

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

201739Orig1s000

CHEMISTRY REVIEW(S)

NDA 201-739

Epinephrine Autoinjector 0.3 mg and 0.15 mg

Summary of the Basis for the Recommended Action from ONDQA Chemistry, Manufacturing, and Controls

Applicant: Intelliject, Inc.
111 Virginia Street, Suite 405
Richmond, VA 23219

Indication: For allergic reactions (type I) including anaphylaxis. The drug product is intended for immediate administration in patients who are at increased risk for, or have a history of anaphylactic reaction.

Presentation: Carton containing epinephrine Auto-Injector 0.15 mg (epinephrine injection USP (1:1000)) and epinephrine Auto- Injector 0.3 mg (epinephrine injection USP (1:1000)) are collectively referred as EAI or individually as EAI 0.15 mg and EAI 0.3 mg.

EER Status: Recommendations:	Acceptable
Consults: EA -	Categorical exclusion provided
CDRH-	Acceptable
Statistics -	N/A
Methods Validation -	Not recommended
DMETS-	Acceptable
Biopharm-	Acceptable
Microbiology -	Satisfactory
Pharm/toxicology -	Satisfactory

Original Submission: 26-Jun-2001
Resubmission: 21-Dec-2010
Resubmission: 07-May-2012

Post-Approval CMC Agreements: None

Background:

This is a resubmission of an NDA for which a Tentative approval was granted by the Agency on July 29, 2011. The main issue with the approval of this application was the 505b(2) patent certification. This drug product is a drug-device combination with electronics that guide the patient with visual and audio prompts on how to use the product. The proprietary name has not been finalized as of this writing and is planned to be finalized.

Reference is also made to the two CMC reviews (6/24/2011 and 7/1/2011) and CDTL memo (7/8/2011) in DARRTS which indicate that the GMP status for the manufacturing facilities is pending. Although the Division Director Memo indicates that all sites have an acceptable recommendation.

This memo is to indicate a final ONDQA recommendation of Approval for the NDA after the final recommendation for the manufacturing, packaging and testing facilities were found acceptable by the Office of Compliance on July 18th, 2011.

Conclusion: The drug product is satisfactory.

CMC issues that are still pending: None

Overall Conclusion: The NDA is recommended for **approval** from CMC standpoint.

