

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**201739Orig1s000**

**PHARMACOLOGY REVIEW(S)**

## Division of Pulmonary, Allergy, and Rheumatology Products Pharmacology/Toxicology Consultation

**NDA:** 201739, Supporting Document 60

**Sponsor:** Intelliject, Inc.

**Drug:** Epinephrine Auto-Injector 0.15 mg (epinephrine injection USP 1:1000) and Epinephrine Auto-Injector 0.3 mg (epinephrine injection USP 1:1000); Auvi-Q®

**Route of Administration:** Intramuscular and subcutaneous

**Reviewer Name:** Jane Sohn, Ph.D.

**Team Leader:** Tim Robison, Ph.D., DABT

**Date of submission:** 5/7/2012

**Date of consult:** 10/3/12

**Review Completion Date:** 10/4/12

**Subject:** Sponsor's request to increase the specification limit of [REDACTED] (b) (4)

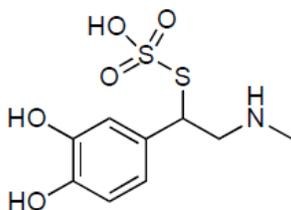
### Recommendations

The requested specification limit of [REDACTED] (b) (4) % for [REDACTED] (b) (4) exceeds the qualification threshold per the ICH Q3B(R2) Guidance. The sponsor should submit their justification for the safety of the higher level of [REDACTED] (b) (4). Justification may be provided based on either (1) comparison of levels of [REDACTED] (b) (4) in approved products towards the end of shelf-life, or (2) completion of toxicology studies (per the ICH Q3B(R2) Guidance).

Toxicology studies recommended are *in vitro* bacterial mutation and chromosomal aberration genetic toxicity assays as well as a 2-week toxicology study in one species with the impurity. Toxicology studies may be conducted using an [REDACTED] (b) (4) enriched (spiked) epinephrine drug product to qualify the impurity.

### Background

This review evaluates the safety of the the sponsor's request to increase the specification limit for [REDACTED] (b) (4) in Auvi-Q®, a epinephrine auto-injector (EAI) that delivers either 0.15 mg or 0.3 mg epinephrine (USP 1:1000) per injection. The consult was requested by Ms. Youbang Liu of ONDQA on October 3, 2012 via email (attached). The CMC reviewer is Dr. Youbang Liu.



Molecular Weight: 217.33 g/mol

Generic chemical name: S-1-(3,4-dihydroxyphenyl)-2-(methylamino)ethyl Ohydrogen sulfthionate

Auvi-Q® is indicated for the emergency treatment of allergic reactions (Type I) including anaphylaxis. The maximum dose delivered is 0.3 mg epinephrine per injection, and the maximum daily recommended dose is 2 injections, which translates to 0.6 mg epinephrine (per discussion with Medical Officer Dr. Peter Starke for self-administered epinephrine products.)

### **Safety Assessment**

The sponsor has proposed to increase the specification for (b) (4) to (b) (4)%. The increase in specification translates into an increase in maximum daily exposure to (b) (4)/day. The proposed level exceeds the qualification threshold of 1% (6 mcg/day) or 5.0 mcg/day (whichever is lower), per ICH Q3B(R2). The sponsor conducted a computational toxicology assessment using Multiple Computer Automated Structure Evaluator (MCASE) to evaluate the potential genotoxicity and carcinogenicity, but this is not adequate as the proposed level exceeds the qualification threshold.

Per the ICH Q3B(R2), the sponsor should submit their justification for the safety of the higher level of (b) (4). Justification may be provided based on comparison of levels of (b) (4) in approved products, or completion of toxicology studies (outlined in the Recommendations above).

**Consult Request via email****From:** Wang, Ying**Sent:** Wednesday, October 03, 2012 12:07 PM**To:** Robison, Timothy W**Cc:** Sohn, Jane; Peri, Prasad; Schroeder, Alan C; Liu, Youbang**Subject:** Quick P/T Question - NDA 201739 -S1 -Auvi-Q Epinephrine

Tim,

We have a quick P/T question that we like to get a quick answer. One of the unidentified impurities has exceeded the original proposed (b) (4) limit during stability. The applicant has provided the following identification data and justification to propose to increase the limit to (b) (4)%. Please let us know if this is acceptable from P/T perspective. This NDA was recently approved in Aug 2012. We need to get this supplement review out soon and would appreciate it if you can get back to us by Oct. 10.

If you need a formal consult, Youband can send you one. Thanks!

