

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204200Orig1s000

204200Orig2s000

OTHER REVIEW(S)

505(b)(2) ASSESSMENT

Application Information		
NDA # 204200/Original 2	NDA Supplement #:	Efficacy Supplement Type SE-
Proprietary Name: Adrenalin Established/Proper Name: Epinephrine Dosage Form: injection Strengths: 1 mg/mL		
Applicant: JHP Pharmaceuticals, LLC		
Date of Receipt: March 7, 2012		
PDUFA Goal Date: December 7, 2012		Action Goal Date (if different):
Proposed Indication(s): Original 2- Induction and maintenance of mydriasis during intraocular surgery		

GENERAL INFORMATION

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES NO

If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

**INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
NDA 19430 (RLD)	Safety
Published literature	Safety and Efficacy

*each source of information should be listed on separate rows

- 3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific “bridge” to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

The applicant states that since the proposed product is administered as an injection solution (b) (4) they request a waiver of in vivo bioequivalence studies. This was agreed at the July 5, 2011, pre-NDA meeting.

RELIANCE ON PUBLISHED LITERATURE

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES NO

If “NO,” proceed to question #5.

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES NO

If “NO,” proceed to question #5.

If “YES”, list the listed drug(s) identified by name and answer question #4(c).

EpiPen auto injector

- (c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES NO

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

- 5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES NO

If "NO," proceed to question #10.

- 6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
EpiPen	NDA 19430	Yes

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A YES NO

If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".

If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved in a 505(b)(2) application: EpiPen

- b) Approved by the DESI process?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved via the DESI process:

- c) Described in a monograph?

YES NO

If "YES", please list which drug(s).

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES NO

If "YES", please list which drug(s) and answer question d) i. below.

If "NO", proceed to question #9.

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES NO

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

This application provides for a new dosage form-Single-use vial whereas the relied-upon EpiPen is an autoinjector (drug-device combination). This application also provides for a new indication: induction and maintenance of mydriasis.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered YES to question #1, proceed to question #12; if you answered NO to question #1, proceed to question #10 below.

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; **and** (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).*

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

YES NO

If "**NO**" to (a) proceed to question #11.
If "**YES**" to (a), answer (b) and (c) then proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

YES NO

If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.

If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES NO

If "**NO**", proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

YES NO

If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in

the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

- 12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s): EpiPen/7449012, 7794432, 8048035

No patents listed proceed to question #14

- 13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES NO

If "NO", list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

- 14) Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

Expiry date(s):

21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the

NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

Method(s) of Use/Code(s):

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s): 7,449,012
7,798,432
8,048,035

(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]? YES NO
If "NO", please contact the applicant and request the signed certification.

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt. YES NO
If "NO", please contact the applicant and request the documentation.

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s): *May 17, 2012*

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.

YES NO Patent owner(s) consent(s) to an immediate effective date of approval

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

12/07/2012

NDA 204200/Original 2-505(b)(2) assessment form

505(b)(2) ASSESSMENT

Application Information		
NDA # 204200-Orig 1	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Adrenalin Established/Proper Name: Epinephrine Dosage Form: Injection Strengths: 1 mL		
Applicant: JHP Pharmaceuticals, LLC		
Date of Receipt: March 7, 2012		
PDUFA Goal Date: January 7, 2013		Action Goal Date (if different): December 7, 2012
Proposed Indication(s): emergency treatment of allergic reactions (TypeI) including anaphylaxis.		

GENERAL INFORMATION

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES NO

If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.



**INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
NDA 19430	Safety and efficacy
Published Literature	Safety and efficacy

*each source of information should be listed on separate rows

- 3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific “bridge” to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

The proposed drug product is an injection solution (b) (4)
 (b) (4) **JHP has requested a waiver of *in vivo* bioequivalence studies under 21 CFR 320.22(d)(2) because the proposed drug product is an injection solution** (b) (4)

The Division agrees with this approach, and considers that further bridging is not required. The BA/BE waiver was granted for the IM and SC routes of administration, see the Product Quality Review and Biopharmaceutics Reviews dated August 13 and November 13, 2012, respectively. (b) (4)

It should be noted that there are critical differences between the proposed product and the referenced product. The proposed product is a drug intended for use in the medical setting by medically trained personnel, whereas the referenced product is a drug-device combination, i.e., an auto-injector, that is intended for emergency self use in the non-medically supervised setting. Because of these differences, the dosing, weight, and age ranges for this product will extend beyond those for the referenced drug-device combination, resulting in different labeling for this product than any of the currently marketed epinephrine auto-injector products. Because this product is not a drug-device combination and is intended for different setting of use with different dosing and administration instructions, there is no need to ensure bioequivalence to any of the currently marketed auto-injector products, and granting of a waiver of bioequivalence studies is both acceptable and appropriate.

To support the nonclinical pharmacology and toxicology, a literature review was conducted supplemented by four studies designed to assess genotoxicity and to qualify (b) (4)
 (b) (4) **as an impurity.**

Relevant literature searches and overview documents were submitted to support efficacy and safety.

RELIANCE ON PUBLISHED LITERATURE

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES NO

If "NO," proceed to question #5.

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

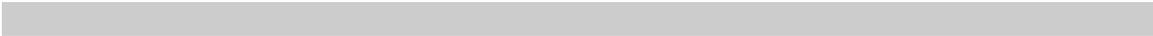
YES NO

If "NO," proceed to question #5.

If "YES", list the listed drug(s) identified by name and answer question #4(c).

- (c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES NO



RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

- 5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES NO

If "NO," proceed to question #10.

- 6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
EpiPen	NDA 19430	Yes

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A YES NO

If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".

If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved in a 505(b)(2) application: EpiPen

- b) Approved by the DESI process?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved via the DESI process:

- c) Described in a monograph?

YES NO

If "YES", please list which drug(s).

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES NO

If "YES", please list which drug(s) and answer question d) i. below.

If "NO", proceed to question #9.

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES NO

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution"). This application

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

This application provides for use in dosages and age ranges beyond those for the referenced approved drug product. Additionally, the approved drug product is a drug-device combination, whereas the proposed drug product is not.

The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered YES to question #1, proceed to question #12; if you answered NO to question #1, proceed to question #10 below.

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

YES NO

If "**NO**" to (a) proceed to question #11.
If "**YES**" to (a), answer (b) and (c) then proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?
YES NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?
YES NO

If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.

If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES NO
If "**NO**", proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?
YES NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?
YES NO

If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in

the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s): EpiPen – 7449012, 7794432, 8048035

No patents listed proceed to question #14

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES NO

If "NO", list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

- No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

Expiry date(s):

- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*
- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the

NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

- (a) Patent number(s): 7449012, 7798432, 8048035
- (b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?
YES NO
If "NO", please contact the applicant and request the signed certification.

- (c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.
YES NO
If "NO", please contact the applicant and request the documentation.

- (d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s): *May 17, 2012*

- (e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.

YES NO Patent owner(s) consent(s) to an immediate effective date of approval

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

Attachment C: Sample PMR/PMC Development Template: Product Quality (CMC)

TO BE USED FOR PMCS NOT REPORTABLE UNDER 506(B)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types.

PMC #1 Description:

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.

PMC Schedule Milestones:	Final Protocol Submission Date:	<u>January 2013</u>
	Study Completion Date:	<u>March 2014</u>
	Final Report Submission Date:	<u>May 2014</u>
	Other: <u>Interim Report</u>	<u>April 2013</u>

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check the reason below and describe.

- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct postapproval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

The NDA provides for a currently marketed unapproved product, Adrenalin® for two indications, 1) emergency treatment of allergic reactions (anaphylaxis), and 2) ophthalmic use for induction and maintenance of mydriasis during cataract surgery. The product has been determined to be safe from clinical perspective. However, from quality perspective, the levels of impurities are considerably high as compared to approved products. During the review cycle, considerable efforts were expended in discussing approaches to reduce the levels of impurities and also achieved to some extent. Since the revised levels provide a better quality product than their currently marketed product, a PMC is adequate to further improve and ensure reliable and consistent quality. Furthermore, the company agrees with the Agency's recommendations to evaluate the existing process and formulation to mitigate the levels of impurities.

2. Describe the particular review issue and the goal of the study.

The NDA at the time of submission provided for a product which potentially could have had as much as (b) (4) impurities. The levels, based on clinical and pharm/tox reviews poses no safety risk. (b) (4)

During the review cycle, the Agency and the company diligently worked together to resolve the issue (b) (4)

Upon further discussions, the company is convinced that further evaluation of process and formulation can help (b) (4) The outcome of the PMC studies is expected to provide a product of reliable and consistent acceptable quality and potentially lower impurities.

3. [OMIT — for PMRs only]
4. What type of study is agreed upon (describe and check the type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

Evaluate formulation and process improvements to reduce the levels of impurities with Adrenalin (epinephrine injection). 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. 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. Using the results from these investigations, re-evaluate the acceptance limits for (b) (4) and (b) (4) and lower the limits for these impurities.

5. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

X This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs only)

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/s/

SALLY M SEYMOUR
12/07/2012

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Final Label, Labeling and Packaging Review

Date: November 19, 2012

Reviewer: Jung Lee, RPh
Division of Medication Error Prevention and Analysis

Team Leader: Jamie Wilkins Parker, PharmD
Division of Medication Error Prevention and Analysis

Drug Name and Strength: Adrenalin (Epinephrine Injection, USP), 1 mg/mL

Application Type/Number: NDA 204200

Applicant/sponsor: JHP Pharmaceuticals

OSE RCM #: 2012-2678

*** This document contains proprietary and confidential information that should not be released to the public.***

1 INTRODUCTION

This review evaluates the revised proposed insert labeling (for both the anaphylaxis and ophthalmic indications) for Adrenalin (Epinephrine Injection, USP), NDA 204200, for areas of vulnerability that could lead to medication errors.

1.1 BACKGROUND AND REGULATORY HISTORY

Adrenalin is currently marketed by JHP Pharmaceuticals as an unapproved epinephrine product. On March 7, 2012, NDA 204200 was submitted by the Applicant as a 505(b)(2) application; the Reference Listed Drug (RLD) is EpiPen (NDA 19430). This application includes two indications and is currently being reviewed by two divisions. The first indication (designated as Original 1) is for the emergency treatment of allergic reactions including anaphylaxis being reviewed by the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) and the second indication (designated as Original 2) is for the induction and maintenance of mydriasis during intraocular surgery under review by the Division of Transplant and Ophthalmology Products (DTOP). Both indications have been incorporated into one insert labeling which is the subject of our review.

1.2 PRODUCT INFORMATION

The following product information is provided in the November 9, 2012 submission.

- Active Ingredient: Epinephrine
- Indication of Use:
 - Hypersensitivity Reactions: Emergency treatment of allergic reactions, including anaphylaxis
 - Ophthalmic Use: Induction and maintenance of mydriasis during intraocular surgery
- Route of Administration: Intramuscular, Subcutaneous (b) (4) or Intraocularly
- Dosage Form: Injection Solution
- Strength: 1 mg/mL
- Dose and Frequency:
 - Anaphylaxis:
 - Adults and Children ≥ 30 kg (66 lbs):
 - 0.3 mg to 0.5 mg (0.3 mL to 0.5 mL) intramuscularly (or subcutaneously) into anterolateral thigh every 5 to 10 minutes as necessary.
 - Children 30 kg (66 lbs) or less:

- 0.01 mg/kg (0.01 mL/kg), up to 0.3 mg (0.3 mL), intramuscularly (or subcutaneously) into anterolateral thigh every 5 to 10 minutes as necessary.
- Intraocular Surgery: Dilute 1 mL with 100 mL to 1000 mL of an ophthalmic irrigation fluid, for ophthalmic irrigation or intracameral injection. After dilution in an ophthalmic irrigating fluid, Adrenalin may also be injected intracamerally as a bolus dose of 0.1 mL at a dilution of 1:100,000 to 1:400,000 (10 mcg/mL to 2.5 mcg/mL).
- How Supplied: Carton containing 25-1 mL solution in a 3 mL single use vials of Adrenalin
- Storage: Store at 20°C to 25°C (68°F to 77°F). [See USP Controlled Room Temperature]. Epinephrine is light sensitive. Protect from light and freezing.
- Container and Closure System: USP Type I glass vials with a rubber stopper (b) (4)

2 MATERIALS REVIEWED

The revised insert labeling incorporating both anaphylactic and ophthalmic indications and OSE Review #2012-1042 were evaluated to assess whether the revisions adequately address our concerns from a medication error perspective.

2.1 LABELS AND LABELING

Using the principles of human factors and Failure Mode and Effects Analysis,¹ along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Revised Insert Labeling for both the anaphylaxis and ophthalmic indications submitted November 9, 2012

3 CONCLUSIONS

DMEPA concludes that the proposed insert labeling can be improved to increase the readability of important information on the label to promote the safe use of the product.

4 RECOMMENDATIONS

Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA:

- A. Comments to the Division
 1. Dosage and Administration (Section 2):

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

- a) Add a unit of measure immediately following all numbers, as appropriate. (For example, revise “0.3 to 0.5 mg” to read “0.3 mg to 0.5 mg”.)
 - b) Replace the symbol for inch (“”) with text. For example, 1/2” to 5/8” should read as follows: 1/2 inch to 5/8 inch.
 - c) Revise the statement “up to a maximum of 0.3 (0.3 mL) mg” to read as follows: up to a maximum of 0.3 mg (0.3 mL).
 - d) Revise the statements “10 mcg to 1 mcg/mL” and “10 mcg to 2.5 mcg/mL” to read as follows: 10 mcg/mL to 1 mcg/mL and 10 mcg/mL to 2.5 mcg/mL, respectively.
2. Under Dosage Forms and Strengths (Section 3), delete the statement “1 mL solution in a 3 mL single use-vial” and relocate to the How Supplied/Storage and Handling section.

If you have further questions or need clarifications, please contact Nichelle Rashid, project manager, at 301-796-3904.

REFERENCES

1. OSE Review #2012-1042, Label and Labeling Review for Adrenalin (Epinephrine Injection, USP), 1 mg/mL September 5, 2012, Lee, J.

APPENDICES

APPENDIX A. DATABASE DESCRIPTIONS

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

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/s/

JUNG E LEE
11/19/2012

JAMIE C WILKINS PARKER
11/21/2012

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: November 9, 2012

To: Carol Hill, Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products
(DPARP)

From: Roberta Szydlo, R.Ph., Regulatory Review Officer, Division of
Professional Drug Promotion (DPDP)

CC: Lisa Hubbard, Group Leader, DPDP
Twyla Thompson, Acting Group Leader, Division of Consumer Drug
Promotion (DCDP)
Matthew Falter, Pharm.D., Regulatory Review Officer, DCDP
Christine Corser, Pharm.D., Regulatory Review Officer, DPDP

Subject: NDA 204200
OPDP labeling comments for Adrenalin[®] (epinephrine injection,
USP) 1 mg/mL (1:1000) for intramuscular, subcutaneous and
intraocular use (Adrenalin)

OPDP has reviewed the proposed Package Insert (PI) and Carton and Container Labeling for Adrenalin submitted for consult on November 5, 2012. Reference is also made to OPDP's consult response dated September 6, 2012, to the Division of Transplant and Ophthalmology Products regarding the PI for Adrenalin. We offer the following comments on the proposed labeling.

OPDP's comments on the PI are based on the proposed draft labeling titled "NDA 204200_SCPI_2012-3-7_DTOP&DPARP_2012-11-2.doc" that was sent via email from DPARP to OPDP on November 2, 2012. OPDP's comments on the PI are provided directly in the marked-up document attached (see below).

OPDP has reviewed the proposed Carton and Container Labeling for the 1 mL package size for Adrenalin located in the EDR at:

- <\\cdsesub1\EVSPROD\NDA204200\0000\m1\us\draft-carton-1ml.pdf>
- <\\cdsesub1\EVSPROD\NDA204200\0000\m1\us\draft-label-1ml.pdf>

OPDP offers the following comments on the proposed carton and container labeling:

-  (b) (4)
- We recommend that the established name be revised on the carton and container labels to a font size that is at least as half as large of that of the proprietary name and a prominence commensurate with the proprietary name, as stated in 21 CFR 201.10(g)(2).

Thank you for the opportunity to comment on the proposed labeling.

If you have any questions please contact Roberta Szydlo at (301) 796-5389 or roberta.szydlo@fda.hhs.gov.

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/s/

ROBERTA T SZYDLO
11/09/2012

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
Division of Professional Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: September 6, 2012

To: Judit Milstein, Chief, Project Management Staff
Division of Transplant and Ophthalmology Products

From: Christine Corser, Pharm.D., Regulatory Review Officer
Division of Professional Drug Promotion (DPDP)

Subject: NDA 204200
Adrenalin® (epinephrine injection, USP) 1 mg/mL (1:1000) for
intramuscular, (b)(4) subcutaneous and intraocular use

As requested in your consult dated May 12, 2012, DPDP has reviewed the draft labeling for Adrenalin® (epinephrine injection, USP) 1 mg/mL (1:1000) for intramuscular, (b)(4) subcutaneous and intraocular use (Adrenalin).

DPDP's comments are based on the substantially complete version of the labeling titled, "Epi_Labeling(2).docx," which was sent via email from Judit Milstein on August 16, 2012.

DPDP's comments are provided in the attached, clean version of the labeling.

If you have any questions about DPDP's comments on the PI, please contact Christine Corser at 6-2653 or at Christine.corser@fda.hhs.gov.

Thank you for the opportunity to provide comments.

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/s/

CHRISTINE G CORSER
09/06/2012

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label, Labeling and Packaging Review

Date: September 5, 2012

Reviewer: Jung Lee, RPh
Division of Medication Error Prevention and Analysis

Acting Team Leader: Jamie Wilkins Parker, PharmD
Division of Medication Error Prevention and Analysis

Associate Director: Scott Dallas, RPh
Division of Medication Error Prevention and Analysis

Division Director: Carol Holquist, RPh
Division of Medication Error Prevention and Analysis

Drug Name and Strength: Adrenalin (Epinephrine Injection, USP), 1 mg/mL

Application Type/Number: NDA 204200

Applicant: JHP Pharmaceuticals

OSE RCM #: 2012-1042

*** This document contains proprietary and confidential information that should not be released to the public.***

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1 INTRODUCTION

This review evaluates the proposed container label, carton, and insert labeling for Adrenalin (Epinephrine Injection, USP), NDA 204200, for areas of vulnerability that could lead to medication errors.

