CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205029Orig1s000

OTHER REVIEW(S)

505(b)(2) ASSESSMENT

Application Information		
NDA # 205029	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: N/A Established/Proper Name: epinephrine injection Dosage Form: injectable for IV administration Strengths: 1 mg/mL		
Applicant: Belcher Pharmaceuticals		
Date of Receipt: 12/4/13 (resubmission received 1/29/14)		
PDUFA Goal Date: 7/29/14	Action Goal Date (if different): 7/25/14	
RPM: Russell Fortney		
Proposed Indication(s): Epinephrine Injection USP, 1:1000 (1 mg/mL) is a solution for intravenous infusion indicated for use in increasing systemic arterial blood pressure in acute hypotensive states associated with septic shock.		

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 by reliance on published literature, or by reliance on a final OTC monograph. *(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 listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
published literature	To support the indication (to increase BP in septic shock)
NDA 20800 Twinject	FDA's previous finding of safety

*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

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)

Because the product is injectable, and is titrated to effect for the new indication, we did not require BA/BE studies.

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 cited reliance on 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 #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)
Twinject	20800	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: NDA 20800 Twinject

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 final OTC drug monograph?

YES ☐ NO ☒

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

Name of drug(s) described in a final OTC drug 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 indication, to increase BP in septic shock.

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 intended for the same route of administration 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), FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the Orange Book)).*

***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?

N/A ☐ YES ☐ NO ☐

*If this application relies only on non product-specific published literature, answer **"N/A"***
*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)?

N/A ☐ YES ☐ NO ☒

*If this application relies only on non product-specific published literature, answer **"N/A"***
*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):
NDA 201739 AUVI-Q
NDA 19430 EPIPEN
NDA 204200 ADRENALIN (approved after the Belcher application was submitted)

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): NDA 20800 Twinject
Patent # 7297136
Patent # 7621891

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): 7297136
7621891

(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): *2/27/13*

***Note**, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided*

(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/

RUSSELL FORTNEY
07/23/2014

LABEL AND LABELING MEMO

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	July 16, 2014
Requesting Office or Division:	Division of Cardiovascular & Renal Products (DCRP)
Application Type and Number:	NDA 205029
Product Name and Strength:	Epinephrine Injection USP, 1 mg/mL (1:1,000)
Product Type:	Single Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Belcher Pharmaceuticals, LLC
Submission Date:	July 1, 2014
OSE RCM #:	2014-310-1
DMEPA Primary Reviewer:	Janine Stewart, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD

1 REASON FOR REVIEW

This review evaluates the revised container label and carton labeling for Epinephrine Injection USP, 1 mg/mL (1:1,000), NDA 205029 received on July 1, 2014 from the Applicant. The Division of Medication Error Prevention and Analysis (DMEPA) previously reviewed the labels and labeling under OSE Review #2014-310 dated May 28, 2014 (See DARRTS NDA 205029 Labeling Review dated 5/29/2014).

2 MATERIALS REVIEWED

The Division of Medication Error Prevention and Analysis (DMEPA) reviewed the following:

- Container Label submitted July 1, 2014
- Carton Labeling submitted July 1, 2014

We compared the revised labels and labeling with our recommendations provided in OSE Review #2014-310 dated May 28, 2014 to assess whether the revised labels and labeling address our concerns from a medication error perspective.

3 CONCLUSION & RECOMMENDATIONS

Belcher Pharmaceuticals, LLC incorporated all of our recommendations so the revised labels and labeling adequately address our concerns from a medication error perspective. We have no additional comments at this time.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact OSE Regulatory Project Manager: Cherye Milburn, at 301-796-2084.

APPENDIX A. LABELS AND LABELING

A.1 List of Labels and Labeling Reviewed

We reviewed the following Epinephrine Injection USP, 1 mg/mL (1:1,000) container label and carton labeling submitted by Belcher Pharmaceuticals, LLC on July 1, 2014.

- Container label
- Carton labeling

A.2 Label and Labeling Images

Container Label

Carton Labeling

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

/s/

JANINE A STEWART
07/16/2014

CHI-MING TU
07/16/2014

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	May 28, 2014
Requesting Office or Division:	Division of Cardiovascular & Renal Products (DCRP)
Application Type and Number:	NDA 205029
Product Name and Strength:	Epinephrine Injection USP, 1 mg/mL (1:1,000)
Product Type:	Single Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Belcher Pharmaceuticals, LLC
Submission Date:	January 29, 2014
OSE RCM #:	2014-310
DMEPA Primary Reviewer:	Janine Stewart, PharmD
DMEPA Team Leader:	Lisa Khosla, PharmD, MHA

1 REASON FOR REVIEW

As part of the approval of this new drug application, this review evaluates the proposed container label, carton, and insert labeling for Epinephrine Injection USP, 1 mg/mL (1:1,000) for areas of vulnerability that can lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
FDA Adverse Event Reporting System (FAERS)	B
Previous DMEPA Reviews	C
Human Factors Study	D- N/A
ISMP Newsletters	E
Background	F
Labels and Labeling	G

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

In 2012, during the previous review, there were discussions between the Division, DMEPA, USP, and ISMP regarding the presentation of the ratio since there were medication error cases which reported confusion between the epinephrine ratio, and one case resulting in death of a patient. DMEPA and ISMP identified cases that would warrant the removal of the ratio from the container and carton labeling, and as such ISMP tried to petition USP for the removal of the ratio from the labeling. USP monograph has no requirement to label epinephrine with a ratio and deferred back to FDA to decide if the ratio would be necessary on the labeling. At that time, the Division wanted to keep the ratio on the labeling since some practicing doctors still use the ratio for prescribing and believes that removal of the ratio would introduce more errors than it would mitigate.