The updated drug stability information is consistent with previously reported results with the exception of recent results for a previously unidentified impurity (b) (4) that exceeded the (b) (4) specification level at the 18 and 21-month long-term storage (i.e., 25 ± 2 °C/60 ± 5% RH) stability sampling time points in Lot 30003 and Lot 10007, respectively. Both of these lots were manufactured according to the Original Process.

Subsequent to these studies the structure (see Table 3.2.P.5.5-1) and correct (b) (4) (see Section 3.2.P.5.6) for unknown impurity (b) (4) were identified. Using the correct (b) (4) (i.e., (b) (4)) the quantity of impurity (b) (4) (now referred to as (b) (4)) in EAI registration batches after 18 months at long-term storage conditions ranges from (b) (4)%.

(b) (4) was qualified according to ICH Q3B(R2) *Impurities in New Drug Products* (see Section 3.2.P.5.6). Based upon a daily dose of 0.3 mg and a limit of NMT (b) (4)% for (b) (4), exposure of (b) (4) per dose would be (b) (4). The absolute amount exceeded the identification threshold but not the qualification threshold according to ICH Q3B(R2) *Impurities in New Drug Products*. The proposed specification by percent (b) (4)%, however, exceeded the qualification threshold ( $\geq 1.0\%$ ). The impurity, (b) (4), was qualified by performing a computational assessment and evaluation of potential genotoxicity and carcinogenicity using Multiple Computer Automated Structure Evaluator (MCASE; MultiCASE Study # 1522-10442 report on file). The assessment employed three regulatory relevant sets for assessing carcinogenic and genotoxic potential and two surrogate tests for rodent carcinogenicity, a Research Cooperative Agreement with FDA ICSAS method expert opinion, and all available Quantitative Structure-Activity Relationship evidence. It was concluded that (b) (4) is negative in the carcinogenicity and genetic toxicity test assessments.

Ying Wang, Ph.D.  
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/s/  
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JANE J SOHN  
10/04/2012

TIMOTHY W ROBISON  
10/04/2012  
I concur

INTEROFFICE MEMO

TO: NDA 201,739  
Sequence number/date/type of submission:  
001/September 29, 2010/Original NDA

FROM: Molly E. Topper, Ph.D.  
Pharmacology/Toxicology Supervisor  
Division of Pulmonary, Allergy and Rheumatology Products

DATE: June 24, 2011

Intelliject, Inc. submitted NDA 201739 under the 505(b)(2) pathway on September 29, 2010 for a patient-actuated epinephrine auto-injector system (EAI) for the emergency treatment of allergic reactions (Type 1). EAI is a new drug-device combination product for the intramuscular or subcutaneous delivery of epinephrine that delivers one dose of either 0.15 mg or 0.3 mg epinephrine. The dose selection is based on body weights with the 0.3 mg dose for patients weighing 30 kg or more and the lower 0.15 mg dose for patients 15-30 kg. The Agency previously agreed that referencing the non-clinical information in the approved labeling for EpiPen<sup>®</sup> would be sufficient to support filing of NDA 201739. This drug-device product differs from the EpiPen<sup>®</sup> by using a self-actuated electronic injector with visual prompts and interactive voice which is proposed to decrease dosing errors. No nonclinical studies, nor any publically available literature, were submitted in support of this NDA.

The nonclinical review of the NDA application included review of impurities, leachables and extractables in collaboration with the review chemist and review of the proposed nonclinical sections of the labeling. The impurities, leachables and extractables were within acceptable ranges. Revisions to the sponsor's proposed nonclinical sections of the labeling were recommended to align with the most recently approved EpiPen label (April 2009) and to align with 21 CFR Part 201.57 labeling recommendations. There are no outstanding toxicology issues.

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Molly E. Topper, Ph.D.  
Pharmacology/Toxicology Supervisor

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/s/  
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MOLLY E TOPPER  
06/24/2011

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

**PHARMACOLOGY/TOXICOLOGY NDA  
MEMO TO FILE**

RE: Three specified impurities in the drug product

Application number: NDA 201739  
Supporting document/s: SDN 0000; SDN 0018  
Applicant's letter date: September 29, 2010; March 11, 2011  
CDER stamp date: September 29, 2010; March 11, 2011  
Product: EAI (Epinephrine Auto-Injector 0.15 mg (epinephrine injection USP 1:1000, EAI) and Epinephrine Auto-Injector 0.3 mg (epinephrine injection USP 1:1000))  
Indication: Emergency treatment of allergic reactions (Type 1)  
Applicant: Intelliject, Inc.  
Review Division: Division of Pulmonary, Allergy and Rheumatology  
Drug Products  
Reviewer: Kathleen Young, Ph.D.  
Supervisor/Team Leader: Molly E. Topper, Ph.D.  
Division Director: Badrul Chowdhury, M.D., Ph.D.  
Project Manager: Angela Ramsey

The Sponsor provided specifications for the three impurities in the proposed drug product EAI (Epinephrine Auto-Injector 0.15 mg (epinephrine injection USP 1:1000, EAI) and Epinephrine Auto-Injector 0.3 mg (epinephrine injection USP 1:1000)), including the recently identified degradation product (b) (4).

