

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204200Orig1s000

204200Orig2s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 204200 - Original 1

SUPPL #

HFD #

Trade Name Adrenalin

Generic Name epinephrine (1:1000) 1 mg/mL

Applicant Name JHP Pharmaceuticals LLC

Approval Date, If Known January 7, 2012

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)

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?

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, Adrenacllick

NDA#

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

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 7, 2012

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
12/07/2012

LYDIA I GILBERT MCCLAIN
12/07/2012

EXCLUSIVITY SUMMARY

NDA # 204200 Original 2

SUPPL #

DTOP

Trade Name Adrenalin

Generic Name epinephrine injection 1 mg/mL

Applicant Name JHP Pharmaceuticals, LLC

Approval Date, If Known: December 7, 2012

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)

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.

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?

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).

The following single ingredient products contain epinephrine:

NDA#	19-430	Epipen
NDA#	201-739	Auvi-Q
NDA#	20-800	Twinject

The following combination products include epinephrine:

NDA#	21-504	Lidosite Topical
NDA#	20-971	Septocaine
NDA#	22-010	Septocaine
NDA#	20-530	Iontocaine
NDA#	21-381	Lidocaine
NDA#	21-383	Prilocaine
NDA#	22-466	Orabloc
NDA#	6-488	Xylocaine and Epinephrine

2. Combination product. N/A

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).

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:

Name of person completing form: William M. Boyd, MD
Title: Clinical Team Leader
Date: 12/10/2012

Name of Division Director signing form: Renata Albrecht, MD
Title: Division Director
Date: 12/11/2012

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/

JUDIT R MILSTEIN
12/11/2012

RENATA ALBRECHT
12/11/2012



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

October 26, 2011

Date

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 204200 Original 1 Original 2	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: Adrenalin Established/Proper Name: Epinephrine injection, USP Dosage Form: Injection, 1 mg.mL		Applicant: JHP Pharmaceuticals Agent for Applicant (if applicable):
RPM: Carol Hill (DPARP), Judit Milstein (DTOP)		Division: DPARP, DTOP
<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)): NDA 19430-EpiPen</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p>This product is an injection; NDA 19430 is a drug-device combination;</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 checked="" type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</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		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>December 7, 2012 for Original 2, and January 7, 2013 for Original 1</u> • Previous actions (<i>specify type and date for each action taken</i>) 	<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR <input checked="" type="checkbox"/> None	

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).

<p>❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____</p>	<input type="checkbox"/> Received
<p>❖ Application Characteristics ³</p>	
<p>Review priority: <input checked="" type="checkbox"/> Standard (Original 1) <input checked="" type="checkbox"/> Priority (Original 2) Chemical classification (new NDAs only): 7</p> <p> <input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC </p> <p> NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies </p> <p> <input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Submitted in response to a Pediatric Written Request </p> <p> BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <input type="checkbox"/> Approval based on animal studies </p> <p> REMS: <input type="checkbox"/> MedGuide <input type="checkbox"/> Communication Plan <input type="checkbox"/> ETASU <input type="checkbox"/> MedGuide w/o REMS <input type="checkbox"/> REMS not required </p> <p>Comments:</p>	
<p>❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)</p>	<input type="checkbox"/> Yes, dates
<p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
<p>❖ Public communications (<i>approvals only</i>)</p>	
<ul style="list-style-type: none"> Office of Executive Programs (OEP) liaison has been notified of action 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Press Office notified of action (by OEP) 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated 	<input checked="" type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ 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 BLAs: 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 <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
---	---

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 and date: Approval December 7, 2012
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 6, 2012 (applicant)
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	March 7, 2012
<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. • Original applicant-proposed labeling • 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 6, 2012
<ul style="list-style-type: none"> ❖ Proprietary Name <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) : July 17, 2012 • Review(s) (<i>indicate date(s)</i>):November 8, 2012, July 17, 2012 • <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.</i> 	
<ul style="list-style-type: none"> ❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>) 	<input checked="" type="checkbox"/> RPM April 27, 2012 <input checked="" type="checkbox"/> DMEPA Consult to OSE: May 12, 2012 Consult Response: September 6, 2012 Review: November 21, 2012 <input type="checkbox"/> DMPP/PLT (DRISK) <input checked="" type="checkbox"/> OPDP (DDMAC) Consult to OPDP May 10, 2012, November 5, 2012---Consult Responses September 6, 2012, November 9, 2012 <input type="checkbox"/> SEALD <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
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>) ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment 	RPM Filing Review: April 27, 2012 <u>Clearance:</u> Original 2-August 6, 2012 Original 1- October 22, 2012 <u>Assessment Forms:</u> Original 1 and Original 2- December 7, 2012
<ul style="list-style-type: none"> ❖ NDAs only: Exclusivity Summary: Original 1-December 7, 2012 ❖ Original 2- December 12, 2012 	<input checked="" 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 	

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

<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 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 June 25, 2012 If PeRC review not necessary, explain: _____ • Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> ❖ 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
<ul style="list-style-type: none"> ❖ Outgoing communications (<i>letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons</i>) 	December 7, 2012 December 6, 2012 December 5, 2012 December 4, 2012 November 29, 2012 November 27, 2012 November 21, 2012 November 2, 2012 October 22, 2012 September 18, 2012 September 7, 2012 August 8, 2012 June 13, 2012 May 24, 2012 May 4, 2012 March 29, 2012
<ul style="list-style-type: none"> ❖ Internal memoranda, telecons, etc. 	August 23, 2012
<ul style="list-style-type: none"> ❖ Minutes of Meetings 	
<ul style="list-style-type: none"> • Regulatory Briefing (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> • 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
<ul style="list-style-type: none"> • Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) 	July 5, 20122 _Pre-NDA meeting
<ul style="list-style-type: none"> • EOP2 meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> • Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>) • CMC Meeting 	July 23, 2012
<ul style="list-style-type: none"> ❖ Advisory Committee Meeting(s) 	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> • Date(s) of Meeting(s) 	
<ul style="list-style-type: none"> • 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>)	December 7, 2012 (2) September 7, 2012
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	November 29, 2012 September 6, 2012
PMR/PMC Development Templates (<i>indicate total number</i>)	December 7, 2012
Clinical Information⁶	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	
• Clinical review(s) (<i>indicate date for each review</i>)	October 29, 2012 September 5, 2012 April 19, 2012 April 11, 2012
• 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 MO review dated October 29, 2012 and September 5, 2012
❖ 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
❖ Risk Management <ul style="list-style-type: none"> • REMS Documents and Supporting Statement (<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>) 	<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>)	August 6, 2012 April 17, 2012 April 12, 2012

⁶ Filing reviews should be filed with the discipline reviews.

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>	November 8, 2012 August 17, 2012 April 26, 2012
❖ 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>	November 16, 2012 October 30, 2012 August 17, 2012 June 1, 2012 CMC Consult request: May 11, 2012 April 17, 2012 April 12, 2012
❖ 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	
<ul style="list-style-type: none"> • ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i> 	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> • Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i> 	September 7, 2012 May 2, 2012
<ul style="list-style-type: none"> • Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i> 	<u>Biopharmaceutics:</u> November 13, 2012 August 13, 2012 April 13, 2012 <u>Product Quality:</u> November 15, 2012 August 14, 2012 April 12, 2012 (2)
❖ Microbiology Reviews <ul style="list-style-type: none"> <input 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 August 8, 2012 Consult from ONDQA- May 10, 2012 April 12, 2012
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	See CMC review dated April 14, 2012, Page 64
<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) <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: August 6, 2012 <input checked="" type="checkbox"/> Acceptable <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 <i>(check box only, do not include documents)</i>	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review) Not provided

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.