Prasad Peri, Ph.D.
Branch Chief,
DPA III/ONDQA

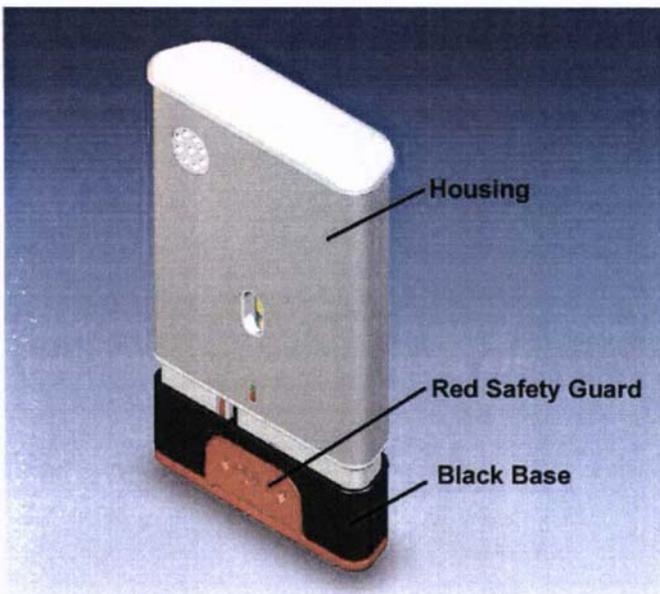


Figure 4: Auto-Injector Components Review

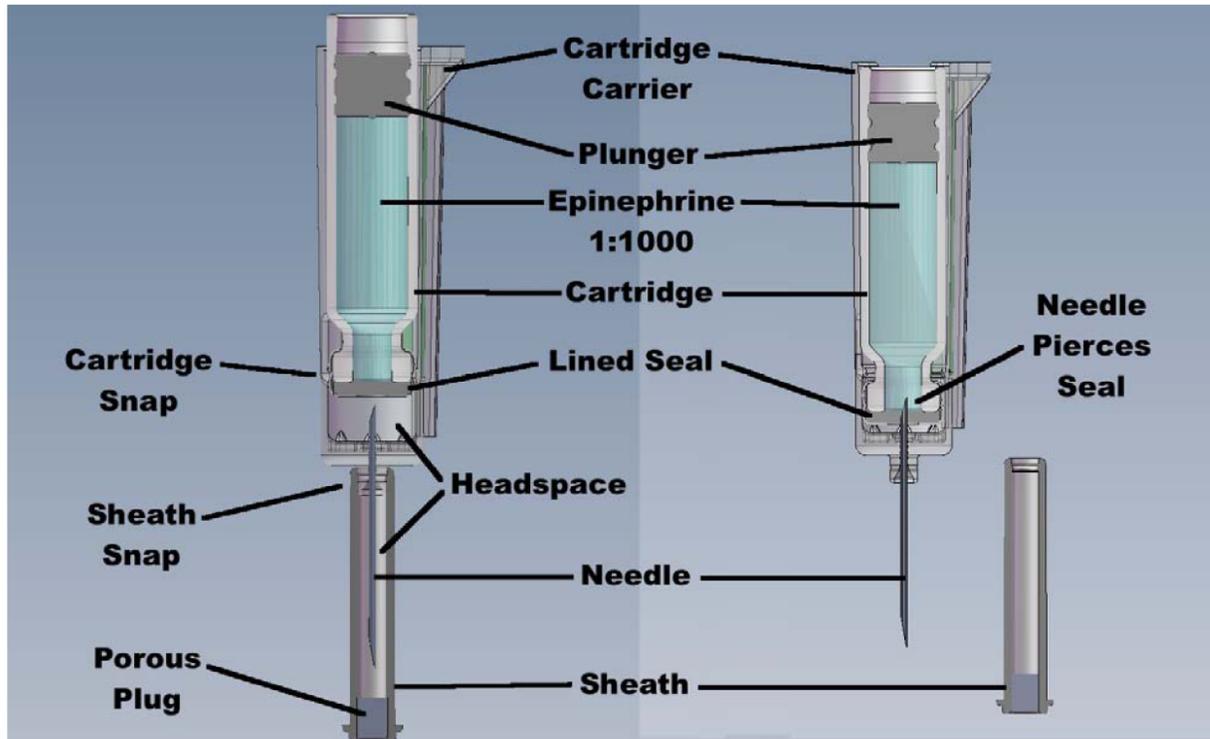


Figure 3.2.P.2.4-4: Components of EAI that form the Drug Fluid Flow Path before (left) and after (right) activation.

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/s/

PRASAD PERI

07/19/2012

EES acceptable previously but not documented

NDA 201-739

e-cue (?) (Epinephrine) Autoinjector 0.3 mg and 0.15 mg

Summary of the Basis for the Recommended Action from Chemistry, Manufacturing, and Controls

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EER Status: Recommendations:	Incomplete
Consults: EA -	Categorical exclusion provided
CDRH-	N/A
Statistics -	N/A
Methods Validation -	Not recommended
DMETS-	Acceptable
Biopharm-	Acceptable
Microbiology -	Satisfactory
Pharm/toxicology -	Satisfactory

Original Submission: 26-Jun-2001
Resubmission: 21-Dec-2010

Post-Approval CMC Agreements: None

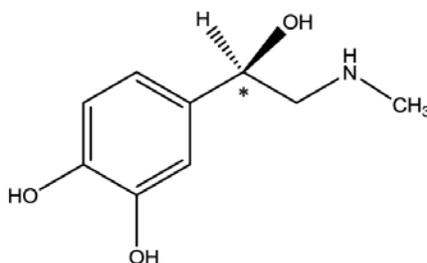
Background:

This is a standard NDA with a 10 month clock. The NDA is in electronic format with labeling provided in SPL format. This drug product is a drug-device combination with electronics that guide the patient with visual and audio prompts on how to use the product. The proprietary name has not been finalized as of this writing.