1.1 BACKGROUND AND REGULATORY HISTORY

Adrenalin is currently marketed by JHP Pharmaceuticals as an unapproved epinephrine product. On March 7, 2012, NDA 204200 was submitted by the Applicant as a 505(b)(2) application. The Reference Listed Drug (RLD) is EpiPen (NDA 19430). NDA 204200 includes two indications which are currently being reviewed by two divisions, the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) and the Division of Transplant and Ophthalmology Products (DTOP). The first indication (designated as Original 1) is for the treatment of anaphylaxis and the second indication (designated as Original 2) is for the induction of mydriasis during cataract surgery. The Divisions determined there should be two separate submissions based upon different indications. Further discussion to determine how the application will be reviewed is forthcoming with the Applicant. A waiver of bioequivalence studies will be granted for the anaphylaxis indication but not for the ophthalmic indication. The new ophthalmic indication is being reviewed under priority status.

1.2 PRODUCT INFORMATION

The following product information is provided in the April 18, 2012 NDA submission.

- Active Ingredient: Epinephrine
- Indication of Use:
 - Hypersensitivity reactions: emergency treatment of severe acute anaphylactic reactions (b) (4)
 - Ophthalmic use: induction of mydriasis during cataract surgery
- Route of Administration: Intramuscular, Subcutaneous (b) (4) or Intraocularly
- Dosage Form: Injection Solution
- Strength: 1 mg/mL
- Dose and Frequency:





o Ophthalmic Use (b) (4)

- In order to maintain mydriasis, Adrenalin may be added to the irrigation fluid at very low doses (1:100,000 to 1: 1,000,000 [10 mcg/mL to 1 mcg/mL]). In adults, Adrenalin may also be injected intraocularly as a bolus dose in 0.1 mL at a dilution of 1:100,000 to 1:400,000 (10 mcg/mL to 2.5 mcg/mL).

• How Supplied:

Strength	(b) (4) 1 mg/mL Adrenalin® Sterile solution containing epinephrine injection, USP, as the hydrochloride in each (b) (4) vial (1:1000)	(b) (4)
Packaging	packages of twenty-five vials	

- Storage: Store at 20°C to 25°C (68°F to 77°F). [See USP Controlled Room Temperature]. Protect from light and freezing. (b) (4)
- Container and Closure System: USP Type I glass vials with a rubber stopper (b) (4)

2 METHODS AND MATERIALS REVIEWED

DMEPA searched the FDA Adverse Event Reporting System (AERS) database for Adrenalin and epinephrine medication error reports. We also reviewed the Adrenalin container labels, carton labeling and package insert labeling submitted by the Applicant.

2.1 SELECTION OF MEDICATION ERROR CASES

We searched the FDA AERS database using the strategy listed in Table 1 below.

Table 1: AERS Search Strategy	
Date	June 13, 2012
Drug Names	Active Ingredient: Epinephrine Verbatim Term: Adrenali%
MedDRA Search Strategy	Medication Errors (HLGT) Product Packaging Issues HLT (HLGT) Product Label Issues HLT Product Quality Issues (NEC) HLT
Time Limitation	From June 17, 2010 (Date of last search in OSE Review # 2010-1226 and 2010-1559) to June 13, 2012

The AERS search strategy identified 84 reports. Each report was reviewed for relevancy and duplication. After individual review, 78 cases were excluded from further analysis for the following reasons:

- Accidental exposure from Epipen, Twinject or epinephrine autoinjectors
- Adverse drug reactions not related to a medication error
- Product quality complaints not related to the labels and labeling of our product
- Cases related to the use of expired epinephrine autoinjectors
- Cases of Benadryl anaphylaxis

2.2 LABELS AND LABELING

Using the principals of human factors and Failure Mode and Effects Analysis,¹ along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted March 7, 2012 (Appendix B)
- Carton Labeling submitted March 7, 2012 (Appendix C)
- Insert Labeling submitted March 7, 2012

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

2.3 PREVIOUSLY COMPLETED REVIEWS

DMEPA previously reviewed epinephrine products in a postmarketing review (OSE # 2010-1226 and 2010-1559). We referenced this review to ensure all of our previous recommendations for labels and labeling were implemented. Although it does not appear that our recommendations were communicated to the Applicant, JHP Pharmaceuticals, we note the labels and labeling submitted by the Applicant contain some changes that were suggested in those previous reviews (OSE # 2010-1226/1559). We will discuss other recommendations from our previous reviews in section 3.2.

3 MEDICATION ERROR RISK ASSESSMENT

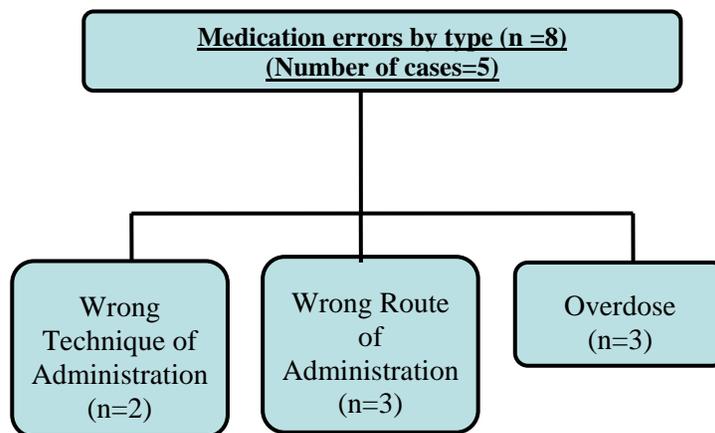
The following sections describe the results of our AERS search and the risk assessment of the Adrenalin product design as well as the associated label and labeling.

3.1 MEDICATION ERROR CASES

Following exclusions as described in section 2.1, five Adrenalin medication error cases remained for our detailed analysis. The NCC MERP Taxonomy of Medication Errors was used to code the type and factors contributing to the errors when sufficient information was provided by the reporter². A total of five medication error cases were identified, of which one case is a literature report that described medication errors for four different patients. Therefore, we note that the sum of the number of medication errors by type (n=8) is higher than the number of AERS cases (n=5).

Figure 1 provides a stratification of the number of cases included in the review by type of error. Appendix D provides listings of all ISR numbers and a detailed listing of cases summarized in this review.

Figure 1: Adrenalin medication errors categorized by type of error (n = 8)



² The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website <http://www.nccmerp.org/pdf/taxo2001-07-31.pdf>. Accessed June 1, 2011.

3.1.1 Wrong Technique of Administration (n=2)

We identified 2 cases involving wrong technique of administration. The first case (ISR #6809235-1) describes a patient who recovered after receiving a high dose of epinephrine by intravenous push instead of the slow, low intravenous dose as recommended. The root cause was reported to be due to inadequate physician knowledge about appropriate dose and route of epinephrine in anaphylaxis, the lack of intramuscular doses in emergency crash carts, complicated dose calculations involving decimals and ratios, and the lack of adequate communication between the physicians and nurses.

The second case of wrong technique of administration (ISR #8162681-9) reports a patient who accidentally received an undiluted (1:1000) dose of 1 mg epinephrine infusion. The patient experienced chest tightness, ST depression and decreased systolic blood pressure as a result of this error. The root cause of the error was not provided in the narrative.

3.1.2 Wrong Route of Administration (n=3)

One case (ISR #6809235-1) that is a literature report describes 3 patients who experienced wrong route of administration errors. All three patients received epinephrine intravenously instead of the prescribed intramuscular route. No further details were provided, but the narrative states the root cause for these errors was attributed to inadequate physician knowledge about appropriate dose and route of epinephrine in anaphylaxis, the lack of intramuscular doses in emergency crash carts, complicated dose calculations involving decimals and ratios, and the lack of adequate communication between the physicians and nurses.

3.1.3 Overdose (n=3)

Three cases of accidental overdose were identified with epinephrine. The reason for the overdose could not be determined in the first two cases (ISR #8395821 and 8044424). Two of the three cases reported an adverse event including hypotension, sinus bradycardia, and death.

The third case (ISR #8418043) identified a patient who received two doses of intramuscular epinephrine 1 mg at an unknown interval for the treatment of anaphylaxis but the recommended dose for anaphylaxis is 0.3 mg. The root cause of this error was attributed to the commercially available ampules of 1:1000 epinephrine containing 1 mg of drug.

3.2 INTEGRATED SUMMARY OF MEDICATION ERROR RISK ASSESMENT

In post-marketing review (OSE #2010-1226/1559), we recommended several labeling revisions to minimize the risk of medication errors involving epinephrine. For example, we recommended the presentation of strength be stated as (b) (4) (1 mg/mL) to comply with the USP labeling requirements for small volume parenterals. Additionally, we recommended that the 1 mg/mL injection product be labeled on the principal display panel to indicate the product must be diluted (b) (4). The proposed labels and labeling submitted by the Applicant in this submission include the strength per total volume as the primary expression followed by the strength per mL in parentheses. (b) (4)

In the post-marketing review, we recommended deleting the ratio strength from the principal display panel. However, we note the proposed labels and labeling includes the ratio (1:1000) in the strength presentation. Since there continues to be ongoing errors attributed to this ratio being included in the label and labeling, we will request this be deleted from this Applicant's label and labeling accordingly.

