CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205029Orig1s000

CHEMISTRY REVIEW(S)

NDA 205029

Epinephrine Injection
1 mg/mL

Belcher Pharmaceuticals

Division of Cardiology and Renal Products, HFD 110

Shastri Bhamidipati, Ph.D.
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment

Submission Date : 29-JAN-2014
PDUFA Goal Date: 28-JUL-2014

Chemistry Review Data Sheet

1. NDA 205029

2. REVIEW #: 3

3. REVIEW DATE: 10-July-2014

4. REVIEWER: Shastri Bhamidipati, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
IND (b) (4)	01-Feb-2012

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
NDA 205029 SD#9	29-JAN-2014
NDA 205029(SD#10)	13-JU N-2014
NDA 205029(SD#11)	01-JUL-2014
NDA 205029(SD#12)	09-JUL-2014

7. NAME & ADDRESS OF APPLICANT:

Name:	Belcher Pharmaceuticals
Representative:	Mihir Taneja Vice President, Regulatory Affairs & Compliance 6911 Bryan Dairy Road Largo, FL 33777 USA
Telephone:	(727) 471-0850 Ext 250

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Epinephrine
c) Code Name/# (ONDQA only): N/A
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 7
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 21 CFR 314.50, 505(b)(2)

10. PHARMACOL. CATEGORY: Cardiology, Septic Shock

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 1.0 mg/mL (1:1000)

13. ROUTE OF ADMINISTRATION: Intravenous

14. Rx/OTC DISPENSED: ___X___ Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

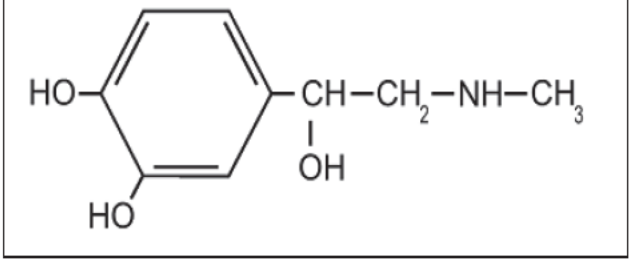
_____SPOTS product – Form Completed

___X___Not a SPOTS product

1. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name(s):

1. Chemical Name: (R)-1-(3,4-dihydroxyphenyl)-2-methylaminoethanol 1,2-Benzenediol, 4-(1 -hydroxy-2-(methylamino)ethyl)-, (R)- (-)-3,4-Dihydroxy- IX -((methylamino)methyl)-benzyl alcohol



Synonym: (-)-Adrenaline

(-)- Epinephrine

(b) (4)

CAS-No: 51 - 43 – 4

Molecular Formula: $C_9H_{13}NO_3$

Molecular Mass: 183.20

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	1	Adequate	06/24/2014	S. Bhamidipati
	III			4			

[1] Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	(b) (4)	Epinephrine

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER(S)	COMMENTS
Biometrics	Not applicable			
EES	Acceptable	Jun-07-2014		E.Dobbin
Pharm/Tox	Not applicable			
Biopharmaceutics	Not applicable			
Methods Validation	Not requested. The methods are conventional and do not qualify for internal validation by FDA labs			
DMEPA	Trade name (b) (4) is acceptable	Aug-07-2013	Kimberly De Fronzo	Trade name may not be used for commercialization
EA	Categorical Exclusion granted			
Microbiology	Recommended approval (1st Cycle).	15-Feb-2013	Steven Donald	No review of the resubmission as there is no change in (b) (4)

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes ____ No If no, explain reason(s) below:
Not Applicable

Chemistry Review for NDA 205029

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA 205029 for Epinephrine Injection 1mg/mL, USP from Belcher Pharmaceuticals is recommended for approval from CMC perspective. Office of Compliance has provided an overall acceptable recommendation for manufacturing and testing facilities for this NDA.

Note: Please refer to Quality Reviews filed for this NDA in DARRTS on Aug-21-2013 and Oct-03-2013 for complete details.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None applicable .

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Review Cycle#1 :The proposed drug product, Epinephrine Injection 1 mg/mL (1:1000) USP is an injectable sterile solution for the treatment of septic shock. The sponsor, Belcher Pharmaceuticals, met with the Agency and agreed to submit the NDA for the proposed indication (septic shock) for a literature based review without conducting any new clinical studies. While Epinephrine injection was marketed as an unapproved drug at the time Belcher Pharmaceuticals submitted their original NDA, Division of Pulmonary, Allergy and Rheumatology Products (DPARP) has subsequently approved NDA 204200 Adrenalin (Epinephrine) injection , 1 mg/mL (1:1000) USP submitted by JH Pharmaceuticals for treatment of allergic reactions and anaphylactic shock in Dec 2012. The proposed drug product in this NDA contains 1 mg/mL of Epinephrine base equivalent as a sterile solution with 1 ml of the solution filled in 2 ml Type I (USP) clear glass ampoule. The only excipients in the product are sodium chloride (tonicity agent), (b) (4) hydrochloric acid (for (b) (4) and pH adjustment) and water for injection (b) (4) The manufacturing process is carried out (b) (4) The manufacturing process is straightforward and consists of (b) (4) The specification provided for the drug product is essentially the same as in USP for epinephrine injection. The only addition is a specification for the related substance, (b) (4) Batch analysis data have been submitted for 3 commercial batches manufactured between 2004 and 2007. Stability data were provided for 4 full scale batches manufactured with (b) (4) Appearance, assay, (b) (4) and particulate matter were tested at every time point whereas sterility and endotoxins were tested annually. Based on the