During our current review of Epinephrine Injection USP, 1 mg/mL (1:1,000) under NDA 205029, we identified additional Institute of Safety Medication Practices (ISMP) reports of confusion between the ratio and strength, including 2 death cases. DMEPA notified the Division of these findings and asked for an update on the Division's position on retaining the ratio expression. The Division remains in favor of retaining the ratio expression.

DMEPA performed a risk assessment of the proposed full prescribing information, container label, and carton labeling to identify deficiencies that may lead to medication errors and areas for improvement. We also compared the labels and labeling with the recommendations provided in OSE Review # 2013-83 for NDA 205029, dated August 7, 2013. While the majority of the recommendations from the previous review have been implemented, we note that the proposed container label and carton labeling present the established name in all capital letters, which may diminish the readability of the product name. We also note that the prominence of the primary strength expression in milligrams per milliliter is diminished by the use of parentheses, which makes the secondary expression of the ratio strength more prominent. This is inconsistent with the way the mg/mL strength and the ratio strength are expressed in the full prescribing information. Additionally, we note the absence of the "Usual Dose:" statement on the container label and the carton labeling. Furthermore, we note the statement (b) (4) can be revised to eliminate redundancy of information on the container label and the carton labeling. Thus, we have provided recommendations in Section 4 to address these deficiencies.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed container label and carton labeling can be improved to increase the readability and prominence of important information on the label and labeling to promote the safe use of the product and to mitigate any confusion.

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

4.1 RECOMMENDATIONS FOR THE APPLICANT

A. General Comments for Container Label and Carton Labeling

1. Revise the presentation of the established name from all caps (i.e. EPINEPHRINE INJECTION, USP) to title case (i.e. Epinephrine Injection, USP) to improve readability of the name. Words set in title case are easier to read than the rectangular shape that is formed by words set in all capital letters.

2. Revise the statement of strength to increase clarity and mitigate confusion between the product strength and product ratio. Express the mg/mL and ratio strength expressions in the manner that is consistent with the way they are expressed in the Full Prescribing Information by placing the parentheses around the ratio strength. For example:

   Epinephrine Injection, USP
   1 mg/mL
   (1:1,000)

3. [redacted] (b) (4) revise the statement [redacted] (b) (4) to "Dilute before use."

B. Carton Labeling

1. Remove the [redacted] (b) (4) statement from the principal display panel to reduce clutter and eliminate redundancy of information. It also appears on the top panel.

2. Include a "Usual Dose: See insert labeling" statement on the principal display panel per 21 CFR 201.55.

C. Container Label

1. Revise the [redacted] (b) (4) statement on the side panel to [redacted] (b) (4)

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Epinephrine Injection, USP that Belcher Pharmaceuticals, LLC submitted on January 29, 2014.

Table 2. Relevant Product Information for Epinephrine Injection, USP	
Active Ingredient	Epinephrine Injection, USP
Indication	To increase mean arterial blood pressure in hypotension associated with septic shock
Route of Administration	Intravenous Infusion
Dosage Form	Injection
Strength	1mg/ mL (1:1,000)
Dose and Frequency	Suggested intravenous infusion rate of 0.05 mcg/kg/min to 2 mcg/kg/min, titrated closely with minimum dose as needed to achieve MAP goal, e.g., ≥ 70 mmHg. Wean dosage down incrementally over time, after stabilization. Dilute Epinephrine (e.g., 1:1000) in 5% dextrose solution or 5% dextrose in sodium solution prior to infusion. Epinephrine should be infused into a large vein, e.g., antecubital or femoral vein, and not with a catheter tie-in technique
How Supplied	A sterile solution containing 1 mg epinephrine as the hydrochloride in each 1 mL ampule. Epinephrine contains no preservatives, such as sulfites. Supplied in a box of 10 ampules (NDC 62250-xxxx-xx)
Storage	Protect from light until ready to use. Do not refrigerate. Protect from freezing. Store at room temperature, between (b) (4) Protect from alkalis and oxidizing agents. Solutions for intravenous use should be inspected visually for particulate matter and discoloration, whenever solution and container permit. Do not use after the expiration date.
Container Closure	The primary packaging is Type I (USP) 2 mL clear colorless glass ampoules with score-break. The ampoules have an adhesive label and are packed, with a leaflet, in lithographed cardboard-boxes. The cardboard-box contains 10 ampoules of Epinephrine USP 1:1000, 1 mg/mL, preservative free and sulphite free.

APPENDIX B. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

B.1 Methods

We searched the FDA Adverse Event Reporting System (FAERS) on March 21, 2014 using the criteria in Table 3, and then individually reviewed each case. We limited our analysis to cases that described errors possibly associated with the label and labeling. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter[2]

Table 3: FAERS Search Strategy	
Date Range	April 30, 2013 (date of last FAERS search in OSE Review #2013-45) to March 21, 2014
Drug Names	Epinephrine, Epinephrine Hydrochloride [active ingredient]
MedDRA Search Strategy	**Medication Errors** [HLGT] **Product Packaging Issues** [HLT] **Product Label Issues** [HLT] **Product Quality Issues** (NEC)[HLT]
Limited by route of administration (included all intravenous terms)	IV;IV BOLUS;IV DRIP;IV NOS;IVB;IVBOL;IVBOLUS;IVD;IVDP;IVDRIP; IVDRP;IVES;IVP;IVPB;IVPICC;INJ;INJECTION;1V

B.2 Results

Our search identified 13 cases, of which 4 described errors possibly associated with the current labels and labeling for Epinephrine. The search was limited by the intravenous route of administration to eliminate cases involving EpiPen (which is approved for the treatment of allergic reactions and administered by intramuscular injection) and racemic epinephrine (which is approved for the treatment of allergic reactions, asthma and croup syndrome and administered by inhalation).

Each case was reviewed for relevancy and duplication. After initial review, 7 duplicate cases and 2 drug interaction reports were excluded from further analysis. Following exclusions, 4 medication errors remain for our detailed analysis:

- Wrong Route of Administration (n=3)

[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.