4 RECOMMENDATIONS

Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA:

4.1 COMMENTS TO THE DIVISION

A. Insert Labeling

1. The inclusion of the ratio strength on labels and labeling serves no purpose as the product is dosed in 'mg'. It has been demonstrated that using the ratio has contributed to miscalculation in dose. Therefore, we recommend deleting the ratio strength (ie. 1:1,000 and 1:100,000) throughout the insert labeling.
2. The abbreviations (b) (4) IM, and SC and the > symbol are utilized in the insert labeling to represent (b) (4) "intramuscular", "subcutaneous", and "greater than," respectively. These dangerous abbreviations and symbol can be misinterpreted and are considered error-prone abbreviations.² Please revise the labeling to replace all symbols with text.
3. Add a unit of measure immediately following all numbers, as appropriate. (b) (4)
4. Delete (b) (4) from the dosage and administration section.
5. In the Dosage and Administration section under section 2.1 ((b) (4) Anaphylaxis (b) (4)), revise the statement as follows: (b) (4)
6. In the Dosage and Administration section under section 2.2 (b) (4), revise the statement as follows: (b) (4) to highlight the correct dosage formulation and de-emphasize the incorrect dosage formulation.

² Institute for Safe Medication Practices (ISMP). ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations. ISMP: 2010.

7. In the Dosage and Administration section under section 2.2 (b) (4) the statement (b) (4) is confusing (b) (4). Revise this statement as appropriate to clearly convey the milligram dose of the milliliter volume that can be injected intraocularly.

4.2 COMMENTS TO THE APPLICANT

A. General Comments (Container Labels 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. The ratio expressed on the labels and labeling has contributed to several calculation and product selection errors. Since the product is dosed in milligrams, we recommend deleting reference to the ratio strength (ie. 1:1,000 (b) (4)) and only expressing the strength in milligrams. For example: 1 mg per 1 mL
3. Your container and carton label contain the abbreviations IM and SC. These abbreviations appear on the ISMP List of Error-Prone Abbreviations, Symbols, and Dose Designations³. The abbreviations IM and SC have been misinterpreted as 'IU' (international units), 'IN' (intranasal), 'IV' (intravenous), and 'SL' (sublingual), respectively. Therefore, we request you revise "For IM or SC Use" to read "For Intramuscular or Subcutaneous Use" throughout the labels and labeling. We also request you increase the prominence of these statements on the container and carton labeling.
4. (b) (4)
5. Debold the "Rx Only" statement.
6. Debold and decrease the prominence of the net quantity statement so it does not have greater prominence than that of the strength statement and the established name.

³ Institute for Safe Medication Practices, "List of Error-Prone Abbreviations, Symbols, and Dose Designations. www.ismp.org.

B.

(b) (4)

C.

D. Carton Labeling-1 mL (25 (b) (4) Vials)

1. Revise (b) (4)
2. Relocate the strength statement below the established name and increase the prominence of the strength statement on the PDP and the side panels. For example:

Adrenalin
(EPINEPHrine Injection, USP)
1 mg per mL
(1 mg/mL)

3. Ensure the lot number and expiration date are printed on the label.
4. Revise the net quantity statement to read (b) (4)
5. Relocate the active ingredient statement "Each mL contains..." on the PDP to the side panel.
6. Relocate the statement (b) (4) on the PDP to the side panel.

(b) (4)

If you have further questions or need clarifications, please contact Karen Townsend, project manager, at 301-796-5413.

APPENDICES

APPENDIX A. DATABASE DESCRIPTIONS

Adverse Event Reporting System (AERS)

The Adverse Event Reporting System (AERS) is a computerized information database designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The FDA uses AERS to monitor adverse events and medication errors that might occur with these marketed products. The structure of AERS complies with the international safety reporting guidance ([ICH E2B](#)) issued by the International Conference on Harmonisation. Adverse events in AERS are coded to terms in the Medical Dictionary for Regulatory Activities terminology (MedDRA).

AERS data do have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive all adverse event reports that occur with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, AERS cannot be used to calculate the incidence of an adverse event in the U.S. population.

Appendix B: Container Labels

(b) (4)

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Appendix D: ISR numbers of cases discussed in this review

<u>ISR Number</u>	<u>Medication Error Type</u>	<u>Narrative</u>
8044424-2	Overdose	<p>This is a literature report from Clinical Toxicology, 2011, Volume 49, Pages 910-941 titled "2010 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 28th Annual Report." This is the 56th of 67 cases from this report. Case data from US poison centers were analyzed. A substance rank was assigned to each suspect drug. The substance rank assigns a number, beginning with one, in ascending order of the substance deemed most likely responsible for the patient's death. Cause rank permits the poison center to judge 2 or more substances as indistinguishable in terms of cause. A 57-year-old male patient (Annual Report ID: 1134a) was administered the following substance [substance rank; cause rank]: epinephrine [1;1] via the parenteral route. The patient experienced an allergic reaction to shellfish and went to the Emergency Department (ED). Patient's past medical history was significant for seafood allergy, hyperlipidemia, hypertension, coronary disease status post coronary stenting x 3, gastroesophageal reflux disease (GERD). Concomitant medications included valsartan, atorvastatin, metoprolol, esomeprazole and methylprednisolone (Solumedrol). In the ED, the patient received an initial 0.3 mg 1:1000 epinephrine subcutaneously and intravenous (IV) Solumedrol. The patient developed recurrence of his symptoms and was inadvertently given 3 mg subcutaneously instead of the intended 0.3 mg. The patient experienced immediate chest pain, tachycardia, ventricular ectopy and vomiting. The patient was given amiodarone with the slowing of the heart rate (HR). He was intubated with a great deal of difficulty due to airway edema. The patient expired after a resuscitation lasting one hour during which he received aspirin, fentanyl, nitroglycerin and morphine. The autopsy findings indicated that the cause of death was global myocardial necrosis due to iatrogenic overdose of epinephrine administered for anaphylaxis. It was reported this was an unintentional therapeutic error and the American Association of Poison Control Center Relative Contribution to Fatality (AAPCC RCF) was reported as 1 (undoubtedly responsible). Chronicity was reported as acute exposure. The outcome of the event is death.</p>
8395821-7	Overdose	<p>This serious literature report, from a publication on a case report from the United States, describes a 44-year-old female who experienced reverse takotsubo cardiomyopathy after administration of an inappropriate high dose of epinephrine. The patient had a history of hypertension and neurogenic bladder. She was having</p>

<u>ISR Number</u>	<u>Medication Error Type</u>	<u>Narrative</u>
		<p>an elective computed tomography (CT) scan of the abdomen and pelvis and was administered intravenous (IV) contrast with which she had developed a mild anaphylactic reaction. Concomitant medications included albuterol and oxygen (which were administered right after the anaphylactic reaction) and dexamethasone and antihistamines. On an unspecified date, the patient was administered 1 mg epinephrine (1:1000) intravenously due to ongoing chest discomfort and respiratory distress despite albuterol and oxygen. Immediately after this injection, she began experiencing severe chest tightness and respiratory distress, developed a headache, became diaphoretic and experienced a transient loss of consciousness lasting a few seconds. Upon arrival to the Emergency Department (ED), blood pressure was 80/71 mmHg with a pulse of 82 beats/min. She was given boluses of normal saline that increased her blood pressure to 100/73 and was administered dexamethasone and antihistamines. Two hours later, the patient still had chest tightness, shortness of breath, began coughing up blood-tinged sputum and became tachycardic to 110 beats/min. Chest radiograph revealed interstitial edema. Electrocardiogram showed normal sinus rhythm at 80 beats/min with non-specific ST-segment changes. Creatinine kinase-MB was 2.9 ng/mL and troponin I level was 0.56 ng/mL. Bedside echocardiography revealed hypokinesis of the mid and basal segments of the anterior, anteroseptal, anterolateral, inferolateral, inferior, and inferoseptal walls. The apical segments were hyperdynamic and the ejection fraction(EJ) was about 35%. She received intravenous furosemide and her symptoms improved. She did continue to complain of non-specific left-sided chest discomfort and her cardiac enzymes peaked on hospital day 2 with a creatinine kinase-MB of 13.4 ng/mL and troponin I level of 3.23 ng/mL. On hospital day 4, the patient was asymptomatic. A repeat echocardiogram revealed an EF of 50% with only minimal regional wall motion abnormalities. Thallium stress test showed no evidence of ischemia, mild generalized hypokinesia, and a left ventricle EF of 54%. The patient was discharged home. On the 3 week follow-up, a CT coronary calcium score was zero. Stress echocardiography showed normal resting wall motion, normal EF and an appropriate augmentation of all left ventricular segments at peak exercise. Cardiac catheterization showed no evidence of coronary artery disease. According to the authors, the delivered dose of epinephrine was too high and there is a risk of stress cardiomyopathy with inappropriate dosing of epinephrine during the treatment of anaphylaxis.Company Medical Assessment (30May12): Stress cardiomyopathy was likely due to catecholaminergic effect of epinephrine. Risk factors include critical illness (anaphylaxis), history of arterial hypertension and inappropriate high epinephrine dosing. Inappropriate dosing is assessed as not</p>

