

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204640Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 204640

SUPPL #

HFD # 570

Trade Name **Adrenalin**

Generic Name **epinephrine, 1 mg/mL**

Applicant Name **JHP Pharmaceuticals LLC**

Approval Date, If Known **December 16, 2013**

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(2) original application

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

There were no BA/BE studies. To support approval, the applicant is relying on the Agency's finding of safety and efficacy for NDA 19430, EpiPen and also literature data.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

NA

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA

#(s).

NDA#	19430	EpiPen
NDA#	20800	Twinject, Adrenaclick
NDA#	204200	Adrenalin

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical

investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or

sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

- b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
!
IND # YES ! NO
! Explain:

Investigation #2 !
!
IND # YES ! NO
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not

identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1
!
!
YES ! NO
Explain: ! Explain:

Investigation #2
!
!
YES ! NO
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES NO

If yes, explain:

Name of person completing form: **Carol F. Hill, M.S.**
Title: Senior Regulatory Health Project Manager
Date: December 18, 2013

Name of Office/Division Director signing form: **Lydia I. Gilbert-McClain, M.D.**
Title: Deputy Director, Division of Pulmonary, Allergy, and Rheumatology Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

/s/

CAROL F HILL
12/18/2013

LYDIA I GILBERT MCCLAIN
12/18/2013



870 Parkdale Road
Rochester, MI 48307

Debarment Certification

This is to certify that JHP Pharmaceuticals LLC (JHP) did not and will not use in any capacity the services of any person debarred under Section 306 subpart (a) or (b) of the Generic Drug Enforcement Act of 1992 and the Federal Food Drug and Cosmetic Act in connection with the manufacturing or testing of pharmaceutical products.

JHP also declares that no one responsible for the development or submission of an ANDA/NDA/NADA has been convicted of a crime as defined by Section 306 subpart (a) or (b) within the last 5 years.

A handwritten signature in black ink, appearing to read 'Adetayo O. Adebisi', is written over a horizontal line.

Adetayo O. Adebisi
Director, Compliance

A handwritten date 'October 26, 2011' is written in black ink over a horizontal line.

Date

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION¹		
NDA # 204640 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: Adrenalin Established/Proper Name: epinephrine Dosage Form: solution		Applicant: JHP Pharmaceuticals, LLC Agent for Applicant (if applicable):
RPM: Carol Hill		Division: DPARP
<p><u>NDA and NDA Efficacy Supplements:</u></p> <p>NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>		<p><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u></p> <p>Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s):</p> <p>NDA 19430 EpiPen</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p>The listed drug is a drug-device combination-auto-injector (0.30 and 0.15 mg/mL) the proposed product is an injection solution (1 mg/mL) in a vial. The proposed product ^{(b)(4)} active ingredients of the listed drug ^{(b)(4)} inactive ingredients. The proposed product is intended for use in the medical setting whereas the reference product is intended for emergency self-use in the non-medical setting.</p> <p><input type="checkbox"/> This application does not rely upon a listed drug. <input checked="" type="checkbox"/> This application relies on literature. <input type="checkbox"/> This application relies on a final OTC monograph. <input checked="" type="checkbox"/> This application relies on NDA 19430 for safety and efficacy</p> <p><u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></p> <p><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></p> <p><input type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check: December 17, 2013</p> <p>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</p>
❖ Actions		

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.

² For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

❖ Exclusivity	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLA: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	<input checked="" type="checkbox"/> Verified, Module 1.3.5 <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. 	21 CFR 314.50(i)(1)(i)(A) <input checked="" type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	<input type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i> 	<input type="checkbox"/> N/A (no paragraph IV certification) <input checked="" type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
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CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist ⁴	Yes
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) December 18, 2013
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	December 16, 2013
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	October 17, 2013
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	

⁴ Fill in blanks with dates of reviews, letters, etc.

<ul style="list-style-type: none"> ❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>) 	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	
<ul style="list-style-type: none"> ❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>) 	
<ul style="list-style-type: none"> • Most-recent draft labeling 	December 9, 2013
<ul style="list-style-type: none"> ❖ Proprietary Name <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) • Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name. 	December 9, 2013 December 9, 2013
<ul style="list-style-type: none"> ❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>) 	<input checked="" type="checkbox"/> RPM September 3, 2013 <input checked="" type="checkbox"/> DMEPA November 20, 2013 <input type="checkbox"/> DMPP/PLT (DRISK) <input checked="" type="checkbox"/> ODPD (DDMAC) December 4, 2013 <input checked="" type="checkbox"/> SEALD December 13, 2013 <input type="checkbox"/> CSS NA <input type="checkbox"/> Other reviews NA
Administrative / Regulatory Documents	
<ul style="list-style-type: none"> ❖ Administrative Reviews (<i>e.g., RPM Filing Review⁵/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>) 	September 30, 2013
<ul style="list-style-type: none"> ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte 	<input type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>) 	<input type="checkbox"/> Not a (b)(2) December 12, 2013
<ul style="list-style-type: none"> ❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>) 	<input type="checkbox"/> Included
<ul style="list-style-type: none"> ❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm 	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC If PeRC review not necessary, explain: Application does not trigger PREA see email dated October 21, 2013 • Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>) 	<input type="checkbox"/> Included

⁵ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent <i>(include certification)</i>	<input checked="" type="checkbox"/> Verified, statement is acceptable, Module 1.3.3 dated September 19, 2013
❖ Outgoing communications <i>(letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons)</i>	December 4, October 9, August 8, 2013, and September 20, 2012
❖ Internal memoranda, telecons, etc.	September 20, and August 23, 2012
❖ Minutes of Meetings	
• Regulatory Briefing <i>(indicate date of mtg)</i>	<input checked="" type="checkbox"/> No mtg
• If not the first review cycle, any end-of-review meeting <i>(indicate date of mtg)</i>	<input checked="" type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting <i>(indicate date of mtg)</i>	<input type="checkbox"/> No mtg Pre-IND July 5, 2011
• EOP2 meeting <i>(indicate date of mtg)</i>	<input checked="" type="checkbox"/> No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) <i>(indicate dates of mtgs)</i>	
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available <i>(do not include transcript)</i>	
Decisional and Summary Memos	
❖ Office Director Decisional Memo <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
Division Director Summary Review <i>(indicate date for each review)</i>	<input type="checkbox"/> None December 18, 2013
Cross-Discipline Team Leader Review <i>(indicate date for each review)</i>	<input type="checkbox"/> None December 17, 2013
PMR/PMC Development Templates <i>(indicate total number)</i>	<input type="checkbox"/> None December 18, 2013
Clinical Information⁶	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) <i>(indicate date for each review)</i>	See CDTL Review dated December 18, 2013
• Clinical review(s) <i>(indicate date for each review)</i>	December 12, November 25, September 11, 2013
• Social scientist review(s) (if OTC drug) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not <i>(indicate date of review/memo)</i>	See Clinical Review for NDA 204200, dated April 11, 2012 page 26
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> Not applicable

⁶ Filing reviews should be filed with the discipline reviews.