We identified 3 cases as wrong route of administration medication errors. The first case involved racemic epinephrine (1:10,000) intended for inhalation but given intravenously to a 13- month old child with croup. The nurse recognized that she had inadvertently administered the racemic epinephrine by intravenous injection instead of by the intended nebulized route. The child required continued emergency care but was successfully extubated 80 hours later. No contributing factors were reported and no additional information was provided.

The second and third case reported epinephrine being administered intravenously instead of through intravenous infusion or by subcutaneous route. The second case reported the nurse rushing and inadvertently administered 0.3 mL of epinephrine intravenously instead of subcutaneously as ordered when patient was presented with anaphylactic reaction. The patient immediately experienced projectile vomiting and became acutely diaphoretic and uncomfortable. The patient was transferred to a critical care bed for further evaluation.

The third case involved a 3-year-old girl who developed ventricular tachycardia during treatment with bupivacaine, and respiratory distress following an inadvertent overdose of lipid emulsion. Bupivacaine toxicity was suspected and her planned course of treatment included Lipid resuscitation for bupivacaine overdose. The child was administered epinephrine 30 mcg/kg by intravenous injection. The outcome of this error was unclear and any contributing factors were not elucidated.

We conclude that having other drugs that are administered simultaneously by the intravenous route appears to contribute to route of administration confusion and not associated with the labels and labeling.

- Wrong drug (n=1)

  A combination of Diazepam 5 mg, 50% Dextrose 50 mL, and Narcan 2 mg was ordered. Mistakenly, 2 mL of 1: 1,000 epinephrine (2 mg) was administered instead of Narcan. No contributing factors were reported and no additional information was available.

The medication errors discussed above are similar to those identified in our previous review (OSE Review # 2013-83 for NDA 205029). The previous review identified errors of wrong route (n=37), wrong drug (n=19), wrong dose (overdose) (n=20), wrong strength (n=1), and drug interaction (n=3). We have already made recommendations to help mitigate these errors and we note the Applicant has implemented the recommendations.

B.3 List of FAERS Case Numbers

Below is a list of the FAERS case number and manufacturer control numbers for the cases relevant for this review.

- 9246918- US-PFIZER INC-2013119417
- 9916010- 2014P1001188
- 9940437- IN-MYLANLABS-2014S1003832
- 9248132- US-PFIZER INC-2013119399

B.4 Description of 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 postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS 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. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm.

APPENDIX C. PREVIOUS DMEPA REVIEWS

C.1 Methods

We searched the L: Drive on March 20, 2014 using the terms, epinephrine NDA 205029 to identify reviews previously performed by DMEPA.

C.2 Results

2013-83 (b) (4) (Epinephrine) Label and Labeling Review NDA.doc, August 7, 2013

2013-45 (b) (4) (Epinephrine Injection USP) Proprietary Name Review NDA (unacceptable), April 2, 2013

APPENDIX D. HUMAN FACTORS STUDY- Not Applicable (N/A)

APPENDIX E. ISMP NEWSLETTERS

E.1 Methods

We searched the Institute for Safe Medication Practices (ISMP) newsletters on April 1, 2014 using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
Date Range	no date range
ISMP Newsletter Search Strategy	Select one of the following: Match Exact word or phrase
Search Terms	Epinephrine Injection

E.2 Results

We retrieved 16 articles related to epinephrine of which 5 described medication errors possibly associated with the current labels and labeling for Epinephrine.

An ISMP Safety Brief reported multiple accidents involving 30 mL vials of epinephrine 1:1,000 and a report of a mix-up between vials of topical epinephrine 30 mL 1:1000 and lidocaine 1% with epinephrine injection 1:100,000. The brief called for careful consideration of how supplies of epinephrine injection are maintained in clinical areas.[1]

Two ISMP articles described a mix-up between topical and injectable epinephrine products that lead to a fatal outcome after inadvertent injection of topical epinephrine. During a procedure, a surgeon requested lidocaine 1% with epinephrine 0.01 mg/mL (1:100,000) to be used as a local anesthetic. The surgeon injected the medication into the surgical site. Immediately afterward, the patient experienced a cardiac arrhythmia leading to full cardiac arrest. Despite resuscitation efforts, the patient died. An investigation revealed that the patient actually received epinephrine 1 mg/mL (1:1,000) from a syringe that a surgical nurse thought contained the local anesthetic. Contributing factors included that vials of epinephrine for topical use look like vials of epinephrine for injection. Although epinephrine for topical use is supplied in pour bottles with a peel-off ferrule, the ferrule on vials of epinephrine for injection look similar. Both contain a rubber port which can be accessed with a syringe needle. The container, container label and container closure of both formulations look similar when compared.[2,3]

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[1] Institute for Safe Medication Practices. Safety briefs: Epinephrine mix-ups. ISMP Med Saf Alert Acute Care. 1996;1(5):2.

[2] Institute for Safe Medication Practices. Safety briefs: Fatal outcome after injection. ISMP Med Saf Alert Acute Care. 2009;14(6):1-2.

[3] Institute for Safe Medication Practices. Nursing Edition: Fatal outcome after injection. ISMP Med Saf Alert Nurse Advise-ERR. 2010;8(2):1-2.

