CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

201739Orig1s000

MEDICAL REVIEW(S)

SUMMARY REVIEW OF REGULATORY ACTION

Date:	July 29, 2011
From:	Badrul A. Chowdhury, MD, PhD Director, Division of Pulmonary, Allergy, and Rheumatology Products, CDER, FDA
Subject:	Division Director Summary Review
NDA Number:	20-1739
Applicant Name:	Intelliject (to manufacture for sanofi-aventis)
Date of Submission:	September 29, 2010
PDUFA Goal Date:	July 29, 2010
Proprietary Name:	(b) (4) (proposal originally), (b) (4) (proposed later), e-cue (accepted by DMEPA)
Established Name:	Epinephrine
Dosage form:	Injection
Strength:	0.3 mg (0.3 mg/0.3 mL) prefilled auto-injector 0.15 mg (0.15 mg/0/3 mL) prefilled auto-injector
Proposed Indications:	Emergency treatment of allergic reactions including anaphylaxis
Action:	Tentative Approval

1. Introduction

Intelliject submitted this 505(b)(2) application for epinephrine injection at doses of 0.3 mg for patients weighing 30 kg or more and 0.15 mg for patients weighting 15 to under 30 kg for emergency treatment of allergic reactions including anaphylaxis. The applicant refers to Meridian Medical's epinephrine auto-injector (marketed as EpiPen 0.3 mg and EpiPen Jr 0.15 mg, NDA 19-430) as the listed drug. Although not required for approval, the applicant has conducted a clinical pharmacology study to show bioequivalence (BE) to the listed drug. This summary review provides an overview of the application. The application cannot be approved because of a patent infringement suit filed by Meridian Medical.

2. Background

Epinephrine has long been used in the treatment of Type I hypersensitivity reactions, including anaphylaxis. Epinephrine auto-injector was first approved for the treatment of Type 1 hypersensitivity reactions, including anaphylaxis, on December 22, 1987 (NDA 19-430, EpiPen® 0.3 mg and EpiPen Jr. ® 0.15 mg). Other epinephrine auto-injector products include Twinject® 0.3 mg and 0.15 mg (NDA 20-800; Approval Letter dated May 3, 2003) and Adrenaclick® 0.3 mg and 0.15 mg (NDA 20-800; November 25, 2009). None of the currently marketed epinephrine auto-injector products included any clinical trials in their respective development programs, and the recommended dosing is based on the published literature and established clinical practice. While some differences exist among these products, they share a similar pen-shaped design, mode of activation for the initial auto-injector dose, and auto-injector needle characteristics. In

contrast to other approved epinephrine auto-injector products, the proposed product from Intellijject has a different shape, design, and an electronic auditory prompt system that provides real-time, verbal and visual cues (in English) to guide the user through the administration steps of the product. However, the needle characteristics (length, gauge, and injection force) of the proposed product and other epinephrine auto-injector products are similar. Therefore, delivery of epinephrine into human body is expected to be similar for the proposed product and other epinephrine auto-injector products.

Meridian Medical has filed a patent infringement suit against Intellijject claiming infringement of US Patent No. 7,794,432 B2. Pursuant to section 505(b)(2) of the FD&C Act, an applicant cannot be approved if an action is brought for infringement of one or more of the patents that were the subject of the Paragraph IV certifications. Therefore, final approval of this application cannot be granted until expiration of the 30-month period or other court action and assurance that there is no new information that would affect whether final approval should be granted.

3. Chemistry, Manufacturing, and Controls

The proposed commercial epinephrine auto-injection product is a drug-device combination product. The drug component is the drug substance epinephrine (manufactured by (b) (4)), formulated with the excipients sodium (b) (4), sodium chloride, hydrochloric acid, and water for injection. The device component is a gas powered, needle-based auto-injector system that delivers the prescribed dose of epinephrine into the user. The auto-injector device is rectangular shape (shape and size approximate that of a deck of cards) and has an automatic retractable needle system and a battery-powered electronic prompt system that provides audible beep and voice instructions and visual cues with red and green blinking LED lights to guide the user. The electronic prompt system works independently from the functional mechanism of the product, meaning that the product will administer epinephrine in the event of a failure of the electronic prompt system. Intellijject's proposed epinephrine auto-injector's needle is similar EpiPen's in terms of needle length, gauge, and injection force. Therefore, delivery of epinephrine into the human body is expected to be similar for Intellijject's proposed product compared to EpiPen. Various DMF's associated with the manufacture of the product are adequate. An expiry date of 18 months from the date of final assembly is supported by submitted stability data.