❖ Risk Management <ul style="list-style-type: none"> REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>) REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	N/A <input checked="" type="checkbox"/> None
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	<input checked="" type="checkbox"/> None requested
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None September 12, 2013
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None December 7, September 17, 2013
❖ DSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>)	<input checked="" type="checkbox"/> None
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
• Supervisory Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	<input type="checkbox"/> None December 9, and August 27, 2013
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)	<input checked="" type="checkbox"/> None requested

Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None December 11, 3, and August 26, 2013 ONDQA BP/December 5, and September 10, 2013
❖ Microbiology Reviews <input checked="" type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i> <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	<input type="checkbox"/> Not needed November 25, and August 21, 2013
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	<input type="checkbox"/> None Nonclinical/October 21, 2013
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	August 2, 2013
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>	
❖ Facilities Review/Inspection	
<input type="checkbox"/> NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report) <i>(date completed must be within 2 years of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁷)</i>	Date completed: <input checked="" type="checkbox"/> Acceptable/November 27, 2013 see EES Summary Report in Product Quality Review dated December 13, 2013 <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER <i>(date of most recent TB-EER must be within 30 days of action date) (original and supplemental BLAs)</i>	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation (check box only, do not include documents) ❖ Per CMC: If assessment of methods is necessary, a list of samples can be requested. Other information necessary to fill out the MV is found in the application.	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed (per review)dated August 26, 2013

⁷ I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

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/s/

CAROL F HILL
12/18/2013



Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: December 16, 2013

To: Carla English Manager, Regulatory Affairs	From: Carol Hill, M.S. Sr. Regulatory Health Project Manager
Company: JHP Pharmaceuticals, LLC	Division of Pulmonary, Allergy, and Rheumatology Drug Products
E-address: carla.english@jhppharma.com	Fax number: 301-796-9728
Phone number: 973-658-3530	Phone number: 301-796-2300

Subject: NDA 204640 – Labeling Revisions II and PMC Information Request

Total no. of pages including cover: 16

Comments: Please acknowledge receipt and note that you are requested to provide your response on Monday 16, 2013.

Document to be mailed: YES xNO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-2300. Thank you.

NDA 204640
JHP Pharmaceuticals
Adrenalin

Dear Ms. English:

Your new drug application, NDA 204640 is currently under review. We have the following comments and proposed recommended revisions to the labeling. We also have additional revisions in the attached package insert. Insertions are underlined and the deletions are in strike-out. Be advised that these labeling changes are not necessarily the Agency's final recommendations and that additional labeling changes may be forthcoming.

HIGHLIGHTS (HL)

1. The length of HL must be one-half page or less unless a waiver has been granted. Revise the HL section such that the length does not exceed one-half page or request a waiver.
2. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic. The reference for Adverse Reactions is "6" where "6.1" may be more appropriate.
3. Include the revision date at the end of the HL.

Table of Contents (TOC)

4. The section and subsection headings in the TOC must match the section and subsection headings in the FPI. For subsections 1.1, 1.2, 2.1 and 2.2, there is information in parentheses following the subheadings in the Full Prescribing Information (FPI) that is missing from the TOC.

Full Prescribing Information

5. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, "[see *Warnings and Precautions (5.2)*]" or "[see *Warnings and Precautions (5.2)*]". Two cross-references in subsection 6.1 do not italicize "see"; it should be in italics. Also, in subsection 5.4 (Disease Interactions), cross-reference is made to "6" where "6.1" may be more appropriate; prescribers should be directed to the most specific numerical identifier

Per your correspondence dated December 6, 2013 to NDA 204200 and cross referenced to NDA 204640 and as discussed at the teleconference held on December 2, 2013, we request that you submit your commitment to conduct a leachable study for the finished product.

2120-1: Conduct a leachable study for the container closure system.

Final Protocol Submission:	<u>Completed</u>
Develop and Validate Analytical Methods:	<u>April 2014</u>

Update Stability Program and Protocols to
Reflect Leachable Testing:
Final Report Submission:

June 2014
December 2014

We request that you submit draft labeling incorporating our recommended changes and your agreement with the postmarketing commitment above on December 16, 2013. You may email your responses to me at carol.hill@fda.hhs.gov. Also formally submit your responses to the NDA. If you have any questions, contact Carol F. Hill, Senior Regulatory Health Project Manager at 301-796-1226.

13 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

CAROL F HILL
12/16/2013



NDA 204640

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

JHP Pharmaceuticals, LLC
One Upper Pond Road
Building D, 3rd Floor
Parsippany, NJ 07054

Attention: Carla English
Manager, Regulatory Affairs

Dear Ms. English:

Please refer to your New Drug Application (NDA) dated March 7, 2012, received March 7, 2012, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Epinephrine Injection, USP, 1 mg/mL.

We also refer to your October 23, 2013, correspondence, received October 23, 2013, requesting review of your proposed proprietary name, Adrenalin. We have completed our review of the proposed proprietary name, Adrenalin, and have concluded that it is acceptable.

If **any** of the proposed product characteristics as stated in your October 23, 2013, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Nichelle Rashid, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3904. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Carol Hill, at (301) 796-1226.