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

/s/

JUDIT R MILSTEIN
12/12/2012
NDA 204200-Action Package Checklist

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 204200 – Original #1 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: Adrenalin Established/Proper Name: epinephrine (1:1000) Dosage Form: solution for injection		Applicant: JHP Pharmaceuticals LLC Agent for Applicant (if applicable):
RPM: Carol F. 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)): NDA 19430, EpiPen</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p>This proposed product is an injection solution of 1 mg/mL whereas the listed drug is an autoinjector, drug device-combination of 0.15 mg/mL and 0.30 mg/ml.. The proposed product is intended for use in the medical setting by medically trained personnel and the referenced drug is for use in a non medical setting. Thus the dosing, weight, and age ranges for the proposed product will extend beyond those for the referenced drug-device combination and is intended for different setting of use with different dosing and administration instructions.</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 type="checkbox"/> This application relies on (explain)</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 checked="" type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check: December 7, 2012</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>	

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 BLAs: 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 <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>	<p><input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</p>
---	---

CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist ⁴	December 7, 2012
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 7, 2012
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 6, 2012
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	
<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. • Original applicant-proposed labeling • 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 6, 2012
<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. 	July 16, 2012 July 17, 2012 November 15, 2012
<ul style="list-style-type: none"> ❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>) 	<input checked="" type="checkbox"/> RPM April 27, 2012 <input checked="" type="checkbox"/> DMEPA September 5, and November 21, 2012 <input type="checkbox"/> DMPP/PLT (DRISK) <input checked="" type="checkbox"/> ODPD (DDMAC) September 6, 2012/November 9, 2012 <input type="checkbox"/> SEALD <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
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>) 	Filing Review April 27, 2012
<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) October 22, 2012
<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 7, 2012
<ul style="list-style-type: none"> ❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>) 	<input checked="" type="checkbox"/> Included December 7, 2012
<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 <u>June 6, 2012</u> If PeRC review not necessary, explain: _____ • Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>) 	<input checked="" 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
❖ Outgoing communications <i>(letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons)</i>	December 7, 6, 5, 4, November 29, 27, 21, 2, October 22, September 18, August 2, June 13, May 24, 4, and March 29, 2012
❖ Internal memoranda, telecons, etc.	August 23 and July 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 7, 2012
Cross-Discipline Team Leader Review <i>(indicate date for each review)</i>	<input type="checkbox"/> None November 29, 2012
PMR/PMC Development Templates <i>(indicate total number)</i>	<input type="checkbox"/> None December 7, 2012
Clinical Information⁶	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) <i>(indicate date for each review)</i>	See CDTL Memo
• Clinical review(s) <i>(indicate date for each review)</i>	October 29 and April 11, 2012
• 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>	N/A on page 26 of Clin Rev dated, April 11, 2012 See DTOP's CDTL review dated, September 6, 2012
❖ 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 Supporting Statement (<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
❖ DSI Clinical Inspection Review Summary(ies) (<i>include copies of DSI 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 checked="" type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
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 November 9 and April 26, 2012
❖ DSI Clinical Pharmacology Inspection Review Summary (<i>include copies of DSI 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 type="checkbox"/> None November 16, 2012
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	<input type="checkbox"/> None October 30 and April 12, 2012, See CMC Consult Reviews, dated June 1, 2012
❖ 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
❖ DSI Nonclinical Inspection Review Summary (<i>include copies of DSI 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 type="checkbox"/> None
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None September 7 and May 2, 2012
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None November 15, August 14, and April 12, 2012 BioPharm: November 13 and April 13, 2012
❖ Microbiology Reviews	<input type="checkbox"/> Not needed August 8, 2012
<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>	
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i> /CONSULT REVIEWS	<input type="checkbox"/> None Non-Clinical dated June 1, 2012
❖ 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>	CMC review page 7, dated August 14, 2012
<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 checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout) <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: August 6, 2012 <input checked="" type="checkbox"/> Acceptable <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 <i>(check box only, do not include documents)</i>	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed (per review)8/14/12

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
12/10/2012



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

FACSIMILE TRANSMITTAL SHEET

DATE: December 7, 2012

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: 973-658-3562	Phone number: 301-796-2300

Subject: NDA 204200 – PMC Agreement Request

Total no. of pages including cover: 3

Comments: Please provide your response by noon on today.

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 204200
JHP Pharmaceuticals, LLC
Adrenalin

Dear Ms. English:

We refer to your NDA submission (NDA 204200) dated March 7, 2012, and also to our correspondence dated November 27, 2012 regarding your commitment to a required post-marketing requirement. Upon further evaluation, we have changed the original post-marketing requirement request and the corresponding time table. We are requesting your agreement to the following post-marketing commitment and timetable.

1. Evaluate formulation and process improvements to reduce the levels of impurities with Adrenalin (epinephrine injection, USP). In your evaluation, conduct at least one study to determine the possible cause(s) of (b) (4) formation and take appropriate measures to minimize the level of this impurity. Using the results from these investigations, re-evaluate the acceptance limits for (b) (4) and (b) (4) and lower the limits for these impurities, as appropriate. As part of an interim report, include your evaluation of the formulation/process improvements undertaken to mitigate the level of impurities, in particular (b) (4) and (b) (4), as well as a summary of all technical work performed using the results of the conducted study(ies). The interim report should also include a proposed development plan for future batches which will ensure consistency and reliability of product quality.

Final Protocol Submission: January 2013
Interim Report Submission: April 2013
Study/Trial Completion: March 2014
Final Report Submission: May 2014

We request your response by noon on today. If you have any questions, contact Carol F. Hill, Senior Regulatory Health Project Manager at 301-796-1226.

Draft: CHill/December 7, 2012
Clearance: Jafari/December 7, 2012
Seymour/December 7, 2012
Shanmugam/December 7, 2012
Schroeder/December 7, 2012
Peri/December 7, 2012
Finalized: Chill/December 7, 2012

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/s/

CAROL F HILL
12/07/2012



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

FACSIMILE TRANSMITTAL SHEET

DATE: December 6, 2012

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 204200 – Labeling Comments and Revisions VI

**Total no. of pages including
cover: 13**

Comments:

Document to be mailed: YES xNO

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NDA 204200
JHP Pharmaceuticals
December 6, 2012

Dear Ms. English:

Your submissions dated March 7 and December 5, 2012, to NDA 204200, Original 1, are currently under review. We have revisions to the attached package insert. Insertions are underlined and deletions are in strike-out. We also have comments below that pertain to the carton and container labeling. Be advised that these labeling changes are not the Agency's final recommendations and that additional labeling changes will be forthcoming specifically regarding the Initial Approval Date in the Highlights of Prescribing Information.

1. On the container label there is insufficient white space between the bottom of the 'j' in injection and the top of the '1' in 1 mg/mL on the line below. For ease of reading the '1' in the 1 mg/mL, revise the container label so there is sufficient white space between the bottom of the 'j' in injection and the top of the '1' in 1 mg/mL.
2. In several panels of the carton label there is not enough white space between the end of the NDC number and the beginning of the Trade Name, Adrenalin. Revise the carton label so there is adequate separation between the NDC number and the beginning of the Trade Name, Adrenalin.

As soon as we provide the correct Initial Approval Date, we ask that you provide full draft labeling by COB December 6, 2012. Your response can be provided by email; however, you will have to formally submit the response to the NDA. If you have any questions, contact Carol F. Hill, Senior Regulatory Health Project Manager at 301-796-1226.

11 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
12/06/2012

Hill, Carol

From: Hill, Carol
Sent: Wednesday, December 05, 2012 6:57 AM
To: 'English, Carla'
Subject: NDA 204200 _ Labeling Revisions V
Attachments: NDA 204200_PI_2012-11-30 with FDA edits (3).doc

Hi Carla:

As mentioned in my correspondence to you on December 4, 2012 regarding FDA labeling revisions and PMRs for NDA 204200, I am providing the additional labeling revisions. These additional edits in yellow highlights are inserted in the marked-up package insert sent to you on December 4, 2012.

We request that you submit draft labeling incorporating all of our recommended changes on December 6, 2012. You may email your responses. Please note that your responses will have to be submitted to the NDA.

If you have any questions, please let me know. Thank you.

Carol

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/s/

CAROL F HILL
12/05/2012



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

FACSIMILE TRANSMITTAL SHEET

DATE: December 4, 2012

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 204200 – Labeling Comments and Revisions IV and PMRs

Total no. of pages including cover: 15

Comments:

Document to be mailed: YES xNO

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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 204200
JHP Pharmaceuticals
December 3, 2012

Dear Ms. English:

Your submission dated March 7, 2012, to NDA 204200, Original 1, is currently under review. We have the following comments and revisions to the attached package insert. Insertions are underlined, the deletions are in strike-out, and several highlighted comments are embedded in the text. Be advised that these labeling changes are not the Agency's final recommendations and that additional labeling changes will be forthcoming. You do not need to respond to the labeling comments until you have received the additional comments within the next two days.

