned above, the NDA provides for two indications and will be reviewed by DPAR and DTOP. For administrative purposes, the NDA has been split into two originals, 1 and 2 for DPAR and DTOP indications, respectively. The submission, including methods validation is all electronic and located in the EDR. The drug product is formulated as a sterile (b) (4) injection for administration as (b) (4) IM or SC for DPAR indication. For the Ophthalmic indication, the drug product is formulated (b) (4) for IO administration. (b) (4)

The proposed commercial packages are 1 mL in 3 mL glass via (b) (4)

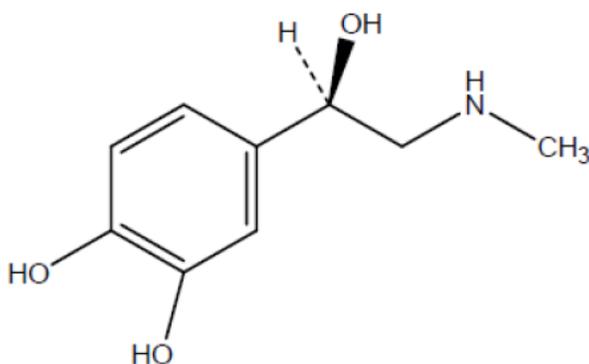
The company is requesting a shelf-life

of (b) (4) when stored at 20-25°C. Draft container, and carton labels and PI has been submitted.

All manufacturing and testing facilities have been entered in EES. Please note that a pre-NDA meeting was held. The minutes of the Pre-NDA meeting is attached to this IQA for quick reference to the reviewer. The CMC filing review is also attached to this IQA.

This NDA will be reviewed on a **Priority** time line.
PDUFA goal date: DTOP: September 07, 2012.
DPARP: January 7, 2013

Drug Substance



All drug substance information related to manufacturing and controls is referenced to DMF (b) (4). The table below provides status of the above mentioned DMF's at the time of writing this IQA. Letters of authorization from the DMF holder has been provided.

Drug Substance	DMF #	LOA provided (Yes/No)	Status	Comments
Epinephrine	(b) (4)	Y	The last review is by Deepika Lakhani, dated January 27, 2012.	Adequate per last review. At the time of writing the IQA, there are no new quality submissions since last review.

Manufacturer:
(b) (4)

Drug Product

Manufacturer:

JHP Pharmaceuticals LLC
870 Parkdale Road
Rochester, MI 48307

The product is a sterile, injectable solution containing 1 mg/mL epinephrine. (b) (4)

(b) (4) Based on the perusal of the NDA, the most critical review components of the NDA which needs careful evaluation are: impurities, stability data along with the proposed acceptance criteria (especially those for the impurities) and analytical methods (especially the HPLC assay. Please see below for observations (b) (4)).

- (b) (4)
The justification provided by the company for the proposed overage should be evaluated and determined if the level is acceptable. It should be noted that per USP the assay is (b) (4) and that USP does not specify limits (b) (4).
- (b) (4)
- All excipients used in the formulation are compendial. The impurities formed are briefly discussed alongside the formulation (b) (4)
- (b) (4)
Although the excipient is compendial, it should be verified if the excipient at the levels proposed has been qualified in pre-clinical studies and also consult Pharm/tox on any potential safety concerns. Also, during review it should be determined if any class of impurities of concern from the excipient should be controlled in the drug product specification to ensure that these impurities are adequately controlled.
- Epinephrine is susceptible to molecular oxygen and is a concern to the stability of the drug product (for discussion, please see 3.2.P.2.2). To stabilize the drug product and prevent oxidation, an antioxidant, sodium metabisulfite is added. (b) (4)
A need for DTOP Pharm/Tox consult on the qualification of the excipient at the proposed level should be evaluated. It may be relevant to note here that all excipients/impurities require evaluation from

an ophthalmic perspective since the exposure is local as opposed to a generally systemic exposure.

- Sodium chloride is used in the formulation for tonicity. However, a test for osmolality is not proposed in the drug product specification. *DTOP clinical input may be sought on the need to control this attribute in the drug product specification.*
- The pH of the formulation, per specification is in the range of 2.2-5.0 (USP range)

(b) (4)

The DTOP Clinical Division was informed of the acidic range and the range is acceptable for ophthalmic application. Another important factor where pH is a key factor is racemization. (b) (4)

- The drug product composition is attached to this review
 - Manufacturing process can be defined broadly (b) (4)
- The scale of the 1 mL product is approximately (b) (4) for a capacity of approximately (b) (4) vials (b) (4).