Sincerely,

{See appended electronic signature page}

Kellie A. Taylor, Pharm.D., MPH
Deputy Director
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TODD D BRIDGES on behalf of KELLIE A TAYLOR
12/09/2013



Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: December 4, 2013

To: Carla English Manager, Regulatory Affairs	From: Carol Hill, M.S. Sr. Regulatory Health Project Manager
Company: JHP Pharmaceuticals, LLC	Division of Pulmonary, Allergy, and Rheumatology Drug Products
E-address: Carla.english@jhppharma.com	Fax number: 301-796-9728
Phone number: 973-658-3530	Phone number: 301-796-2300

Subject: NDA 204640 – Labeling Comments and Revisions I

Total no. of pages including cover: 15

Comments: Please acknowledge receipt and note that you are requested to provide your response on Monday 9, 2013.

Document to be mailed: YES xNO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-2300. Thank you.

NDA 204640
JHP Pharmaceuticals
Adrenalin

Dear Ms. English:

Your NDA 204640, is currently under review. We have the following comments and proposed recommended revisions to the labeling. We also have additional revisions noted in the attached package insert. Insertions are underlined and the deletions are in strike-out. Be advised that these labeling changes are not necessarily the Agency's final recommendations and that additional labeling changes may be forthcoming.

A. General Comments (Container Labels and Carton Labeling)

1. After the "For Intramuscular or Subcutaneous Use" statement add the "Not for Ophthalmic Use" statement in a smaller font as follows:

For Intramuscular or Subcutaneous Use

Not for Ophthalmic Use

2. Reverse the order for the statements of concentration as follows:

1 mg/mL

(30 mg/30 mL)

1:1000

Keep the red background in the same location, so that it will be behind the "1 mg/mL" designation.

B. Container Label-30 mL Vial (All)

1. The 30 mL vial is a multiple dose vial that must be discarded after 30 days after initial use. Include the statement "Discard 30 days after initial use: Discard on _____" (space to write in discard date) on the side panel. If space is needed, consider deleting the "Note-Do not use the solution if it is colored or cloudy, or if it contains particulate matter" and "A sterile solution for intramuscular or subcutaneous use" statements because this information is redundant or can be found in the full prescribing information.

C. Carton Labeling-30 mL (All)

1. Ensure the lot number and expiration date are printed on the labeling.
2. Revise, relocate, and bold the "Vial and contents must be discarded 30 days after initial use" statement to "Discard 30 days after initial use: Discard on _____" (space to write in discard date) on the principal display panel (front and back).

D. Carton Labeling-30 mL (One Unit Multiple Dose Vial)

1. Add the "30 mL Multiple Dose Vial" statement to the back panel.

We request that you submit draft labeling incorporating our recommended changes by COB on December 9, 2013. You may email your responses to me at carol.hill@fda.hhs.gov. Also formally submit your responses to the NDA. If you have any questions, contact Carol F. Hill, Senior Regulatory Health Project Manager at 301-796-1226.

12 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

CAROL F HILL
12/04/2013

Hill, Carol

From: Inglese, Jane
Sent: Monday, October 21, 2013 9:53 AM
To: Starke, Peter; Greeley, George
Cc: Hill, Carol; Maynard, Janet
Subject: RE: PeRC schedule: NDA 204640 Adrenalin (Full Waiver)

Peter,

This is to confirm that NDA 204640 does not trigger PREA. We will remove the review scheduled for December 11, 2013 from the PeRC calendar.

Jane

From: Starke, Peter
Sent: Friday, October 18, 2013 1:50 PM
To: Greeley, George; Inglese, Jane
Cc: Hill, Carol; Maynard, Janet
Subject: RE: PeRC schedule: NDA 204640 Adrenalin (Full Waiver)

George and Jane,

This application is for the 30 mL vial of Adrenalin (epinephrine injection). Recall that we already approved a 1 mL vial of Adrenalin last December, and this presentation was split off from the original application for several reasons (including that it was only for one of the two previous indications and it contains a preservative because it is a multiple-dose vial). Because of the preservative it will only get the anaphylaxis indication and not the mydriasis indication that the first one got as well. That said, my understanding is that this application does not trigger PREA, because it contains no new active ingredients, indications, routes, dosage forms, or dosing regimens. So, I suspect that we do not need to come to PeRC. Please confirm.

Also, for the previous application PeRC agreed with the two Divisions that the assessment was complete and we labeled it for all ages. This one will be labeled for all ages as well.

Thank you,
--Peter



NDA 204640

**FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED**

JHP Pharmaceuticals, LLC
One Upper Pond Road
Building D, 3rd Floor
Parsippany, NJ

Attention: Carla English
Manager, Regulatory Affairs

Dear Ms. English:

Please refer to your New Drug Application (NDA) dated August 2, 2013, received August 2, 2013, pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Adrenalin (epinephrine) Injection, 1 mg/mL (1:1000).

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is June 2, 2014.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by May 5, 2014.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

We request that you submit the following information:

1. As per 21 CFR § 320.22 (b)(1), FDA shall waive the requirement for the submission of data demonstrating bioequivalence if the drug product is a parenteral solution for injection and contains the same active and inactive ingredients in the same concentration as a drug product that is the subject of an approved full new drug application. However, since your product contains chlorobutanol and the reference listed drug (RLD) does not, provide justification with supportive data (e.g., published literature, study data, etc.) demonstrating that the presence of chlorobutanol will not have any impact on the pharmacokinetics, efficacy, and safety of your product. Also provide a side-by-side summary table comparing your proposed product vs. the reference product (including description, formulation, pH, osmolarity, tonicity etc.).
2. You describe the use of [REDACTED] (b) (4)
3. Provide the results of the most recent requalification studies performed with [REDACTED] (b) (4) vials.
4. Provide results from the most recent media fills performed [REDACTED] (b) (4).
5. Submit a request for evaluation of your proprietary name, Adrenalin. Refer to the guidance entitled: *Guidance for Industry: Contents of a Complete Submission for the Evaluation of Proprietary Name* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>.

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

1. In the Highlights and Adverse Reactions sections of the package insert, remove the underline that appears in the FDA website listing.
2. The bolded heading for the Table of Contents is required to be placed on one line.