stability data , the applicant proposed an expiration dating of [redacted] for the product. The drug product is recommended to be stored at [redacted] However, batch analysis and stability data presented did not include evaluation of the drug product for [redacted] at release or during storage. Based on the applicant's response that a minimum of [redacted] of Epinephrine was observed at the end of proposed commercial manufacturing process with [redacted] with the current manufacturing process is considered not justified. In addition, the analytical methods employed for assay and degradation products were considered not adequately validated to ensure the drug product quality characteristics at release and on stability. A Complete Response letter was sent to the Applicant with CMC deficiency items on 4-Oct-2013.

Review Cycle# 2 (Resubmission): The drug product formulation was revised to contain [redacted] The proposed commercial manufacturing process entails [redacted] The drug product specification was revised for assay to [redacted] and included acceptance limits of no more than [redacted] and [redacted] for [redacted] at release and on stability respectively. The HPLC analytical method employed for assay and related substances was adequately revised. Additionally, description and validation results of chiral HPLC method employed for quantitation of [redacted] content were provided. Stability data for one batch of drug product manufactured with revised formulation and manufacturing process stored at long term storage conditions (25°C) up to 9 months were provided. Based on the levels of [redacted] observed on stability, the Applicant proposed a shelf-life of [redacted] for the drug product.

The proposed commercial manufacturing process which consists of [redacted] is considered acceptable. It was noted that the proposed drug product shelf-life of [redacted] lacks adequate scientific justification since stability data presented are limited to nine months for one batch in the resubmission. Stability data submitted in the original NDA (three batches manufactured with [redacted]) manufactured at [redacted] cannot be considered to be supportive data due to [redacted] The NDA is recommended for approval based on changes to the manufacturing process and formulation reducing the level of [redacted] impurity in the final drug product, which should provide reduced risk to the patient. The stability data for a single batch [redacted] show the drug product maintains the critical quality attributes up to 12 months and hence a shelf-life of 12 months for the drug product is recommended. Following a discussion of limited stability data during the Teleconference held on July 2nd 2014, the Applicant submitted the following information to the NDA(SD#12 dated 09-JUL-2014)

> The Applicant has agreed to submit long term storage stability data for three commercial batches for expiration dating extension of the drug product [redacted].
>
> The Applicant revised the drug product specification to include appropriate acceptance limits for total impurities/degradants (including [redacted]) at release and on stability

Drug Substance:

The drug substance, epinephrine, commonly known as adrenaline is a white to almost white crystalline powder which is practically insoluble in water, ethanol or methylene chloride but is soluble in HCl. It is an endogenous hormone and neurotransmitter. Epinephrine has one chiral center and is a pure enantiomer with the R configuration. It is manufactured by (b) (4) in (b) (4) by a (b) (4) and all CMC information is cross-referenced to DMF (b) (4) This DMF has been deemed adequate to support this NDA for an injectable dosage form. Specifications for epinephrine are provided in the NDA based on the USP monograph with the addition of tests for residual solvents (b) (4) and bacterial endotoxins. Batch analysis data have been provided for 2 representative batches. It was stated that DMF holder, (b) (4) has assigned a retest period of (b) (4) based on stability data submitted to the DMF.

B. Description of How the Drug Product is Intended to be Used

Epinephrine Injection 1 mg/mL (1:1000) USP is a sterile solution consisting of 1 mg/mL of Epinephrine base equivalent and one ml of the solution is filled in 2 ml Type I (USP) clear glass ampoule (b) (4). The ampoules (b) (4) are packed in (b) (4) cardboard boxes. Each cardboard-box contains 10 ampoules of Epinephrine Injection . The drug product is diluted further in saline for intravenous administration. The recommended storage conditions for the drug product are:

"Store at room temperature, between 20°C and 25°C (68° and 77°F) (b) (4)

C. Basis for Approvability or Not-Approval Recommendation

This NDA 205029 for Epinephrine Injection, 1 mg/mL (1:1000) USP is approvable based on the evaluation of quality information submitted in the resubmission. The proposed commercial manufacturing process which consists of (b) (4) is acceptable because the (b) (4) and manufacturing changes in this resubmission assure adequate L-epinephrine is present in the drug product to assure clinical efficacy while minimizing drug product impurities that were present with the previous process. However, based on limited stability data submitted in the resubmission, a shelf-life of 12 months is recommended for the drug product.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Chemist Name/Date: Shastri Bhamidipati, Ph.D.

Chemistry Team Leader Name/Date: Kasturi Srinivasachar, Ph.D.

