

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

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PHARMACOLOGY REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number: NDA 204,640
Supporting document/s: SD #1
Applicant's letter date: 3/7/12
CDER stamp date: 3/7/12
Product: Adrenalin® (epinephrine injection), 30 ml
Indication: Treatment of anaphylaxis
Applicant: JHP Pharmaceuticals LLC
Review Division: Division of Pulmonary, Allergy and Rheumatology
Products
Reviewer: Matthew Whittaker, Ph.D.
Supervisor/Team Leader: Timothy Robison, Ph.D.
Division Director: Badrul Chowdhury, M.D., Ph.D.
Project Manager: Carol Hill

Template Version: September 1, 2010

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1 Executive Summary

1.1 Introduction

NDA 204,640 is a 505(b)(2) application from JHP Pharmaceuticals, LLC for the **30 ml** vial presentation of Adrenalin® (epinephrine). This product is intended to be used via the intramuscular (IM) or subcutaneous (SC) route for the emergency treatment of allergic reactions including anaphylaxis. Adrenalin® is currently marketed, but without an approved NDA. The reference product for the current application is EpiPen®, an epinephrine auto-injector product approved for the treatment of anaphylaxis via the IM and SC routes, and marketed under NDA 19,430.

The **1 ml** vial presentation of Adrenalin® was approved on December 7, 2012 for IM and SC administration (NDA 204,200). The current application cross-references data from NDA 204,200 to support the safety, efficacy, and manufacturing controls for the 30 ml vial presentation. The proposed 30 ml adrenalin® product differs from the 1 ml product with respect to (1) drug product formulation and (2) acceptance criteria for drug product impurities. Nonclinical studies were conducted to support the safety of a specific degradant. A safety assessment of the degradant level from a nonclinical perspective was conducted (Nonclinical Chemistry Consultation dated 10/21/13).

The 30 ml adrenalin® product has several differences from EpiPen® including: (1) there is no auto-injector device associated with the proposed product, (2) epinephrine doses are increased in the proposed product, (3) the impurity profiles differ between the two products. The safety of epinephrine is based on extensive previous clinical experience, which is supported in the literature. The Agency accepts reference to nonclinical information in the approved label for EpiPen® as well as the public literature to provide nonclinical support for NDA 204,640.

1.2 Brief Discussion of Nonclinical Findings

No nonclinical studies were submitted to or required for NDA 204,640. The current application cross-references data from NDA 204,200 to support the safety, efficacy, and manufacturing controls for the 30 ml adrenalin® product. The sponsor also references nonclinical information in the approved label for EpiPen® as well as publicly available literature to provide nonclinical support for the proposed product.

1.3 Recommendations

1.3.1 Approvability

NDA 204,640 is recommended for approval from the nonclinical perspective.

1.3.2 Additional Non Clinical Recommendations

None.

1.3.3 Labeling

There are no recommended changes to the current unified label for adrenalin® 1 ml and 30 ml vial presentations.

2 Drug Information

2.1 Drug

CAS Registry Number (Optional)

51-3-4

Generic Name

Epinephrine injection

Code Name

None

Chemical Name

(-)-3,4-Dihydroxy- α -[(methylamino)methyl]benzyl alcohol

Molecular Formula/Molecular Weight

C₉H₁₉NO₃

MW: 183.20 (free base)

Structure or Biochemical Description

Figure 1. Chemical structure of epinephrine

Pharmacologic Class

Sympathomimetic catecholamine

2.2 Relevant INDs, NDAs, BLAs and DMFs

NDA 204,200, the 1 ml presentation of adrenalin® from JHP Pharmaceuticals, was approved on 12/7/12.

2.3 Drug Formulation

The adrenalin® 30 ml drug product has a higher sodium metabisulfite concentration than the approved 1 ml drug product. Additionally, the 30 ml presentation contains the antibacterial/antifungal preservative, chlorobutanol (Table 1).

Table 1. Drug product formulation for 30 ml vial presentation of adrenalin®.