1. Revise the Package Insert so that the Highlights of Prescribing Information and the Full Prescribing Information: Contents appears on one single page.
2. Confirm that the Trademark "Adrenalin" is a Trademark that includes the injection dosage form rather than just the active ingredient.

We also refer to our correspondence dated November 27, 2012 regarding your agreement to fulfill the Post-Marketing Requirement. The timetable for the submission of the components of the post-marketing requirement has been revised as follows:

Final Protocol Submission: January 30, 2013
Interim Report: April 1, 2013.
Study/Trial Completion: March 1, 2014
Final Report Submission: May 1, 2014

We request that you submit your agreement to the timetable for the Post-Marketing Requirement by COB on December 5, 2012. Submit revised labeling by COB December 6, 2012, once you have received our additional labeling comments. You may email your response and you must 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.

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/s/

CAROL F HILL
12/04/2012

NDA 204200
JHP Pharmaceuticals
November 29, 2012

Dear Ms. English:

Your submission dated March 7, 2012, to NDA 204200, Original 1, 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, the deletions are in strike-out, and several highlighted comments are embedded in the text. Be advised that these labeling changes are not necessarily the Agency's final recommendations and that additional labeling changes may be forthcoming.

Package Insert

Highlights (HL) Section

1. Reformat the margins of the HL section to ½ inch and change the font to an 8 point font in order to meet the regulatory requirement of a half page in size.
2. Insert a horizontal line across the page between the HL and the TOC (see 21 CFR 201.57(d)(2)).
3. The proprietary name should be capitalized three times in the HL section (twice in the Highlights limitation statement and once in the Product title). This is for consistency to recognize the drug product name.
4. Remove USP, which should not appear after the proprietary name.
5. The dosage form is Injection, and the strength is 1 mg/mL (1:1000).
6. Insert the Revision Date at the end of the HL section.

Note other formatting changes and edits to the accompanying labeling text.

Table of Contents (TOC) and Full Prescribing Information (FPI) Sections

1. Insert a horizontal line between the TOC and the FPI.
2. Delete section 14.1 (b)(4) and change the section (b)(4) "Induction and Maintenance of Mydriasis during Intraocular Surgery" to 14.1. Revise the TOC to reflect this change.
3. In Section 16, change (b)(4) to 3 mL vial following the NDA number.
4. Delete the Approval Date at the end of the FPI.

Note other edits to the accompanying labeling text.

Carton Labeling

1. Replace (b)(4) with "Single-Use Vial" in two locations.

We request that you submit the draft labeling incorporating our recommended changes by NLT noon on Monday, December 03, 2012. You may email your responses to Ms. Philantha Bowen who will be the contact person. Please also copy me on any email or correspondence forwarded to Ms. Bowen. Also formally submit your responses to the NDA.

Sadaf Nabavian, Pharm.D.
Regulatory Project Manager

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/s/

SADAF NABAVIAN
11/29/2012



NDA 204200

INFORMATION REQUEST

JHP Pharmaceuticals, LLC
Attention: Steve Richardson
Vice President, Scientific and Regulatory Affairs
One Upper Pond Road, Building D, 3rd Floor
Parsippany, NJ 07054

Dear Mr. Richardson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) (2) of the Federal Food, Drug, and Cosmetic Act for Adrenalin® (epinephrine) Injection, 1 mg/mL.

We are reviewing this NDA. You are required to fulfill the following Post-Marketing Requirement:

1. Conduct studies to determine the possible cause(s) of (b) (4) formation and take appropriate measures to minimize the level of this impurity.
2. Reevaluate the acceptance limit for (b) (4) to lower the limits based on additional study results.
3. Submit an interim report providing information on the following to the Agency before April 1, 2013.
 - Evaluation of formulation/process improvements undertaken to mitigate the level of impurities, in particular (b) (4) and (b) (4).
 - Summary of all technical work conducted with results of the studies conducted
 - Proposed development plan for future batches which will ensure consistency and reliability of product quality

At the time of submission of the interim report, we recommend that you request a meeting with the Agency to discuss the required manufacturing changes to improve product quality, and implementation plans. Target date for completing the post-marketing requirement: March 2014.

Please provide responses to the above Information Request by November 29, 2012. If you have any questions, call Youbang Liu, Regulatory Project Manager, at (301) 796-1926.

Sincerely,

{See appended electronic signature page}

Eric P. Duffy, Ph.D.
Director
Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

ERIC P DUFFY
11/27/2012



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

FACSIMILE TRANSMITTAL SHEET

DATE: November 21, 2012

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 204200 – Labeling Comments and Revisions II

**Total no. of pages including
cover: 16**

Comments: We request your response by November 28, 2012. Please send your response to philantha.bowen@fda.hhs.gov and copy me.

Document to be mailed: YES xNO

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NDA 204200
JHP Pharmaceuticals
November 21, 2012

Dear Ms. English:

Your submission dated March 7, 2012, to NDA 204200, Original 1, 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, the deletions are in strike-out, and several highlighted comments are embedded in the text. Be advised that these labeling changes are not necessarily the Agency's final recommendations and that additional labeling changes may be forthcoming.

Package Insert

1. Replace the abbreviations IM and SC, and the \geq and unit of measure ("") symbols in the package insert, carton, and container labeling with text because the abbreviations can be misinterpreted and are considered error-prone.
2. Revise the Adverse Reactions section to include the common adverse reactions expected with use of the product at therapeutic doses, and separately, adverse reactions reported in observational trials and case reports.
3. Once the NDC information is available, replace the NDC place-holder with the actual NDC number in both the package insert and the carton/container labels. Include the vial size next to the NDC number in the How Supplied section of the Package Insert.
4. Replace the month place-holder at the end of the package insert with the month of approval.

Container and Carton Labeling

1. Ensure that the established name is at least half the size of the proprietary name. Ensure the established name has prominence commensurate with the proprietary name taking into account all pertinent factors including typography, layout, contrast and other printing features per 21 CFR 201.10(g)(2).
2. Do not use TALL MAN labeling for the established name.
3. Revise (b) (4) to read "For Intramuscular, Subcutaneous, and Intraocular Use" and "Dilute Before Intraocular Use" and increase the prominence of these statements.
4. Debold the Rx Only statement.
5. Decrease the prominence of the NDC number.

Carton Labeling

1. Relocate the strength statement below the established name and increase the prominence of the strength statement on the primary display panel (PDP) and the side panels. For example:

Adrenalin
(epinephrine injection, USP)
1 mg / mL
(1:1000)

2. Relocate the active ingredient statement “Each mL contains...” from the PDP to the side panel.
3. Relocate the statement [REDACTED] (b) (4) on the PDP to the side panel, and replace it with the following statement: “Do not use the solution if it is colored or cloudy, or if it contains particulate matter.”
4. Ensure the lot number and expiration date are printed on the carton label.

Container Labeling

1. Delete [REDACTED] (b) (4) and change [REDACTED] (b) (4) to “1 mL Solution in a 3 mL Single-Use Vial”.

We request that you submit draft labeling incorporating our recommended changes by COB on November 28, 2012. You may email your responses to Philantha Bowen who will be the contact person during my absence. Please copy me on any email or correspondence forwarded to Cmdr. Bowen. Also formally submit your responses to the NDA.