Project Manager Name/Date: R. Fortney

C. CC Block

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

/s/

SHASTRI P BHAMIDIPATI
07/11/2014

OLEN M STEPHENS
07/14/2014

NDA 205029

[redacted] (b) (4)

(Epinephrine) Injection
1 mg/mL

Belcher Pharmaceuticals

Division of Cardiology and Renal Products, HFD 110

Shastri Bhamidipati, Ph.D.
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment

Submission Date : 04-DEC-2012
PDUFA Goal Date: 04-OCT-2013

Chemistry Review Data Sheet

1. NDA 205029

2. REVIEW #: 2

3. REVIEW DATE: 03-Oct-2013

4. REVIEWER: Shastri Bhamidipati, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
IND (b) (4)	01-Feb-2012

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
NDA 205029 Original Submission	04-DEC-2012
NDA 205029 SD#7	08-MAR-2013

7. NAME & ADDRESS OF APPLICANT:

Name: Belcher Pharmaceuticals

Address: 6911 Bryan Dairy Road
Largo, FL 33777 USA

Chemistry Review Data Sheet

Representative:	Mihir Taneja Vice President, Regulatory Affairs & Compliance 6911 Bryan Dairy Road Largo, FL 33777 USA
Telephone:	(727) 471-0850 Ext 250

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: (b) (4)
b) Non-Proprietary Name (USAN): Epinephrine
c) Code Name/# (ONDQA only): N/A
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 7
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 21 CFR 314.50, 505(b)(2)

10. PHARMACOL. CATEGORY: Cardiology, Septic Shock

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 1.0 mg/mL (1:1000)

13. ROUTE OF ADMINISTRATION: Intravenous

14. Rx/OTC DISPENSED: ___X__ Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

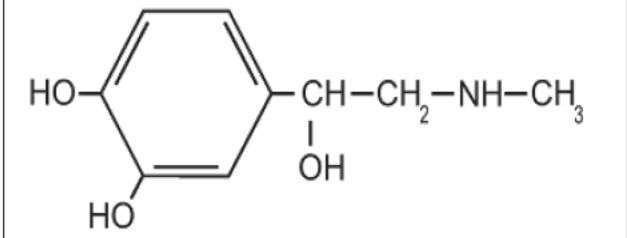
_____SPOTS product – Form Completed

___X___Not a SPOTS product

1. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name(s):

1. Chemical Name: (R)-1-(3,4-dihydroxyphenyl)-2-methylaminoethanol 1,2-Benzenediol, 4-(1 -hydroxy-2-(methylamino)ethyl)-, (R)- (-)-3,4-Dihydroxy- IX -((methylamino)methyl)-benzyl alcohol



Synonym: (-)-Adrenaline
(-)- Epinephrine
(b) (4)
CAS-No: 51 - 43 – 4
Molecular Formula: $C_9H_{13}NO_3$
Molecular Mass: 183.20

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	1	Adequate	03/01/2013 07/15/2013	S. Bhamidipati E.Englund
	III			4			

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application

5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	(b) (4)	Epinephrine

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER(S)
Biometrics	Not applicable		
EES	Acceptable	Oct-03-2013	Christina Capacci-Daniel
Pharm/Tox	Not applicable		
Biopharmaceutics	Not applicable		
Methods Validation	Not requested. The methods are conventional and do not qualify for internal validation by FDA labs		
DMEPA	Trade name (b) (4) is acceptable	Aug-07-2013	Kimberly De Fronzo
EA	Categorical Exclusion granted		
Microbiology	Recommended approval	Feb-15-2013	Steven Donald

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes ____ No If no, explain reason(s) below:

Chemistry Review for NDA 205029

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA 205029 for (b) (4) (Epinephrine) Injection 1mg/mL USP from Belcher Pharmaceuticals is not recommended for approval from CMC perspective due to significant issues in regards to quality of the drug product resulting from the proposed commercial manufacturing process. A list of CMC deficiencies and recommendations are provided at the end of this Executive summary. The Office of Compliance has provided overall acceptable recommendation for manufacturing and testing facilities for this NDA (see Attachment).

Note: Please refer to Quality Review filed for this NDA in DARRTS on Aug-21-2013 for complete details.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None applicable .

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The proposed drug product, (b) (4) (Epinephrine) Injection 1 mg/mL (1:1000) USP is an injectable sterile solution for the treatment of septic shock. Currently, Epinephrine injection is marketed as an unapproved drug and the sponsor , Belcher Pharmaceuticals, agreed at the pre-NDA meeting to a literature based review to support the proposed indication was considered sufficient in lieu of clinical studies. The drug product contains 1 mg/mL of Epinephrine base equivalent and 1 ml of the solution is filled in 2 ml Type I (USP) clear glass ampoule. The only excipients in the product are sodium chloride (tonicity agent), (b) (4) hydrochloric acid (for (b) (4) and pH adjustment) and water for injection. This is a (b) (4) formulation. The manufacturing process is carried out (b) (4) The manufacturing process is straightforward and consists of (b) (4) The specification provided for the drug product is essentially the same as in USP for epinephrine injection. The only addition is a specification for the related substance, (b) (4) Batch analysis data have been submitted for 3 commercial batches manufactured between 2004 and 2007. Stability data were provided for 4 full scale batches manufactured with (b) (4) Appearance, assay, (b) (4) and particulate matter were tested at every

time point whereas sterility and endotoxins were tested annually. Based on the stability data , the applicant proposed an expiration dating of [redacted] for the product. The drug product is recommended to be stored at [redacted] However, batch analysis and stability data presented did not include evaluation of the drug product for [redacted] at release or during storage. Based on the applicant's response that a minimum of [redacted] of Epinephrine was observed at the end of proposed commercial manufacturing process with [redacted] with the current manufacturing process is considered not justified. In addition, the analytical methods employed for assay and degradation products were considered not adequately validated to ensure the drug product quality characteristics at release and on stability.

