

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204640Orig1s000

CHEMISTRY REVIEW(S)

NDA 204640

Adrenalin (Epinephrine) 30 mL

JHP Pharmaceuticals LLC

Ying Wang, PhD

Review Chemist

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

**CMC REVIEW OF NDA 204640
For Pulmonary, Allergy and Rheumatology Products Division**

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CMC Review Data Sheet

CMC Review Data Sheet

1. NDA 204640
2. REVIEW #: 1
3. REVIEW DATE: 10-December-2013
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	8/2/2013
Correspondence (C)	
Amendment (BC)	8/15/2013
Amendment (BC)	12/7/2013

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: Standard

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

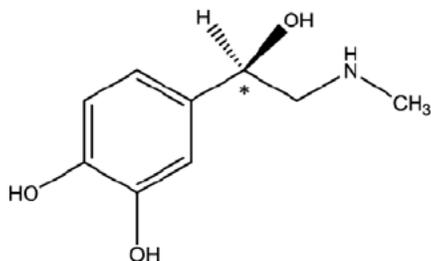
10. PHARMACOL. CATEGORY: Sympathomimetic catecholamine

CMC Review Data Sheet

11. DOSAGE FORM: Injection
12. STRENGTH/POTENCY: 1 mg/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

1. 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	July 15, 2013	Reviewed by Dr. Erika Englund
	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	11/27/2013	
Pharm/Tox	Acceptable	10/21/2013	Matthew Whittaker, Ph.D.
Biopharm	Acceptable	12/5/2013	Assadollah Noory, Ph.D.
LNC	N/A		
Methods Validation	Not recommended currently but may be reevaluated later		
DMEPA	See Review	Nov 19, 2013	Teresa McMillan, PharmD
EA	Categorical exclusion acceptable (see NDA review)		Ying Wang, Ph.D.
Microbiology	Acceptable	11/25/2013	Erika Pfeiler, Ph.D.

Executive Summary Section

The CMC Review for NDA 204640

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA is recommended for APPROVAL from the chemistry, manufacturing and control (CMC) perspective.

The proposed expiry of 14 months when stored at controlled room temperature (20 – 25°C; 68 – 77°F) is granted.

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

The proposed post marketing commitments from the applicant for a leachable study for the drug product solution with the stopper used in the container closure system are acceptable and are listed below:

1. Develop and validate analytical method(s) if applicable for leachable testing – April 2014
2. Update ongoing stability program and protocols to reflect leachable testing – June 2014
3. Test retained samples at or near end of shelf life for leachables. Report results in NDA – Dec. 2014.
4. Revise drug product specification to include leachable testing if necessary – Dec. 2014

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)

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.

(b) (4) nced in DMF (b) (4) for which (b) (4) is the holder. See the DMF status table earlier in

Executive Summary Section

(2) Drug Product

The drug product, Adrenalin® (epinephrine injection, USP, 1:1000), is a sterile injectable solution and is packaged in 30 mL multi-dose vials (30 mg/30mL). The formulation of Adrenalin 30 mL is similar to Adrenalin 1 mL presentation (approved in December 2012, NDA 204200) with the addition of chlorobutanol preservative. The drug product is manufactured by JHP Pharmaceuticals, LLC according to a standard manufacturing process ((b)(4)) that meets current GMP requirements for parenteral products. This 30 mL presentation of Adrenalin has been marketed for over 100 years before submitting in this NDA for approval. There is no pharmaceutical development information in the submission for the manufacturing process of the drug product. The quality is controlled by the end product testing according to the specification. The approved Adrenalin 1 mL presentation has the same approach. The storage condition for the drug product is 20°C to 25°C (68°F to 77°F). Protect from light and freezing.

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

The 30 mL Adrenalin is only indicated for emergency treatment of allergic reaction (type 1), including anaphylaxis. Please note the 30 mL Adrenalin presentation is not indicated for induction and maintenance of mydriasis during intraocular surgery.