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
11/21/2012

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/s/

CAROL F HILL
11/08/2012

**REQUEST FOR OPDP (previously DDMAC) LABELING REVIEW
CONSULTATION**

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

****Please send immediately following the Filing/Planning meeting****

TO: CDER-DDMAC-RPM	FROM: (Name/Title, Office/Division/Phone number of requestor) Carol Hill/ODEII/DPARP/301-796-1226
------------------------------	--

REQUEST DATE November 2, 2012	IND NO.	NDA/BLA NO. 204200/Original 1	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)
----------------------------------	---------	----------------------------------	---

NAME OF DRUG Adrenalin	PRIORITY CONSIDERATION Standard	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting) November 16, 2012
---------------------------	------------------------------------	------------------------	---

NAME OF FIRM: JHP Pharmaceuticals	PDUFA Date: January 7, 2013 (Division Goal: 12-7-12)
--------------------------------------	--

TYPE OF LABEL TO REVIEW

TYPE OF LABELING: (Check all that apply) <input checked="" type="checkbox"/> PACKAGE INSERT (PI) <input type="checkbox"/> PATIENT PACKAGE INSERT (PPI) <input checked="" type="checkbox"/> CARTON/CONTAINER LABELING <input type="checkbox"/> MEDICATION GUIDE <input type="checkbox"/> INSTRUCTIONS FOR USE (IFU)	TYPE OF APPLICATION/SUBMISSION <input type="checkbox"/> ORIGINAL NDA/BLA <input type="checkbox"/> IND <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> SAFETY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> PLR CONVERSION	REASON FOR LABELING CONSULT <input type="checkbox"/> INITIAL PROPOSED LABELING <input checked="" type="checkbox"/> LABELING REVISION
---	---	---

EDR link to submission: <\\CDSESUB1\EVSPROD\NDA204200\204200.enx>

Please Note: There is no need to send labeling at this time. OPDP reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to OPDP. Once the substantially complete labeling is received, OPDP will complete its review within 14 calendar days.

COMMENTS/SPECIAL INSTRUCTIONS:

Milestone dates have all been reached. We did not consult earlier because this was a joint application for DTOP/DPARP. The application was later split into Original 1 (DPARP) and Original 2 (DTOP). After our wrap up meeting on Friday, November 2, 2012, it was decided that we should consult DMEPA because of the revisions made to the applicant's original label and DTOP's version of the label. We ask that you review the SCPI labeling (package insert) that we submitted to you on Friday, November 2, 2012 and the carton and container labels. Please note that Christine Corser reviewed the label for DTOP/Original 2.

SIGNATURE OF REQUESTER Carol Hill

SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> eMAIL <input type="checkbox"/> HAND
-----------------------	--

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/s/

CAROL F HILL
11/05/2012



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

FACSIMILE TRANSMITTAL SHEET

DATE: November 2, 2012

To: Carla English Manager, Regulatory Affairs	From: Carol Hill, M.S. 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 204200 – Label Comments and Revisions I

Total no. of pages including cover: 25

Comments:

Document to be mailed: YES xNO

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JHP Pharmaceuticals, LLC
Adrenalin
NDA 204200

Dear Ms. English:

Your submission dated March 7, 2012, to NDA 204200, Original 1, is currently under review. We have the following comments and proposed recommended revisions to the labeling. Be advised that these labeling changes are not necessarily the Agency's final recommendations and that additional labeling changes may be forthcoming. In the attached package insert, insertions are underlined and the deletions are in strike-out.

1. As noted in the August 4, 2011 meeting minutes, for pre-IND 111712, each proposed dosing regimen and indication will require adequate support. (b) (4)

2. We have made significant changes to the labeling to match a number of sections, as appropriate, with that of the currently approved epinephrine products, and to conform to the Physician Labeling Rule (PLR) requirements.
3. In Section 6.1, you have listed the adverse reactions by body system and alphabetical order. Per 21CFR201.57, adverse reactions must be categorized by body system, by severity of reaction, or in order of decreasing frequency, or a combination of these. Revise the order of listing of adverse reactions to match this requirement.

We request that you provide revised draft labeling to incorporate these changes on or before November 9, 2012. If you have any questions, please contact Carol F. Hill, Senior Regulatory Health Project Manager, at 301-796-1226.

23 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
11/02/2012



NDA 204200

INFORMATION REQUEST

JHP Pharmaceuticals, LLC
Attention: Steve Richardson
Vice President, Scientific and Regulatory Affairs
One Upper Pond Road, Building D, 3rd Floor
Parsippany, NJ 07054

Dear Mr. Richardson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) (2) of the Federal Food, Drug, and Cosmetic Act for Adrenalin® (epinephrine) Injection, 1 mg/mL.

We also refer to your October 15, 2012 submission to the Agency's deficiency letter dated September 18, 2012.

We have reviewed the referenced material and have the following comments:

1. The proposed acceptance criterion of NMT [REDACTED] (b) (4)
[REDACTED]
This impurity in your drug product is also significantly higher than levels you reported for approved epinephrine drug products. We recommend that you provide a post marketing commitment with a defined timeline to investigate the causes for this high level [REDACTED] (b) (4)
[REDACTED]
[REDACTED] take necessary measures to minimize this impurity in your future production lots of epinephrine, and revise the acceptance criteria further from what is recommended below in Table 1. The journal articles referenced in your original submission, and other publications may provide useful information. The reporting of any changes to the manufacturing process or formulation resulting from this study should follow 21 CFR 314.70.
2. We have considered your justification, updated stability data, and data you submitted on other approved epinephrine drug products and recommend that you revise the specification as follows:

Table 1. Recommended Acceptance Criteria for the Drug Product (1 mL)

Test	Acceptance Criteria at Stability
(b) (4)	

3. Provide updated stability data for the 3 registration batches with the format as following:
 - Report actual levels for all impurities above (b) (4)
 - Include all impurities (including (b) (4)) in the Total Impurities category
4. Clearly list all identified impurities in the drug substance or drug product specifications as appropriate. The proposal of deleting known impurity (b) (4) from the drug product specification is not appropriate at this time. The acceptance criterion for this impurity should be consistent with manufacturing capabilities, observed levels and risk.

Please provide responses to the above information requests by November 9, 2012, in order for us to continue our review.

If you have any questions, call Youbang Liu, Regulatory Project Manager, at (301) 796-1926.

Sincerely,

{See appended electronic signature page}

Prasad Peri, Ph.D.
Branch Chief, Branch VIII
Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

PRASAD PERI
11/02/2012



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

FACSIMILE TRANSMITTAL SHEET

DATE: October 22, 2012

To: Carla English Manager, Regulatory Affairs	From: Carol Hill, M.S. Sr. Regulatory Health Project Manager
Company: JHP Pharmaceuticals	Division of Pulmonary, Allergy, and Rheumatology Drug Products
E-Address: Carla.English@JHPPharma.com	Fax number: 301-796-9728
Phone number: 973-658-3562	Phone number: 301-796-2300

Subject: NDA 204200 – Reference Listed Drug Information Request

Total no. of pages including cover: 3

Comments: Please provide your response by 12 noon on today.

Document to be mailed: YES xNO

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NDA 204200
JHP Pharmaceuticals, LLC
Adrenalin

Dear Ms. English

Your NDA 204200, submitted on March 7, 2012, is currently under review. We have the following comments or request(s) for information:

We note that in your annotated draft labeling, section 3, Dosage Forms and Strengths, you reference Twinject. Please clarify why Twinject is listed as a reference and whether or not you are relying on Twinject as an additional RLD for your product.

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

Drafted by: CHill/October 22, 2012
Clearance: Jafari/October 22, 2012
Finalized: CHill/October 22, 2012

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/s/

CAROL F HILL
10/22/2012



NDA 204200

INFORMATION REQUEST

JHP Pharmaceuticals, LLC
Attention: Steve Richardson
Vice President, Scientific and Regulatory Affairs
One Upper Pond Road, Building D, 3rd Floor
Parsippany, NJ 07054

Dear Mr. Richardson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) (2) of the Federal Food, Drug, and Cosmetic Act for Adrenalin® (epinephrine) Injection, 1 mg/mL.

We also refer to your August 2, 2012 and August 21, 2012 submissions, containing revised acceptance criteria and updated 12 month stability data for the drug product.