Ingredient	Function	Amount	
		mg/ml	mM
Epinephrine	Active ingredient	(b) (4)	(b) (4)
Chlorobutanol	Preservative	5.4	(b) (4)
Sodium chloride	(b) (4)	9.0	(b) (4)
Sodium metabisulfite	(b) (4)	1.5	(b) (4)
(b) (4) HCl	pH adjustor	(b) (4)	(b) (4)

2.4 Comments on Novel Excipients

The safety of the excipients used in the drug product formulation was evaluated in a Nonclinical Chemistry Consultation submitted to DARRTS on 10/21/13. The excipient levels in adrenalin®, 30 ml at the maximum recommended dose are below levels in currently approved injectable products.

2.5 Comments on Impurities/Degradants of Concern

The safety of degradants at the proposed specifications provided in the original NDA submission (3/7/12) was reviewed in a Nonclinical Chemistry Consultation dated 10/21/13.

2.6 Proposed Clinical Population and Dosing Regimen

For treatment of anaphylaxis, the sponsor proposes 0.3 – 0.5 mg IM or SC every 5 -10 minutes as necessary in adults. In children < 30 kg, (b) (4) 0.3 mg IM or SC every 5-10 minutes as necessary is proposed. No maximum dosage is proposed by the sponsor.

During review of NDA 204,200, medical officer Peter Starke, MD recommended up to 3 x 0.5 mg IM/SC doses in adults and adolescents weighing greater than 30 kg, corresponding to a maximum dose of (b) (4). Dr. Starke recommends up to 3 x 0.3 mg IM/SC injections in children weighing less than or equal to 30 kg ((b) (4)) (See NDA 204,200 nonclinical review, Jane Sohn, Ph.D., 10/30/12).

2.7 Regulatory Background

On March 7, 2012, JHP Pharmaceuticals submitted NDA 204,200, a 505(b)(2) application for 1 ml and 30 ml presentations of Adrenalin® (epinephrine) for treatment of allergic reactions and

anaphylaxis, and for intraocular use during eye surgery to induce and maintain mydriasis. The reference product for this application was EpiPen®, an epinephrine auto-injector product marketed under NDA 19,430. The 1 ml and 30 ml Adrenalin® presentations were judged by the FDA CMC review team to not be qualitatively or quantitatively equivalent. Per the bundling policy, the 30 ml vial presentation was separated into a new application, NDA 204,640 (see FDA Information Request, 8/2/12; Memorandum to File 8/23/12). This action required submission of separate NDAs and separate user fees for the two products. NDA 204,200 (1 ml presentation only) was subsequently approved on December 7, 2012 for IM and SC administration only. The current review pertains only to the 30 ml vial presentation.

3 Studies Submitted

3.1 Studies Reviewed

No nonclinical studies were submitted or required for the active ingredient, epinephrine. Studies were submitted to NDA 204,200 to support the safety of degradants and preservatives which were reviewed under a Nonclinical Chemistry Consultation dated 10/21/13.

3.2 Studies Not Reviewed

None.

3.3 Previous Reviews Referenced

Nonclinical review for NDA 204,200. Jane Sohn, Ph.D. 10/30/12.

Nonclinical Chemistry Consultation for NDA 204,200. Jane Sohn, Ph.D. 6/1/12.

Nonclinical Chemistry Consultation for NDA 204,640. Matthew Whittaker, Ph.D. 10/21/13.

4 Integrated Summary and Safety Evaluation

NDA 204,640 is a 505(b)(2) application from JHP Pharmaceuticals, LLC for the **30 ml** vial presentation of Adrenalin® (epinephrine) for the emergency treatment of allergic reactions including anaphylaxis. The reference product for the current application is EpiPen®, an epinephrine auto-injector (NDA 19,430). The **1 ml** vial presentation of Adrenalin® was approved on December 7, 2012 for IM and SC administration (NDA 204,200)

The formulation of the 30 ml adrenalin® drug product proposed in NDA 204,640 differs from the approved 1 ml adrenalin® product. However, the levels of all excipients are within the range of currently approved injectable products. The proposed acceptance criteria for degradants in the 30 ml adrenalin® drug product also differ from the 1 ml product. The proposed acceptance criteria allow for adequate safety margins and are considered safe from the nonclinical perspective.