We request that you resubmit labeling that addresses these issues by October 18, 2013. The resubmitted labeling will be used for further labeling discussions.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

If you have any questions, call Carol F. Hill, Senior Regulatory Health Project Manager, at (301) 796-1226.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, M.D., Ph.D.
Director
Division of Pulmonary, Allergy, and Rheumatology
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

LYDIA I GILBERT MCCLAIN
10/09/2013



NDA 204640

**NDA ACKNOWLEDGEMENT
USER FEES RECEIVED**

JHP Pharmaceuticals LLC
One Upper Pond Road
Building D, 3rd Floor
Parsippany, NJ 07054

Attention: Carla English
Manager, Regulatory Affairs

Dear Ms. English:

Please refer to your new drug application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug and Cosmetic Act for Adrenalin (epinephrine injection) 1 mg/mL.

You were notified in our letter dated September 20, 2012, that your application was not accepted for filing due to non-payment of fees. This is to inform you that the Agency has received all required fees and your application has been accepted as of August 2, 2013.

Unless we notify you within 60 days of the above date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on October 1, 2013 in accordance with 21 CFR 314.101(a).

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number cited above should be included at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Pulmonary, Allergy, and Rheumatology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, contact Carol F. Hill, Senior Regulatory Health Project Manager, at (301) 796-7.

Sincerely,

{See appended electronic signature page}

Ladan Jafari
Chief, Project Management Staff
Division of Pulmonary, Allergy, and Rheumatology
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

CAROL F HILL
08/08/2013

LADAN JAFARI
08/08/2013



NDA 204640

UNACCEPTABLE FOR FILING

JHP Pharmaceuticals, LLC
One Upper Pond, Building D, 3rd Floor
Parsippany, NJ 07054

Attention: Steve Richardson
Vice President, Scientific and Regulatory Affairs

Dear Mr. Richardson:

We have received your new drug application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Adrenalin ®, (epinephrine, USP) Solution, 1 mg/mL/30 mL

Date of Application: March 7, 2012

Date of Receipt: March 7, 2012

Our Reference Number: NDA 204640

We have not received the appropriate user fee for this application. An application is considered incomplete and cannot be accepted for filing until all fees owed have been paid. Therefore, this application is not accepted for filing. We will not begin a review of this application's adequacy for filing until FDA has been notified that the appropriate fee has been paid. Payment should be submitted to the following address:

Food and Drug Administration
P.O. Box 979107
St. Louis, MO 63197-9000

Checks sent by courier should be addressed to:

(b) (4)
[Redacted address information]

When submitting payment for an application fee, include the User Fee I.D. Number, the Application number, and a copy of the user fee coversheet (Form 3397) with your application fee payment. When submitting payment for previously unpaid product and establishment fees, please include the Invoice Number(s) for the unpaid fees and the summary portion of the invoice(s) with your payment. The FDA P.O. Box number (P.O. Box 979107) should be included on any check you submit.

The receipt date for this submission (which begins the review for filability) will be the date the review division is notified that payment has been received by the bank.

Please cite the NDA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Pulmonary, Allergy, and Rheumatology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you wish to send payment by wire transfer, or if you have any other user fee questions, please call Bev Friedman or Mike Jones at 301-796-3602.

If you have any questions regarding this application, contact Carol F. Hill, Senior Regulatory Health Project Manager, at (301) 796-1226.

Sincerely,

{See appended electronic signature page}

Ladan Jafari
Chief, Project Management Staff
Division of Pulmonary, Allergy, and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

LADAN JAFARI
09/20/2012

MEMORANDUM

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

DATE: September 20, 2012

SUBJECT: Application History

APPLICATION/DRUG: NDA 204640/Adrenalin/JHP Pharmaceuticals, Inc.

BACKGROUND:

On March 7, 2012, JHP Pharmaceuticals, Inc. submitted NDA 204200 for Adrenalin (epinephrine) injection, 1mg/mL in a 1 mL vial and a 30 mL vial for the proposed indications of severe acute anaphylactic reaction and maintenance of mydriasis in cataract surgery. It was determined that the original application should be split because the indications were in two different divisions. Administratively, the application was split into Original 1, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP), for severe acute anaphylactic reaction and Original 2, Division of Transplant and Ophthalmology Products (DTOP) for maintenance of mydriasis in cataract surgery. DTOP instituted a priority review with a due date of September 7, 2012 and DPARP's review timeline was standard with a due date of January 7, 2013. Upon further review, the CMC team determined that the 1 mL and 30 mL vial presentations were not quantitatively and qualitatively the same; therefore, per the bundling policy, the 30 mL vial had to be separated to a new application, NDA 204640.

The applications and indications are as follows:

NDA 204200 - Original 1, 1 mL - indicated for severe acute anaphylactic reaction
NDA 204200 - Original 2, 1 mL - indicated for maintenance of mydriasis in cataract surgery
NDA 204640 30 mL - indicated for severe acute anaphylactic reaction

During a teleconference on July 24, 2012, FDA advised JHP Pharmaceuticals Inc. that the Adrenalin 30 mL vial presentation, as filed in NDA 204200, was considered a new NDA (NDA 204640) and would require the submission of appropriate user fees in order to continue the review of the application. An Information Request/Advice Letter dated August 2, 2012 from the FDA provided comments in response to JHP's email correspondences dated July 26 and 27, 2012 regarding user fees and a path forward for the 30 mL product so that the Agency could proceed with appropriate administrative actions. JHP informed the Agency in a correspondence dated August 22, 2012 that the 30 mL vial product would not be pursued. Although the application would not be pursued, JHP confirmed that they would not withdraw the application reserving the right to activate on payment of the appropriate user fees.

Note that the data included in NDA 204200 is identical to those included in NDA 204640. However, due to technical limitations, the data in NDA 204200 could not be copied to NDA 204640. Therefore in order to appropriately process NDA 204640, JHP had to submit a letter to cross reference NDA 204200. Thus, the original receipt and goal dates for NDA 204640 are the same as NDA 204200.