In the original NDA 201739 submission (SDN 0000, September 29, 2010), the potential degradation products were identified as (b) (4) and an unidentified (b) (4) (see table below, from the Sponsor).

**Table 3.2.P.5.5-1: Potential Degradation Products in Epinephrine Injection**

Description	Chemical Structure and Chemical Name	Source/Method of Detection
(b) (4)		

<sup>a</sup> Impurity observed at higher levels in LD (see (b) (4)). Further work is ongoing to identify the structure.

This amendment (NDA 201,739, SDN 0018, March 11, 2011) provided identification of the previously unidentified impurity as (b) (4) (see figure below), found in both the reference listed drug (LD) and the proposed drug.



The specification levels were listed with those for the referenced product EpiPen<sup>®</sup> and EpiPen<sup>®</sup> Jr epinephrine auto-injector (NDA 19-430). The data for the listed drug (LD, referenced product) were obtained by stability assays on the marketed product. The specifications for the three identified degradation products are presented in the following table:

<b>Specified Impurity</b>	(b) (4)
<b>Release Spec</b>	
<b>Actual Batch at release</b>	
<b>18 month Stability Spec</b>	
<b>Actual Batch at 18 month</b>	
<b>LD at Release</b>	
<b>LD at stability (12 month)</b>	
<b>LD at stability (18 month)</b>	

The specification for (b) (4) in the proposed drug product, EAI, was set at the level of NMT (b) (4) at release and in the 18-month stability assay, and found in the actual batch at 18 months at (b) (4). (b) (4) was found at higher levels in the referenced drug product, at (b) (4) in the 18 months stability assay. At the NMT (b) (4) level, the maximum exposure to (b) (4) in EAI will be (b) (4) at the highest proposed dose of 0.3 mg. This level is below the identification threshold of (b) (4) (b) (4) for a maximum daily dose of <1 mg (refer to ICH Q3B (R2) Guidance).

(b) (4) specification in the proposed drug product is NMT (b) (4) at release and NMT (b) (4) at 18 months stability testing, and found in the stability assays to be (b) (4) at release and (b) (4) at 18 months, below the levels found for the referenced drug of (b) (4) at release and up to (b) (4) at 18 months stability testing. At these levels, the maximum exposure to (b) (4) in the proposed drug product will be (b) (4) in the proposed high dose of 0.3 mg EAI.

(b) (4) was found in the 18-month stability assay at (b) (4) in the referenced drug product, EpiPen. The specification level is NMT (b) (4) in the proposed product, EAI; however stability testing at 18 months showed (b) (4)

(b) (4) is well below the Q3B (R2) Guidance identification threshold of (b) (4) for a maximum daily dose of <1 mg. At this level, the maximum (b) (4) clinical dose is (b) (4)

### **CONCLUSIONS**

The levels of the identified degradation products in EAI, (b) (4) were found at levels within the ICH Q3B (R2) Guidance limits for the highest proposed dose (0.3 mg) after 12 months and 18 months on stability. Additionally, these two degradants were observed at lower levels in the proposed EAI product than the reference EpiPen product after 12- and 18- months stability. (b) (4) was observed (b) (4)%, which exceeds recommendations per ICH Q3B (R2) Guidance. However, (b) (4) was found (b) (4)% in the referenced and approved product EpiPen. Based on these findings, the three degradation products in the proposed drug product are acceptable from a pharmacology and toxicology perspective and require no further nonclinical qualification studies.

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/s/  
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KATHLEEN A YOUNG  
06/24/2011

MOLLY E TOPPER  
06/24/2011  
I concur.