The Agency agrees that referencing the nonclinical information in the approved labeling for EpiPen® and publicly available published scientific literature are sufficient to support the filing of NDA 204,640. The nonclinical sections (Section 8.1 for Pregnancy, Section 8.3 for Nursing Mothers, Section 12.1 for Mechanism of Action, and Section 13.1 for Carcinogenesis, Mutagenesis, Impairment of Fertility) of the current label for Adrenalin®, 1 ml (NDA 204,200) require no changes for the Adrenalin®, 30 ml vial presentation (NDA 204,640).

NDA 204,640 is recommended for approval from the nonclinical perspective.

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/s/

MATTHEW T WHITTAKER
12/09/2013

TIMOTHY W ROBISON
12/09/2013
I concur

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

PHARMACOLOGY/TOXICOLOGY NDA CHEMISTRY CONSULTATION

Application number: NDA 204,640
Supporting document/s: SD #1
Sponsor's letter date: 3/7/12
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Product: Adrenalin® (epinephrine injection)
Indication: Treatment of anaphylaxis
Sponsor: JHP Pharmaceuticals LLC
Review Division: Division of Pulmonary, Allergy and Rheumatology
Products
Reviewer: Matthew Whittaker, Ph.D.
Supervisor/Team Leader: Timothy Robison, Ph.D.
Division Director: Badrul Chowdhury, M.D., Ph.D.
Project Manager: Carol Hill, Youbang Liu

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Table 3. Sponsor’s proposed specifications for Adrenalin® 30 ml drug product. 8

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1 Executive Summary

1.1 Introduction

NDA 204,640 is a 505(b)(2) application for the **30 ml** vial presentation of Adrenalin® (epinephrine) for intramuscular or subcutaneous administration for emergency treatment of allergic reactions including anaphylaxis. The reference product for this application is EpiPen®, an epinephrine auto-injector product marketed under NDA 19-430.

The **1 ml** presentation of Adrenalin® was approved on December 7, 2012 for IM and SC administration (NDA 204,200). The 30 ml Adrenalin® product differs from the 1 ml product in several respects, including: (1) excipients used, and (2) the acceptance criterion for the impurity (b) (4) CMC project manager Youbang Liu requested a nonclinical consultation (9/30/13, Appendix 1) to evaluate the proposed acceptance criterion of not more than (NMT) (b) (4) for (b) (4) in the 30 ml Adrenalin® drug product.

1.2 Brief Discussion of Nonclinical Findings

The sponsor evaluated the safety of (b) (4) in two genetic toxicology studies (bacterial mutation assay, chromosomal aberration assay) in support of NDA 204,200. A comprehensive genetic toxicology evaluation was also conducted by the FDA CDER Computational Toxicology Group. Based on the evidence from these studies, (b) (4) is considered to be genotoxic (Reviewed in: nonclinical CMC consultation, NDA 204,200; Jane Sohn, Ph.D., 6/1/2012).

A 14 day (b) (4) study (Study (b) (4)) in Sprague Dawley rats was also conducted to evaluate the toxicity of (b) (4) when co-administered with epinephrine. The (b) (4) NOAEL was judged to be (b) (4), the highest dose tested (Sohn, 2012). Safety margins for (b) (4) at the upper limit of the proposed (b) (4)% acceptance level were calculated on a mg/m² basis. Based on the results of the 2 week rat study, the (b) (4) acceptance criterion of NMT (b) (4)% is considered safe from the nonclinical perspective.

1.3 Recommendations

The acceptance criterion of NMT (b) (4)% for the impurity (b) (4) in the 30 ml presentation of adrenalin® is considered safe from the nonclinical perspective.