The 30 mL vials of epinephrine for injection may lead to medication errors. An ISMP Safety brief described a mix- up between topical and injectable epinephrine products which happened to be the same strength (1 mg/mL; 1:1000). There was no harm to the patient but the potential for error exists due to the look-alike packaging and container labels across product strengths. The products are supplied in 30 mL multiple dose vials including epinephrine injection, 1:100,000. This can easily lead to a 10 fold dosing error if a 1mg dose is ordered and a healthcare professional uses 10 ml of a 1:1,000 solution instead of 10 mL of a 1:100,000. There is enough volume in a 30 mL vial to administer an overdose. When epinephrine injection 1 mL vials/ ampules are available, an error like this would require 10 vials which would likely alert the user of the potential error.[4]

The death of a 16-year-old boy due to an epinephrine overdose highlighted problems with epinephrine labeling and nomenclature. Factors contributing to the error included: (1) lack of understanding of the difference between dose concentrations (such as 1:1,000 or 1mg/mL and 1:10,000 or 0.1 mg/mL) and (2) numerical similarities between the ratio expressions (1:1,000 vs. 1:100,000). Since this drug product has a USP monograph, ISMP has petitioned the USP asking for the elimination of ratio expressions on labels of epinephrine injection products. In its petition, ISMP stressed that the drug should only be expressed in milligrams. USP proposed an exception to allow the use of ratio strength expressions only when the drug is mixed with local anesthetics such as lidocaine as indicated for the prolongation of local anesthesia.[5]

[4] Institute for Safe Medication Practices. Safety briefs: Epinephrine mix-ups. ISMP Med Saf Alert Acute Care. 2014;19(1):1-3.

[5] Institute for Safe Medication Practices. Safety briefs: Topical and injectable epinephrine. ISMP Med Saf Alert Acute Care. 2004;9(16):1-3.

APPENDIX F. BACKGROUND

Belcher Pharmaceuticals, LLC originally submitted Epinephrine Injection, USP on December 4, 2012 as a 505(b)(2) application under "Type 7- Drug Already Marketed Without Approved NDA". Epinephrine currently is not approved and the Applicant is seeking approval for the proposed indication of increasing arterial blood pressure in patients with hypotension associated with septic shock. The original application received a complete response on October 4, 2013 due to issues related to product quality, labels and labeling, pediatric assessments, and product safety. This resubmission of the container label, and carton and insert labeling is part of Belcher's response to the FDA's complete response letter.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[6] along with postmarket medication error data, we reviewed the following Epinephrine, USP labels and labeling submitted by Belcher Pharmaceuticals, LLC on January 29,2014.

- Container label
- Carton labeling
- Full Prescribing Information (no image)

G.2 Label and Labeling Images

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

1 Page of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page.

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

/s/

JANINE A STEWART
05/28/2014

LISA V KHOSLA
05/29/2014

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:	August 7, 2013
Reviewer:	Kimberly DeFronzo, RPh, MS, MBA Division of Medication Error Prevention and Analysis
Team Leader:	Irene Z. Chan, PharmD, BCPS 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:	(b) (4) (Epinephrine Injection, USP), 1 mg/mL
Application Type/Number:	NDA 205029
Applicant:	Belcher Pharmaceuticals, LLC
OSE RCM #:	2013-83

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

Contents

1 INTRODUCTION

This review evaluates the proposed container label, carton, and insert labeling for (b) (4) (Epinephrine Injection, USP), 1 mg/mL, for areas of vulnerability that can lead to medication errors.

1.1 BACKGROUND

Epinephrine is currently approved for the indications of emergency treatment of allergic reactions, including anaphylaxis, for induction and maintenance of mydriasis during intraocular surgery, and asthma. Epinephrine is not FDA-approved for the indication of hemodynamic stabilization in septic shock patients.

On December 4, 2012, Belcher Pharmaceuticals submitted this 505(b)(2) New Drug Application (NDA 205029) under "Type 7- Drug Already Marketed without Approved NDA" for Epinephrine Injection, USP 1:1000 (1 mg/mL). This is a literature-only based submission seeking approval for the indication of increasing systemic arterial blood pressure in acute hypotensive states associated with septic shock.

1.2 PRODUCT INFORMATION

The following product information is provided in the December 4, 2012 draft labeling submission.

- Active Ingredient: Epinephrine
- Indication of Use: Increasing systemic arterial blood pressure in acute hypotensive states associated with septic shock
- Route of Administration: Intravenous infusion
- Dosage Form: Injection
- Strength: 1:1000 (1 mg/mL)
- Dose and Frequency: Suggested intravenous infusion rate of 0.05 mcg/kg/min to 2 mcg/kg/min, titrated closely with minimum dose as needed to achieve MAP goal, e.g., ≥ 70 mmHg. Wean dosage down incrementally over time, after stabilization. Dilute (b) (4) (e.g., 1:1000) in dextrose solution prior to infusion. (b) (4) should be infused into a large vein, e.g., antecubital or femoral vein, and not with a catheter tie-in technique
- How Supplied: a sterile solution containing 1 mg epinephrine as the hydrochloride in each 1 mL ampule. (b) (4) contains no preservatives, such as sulfites. Supplied in a box of 10 ampules (NDC 62250-xxxx-xx)
- Storage: Protect from light until ready to use. Do not refrigerate. Protect from freezing. Store at room temperature, between (b) (4) Protect from alkalis and oxidizing agents. Solutions for intravenous use should be inspected visually

for particulate matter and discoloration, whenever solution and container permit. Do not use after the expiration date.

- Container and Closure Systems: The primary packaging is Type I (USP) 2 mL clear colorless glass ampoules [redacted] The ampoules [redacted] are packed, [redacted] in [redacted] cardboard-boxes. The cardboard-box contains 10 ampoules of Epinephrine USP 1:1000, 1 mg/mL, preservative free and sulphite free.

2 METHODS AND MATERIALS REVIEWED

DMEPA searched the FDA Adverse Event Reporting System (FAERS) database for epinephrine injectable medication error cases. We also reviewed the [redacted] container label, carton labeling and package insert labeling submitted by the Applicant.