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

**PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION**

Application number: NDA 201739  
Supporting document/s: SDN 0000  
Applicant's letter date: September 29, 2010  
CDER stamp date: September 29, 2010  
Product: EAI (Epinephrine Auto-Injector 0.15 mg (epinephrine injection USP 1:1000, EAI) and Epinephrine Auto-Injector 0.3 mg (epinephrine injection USP 1:1000))  
Indication: Emergency treatment of allergic reactions (Type 1)  
Applicant: Intelliject, Inc.  
Review Division: Division of Pulmonary, Allergy and Rheumatology Drug Products  
Reviewer: Kathleen Young, Ph.D.  
Supervisor/Team Leader: Molly E. Topper, Ph.D.  
Division Director: Badrul Chowdhury, M.D., Ph.D.  
Project Manager: Angela Ramsey

**Disclaimer**

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 201739 are owned by Intelliject or are data for which Intelliject has obtained a written right of reference. Any information or data necessary for approval of NDA 201739 that Intelliject does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 201739.

# 1 Executive Summary

## 1.1 Introduction

This 505(b)(2) application is for Epinephrine Auto-Injector (EAI), a patient-actuated auto-injection system (drug-device combination product) for the intramuscular or subcutaneous delivery of epinephrine in the emergency treatment of allergic reactions including anaphylaxis. Epinephrine is an alpha and beta adrenergic receptor agonist that inhibits vasodilation and increases vascular permeability via alpha adrenergic activity, and relaxes smooth muscle in the bronchial, gastrointestinal and genitourinary tracts. EAI is a patient actuated autoinjection system that delivers one dose of either 0.15 mg or 0.3 mg epinephrine for the emergency treatment of allergic reactions (Type 1). The dose selection is based on body weights with the 0.3 mg dose for patients weighing 30 kg or more and the lower 0.15 mg dose for patients 15-30 kg.

Intelliject, Inc. is cross referencing the approved product label for NDA 19-430 (EpiPen<sup>®</sup> and EpiPen<sup>®</sup> Jr epinephrine auto-injector, Meridian Medical Technologies, approved on December 22, 1987) for the nonclinical information in support of the proposed label. No nonclinical studies were conducted in support of this NDA. Additionally, the Sponsor did not provide nonclinical literature in their submission. This is acceptable for this submission from a pharmacology and toxicology perspective. This drug-device product differs from the EpiPen<sup>®</sup> by using a self-actuated electronic injector with visual prompts and interactive voice to decrease dosing errors. The Agency agreed that referencing the non-clinical information in the approved labeling for EpiPen<sup>®</sup> would be sufficient to support filing of NDA 201739 (see Responses to Questions in Meeting Package, March 9, 2007).

## 1.3 Recommendations

The Agency agreed that referencing the non-clinical information in the approved labeling for EpiPen<sup>®</sup> would be sufficient to support filing of NDA 201739 (see Responses to Questions in Meeting Package, March 9, 2007). No additional non-clinical studies are needed.

### 1.3.1 Approvability

NDA 201739 can be approved from a pharmacology and toxicology perspective, pending the suggested revisions to the proposed label (see below).

**1.3.2 Additional Non Clinical Recommendations:** Recommended changes to the proposed product label are presented below.

### 1.3.3 Labeling:

The following changes to the proposed labeling for sections 8.1, 8.3, 10, and 13 are presented below with changes presented as ~~strikethroughs~~ for deletions or in **red** font for additions.

## **8 Use in Specific Populations**



(b) (4)



## 2 Drug Information

2.1 **Drug:** Proposed Proprietary Name: (b) (4) (Epinephrine Auto-Injector 0.15 mg and Epinephrine Auto-Injector 0.3 mg)

2.1.1 **CAS Registry Number:** 51-43-4

2.1.2 **Generic Name:** Epinephrine Injection USP 1:1000

2.1.3 **Code Name:** 56845

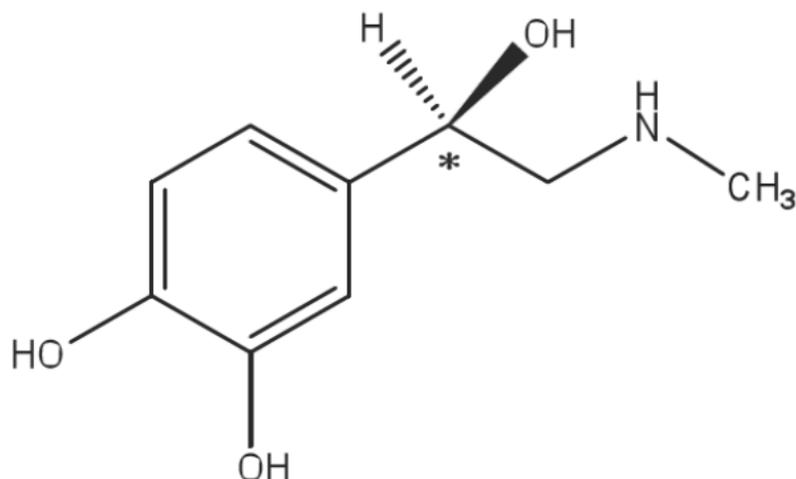
2.1.4 **Chemical Name:** 1,2-Benzenediol, 4-[1-hydroxy-2-(methylamino)ethyl]-, (R) (USP)