2 Drug Information

2.1 Drug

CAS Registry Number (Optional)

51-43-4

Generic Name:

Epinephrine injection

Code Name

None

Chemical Name

(-)-3,4-Dihydroxy- α -[(methylamino)methyl]benzyl alcohol

Molecular Formula/Molecular Weight

C₉H₁₉NO₃

MW: 183.20 (free base)

Structure or Biochemical Description

Figure 1. Chemical structure of epinephrine



Pharmacologic Class

Epinephrine: Sympathomimetic catecholamine

2.4 Comments on Novel Excipients

Sodium metabisulfite

The 30 ml vial presentation has a higher concentration of **sodium metabisulfite** (antioxidant) than the 1 ml presentation (1.5 mg/ml vs. 1.0 mg/ml). (b) (4)

The maximum recommended dose of Adrenalin® in adults is 1.5 ml (see section 2.6). This corresponds to a maximum total sodium metabisulfite dose of (b) (4)

The approved injectable product Septocaine® [articaine HCl (40 mg/ml) plus epinephrine (b) (4) (b) (4)], NDA 020971, 1/12/11; Septodont, Inc.] contains sodium metabisulfite at 0.5 mg/ml.

The maximum recommended articaine dose is 7 mg/kg according to the drug product label. In a 60 kg adult, this would result in a total dose of 420 mg. Given that articaine is present at 40 mg/ml, the maximum sodium metabisulfite dose is calculated as follows:

$$420mg * \frac{1ml}{40mg} = 10.5ml$$

$$10.5ml * \frac{0.5mg}{ml} = 5.3mg$$

The maximum sodium metabisulfite exposure in this approved product is **5.3 mg**. This exceeds the sodium metabisulfite exposure at the maximal Adrenalin® dose. Therefore, the proposed sodium metabisulfite concentration is considered acceptable.

Chlorobutanol

The 30 ml vial Adrenalin® presentation also contains the antibacterial/antifungal preservative **chlorobutanol** at a concentration of 5.4 mg/ml. The maximum recommended dose of Adrenalin® in adults is (b) (4) (see section 2.6). This corresponds to a maximum total sodium metabisulfite dose of (b) (4)

Testosterone enanthate is an approved intramuscular product (ANDA 040475, 8/2/2007; Paddock Laboratories) for the treatment of male hypogonadism, delayed puberty in males, and palliation of inoperable mammary cancer in women. Testosterone enanthate is present at 200 mg/ml and chlorobutanol is present at (b) (4) in this drug product. The maximum recommended testosterone dose for all indications is 400 mg given once every 2 – 4 weeks. The resulting maximum chlorobutanol dose is calculated as follows:

(b) (4)

The maximum chlorobutanol exposure in this approved product is (b) (4). This exceeds the chlorobutanol exposure at the maximal Adrenalin® dose. Therefore, the proposed chlorobutanol concentration is considered acceptable.

2.5 Comments on Impurities/Degradants of Concern

The release and shelf-life limit specifications for the Adrenalin® 30 ml drug product are listed in Table 3. The sponsor has carried out 24 months of long term stability, 6 months of accelerated stability, and 12 months of intermediate stability testing on upright and inverted orientations of the 30 ml Adrenalin® presentation. The specifications for total impurities (NMT (b) (4)%) and (b) (4) (NMT (b) (4)) both had less than 15 months of maximum supported shelf life. The sponsor is proposing an expiration date of 14 months for Adrenalin® 30 ml vials. The current review addresses the nonclinical support for the safety of (b) (4) (Figure 2) at the upper limit of the proposed specification ((b) (4)). It is noted that the original specification for (b) (4) in the 30 ml presentation in NDA 204,200 was (b) (4)%. (b) (4) forms as a product of the reaction of the excipient sodium metabisulfite with the active ingredient epinephrine.

Table 3. Sponsor’s proposed specifications for Adrenalin® 30 ml drug product.

Test	Specification 30 mL Release Limit	Specification 30 mL Shelf-Life Limit
Description		(b) (4)
Assay		(b) (4)
	(b) (4)	(b) (4)
Individual Unidentified Impurities		
Total Impurities*		
Identification	Positive	N/A
pH	2.2 - 5.0	2.2 - 5.0
Sodium Bisulfite		(b) (4)
Chlorobutanol		(b) (4)
Total Acidity	NMT (b) (4)	N/A
Color & Clarity	Meets USP	Meets USP
Sterility	Meets Test USP<71>	Meets Test USP<71>
Particulate Matter	Meets USP <788>	Meets USP <788>
Bacterial Endotoxin		(b) (4)
AME**	Pass	Pass

* Total Impurities include (b) (4)

**Antimicrobial Effectiveness Testing will be performed at release and end of shelf life for the registration batches : validation batches only. Thereafter, annual stability lots will be tested for preservative content in lieu of antimicrobial effectiveness testing.