Drug Substance:

Drug substance epinephrine is a white to off-white crystalline powder. It darkens on exposure to light and air. It is very slightly soluble in water and ethanol. With acid it forms salts that are readily soluble in water. The drug substance is manufactured by (b) (4) and all CMC information is referenced to DMF (b) (4). The DMF was found acceptable. An overall Office of Compliance (OC) recommendation for this application is not provided as of this writing.

Specifications which are provided in the NDA for the drug substance epinephrine mostly follow the USP monograph. Additional specifications for related substances meet the ICH Q3A guideline. Note that the USP monograph indicates that this is R-epinephrine although there is no chiral HPLC method that confirms the enantiomeric excess (EE). Specific optical rotation may control the EE to a certain extent.



The drug substance is controlled by testing for appearance, identification (titrimetric), optical rotation, loss on drying, residue on ignition, chromatographic purity, total impurities, assay and residual solvents.

Conclusion: The drug substance is satisfactory, pending acceptable an OC recommendation.

Drug Product:

Epinephrine Auto-Injector 0.15 mg (epinephrine injection USP (1:1000)) and Epinephrine Auto-Injector 0.3 mg (epinephrine injection USP (1:1000)) are collectively referred as EAI or individually as EAI 0.15 mg and EAI 0.3 mg. EAI is a drug-device combination product. The combination product is a prefilled epinephrine drug delivery system. The formulation for the epinephrine injection USP 1:1000 is based on the EpiPen® 0.3 mg Auto-Injector device which is the listed drug (LD). The excipients include sodium bisulfite, sodium chloride, and hydrochloric acid and water for injection.

The device constituent component of EAI is a gas powered, needle-based system that delivers the prescribed dose of epinephrine into the user. When activated, the EAI 0.3 mg will inject a single dose of 0.3 mL (0.3 mg of epinephrine) of epinephrine injection and EAI 0.15 mg will inject a single dose of 0.15 mL (0.15 mg of epinephrine) of epinephrine injection. Epinephrine Auto-injector includes battery operated, electronic voice instructions, together with red/green blinking LED lights, and audible beeps as

additional features to reinforce the written directions for use. The device information is referenced to a Device Master File MAF (b) (4) which was evaluated and found acceptable by CDRH reviewers.

The epinephrine solution is manufactured and filled into cartridges at (b) (4), is responsible for assembling the needle with the drug cartridge. The device components manufacture and final drug product assembly, packaging and labeling are performed at (b) (4). Intelliject Inc. is responsible for the final product release for distribution. A final overall recommendation has not been provided by the Office of Compliance as of this writing.

The drug product has been evaluated for impurities, degradants, compatibility of the formulation with the container closure system, and leachables. The pharm/tox review team has found the proposed acceptance criteria for impurities and leachables acceptable from a safety perspective.

A biowaiver was requested for the EAI 0.15 strength and was granted by the biopharm review team.

The drug product is controlled by testing for the following attributes: appearance, color and clarity of solution, identity, assay, impurities, bisulfite content, pH, particulate matter, total acidity, bacterial endotoxins, sterility, residual solvents, activation force, volume dispensed, dispensing time, and needle length exposed.

Stability data for the 18 month long-term storage condition (25°C/60% RH), 12 month intermediate storage condition (30°C/65% RH) and 6 month accelerated storage condition (40°C/75% RH) are provided in the submission for the drug constituent component. Stability data for the device performance test parameters are provided in MAF (b) (4). The stability data support the **proposed expiry of earlier of 20 months from the manufacturing date for the drug constituent component of EAI and 18 months from the date of final assembly, packaging and labeling of EAI.**

Conclusion: The drug product is satisfactory pending an acceptable OC recommendation.
CMC issues that are still pending: Acceptable OC recommendation.

Overall Conclusion: The NDA is recommended for **approval** from CMC standpoint pending an acceptable overall acceptable recommendation from the Office of Compliance.