(-)-3,4,-Dihydroxy- $\alpha$ -[(methylamino)methyl]benzyl alcohol (CAS)

R-1-(3,4-dihydroxyphenyl)-2-methylaminoethanol (BP)

2.1.5 **Molecular Formula/Molecular Weight:** C<sub>9</sub>H<sub>13</sub>NO<sub>3</sub> / 183.20

2.1.6 **Structure:**



**2.1.7 Pharmacologic class:** Sympathomimetic catecholamine

**2.2 Relevant IND/s, NDA/s, and DMF/s:** IND 76367 and the DMF (b)(4) (drug-device combination was developed) are referenced. EpiPen's<sup>®</sup> approved label (NDA 019430) is the reference product that is the basis for this submission.

### 2.3 Clinical Formulation

**2.3.1 Drug Formulation:** Pre-filled Auto-Injection device containing the following drug product:

Component	Function	Amount (mg) per mL/%W/V	EAI 0.3 mg Amount per 0.3 mL	EAI 0.15 mg Amount per 0.15 mL	Reference to Quality Standards
Epinephrine	Active ingredient	1.12/0.11% <sup>a</sup>	0.300 mg	0.150 mg	USP
Sodium Bisulfite					(b)(4) FCC (Section 3.2.P.4.1)
Sodium Chloride					USP
Hydrochloric Acid					NF

Component	Function	Amount (mg) per mL/%W/V	EAI 0.3 mg Amount per 0.3 mL	EAI 0.15 mg Amount per 0.15 mL	Reference to Quality Standards
Water for Injection	(b) (4)	<i>qs ad</i> 1 mL/100%	<i>qs ad</i> 1 mL/100%	<i>qs ad</i> 1 mL/100%	USP
	(b) (4)				NF
(b) (4)					

### 2.3.2 Comments on Novel Excipients: No novel excipients

**2.3.3 Comments on Impurities/Degradants of Concern:** Two degradants from the EAI drug-device were reported after 18 months storage, at levels (b) (4)%, corresponding to exposure of up to (b) (4)/day and (b) (4)/day in the 0.3 mg and 0.15 mg products, respectively. These levels were below the identification threshold of 1.0% or 5 mcg/mg/day for a maximum daily dose of <1 mg (refer to the ICH Q3B (R2) Guidance), and the genotoxic limit of (b) (4)/day (refer to the Draft Genotoxic Impurities Guidance). Further investigation was deemed to be not necessary by the Agency. Leachables and extractables found in placebo and drug product solutions stored for 12 months were also found, although at levels below those requiring qualification. (b) (4) from the (b) (4) was below the acceptance criteria of (b) (4) cartridge. Per the chemistry reviewer, Dr. Ying Wang, there were no outstanding CMC issues for the application.

**2.4 Proposed Clinical Population and Dosing Regimen:** Epinephrine Auto-Injector is proposed for the emergency supportive therapy of allergic reactions, including anaphylaxis at single doses of 0.15 mg (0.15 mL, in patients weighing 15-30 kg) or 0.3 mg (0.3 mL, in patients weighing 30 kg or more).

**2.5 Regulatory Background:** The FDA agreed that it would be sufficient to reference the nonclinical information in the approved labeling for the reference listed drug (RLD), Twinject® for filing of the IND because Epinephrine Injection, USP 1:1000 is a well established commercial drug in pIND (communication to the Sponsor of March 9, 2007 for the pIND meeting of February 1, 2007) and pNDA (communication to the Sponsor nonclinical question for the October 26, 2009) meetings. The FDA confirmed that it would be acceptable to change the referenced listed drug from Twinject® to EpiPen® in a communication to the Sponsor of October 20, 2008. A 505(b)(2) application was filed on September 29, 2010.