Recommended dosage for Anaphylaxis (Adrenalin 1 mL and 30 mL vials):

- *Adults and Children 30 kg (66 lbs) or more:* 0.3 to 0.5 mg (0.3 to 0.5 mL) intramuscularly or subcutaneously into anterolateral aspect of the thigh every 5 to 10 minutes as necessary
- *Children 30 kg (66 lbs) or less:* 0.01 mg/kg (0.01 mL/kg), (b)(4) 0.3 mg (0.3 mL), intramuscularly or subcutaneously into anterolateral aspect of the thigh every 5 to 10 minutes as necessary.

C. Basis for Approvability or Not-Approval Recommendation

Adrenalin 1 mL presentation (NDA 204200) had been extensively reviewed in 2012 for the CMC aspects. This Adrenalin 30 mL presentation is an extension of the 1 mL presentation. The main difference in the composition is the addition of chlorobutanol preservative in 30 mL for multi-dose use purpose. There is no safety concern per pharm/tox reviewer for this preservative. High level of degradants in the drug product was a major concern in the review of NDA 204200. The approved drug product specification for 1 mL has the total impurities limit of no more than (b)(4)%. The proposed specification for the 30 mL presentation is similar to that of approved 1 mL presentation. The only exception is the slight increase of the limit for degradant (b)(4) proposed by JHP, which is increased from (b)(4)% during stability.

Executive Summary Section

The proposal is acceptable since there is no safety concern (per P/T) for this increase in ^{(b) (4)} and the total impurities level remain the same.

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

Ying Wang, PhD

B. Endorsement Block:

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

C. CC Block: entered electronically in DFS

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/s/

YING WANG
12/11/2013

PRASAD PERI
12/11/2013
I concur

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

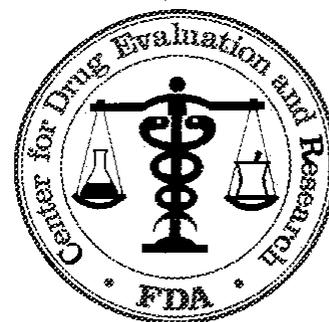
DATE: 03-DEC-2013

TO: N204640 File

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

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

SUBJECT: Update on Establishment Evaluation Request for N204640 Adrenalin®
(epinephrine) Injection



SUMMARY:

The Office of Compliance issued an overall recommendation of ACCEPTABLE for the application on 27-NOV-2013. The summary report from the Establishment Evaluation System is attached below.

Craig M. Bertha, Ph.D.
Chemist and Acting CMC Lead

cc:
ONDQA/DIV 3/CBertha/03-DEC-2013
ONDQA/DIV 3/EDuffy
ONDQA/DIV 3/PPeri _____
ONDQA/DIV3/YWang
ONDQA/DIV 3/YLiu
OND/DPARP/PStark
OND/DPARP/CHill
OND/DPARP/MWhittaker
OB/DBII/RABugov

FDA CDER EES ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application: NDA 204640/000 Sponsor: JHP PHARMS
Org. Code: 570 1 UPPER POND RD BLDG D 3RD FL
Priority: 7 PARSIPPANY, NJ 07054
Stamp Date: 07-MAR-2012 Brand Name: ADRENALIN®
PDUFA Date: 02-JUN-2014 Estab. Name:
Action Goal: Generic Name: EPINEPHRINE INJECTION USP
District Goal: 03-APR-2014 Product Number; Dosage Form; Ingredient; Strengths
001; INJECTION; EPINEPHRINE; 1MG

FDA Contacts: Y. WANG Prod Qual Reviewer 3017961479
E. PFEILER Micro Reviewer (HF-22) 3017960642
Y. LIU Product Quality PM 3017961926
C. HILL Regulatory Project Mgr (HFD-570) 3017961226
C. BERTHA Team Leader 3017961646

Overall Recommendation: ACCEPTABLE on (b) (4) by J. WILLIAMS () 3017964196

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)
DMF No: AADA:
Responsibilities: FINISHED DOSAGE OTHER TESTER
Profile: CONTROL TESTING LABORATORY OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: (b) (4)
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)
DMF No: AADA:
Responsibilities: DRUG SUBSTANCE MANUFACTURER
Profile: NON-STERILE API BY CHEMICAL SYNTHESIS OAI Status: POTENTIAL OAI
Last Milestone: OC RECOMMENDATION
Milestone Date: (b) (4)
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment: CFN: 1818977 FEI: 1818977
JHP PHARMACEUTICALS, LLC