Prasad Peri, Ph.D.
Branch Chief,
DPA III/ONDQA

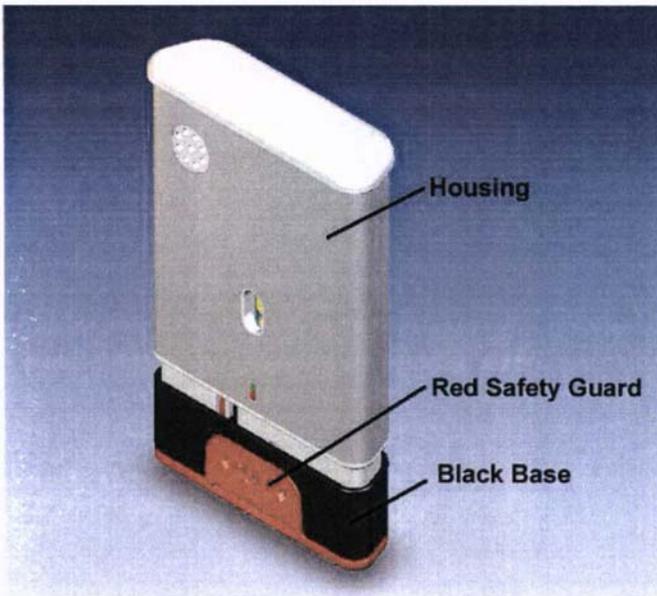


Figure 4: Auto-Injector Components Review

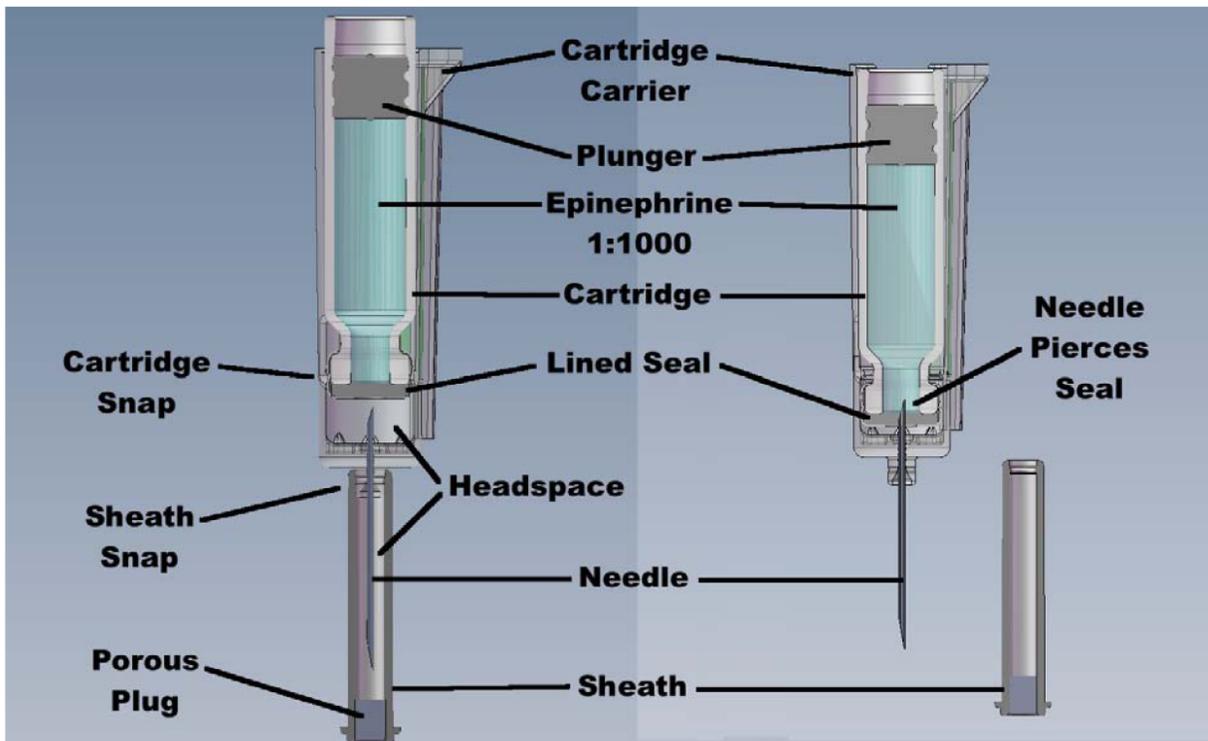


Figure 3.2.P.2.4-4: Components of EAI that form the Drug Fluid Flow Path before (left) and after (right) activation.