2.1 SELECTION OF MEDICATION ERROR CASES

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

Table 1: FAERS Search Strategy*	
Date	April 30, 2013
Product	Active Ingredients: Epinephrine, Epinephrine Hydrochloride
MedDRA Search Strategy	Medication Errors (HLGT) Product Packaging Issues HLT (HLGT) Product Label Issues HLT Product Quality Issues (NEC) HLT
Limited by route of administration (included all intravenous terms)	Iv; Iv Bolus; Iv Drip; Iv Nos; Ivb; Ivbol; Ivbolus; Ivd; Ivdp; Ivdrip; Ivdrp; Ives; Ivp; Ivpb; Ivpicc; Iv; 1v; Inj; Injection

*Appendix A provides a description of FAERS

The AERS search identified 118 cases. The search was limited by the intravenous route of administration in attempts to eliminate cases of EpiPen or other similar epinephrine products used for treating allergic reactions that are approved for intramuscular or subcutaneous administration. Each case was reviewed for relevancy and duplication. After individual review, 38 cases were excluded from further analysis for the following reasons:

- Intentional overdose or suicide attempt
- Adverse drug reactions not related to a medication error
- Medication error not relating to epinephrine
- Product quality complaints (e.g., defective plunger on Autoinjectors or ineffective lot/batch)
- Cases related to errors with a pump setting or defective pump
- Dose omission due to delay in obtaining the drug

- Improper dose errors where rate of infusion was incorrectly programmed
- Unapproved uses of epinephrine (e.g., used for vasovagal syncope)
- Duplicate cases

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 Label submitted December 4, 2012 (Appendix B)
- Carton Labeling submitted December 4, 2012 (Appendix C)
- Insert Labeling submitted December 4, 2012 (no image)

2.3 PREVIOUSLY COMPLETED REVIEWS

DMEPA previously conducted postmarketing reviews evaluating medication errors associated with epinephrine injection, inhalation solution, and nasal solution products (see OSE #2010-1226/1559 dated October 12, 2011, OSE #2012-1042 dated September 5, 2012, and OSE #2012-2678 dated November 19, 2012).

We reviewed these previous reviews to ensure all applicable recommendations that relate to the labels and labeling of injectable epinephrine are reflected in this review.

3 MEDICATION ERROR RISK ASSESSMENT

The following sections describe the results of our FAERS search and the risk assessment of the (b) (4) product design as well as the associated label and labeling.

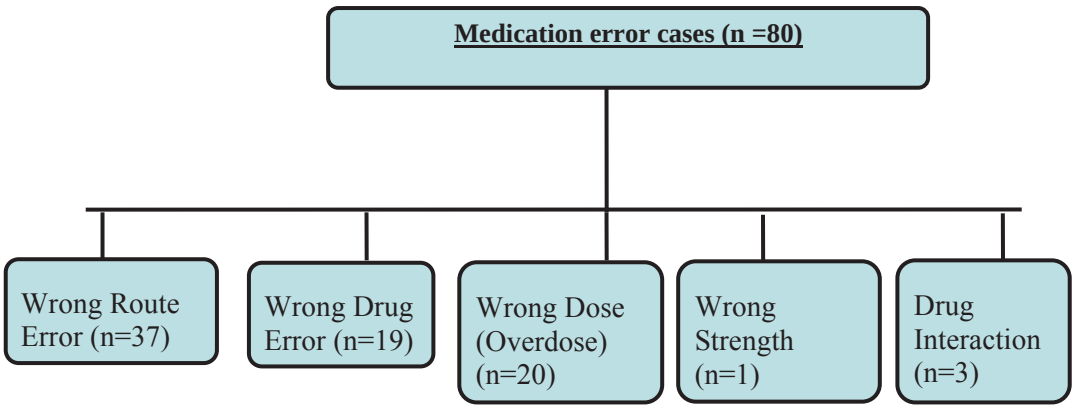
3.1 MEDICATION ERROR CASES

Following exclusions as described in section 2.1, a total of 80 epinephrine medication error cases remained for our detailed analysis. Duplicates were merged into a single case. 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 reporter[2]. Figure 1 provides a stratification of the number of cases included in the review by type of error. Appendix D provides listings of all case numbers for the cases summarized in this review.

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

[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.

Figure 1: Epinephrine medication error cases (n = 80) categorized by type of error



3.1.1 Wrong Route of Administration (n=37)

We identified 37 wrong route of administration cases where epinephrine was inadvertently given intravenously (n=28), intramuscularly (n=5), by inhalation (n=2), intravascularly (n=1) or as a bolus instead of infusion (n=1). All of these cases resulted in adverse events. The reported outcomes included ventricular tachycardia, ventricular fibrillation, chest pain, mild ST elevation, seizure, ataxia, tremors, had loss of muscle control, coronary artery vasospasm, and shortness of breath. Contributing factors were not reported.

3.1.2 Wrong Drug (n=19)

We identified 19 wrong drug cases where epinephrine was confused with other injectable products including atropine, Benadryl, calcium chloride, ephedrine, furosemide, morphine, naloxone, oxytocin, sulfamethoxazole/ trimethoprim, and Xylocaine. Most of the cases did not report contributing factors; however, some of the narratives did indicate that similarities in labeling and packaging contributed to the error. Reported outcomes of these cases included death, circulatory collapse and status asthmaticus, tachypnea, cyanosis, and severe retractions.

3.1.3 Wrong Dose/Overdose (n=20)

We identified 20 cases of overdose. Reported contributing factors included not diluting the injection prior to infusion, overlooking decimal points, confusion between the mcg and mg, confusion between the mL and mg, and calculation errors. Reported outcomes of these cases included hypertension, seizure, loss of consciousness, headache, nausea, vomiting, multi-focal ventricular arrhythmias, chest pain, mild decrease in blood pressure, mild EKG changes, supraventricular tachycardia, ventricular fibrillation, severe chest tightness, respiratory distress, and diaphoretic.