DMF No: ROCHESTER, , UNITED STATES 48307 **AADA:**

Responsibilities: FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE OTHER TESTER

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

Last Milestone: OC RECOMMENDATION

Milestone Date: (b) (4)

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

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

DMF No: (b) (4) **AADA:**

Responsibilities: FINISHED DOSAGE OTHER TESTER

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: (b) (4)

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

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/s/

CRAIG M BERTHA
12/03/2013

PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

NDA Number	NDA 204-640
Submission Date	8/14/2013
Product name, generic name of the active	Epinephrine Injection, USP
Dosage form and strength	Injection, 1 mg/mL. 30 mL
Route of Administration	Intramuscular, Subcutaneous
Indication	Emergency treatment of allergic reactions (Type 1), including anaphylaxis.
Applicant	JHP Pharmaceuticals, LLC
Clinical Division	Division of Pulmonary, Allergy and Rheumatology Products
Type of Submission	505 (b) (2)
Biopharmaceutics Reviewer	Banu S. Zolnik, Ph.D.
Biopharmaceutics Team Leader	Tapash Ghosh, Ph.D.
Acting Supervisor	Richard Lostritto, 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</u> OVERVIEW OF THE NDA APPLICATION FOR FILING				
	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 contain in vitro alcohol induced dose dumping studies?		X	Not Applicable
6.	Does the application include a biowaiver request?		X	The Applicant did not request a waiver of in vivo bioequivalence studies.
7.	Is there information provided to support the biowaiver request?		X	See Comment below
8.	Does the application include an IVIVC model?		X	Not Applicable
9.	Is information such as BCS classification mentioned, and supportive data provided?		X	

PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

10.	Is information on mixing the product with foods or liquids included?		X	Not Applicable
11.	Is there any <i>in vivo</i> BA or BE information in the submission?		X	The Application is referenced to the approved NDA 204200 (1 mL single dose vial without preservative)
12.	Are there any manufacturing changes implemented to the clinical trial and bio batch formulations?		X	
13.	Is there any data to submitted to support the manufacturing changes		X	Not Applicable
14.	Is there any data submitted to support the proposed dissolution specification?		X	Not Applicable

B. FILING CONCLUSION				
	Parameter	Yes	No	Comment
15.	IS THE BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?	X		The need for biowaiver request will be conveyed to the Applicant
16.	If the NDA is not fileable from the product quality-biopharmaceutics perspective, state the reasons and provide filing comments to be sent to the Applicant.	-	-	Not Applicable
17.	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
18.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?	X		See Comment below

PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

BIOPHARMACEUTICS INITIAL ASSESSMENT

SUMMARY

This submission contains 505 (b) 2 Application for Adrenaline (epinephrine injection, USP) 1mg/mL, 30 mL multi-use vials. The Applicant made reference to the approved NDA 204200, a 1 mL single dose vial version of the drug product with similar formulation (b) (4) without chlorobutanol preservative. Table 2 below shows the comparative formulation information of the approved 1 mL single vial and the proposed 30 mL multi-use vial.

Table 1: Formulation of Adrenalin Injection 1 mg/mL, 30 mL

Batch formula for Adrenalin® Injection 1mg/mL, 30 mL vial:

Quantitative Composition for 30mL Vial:

Component	Grade	Batch Quantity	Unit Dose	Function
Epinephrine	USP	(b) (4)	(b) (4)	Active
Chlorobutanol	NF	(b) (4)	5.4 mg (b) (4) % overage)	Antimicrobial Preservative
Sodium Chloride	USP	(b) (4)	9.0 mg	(b) (4)
Sodium Metabisulfite (b) (4)	NF	(b) (4)	1.5 mg	(b) (4)
Hydrochloric Acid	USP	(b) (4)	(b) (4)	(b) (4)
Water for Injection	USP	(b) (4)	(b) (4)	(b) (4)

PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

Table 2: Comparative formulation information of 1 mL single vial approved NDA 204200 and the proposed formulation

JHP Adrenalin[®] Drug Product Formulations

Ingredient	Function	30 mL		1 mL	
		mM	mg/mL	mM	mg/mL
Chlorobutanol	Preservative		(b) (4)	--	--
NaCl	(b) (4)		9.00		9.00
Sodium Metabisulfite	(b) (4)	(b) (4)	1.50	(b) (4)	1.00
(b) (4)			(b) (4)		(b) (4)
HCl (b) (4)	pH Adjustment		---		---
Epinephrine (b) (4)	Active Ingredient				(b) (4)

RECOMMENDATION:

From the ONDQA-Biopharmaceutics perspective, NDA 204-640 is fileable. The following comments should be conveyed to the Applicant in the 74-Day Letter.

The applicant needs to request the Agency for a biowaiver for their proposed product as per the CFR requirement to provide in vivo bioequivalence data.

We recommend that in your NDA submission, provide adequate scientific information (e.g. published literature, study data, etc.) supporting the bridging of your proposed product to the reference product (to be clarified by the Applicant) with a side-by-side summary table comparing your proposed product vs. the reference product (including description, formulation, pH, osmolarity, tonicity etc.). Provide justification that any difference(s) between your proposed product and the reference product would not affect the safety and effectiveness of your proposed product.

{See appended electronic signature page}

Banu S. Zolnik, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

09/10/13
Date

{See appended electronic signature page}

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

09/10/13
Date

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/s/

BANU S ZOLNIK
09/10/2013

TAPASH K GHOSH
09/10/2013

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

NDA #: 204640

Received Date: 02-AUG-2013

APPLICATION INFORMATION

1. NEW DRUG APPLICATION NUMBER: N204640

The application is submitted for Adrenalin® (epinephrine injection, USP, 1:1000). It is a sterile injectable solution that is packaged in a 30 mL multi-dose presentation. The drug formulation is similar to the reference drug Epipen and is manufactured by JHP Pharmaceuticals, LLC. A 1 mL single dose vial version of the drug product has already been approved under NDA 204200 (similar formulation of same strength but without chlorobutanol preservative). Thus, it is recommended that the reviewer familiarize him or herself with the CMC related information approved for that application. Information regarding the epinephrine drug substance is mostly provided by reference to DMF ^{(b) (4)} from ^{(b) (4)} ^{(b) (4)} DMF ^{(b) (4)} was most recently reviewed in support of injection drug products on 15-JUL-2013, and was found to be adequate.

2. Drug Name: Arenalin® Injection (epinephrine injection, USP)

The chemistry classification code is **type 5 – New Formulation or New Manufacturer, Same or New Indication**. There is a single strength of the drug product, 1 mg epinephrine/mL. The formulation is for multi-dose use, thus it contains chlorobutanol as a preservative.

3. RECEIVED DATE: 02-AUG-2013 (Applicant: JHP Pharmaceuticals, LLC)

4. RELATED REVIEW DOCUMENTS:

a. Drug Master Files listed on 356h form:

**ONDQA Initial Quality Assessment (IQA) and Filing Review
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NDA #: 204640

Received Date: 02-AUG-2013

DMF #	TYP E	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)	2	(b) (4)	epinephrine API	05-JAN-2012	Last reviewed 15- JUL-2013; Check DMF for LOA (not listed in DARRTS)
	3	(b) (4)	(b) (4)	12-AUG-2012	Last reviewed for (b) (4) 25-APR- 2013; Check DMF for LOA (not listed in DARRTS)
	3	(b) (4)	(b) (4)	10-MAY-2012 & 09-MAY- 2012	Last reviewed for (b) (4) MAY-2011 & 06- JUN-2011 (DMFs (b) (4)); Check DMFs for LOA (not listed in DARRTS)