2.6 Proposed clinical population and dosing regimen

For treatment of anaphylaxis, the sponsor proposes 0.3 – 0.5 mg IM or SC every 5 -10 minutes as necessary in adults. In children < 30 kg, (b) (4) 0.3 mg IM or SC every 5-10 minutes as necessary is proposed. No maximum dosage is proposed by the sponsor.

During review of NDA 204,200, medical officer Peter Starke, MD recommended up to 3 IM/SC doses in adults and adolescents > 12 years old, corresponding to a maximum dose of **1.5 mg**. The maximum recommended dose is **0.9 mg** for children 6 – 12 years old, and **0.45 mg** for children <6 years old (Sohn, 2012).

2.8 Regulatory Background

On March 7, 2012, JHP Pharmaceuticals submitted NDA 204,200, a 505(b)(2) application for 1 ml and 30 ml presentations of Adrenalin® (epinephrine) for treatment of allergic reactions and anaphylaxis, and for intraocular use during eye surgery to induce and maintain mydriasis. The reference product for this application was EpiPen®, an epinephrine auto-injector product marketed under NDA 19-430. The 1 ml and 30 ml Adrenalin® presentations were judged by the FDA CMC review team to not be qualitatively or quantitatively equivalent and required submission of separate NDAs for the two products (August 23, 2012). The 30 ml presentation was assigned NDA number 204,640. JHP declined to pay the separate user fee for the 30 ml formulation at that time. NDA 204,200 (1 ml presentation only) was subsequently approved on December 7, 2012 for IM and SC administration only.

JHP submitted payment of the user fee for NDA 204,640 (30 ml presentation) on 8/2/13.

6 General Toxicology

6.2 Repeat-Dose Toxicity

JHP completed a 14 day study (Study (b) (4)) in Sprague Dawley rats to evaluate the toxicity of (b) (4) when co-administered with epinephrine in support of NDA 204,200. This study was reviewed in detail in a nonclinical chemistry consultation for NDA 204,200 (Sohn, 2012). Briefly, animals received daily intravenous doses of 20 µg/kg epinephrine + (b) (4) (b) (4) for 14 days. The no observed adverse effect level (NOAEL) for (b) (4) was judged to be (b) (4) (b) (4) the highest dose tested.

7 Genetic Toxicology

(b) (4) was evaluated by the sponsor in a bacterial mutation assay and an *in vitro* chromosomal aberration assay. These studies were reviewed in detail in a nonclinical chemistry consultation for NDA 204,200 (Sohn, 2012). Briefly, (b) (4) was negative for induction of genotoxic responses in the bacterial reverse mutation assay using both the plate incorporation and preincubation methods, in the presence and absence of metabolic activation.

In the chromosomal aberration assay, (b) (4) induced chromosomal aberrations at the highest dose tested (b) (4) with 3 hr exposure and metabolic activation. The percentage of cells with

structural aberrations was (b) (4)%, significantly higher (b) (4) than the observed (b) (4)% in negative controls. (b) (4) without metabolic activation, with 3 hr and 19 hr exposure, did not induce an increase in cells with structural aberrations, but dosing was not appropriate as the sponsor did not dose to cytotoxic levels.

The FDA CDER Computational Toxicology Group evaluated the genotoxic potential of (b) (4) using three separate genetic toxicity prediction programs: Derek (b) (4). (b) (4) was predicted to be positive for *Salmonella* mutagenicity while no prediction was made for *E. coli* mutagenicity based on the lack of representation in the model training data sets. Based on the totality of the data, (b) (4) is considered genotoxic (Sohn, 2012).