3.1.4 Wrong Strength (n=1)

We identified one case (#3383422v.1 received 11/10/1999) where the 1 mg/mL (1:1000) strength was confused with the 0.1 mg/mL (1:10,000) strength of epinephrine injection. Contributing factors were not reported. The reported outcomes included hypertension, tachycardia, and further intervention required to preclude harm.

3.1.5 Drug Interaction (n=3)

We identified three cases of potential epinephrine-quetiapine interaction reported in the scientific literature. The publication reported that three patients developed hypotension after receiving an overdose of quetiapine. All patients were treated with epinephrine [adrenaline] infusion, which resulted in worsening of hypotension. The authors concluded that there is potential deleterious interaction between quetiapine and epinephrine. This potential drug-drug interaction is not listed in the insert labeling for this product; therefore, we forwarded these cases to the Division of Pharmacovigilance (DPV) for their evaluation.

3.2 INTEGRATED SUMMARY OF MEDICATION ERROR RISK ASSESMENT

Our FAERS search identified wrong route errors, wrong drug errors, wrong dose errors, and wrong strength errors.

Historically, epinephrine has been used via intramuscular, subcutaneous, and intravenous routes of administration. However, for the proposed indication of acute hypotensive states associated with septic shock, epinephrine should only be administered as an intravenous infusion. The intended intravenous route of administration should be clearly noted on the principal display panel of the container label and carton labeling to minimize the risk of wrong route of administration errors. Our review of the proposed labels and labeling determined that the route of administration is clearly stated in the insert labeling, although the use of the dangerous abbreviation IV is utilized to designate 'intravenous'; therefore, we will request that the Applicant replace all dangerous abbreviations with their intended meaning. Our review also determined the route of administration can be more prominently stated on the ampule label and carton labeling. Additionally, we recommend adding a statement similar to "Dilute Before Intravenous Use". We provide recommendations in Section 4 below.

The wrong drug errors that were attributed to label and labeling confusion between epinephrine with other injectable products on the market are difficult to mitigate since there are many vial sizes and cap colors for the various products cited in the cases. Therefore, requesting the Applicant or other drug manufacturers to relabel or repackage their respective product(s) may create a different look-alike situation with another drug on the market that did not previously exist. Our main strategy for minimizing wrong drug or wrong strength errors is to ensure clear labels and labeling for our product with easily identifiable important information such as the drug name and strength.

We also reviewed the insert labeling to ensure the dosage and administration instructions are not vulnerable to confusion that can result in wrong dose errors. We determined the dosage and administration instructions can be improved by eliminating the use of error-prone abbreviations and providing units of measure for the recommended doses. We note there is a discrepancy between the expressions of the dose and the strength. The recommended dose is written in mcg/kg/min but the strength is expressed as mg/mL. However, given the historical use of this product, any attempt to change the established dosing instructions may result in more confusion. Therefore, we do not recommend changing the strength expression or dose expression at this time. Furthermore, during an internal division meeting held on October 3, 2012 with cross representation from the different disciplines that manage the different indications for epinephrine, the Divisions did not agree with DMEPA's recommendation to delete the ratio strength (i.e. 1:1000 and 1:10,000) from the labels and labeling. They stated that users reference

the ratio during the use of this product. It was agreed that both the ratio and 1 mg/mL will appear on the labels.

4 CONCLUSIONS

DMEPA concludes that the proposed label and labeling can be improved to add important labeling statements and increase the clarity, readability, and prominence of important information on the label to promote the safe use of the product. We provide recommendations below.

If you have further questions or need clarifications, please contact Cherye Milburn, OSE Project Manager, at 301-796-2084.

4.1 COMMENTS TO THE DIVISION

We provide the following recommendations for consideration by the review division prior to approval of this application.

A. Insert Labeling

1. The abbreviation 'IV' and symbol '≥', which appear on the ISMP list of Error-Prone Abbreviations, Symbols, and Dose Designations, can be found throughout the Dosage and Administration section of the insert labeling for this product. We recommend replacing the symbol '≥'with the appropriate term "greater than or equal to" as symbols have been mistaken as the opposite of its intended meaning and practitioners have mistakenly used the incorrect symbol. Similarly, the use or of abbreviations such as 'IV' should be replaced with the appropriate full meaning of 'intravenous'.
2. Trailing zeros are also error-prone and can result in ten-fold dosing error if the decimal is not seen (i.e. '2.0' can be misinterpreted as '20'); thus, we recommend removing the trailing zeros where they appear in the Dosage and Administration section of the insert labeling.
3. Add a unit of measure immediately following all numbers, as appropriate. For example, revise (b) (4) to read "0.05 mcg/kg/min to 2 mcg/kg/min" under the Dosage and Administration section.
4. In the Dosage and Administration section under the Highlights of Prescribing Information, add the word "Must" to the third bullet point that starts with the statement "Dilute (b) (4)" to read "Must dilute (b) (4) to help emphasize this important dilution step.
5. Revise the storage condition statement in section 16 to include the units °C or °F, respectively, and replace the hyphen within the temperature designations with the word "to" for improved clarity and to be consistent with USP standards. We recommend not using the hyphen between the numbers because a hyphen can be misinterpreted as a minus sign when discussing temperatures. Therefore, revise the storage statement to read "Store between (b) (4)

4.2 COMMENTS TO THE APPLICANT

We recommend the following be implemented prior to approval of this NDA.