b. Recommended Consults

CONSULT	YES	NO	COMMENTS: (list date of request if already sent)
Biometrics	X	<input type="checkbox"/>	Request evaluation of stability data analysis provided in P.8.1 to support the proposed 14 month shelf life
Clin Pharm	<input type="checkbox"/>	X	
EES	X	<input type="checkbox"/>	PM to submitted EER on 21-AUG-2013
Pharm/Tox	<input type="checkbox"/>	X	Compare controls (tests/acceptance criteria) for drug product impurities and leachables to that applied to the 1 mL unit dose product of NDA 204200. If comparable, then there would be no need to request the pharmacology/toxicology team evaluate these controls, unless the presence of chlorobutanol alters the leachables profile.

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

NDA #: 204640

Received Date: 02-AUG-2013

			Excipients evaluated in 30-OCT-2012 review for NDA 204200.
Methods Validation	<input type="checkbox"/>	X	Left to reviewer discretion if any drug product methods are questionable, but drug is not an NME so it is not mandatory that any methods be assessed by the Agency laboratory.
EA	X	<input type="checkbox"/>	Applicant claims categorical exclusion as per 21 CFR 25.31(a) on the basis that approval will not increase the use of the active moiety. Request evaluation/advice from Dr. Ranaan Bloom of OPS if team does not believe that use will not increase upon approval.
New Drug Micro	<input type="checkbox"/>	X	The microbiology team was informed via the CDER OPS IO MICRO e-mail address of this application for a sterile injection drug product, and will determine if any microbiology review is needed.
CDRH	<input type="checkbox"/>	X	N/A
Other	<input type="checkbox"/>	X	N/A

c. Other Applications or Submissions to note (if any):

DOCUMENT NAME	DATE	APPLICATION NUMBER	DESCRIPTION
NDA		204200	Unit dose version of drug product w/o chlorobutanol preservative (approved 07-DEC-2012)

d. Previous Communications with the Applicant to note (see module 1.6.3 for complete detail):

DOCUMENT NAME	DATE	APPLICATION NUMBER	DESCRIPTION
Teleconference minutes	23-JUL-2012 (telecon date 21-JUN-2012)	NDA 204200	Discussion of impurities and leachables
Information Request	02-AUG-2012	NDA 204200	Designation of preserved multi-dose presentation as

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

NDA #: 204640

Received Date: 02-AUG-2013

			distinct product (separate user fee)
Information Request	18-SEP-2012	NDA 204200	Miscellaneous CMC deficiencies
Information Request	02-NOV-2012 & 27-NOV-2012	NDA 204200	Impurities-related deficiency comments

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

NDA #: 204640

Received Date: 02-AUG-2013

OVERALL PRODUCT QUALITY CONCLUSIONS AND RECOMMENDATIONS

Is the Product Quality Section of the application fileable from a CMC perspective?		
Yes	No	CMC Filing Issues
X	<input type="checkbox"/>	1.

Are there potential CMC review issues to be forward to the Applicant with the 74 day letter?		
Yes	No	
<input type="checkbox"/>	X	Not based on this IQA.

Is the Product Quality Section of the application fileable from a biopharmaceutics perspective?		
Yes	No	Biopharmaceutics Filing Issues
<input type="checkbox"/>	<input type="checkbox"/>	To be separately assessed by the biopharmaceutics team, but unlikely considering the routes of administration (IM or SC).

Are there potential biopharmaceutics review issues to be forward to the Applicant with the 74 day letter?		
Yes	No	
<input type="checkbox"/>	<input type="checkbox"/>	See above

Does the submission contain any of the following elements?

	Yes	No	Comments
Botanical Products	<input type="checkbox"/>	X	
Combination Products	<input type="checkbox"/>	X	
Nanotechnology	<input type="checkbox"/>	X	
PET	<input type="checkbox"/>	X	
QbD Elements	<input type="checkbox"/>	X	
SPOTS	<input type="checkbox"/>	X	

Is a team review recommended?		
Yes	No	Suggested expertise for team
<input type="checkbox"/>	X	

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

NDA #: 204640

Received Date: 02-AUG-2013

CMC Summary: Critical Issues and Complexities

(This section is formatted to expand as far as needed by author.)