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/s/

CAROL F HILL
09/20/2012

MEMORANDUM

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

DATE: August 23, 2012

SUBJECT: Application History for NDA 204200 and 204640

**APPLICATION/DRUG: NDA 204200, Original 1, NDA 204200, Original 2 and
NDA 204640/Adrenalin**

BACKGROUND:

On March 7, 2012, JHP Pharmaceuticals, Inc. submitted NDA 204200 for Adrenalin (epinephrine) injection, 1mg/mL in a 1 mL vial and a 30 mL vial for the proposed indications of severe acute anaphylactic reaction and maintenance of mydriasis in cataract surgery. It was determined that the original application should be split because the indications were in two different divisions. Administratively, the application was split into Original 1, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP), for severe acute anaphylactic reaction and Original 2, Division of Transplant and Ophthalmology Products (DTOP) for maintenance of mydriasis in cataract surgery. DTOP instituted a priority review with a due date of September 7, 2012 and DPARP's review timeline was standard with a due date of January 7, 2013. Upon further review, the CMC team determined that the 1 mL and 30 mL vial presentations were not quantitatively and qualitatively the same; therefore, per the bundling policy, the 30 mL vial had to be separated to a new application, NDA 204640.

The applications and indications are as follows:

NDA 204200 - Original 1, 1 mL - indicated for severe acute anaphylactic reaction
NDA 204200 - Original 2, 1 mL - indicated for maintenance of mydriasis in cataract surgery
NDA 204640 30 mL - indicated for severe acute anaphylactic reaction

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/s/

CAROL F HILL
08/23/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

PIND 111712

MEETING MINUTES

JHP Pharmaceuticals, LLC
One Upper Pond Road
Building D, #rd Floor
Parsippany, NJ 07054

Attention: Steve Richardson
Vice President, Scientific and Regulatory Affairs

Dear Mr. Richardson:

Please refer to your Pre-Investigational New Drug Application (PIND) file for Adrenalin.

We also refer to the teleconference between representatives of your firm and the FDA on July 5, 2011. The purpose of the meeting was to discuss requirements for filing a 505(b)(2) new drug application (NDA) and to seek the Agency's agreement to allow the continued marketing of Adrenalin® during the filing process.

A copy of the official minutes of the meeting/telecon is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me, at (301) 796-1226.

Sincerely,

{See appended electronic signature page}

Carol F. Hill, M.S.
Senior Regulatory Health Project Manager
Division of Pulmonary, Allergy, and Rheumatology
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B Meeting
Meeting Category: Pre-IND

Meeting Date and Time: July 5, 2011
Meeting Location: Teleconference

Application Number: PIND 111712
Product Name: Adrenalin
Sponsor/Applicant Name: JHP Pharmaceuticals, LLC

Meeting Chair: Badrul A. Chowdhury, M.D., Ph.D.
Meeting Recorder: Carol F. Hill, M.S.

FDA ATTENDEES

Badrul A. Chowdhury, M.D., Ph.D., Director, DPARP
Lydia I. Gilbert McClain, M.D., F.C.C.P., Deputy Director
Susan Limb, M.D., Clinical Team Leader
Jennifer R. Pippins, M.D., Clinical Reviewer
Molly Topper, Ph.D., Pharmacology/Toxicology Supervisor
Alan Schroeder, Ph.D., CMC Lead, ONDQA
Angelica Dorantes, Ph.D., Biopharmaceutics Team Leader, ONDQA
Kiya Hamilton, Ph.D., Statistical Reviewer, DOBII
Suresh Doddapaneni, Ph.D., Acting Team Leader, Clinical Pharmacology, DOCP2
Liang Zhao, Ph.D., Clinical Pharmacology Reviewer
Sally Loewke, M.D., Associate Director, GPT
Shari Targum, M.D., DCRP
Quynh M. Nguyen, Pharm.D., DCRP
Wiley A. Chambers, M.D., Deputy Director, DTOP
Astrid Lopez-Goldberg, J.D., DNDLC
Carol F. Hill, M.S., Senior Regulatory Health Project Manager

SPONSOR ATTENDEES

Steve Richardson, VP, Scientific and Regulatory Affairs
Carla English, Manager, Regulatory Affairs
Mike Bergren, Director, Chemistry and Analytical Development

(b) (4)

Meeting Minutes
[Insert Meeting Type]
DATE

[Insert Office/Division]



(b) (4)

1.0 BACKGROUND

On March 10, 2011, JHP Pharmaceuticals submitted a type B meeting request to discuss and obtain the FDA's concurrence regarding the filing strategy proposed by JHP for the submission of a 505(b)(2) application for Adrenalin (epinephrine injection, USP). The product, Adrenalin currently marketed by JHP received on July 23, 2009, a Notice of FDA Action for the Office of Compliance regarding shipment of the active pharmaceutical ingredient (API), epinephrine pending release from US Customs. Subsequently, JHP was requested to provide documentation of grandfather status of their Adrenalin drug products and to clarify the lineage of the Adrenalin drug product marketed initially by Parke-Davis prior to June 25, 1938 and that of the drug product currently marketed by JHP. JHP provided the requested information and the API was released from customs on October 9, 2009. After which, the Office of Compliance urged JHP to contact the Center for Drug Evaluation, Office of New Drugs to discuss the filing of a new drug application for the Adrenalin drug product.

The FDA granted a pre-IND meeting request on March 24, 2011. JHP provided the background materials for the meeting on June 3, 2011 and requested a teleconference in lieu of a face-to-face meeting. After review of the briefing document, the FDA forwarded their preliminary responses to the briefing document questions on June 30, 2011. A revised copy of the preliminary responses was sent to JHP on July 1, 2011 to reflect the revision to question 9 in the June 30, 2011 copy. In the July 1, 2011 version, paragraph one, the words "**administered subcutaneously or intramuscularly**" were deleted from the sentence, "*Your outlined approach, presuming supportive CMC information and an appropriate request for biowaiver, appears acceptable for the proposed doses of (b) (4) and 0.3 mg epinephrine administered subcutaneously or intramuscularly for the treatment of anaphylaxis*". JHP submitted their intention to continue with the teleconference on July 5, 2011 and provided the FDA with its discussion guide for the teleconference (see attachments, section 6 below). JHP noted in the guide a request to discuss for clarification questions 5 (including questions 8 and additional non-clinical comments 1 and 2), 9, 17 and Biopharmaceutical comments 1 and 2.

Note: JHP's questions are in bold italics, FDA responses are in italics and the discussion appears in normal font.