The epinephrine solution is manufactured and filled into cartridges at (b) (4). The needle-drug cartridge assembly is performed by (b) (4). The device components manufacture and final product assembly, packaging and labeling are performed at (b) (4). The current proposed assembly of the device is semi-automated and Intellijject plans to use a fully automated assembly system for the device in the future. Intellijject Inc., located in Richmond, VA, is responsible for the final product release for distribution. Various manufacturing and testing facilities associated with this application have acceptable inspection status.

CDRH completed a consultative review of device performance (bench testing), biocompatibility, sterilization, software, electrical safety/electromagnetic compatibility (EMC), and human factors studies. Performance testing demonstrated that Intellijject's epinephrine auto-injector is functionally safe and effective for its intended use. No issues were identified in terms of sterility, software, or EMC testing. Human factors testing systematically evaluated use-related risks and validated user-performance of the highest priority tasks pertinent to the proposed product, and the findings were acceptable. Biocompatibility findings were also acceptable.

4. Nonclinical Pharmacology and Toxicology

No new nonclinical toxicology studies were required or performed for this application.

5. Clinical Pharmacology and Biopharmaceutics

Intellijject conducted a comparative bioavailability study (INT0802) to demonstrate the bioequivalence of its epinephrine auto-injector with EpiPen. Demonstration of such bioequivalence is not required because Intellijject's epinephrine auto-injector's needle is similar to EpiPen's in terms of needle length, gauge, and injection force, and therefore, delivery of epinephrine into the human body is expected to be similar for the two products. Intellijject planned and conducted the bioequivalence study early in the development phase when the needle characteristics for the product were not available to the Agency. The study was crossover in design and conducted in 66 subjects ages 18 to 45 years. Given the high intra-subject variability of epinephrine, a reference-scaling approach (Haidar SH et al. *Pharm Res*. 2008 Jan; 25:237-41) was used to assess bioequivalence. This approach was acceptable. The main results of the bioequivalence analyses are summarized in Table 1. The study provides useful information in that it confirms that delivery of epinephrine for the two products was the same.

Table 1. Bioequivalence analysis results

Parameter	Ratio	90% confidence interval		$\mu_T-\mu_R$	σ_{WR}^2	Upper 95% confidence limit for $(\mu_T-\mu_R)^2-0.8\,\sigma_{WR}^2$	CV_{WR}(%)	Criterion 1: Confidence limit	Criterion 2: Point estimate	BE
		Lower	Upper							
Observed dataset										
Cmax	0.9448	0.8349	1.0842	-0.0568	0.1888	-0.1019	43.45	Pass	Pass	Yes
AUC(0-t)	1.1586	1.0602	1.2776	0.1472	0.1091	-0.0231	33.03	Pass	Pass	Yes
AUC(inf)	1.1864	1.1035	1.3790	0.1709	0.1003	0.0034	31.68	Fail	Pass	No
Baseline-corrected dataset										
Cmax	0.9446	0.8439	1.0844	-0.0570	0.1931	-0.1046	43.94	Pass	Pass	Yes
AUC(0-t)	1.1544	1.0575	1.2774	0.1436	0.1279	-0.0373	35.76	Pass	Pass	Yes
AUC(inf)	1.1747	1.0915	1.3693	0.1610	0.1250	-0.0179	35.36	Pass	Pass	Yes

6. Clinical Microbiology

The final product is not sterile, which is acceptable. The manufacturing process is adequate from a microbiological perspective.

7. Clinical and Statistical – Efficacy

No clinical studies were required or conducted to support this application.

8. Safety

The safety of the proposed product is based primarily on the Agency's previous findings of the safety of epinephrine in the treatment of Type I hypersensitivity reactions including anaphylaxis. Limited adverse event data from the bioequivalence study INT0802 were also supportive of safety.

9. Advisory Committee Meeting

An advisory committee was not convened for this application. Epinephrine is not a new molecular entity and there is a long history of its use in the treatment of Type I hypersensitivity reactions, including anaphylaxis. There were no specific issues to warrant discussion at an Advisory Committee Meeting.

10. Pediatric

This application does not trigger PREA requirements and therefore was not formally discussed at a PeRC meeting. The Agency has previously encouraged Intelliject to explore dosing in lower weight patients and is amenable to issuing a Written Request for studies in young children.