Drug Substance:

The drug substance, epinephrine, commonly known as adrenaline is a white to almost white crystalline powder which is practically insoluble in water, ethanol or methylene chloride but is soluble in HCl. It is an endogenous hormone and neurotransmitter. Epinephrine has one chiral center and is a pure enantiomer with the R configuration. It is manufactured by [redacted] in [redacted] by a [redacted] and all CMC information is cross-referenced to DMF [redacted] This DMF has been reviewed numerous times and the most recent review dated 15-Jul-2013 concludes that it is adequate to support an NDA for an injectable dosage form. Specifications for epinephrine are provided in the NDA based on the USP monograph with the addition of tests for residual solvents [redacted] and bacterial endotoxins. Batch analysis data have been provided for 2 representative batches. It was stated that DMF holder, [redacted] has assigned a retest period of [redacted] based on stability data submitted to the DMF. However, the Office of Compliance has put the Epinephrine HCl drug substance manufacturing site in [redacted] on a "withhold" status.

B. Description of How the Drug Product is Intended to be Used

Epinephrine Injection 1 mg/mL (1:1000) USP is a sterile solution consisting of 1 mg/mL of Epinephrine base equivalent and one ml of the solution is filled in 2 ml Type I (USP) clear glass ampoule [redacted]. The ampoules [redacted] are packed in [redacted] cardboard boxes. Each cardboard-box contains 10 ampoules of Epinephrine Injection . The drug product is diluted further in saline for intravenous administration. The recommended storage conditions for the drug product are:

"Store at room temperature, between 20°C and 25°C (68° and 77°F) [redacted]

C. Basis for Approvability or Not-Approval Recommendation

The recommendation for non-approvability of this NDA 205029 for [redacted] (Epinephrine) Injection is based on the evaluation of quality information submitted in the original application and the supporting documents. The proposed commercial manufacturing process which consists of [redacted] in considered not justified. In addition, the analytical methods employed for assay

and degradation products were considered not adequately validated to ensure the drug product quality characteristics at release and on stability.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Chemist Name/Date: Shastri Bhamidipati, Ph.D.
Chemistry Team Leader Name/Date: Kasturi Srinivasachar, Ph.D.
Project Manager Name/Date: R. Fortney

C. CC Block

(b) (4)

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

/s/

SHASTRI P BHAMIDIPATI
10/03/2013

RAMESH K SOOD
10/03/2013

NDA 205029

[redacted] (b) (4)
(Epinephrine) Injection
1 mg/mL

Belcher Pharmaceuticals

Division of Cardiology and Renal Products, HFD 110

Shastri Bhamidipati, Ph.D.
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment

Submission Date : 04-DEC-2012
PDUFA Goal Date: 04-OCT-2013

Chemistry Review Data Sheet

1. NDA 205029

2. REVIEW #: 1

3. REVIEW DATE: 20-Jan-2013

4. REVIEWER: Shastri Bhamidipati, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
IND (b) (4)	01-Feb-2012

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
NDA 205029 Original Submission	04-DEC-2012
NDA 205029 SD#7	08-MAR-2013

7. NAME & ADDRESS OF APPLICANT:

Name: Belcher Pharmaceuticals

Address: 6911 Bryan Dairy Road
Largo, FL 33777 USA

Chemistry Review Data Sheet

Representative:	Mihir Taneja Vice President, Regulatory Affairs & Compliance 6911 Bryan Dairy Road Largo, FL 33777 USA
Telephone:	(727) 471-0850 Ext 250

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: (b) (4)
b) Non-Proprietary Name (USAN): Epinephrine
c) Code Name/# (ONDQA only): N/A
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 7
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 21 CFR 314.50, 505(b)(2)

10. PHARMACOL. CATEGORY: Cardiology, Septic Shock

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 1.0 mg/mL (1:1000)

13. ROUTE OF ADMINISTRATION: Intravenous

14. Rx/OTC DISPENSED: ___X__ Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

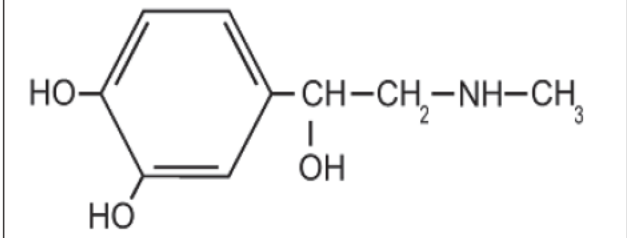
_____SPOTS product – Form Completed

___X___Not a SPOTS product

1. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name(s):