<u>ISR Number</u>	<u>Medication Error Type</u>	<u>Narrative</u>
		related as there is no direct cause and effect relationship. Company Causality (30May12): Probable
8418043-X	Overdose	<p>This case was received by (b) (4) via reactions weekly with literature reference: McCann JQ, Cook A, Stover J, Venis R. Case report - Apparent epinephrine toxicity in the treatment of anaphylaxis: A patient case of prolonged hypotension. Hospital Pharmacy 47: 124-128, No. 2, Feb 2012. It concerns a 29 year old female patient. Patient's past medical history and drug history were unknown. Concomitant medications were not provided. On an unspecified date patient developed anaphylaxis after taking cotrimoxazole for an upper respiratory tract infection. She then received a high dose of epinephrine for anaphylaxis, and experienced hypotension and sinus bradycardia [times to onset of reactions not stated]. One hour after ingesting her first cotrimoxazole dose [trimethoprim/sulfamethoxazole; dose not stated], the woman presented with shakiness, headache and throat tightness. She was treated for anaphylaxis. The woman received oxygen, sodium chloride, methylprednisolone and diphenhydramine, and two doses of intramuscular epinephrine 1mg (1:1000) which were separated by an unknown interval. She was subsequently transferred to an emergency department where, on arrival, she had headache, pain in her abdomen and muscles, diffuse erythema, and pleuritic chest pain. Initial investigations revealed a blood pressure of 105/49 mm Hg and a heart rate of 111 beats/min; an ECG showed nonspecific ST changes. She received potassium chloride but while still in the emergency department she became hypotensive, with a blood pressure of 70/30 mm Hg . The woman received 5L of saline over 6 hours but her hypotension persisted. She was admitted to an intensive care unit (ICU) with a diagnosis of hypotension and epinephrine toxicity. She received a further 5L of saline over 10 hours, and improved. While in the ICU, she experienced episodes of sinus bradycardia with a heart rate as low as 48 beats/min; they resolved spontaneously. She received potassium phosphate and was discharged 48 hours after presentation. The outcome of the case was "Unknown". Follow-up: (22-May-2012): Follow-up information was received based on the full-text article received by (b) (4) Reporter information, lab data, additional events, treatment description, outcome of the case and narrative was updated. A 29-year-old female with no significant past medical history presented to an immediate care facility 1 hour after ingesting a first dose of sulfamethoxazole/ trimethoprim prescribed for the treatment of an upper respiratory infection. The patient presented to the care center complaining of shakiness, headache, and tightness in her throat. She was found to have a blood pressure of 80/40 mmHg, heart rate of 150 beats per minute, respiratory rate of 16 breaths per minute, temperature 36.6 C (97.9 F), and an</p>

<u>ISR Number</u>	<u>Medication Error Type</u>	<u>Narrative</u>
		<p>oxygen saturation of 99% on room air. The immediate care physician initiated treatment for anaphylaxis with 2 L oxygen via nasal cannula, 2 L intravenous (IV) bolus of sodium chloride 0.9%, methylprednisolone 80 mg IV, diphenhydramine 25 mg IV, and epinephrine 1 mg (1:1000) IM into the right deltoid muscle. A repeat epinephrine dose of 1 mg IM was administered following an unknown interval, and the patient was subsequently transported via ambulance to our adult emergency department. Upon arrival to the emergency department, the patient was awake, alert, and complaining of headache, abdominal and muscle pain, diffuse erythema, and pleuritic chest pain. Vital signs on arrival included blood pressure of 105/49 mm Hg, heart rate of 111 beats per minute, respiratory rate of 18 breaths per minute, temperature 37.2 °C (99 °F), and oxygen saturation of 98% on room air. A 12-lead EKG was performed and revealed nonspecific ST segment changes. Pertinent laboratory measures included sodium 134 mmol/L, potassium 2.3 mmol/L, carbon dioxide 19 mmol/L, glucose 166 mg/dL, CPK 253 units/L, mass CKMB 1.4 ng/mL, and troponin , 0.04 ng/mL. One dose of potassium chloride 50 mEq was administered orally, and 2 additional sets of cardiac enzymes were ordered at 6-hour intervals. The patient became hypotensive (blood pressure 70/30 mm Hg) in the emergency department and persisted despite the administration of 5 L of normal saline over a 6-hour period. The patient was subsequently admitted to the medical intensive care unit with a diagnosis of profound hypotension and epinephrine toxicity. Blood pressure improved in the intensive care unit after the administration of an additional 5 L of normal saline over a 10-hour period. Episodes of sinus bradycardia were reported during the patient's stay in the intensive care unit with a heart rate as low as 48 beats per minute, which resolved spontaneously. Potassium phosphate 20 mmol IV was administered to the patient after arrival to the intensive care unit resulting in a normal serum repeat potassium (4 mmol/L). A repeat 12-lead EKG was normal. Two repeat cardiac enzymes were drawn at 6-hour intervals and both sets were reported negative. The echocardiogram revealed an estimated elevation in the right ventricular systolic pressure, mild tricuspid regurgitation, and a reported ejection fraction of 50% to 55%. The patient was ultimately discharged from the hospital in a normal state of health, 48 hours from presentation to the adult emergency department. Discussion The therapeutic use of epinephrine, as well as epinephrine toxicity, has been well described in the literature as causing an array of serious adverse effects including lactic acidosis, hypertensive crisis, tachyarrhythmias, pulmonary edema, myocardial infarction, ischemic and hemorrhagic stroke, and death. The delayed and prolonged hypotensive and bradycardic effects associated with epinephrine administration, as observed in the case study patient, has not been documented. Intramuscular</p>

<u>ISR Number</u>	<u>Medication Error Type</u>	<u>Narrative</u>
		<p>epinephrine administration exhibits a rapid onset of action similar to that observed with intravenous administration. The immediate effect of epinephrine administration is vasoconstriction, resulting from peripheral stimulation of alpha adrenergic receptors, causing a marked hypertensive response. In addition, epinephrine stimulates beta 1 receptors, resulting in cardiac stimulation and dilation of skeletal muscle arteries. The hypertensive and tachycardic response is short lived, as epinephrine is rapidly cleared. Residual stimulation of the more sensitive beta receptors may result in continued vasodilation and ultimately hypotension. Because this patient was administered a high dose of epinephrine (total of 2 mg), the prolonged hypotensive response and episodes of bradycardia are believed to be the result of stimulation of the beta receptors. Based on the Naranjo scale, a validated probability scoring tool, the reaction noted in this patient indicates a probable reaction in which a temporal sequence with epinephrine initiation was observed followed by a recognized pattern of response that could not be reasonably explained by known characteristics of the patient's clinical course. The Institute for Safe Medication Practices includes epinephrine among the list of high-alert medications defined as a drug that bears a heightened risk of causing significant patient harm when used in error. Special precautions should be taken to minimize the risk of error with high-alert medications. Epinephrine presents a unique challenge for anaphylaxis treatment: commercially available ampoules of 1:1000 epinephrine contain 1 mg of drug, but the dose recommended for anaphylaxis is 0.3 mg. Furthermore, once epinephrine is prepared from the ampoule into a syringe, it can be administered intramuscularly or incorrectly administered via the intravenous route. As a result of this potentially preventable medication error that occurred at an immediate care center, a comprehensive evaluation of our institution's epinephrine 1:1000 medication management was completed and revealed a compelling case for internal improvements in medication safety. This evaluation resulted in the Medication Safety, Resuscitation, and Pharmacy and Therapeutics Committees' approval for the removal of 1:1000 epinephrine ampoules from the emergency departments and inpatient areas. Epinephrine prefilled auto-injector devices were supplied in place of the ampoules. This epinephrine product is available as a standard dose of 0.3 mg (1:1000) for adults and can only be administered through an intramuscular injection, consistent with the ACLS guidelines for management of anaphylaxis. Though the prefilled auto-injector device is significantly more expensive than the ampoules, it may prevent dosing and wrong route administration errors from occurring in the future and improve the safe care of the emergent patient. Conclusion</p>

<u>ISR Number</u>	<u>Medication Error Type</u>	<u>Narrative</u>
		<p>Epinephrine is a high-alert medication that is widely used for the treatment of anaphylaxis in addition to its cardiac uses. Proactive evaluation of current hospital processes and procedures are recommended to maximize the safe use of epinephrine, as prescribing errors for dose and route of administration may be more common than anticipated. The use of more costly medication delivery devices of epinephrine in conjunction with a comprehensive medication safety improvement plan should be considered to prevent errors that can lead to substantial harm to patients.</p>
6818780-4	Wrong Technique of Administration	<p>This case was reported in a literature article and described the occurrence of anaphylaxis in a 37-year-old female patient who received Amoxicillin trihydrate (Amoxicillin, brandname/trandname unknown) tablet for an unknown drug indication. Concurrent medical conditions included smoker. Co-suspect medication included Epinephrine. On an unknown date, the patient started Amoxicillin trihydrate (oral) at 500 mg (single dose). Approximately 30 minutes after starting Amoxicillin trihydrate, the patient experienced anaphylaxis with symptoms including generalized erythema, flushing, itching, abdominal pain, respiratory distress and disturbed consciousness. Within seconds of her presentation to the emergency department, her clinical status deteriorated rapidly and she collapsed. Her systolic blood pressure was 40 mm Hg and pulse rate was 82 beats/min. She was immediately placed in the Trendelenburg position, nasal oxygen was started, an intravenous (IV) line was promptly established, and rapid saline infusion was started. Two doses of .5 mg epinephrine (diluted; 1:10,000) bolus administered 5 minutes apart by the IV route failed to restore an adequate blood pressure. A third dose of 1 mg epinephrine, which was accidentally infused undiluted (1:1000), restored the blood pressure to 105/65 mm Hg. However, immediately after the last epinephrine infusion and restoration of blood pressure, the patient had chest tightness, and ST depression was observed on the monitor. A 12-lead electrocardiogram (ECG) revealed marked ST changes, suggesting diffuse myocardial ischemia. Ischemia was presumed to occur secondary to coronary artery spasm induced by epinephrine, but coronary vasodilators were not used because of concern about precipitating systemic vasodilation and hypotension. After 20 minutes of watchful waiting (a duration compatible with the half-life of IV epinephrine), her chest pain and ECG changes resolved. The troponin T levels (peak .53 ng/mL; N: less than 03 ng/mL) and creatine kinase-MB levels (peak 26 IU/L; N: less than 24 IU/L) increased during the next 24 hours. Transthoracic echocardiography revealed normal left ventricular systolic function and segmental wall motion. The patient did not have any dynamic ECG changes suggesting recurrent ischemia after the acute event. A 12-lead ECG</p>