11. Other Relevant Regulatory Issues

a. DSI Audits

DSI conducted an audit of the clinical pharmacology study site and the associated analytical site. The inspection did not reveal any significant deficiencies. During review of this submission no irregularities were found that would raise concerns regarding data integrity. No ethical issues were present. All studies were performed in accordance with acceptable ethical standards.

b. Financial Disclosure

The applicant submitted acceptable financial disclosure statements.

c. Others

There are no outstanding issues with consult reviews received from DDMAC or from other groups in CDER.

12. Labeling

a. Proprietary Name

Intelliject originally proposed (b) (4) and later (b) (4) as the trade name for this product. These names were not accepted by DMEPA. Intelliject later proposed e-cue as the trade name, which was found acceptable by DMEPA.

b. Physician Labeling

Intelliject submitted labeling that includes a product label in the Physician's Labeling Rule format, and a patient labeling with instructions for use. When approved, this will be the first label of an epinephrine auto-injector in the Physician's Labeling Rule format. The label was reviewed by various disciplines of this Division, DRISK, DMEPA, and by DDMAC. The language of various sections of the label is consistent with the label language of other epinephrine auto-injector products, except product and device specific information. The Division and Intelliject have agreed on the final labeling language.

c. Carton and Immediate Container Labels

These were reviewed by various disciplines of this Division, ONDQA, and DMEPA, and were found to be acceptable.

d. Patient Labeling and Medication Guide

There is no separate medication guide for this product.

13. Action and Risk Benefit Assessment

a. Regulatory Action

Intelliject has submitted adequate data for approval of its epinephrine auto-injector drug-device combination product for emergency treatment of allergic reactions including anaphylaxis. There is a patent infringement lawsuit that has resulted in a 30 months stay on the application. Therefore, the regulatory action on this application will be a Tentative Approval until the court decides that the patent is not infringed as described in section 505(c)(3)(C)(i), (ii) or (iv) and that there is no new information that would affect whether final approval should be granted.

b. Risk Benefit Assessment

The risk and benefit assessment of Intelliject's epinephrine auto-injector supports its approval. The efficacy and safety of epinephrine auto-injector in the treatment of allergic reactions including anaphylaxis are know from the clinical literature and established clinical practice. There are no device specific issues with the Intelliject's auto-injector product. This application can be approved till resolution of the patent infringement lawsuit.

c. Post-marketing Risk Management Activities

None.

d. Post-marketing Study Commitments

None.

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/s/

BADRUL A CHOWDHURY
07/29/2011

Cross-Discipline Team Leader Review

Date	July 8, 2011
From	Susan Limb, MD, Clinical Team Leader, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	NDA 201739
Applicant	Intellijject
Date of Submission	September 29, 2010
PDUFA Goal Date	July 29, 2011
Proprietary Name / Established (USAN) names	e-cue (under review)/epinephrine
Dosage forms / Strength	Epinephrine auto-injector 0.15 mg and 0.3 mg (epinephrine injection USP 1:1000)
Proposed Indication(s)	1. Emergency treatment of allergic reactions including anaphylaxis
Recommended:	Approval pending: 1) final inspection report 2) resolution of patent infringement suit

1. Introduction

Intellijject has submitted a 505(b)(2) new drug application (NDA 201739) for a new drug-device combination product, epinephrine auto-injector 0.15 mg and 0.3 mg (epinephrine injection USP 1:1000). The application proposes the use of epinephrine auto-injector (EAI) for the following indication:

> *EAI is indicated in the emergency treatment of allergic reactions (Type I) including anaphylaxis to stinging insects (e.g. order Hymenoptera, which include bees, wasps, hornets, yellow jackets, and fire ants) and biting insects (e.g. triatoma, mosquitoes), allergen immunotherapy, foods, drugs (e.g. penicillin, omalizumab), diagnostic testing substances (e.g. radiocontrast media) and other allergens, as well as idiopathic anaphylaxis or exercise-induced anaphylaxis.*

The proposed dosing varies by patient weight. For patients 15 kg to 30 kg, EAI 0.15 mg subcutaneously or intramuscularly is recommended, while EAI 0.3 mg is indicated for patients >30 kg. There is no proposed dosage form for patients <15 kg. The NDA references NDA 19-430 for EpiPen® Auto-injector 0.3 mg and EpiPen Jr® Auto-injector 0.15 mg. In contrast to the reference product and other approved epinephrine auto-injector products, the proposed EAI has a different shape and design, highlighted by an electronic auditory prompt system that provides real-time, verbal and visual cues to guide the user through the administration steps of

the product. The proposed tradename is "e-cue," which is currently under review by the Division of Medication Error Prevention and Analysis (DMEPA). The proposed EAI is not currently marketed anywhere.