2. DISCUSSION

Introductory Comment

The briefing materials indicate a number of different dosing regimens and indications. Each proposed dosing regimen and indication will require adequate support. With the exception of the response to clinical question 1, the comments below pertain to the indications specific to the Division of Pulmonary, Allergy, and Rheumatology Products, namely anaphylaxis. (b) (4)

1. We refer you to the Division of Cardio-Renal Products, the Division of Anesthesia and Analgesic Products, and the Division of Anti-Infective and Ophthalmology Products for additional feedback regarding the other indications.

JHP Pharmaceutical Introductory Comments

JHP stated that the proposed product acquired from Parke-Davis has the same formulation as when it was originally marketed. Their goal is to comply with FDA regulations and legitimize the product on the market place thus avoiding any future issues regarding the sale or transport of their product and its active ingredient.

CHEMISTRY, MANUFACTURING AND CONTROLS

Question 1

Does FDA agree that the drug product assay limits of (b) (4)% (b) (4) are acceptable to gain approval?

FDA Response

This is a review issue and it is premature to consider approvability issues at this time.

Discussion

The sponsor accepted FDA's response, no discussion occurred.

Question 2

Does FDA expect JHP to propose a limit on (b) (4) to gain approval?

FDA Response:

See our response to question 1. (b) (4)

Discussion

The sponsor accepted FDA's response, no discussion occurred.

Question 3

Does FDA agree that the pH limit for the drug product should be based on a range that achieves enantiomeric stability even though the limits may conflict with the USP monograph?

FDA Response

If the pH range chosen is within the USP monograph range, this may not pose a problem. If not, the drug product may have to be labeled as not USP. This is only a preliminary response as it will require further evaluation. See our response to question 1.

Discussion

The sponsor accepted FDA's response, no discussion occurred.

Question 4

Does FDA agree that our proposed overage of (b) (4)% is acceptable to gain approval?

FDA Response

See our response to question 1. Nevertheless, (b) (4) % overage may be acceptable, depending on your data.

Discussion

The sponsor accepted FDA's response, no discussion occurred.

Question 5

Assuming stability studies support limits of NMT (b) (4) does FDA anticipate that any additional supporting information would be required from JHP for approval of these limits?

FDA Response

It is possible that additional qualification data would be required to support the proposed limits. This will be evaluated during review of your NDA, along with the involvement of the pharmacology/toxicology reviewers. See our non-clinical comments.

Discussion

JHP requested the FDA to clarify its comments regarding (b) (4) limits (b) (4) and also the data needed to support the specification levels (b) (4) in the proposed drug product. (b) (4)

The Agency commented about testing of approved products for (b) (4): the sponsor would have to demonstrate that their results were representative of the marketed products (and not outliers). JHP stated that they feel that the (b) (4) results on stability are similar across other products.

The FDA advised the sponsor to submit their justification (b) (4)

The justification to support safety may come from publically available literature, comparisons of impurity levels in currently approved products or completion of toxicology studies. FDA referred JHP to ICH Q3 guidelines for useful information regarding specifications and information needed to support safety. In the absence of adequate public literature or adequate coverage of the impurities in currently approved products, a 2-week toxicology study conducted in one species is necessary for each impurity that exceeds approved specifications. The 2-week duration of the toxicology study is necessary to support the acute indication. The FDA agreed that the toxicology studies may be conducted using an (b) (4) enriched (spiked) epinephrine

drug product to qualify the impurity. Alternatively, JHP can assay (b) (4) alone. JHP asked (b) (4) would this information be adequate to qualify (b) (4) in their product. The FDA agreed that this would qualify (b) (4) as long as the results represent the batch production lots.

(b) (4)
(b) (4)
(b) (4). FDA reminded JHP that the toxicology studies are not solely looking at expected pharmacological effects but also off-target toxicities. The FDA recommended that JHP submit a justification with supportive data to support the safe use of (b) (4) at the levels proposed. These data will be reviewed and if found the data are not adequate, a 2-week toxicity study to qualify the proposed specifications will be needed. JHP inquired if the proposal for justification could be submitted for preliminary review before submission of the NDA. The FDA replied that it would be more appropriate to submit the data in the NDA.

Question 6

Does FDA have any other concerns with the specification for the 1 mL and 30 mL vial presented in Briefing Package?

FDA Response

Specifications should be developed for identification, residual solvents, and extractables/leachables as appropriate (see the ICH Q6A guidance). Numerical limits for specifications are a review issue. Justification of the differences in specifications between the two presentations will need to be provided.

Discussion

The sponsor accepted FDA's response, no discussion occurred.

Question 7

Does FDA concur that real time stability data at controlled room temperature out to 18 months, along with 3 months accelerated data tested (b) (4), is acceptable for filing?

FDA Response

The question is premature, as our response will depend on multi-disciplinary review of data and consideration of the issue of (b) (4) on stability. Additional room temperature stability data may be required for the future NDA.

Discussion

The sponsor accepted FDA's response, no discussion occurred.

NON-CLINICAL QUESTION

Question 8

JHP believes there is adequate information available in the literature to describe the nonclinical activity of epinephrine in support of all of the proposed clinical indications. JHP believes it is appropriate for the NDA Nonclinical sections and the Package Insert to be based solely on the literature and also based on the Agency's finding of safety and effectiveness of EpiPen® and Twinject®.

Does FDA agree this is acceptable?

FDA Response:

We agree that the NDA nonclinical section and the Package Insert may reference the publically available literature to support use of epinephrine for currently approved doses and routes of administration. Provide this information for each route of administration and doses for these routes in your IND.

Additional Nonclinical Comments:

- 1. Based on the summary information in your briefing package, (b) (4) (b) (4) exceed levels in currently approved epinephrine products. Provide information from nonclinical studies and/or the publically available literature to support the safety of the specification levels in the proposed drug product.*
- 2. Additional nonclinical studies may be needed to support the safety of leachables and extractables from any new component(s) in which the drug solution comes into contact.*

Discussion

See discussion for question 5.

CLINICAL

Question 9

For the clinical section of the NDA, JHP will review the major guidelines, textbooks, and current relevant literature outlining current consensus on standard of use. This information will be summarized in Module 2.

Does FDA agree this is acceptable?

FDA Response:

Your outlined approach, presuming supportive CMC information and an appropriate request for biowaiver, appears acceptable for the proposed doses of (b) (4) and 0.3 mg epinephrine for the treatment of anaphylaxis. (b) (4)

(b) (4)

(b) (4)

Discussion

See the Discussion for Question 10.