A. General Comments for Container Labels and Carton Labeling

1. Revise the proprietary name and established name to appear in title case.
2. Revise the order for the statement of strength so the mg/mL is the primary expression of strength (not the ratio 1:1000).
3. Present the number 1000 with a comma to help differentiate it from the number 10000 (the other strength of epinephrine).
4. Present the proprietary name, established name, and strength in a stacked format, similar to the following:

[redacted] (b) (4)

(Epinephrine Injection, USP)

1 mg/mL

(1:1,000)

5. 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).
6. Increase the prominence of the route of administration statement and relocate it directly below the strength statement. In addition, replace the word [redacted] (b) (4) with the word "Infusion" in the statement that begins with "For Intravenous [redacted] (b) (4) to improve clarity of the intended route of administration given that epinephrine is currently given by multiple routes of administration for other indications.
7. Delete the phrase [redacted] (b) (4) (that follows the route of administration statement) to reduce clutter on this small label. Accordingly, revise the statement to read "For Intravenous Infusion."
8. In order to ensure proper administration of epinephrine of diluting prior to intravenous infusion, we recommend adding the statement "Dilute Before Intravenous Infusion". If space permits, prominently display this statement on the principal display panel under the strength statement.
9. Decrease the prominence of the "Rx Only" statement and relocate the statement to the side panel to minimize distraction from other more important information on the principle display panel.
10. Delete the manufacturer name "Belcher" located on the principal display panel since it's redundant as it is already found on the side panel.
11. Delete the statement "Contains No Sulfites" found on the principle display panel to reduce clutter on a crowded small label.

12. Add the statement “Single Dose Ampule” to the bottom of the principle display panel.

13. Remove the color block from the proprietary name and strength expressions to enhance the contrast and improve readability of the establish name since it is currently difficult to read the established name.

B. Container Label-1 mL Ampule

1. Relocate the (b) (4) statement to the side panel to reduce clutter on a crowded small label.

2. Consider deleting the (b) (4) statement which will provide additional space to enlarge the area of the principle display panel.

C. Carton Labeling-1 mL (10 Ampules)

1. Unbold and revise the net quantity statement to read “10 Single-Dose Ampules x1 mL each”. Relocate this statement to the lower portion of the principle display panel to avoid competing with the strength statement.

2. Relocate the “preservative free” statement from the top to the bottom of the principal display panel. Delete the “Contains no sulfites” statement.

3. Delete or minimize and relocate the graphic away from the proprietary name to avoid misinterpretation as a letter ‘O’ in the proprietary name.

4. Increase the prominence of the strength statement since the purple box is difficult to discern against a dark blue background.

5. Relocate the storage condition statement to the side panel to reduce clutter on the principal display panel.

6. If space is needed to accommodate the additional statements, consider relocating the “Each mL contains…” statement from below the strength statement to the side panel.

7. Revise the storage condition statement to include the units °C or °F, respectively, and replace the hyphen within the temperature designations with the word “to” for improved clarity and to be consistent with USP standards. We recommend not using the hyphen between the numbers because a hyphen can be misinterpreted as a minus sign when discussing temperatures. Therefore, revise the storage statement to read “Store between (b) (4)

8. Revise the statement after the word” WARNINGS” to appear in mixed case to enhance the readability of the statement “Do not use if discolored or precipitated.”

9. Debold the storage statement “Store between …” to improve readability.

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.

Appendix B: 1 mL (Single Dose Ampule) Container Label

Appendix C: 1 mL Carton Labeling (10 Single Dose Ampules)

Appendix D: Case numbers discussed in this review

3003405 3030642 3133019 3307660 3383422 3437242 3652510 3759144 3762821 3772891 3808662 3863342 3875977 3877324 3878394 3883272 4015074 4107111 4124810 4128104 4136755 4139673 4584068 4792266 4792340 4815084 4839858 5036556 5058738 5090765 5090774 5090796 5095538 5150183 5267396 5336783 5421240 5445082 5445093 5524092 5603654 5652256 5681774 5728957 5728966 5796861 5805588 5855103 5863446 5873845 5884502 5915145 5916161 5922075 6000684 6114929 6158465 6320417 6397797 6620592 6659344 6721942 6724825 6724838 6724841 6784567 6796779 6995113 6999531 6999532 7008428 7008430 7036637 7126019 7147080 7152797 7160750 7177120 7179849 7261054 326232 7327259 7363759 7381759 7382347 7384945 7453831 457027 7466250 7468792 7498141 7567724 7746501 7748124 7795547 7940259 8029816 8031847 8225872 8323230 8586280 8636993 9246918 9248132 8685085 883272 9124416 090774 6840581 6863774 6935934 6962418 6966843 6992649 992651 993199 6993738 6995104

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

/s/

IRENE Z CHAN on behalf of KIMBERLY A DE FRONZO
08/07/2013

IRENE Z CHAN
08/07/2013

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 # 205029 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: (b) (4) Established/Proper Name: Epinephrine Dosage Form: injection Strengths: 1 mg/mL		
Applicant: Belcher Pharmaceuticals, LLC Agent for Applicant (if applicable): N/A		
Date of Application: November 30, 2012 Date of Receipt: December 4, 2012 Date clock started after UN:		
PDUFA Goal Date: October 4, 2013	Action Goal Date (if different): N/A	
Filing Date: February 1, 2013	Date of Filing Meeting: January 23, 2013	
Chemical Classification: (1,2,3 etc.) (original NDAs only)		
Proposed indication(s)/Proposed change(s): for use in increasing systemic arterial blood pressure in acute hypotensive states associated with septic shock		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499*** ***and refer to Appendix A for further information.***	☐ 505(b)(1) ☒ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)	
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***	☒ Standard ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted	
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐	
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)	

☐ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): P-IND (b) (4)	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	**X**			
Are the proprietary, established/proper, and applicant names correct in tracking system? ***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.***	**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)? ***For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	**X**			
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***		**X**		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? **If yes,** date notified:				
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	**X**			

User Fee Status ***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.***	Payment for this application: ☐ Paid ☐ Exempt (orphan, government) ☒ Waived (e.g., small business, public health) ☐ Not required
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.	Payment of other user fees: ☒ Not in arrears ☐ In arrears

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		**X**		
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)].**		**X**		
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)]?** ***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 505(b)(2) review staff in the Immediate Office of New Drugs***		**X**		
Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:		**X**		

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

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 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***		**X**		