The clinical development program for the proposed EAI was comprised of a comparative pharmacokinetics trial and three human factor studies. No efficacy and safety trials were conducted for the application. The PK trial, which was not a requirement for the application, demonstrated bioequivalence (BE) between EAI 0.3 mg and the reference 0.3 mg product using a scaled BE approach, which is an analytic approach that may be applied in situations of high intra- and inter-individual variability. Satisfactory review of the drug constituent and device components, in conjunction with the Agency's prior findings of efficacy and safety for epinephrine in the proposed indication, form the basis of the Approval recommendation for EAI. Supplementary information from the pharmacokinetic trial provides added support for the recommendation of approval.

However, the recommendation for Approval is contingent upon: 1) acceptable final inspections and 2) resolution of a patent infringement suit. At the time of this memorandum, a final recommendation from the Office of Compliance remains pending. A preliminary report of the inspection of the drug-device assembly process indicates potential deficiencies, but further information is not available at this time, and the final recommendation from the Office of Compliance has yet to be determined. In addition, the Applicant has been placed on a 30-month-stay due to a patent infringement suit initiated by Meridian Medical Technologies, claiming infringement of US Patent No. 7,794,432 B2. Section 505(c)(3)(C) of the Act provides that approval of a new drug application submitted pursuant to section 505(b)(2) of the Act shall be made effective immediately, unless an action is brought for infringement of one or more of the patents that were the subject of the Paragraph IV certifications. Final approval cannot be granted until expiration of the 30-month period or other court action and assurance that there is no new information that would affect whether final approval should be granted. Therefore, even with an acceptable recommendation from the Office of Compliance, the regulatory action would be a Tentative Approval. These issues are discussed in further detail in Sections 3 and 11, respectively, of this memorandum.

This CDTL review focuses on the similar and distinguishing characteristics of the proposed EAI product in comparison to other approved epinephrine auto-injectors and addresses the 505(b)(2) references relevant to the Approval recommendation.

2. Background

Epinephrine is a non-specific adrenergic agonist. Epinephrine has long been used in the treatment of Type I hypersensitivity reactions, including anaphylaxis. Epinephrine auto-injector was first approved for the treatment of Type 1 hypersensitivity reactions, including anaphylaxis, on December 22, 1987 (NDA 19-430, Epipen® 0.3 mg and EpiPen Jr. ® 0.15 mg). Other epinephrine auto-injector products include Twinject® 0.3 mg and 0.15 mg (NDA 20-800; Approval Letter dated May 3, 2003) and Adrenaclick® 0.3 mg and 0.15 mg (NDA 20-800; November 25, 2009). None of the currently marketed epinephrine auto-injector products included any clinical trials in their respective development programs, and the

recommended dosing is based on the published literature and established clinical practice. While some differences exist among these products, they share a similar pen-shaped design, mode of activation for the initial auto-injector dose, and auto-injector needle characteristics. The Twinject product is distinguished by the inclusion of a second dose in the barrel of the pen which may be manually administered. Epipen and Adrenaclick do not contain a second dose, and none of the products contains an electronic auditory prompt system like the proposed EAI.

The regulatory history of the proposed EAI dates to an initial planning meeting on July 21, 2005 (IND 76,367), which established that CDER would be the designated lead review center for the NDA with support from CDRH. A 505(b)(2) application was deemed appropriate given the novelty of the device. A Pre-IND meeting held on March 9, 2007, included discussion of the appropriate reference product, at which time the Agency agreed that non-clinical information from the reference product label would be sufficient to support filing of EAI. The Applicant also outlined the proposed bioequivalence (BE) trial to be included in the initial IND submission. Of note, a BE trial was not a requirement for the clinical program. However, given the lack of information about the device available at the time, such as needle dimensions, the Agency accepted the Applicant's proposal to conduct the BE trial.

In addition, the need for human factor studies in both adult and pediatric users was discussed at the March 9, 2007, meeting. (b) (4) Later discussion in October 2009 established that a pediatric assessment was not likely to be required, since EAI did not contain any new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration (written communication dated October 22, 2009). However, the Agency encouraged the Applicant to explore dosing in lower weight patients given an existing public health need (written response to pre-NDA briefing package; dated October 23, 2009).

There is no foreign marketing experience with EAI to date.