1. Chemical Name: (R)-1-(3,4-dihydroxyphenyl)-2-methylaminoethanol 1,2-Benzenediol, 4-(1 -hydroxy-2-(methylamino)ethyl)-, (R)- (-)-3,4-Dihydroxy- IX -((methylamino)methyl)-benzyl alcohol



Synonym: (-)-Adrenaline

(-)- Epinephrine

(b) (4)

CAS-No: 51 - 43 – 4

Molecular Formula: $C_9H_{13}NO_3$

Molecular Mass: 183.20

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	1	Adequate	03/01/2013 07/15/2013	S. Bhamidipati E.Englund
	III			4			

[1] Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	(b) (4)	Epinephrine

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER(S)
Biometrics	Not applicable		
EES	Final Recommendation pending		
Pharm/Tox	Not applicable		
Biopharmaceutics	Not applicable		
Methods Validation	Not requested. The methods are conventional and do not qualify for internal validation by FDA labs		
DMEPA	Trade name (b) (4) is acceptable	Aug-07-2013	Kimberly De Fronzo
EA	Categorical Exclusion granted		
Microbiology	Recommended approval		Steven Donald

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes ____ No If no, explain reason(s) below:

Chemistry Review for NDA 205029

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA 205029 for (b) (4) (Epinephrine) Injection 1mg/mL USP from Belcher Pharmaceuticals is not recommended for approval from CMC perspective due to significant issues in regards to quality of the drug product resulting from the proposed commercial manufacturing process. A list of CMC deficiencies and recommendations are provided at the end of this Executive summary. Additionally, the Office of Compliance has not provided a final recommendation as to the acceptability of manufacturing and testing facilities for this NDA.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None applicable .

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The proposed drug product, (b) (4) (Epinephrine) Injection 1 mg/mL (1:1000) USP is an injectable sterile solution for the treatment of septic shock. Currently, Epinephrine injection is marketed as an unapproved drug and the sponsor , Belcher Pharmaceuticals, agreed at the pre-NDA meeting to a literature based review to support the proposed indication was considered sufficient in lieu of clinical studies. The drug product contains 1 mg/mL of Epinephrine base equivalent and 1 ml of the solution is filled in 2 ml Type I (USP) clear glass ampoule. The only excipients in the product are sodium chloride (tonicity agent), (b) (4) hydrochloric acid (for (b) (4) and pH adjustment) and water for injection. This is a (b) (4) formulation. The manufacturing process is carried out (b) (4) The manufacturing process is straightforward and consists of (b) (4) The specification provided for the drug product is essentially the same as in USP for epinephrine injection. The only addition is a specification for the related substance, (b) (4) Batch analysis data have been submitted for 3 commercial batches manufactured between 2004 and 2007. Stability data were provided for 4 full scale batches manufactured with (b) (4) Appearance, assay, (b) (4) and particulate matter were tested at every time point whereas sterility and endotoxins were tested annually. Based on the stability data , the

applicant proposed an expiration dating of [redacted] for the product. The drug product is recommended to be stored at [redacted] However, batch analysis and stability data presented did not include evaluation of the drug product for [redacted]n at release or during storage. Based on the applicant's response that a minimum of [redacted] of Epinephrine was observed at the end of proposed commercial manufacturing process with [redacted] with the current manufacturing process is considered not justified. In addition, the analytical methods employed for assay and degradation products were considered not adequately validated to ensure the drug product quality characteristics at release and on stability.

Drug Substance:

The drug substance, epinephrine, commonly known as adrenaline is a white to almost white crystalline powder which is practically insoluble in water, ethanol or methylene chloride but is soluble in HCl. It is an endogenous hormone and neurotransmitter. Epinephrine has one chiral center and is a pure enantiomer with the R configuration. It is manufactured by [redacted] in [redacted] by a [redacted] and all CMC information is cross-referenced to DMF [redacted] This DMF has been reviewed numerous times and the most recent review dated 15-Jul-2013 concludes that it is adequate to support an NDA for an injectable dosage form. Specifications for epinephrine are provided in the NDA based on the USP monograph with the addition of tests for residual solvents [redacted] and bacterial endotoxins. Batch analysis data have been provided for 2 representative batches. It was stated that DMF holder, [redacted] has assigned a retest period of [redacted] based on stability data submitted to the DMF. However, the Office of Compliance has put the Epinephrine HCl drug substance manufacturing site in [redacted] on a "withhold" status.

B. Description of How the Drug Product is Intended to be Used

Epinephrine Injection 1 mg/mL (1:1000) USP is a sterile solution consisting of 1 mg/mL of Epinephrine base equivalent and one ml of the solution is filled in 2 ml Type I (USP) clear glass ampoule [redacted]. The ampoules [redacted] are packed in [redacted] cardboard boxes. Each cardboard-box contains 10 ampoules of Epinephrine Injection . The drug product is diluted further in saline for intravenous administration. The recommended storage conditions for the drug product are:
"Store at room temperature, between 20°C and 25°C (68° and 77°F) [redacted]