## 11 Integrated Summary and Safety Evaluation

Intelliject, Inc. submitted NDA 201739 for their new patient-actuated epinephrine auto-injector (EAI) under the 505(b)(2) pathway on September 29, 2010. Epinephrine is an alpha and beta adrenergic receptor agonist that inhibits vasodilation and increases vascular permeability via alpha adrenergic activity, and relaxes smooth muscle in the bronchial, gastrointestinal and genitourinary tracts. The proposed injection is for emergency treatment of allergic reactions (Type 1). The proposed dosages are based on patient body weights. The 0.3 mg epinephrine injection strength is proposed for patients who weigh 30 kg or more and the 0.15 mg strength is for patients between 15 and 30 kg. Administration is proposed for the intramuscular or subcutaneous delivery.

No new nonclinical studies or information from the public literature were provided upon submission of this NDA. The Agency agreed that referencing the non-clinical information in the approved labeling for EpiPen® (NDA 19-430) would be sufficient to support filing of NDA 201739 (see Responses to Questions in Meeting Package, March 9, 2007). Nonclinical review of this NDA submission included proposed labeling (nonclinical sections) and review of impurities, leachables and extractables in consultation with the chemistry reviewer. The nonclinical sections of the Sponsor's originally proposed labeling were updated to reflect the most currently available epinephrine information contained in the EpiPen approved label (April 2009) and to align with 21 CFR Part 201.57 labeling recommendations. No impurities, leachables and extractables requiring nonclinical evaluation were identified by the chemistry reviewer.

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KATHLEEN A YOUNG  
06/22/2011

MOLLY E TOPPER  
06/22/2011  
I concur.

**OND Division of Pulmonary Allergy and Rheumatology Products**  
**Initial Quality Assessment**  
**Date: November 9, 2010**

**NDA: 201-739**

Epinephrine Auto-Injector, 0.15 mg and 0.3 mg

**Applicant:** Intelliject Inc.

**Stamp Date:** September 29, 2010

**PDUFA Date:** July 29, 2011

**ONDQA 5 month date:** February 28, 2011

**Proposed Proprietary Name:** (b) (4)

**Established Name:** epinephrine auto-injector (epinephrine injection)

**Dosage form and strength:** injection 0.15 mg and 0.3 mg

**Route of Administration:** s.c./i.m.

**Indications:** The emergency treatment of allergic reactions.

**CMC Lead (acting):** Alan C. Schroeder, Ph.D. /DNDQA III/ONDQA

**Filability recommendation:** Acceptable for filing

**Review team recommendation:** Single primary reviewer (Ying Wang, PhD)

**Time goals:**

- Initial Quality Assessment in DFS: by November 29, 2010
- Filing decision “Day 45”: November 13, 2010
- Filing review issues “Day 74”: December 12, 2010
- **Chemistry Review (DR/IR) letter: by February 28, 2011**
- Mid-cycle meeting “Month 5”: March 2, 2011
- Wrap Up: June 22, 2011
- **Final Chemistry Review “Month 8” in DFS: by May 29, 2011**
- PDUFA: July 29, 2011

<b>CONSULTS/ CMC RELATED REVIEWS</b>	<b>COMMENT</b>
Biopharm	Review needed; biowaiver requested for 0.15 mg dose
CDRH	Review of device and device master file (MAF (b) (4)) needed, for human factors studies, device manufacture and control, device performance, device stability, sterilization, software, electrical safety, electromagnetic compatibility, etc.
EA	To be assessed by Primary Reviewer
EES	EER sent to Office of Compliance on October 28, 2010
DMETS	Labeling consult request will be sent as part of DPARP’s request.
Methods Validation	Validation may be requested of FDA labs after test methods are finalized.
Microbiology	Review needed for (b) (4) manufacturing process and all stability aspects (except for sterilization of the device as described in the Device Master File, to be evaluated by CDRH)
Pharm/Tox	DS and DP impurities/degradants/leachables to be evaluated for safety.

**Notes:**

Part of this IQA consists of the filing meeting slides, which are archived separately in DARRTS (on November 4, 2010). The filing table is repeated later in this memo.

Drug substance

The drug substance, epinephrine, is manufactured by (b) (4) and information pertaining to its manufacture and controls is referenced to DMF (b) (4). A LOA (dated June 24, 2010) to DMF (b) (4) is provided. This DMF was last reviewed by Mike Darj and entered into DARRTS on April 2, 2009. The DMF was reviewed for another Auto-Injector product and it was found to be adequate. Subsequent to the last review of this DMF, a quality information amendment was submitted and three annual reports. These newer submissions need to be reviewed.