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/s/

PRASAD PERI
07/01/2011

NDA 201739

Drug Name (Epinephrine) Auto-Injector

Intelliject, Inc.

Ying Wang, PhD
Review Chemist

Office of New Drug Quality Assessment
Division III, Branch VIII

CMC REVIEW OF NDA 201739
For the Division of Pulmonary, Allergy, and Rheumatology
Products (HFD-570)

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CMC Review Data Sheet

CMC Review Data Sheet

1. NDA 201739
2. REVIEW #: 1
3. REVIEW DATE: 23-June-2011
4. REVIEWER: Ying Wang, PhD
5. PREVIOUS DOCUMENTS: N/A
6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Original Submission
Correspondence (C)
Amendment (BC)

Document Date

Sept. 29, 2010
March 11, 2011

7. NAME & ADDRESS OF APPLICANT:

Name: Intelliject, Inc
Address: 111 Virginia Street
Representative: Ronald D. Gunn
Telephone: 804-545-6376

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: **To be determined**
- b) Non-Proprietary Name: Epinephrine Injection USP 1:1000
- c) Code Name/# (ONDQA only): N/A
- d) Chem. Type/Submission Priority (ONDQA only):
 - Chem. Type: 5
 - Submission Priority: Standard

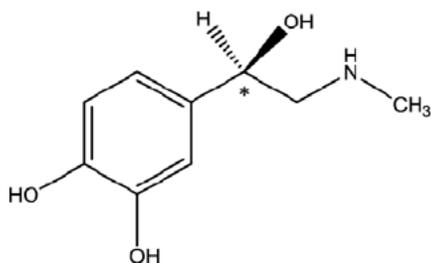
9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: Sympathomimetic

11. DOSAGE FORM: Auto-injector

CMC Review Data Sheet

12. STRENGTH/POTENCY: 0.15 mg and 0.3 mg
13. ROUTE OF ADMINISTRATION: IM or SC
14. Rx/OTC DISPENSED: Rx OTC
15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#):
 SPOTS product – Form Completed
 Not a SPOTS product
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
1,2-Benzenediol, 4-[1-hydroxy-2-(methylamino)ethyl]-, (R) (USP)
(-)-3,4-Dihydroxy- α -[(methylamino)methyl]benzyl alcohol (CAS)
R-1-(3,4-dihydroxyphenyl)-2-methylaminoethanol (BP)

**Molecular Formula** $C_9H_{13}NO_3$ **Relative Molecular Mass**

183.20

CMC Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	1	Adequate	Apr 5, 2011	DMF update reviewed
	III		4	N/A		See container closure review in NDA	
	III		1	Adequate	Dec. 15, 2008	Reviewed by Steven Donald from microbiology	
	III		4	N/A		See container closure review in NDA	
			1	Adequate	March 1, 2011 & May 19, 2011	Reviewed by CDRH Nikhil Thakur	

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: N/A

CMC Review Data Sheet

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Pending		
Pharm/Tox	N/A		
Biopharm	Approve	May 26, 2011	Sandra Suarez
LNC	N/A		
Methods Validation	N/A, according to the current ONDQA policy		
DMEPA	See review for comments to the applicant	April 28, 2011	Colleen Brennan
EA	Categorical exclusion acceptable (see NDA review)		Ying Wang
Microbiology	Approve	May 13, 2011	Steve Fong
CDRH	Comparability Protocol (CP) Review. Based on the review comments applicant withdrew the CP	April 7, 2011	Isabel Tejero

Executive Summary Section

The CMC Review for NDA 201739

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA is recommended for APPROVAL from the chemistry, manufacturing and control (CMC) perspective pending overall ACCEPTABLE recommendation from the Office of Compliance.