Question 10

Does FDA have any concerns or guidance regarding the list of proposed indications?

FDA Response:

See the Introductory Comment and the response to clinical question 9. The Division has conceptual concerns regarding the proposed indications (b) (4)

Given the availability of alternative treatments with less toxic profiles, the Division questions the risk-benefit profile of your proposed product for these indications. If you decide to pursue these indications, the application must provide adequate justification.

Discussion

JHP asked for clarification of the Divisions responsible for the various proposed indications (b) (4). The FDA stated that it is not immediately apparent which Division would be designated to review an (b) (4) indication, however, as noted in the FDA's response to question 9, the FDA's comments were intended to highlight which indications would be most readily supported without the need for additional clinical trial data. While the choice of which indications to pursue is at JHP's discretion, FDA encourages the Sponsor to pursue those indications that present a straightforward pathway for NDA submission and review.

JHP asked if a 505(b)(2) submission with a request for a biowaiver would be the appropriate pathway for an anaphylaxis indication. The FDA replied that this would be an appropriate and straightforward approach, as the information on dosing and indications for an approved product such as EpiPen or Twinject would constitute adequate data.

[REDACTED] (b) (4)

JHP asked if an ophthalmic indication could be based solely on the literature, to which FDA replied yes. [REDACTED] (b) (4)

[REDACTED]

JHP asked if it would be possible to meet with the Division of Transplant and Ophthalmology Products, to which FDA replied that a meeting would be entertained if appropriate. To assist JHP in determining the appropriate clinical data to support the ophthalmic indication, JHP requested that the FDA provide literature references for review. The FDA stated that they would consider the request and provide available references.

JHP summarized this portion of the discussion by stating that the most straightforward pathway to approval would be to seek the anaphylaxis and ophthalmic indications.

Regarding the information needed to address submission of multiple indications for a single NDA submission, it was agreed that follow-up would be sought from the regulatory project manager for the Division of Pulmonary, Allergy, and Rheumatology Products.

Question 11

Does FDA agree the proposed update to the JHP Package Insert is acceptable?

FDA Response:

It is premature at this time to discuss labeling. Labeling will depend on the specific indications which are approved.

Discussion

The sponsor accepted FDA's response, no discussion occurred.

Question 12

JHP believes there is adequate information available in the literature to describe the use of epinephrine in the pediatric population. JHP believes it is appropriate for any discussion of pediatric use of epinephrine in the NDA clinical sections and the Package Insert to be based solely on the literature and also based on the agency's finding of safety and effectiveness of EpiPen® and Twinject®.

Does the FDA find this acceptable?

FDA Response:

In principle, published literature may be sufficient to support certain indications. The adequacy of the literature for a pediatric indication will be a review issue.

Discussion

The sponsor accepted FDA's response, no discussion occurred.

Question 13

JHP has provided a draft Package Insert with this Information Package which incorporates information from the approved EpiPen[®] and Twinject[®] Package Inserts as well as current language from the AHFS, recent guidelines, and peer-reviewed literature. In addition, JHP has provided postmarketing safety data received and reported to FDA as individual case reports between October 2003 and April 2011. During that period events were most frequently reported in the Cardiac Disorders System Organ Class. JHP plans to assess these events in more detail as part of the safety evaluations of epinephrine for the future NDA. Although there are confounding factors that contributed to the majority of these disorders, JHP believes it will be appropriate to add to the label those terms most frequently attributed to epinephrine use in postmarketing surveillance reports.

Does the FDA agree or have any comment?

FDA Response:

In principle, we agree with the inclusion of adverse events commonly associated with epinephrine. Discussion regarding specific labeling is premature at this time. See our response to question 11.

Discussion

The sponsor accepted FDA's response, no discussion occurred.

Question 14

Adrenalin[®] is used in multiple indications with different routes, doses, and schedules. JHP is concerned that condensing dosing instructions for multi-indication to comply with the package insert space limitation for the HIGHLIGHTS section may lead to dosing errors. Accordingly, JHP proposes to insert the following or similar statement into the HIGHLIGHTS OF PRESCRIBING INFORMATION / DOSAGE AND ADMINISTRATION section of the proposed Package Insert:

 (b) (4)

Does FDA agree or have any comments or suggestions?

FDA Response:

In principle, complete dosing information for each approved indication should be included in the Highlights section of the label. Discussion regarding specific labeling is premature at this time. See our response to question 11.

Discussion

The sponsor accepted FDA's response, no discussion occurred.

ADMINISTRATIVE

Question 15

Because of the long history of use of Adrenalin[®] as treatment of anaphylaxis, JHP proposes that the planned NDA is submitted to and reviewed within the Division of Pulmonary and Allergy Products. Additional expertise from other Divisions would be consulted per the FDA's discretion.

Does the FDA find this acceptable?

FDA Response:

The proposed submission of the NDA to DPARP is acceptable. Involvement of other review divisions in the NDA review will depend on the indications sought. However, we recommend discussion with the other relevant review divisions prior to NDA submission. Refer to the Introductory Comment and the response to clinical question 9.

Discussion

The sponsor accepted FDA's response, no discussion occurred.

Question 16

Does FDA agree the proposed filing format is acceptable?

FDA Response:

The NDA will need to include information as outlined in 21 CFR 314.50. While the proposed format may be acceptable in principle, a submission based solely on literature references is unlikely to support all of the various proposed indications and routes of administration. See the Introductory Comment and the response to clinical question 9.

Discussion

The sponsor accepted FDA's response, no discussion occurred.

Question 17

Does FDA believe that JHP will qualify for an application fee waiver under the FD&C Act section 736(d)(1)(D)?

FDA Response:

We believe that your planned application(s) will require clinical data for approval and would be subject to the fee for applications that require clinical data for approval (the FY 2011 fee rate is \$1,542,000). For more details regarding application fees and waivers, including how to request a waiver, we suggest you contact Mr. Mike Jones, in CDER's Office of Regulatory Policy at 301-796-3602.