11 Integrated Summary and Safety Evaluation

The CMC consultation request from Youbang Liu (9/30/13) specifically inquired about the safety of the impurity (b) (4) at the proposed (b) (4) upper acceptance limit. (b) (4) forms as a product of the reaction of the excipient sodium metabisulfite with the active ingredient epinephrine. Sodium metabisulfite is included in the drug product formulation (b) (4) epinephrine.

The 30 ml adrenalin® drug product proposed in NDA 204,640 differs from the approved 1 ml adrenalin® product (NDA 204,200) in formulation. The sodium metabisulfite concentration is increased, and the preservative chlorobutanol is included. The levels of each of these excipients are within the range of currently approved injectable products.

(b) (4) is considered genotoxic based on positive results in an *in vitro* chromosome aberration assay carried out by the sponsor as well as an *in silico* Computational Toxicology assessment conducted by the FDA. However, given the acute use of the drug product and the nature of the proposed indication, the positive genotoxic results are not considered to represent a significant risk to patients (Sohn, 2012).

In a 14 day (b) (4) study in rats, the (b) (4) NOAEL was judged to be (b) (4), the highest dose tested. A dose of (b) (4) is used for safety margin calculations. This value is based on the actual measured values (LC/MS/MS) of (b) (4) concentration from dose formulation samples on days 2 and 13 of the study. This dose is multiplied by the conversion factor (b) (4) (FDA *Guidance for Industry: Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers*) to obtain the NOAEL dose relative to body surface area in the rat: (b) (4)

(b) (4)

Body surface area values for human adults and children 6 -12 years old were obtained from the FDA *Guidance for Industry: Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers*. The body surface area for children <6 years old was estimated using a body weight of 14 kg. This body weight was derived from the average weight of 3 year old boys and girls in the 50th percentile (www.cdc.gov/growthcharts). The body surface area for a 14 kg child is estimated to be 0.62 m² based on published literature (Sharkey et al. 2001).

Table 4. Safety margins for (b) (4) at the maximum recommended Adrenalin® dose.

	Body surface area (m ²)	Maximum IM/SC adrenalin® dose (mg) ^c	Maximum IM/SC adrenalin® dose (mg/m ²)	(b) (4) dose at (b) (4) limit (mg/m ²)	(b) (4) NOAEL in 2 wk. rat study (mg/m ²)	Safety Margin
Adults & children > 12 years old	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Children 6-12 years old						
Children < 6 years old						

^a Body surface area value from: *Guidance for Industry: Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers*.

^b Body surface area estimate for 14 kg child from (b) (4) Body weight is estimated from the average weight of 3 year old boys and girls in the 50th percentile (www.cdc.gov/growthcharts)

^c Maximum recommended Adrenalin® dose established by Medical Officer Peter Starke, MD (NDA 204,200).

The (b) (4) safety margin for children aged 6-12 is below the desired value of (b) (4) when dose is normalized to body surface area. However, the safety margins for all 3 clinical populations are larger than the safety margins for (b) (4) in the approved 1 ml adrenalin® presentation (Sohn, (b) (4)). The acceptance criterion of NMT (b) (4) for (b) (4) is considered safe from the nonclinical perspective.

References

[Redacted] (b) (4)
[Redacted]

Sohn, J. Nonclinical consultation (CMC) for NDA 204,200. 6/1/12.

12 Appendix/Attachments

Appendix 1. Chemistry consultation request from Youbang Liu, dated 9/30/13.