<u>ISR Number</u>	<u>Medication Error Type</u>	<u>Narrative</u>
		<p>was normal at discharge. The patient was discharged on the third day of hospital stay and was doing well without any medication at her 1-year follow-up. This case was assessed as medically serious by GSK. At the time of reporting, the events were resolved. The author considered the anaphylactic reaction was related to treatment with Amoxicillin trihydrate. The authors' commented that "Our patient was diagnosed with anaphylactic shock approximately 30 minutes after the ingestion of amoxicillin. She did not report any chest pain, and an ECG was not done before the third dose of epinephrine. She started to have chest tightness and accompanying ECG changes immediately after the accidental infusion of concentrated epinephrine. Her symptoms resolved without using steroids, antihistamines, or vasodilators. Although the diagnosis of Kounis syndrome cannot be ruled out, this case most likely represents an acute coronary syndrome secondary to epinephrine overdose. The Naranjo adverse drug reaction score was 9, suggesting epinephrine was the definite culprit for this insult." Izgi C et al. Severe myocardial ischemia after concentrated epinephrine use for the treatment of anaphylaxis: Kounis syndrome or epinephrine effect? Heart and Lung 2010; 39(2):160-163</p>
8162681-9	<p>Wrong Technique of Administration (Duplicate case to ISR #6818780-4)</p>	<p>This case, manufacturer control number 2010US-33529 from UNITED STATES refers to a Female, 37 Years-old who had an Accidental overdose of adrenaline, unk which led to myocardial ischemia. The patient was administered adrenaline, unk for amoxicillin induced anaphylaxis. The patient took amoxicillin 500 mg, unk, for an unknown indication. The events required hospitalization of the patient. An event of medication error was assessed by the medical reviewer. This case was reported in literature. Per the report, a 37-year-old woman with a history of smoking developed severe myocardial ischaemia after an inadvertent epinephrine [adrenaline] overdose for treatment of amoxicillin-induced anaphylaxis. The woman presented to the emergency room with generalized erythema, abdominal pain, flushing, pruritus, respiratory distress, and disturbed consciousness, that developed about 30 minutes after ingestion of amoxicillin 500mg. Within seconds of presentation, her status deteriorated; her systolic BP was 40mm Hg. Two doses of IV epinephrine 0.5mg (diluted 1:10,000) were given, 5 minutes apart. The woman received a third dose of 1mg, that was accidentally infused undiluted. Her BP resolved, but she immediately developed chest tightness and ST depression. An ECG revealed ST-segment changes, indicating diffuse myocardial ischaemia, presumed secondary to coronary spasm induced by epinephrine. Her chest pain and ECG changes resolved after 20 minutes of monitoring. Over the next 24 hours, her troponin T and creatine kinase MB isoenzyme levels increased. She was discharged on hospital day 3; at 1 year follow-up, she was doing well</p>

<u>ISR Number</u>	<u>Medication Error Type</u>	<u>Narrative</u>
		<p>without any medication. Author Comment: "The Naranjo adverse drug reaction score was 9; suggesting epinephrine was the definite culprit for this insult."</p> <p>The events outcome was reported as resolved at the time of this report. The case is deemed serious. Anaphylaxis is expected while all the other events are unexpected as per the USPI of amoxicillin. Medical Reviewer considered the case to be possibly related to the overdose of epinephrine due to its temporal association as per WHO UMC system for standardized causality assessment. Case Outcome: Resolved Follow up#1: 10-Feb-2012 (Significant) The follow up (Full text article) was received which contained significant information regarding medications, medical history and lab investigations. The author details, medical history and lab investigations were updated. The suspect product 'Amoxicillin' and the event 'anaphylaxis' have been removed. As per the report, a 37 year old woman presented to the emergency department with generalized erythema, flushing, pruritus, abdominal pain, respiratory distress, and disturbed consciousness. Her symptoms had started acutely approximately 30 minutes after ingestion of a tablet of amoxicillin (500 mg). Within seconds of her presentation to the emergency department, her clinical status deteriorated rapidly and she collapsed. Her systolic blood pressure was 40 mm Hg and pulse rate was 82 beats/min. She was immediately placed in the Trendelenburg position, nasal oxygen was started, an intravenous (IV) line was promptly established, and rapid saline infusion was started. Two doses of .5 mg epinephrine (diluted; 1:10,000) bolus administered 5 minutes apart by the IV route failed to restore an adequate blood pressure. A third dose of 1 mg epinephrine, which was accidentally infused undiluted (1:1000), restored the blood pressure to 105/65 mm Hg. However, immediately after the last epinephrine infusion and restoration of blood pressure, the patient had chest tightness, and ST depression was observed on the monitor. A 12-lead electrocardiogram (ECG) revealed marked ST changes, suggesting diffuse myocardial ischemia. Ischemia was presumed to occur secondary to coronary artery spasm induced by epinephrine, but coronary vasodilators were not used because of concern about precipitating systemic vasodilation and hypotension. After 20 minutes of watchful waiting (a duration compatible with the half-life of IV epinephrine), her chest pain and ECG changes resolved. The troponin T levels (peak .53 ng/mL; N: <.03 ng/mL) and creatine kinase-MB levels (peak 26 IU/L; N: <24 IU/L) increased during the next 24 hours. The patient later reported that she did not have any history of coronary artery disease, and her only risk factor was smoking. Transthoracic echocardiography revealed normal left ventricular systolic function and segmental wall motion. The patient did not have any dynamic ECG changes suggesting</p>

<u>ISR Number</u>	<u>Medication Error Type</u>	<u>Narrative</u>
		<p>recurrent ischemia after the acute event. A 12-lead ECG was normal at discharge. Coronary angiography and cardiac stress test were deferred according to the patient's preference. The patient was discharged on the third day of hospital stay and was doing well without any medication at her 1-year follow-up. Author's Comments: Chemical mediators including norepinephrine have been implicated in the pathogenesis of tako-tsubo syndrome, and this could help explain our patient's findings after the administration of high-dose epinephrine. However, the echocardiogram before discharge in our patient did not reveal apical ballooning, and the diagnosis of tako-tsubo cardiomyopathy was unlikely. This patient was diagnosed with anaphylactic shock approximately 30 minutes after the ingestion of amoxicillin. She did not report any chest pain, and an ECG was not done before the third dose of epinephrine. She started to have chest tightness and accompanying ECG changes immediately after the accidental infusion of concentrated epinephrine. Her symptoms resolved without using steroids, antihistamines, or vasodilators. Although the diagnosis of Kounis syndrome cannot be ruled out, this case most likely represents an acute coronary syndrome secondary to epinephrine overdose. The Naranjo adverse drug reaction score was 9, suggesting epinephrine was the definite culprit for this insult. Author's Conclusion: Although anaphylaxis is not uncommon, most physicians rarely see cases. This may lead to diagnostic and treatment errors. Anaphylactic mediators and, more important, epinephrine used for the treatment of anaphylaxis can induce serious cardiac ischemia. This side effect, however, should not preclude the use of epinephrine for the treatment anaphylaxis when needed. Proper administration of epinephrine will minimize the risk of its potential cardiovascular side effects, which are myocardial ischemia, lifethreatening ventricular arrhythmia, and uncontrolled increase in blood pressure with the risk of intracerebral hemorrhage. The dose, concentration (dilution), and route of administration of epinephrine should be decided according to the severity of anaphylactic reaction. The intramuscular route seems safer and appropriate for milder anaphylactic reactions. However, anaphylactic shock necessitates IV epinephrine administration with aggressive fluid resuscitation. IV preparations of epinephrine should be diluted to at least 1:10,000 and better to 1:100,000 (i.e, 10 and 100 times diluted, respectively), and should never be given undiluted (1:1000). Even after the appropriate dilution, IV administration should be given as slowly as possible and with close cardiac and blood pressure monitoring. Case Outcome: Resolved The case is deemed serious. Medical Reviewer considered the events to be possibly related to the suspect drug due to its temporal association as per WHO UMC system for standardized causality assessment.</p>