Background: This application is a multi-dose (preserved) version of the 1 mg/mL Adrenalin® (epinephrine injection) of NDA 204200 that was approved for treatment of anaphylaxis 07-DEC-2012. The only differences in the formulations is that the multi-dose product in a 30 mL vial contains 1.5 mg/mL of sodium metabisulfite (b) (4) and 5.4 mg/mL chlorobutanol (antimicrobial preservative), as compared to the 1 mL vial for unit dosing that only contains sodium metabisulfite at 1 mg/mL concentration. There were significant issues related to impurities/shelf life that were resolved for the unit dose drug product of NDA 204200 and it is suspected that similar issues will be pertinent for the multi-dose product. It is recommended that the reviewer familiarize him/herself with the resolution of those issues for the unit dose product when evaluating this NDA.

Description of Facility Related Risks or Complexities (i.e. foreign sites, large number of sites involved, etc.)

See EES for complete list of facilities related to this application.

Five sites have been entered into the EES and the PM has submitted the EER to the Office of Compliance on 21-AUG-2013. The drug substance manufacture takes place at a (b) (4) and the drug product is manufactured by the applicant at its facility in Michigan.

Biopharmaceutics Filing Review: Summary, Critical Issues and Complexities

(This section can expand as far as needed by author.)

Note: A separate filing review may be provided by the biopharmaceutics team.

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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	N/A	Comment
1.	Is the CMC section organized adequately?	X	<input type="checkbox"/>	<input type="checkbox"/>	
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X	<input type="checkbox"/>	<input type="checkbox"/>	
3.	Are all the pages in the CMC section legible?	<input type="checkbox"/>	<input type="checkbox"/>		All pages examined for production of this IQA were legible.
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X	<input type="checkbox"/>	<input type="checkbox"/>	The adequacy of the provided data will be determined during review.

B. FACILITIES*					
	Parameter	Yes	No	N/A	Comment
5	Is a single, comprehensive list of all involved facilities available in one location in the application?	<input type="checkbox"/>	X	<input type="checkbox"/>	See module 1.1.2 of Sequence # 0001 (attachment to Form 356h) and P.3.1
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.	<input type="checkbox"/>	<input type="checkbox"/>	X	

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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 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	<input type="checkbox"/>	<input type="checkbox"/>	Identified in S.2.1, not on Form 356h
8	<p>Are drug product 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 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	<input type="checkbox"/>	<input type="checkbox"/>	

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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) 	X	<input type="checkbox"/>	<input type="checkbox"/>	Various testing sites are also included in P.3.1.
1	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X	<input type="checkbox"/>	<input type="checkbox"/>	Statement not provided for (b) (4) API manufacturing site, but in lieu of this a cGMP certification statement is provided.

* 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	N/A	Comment
11.	Has an environmental assessment report or categorical exclusion been provided?	X	<input type="checkbox"/>	<input type="checkbox"/>	It is left to the reviewer to decide whether or not supportive information or data is needed for the request for categorical exclusion under 21 CFR 25.31(a) based on input from the clinical division about potential changes in usage rate of epinephrine with approval of the application.

D. MASTER FILES (DMF/MAF)					
	Parameter	Yes	No	N/A	Comment

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12.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X	<input type="checkbox"/>	<input type="checkbox"/>	<i>See table on cover page.</i>
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E. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)					
	Parameter	Yes	No	N/A	Comment
13.	Does the section contain a description of the DS manufacturing process?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Yes, by reference to DMF (b)(4)
14.	Does the section contain identification and controls of critical steps and intermediates of the DS (in process parameters)?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	See comment for 13 above.
15.	Does the section contain information on impurities?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	See comment for 13 above.
16.	Does the section contain information regarding the characterization of the DS?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	See comment for 13 above.
17.	Does the section contain controls for the DS?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	See comment for 13 above; the NDA contains the specification sheet for the drug substance.
18.	Has stability data and analysis been provided for the drug substance?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	See comment for 13 above.
19.	Does the application contain Quality by Design (QbD) information regarding the DS?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	See comment for 13 above.
20.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	See comment for 13 above.
21.	Does the section contain container and closure information?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	See comment for 13 above.