We have reviewed the referenced materials. Based on the CMC information provided in the original NDA submission as well as in the amendments the Agency has the following CMC deficiencies:

- A. [REDACTED] (b) (4)
[REDACTED] Clarify the definition of your claimed historic manufacturing batches (years and total number of batches). Indicate if there were any manufacturing and control differences between these registration batches and previous historic batches, [REDACTED] (b) (4)
[REDACTED] Provide this information in a tabular format. Discuss if there are any measures in place for the manufacturing and control of the drug product that will adequately control the level of this major degradant.
- B. Provide the rationale and data for the proposed limits for in-process controls in your section 3.2.P.3.4 (Control of Critical Steps and Intermediates).
- C. Provide mass balance data for the 3 registration batches at every stability test point under the 25°C/60% RH storage condition. Provide summary tables that list overall mass balance and detailed tables that list each individual component (impurities as well as [REDACTED] (b) (4)) mass that has been analyzed. Provide these tables in Excel format in electronic form in addition to the eCTD submission. Additionally provide a chromatogram for each [REDACTED] (b) (4) sample at every stability time point under the 25°C/60%RH storage condition.
- D. The proposed acceptance criteria for the total impurities [REDACTED] (b) (4) as amended are not acceptable. Include [REDACTED] (b) (4)

(b) (4) in the total impurities and exclude it from the assay value. We recommend that you use a chiral method to quantify the amount (b) (4) in your drug product. We propose the following drug product acceptance criteria based on your registration stability batches.

Recommended Acceptance Criteria for the Drug Product (1 mL)	
Test	Acceptance Criteria at Stability
	(b) (4)

- E. The analytical methods (b) (4) are not adequate. Per ICH Q3A and Q3B guidelines, report the actual results when the impurity is above its reporting threshold (0.1%). Develop adequate analytical methods that are capable of detecting the actual levels of these impurities.
- F. The analytical method for sodium bisulfite with the level of quantification (LOQ) Limit (b) (4) is not adequate. This LOQ is (b) (4) currently proposed for the acceptance criterion. Develop an adequate analytical method that is capable of analyzing the sodium bisulfite concentration accurately throughout the proposed range.

Provide additional information and/or clarification for the following analytical method deficiencies:

1. The drug substance analytical procedures section (3.2.S.4.2) provides a table listing all methods which you have used for the incoming drug substance testing, however, the actual descriptions of the test methods are not provided. Provide the specific methods used for description, identification, assay, impurities, residual solvents, and bacterial endotoxins testing.
2. Provide method validation/verification results for the bacterial endotoxins testing method used for incoming drug substance testing (method (b) (4)).
3. The drug product test method for description (method (b) (4)) is not clear. Revise the method description to record the actual observations of the test samples by the analyst and indicate whether the test results are satisfactory or unsatisfactory.
4. Indicate the specified grade (b) (4) used in the assay, epinephrine, and impurities method (method (b) (4) 9). The defined grade (b) (4) is not acceptable. It is also noted that the instructions for this method requires (b) (4) Include an additional separately prepared check standard in each sample set to verify that the standard solution used to

- quantify the samples are correctly prepared. Specify the solvent used to prepare the (b) (4) resolution solution.
5. The method for pH determination of the epinephrine drug product (method number (b) (4)) does not have any information related to how the pH is determined except for a reference to an SOP that is not provided in the NDA. Submit the referenced SOP or alternatively, update the method with the required information.
 6. Regarding the method validation report 703-0090
 - a. Provide method precision validation results (b) (4)
 - b. Provide robustness validation results to demonstrate that the resolution between the impurity peaks are still acceptable with the variations of the proposed run parameters.
 - c. Provide stability data for the impurities in the test sample; these data may also affect the sample stability period.
 - d. Note that the stability data only support 24 hour stability for the epinephrine in the test samples.
 7. Provide an updated method validation report.

Please provide responses to the above deficiencies by October 15, 2012, in order for us to continue our review.

If you have any questions, call Youbang Liu, Regulatory Project Manager, at (301) 796-1926.

Sincerely,

{See appended electronic signature page}

Prasad Peri, Ph.D.
Branch Chief, Branch VIII
Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

PRASAD PERI
09/18/2012



NDA 204200/Original 2

**REVIEW EXTENSION –
MAJOR AMENDMENT**

JHP Pharmaceuticals, LLC
Attention: Steve Richardson
Vice President, Scientific and Regulatory Affairs
One Upper Pond Road, Building D, 3rd Floor
Parsippany, NJ 07054

Dear Mr. Richardson:

Please refer to your March 7, 2012, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Adrenalin (epinephrine injection), 1 mg/mL.

On August 21, 2012 and September 6, 2012, we received your solicited major amendments to this application for the indication of induction and maintenance of mydriasis. The receipt date is within three months of the user fee goal date. Therefore, we are extending the goal date for this application by three months to provide time for a full review of the submissions. The extended user fee goal date is December 7, 2012.

In addition, we are establishing a new timeline for communicating labeling changes and/or postmarketing requirements/commitments in accordance with “PDUFA Reauthorization Performance Goals and Procedures-Fiscal Years 2008 through 2012.” If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by November 7, 2012.

If you have any questions, call Judit Milstein, Chief, Project Management Staff, at (301) 796-0763.

Sincerely,
{See appended electronic signature page}

Renata Albrecht, MD
Director
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

RENATA ALBRECHT
09/07/2012

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 (b) (4)

APPLICATION/DRUG: NDA 204200, Original 1, NDA 204200, Original 2 (b) (4)

BACKGROUND:

On March 7, 2012, JHP Pharmaceuticals, Inc. submitted NDA 204200 for Adrenalin (epinephrine) injection, 1mg/mL (b) (4) 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. (b) (4)

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

(b) (4)

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/s/

CAROL F HILL
08/23/2012



Food and Drug Administration
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 Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: August 2, 2012

To: Steve Richardson, VP, Scientific & Regulatory Affairs	From: Carol Hill, M.S. Sr. Regulatory Health Project Manager
Company: JHP Pharmaceuticals, LLC	Division of Pulmonary, Allergy, and Rheumatology Drug Products
Fax: 973-658-3582	Fax number: 301-796-9728
Phone number: 973-658-3561	Phone number: 301-796-2300
Subject: NDA 204200 [REDACTED] (b) (4) – Information Request/Advice	

Total no. of pages including cover: 3

Comments:

Document to be mailed: YES xNO

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NDA 204200

(b) (4)

Dear Mr. Richardson:

We refer to your NDA submission (NDA 204200) dated March 7, 2012, and to our telephone conversation on July 24, 2012

(b) (4)

(b) (4)

Let us know of your decision as soon as possible so we can take appropriate administrative actions.

I may be reached at 301-796-1226 for any questions.

Carol Hill
Senior Regulatory Health Project Manager

Draft: CHill/August 1, 2012
Clearance: Jafari/August 2, 2012
Peri/August 2, 2012
Jones/August 2, 2012
Gilbert-McClain/August 2, 2012
Chowdhury/August 2, 2012
Finalized: Chill/August 2, 2012

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/s/

CAROL F HILL
08/02/2012



NDA 204200

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

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

ATTENTION: Steve Richardson
VP Scientific and Regulatory Affairs

Dear Mr. Richardson:

Please refer to your New Drug Application (NDA) dated, March 07, 2012, received, March 07, 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 April 18, 2012, correspondence, received April 18, 2012, 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.

The proposed proprietary name, Adrenalin, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If any of the proposed product characteristics as stated in your April 18, 2012, 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}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
07/17/2012

MEMORANDUM OF MEETING MINUTES

MEETING DATE: June 21, 2012
TIME: 9:30 am to 10:00 am
LOCATION: Teleconference
APPLICATION: NDA 204200
DRUG NAME: Adrenalin
TYPE OF MEETING: Guidance

MEETING CHAIR: Eric Duffy

MEETING RECORDER: Carol F. Hill

FDA ATTENDEES:

Terrance Ocheltree, PhD, Director, DNDQAII
Rapti Madurawe, PhD, Branch Chief, Branch V, DNDQAII
Balajee Shanmugam, PhD, CMC Reviewer, DNDQAII
Eric Duffy, PhD, Director, DNDQA III
Prasad Peri, PhD, Branch Chief, Branch VIII, DNDQA III
Ying Wang, PhD, CMC Reviewer, DMDQA III
Renata Albrecht, MD, Director, DTOP
Wiley Chambers, MD, Deputy Director, DTOP
William Boyd, MD, Clinical Team Leader, DTOP
Theresa Michele, MD, Clinical Team Leader, DPARP
Peter Starke, MD, Clinical Reviewer, DPARP
Molly Shea, PhD, Supervisor, Non-Clinical, DPARP
Jane Sohn, PhD., Non-Clinical Reviewer, DPARP
Carol Hill, MS, Senior Regulatory Health Project Manager, DPARP

EXTERNAL CONSTITUENT ATTENDEES:

Steve Richardson – VP, Scientific and Regulatory Affairs
Mike Bergren – Director, Chemistry and Analytical Development
Marty Joyce – VP, Product Development
(b) (4) (Non-Clinical Consultant)
(b) (4) (Director, Regulatory Affairs – Consultant)
(b) (4) (Director, Regulatory Science – Consultant)
Carla English – Manager, Regulatory Affairs

BACKGROUND:

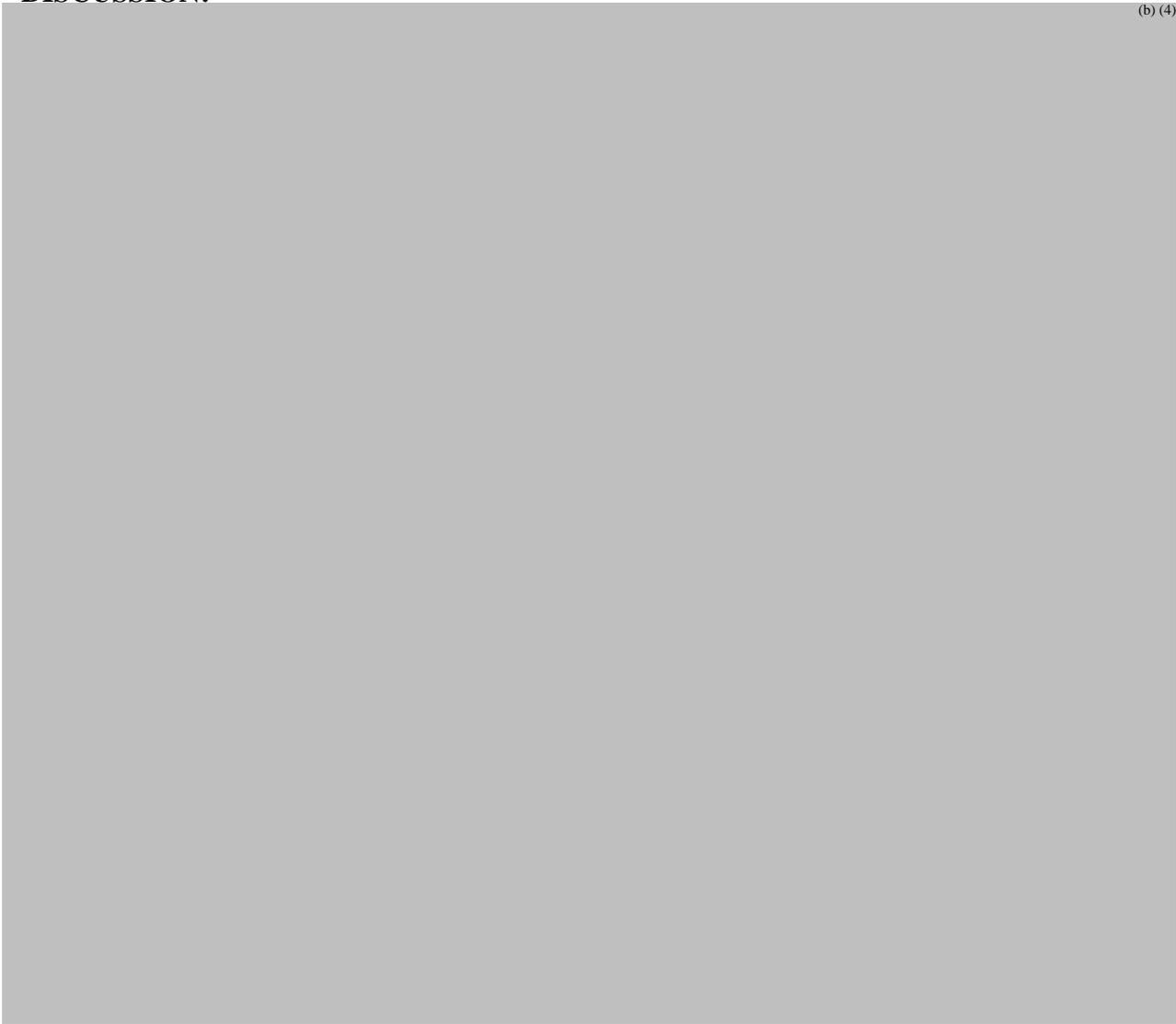
A CMC information request dated June 13, 2012 was forwarded to JHP Pharmaceuticals. The information request asked JHP to reduce the total impurities and submit a revised acceptance criterion for total impurities and for each individual identified impurity along with supporting data; reduce the acceptance criterion limit for unidentified impurities to NMT 0.5% or identify these impurities; for the 1 mL drug product presentation for ophthalmic use, revise the acceptance criteria to meet USP<789>; and conduct a leachable study for the container closure system when stored at the long –term storage condition in the worst-case orientation with test

time points according to the approved stability protocol until the end of the product shelf-life (submit available study data now and update the NDA when additional data is available). After receiving the information request, JHP Pharmaceuticals requested a teleconference with the Agency to gain clarity regarding the Agency's request.

MEETING OBJECTIVES:

See the agenda and presentation submitted by JHP Pharmaceuticals in the Attachments and Handouts section below.

DISCUSSION:



Since the September 7, 2012 (PDUFA goal) date is near for the ophthalmic indication, JHP stated that they would like to proceed in the approval process with the product as it currently exists based on the history of the product and provide a stable quality product including the FDA's requirements as post approval commitments. The FDA mentioned that further internal discussed is needed and that comment would be reserved until a proposal is submitted for

review. The FDA requested JHP to include in the proposal data accrued from other marketed products. JHP stated that a proposal would be submitted within 2 weeks and the requested data would be included.

ATTACHMENTS/HANDOUTS:

Meeting agenda and slide presentation submitted by JHP Pharmaceuticals.

11 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

CAROL F HILL
07/23/2012



NDA 204200/Original 1
NDA 204200/Original 2

INFORMATION REQUEST

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

Attention: Steve Richardson
Vice President, Scientific and Regulatory Affairs

Dear Mr. Richardson:

Please refer to your New Drug Application (NDA) submitted on March 3, 2012, received on March 7, 2012, under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Adrenalin (epinephrine injection), 1 mg/mL.

(b) (4)
After evaluating the drug product release and stability data, specifications and the justifications for specifications provided in your application, we have concluded that in order to completely assess the identity, strength, quality, and purity attributes of your drug products, we will need additional information. Provide responses to the following comments and information requests by July 20th.

1. (b) (4)
Reduce the total impurities; this can be achieved through reformulation, process improvement, or by other means. Submit a revised acceptance criterion for total impurities along with the supporting data.

We also recommend that you revise the acceptance criteria for each individual identified impurity (b) (4) in order to meet the revised total impurities limit. Submit the revised acceptance criteria for each individual identified impurity along with the supporting data and justification.

2. Your proposed acceptance criterion for individual unidentified impurity of NMT (b) (4) is high. Per ICH guidance Q3B(R) we recommend that you either reduce this limit to NMT 0.5% or identify these impurities.

3. Your 1 mL drug product presentation has an indication for ophthalmic use. Therefore the proposed acceptance criteria for particulate matter should meet USP <789>. Revise the acceptance criteria for 1 mg/mL presentation to meet USP <789>.
4. As the proposed container closure system has a (b) (4) stopper, conduct a leachable study (based on results obtained for extractables from the stopper) using screening analytical methods for the drug product solution in the proposed container closure system when stored at the long-term storage condition in the worst-case orientation. Test time points should be according to the approved stability protocol until the end of product shelf-life. Submit available study data now and update the NDA when additional data become available.

If you have any questions, call Judit Milstein, Chief Project Management Staff in the Division of Transplant and Ophthalmology Products (301-796-0763) or Carol Hill, Regulatory Project Manager in the Division of Pulmonary, Allergy and Rheumatology Products (301-796-1226). They will be able to set up a teleconference if you need further clarification on the requests described above

Sincerely,

{See appended electronic signature page}

Prasad Peri, Ph.D.
Branch Chief, Branch VIII
Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

PRASAD PERI
06/13/2012

NDA 204200/Original 1 and Original 2
Adrenalin (epinephrine injection)
JHP Pharmaceuticals

Dear Mr. Richardson,

In order to continue with the timely review of NDA 204200, please respond to the following request for information by no later than June 8, 2012.