<u>ISR Number</u>	<u>Medication Error Type</u>	<u>Narrative</u>
6809235-1	Wrong Technique of Administration	<p>On June 8, 2010, a scientific literature case was received concerning Epinephrine injectable (reference: Kanwar M, Irvin CB, Frank JJ, Weber K, Rosman H. Confusion About Epinephrine Dosing Leading to Iatrogenic Overdose: A Life-Threatening Problem With a Potential Solution. <i>Annals of Emergency Medicine</i> 55: 341-344, No. 4, Apr 2010). Four patients developed heart disorders after receiving iatrogenic overdoses of epinephrine [adrenaline] for anaphylaxis. In the first 3 cases, the patients received IV doses instead of the IM doses indicated (MedDRA coded as medication error). The last patient received a high dose IV push instead of the slow, low IV dose recommended. This involved a 52-year-old woman who was hospitalised for respiratory distress and angioedema after ingesting catfish. A 0.3 mg (1:1000) dose of epinephrine was administered intravenously. Minutes later, she developed severe left-sided chest pain (MedDRA coded as angina pectoris) and ST elevations in leads II, III, and aVF (MedDRA coded electrocardiogram ST segment elevation). Her symptoms resolved after treatment with morphine and nitroglycerin. Cardiac catheterisation revealed no significant coronary artery disease. The author commented "Contributions to these errors were multifactorial and included inadequate physician knowledge about appropriate dose and route of epinephrine in anaphylaxis, lack of intramuscular doses in emergency crash carts, complicated dose calculations involving decimals and ratios, and lack of adequate communication between physicians and nurses". This case has been linked to 2010-0258, 2010-0259, and 2010-0261.</p>

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

/s/

JUNG E LEE
09/05/2012

JAMIE C WILKINS PARKER
09/05/2012

SCOTT M DALLAS
09/06/2012

CAROL A HOLQUIST
09/06/2012

REGULATORY PROJECT MANAGER PLR FORMAT LABELING REVIEW

Application: NDA 204-200
Name of Drug: Adrenalin (epinephrine injection, USP) 1 mg/mL
Applicant: JHP Pharmaceuticals

Labeling Reviewed

Submission Date: March 7, 2012
Receipt Date: March 7, 2012

Background and Summary Description

This original New Drug Application (NDA) provides for the following indications:

1. The emergency treatment of severe acute anaphylactic reactions (b) (4)
Epinephrine is used to treat systemic symptoms, particularly hypotension, airway swelling or breathing difficulty, and symptoms such as urticaria, pruritus, angioedema, and swelling of the eyelids, lips, and tongue which may result from hypersensitivity reactions to drugs, sera, insect stings, food or other allergens.
2. The induction of mydriasis during cataract surgery.

Review

The submitted labeling was reviewed in accordance with the labeling requirements listed in the “Selected Requirements for Prescribing Information (SRPI)” section of this review. Labeling deficiencies are identified in this section with an “X” in the checkbox next to the labeling requirement.

Conclusions/Recommendations

It is premature to request the applicant to revise the labeling as listed in this review, considering the contents of the labeling will still be modified as the review is progressing. The 74 day letter will state that formatting deficiencies were identified and that they will be addressed at the time of labeling discussions.

Leanna M. Kelly

April 9, 2012

Consumer Safety Officer

Date

Judit Milstein

Chief, Project Management Staff

Date

Selected Requirements for Prescribing Information (SRPI)

This document is meant to be used as a checklist in order to identify critical issues during labeling development and review. For additional information concerning the content and format of the prescribing information, see regulatory requirements (21 CFR 201.56 and 201.57) and labeling guidances. When used in reviewing the PI, only identified deficiencies should be checked.

Highlights (HL)

- **General comments**

- HL must be in two-column format, with ½ inch margins on all sides and between columns, and in a minimum of 8-point font.
- HL is limited in length to one-half page. If it is longer than one-half page, a waiver has been granted or requested by the applicant in this submission.
- There is no redundancy of information.
- If a Boxed Warning is present, it must be limited to 20 lines. (Boxed Warning lines do not count against the one-half page requirement.)
- A horizontal line must separate the HL and Table of Contents (TOC).
- All headings must be presented in the center of a horizontal line, in UPPER-CASE letters and **bold** type.
- Each summarized statement must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.
- Section headings are presented in the following order:

• Highlights Limitation Statement (required statement)
• Drug names, dosage form, route of administration, and controlled substance symbol, if applicable (required information)
• Initial U.S. Approval (required information)
• Boxed Warning (if applicable)
• Recent Major Changes (for a supplement)
• Indications and Usage (required information)
• Dosage and Administration (required information)
• Dosage Forms and Strengths (required information)
• Contraindications (required heading – if no contraindications are known, it must state “None”)
• Warnings and Precautions (required information)
• Adverse Reactions (required AR contact reporting)

statement)
• Drug Interactions (optional heading)
• Use in Specific Populations (optional heading)
• Patient Counseling Information Statement (required statement)
• Revision Date (required information)

- **Highlights Limitation Statement**

- Must be placed at the beginning of HL, **bolded**, and read as follows: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”

- **Product Title**

- Must be **bolded** and note the proprietary and established drug names, followed by the dosage form, route of administration (ROA), and, if applicable, controlled substance symbol.

- **Initial U.S. Approval**

- The verbatim statement “Initial U.S. Approval” followed by the 4-digit year in which the FDA initially approved of the new molecular entity (NME), new biological product, or new combination of active ingredients, must be placed immediately beneath the product title line. If this is an NME, the year must correspond to the current approval action.

- **Boxed Warning**

- All text in the boxed warning is **bolded**.
- Summary of the warning must not exceed a length of 20 lines.
- Requires a heading in UPPER-CASE, **bolded** letters containing the word “**WARNING**” and other words to identify the subject of the warning (e.g., “**WARNING: LIFE-THREATENING ADVERSE REACTIONS**”).
- Must have the verbatim statement “*See full prescribing information for complete boxed warning.*” If the boxed warning in HL is identical to boxed warning in FPI, this statement is not necessary.

- **Recent Major Changes (RMC)**

- Applies only to supplements and is limited to substantive changes in five sections: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.
- The heading and, if appropriate, subheading of each section affected by the recent change must be listed with the date (MM/YYYY) of supplement approval. For example, “Dosage and Administration, Coronary Stenting (2.2) --- 2/2010.”
- For each RMC listed, the corresponding new or modified text in the FPI must be marked with a vertical line (“margin mark”) on the left edge.
- A changed section must be listed for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year.
- Removal of a section or subsection should be noted. For example, “Dosage and

Administration, Coronary Stenting (2.2) --- removal 2/2010.”

- **Indications and Usage**

- If a product belongs to an established pharmacologic class, the following statement is required in HL: [Drug/Biologic Product) is a (name of class) indicated for (indication(s)].” Identify the established pharmacologic class for the drug at:

<http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.htm>.

- **Contraindications**

- This section must be included in HL and cannot be omitted. If there are no contraindications, state “None.”
- All contraindications listed in the FPI must also be listed in HL.
- List known hazards and not theoretical possibilities (i.e., hypersensitivity to the drug or any inactive ingredient). If the contraindication is not theoretical, describe the type and nature of the adverse reaction.
- For drugs with a pregnancy Category X, state “Pregnancy” and reference Contraindications section (4) in the FPI.

- **Adverse Reactions**

- Only “adverse reactions” as defined in 21 CFR 201.57(a)(11) are included in HL. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided. Note the criteria used to determine their inclusion (e.g., incidence rate greater than X%).
- For drug products other than vaccines, the verbatim **bolded** statement, “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**” must be present. Only include toll-free numbers.

- **Patient Counseling Information Statement**

- Must include the verbatim statement: “**See 17 for Patient Counseling Information**” or if the product has FDA-approved patient labeling: “**See 17 for Patient Counseling Information and (insert either “FDA-approved patient labeling” or “Medication Guide”)**”.

- **Revision Date**

- A placeholder for the revision date, presented as “Revised: MM/YYYY or Month Year,” must appear at the end of HL. The revision date is the month/year of application or supplement approval.

Contents: Table of Contents (TOC)

- The heading **FULL PRESCRIBING INFORMATION: CONTENTS** must appear at the beginning in UPPER CASE and **bold** type.
- The section headings and subheadings (including the title of boxed warning) in the TOC must match the headings and subheadings in the FPI.
- All section headings must be in **bold** type, and subsection headings must be indented and not bolded.
- When a section or subsection is omitted, the numbering does not change. For example, under Use in Specific Populations, if the subsection 8.2 (Labor and Delivery) is omitted, it must read:
 - 8.1 Pregnancy
 - 8.3 Nursing Mothers (not 8.2)
 - 8.4 Pediatric Use (not 8.3)
 - 8.5 Geriatric Use (not 8.4)
- If a section or subsection is omitted from the FPI and TOC, the heading “**Full Prescribing Information: Contents**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”

Full Prescribing Information (FPI)

- **General Format**

- A horizontal line must separate the TOC and FPI.
- The heading – **FULL PRESCRIBING INFORMATION** – must appear at the beginning in UPPER CASE and **bold** type.
- The section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1).

- **Boxed Warning**

- Must have a heading, in UPPER CASE, **bold** type, containing the word “**WARNING**” and other words to identify the subject of the warning. Use **bold** type and lower-case letters for the text.
- Must include a brief, concise summary of critical information and cross-reference to detailed discussion in other sections (e.g., Contraindications, Warnings and Precautions).

- **Contraindications**

- For Pregnancy Category X drugs, list pregnancy as a contraindication.

- **Adverse Reactions**

- Only “adverse reactions” as defined in 21 CFR 201.57(c)(7) should be included in labeling. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided.

- For the “Clinical Trials Experience” subsection, the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”

- For the “Postmarketing Experience” subsection, the listing of post-approval adverse reactions must be separate from the listing of adverse reactions identified in clinical trials. Include the following verbatim statement or appropriate modification:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

- **Use in Specific Populations**

- Subsections 8.4 Pediatric Use and 8.5 Geriatric Use are required and cannot be omitted.

- **Patient Counseling Information**

- This section is required and cannot be omitted.