C. Basis for Approvability or Not-Approval Recommendation

The recommendation for non-approvability of this NDA 205029 for [redacted] (Epinephrine) Injection is based on the evaluation of quality information submitted in the original application and the supporting documents. The proposed commercial manufacturing process which consists of [redacted] in considered not justified. In addition, the analytical methods employed for assay

and degradation products were considered not adequately validated to ensure the drug product quality characteristics at release and on stability.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Chemist Name/Date: Shastri Bhamidipati, Ph.D.
Chemistry Team Leader Name/Date: Kasturi Srinivasachar, Ph.D.
Project Manager Name/Date: R. Fortney

C. CC Block

Original NDA 205029
DNP (HFD-110)/NDA Division File
DNP(HFD-110)/CSO/R. Fortney
ONDQA/DNDQAI/Chemist/S. Bhamidipati
ONDQA/DNDQAI /Lead/K.Srinivasachar
ONDQA/DNDQAI RPM/T. Bouie
ONDQA/DNDQAI /Branch Chief/R. Sood

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

/s/

SHASTRI P BHAMIDIPATI
08/21/2013

RAMESH K SOOD
08/21/2013

PRODUCT QUALITY - BIOPHARMACEUTICS
FILING REVIEW

NDA Number	205029
Submission Date	12/4/12
Product name, generic name of the active	(b) (4) (epinephrine) Injection
Dosage form and strength	Solution for Injection – 1 mg per mL
Route of Administration	IV infusion
Applicant	Belcher Pharmaceuticals LLC
Clinical Division	Division of Cardiovascular and Renal Products
Type of Submission	Original NDA – 505(b)(2)
Biopharmaceutics Reviewer	Elsbeth Chikhale, Ph.D.
Biopharmaceutics Team Leader	Angelica Dorantes, Ph.D.

The following parameters for the ONDQA's Product Quality-Biopharmaceutics filing checklist are necessary in order to initiate a full biopharmaceutics review (i.e., complete enough to review but may have deficiencies).

ONDQA-BIOPHARMACEUTICS
A. INITIAL OVERVIEW OF THE NDA APPLICATION FOR FILING

	Parameter	Yes	No	Comment
1.	Does the application contain dissolution data?		x	NA
2.	Is the dissolution test part of the DP specifications?		x	NA
3.	Does the application contain the dissolution method development report?		x	NA
4.	Is there a validation package for the analytical method and dissolution methodology?		x	NA
5.	Does the application include a biowaiver request?		x	A BA/BE waiver request is not included in this submission. However, a biowaiver is not applicable for this product. The Applicant relies on published literature to support the efficacy and PK of the proposed drug product. The published information/data will be evaluated by the Clinical and ClinPharm Reviewers.
6.	Does the application include an IVIVC model?		x	
7.	Is information such as BCS classification mentioned, and supportive data provided?		x	
8.	Is information on mixing the product with foods or liquids included?		x	

B. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
9.	Is there any in *vivo* BA or BE information in the submission?	x		This is a literature based NDA. The PK information included in the published references will be evaluated by the Office of Clinical Pharmacology.
10.	**IS THE BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?**	x		
11.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			NA
12.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?		x	

PRODUCT QUALITY - BIOPHARMACEUTICS
FILING REVIEW

BIOPHARMACEUTICS INITIAL ASSESSMENT

SUMMARY:

The proposed drug product needs to be diluted [redacted] (b) (4) before I.V. administration by infusion. The proposed drug product is a currently marketed unapproved drug product. The proposed indication is to increase systemic arterial blood pressure in acute hypotensive states associated with septic shock.

The proposed drug product formulation is:

Material	Function	Quantity mg/ml	Quantity mg/1ml ampoule	Reference
Epinephrine Base	Drug Substance	[redacted] (b) (4)		USP
Sodium Chloride	Tonicity Agent			USP
[redacted] (b) (4)				USP
Hydrochloric Acid (b) (4)	pH Adjuster			USP
Water for Injection	[redacted] (b) (4)			USP
[redacted] (b) (4)				USP

This NDA contains published literature references in lieu of clinical studies. The Applicant is relying on published literature (for efficacy and PK) and safety information from Twinject (NDA 20800, approved 30 May 2003) as the listed drug. Twinject is an approved epinephrine (1 mg/mL) product, administered by subcutaneous or intramuscular injection, for use in the emergency treatment of severe allergic reactions (Type I). Several published articles submitted in this NDA provide human PK data. The review of these articles indicates that the epinephrine drug product formulations used in the published studies are very similar to the proposed drug product formulation. Whenever mentioned in the publication, the epinephrine base concentration is 1 mg/mL before dilution. In addition, NaCl is used in some published studies to adjust the tonicity and small amounts of sodium metabisulfate, ascorbic acid or chlorobutanol are used as antioxidants in some of the provided published studies.

Epinephrine base is insoluble in water but is soluble in HCl, which is used in the proposed drug product formulation. The solubility is also greatly increased by preparation of the hydrochloride salt, which was used in some of the publications. The current USP contains a monograph for epinephrine injection which states that epinephrine injection is a sterile solution of epinephrine in water for injection prepared with the aid of HCl or other suitable buffer. The USP states that the pH of the epinephrine solution should be between pH 2.2 and 5.0. The proposed drug

product meets the USP requirements for epinephrine injection. The proposed drug product and the drug products used in the published studies were all diluted (b) (4) before administration. The differences between the drug product formulations used in the published PK studies and the proposed drug product formulation are minor and are not expected to change the bioavailability of the drug after dilution and I.V. infusion. The evaluation and acceptability of the human PK data from the literature will be determined by the Clinical Pharmacology Reviewer from OCP. The Applicant has stated that dosing of the proposed drug product will be based on blood pressure measurements.