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F. DRUG PRODUCT (DP)					
	Parameter	Yes	No	N/A	Comment
22.	Does the section contain quality controls of excipients?	X	<input type="checkbox"/>	<input type="checkbox"/>	
23.	Does the section contain information on composition?	X	<input type="checkbox"/>	<input type="checkbox"/>	
24.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X	<input type="checkbox"/>	<input type="checkbox"/>	
25.	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	<input type="checkbox"/>	<input type="checkbox"/>	Refer to P.3.4 for control of critical steps; there are no intermediate products associated with the drug product manufacture
26.	Is there a batch production record and a proposed master batch record?	<input type="checkbox"/>	X	<input type="checkbox"/>	Although a "representative" executed batch record is provided, no master production record is provided: Note the application is submitted under 505(b)(2), so technically the inclusion of the actual master production record is required. However, as the applicant states that "the commercial manufacturing batch records will be the same as the batch records used to manufacture the registration batches in [the] application," and the representative executed record for one of the registration batches (b)(4) is provided, a master production record will not need to be requested.
27.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	<input type="checkbox"/>	X	<input type="checkbox"/>	No, however, the formulation is similar to the approved unit dose formulation of NDA 204200 but with preservative (b)(4)
28.	Have any biowaivers been requested?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	The biopharmaceutics team will address any biowaiver requests, but likely N/A.

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29.	Does the section contain description of to-be-marketed container/closure system and presentations?	X	<input type="checkbox"/>	<input type="checkbox"/>	DMF references are provided for the CCS components.
30.	Does the section contain controls of the final drug product?	X	<input type="checkbox"/>	<input type="checkbox"/>	
31.	Has stability data and analysis been provided to support the requested expiration date?	X	<input type="checkbox"/>	<input type="checkbox"/>	A consult to biometrics is warranted to evaluate the statistical analysis of the stability data provided in P.8.
32.	Does the application contain Quality by Design (QbD) information regarding the DP?	<input type="checkbox"/>	X	<input type="checkbox"/>	Unless QbD related information are contained in the referenced DMFs associated with the application. Review of DMFs should only be done if new information has been submitted that has not previously been evaluated and found to be adequate for an injection dosage form.
33.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?	<input type="checkbox"/>	X	<input type="checkbox"/>	

G. METHODS VALIDATION (MV)

	Parameter	Yes	No	N/A	Comment
34.	Is there a methods validation package?	<input type="checkbox"/>	X	<input type="checkbox"/>	If assessment of methods is deemed necessary by the reviewer, a list of samples can be requested. Other information necessary to fill out the MV request is found in the application.

H. MICROBIOLOGY

	Parameter	Yes	No	N/A	Comment
35.	If appropriate, is a separate microbiological section included discussing sterility of the drug product?	<input type="checkbox"/>	<input type="checkbox"/>		The microbiology team has been informed of the submission of this application and will make a determination of any review necessary, as per the pilot.

I. LABELING

	Parameter	Yes	No	N/A	Comment
36.	Has the draft package insert been provided?	X	<input type="checkbox"/>	<input type="checkbox"/>	

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37.	Have the immediate container and carton labels been provided?	X	<input type="checkbox"/>	<input type="checkbox"/>	
38.	Does section contain trademark and established name?	X	<input type="checkbox"/>	<input type="checkbox"/>	

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J. FILING CONCLUSION					
	Parameter	Yes	No	N/A	Comment
39.	IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
40.	If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Describe filing issues here or on additional sheets
41.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Describe potential review issues here or on additional sheets

REVIEW AND APPROVAL

This document will be signed in DARRTS by the following:

Craig M. Bertha, Ph.D., Acting CMC Lead
Prasad S. Peri, Ph.D., Branch Chief

{See appended electronic signature page}

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
08/22/2013

PRASAD PERI
08/26/2013
I concur