1. Please describe the sterilization [REDACTED] (b) (4)
2. Confirm [REDACTED] (b) (4)
3. The table 'Location of Operations' (3.2.P.3.3, Description of Manufacturing Process and Process Controls, Page 10) states [REDACTED] (b) (4)

Call me or Carol Hill if you have any questions regarding this request.

Thank you

Judit Milstein
Chief, Project Management Staff
Division of Transplant and Ophthalmology Products
Center for Drug Evaluation and Research
301-796-0763

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/s/

JUDIT R MILSTEIN

05/24/2012

NDA 204200-Information Request

REQUEST FOR CONSULTATION

TO (Office/Division):

Jane Sohn
Division Of Pulmonary, Allergy, And Rheumatology
Products

FROM (Name, Office/Division, and Phone Number of Requestor):

Youbang Liu, ONDQA/Division III,
301-796-1926

DATE
5/11/12

IND NO.

NDA NO.
204200

TYPE OF DOCUMENT
New NDA (priority)

DATE OF DOCUMENT
3/7/2012

NAME OF DRUG
Adrenaline Solution,
Injection

PRIORITY CONSIDERATION

CLASSIFICATION OF DRUG

DESIRED COMPLETION DATE
6/5/12

NAME OF FIRM: JHP PHARMACEUTICALS LLC

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|---|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input checked="" type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

- | | |
|---|--|
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input checked="" type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--|--|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

- | | |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|---|
| <input type="checkbox"/> CLINICAL | <input checked="" type="checkbox"/> NONCLINICAL |
|-----------------------------------|---|

COMMENTS / SPECIAL INSTRUCTIONS:

Attached are proposed DP specification for various impurities and characterization for impurities. Some of these impurities (b) (4) have very high limits for stability. Please evaluation and let us know if these proposed limits for individual identified impurities are acceptable from safety perspective.

This NDA is priority review for DTOP and mid-cycle is June 18. We need preliminary assessment by June 5.

SIGNATURE OF REQUESTOR
Youbang Liu

METHOD OF DELIVERY (Check one)
 DFS EMAIL MAIL HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

3.2.P.5 – Control of Drug Product

JHP Pharmaceuticals LLC - Adrenalin® - NDA 204200, SN 0000

3.2.P Drug Product

3.2.P.5 Control of Drug Product

3.2.P.5.1 Specifications

JHP proposes to utilize the following Test and Acceptance Criteria for release and end of shelf life for the drug product, Adrenalin® Injection 1 mg/mL, as indicated below.

Test	Specification	Specification (b) (4)
Description	Release	Stability (b) (4)
Assay	(b) (4)	(b) (4)
Individual Unidentified Impurity	(b) (4)	(b) (4)
Total Impurities*	(b) (4)	(b) (4)
Identification	(b) (4)	(b) (4)
pH	(b) (4)	(b) (4)
Sodium Bisulfite	(b) (4)	(b) (4)
Total Acidity	(b) (4)	(b) (4)
Color & Clarity	(b) (4)	(b) (4)
Sterility	(b) (4)	(b) (4)
Particulate Matter	(b) (4)	(b) (4)
Bacterial Endotoxin	(b) (4)	(b) (4)
AME	(b) (4)	(b) (4)

* Total Impurities

3.2.P.5 – Control of Drug Product

3.2.P.5.5 Characterization of Impurities

See table below for the potential degradation impurities, which will be monitored during the release and stability testing of Adrenalin® Injection 1mg/mL.

Impurity (IUPAC; Common Name)	Origin	Structure
(b) (4)		

The method of analysis for related substances in Adrenalin® Injection 1 mg/mL is stability indicating and capable of detecting and quantifying all the known and unknown impurities.

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/s/

YOUBANG LIU
05/11/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION		
TO (Division/Office): Mail: OSE		FROM: Judit Milstein, CPMS Division of Transplant and Ophthalmology Products		
DATE: May 10, 2012	IND NO.	NDA NO 204200.	TYPE OF DOCUMENT New NDA	DATE OF DOCUMENT March 7, 2012
NAME OF DRUG Adrenalin (epinephrine)	PRIORITY CONSIDERATION Priority-6 months	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE August 7, 2012	
NAME OF FIRM: JHP Pharmaceuticals				
REASON FOR REQUEST				
I. GENERAL				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE--NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW):				
II. BIOMETRICS				
STATISTICAL EVALUATION BRANCH		STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):		<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):		
III. BIOPHARMACEUTICS				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES		<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
IV. DRUG EXPERIENCE				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP		<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
V. SCIENTIFIC INVESTIGATIONS				
<input type="checkbox"/> CLINICAL		<input type="checkbox"/> PRECLINICAL		
COMMENTS/SPECIAL INSTRUCTIONS: This NDA includes two indications reviewed in different Divisions and therefore, for tracking purposes, it was split in DARRTS as Original 1-Treatment of severe acute anaphylaxis ^{(b) (4)} - Will be reviewed in DPARP Original 2-Induction of mydriasis during cataract surgery-Will be reviewed in DTOP This NDA will have a joint review for all disciplines, other than clinical and stats, on a priority review clock. We request a review of one labeling with both indications, and labels for carton and container. We will provide a substantially complete labeling as review is progressing. We request that the response to this consult be linked to both originals Electronic submission can be located at: \\CDSESUB1\EVSPROD\NDA204200\204200.enx Mid Cycle meeting: June 18, 2012 Wrap Up Meeting: August 7, 2012				
SIGNATURE OF REQUESTER		METHOD OF DELIVERY -DARRTS		
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER		

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/s/

JUDIT R MILSTEIN
05/10/2012
NDA 204200-OSE Consult

**REQUEST FOR OPDP (previously DDMAC) LABELING REVIEW
CONSULTATION**

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

****Please send immediately following the Filing/Planning meeting****

TO: CDER-DDMAC-RPM	FROM: (Name/Title, Office/Division/Phone number of requestor) Judit Milstein Chief, Project Management Staff, Division of Transplant and Ophthalmology Products, (6-0763)
------------------------------	--

REQUEST DATE May 10, 2012	IND NO.	NDA/BLA NO. 204200	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)
-------------------------------------	---------	-----------------------	---

NAME OF DRUG Adrenalin (epinephrine)	PRIORITY CONSIDERATION Priority-6 months	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting) July 31, 2012
--	---	------------------------	--

NAME OF FIRM: JHP Pharmaceuticals	PDUFA Date: September 7, 2012
---	-------------------------------

TYPE OF LABEL TO REVIEW

TYPE OF LABELING: (Check all that apply) <input checked="" type="checkbox"/> PACKAGE INSERT (PI) <input type="checkbox"/> PATIENT PACKAGE INSERT (PPI) <input type="checkbox"/> CARTON/CONTAINER LABELING <input type="checkbox"/> MEDICATION GUIDE <input type="checkbox"/> INSTRUCTIONS FOR USE(IFU)	TYPE OF APPLICATION/SUBMISSION <input checked="" type="checkbox"/> ORIGINAL NDA/BLA <input type="checkbox"/> IND <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> SAFETY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> PLR CONVERSION	REASON FOR LABELING CONSULT <input checked="" type="checkbox"/> INITIAL PROPOSED LABELING <input type="checkbox"/> LABELING REVISION
---	--	---

EDR link to submission: <\\CDSESUB1\EVSPROD\NDA204200\204200.enx>

Please Note: There is no need to send labeling at this time. Once the substantially complete labeling is received, OPDP will complete its review within 14 calendar days.

COMMENTS/SPECIAL INSTRUCTIONS:

Mid-Cycle Meeting: June 18, 2012
 Labeling Meetings: TBD
 Wrap-Up Meeting: August 7, 2012
 Labeling to applicant: August 17, 2012

SIGNATURE OF REQUESTER: Judit Milstein, CPMS, DTOP

SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one)- <input type="checkbox"/> DARRTS
-----------------------	---

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/s/

JUDIT R MILSTEIN

05/10/2012

NDA 204200- DDMAC Consult

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

CMC MICRO & STERILITY ASSURANCE REVIEW REQUEST

TO (*Division/Office*): **New Drug Microbiology Staff**

***E-mail to:* CDER OPS IO MICRO**

***Paper mail to:* WO Bldg 51, Room 4193**

FROM: Youbang Liu, Project Manager, ONDQA

PROJECT MANAGER (*if other than sender*):

REQUEST DATE
5/8/12

IND NO.