Epinephrine Auto-Injector (EAI) is stored at 25°C (77 °C); excursions permitted to 15-30°C (59–86°F). Expiry of earlier of 20 months from the manufacturing date for the drug constituent component of EAI and 18 months from the date of final assembly, packaging and labeling of EAI is proposed and granted.

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

N/A

II. Summary of CMC Assessments

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

(1) Drug Substance

Drug substance epinephrine is a white to off-white crystalline powder. It darkens on exposure to light and air. It is very slightly soluble in water and ethanol. With acid it forms salts that are readily soluble in water. Drug substance information is referenced in DMF (b) (4) for which (b) (4) is the holder. Specifications which are provide in the NDA for drug substance epinephrine mostly follow USP monograph. Additional specifications for related substance meet ICH Q3A guideline.

(2) Drug Product

Epinephrine Auto-Injector 0.15 mg (epinephrine injection USP (1:1000) and Epinephrine Auto-Injector 0.3 mg (epinephrine injection USP 1:1000) are collectively referred as EAI or individually as EAI 0.15 mg and EAI 0.3 mg. EAI is a drug-device combination product. The combination product is a prefilled epinephrine drug delivery system. The formulation for the epinephrine injection USP 1:1000 is based on the EpiPen® 0.3 mg Auto-Injector device which is the listed drug (LD).

Executive Summary Section

The device constituent component of EAI is a gas powered, needle-based system that delivers the prescribed dose of epinephrine into the user. When activated, the EAI 0.3 mg will inject a single dose of 0.3 mL (0.3 mg of epinephrine) of Epinephrine Injection and EAI 0.15 mg will inject a single dose of 0.15 mL (0.15 mg of epinephrine) of Epinephrine Injection. Epinephrine Auto-injector includes battery operated, electronic voice instructions, together with red/green blinking LED lights, and audible beeps as additional features to reinforce the written directions for use.

Stability data for 18 month long term storage condition (25°C/60% RH), 12 month intermediate storage condition (30°C/65% RH) and 6 month accelerated storage condition (40°C/75% RH) are provided in the submission for the drug constituent component. Stability data for the device performance test parameters are provided in MAF (b) (4). The stability data support the proposed expiry of earlier of 20 months from the manufacturing date for the drug constituent component of EAI and 18 months from the date of final assembly, packaging and labeling of EAI.

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

Epinephrine Auto- Injector is indicated for allergic reactions (type I) including anaphylaxis and is intended for immediate administration in patients who are at increased risk for, or have a history of anaphylactic reaction. Epinephrine Auto- Injector is be injected intramuscularly or subcutaneously into the anterolateral aspect of the thigh, through clothing if necessary. Each device is a single-use injection. There are two strengths of the drug product. Epinephrine 0.3 mg is for patients weigh 30 kg or more. Epinephrine 0.15 mg is for patients weigh 15 to 30 kg.

C. Basis for Approvability or Not-Approval Recommendation

This NDA is a 505(b)(2) application. The drug constituent component is very similar to the approved drug EpiPen which is the reference list drug. The aseptic manufacturing process for the drug constituent component is considered acceptable by microbiology reviewer. The proposed acceptance criteria for the drug product are similar to that of the list drug EpiPen. The device constituent component is deemed adequate by CDRH reviewer.

(b) (4)
Upon consult review by CDRH it was determined that assembly line change needs to be inspected prior to approval. (b) (4)

This was communicated to the applicant via telecom on May 19, 2011. The applicant withdrew the comparability protocol on May 26, 2011.

The labeling review and negotiation with the applicant is still in process and has not been finalized, so is the proprietary name of the drug.

Executive Summary Section

Prior approval inspection is still on going and the Office of Compliance has not issued an overall recommendation for this NDA as of this writing.

III. Administrative**A. Reviewer's Signature:**

(See appended electronic signature page)

Ying Wang, PhD

B. Endorsement Block:

(See appended electronic signature page)

Prasad Peri, PhD, Branch Chief, Branch VIII, ONDQA

C. CC Block: entered electronically in DFS

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/s/

YING WANG
06/23/2011

PRASAD PERI
06/24/2011
I concur