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION		
TO (Office/Division): Marcie Wood Division Of Pulmonary, Allergy, And Rheumatology Products		FROM (Name, Office/Division, and Phone Number of Requestor): Youbang Liu, ONDQA/Division III, 301-796-1926		
DATE 9/30/13	IND NO.	NDA NO. 204640	TYPE OF DOCUMENT New NDA	DATE OF DOCUMENT 8/2/13
NAME OF DRUG Adrenalin® Injection	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE	
NAME OF FIRM: JHP Pharmaceuticals				
REASON FOR REQUEST				
I. GENERAL				
NEW PROTOCOL PROGRESS REPORT NEW CORRESPONDENCE DRUG ADVERTISING ADVERSE REACTION REPORT MANUFACTURING CHANGE / ADDITION MEETING PLANNED BY		PRE-NDA MEETING END-OF-PHASE 2a MEETING END-OF-PHASE 2 MEETING RESUBMISSION <input checked="" type="checkbox"/> SAFETY / EFFICACY PAPER NDA CONTROL SUPPLEMENT	RESPONSE TO DEFICIENCY LETTER FINAL PRINTED LABELING LABELING REVISION ORIGINAL NEW CORRESPONDENCE FORMULATIVE REVIEW OTHER (SPECIFY BELOW):	
II. BIOMETRICS				
PRIORITY P NDA REVIEW END-OF-PHASE 2 MEETING CONTROLLED STUDIES PROTOCOL REVIEW OTHER (SPECIFY BELOW):		CHEMISTRY REVIEW <input checked="" type="checkbox"/> PHARMACOLOGY BIOPHARMACEUTICS OTHER (SPECIFY BELOW):		
III. BIOPHARMACEUTICS				
DISSOLUTION BIOAVAILABILTY STUDIES PHASE 4 STUDIES		DEFICIENCY LETTER RESPONSE PROTOCOL - BIOPHARMACEUTICS IN-VIVO WAIVER REQUEST		
IV. DRUG SAFETY				

PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES CASE REPORTS OF SPECIFIC REACTIONS (List below) COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP		REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY SUMMARY OF ADVERSE EXPERIENCE POISON RISK ANALYSIS	
V. SCIENTIFIC INVESTIGATIONS			
CLINICAL		X NONCLINICAL	
COMMENTS / SPECIAL INSTRUCTIONS: Please evaluate the proposed acceptance criterion of NMT (b)(4) for impurity (b)(4) in the drug product from the P/T perspective. The document can be located through DARRTS.			
SIGNATURE OF REQUESTOR Youbang Liu		METHOD OF DELIVERY (Check one) DFS X EMAIL MAIL HAND	
PRINTED NAME AND SIGNATURE OF RECEIVER		PRINTED NAME AND SIGNATURE OF DELIVERER	

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/s/

MATTHEW T WHITTAKER
10/21/2013

TIMOTHY W ROBISON
10/21/2013
I concur

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 204,640 **Applicant:** JHP Pharmaceuticals, LLC **Stamp Date:** August 2, 2013

Drug Name: Adrenalin® injection, 30 ml **NDA/BLA Type:** 505(b)(2)

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		The Sponsor has cross-referenced NDA 204-200 for nonclinical pharmacology and toxicology studies.
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	X		The literature review conducted in support of NDA 204,200 (1 ml Adrenalin® DP) was considered adequate.
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).		X	The formulation of 30 ml Adrenalin® DP contains an increased concentration of the (b)(4) sodium metabisulfite relative to the 1 ml formulation ((b)(4)). The acceptability of this change will be a review issue. Chlorobutanol is present (b)(4) in the 30 ml Adrenalin® DP and not the 1 ml DP. The acceptability of this change will be a review issue. Toxicology studies have not been conducted with the 30 ml formulation.
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?	X		The IV route was used to qualify the (b)(4) impurity in NDA 204,200. This was considered acceptable.

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7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?	X		
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			Not applicable.
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	X		
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	X		Impurity issues were addressed for the 1 ml drug product formulation. Issues related to impurities and leachables in the current 30 ml product formulation will be evaluated during review in consultation with the Chemist.
11	Has the applicant addressed any abuse potential issues in the submission?	X		The sponsor states: “No reports of addiction to Adrenalin have been found in the literature” in section 2.5.10.2 of the Clinical Overview for NDA 204,200.
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			Not applicable

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? *Yes.*

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

Not applicable

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

There are no nonclinical review issues.

Matthew Whittaker, Ph.D.

8/27/13

Reviewing Pharmacologist

Date

Timothy Robison, Ph.D.

8/27/13

Team Leader/Supervisor

Date

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement 010908

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR
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APPEARS THIS WAY ON ORIGINAL

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