NDA NO.
204200

TYPE OF DOCUMENT
New NDA

DATE OF DOCUMENT
3/7/12

NAMES OF DRUG
Adrenalin (epinephrine)

PRIORITY CONSIDERATION
Priority-6 months

PDUFA DATE
9/7/12

DESIRED COMPLETION DATE
6/18/12

NAME OF APPLICANT OR SPONSOR: **JHP Pharmaceuticals**

GENERAL PROVISIONS IN APPLICATION

- | | |
|---|---|
| <input type="checkbox"/> 30-DAY SAFETY REVIEW NEEDED | <input type="checkbox"/> CBE-0 SUPPLEMENT |
| <input type="checkbox"/> NDA FILING REVIEW NEEDED BY: _____ | <input type="checkbox"/> CBE-30 SUPPLEMENT |
| <input type="checkbox"/> BUNDLED | <input type="checkbox"/> CHANGE IN DOSAGE, STRENGTH / POTENCY |
| <input type="checkbox"/> DOCUMENT IN EDR | |

COMMENTS / SPECIAL INSTRUCTIONS:

This is an injection drug product. Please evaluate the sterile manufacturing process, specifications for sterility, bacterial endotoxins and antimicrobial effectiveness testing, and preservative effectiveness testing. Midcycle meeting is on June 18, 2012. Please provide a preliminary evaluation by then. This is a priority NDA.

SIGNATURE OF REQUESTER

Youbang Liu

REVIEW REQUEST DELIVERED BY (Check one):

DARRTS EDR E-MAIL MAIL HAND

DOCUMENTS FOR REVIEW DELIVERED BY (Check one):

EDR E-MAIL MAIL HAND

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/s/

YOUBANG LIU
05/10/2012



NDA 204200/Original 1
NDA 204200/Original 2

FILING COMMUNICATION

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

Attention: Steve Richardson
Vice President, Scientific and Regulatory Affairs

Dear Mr. Richardson:

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

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 will be considered filed 60 days after the date we received your application. As noted in our communication dated March 29, 2012, this application was administratively split into NDA 204200/Original 1 and NDA 204200/Original 2. Their review classification and user fee goals are listed below.

NDA Number	Indication	Review Classification	User fee Goal
204200/Original 1	treatment of severe acute anaphylactic reactions. (b) (4)	Standard	January 7, 2013
204200/Original 2	induction of mydriasis during cataract surgery	Priority	September 7, 2012

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 requirement/commitment requests by August 17, 2012, for NDA 204200/Original 2 and December 10, 2012, for NDA 204200/Original 1.

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.

To assist in our review, we request that you submit the following information:

CHEMISTRY, MANUFACTURING and CONTROLS

1. Section 3.2.P.3.3., (b) (4) the manufacturing process description mentions inspection of the (b) (4) 3 mL vials. (b) (4)
2. Please confirm that the currently marketed 1 mL and 30 mL formulations and container closure systems are identical to the proposed commercial formulation and container closure system.
3. The analytical method for determining (b) (4) (Procedure Number (b) (4)) appears to be missing. Please submit the above mentioned method along with validation details or indicate where in the NDA this information is provided.
4. Based on the preliminary assessment of the drug product specifications, the proposed acceptance criteria for (b) (4) Individual Unidentified Impurity, and Total Impurities are unacceptably high. We recommend that these criteria (b) (4) meet the current standards of approved drug products. In addition, please provide adequate mass balance information (b) (4) at release and on stability. For additional information please refer to the ICH guidance for industry, "*Q3B (R2) Impurities in New Drug Products*," available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073389.pdf>

PRODUCT QUALITY MICROBIOLOGY

5. Please clarify whether stoppers are supplied endotoxin-free. If stoppers are not supplied endotoxin free, please provide a protocol and validation studies for the depyrogenation of the stoppers (b) (4) of the drug product.
6. Please provide personnel monitoring protocols and schedules.

7. For container closure studies, describe how stoppers for both vial sizes are processed prior to insertion in test vials. Are the sterilization parameters the same or different from stoppers used in production?
8. Please provide endotoxin and bioburden alert/action levels for WFI [REDACTED] (b) (4) used in manufacturing.
9. Please clarify whether [REDACTED] (b) (4) is used in manufacturing the drug product. If so, provide media fill and sterilization/endotoxin validation studies for this line.
10. Please provide the most recent requalification reports [REDACTED] (b) (4) [REDACTED]
11. Please provide data from inhibition/enhancement studies used to determine the dilution used in endotoxin testing of the drug product. [REDACTED] (b) (4)
12. Please provide the sampling plan for the drug product including the number of articles that will be tested for sterility and endotoxin levels in each production batch of drug product.

Please respond 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.

LABELING

During our preliminary review of your submitted labeling, we have identified labeling formatting issues. We will be addressing these issues at the time we communicate proposed labeling.

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.

PEDIATRIC RESEARCH EQUITY ACT (PREA)

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 of our decision.

If you have any questions, call the following Regulatory Project Managers:

For NDA 204200/Original 1 – Carol F. Hill at (301) 796-1226
For NDA 204200/Original 2 – Judit Milstein at (301) 796-0763

Sincerely,

{See appended electronic signature page}

Renata Albrecht, MD
Director
Division of Transplant and
Ophthalmology Products
Office of Antimicrobial Products
Office of New Drugs
Center for Drug Evaluation and Research

Lydia Gilbert MacClain
Deputy Director
Division of Pulmonary, Allergy and
Rheumatology Products
Office of Drug Evaluation II
Office of New Drugs
Center for Drug Evaluation and Research

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/s/

WILEY A CHAMBERS
05/04/2012
For Renata Albrecht

LYDIA I GILBERT MCCLAIN
05/04/2012



NDA 204200/Original 1
NDA 204200/Original 2

NDA ACKNOWLEDGMENT

JHP Pharmaceuticals, LLC
One Upper Pond Road, 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 (FDCA) for the following:

Name of Drug Product: Adrenalin (epinephrine injection), 1 mg/mL

Date of Application: March 7, 2012

Date of Receipt: March 7, 2012

Our Reference Number: NDA 204200

NDA 204200 provides for the use of Adrenalin (epinephrine injection), 1 mg/mL for the following indications which, for administrative purposes, we have designated as follows:

- NDA 204200/Original 1 – indicated for the treatment of severe acute anaphylactic reactions (b) (4)
- NDA 204200/Original 2 – indicated for the induction of mydriasis during cataract surgery.

NDA 204200/Original 1 will be reviewed by the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) and NDA 204200/Original 2 will be reviewed by the Division of Transplant and Ophthalmology Products (DTOP).

All future submissions to your NDA should specify the NDA number and all Original numbers to which each submission pertains.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on May 6, 2012, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

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 and all pertinent Original numbers provided above should be cited 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 addresses. For administrative purposes submissions for NDA 204200/Original 1 should be forwarded to:

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

For administrative purposes submissions for NDA 204200/Original 2 should be forwarded to:

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

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information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call the following Regulatory Project Managers:

For NDA 204200/Original 1 – Carol F. Hill at (301) 796-1226
For NDA 204200/Original 2 – Judit Milstein at (301) 796-0763

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

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
03/29/2012



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) Nonclinical Consultant
(b) (4) regulatory Consultant
(b) (4) Regulatory Consultant

Meeting Minutes
[Insert Meeting Type]
DATE

[Insert Office/Division]

[REDACTED] ^{(b) (4)} via telephone, Medical Safety Consultant
[REDACTED] ^{(b) (4)} Medical Consultant , Emergency Medicine Physician

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 (b)(4) 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)
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 [REDACTED] (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 [REDACTED] (b) (4) to gain approval?

FDA Response:

See our response to question 1. [REDACTED] (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 [REDACTED] (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)

(b) (4)

The Agency commented about testing of approved products (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)
(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 (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 (b)(4) 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 (b)(4) 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 (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)
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 (b) (4) 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)

(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:

[REDACTED] (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