- The DP specification is attached to serve as a quick reference for the reviewer. The table does not provide the analytical method used to test the various quality attributes which makes it inconvenient to cross check the methods used. The regulatory specification proposes different acceptance criteria for a few quality attributes.

- a) (b) (4)
Changes in color, if any, over the shelf-life and during in-use stability studies should be evaluated.
- b) Assay for shelf-life is proposed (b) (4) *Is the lower limit acceptable from quality and clinical?*
- c) The acceptance criteria (b) (4) in DP specification is mentioned as NMT (b) (4) (Section 3.2.P.5.1) while the for the same quality attribute in the stability section (see Section 3.2.P.8.3) it reads, (b) (4). *Perhaps a clarification from the company will resolve this issue.*
- d) *As noted above, there is a test proposed (b) (4) The analytical method (Procedure (b) (4)) seems to be missing in the NDA. This will be requested in the 74-day comment to the company. Questions to be considered during the review of this NDA: Is the proposed level (b) (4) qualified (need to consult Pharm/Tox)? Is there a justification (b) (4)? How do the levels (b) (4) compare to the levels in other approved and*

currently marketed unapproved products? A perusal of the above referenced report indicates that the 1 mL ampoule of Hospira has the maximum level (b) (4). Please note that some of the marketed products use ampoules.

- e) DP stability specification proposes for total impurities an acceptance limit NMT (b) (4) and note that this does not include the NMT (b) (4)
- f) As indicated above, (b) (4) is the main degradant which is controlled in the DP specification (b) (4)
- g) The proposed acceptance criteria for (b) (4) sodium bisulfite acceptance limit for the 1mL fill volume stability specification is (b) (4).
- h) A number of “unknown impurities” are reported (it should be communicated to the company that ICH language be used in reporting impurities) and should be checked with Pharm/Tox if these impurities are qualified. (b) (4)
This should be verified and decided whether the company should be requested to comply with ICH guidelines for reporting/identifying/qualifying threshold or if a reasonable scientific justification is acceptable. (b) (4)
- i) (b) (4) *The specification does not meet the requirements for ophthalmic products which is set per USP <789>. This quality attribute should be evaluated and perhaps recommend establishing a different specification for ophthalmic.*
- j) The proposed acceptance criteria for the quality attributes should be evaluated (b) (4) based on the evaluation of batch analyses and stability data.
- k) (b) (4)

- Based on the perusal of the analytical methods, it appears that the method for estimating (b) (4) has not been submitted. The method, identified as “procedure number (b) (4)” in several places (example, Report DEV 11-006R) is not mentioned in Section 3.2.P.5.2 or 3.2.P.5.3. (b) (4)
The company should submit details of the analytical method, including validation. Since this

information will be immediately needed, this comment should be communicated either in the 74-day letter or earlier.

- In addition to the registration stability data for three batches under accelerated and long-term storage conditions, the NDA provides supportive stability for the currently marketed unapproved products. Please see Table below for a summary of stability information provided in the NDA.

Stability	Marketed Product ^{†⊗} (Supportive Stability)		Registration Batches ^{*⊗} (Primary Stability)	
	Long-term (25°C/60%RH)**	Accelerated (40°C/75%RH)	Long-term (25°C/60%RH)	Accelerated (40°C/75%RH)
Storage Condition				
Packaging Configuration	(b) (4)			
Number of batches tested				
Vial Orientation				
Available Stability Data				

[†]Need confirmation that the formulation & container closure are the same as proposed for commercial

* (b) (4)

⊗ Limited stability study of commercial epinephrine injections from different manufacturers is provided in the report DEV-12-011

**The stability protocol mentions (b) (4) (needs to be clarified). Reports: DEV-11-021 and 022.

a) (b) (4)

b) Reports on the investigations of several deviations during stability have been provided which needs careful evaluation.

- The container closure system used in this NDA is commonly used for the injectable dosage form. The company has provided LOA for the DMF's referenced. (b) (4)
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- [REDACTED] (b) (4)
- [REDACTED] (b) (4)
- Draft container and carton labels have been provided. [REDACTED] (b) (4)
- *The “Description” part of the PI can be reworded to give better clarity on the inactive ingredients* [REDACTED] (b) (4)
- Section 16 of the PI, “How supplied/storage and handling” may need input from DMEPA. *The description of the packaging part can better represent the number of vials per pack.*
- [REDACTED] (b) (4)

Early action needed:

- 1) Reviewer should evaluate items identified *in italics* in this IQA.