RECOMMENDATION:
From the ONDQA-Biopharmaceutics perspective, NDA 205029 is fileable. However, this NDA does not require further assessment by the ONDQA-Biopharmaceutics team.

{See appended electronic signature page}
Elsbeth Chikhale, Ph.D.
Biopharmaceutics Reviewer Date
Office of New Drug Quality Assessment

{See appended electronic signature page}
Angelica Dorantes, Ph.D.
Biopharmaceutics Team Leader Date
Office of New Drug Quality Assessment

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

/s/

ELSBETH G CHIKHALE
01/28/2013

ANGELICA DORANTES
01/28/2013

Initial Quality Assessment
Branch I

OND Division:	Division of Cardiovascular and Renal Products
NDA:	205029
Applicant:	Belcher Pharmaceuticals
Letter Date:	Dec 4, 2012
Stamp Date:	Dec 4, 2012
PDUFA Date:	Oct 4, 2013
Tradename:	(b) (4)
Established Name:	Epinephrine Injection
Dosage Form:	Sterile solution (injection), 1 mg/mL (1:1000)
Route of Administration:	IV infusion
Indication:	Increasing systemic arterial blood pressure in acute hypotensive states associated with septic shock
Assessed by:	Kasturi Srinivasachar
ONDQA Fileability:	Yes, pending receipt of complete establishment information

(b) (4)

Summary

This is an e-CTD 505(b)(2) NDA application for epinephrine injection. Epinephrine injection is a marketed unapproved drug and as agreed to at the pre-NDA meeting, a literature based review to support the proposed indication was considered sufficient in lieu of clinical studies. Only one meeting, a pre-IND teleconference, was held with the Applicant on Feb 3, 2012 where CMC issues were discussed. The issues were mainly concerned with the adequacy of the drug product release and stability specifications and the sponsor was advised that the USP requirements were considered the minimum standards that have to be met and that they should conform to current ICH recommendations for degradant specifications. They were also told that (b) (4)

Drug Substance

The drug substance, epinephrine, commonly known as adrenaline is a white to almost white crystalline powder which is practically insoluble in water, ethanol or methylene chloride but is soluble in HCl. It is an endogenous hormone and neurotransmitter. Epinephrine has one chiral center and is a pure enantiomer with the R configuration. It is manufactured by (b) (4) in (b) (4) by a (b) (4) and all CMC information is cross-referenced to DMF (b) (4) This DMF has been reviewed numerous times and the most recent review dated 27 Jan 2012 concludes that it is adequate to support an NDA (b) (4) for an injectable dosage form. Specifications for epinephrine are provided in the NDA based on the USP monograph with the addition of tests for residual solvents (b) (4) and bacterial endotoxins. Batch analysis data have been provided for 2 representative batches. It is stated that (b) (4) has assigned a retest period of (b) (4) based on stability data submitted to the DMF.

Drug Product

The drug product is an injectable sterile solution of epinephrine, 1mg/mL. 1mL of the solution is contained in a 2mL glass ampoule. The only excipients in the product are sodium chloride (tonicity agent), (b) (4) hydrochloric acid (for (b) (4) and pH adjustment) and water for injection. This is a preservative free formulation. The manufacturing process is carried out (b) (4) The manufacturing process is straightforward and consists of (b) (4)

The specification provided for the drug product is essentially the same as in USP for epinephrine injection. The only addition is a specification for the related substance, (b) (4) Batch analysis data have been submitted for 3 commercial batches manufactured between 2004 and 2007. Stability data have been provided for 4 full scale batches manufactured with (b) (4) 24 months' long term data are available for 3 batches and 48 months' data have been submitted for the 4th batch. In all cases 6 months of accelerated data have been provided. These studies were carried out without humidity control since the product is packaged in sealed ampoules. Appearance, assay, (b) (4) and particulate matter were tested at every time point whereas sterility and endotoxins were tested at

the beginning and end of the studies. The Applicant claims that a shelf-life of [redacted] is supported by these data.

Critical Review Issues

Drug Substance

- The DMF Annual Report dated May 30, 2012 has not been previously reviewed
- The specification provided in the NDA follow the USP monograph with the addition of a test for residual [redacted] The impurity specification is not in the ICH format e.g. specified, unspecified and total. Is this acceptable?
- CoAs from the supplier of epinephrine have not been submitted; instead only the results of testing of the batches received by the drug product manufacturer are provided. Is this adequate? The DMF holder's specification should be scrutinized to see if process impurities are specified.
- Is the bacterial endotoxin test a suitable substitute for the customary microbial limits test performed on drug substances for parenteral formulations?