The NDA contains specifications for the drug substance, based in part on the USP monograph for epinephrine but with (b) (4) limits for a number of attributes, and with additional specifications for impurities and residual solvents (b) (4). The applicant has provided their own methods for impurities and residual solvents. Validation reports are provided for the applicant's own methods. The drug substance tests will be conducted by the drug product manufacturer, (b) (4), for each incoming lot of drug substance used in drug product manufacture. Batch analyses data are provided for the drug substance, as are justification of specifications, and information pertaining to the reference standards. A brief description of the container closure system is provided. Based on stability studies for the drug substance (which are cross referenced to the drug substance DMF (b) (4)), the recommended storage condition is at 25°C and with protection from light. The proposed drug substance retest period is (b) (4) from the date of manufacture.

Drug product

The drug products (Epinephrine Auto-Injector, or EAI), deliver 0.15 mg and 0.3 mg of epinephrine. The formulation is the same for the two strengths, however, the amount of the solution formulation delivered is different (0.3 mL contains 0.300 mg, whereas 0.15 mL contains 0.150 mg). See the drug product composition table in the filing meeting slides. Thus, both strengths contain the same drug solution formulation at the same concentration; it is the device which delivers either 0.3 mg or 0.15 mg of the drug (i.e., 0.3 mL or 0.15 mL, respectively, of the solution formulation) to the patient.

The applicant defines the “drug constituent component” of the drug product as the drug solution formulation contained “in a glass cartridge fitted with a (b) (4).” See the filing meeting slides for a drawing of the cartridge system (along with the “needle hub”).

See the filing meeting slides for a table comparing the formulation of the EAI with that of EpiPen.

The applicant defines the “device constituent component” as “a gas powered, needle-based system that delivers the prescribed dose of epinephrine into the user. The slides contain a photo of the device and a schematic drawing of the device components. The slides also contain a table comparing the device characteristics with the EpiPen. After the EAI is used, there remains residual drug formulation in the product which cannot be injected. The residual amount is approximately (b) (4) for the EAI 0.3 mg and EAI 0.15 mg, respectively. The glass cartridge is (b) (4) USP Type I glass and the (b) (4) aluminum crimp seal and the (b) (4). The filing meeting slides provide the drug product specifications and a brief description of the drug product appearance and how it is used.

The filing meeting slides also provide brief descriptions of the leachables studies on the (b) (4) of the cartridge and on the (b) (4) used in drug product manufacture.

See Table 2.3P.2.4 (in Section 2.3.P.2 of Quality Overall Summary, pg. 6) for a comparison of the registration/stability and proposed commercial manufacturing processes. There are a few differences, but they don't seem to be major differences.

18 months of drug product stability data are provided. The requested expiration dating period is 18-20 months. [Specifically, the expiry period is the earlier of 20 months from the manufacturing date for the drug constituent component, i.e., formulation and (b) (4) filling of EAI, or 18 months from the date of final assembly, packaging and labeling of EAI.] The assay clearly drops over 18 months on stability by more than (b) (4)

(b) (4) 18 months on stability. See the filing meeting slides for stability graphs of the assay and of (b) (4).

Drug product stability data are said to include “seven registration lots (10005, 10006, 10007, 10009, 20001, 20002, and 20003) of EAI [which] were produced using two different drug constituent component lots manufactured at the intended bulk commercial scale ((b) (4) bulk formulation) at the intended commercial sites, using the same commercial manufacturing processes and controls, commercial cartridge filling and sealing machine and container closure components. The stability studies were performed on the combination product (i.e., fully assembled product) including the outer case except without the electronic prompt system.” The drug constituent lots are identical for EAI 0.15 mg and 0.3 mg since it is the device which is set to control the amount of solution delivered. Therefore the applicant performed physicochemical and microbiological stability testing only on the EAI 0.3 mg lots. Nevertheless, device performance testing (i.e., volume dispensed) were performed on all seven NDA stability lots. It appears that a single lot of drug substance was used to manufacture the drug product for all NDA

stability lots. Two batches of filled cartridges were used to manufacture drug product for all NDA stability lots. This approach to the stability batches is not considered to be a filing issue; this is a known drug and it is very close to a known drug product formulation for a marketed Auto-Injector. The applicant indicates stability trends only in the following attributes: assay, impurities, and bisulfite. The applicant also notes three out of specification results for “volume dispensed” said to be due to a premature puncture of the crimp seal and leakage of drug formulation solution. This is said to have been corrected by “minor refinements” and this is said to be described in MAF (b) (4).

Additional device performance stability studies are indicated to have been reported in the device master file (MAF (b) (4)).