*Please note that your proposed epinephrine products may need to be submitted in multiple applications. FDA's guidance for industry, *Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees* (available on the Internet) describes what should be considered separate marketing applications and what is considered clinical data for the purposes of the user fee provisions of the FD&C Act. Issues that the guidance document covers that may be more pertinent for your submission(s) may include, but are not necessarily limited to: different routes of administration, different strengths/concentrations, excipients, and indications (e.g., a pending application should not be amended to add a new indication or claim). In addition, you should be aware that literature can be considered clinical data for user fee purposes.*

Discussion

The sponsor accepted FDA's response, no discussion occurred.

Question 18

Does FDA believe there will be any concerns with granting approval of the name Adrenalin[®] for our proposed NDA?

FDA Response:

We refer you to the "Guidance for Industry: Contents of a Complete Submission for the Evaluation of Proprietary Names," February 2010, for a description of the FDA's approach to the review of proposed proprietary names.

Discussion

The sponsor accepted FDA's response, no discussion occurred.

Question 19

Does FDA have any other concerns or suggestion regarding our proposed submission?

FDA Response:

Presuming that a 505(b)(2) application is an acceptable approach, the Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 C.F.R. 314.54, and the October 1999 Draft Guidance for Industry "Applications Covered by Section 505(b)(2)" available at <http://www.fda.gov/cder/guidance/index.htm>. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions challenging the agency's interpretation of this statutory provision. See Dockets 2001P-0323, 2002P-0447, and 2003P-0408 (available at <http://www.fda.gov/ohrms/dockets/dailys/03/oct03/102303/02p-0447-pdn0001-vol1.pdf>).

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that the regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

However, circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a duplicate of that drug and eligible for approval under section 505(j) of the act, we may refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an ANDA that cites the duplicate product as the reference listed drug.

Discussion

The sponsor accepted FDA's response, no discussion occurred.

Compliance

JHP Meeting Request (March 10, 2011) Comment 1

JHP will also seek the Agency's agreement to allow the continued marketing of Adrenalin (epinephrine injection, USP) during this process.

FDA Response:

We have evaluated your request in accordance with the priorities stated in the Marketed Unapproved Drugs – Compliance Policy Guide (CPG) (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070290.pdf>). In deciding our priorities, medical necessity is one factor we consider when addressing whether to make a product a higher or lower priority under our CPG. See, Notice of Enforcement Action and Continued Marketing of Unapproved Drugs, CPG section III B. Based on the current information we have regarding your epinephrine product, and applying the CPG criteria, at this point in time, this is a low priority.

We support your continued pursuit of an application and encourage you to follow-through with the application process for this important drug.

Discussion

The sponsor accepted FDA's response, no discussion occurred.

JHP Meeting Request (March 10, 2011) Comment 2

JHP submitted a response to the Office of Compliance on August 29, 2009 providing examples of some of the ample evidence in its possession, demonstrating the grandfather status of Adrenalin. JHP also provided support that Adrenalin is medically necessary.

FDA Response

We want to make it clear that the Agency has not made a determination that your Epinephrine product is grandfathered at this time. The type and extent of documentation required to support a claim of "grandfather" status for a drug product includes, but is not limited to, pre-1938 or pre-1962 labeling, to demonstrate that the specific drug product being marketed meets all the criteria for grandfather status. These criteria include establishing that each specific product marketed today has the same formulation, strength, dosage form, routes of administration, indication, intended patient populations, and other conditions of use as the pre-1938 or pre-1962 product.

Also, an inquiry into whether a drug is "grandfathered" is necessarily specific to the individual finished product, because products identical in, for instance, their formulation with pre-1938 or pre-1962 active ingredients, could nevertheless have labels that bear different conditions of use. Please refer to 21 CFR 314.200(e) for a description of the documentation that would need to be provided in order to demonstrate that the finished drug product is exempt from the Act's application requirements (i.e., grandfathered). This information would be required separately for each individual product.

Should you choose to submit documentation in support of your claim of "grandfather" status, we request that the supporting information be submitted in two formats: (1) a hard copy in a tabbed and indexed three ring notebook; and, (2) a CD or DVD with pdf files of the same material, including the cover letter detailing the description of the attached material and an explanation of as to why each individual drug product should be considered "grandfathered." The paper submission for each drug product should be in a separate binder(s) but the electronic copy may be combined on one or more disks but each drug product should be identified as a separate folder on the disk(s).

Please forward the information to:

*Lesley Frank, J.D., Regulatory Counsel
Office of Unapproved Drugs and Labeling Compliance
Food and Drug Administration, Center for Drug Evaluation and Research
10903 New Hampshire Avenue
WO 51, Room 5192
Silver Spring, MD 20993*

Discussion

The sponsor accepted FDA's response, no discussion occurred.

Biopharmaceutics

Additional Comments

1. The to-be-submitted 505 (b)(2) NDA submission for the proposed drug product should include data from a Bioavailability or Bioequivalence (BA/BE) study comparing the proposed drug product to a RLD product (EpiPen® or Twinject®) [§320.21(a)(1)]. Or, you may request a BA/BE waiver and provide the supportive data [§320.21(a)(2)].

2. A BA/BE waiver may be granted for the proposed product for the SC or IM routes if the following supportive information is provided:

- Qualitative/quantitative comparison of formulations;
- Justification for differences in the inactive ingredients, if any;
- A head to head comparison table (proposed product vs. RLD) listing strengths, (b) (4), label indications, etc.); and
- Evidence of similar mode of delivery (needle dimensions, etc.) as the RLD product.

(b) (4)

Discussion

(b) (4)

JHP commented that their product will be sold in a vial with no needle or syringe and asked the FDA to clarify its recommendation to provide evidence of similar mode of delivery (needle dimension, etc) as the reference listed drug. The FDA reminded JHP that they intend to refer to Twinject or EpiPen; if the proposed product is to be recommended for use with a syringe or needle, then the needle size has to be listed in the package insert and should have the same dimensions as that for Twinject or EpiPen.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

It was agreed by both FDA and JHP that additional information would be sought from FDA at a later date regarding the inclusion of multiple indications in one NDA submission.

5.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Literature References regarding an ophthalmic indication	FDA	No due date was established

6.0 ATTACHMENTS AND HANDOUTS

There were no attachments or handouts for the meeting.

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

/s/

CAROL F HILL
08/04/2011