Drug Product

- Since this is a parenteral dosage form, the major critical issue is sterility assurance of the product after manufacture and maintenance of sterility over the shelf-life. These aspects are expected to be covered by the microbiology reviewer.
- [redacted] is used in the formulation. Has this been adequately justified? In general, [redacted] It should be noted that the USP assay limits of [redacted] of label claim seems to allow for [redacted]
- The Master Batch Record for commercial production of drug product should be evaluated in accordance with 21CFR 314.54 for a 505(b)(2) application.
- Regarding the specification:
  - The specification for degradation products is not in ICH Q3B format (specified, unspecified and total). Is the proposed limit for [redacted] of NMT [redacted] justified?
  - Should USP Identification Test A be performed in addition to the HPLC retention time and UV tests proposed?
  - Is the USP pH limit of [redacted] appropriate given that 1) the in-process limit during manufacture is [redacted]) the stability data show that pH doesn't increase beyond [redacted]) stability of the formulation is better at lower pH as claimed in the Pharmaceutical Development Report?
- Regarding Stability
  - Since the stability data presented in the NDA were from batches manufactured [redacted] years back, is it known if the identical formulation and manufacturing process were used as proposed for marketing [redacted]? Otherwise, these cannot be considered primary stability data.
  - Is the proposed shelf-life of [redacted] acceptable based on the data submitted?

Comments and Recommendations

The application is fileable -- see attached Filing Check List for pending information. Facilities will be entered into EES as soon as the Applicant amends the NDA with a complete list of facilities for both drug substance and drug product; the reviewer should confirm the completeness and accuracy of the entries. A microbiology reviewer has been assigned. Methods Validation by DPA is not deemed necessary based on a preliminary review since the 7 criteria in IQP 5105 are not met; however, the reviewer may choose to initiate MV if the in-depth review reveals concerns with any of the analytical methods. A categorical exclusion from environmental assessment has been requested. A single CMC reviewer is recommended since the drug substance information is in a DMF which has been previously reviewed and much of the drug product information pertains to sterility assurance which will be reviewed by the microbiologist.

Kasturi Srinivasachar — Dec. 19, 2012
CMC Lead — Date

Ramesh Sood — Dec. 19, 2012
Branch Chief — Date

PRODUCT QUALITY -- CMC and BIOPHARMACEUTICS
FILING REVIEW FOR NDA

NDA Number:	**NDA Type: 7**	**Established/Proper Name:**
205029	**Original NDA, N-000**	**Epinephrine Injection/** (b) (4)
Applicant:	**Letter Date: Dec 4, 2012**	**PDUFA Goal: Oct 4, 2013**
Belcher Pharmaceuticals	**Stamp Date: Dec 4, 2012**	

CMC Reviewer: Shastri Bhamidipati

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	**Yes**	**No**	**Comment**
1.	Is the CMC section organized adequately?	X		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X		
3.	Are all the pages in the CMC section legible?	X		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		

B. FACILITIES*				
	Parameter	**Yes**	**No**	**Comment**
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?		X	Requested from Applicant
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? **This question is not applicable for synthesized API.**			NA

7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)		X	Requested
8.	Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		
9.	Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)		X	Requested

10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?		X	Only 1 facility listed. Complete list of facilities requested

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
	Parameter	**Yes**	**No**	**Comment**
11.	Has an environmental assessment report or categorical exclusion been provided?	X		Categorical exclusion requested

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	**Yes**	**No**	**Comment**
12.	Does the section contain a description of the DS manufacturing process?	X		Information in DMF (b) (4)
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		Information in DMF (b) (4)
14.	Does the section contain information regarding the characterization of the DS?	X		Information in DMF (b) (4)
15.	Does the section contain controls for the DS?	X		
16.	Has stability data and analysis been provided for the drug substance?	X		Information in DMF (b) (4)
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		X	
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	

E. DRUG PRODUCT (DP)				
	Parameter	**Yes**	**No**	**Comment**
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X		
21.	Is there a batch production record and a proposed master batch record?	X		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?		X	
23.	Have any Comparability Protocols been requested?		X	
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	X		
25.	Does the section contain controls of the final drug product?	X		
26.	Has stability data and analysis been provided to support the requested expiration date?	X		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		X	
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	

F. METHODS VALIDATION (MV)				
	Parameter	**Yes**	**No**	**Comment**
29.	Is there a methods validation package?	X		

G. MICROBIOLOGY				
	Parameter	**Yes**	**No**	**Comment**
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?		X	Included in Drug Product Manufacturing Section

H. MASTER FILES (DMF/MAF)				
	Parameter	**Yes**	**No**	**Comment**
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X		DMF (b) (4) for drug substance

I. LABELING				
	Parameter	**Yes**	**No**	**Comment**
32.	Has the draft package insert been provided?	X		
33.	Have the immediate container and carton labels been provided?	X		

J. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
34.	**IS THE PRODUCT QUALITY AND BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?**	X		Fileable for Product Quality pending receipt of complete establishment information A separate filing review will be submitted for Biopharmaceutics
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			NA
36.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			See Biopharmaceutics Filing Review
37.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?		X	

APPEARS THIS WAY ON ORIGINAL

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

/s/

KASTURI SRINIVASACHAR
12/19/2012

RAMESH K SOOD
12/26/2012