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)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***			**X**	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*		**X**		
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?		**X**		
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)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***			**X**	

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

[1] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #			**X**	
Applications in "the Program" (PDUFA V) (NME NDAs/Original BLAs)	**YES**	**NO**	**NA**	**Comment**
Was there an agreement for any minor application components to be submitted within 30 days after the original submission?			**X**	
• If yes, were all of them submitted on time?			**X**	
Is a comprehensive and readily located list of all clinical sites included or referenced in the application?			**X**	**This is a literature-based application**
Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?			**X**	
Forms and Certifications				
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.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	**X**			
Are all establishments and their registration numbers listed on the form/attached to the form?		**X**		Additional facilities info submitted upon request
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**			Additional patent information requested and submitted
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)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies*			**X**	Literature-based application

that are the basis for approval.				
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***			**X**	
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act 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…"*	**X**			
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***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)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***			**X**	

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

Pediatrics	**YES**	**NO**	**NA**	**Comment**

PREA Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***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.*	**X**			
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?	**X**			Full waiver requested
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? ***If no, request in 74-day letter***			**X**	
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)? ***If no, request in 74-day letter***			**X**	
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]		**X**		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	**X**			
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***		**X**		
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labels ☒ Immediate container labels			

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm
[3] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm

	☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	**X**			
Is the PI submitted in PLR format?[4]	**X**			
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? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***			**X**	
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	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***			**X**	
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***			**X**	
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***			**X**	
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?			**X**	
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT		**X**		

[4] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576 htm

study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***				
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***			**X**	
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** Letter dated 10/15/13 ***If yes, distribute minutes before filing meeting***		**X**		Sponsor requested written feedback on several pre-NDA questions.
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***			**X**	

ATTACHMENT

MEMO OF FILING MEETING

DATE: January 23, 2013

BLA/NDA/Supp #: 205029

PROPRIETARY NAME: (b) (4) (proposed)

ESTABLISHED/PROPER NAME: Epinephrine

DOSAGE FORM/STRENGTH: injection 1 mg/ml

APPLICANT: Belcher Pharmaceuticals

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): treatment of hypotensive states associated with septic shock

BACKGROUND: Belcher Pharmaceuticals is proposing approval of epinephrine injection based on literature reports. Epinephrine is currently marketed by multiple firms for various cardiac uses. While epinephrine was recently approved for use in the treatment of allergic reactions and for use during ocular surgery, it has never been approved for cardiac uses.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Russell Fortney	Y
	CPMS/TL:	Edward Fromm	N
Cross-Discipline Team Leader (CDTL)	Shari Targum		Y
Clinical	Reviewer:	Gail Moreschi	Y
	TL:	Avi Karkowsky	N

Clinical Pharmacology	Reviewer:	Sudarsha Hariharan	Y
	TL:	Raj Madabushi	Y
Biostatistics	Reviewer:	Steve Bai	Y
	TL:	Jim Hung	N
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Rama Dwivedi	N
	TL:	Tom Papoian	Y
Product Quality (CMC)	Reviewer:	Shastri Bhamidipati	Y
	TL:	Kasturi Srinivasachar	Y
Quality Microbiology *(for sterile products)*	Reviewer:	Steve Donald	Y
	TL:	Stephen Langille	N
Facility Review/Inspection	Reviewer:	Vibhakar Shah	Y
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Kim Defronzo	N
	TL:		
OSE/DRISK (REMS)	Reviewer:	N/A	
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:	N/A	
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:	N/A	
	TL:		
Controlled Substance Staff (CSS)	Reviewer:	N/A	
	TL:		

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues? **If yes,** list issues:	☐ Not Applicable ☐ YES ☒ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**: None	☐ Not Applicable
CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☐ YES ☒ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA , include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***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***	☐ YES Date if known: ☒ NO ☐ To be determined Reason: AC recently convened for similar marketed unapproved product (b) (4).

disease	
• Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• 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? **Comments**:	☐ Not Applicable ☐ YES ☒ NO
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
Environmental Assessment • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**: Per CMC, consult not needed.	☐ Not Applicable ☐ YES ☒ NO ☒ YES ☐ NO ☐ YES ☒ NO
Quality Microbiology (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	☐ Not Applicable ☒ YES ☐ NO
Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? **Comments**: Additional facility information requested; sponsor submitted information on 1/4/13. Two of the facilities used for drug substance manufacture were recently issued an FDA-483s (see attached for). There was some discussion that this could be a filing issue, but it was not resolved by the filing date, so it will be a review issue.	☐ Not Applicable ☒ YES ☐ NO ☒ YES ☐ NO

<u>Facility/Microbiology Review</u> (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT
Signatory Authority: Division

	REGULATORY CONCLUSIONS/DEFICIENCIES
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. List (optional): <u>Review Classification:</u> ☒ Standard Review ☐ Priority Review

	ACTIONS ITEMS
☒	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).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	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.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☐	If priority review: • 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)
☒	Send review issues/no review issues by day 74
☐	Update the PDUFA V DARRTS page (for NME NDAs in "the Program")
☐	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 in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

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

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

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

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

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

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

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

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

NDA 205029
(b) (4) (epinephrine injection) USP 1 mg/mL
Filing Meeting

Wednesday January 23, 2013
11: 00 AM– 12:00 PM

Last CGMP Status for NDA-listed Establishments/Facilities

Establishments	Last Inspection Status	Profiles covered	Inspection Classification	OC/OMPQ Recommendation
(b) (4)			FDA-483 issued OAI (11/26/2012)	Pending EIR under review
			FDA-483 issued VAI (11/30/2012)	Pending EIR under review
			NAI (11/30/2012)	Pending EIR under review

OAI: Official Action Indicated; **VAI**: Voluntary Action Indicated; **NAI**: No Action Indicated

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

/s/

RUSSELL FORTNEY
03/12/2013