Supporting DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED
(b) (4)	II	(b) (4)	epinephrine drug substance
	III		(b) (4)
	III		

Supporting Device Master File (MAF):

MAF (b) (4) (owned by Intelliject, Inc.)

Letters of authorization are provided for the above listed DMFs and the MAF (Section 1.4 of the NDA).

IND for this drug product: IND 76,367

Filing Check List (reproduced from filing meeting slides):

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	x		eCTD format
2	Is the section indexed and paginated adequately?	x		
3	On its face, is the section legible?	x		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	x		
5	Is a statement provided that all facilities are ready for GMP inspection?	x		pg. 3 of cover letter
6	Has an environmental assessment report or categorical exclusion been provided?	x		Section 1.12.14. Claim of categorical exclusion.

7	Does the section contain controls for the drug substance?	x		
8	Does the section contain controls for the drug product?	x		
9	Have stability data and analysis been provided to support the requested expiration date?	x		Full stability shelf life data are provided, but there is no statistical analysis
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	some		Review issue.
11	Have draft container labels been provided?	x		
12	Has the draft package insert been provided?	x		
13	Has an investigational formulations section been provided?	x		It does not appear that other formulations were used clinically; multiple formulations are described for studies of optimization of the formulation and chemical stability.
14	Is there a Methods Validation package?	x		Yes, except that there is no listing of samples to be provided (“samples available upon request”)

Certain review issues which were noted are listed below for consideration by the reviewer (some from the filing meeting slides):

An overage of epinephrine in the formulation was previously agreed to by FDA (see our response to Q7 in pre-meeting comments sent on 10/23/2009 for IND 76367).

Assess the adequacy of (b) (4) specifications for the non-compendial excipient, (b) (4)

Include CDRH along with CMC in evaluation of the comparability protocol for automated vs. semi-automated device assembly (refer to Section 2.4 of Regional Information)

Ask the applicant to define battery life of the device after 18 months stability storage.

Discuss with CDRH as necessary whether there are any safety concerns due to the compressed gas container in the device (e.g., with regard to increases in pressure if the drug product is stored at higher temperatures, even for a shorter time period).

It may be worthwhile in part for safety assurance, to verify whether the (b) (4) components used in the EAI were also used in other parenteral drug products.

The draft container and carton labels contain the statement “do not refrigerate or freeze.” It is understandable why the product should not be frozen, but it should be asked why refrigerating the product is not advised.

IND 76367 Information relevant to CMC and CDRH review:

See the Agency’s answers to questions raised in a meeting package: the answers were sent to the sponsor on October 23, 2009. See also comments sent to the sponsor on April 28, 2009 and March 2, 2009.

Recommendation: Fileable from a CMC perspective.

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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.**  
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/s/  
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ALAN C SCHROEDER  
11/16/2010

PRASAD PERI  
11/16/2010  
I concur

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR  
NDA201739**

**NDA Number: 201739**

**Applicant: Intelliject, Inc.**

**Stamp Date: September 29,  
2010**

**Drug Name: Epinephrine Auto-Injector 0.15 mg (epinephrine injection USP 1:1000) and Epinephrine Auto-Injector 0.3 mg (epinephrine injection USP 1:1000)**  
**NDA Type: Original Application**

On **initial** overview of the NDA/BLA application for filing:

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?			NA: no nonclinical study reports submitted; Applicant references the nonclinical information in the approved labeling for EpiPen (agreed to by Agency letter of September 25, 2009 submission for the nonclinical pharmacology and toxicology support
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?			NA
3	Is the pharmacology/toxicology section legible so that substantive review can begin?			NA
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	x		See referenced drug product and referenced MAF (b)(4)
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).			NA; no formulation change from referenced product
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?	x		

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR  
NDA201739**

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?			NA: no nonclinical studies; reference approved labeling for EpiPen
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	x		Yes
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	x		Yes
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)			To be determined: Review issues regarding CMC identification of residues of concern from new cartridge/needle sterilization
11	Has the applicant addressed any abuse potential issues in the submission?			See referenced Drug Product
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			NA

**IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? \_\_\_\_\_ Yes\_\_\_\_\_**

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

There are no pharmacology and toxicology review issues at this time.

\_\_\_\_\_  
Reviewing Pharmacologist

\_\_\_\_\_  
Date

\_\_\_\_\_  
Team Leader/Supervisor

\_\_\_\_\_  
Date

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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.**  
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/s/  
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KATHLEEN A YOUNG  
11/04/2010

MOLLY E TOPPER  
11/04/2010