Comments for 74-day letter

1. Section 3.2.P.3.3., [REDACTED] (b) (4) manufacturing process description mentions inspection of the [REDACTED] (b) (4) 3 mL vials. [REDACTED] (b) (4)
2. Please confirm that the currently marketed 1mL [REDACTED] (b) (4) and container closure systems are identical to the proposed commercial formulation and container closure system.
3. The analytical method for estimating [REDACTED] (b) (4) (Procedure Number [REDACTED] (b) (4)) seems to be missing. Please submit the method along with validation details or indicate where in the NDA this information is provided.

Comments and Recommendation:

Based on the perusal of this NDA, it is determined to be complete and therefore filable from CMC perspective. Drs. Milton Sloan and Ying Wang have been assigned to review the drug substance and drug product components, respectively.

Balajee Shanmugam
CMC Lead

See DARRTS
Date

Rapti Madurawe, Ph.D.
Branch Chief

See DARRTS
Date

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/s/

BALAJEE SHANMUGAM
04/12/2012

RAPTI D MADURawe
04/12/2012

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

7.	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered 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) 	✓		<p>Yes, as noted in item 5 of this review, the required information has been submitted. The Drug substance is referenced to DMF (b) (4) and a. LOA has been provided.</p>
8.	<p>Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • 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) 	✓		

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

9.	<p>Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • 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) 	✓	
10.	<p>Is a statement provided that all facilities are ready for GMP inspection at the time of submission?</p>	✓	<p>The statement in Section 1.1.2 of the NDA mentions that JHP Pharmaceuticals (drug product manufacturer) is ready for inspection and Section 3.2.P.3.1 indicates the readiness of the testing facilities for inspection. However, there is no statement about the preparedness of the drug substance manufacturing facility for inspection.</p>

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
	Parameter	Yes	No	Comment
11.	<p>Has an environmental assessment report or categorical exclusion been provided?</p>	✓		

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	Yes	No	Comment
12.	Does the section contain a description of the DS manufacturing process?	✓		The drug substance is referenced to DMF (b) (4) (last reviewed in Jan 2012). A LOA has been provided in the NDA.
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?			Referenced to DMF
14.	Does the section contain information regarding the characterization of the DS?			Referenced to DMF
15.	Does the section contain controls for the DS?			Referenced to DMF
16.	Has stability data and analysis been provided for the drug substance?			Referenced to DMF
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		✓	
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		✓	

**PRODUCT QUALITY (Small Molecule)
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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?	✓		
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?	✓		
21.	Is there a batch production record and a proposed master batch record?	✓		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	✓		
23.	Have any biowaivers been requested?	✓		The company is requesting biowaiver based on the similarity of the presented formulation to the RLD, EpiPen® (see Section 1.12.15 in the NDA)
24.	Does the section contain description of to-be-marketed container/closure system and presentations?	✓		The NDA references the following DMF's for the container closure: a) DMF (b) (4) b) DMF (b) (4) c) DMF (b) (4) d) DMF (b) (4) LOA's have been provided in the NDA.
25.	Does the section contain controls of the final drug product?	✓		
26.	Has stability data and analysis been provided to support the requested expiration date?	✓		The NDA provides 18-24 months accelerated and 6-months long-term supportive stability data for multiple historical (b) (4) batches and 6-months long-term and 6-months accelerated stability data for three registration batches. The requested expiration date is (b) (4)
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		✓	NA

**PRODUCT QUALITY (Small Molecule)
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28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		✓	NA
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F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
29.	Is there a methods validation package?	✓		

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?	✓		Yes. Product Quality Microbiology will provide an evaluation.

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?	✓		Yes, as noted above, DMFs have been referenced for the drug substance and container closures. LOA's have been provided from the respective DMF holders.

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)	II	(b) (4)	Epinephrine	5-Jan-12	
	III		(b) (4)	3-Feb-09	
	III			12-Aug-10	
	III			16-Sep-10	
	III			16-Sep-10	

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

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

J. FILING CONCLUSION				
	Parameter	Yes	No	Comment
34.	IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?	✓		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.			NA
36.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?	✓		<div style="background-color: #cccccc; height: 80px; width: 100%;"></div> <p>3. The analytical method for estimating ^{(b) (4)} (Procedure Number ^{(b) (4)}) is missing. Please submit the above mentioned method along with validation details or indicate where in the NDA this information is provided.</p>

{See appended electronic signature page}

Balajee Shanmugam
CMC Lead
Division of Pre-Marketing Assessment, DNDQ II
Office of New Drug Quality Assessment

Date

{See appended electronic signature page}

Rapti Madurawe Ph.D.
Branch Chief
Branch V
Division of Pre-Marketing Assessment
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment

Date

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/s/

BALAJEE SHANMUGAM
04/12/2012

RAPTI D MADURawe
04/12/2012