- Must reference any FDA-approved patient labeling, including the type of patient labeling. The statement “See FDA-approved patient labeling (insert type of patient labeling).” should appear at the beginning of Section 17 for prominence. For example:

- “See FDA-approved patient labeling (Medication Guide)”
- “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information)”
- “See FDA-approved patient labeling (Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

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

/s/

LEANNA M KELLY
04/27/2012

JUDIT R MILSTEIN
04/27/2012
MDA 204200-RPM Labeling review

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 204200 Original 1 and 2	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: Adrenalin Established/Proper Name: epinephrine Dosage Form: injection Strengths: 1 mg/mL		
Applicant: JHP Pharmaceuticals Agent for Applicant (if applicable):		
Date of Application: March 7, 2012 Date of Receipt: March 7, 2012 Date clock started after UN: N/A		
PDUFA Goal Date: Original 1- January 7, 2013 Original 2- September 7, 2012	Action Goal Date (if different):	
Filing Date: May 6, 2012	Date of Filing Meeting: April 11, 2012	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 7		
Proposed indication(s)/Proposed change(s): Original 1- Emergency treatment of severe acute anaphylactic reactions (b) (4) Original 2- Induction of mydriasis during cataract surgery		
Type of Original NDA: AND (if applicable)	<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2)	
Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.</i>		
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>	<input checked="" type="checkbox"/> Standard for Original 1 <input checked="" type="checkbox"/> Priority for Original 2 <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? NO <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system <input type="checkbox"/> Pre-filled biologic delivery device/system <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	

<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product): No				
List referenced IND Number(s): PIND 111712				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	X			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		X		
<i>If yes, explain in comment column.</i>				
<i>If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:</i>				
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears</p>																			
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>		<p>X</p>																		
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>		<p>X</p>																		
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs</i></p>		<p>X</p>																		
<p>Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? Check the <i>Electronic Orange Book</i> at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p> <table border="1" data-bbox="203 1446 1349 1587"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration														<p>X</p>		
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>	<p>Exclusivity</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>															
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at:</i> http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</p>		<p>X</p>																		

<p>If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i></p>				
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p>If yes, # years requested:</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>		X		
<p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?</p>		X		
<p>If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>				

Format and Content				
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<p>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</p>				
Overall Format/Content	YES	NO	NA	Comment
<p>If electronic submission, does it follow the eCTD guidance?¹ If not, explain (e.g., waiver granted).</p>	X			
<p>Index: Does the submission contain an accurate comprehensive index?</p>	X			
<p>Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:</p>	X			

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?				
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	X			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	X			
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	X			
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature?	X			

<p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FDCA Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i></p>				
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>			X	Electronic Submission

Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>			X	

Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)²</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	X			
<p>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>	X			

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

If studies or full waiver not included , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>			X	Request for full waiver was submitted on April 9, 2012 for both indications
If a request for full waiver/partial waiver/deferral is included , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>	X			
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>		X		
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	X			Request for tradename was submitted on April 18, 2012
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the DCRMSRMP mailbox</i>			X	
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	X			
Is the PI submitted in PLR format? ⁴	X			

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

⁴ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)			X	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>		X		
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s) Date(s): <i>If yes, distribute minutes before filing meeting</i>		X		

Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): July 5, 2011 under PIND 111712 <i>If yes, distribute minutes before filing meeting</i>	X			
Any Special Protocol Assessments (SPAs)? Date(s): <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>		X		

ATTACHMENT

MEMO OF FILING MEETING

DATE: April 11, 2012

NDA#: 204200

PROPRIETARY NAME: Adrenalin

ESTABLISHED/PROPER NAME: epinephrine

DOSAGE FORM/STRENGTH: injection, 1 mg/mL

APPLICANT: JHP Pharmaceuticals

PROPOSED INDICATION(S)/PROPOSED CHANGE(S):

Original 1-DPARP-Emergency treatment of severe acute anaphylactic reactions (b) (4)

Original 2- DTOP-Maintenance of mydriasis during cataract surgery

BACKGROUND: NDA 204200 was submitted on March 7, 2012 as a 505(b)(2) application, using EpiPen (NDA 19430) as the RLD. As the two indications sought in the original submission are reviewed by separate divisions, this NDA was split into two originals as described above.

(b) (4)

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Judit Milstein, DTOP Carol Hill, DPARP	Y
	CPMS/TL:	Ladan Jafari, DPARP	Y
Cross-Discipline Team Leader (CDTL)	Theresa Michelle		Y
Clinical	Reviewer:	Wiley Chambers, DTOP Peter Starke, DPARP	Y Y
	TL:	William Boyd, DTOP Theresa Michele, DPARP	Y Y
Social Scientist Review (for OTC)	Reviewer:	None	

<i>products)</i>			
	TL:		
OTC Labeling Review (<i>for OTC products)</i>	Reviewer:		
	TL:		
Clinical Microbiology (<i>for antimicrobial products)</i>	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Sheetal Agarwal, OCP, OTS	Y
	TL:	Suresh Doddapaneni, OCP, OTS	Y
Biostatistics	Reviewer:	Yunfan Deng, DTOP Robert Abugov, DPARP	Y Y
	TL:	Yan Wang, DTOP Joan Buenconsejo, DPAPR	Y N
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Conrad Chen, DTOP Jane Sohn, DPARP	Y Y
	TL:	Lori Kotch, DTOP Molly Shea (Topper), DPARP	Y Y
Statistics (carcinogenicity)	Reviewer:	None	
	TL:		
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:	None	
	TL:		
Product Quality (CMC), ONDQA	Reviewer:	Milton Sloan Ying Wang Karen Riviere (Bioequivalence)	Y Y Y
	TL:	Balajee Shanmugam Alan Schroeder	Y Y
Quality Microbiology (<i>for sterile products</i>) OPS/NDMS	Reviewer:	Erika Pfeiler	Y
	TL:	Brian Riley	Y
CMC Labeling Review	Reviewer:	Leanna Kelly, DTOP	Y
	TL:		
Facility Review/Inspection	Reviewer:	Allison Aldridge, OMPQ	Y

	TL:		
OSE/DMEPA (proprietary name)	Reviewer:		
	TL:		
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		
Bioresearch Monitoring (OSI)	Reviewer:	Kassa Ayalew	Y
	TL:		
Controlled Substance Staff (CSS)	Reviewer:	N/A	
	TL:		
Other reviewers			
Other attendees			

In addition to the reviewers listed above, the meeting was attended by
Renata Albrecht, Director, DTOP
Badrul Chowdhury, Director, DPARP
Lydia Gilbert-McClain, Deputy Director, DPARP
Sally Seymour, Deputy Director for Safety, DPARP
Hyun Son, Safety RPM
Leah Ripper, ADRA, ODE II
David Roeder, ADRA, OAP
Daphne Lin, DB4
Prasad Peri, Branch Chief, ONDQA
Lucious Lim, Clinical Reviewer, DTOP
Martin Nevitt, Clinical Reviewer, DTOP
Jennifer Harris, Clinical Reviewer, DTOP
Rhea Lloyd, Clinical Reviewer, DTOP
Sonal Wadhwa, Clinical Reviewer, DTOP
Susan Limb, Clinical Reviewer, DTOP
Gerlie Gieser, Clinical Pharmacology Reviewer
Karen Townsend, OSE

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> 505(b)(2) filing issues? <p>If yes, list issues:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Electronic Submission comments <p>List comments: None</p>	<input type="checkbox"/> Not Applicable
<p>CLINICAL</p> <p>Comments: None</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain: This a 505(b)(2) Application-No clinical studies conducted by the applicant</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason: This is not an NME; In addition, no safety or efficacy issues are raised
<ul style="list-style-type: none"> Abuse Liability/Potential 	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE

Comments:	<input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
CLINICAL MICROBIOLOGY	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE
Comments:	<input type="checkbox"/> Review issues for 74-day letter
CLINICAL PHARMACOLOGY	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE
Comments: None	<input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
BIOSTATISTICS	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE
Comments: None	<input type="checkbox"/> Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE
Comments: None	<input type="checkbox"/> Review issues for 74-day letter
IMMUNOGENICITY (BLAs/BLA efficacy supplements only)	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE
Comments:	<input type="checkbox"/> Review issues for 74-day letter
PRODUCT QUALITY (CMC)	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE
Comments: See filing review dated 4/12/12	<input checked="" type="checkbox"/> Review issues for 74-day letter

<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments: Comments for the 74 day letter are included in the review dated 4/12/12</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><u>CMC Labeling Review</u></p> <p>Comments: None</p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>
REGULATORY PROJECT MANAGEMENT	
<p>Signatory Authority: Renata Albrecht, Director, DTOPT Lydia Gilbert-MacClain, DPARP</p> <p>21st Century Review Milestones (see attached) (listing review milestones in this document is</p>	

optional):	
Comments:	
ACTIONS ITEMS	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):</p> <p><u>Review Classification:</u></p> <p><input checked="" type="checkbox"/> Standard Review- Original 1- (b) (4)-DPARP</p> <p><input checked="" type="checkbox"/> Priority Review – Original 2- Maintenance of mydriasis during cataract surgery-DTOP</p>
<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input checked="" type="checkbox"/>	<p>If priority review:</p> <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822]

Judit Milstein, Chief, Project Management Staff, DTOP
Carol Hill, Senior Regulatory Project Manager, DPARP
Ladan Jafari, Chief, Project Management Staff, DPARP

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
04/27/2012

CAROL F HILL
04/27/2012

LADAN JAFARI
04/27/2012