3. CMC/Device

- **General product quality considerations**
  The proposed EAI product is a pre-filled auto-injector drug-device combination product containing a single dose of 0.3 mg/0.3 ml epinephrine injection [USP 1:1000] or 0.15 mg/0.15 ml epinephrine injection [USP 1:1000]. The drug substance, epinephrine, is a USP monograph compound product, and the application references information from DMF (b) (4), which was last reviewed in March 2009 and found to be Adequate. In addition to epinephrine, the drug constituent component includes (b) (4)% sodium chloride, (b) (4)% sodium bisulfite, hydrochloric acid *qs ad* pH 2.2 – 5.0, and water for injection *qs ad* 1 ml. The composition is similar to the reference drug,

Epipen, with the exception of the antioxidant sodium bisulfite (EpiPen contains sodium metabisulfite).

In general, the specifications for the quality attributes of the drug constituent are the same as for the reference product, EpiPen. There appears to be substantial oxidative degradation during storage similar to EpiPen. Also, three stability samples were noted to have loss of volume. The Applicant attributed the lower volume to the device and modified the device accordingly. The device refinement and related study were found to be acceptable.

The application included stability data for 18-month long-term storage conditions (25ºC/65% RH), 12-month intermediate storage conditions (30ºC/65% RH), and 6-month accelerated storage conditions (40ºC/75% RH) 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. The product is recommended for storage at 25ºC with excursions permitted to 15-30ºC.

In terms of device attributes, EAI is similar to EpiPen in terms of needle length, gauge, and injection force. However, the EAI device is distinguished from currently marketed epinephrine auto-injectors by its automatic retractable needle system, intended to reduce post-injection sharps injury, and a battery-powered electronic prompt system that provides audible instructions and visual cues with red/green blinking LED lights to guide the user. The electronic system works independently from the functional mechanism of the device, i.e. the device will still administer epinephrine in the event of a failure of the electronic prompt system. Physically, EAI differs from the approved auto-injector products in appearance. The EAI device has a shape and size that approximates a deck of cards, whereas the auto-injectors are cylindrical. Given the novelty of the device design, the NDA included human factors studies.

CDRH completed a consultative review of device performance (bench testing), biocompatibility, sterilization, software, electrical safety/electromagnetic compatibility (EMC), and human factors studies. CDRH concluded that the performance testing demonstrated that the EAI is functionally safe and effective for its intended use, meeting the applicable ISO Standards and FDA Guidances. No issues were identified in terms of sterility, software, or EMC testing. In terms of the human factors testing, CDRH concluded that the studies systemically evaluated use-related risks and validated user-performance of the highest priority tasks pertinent to the proposed product. Regarding biocompatibility, CDRH initially noted deficiencies in the testing of the final finished materials of construction. However, following further discussion with the CMC review team, CDRH concluded that biocompatibility issues were addressed in the stability testing.

The application also included a comparability protocol for a proposed post-marketing change of the device assembly line from manual to automated. CDRH determined that

the proposed assembly line change would require inspection prior to approval. Therefore, a comparability protocol for the proposed change is not appropriate at this time. Following communication with the Applicant via teleconference on May 19, 2011, the comparability protocol was withdrawn by the Applicant on May 26, 2011.

Overall, the CMC review recommends Approval pending an overall Acceptable recommendation from the Office of Compliance.

- **Facilities review/inspection**
  The drug constituent component is manufactured by (b) (4), which was deemed acceptable by the Office of Compliance on April 27, 2011. The needle-drug cartridge assembly is performed by (b) (4), in facilities located in (b) (4), which were deemed acceptable by the Office of Compliance on October 29, 2010. The final drug-device assembly is performed by (b) (4) in facilities located in (b) (4) is the release and stability test lab for drug substance and drug product and was deemed acceptable by the Office of Compliance on October 29, 2010. Intelliject Inc. (Richmond, VA) conducts final product COA and approval of release of final product for distribution.

  Inspection status for (b) (4) and Intelliject remains pending at the time of this memorandum. However, a preliminary report of the inspection of the drug-device assembly process indicates potential deficiencies which may warrant a Withhold recommendation from the Office of Compliance. Further details about the nature of the deficiencies are unavailable at this time, and the final recommendation from the Office of Compliance is pending.

- **Other notable issues (resolved or outstanding)**
  None.

4. Nonclinical Pharmacology/Toxicology

The Agency previously agreed that referencing nonclinical information in the approved EpiPen label would be sufficient to support the EAI application. No new nonclinical data were submitted in the application. The nonclinical review included review of impurities, leachables, and extractables, in conjunction with the CMC review. The levels of the three identified degradation products (b) (4) were found to be similar to levels found in the reference product and did not warrant further nonclinical qualification studies. No new issues were identified, and there are no outstanding toxicology issues. The recommended action from the nonclinical pharmacology/toxicology perspective is Approval.

5. Clinical Pharmacology/Biopharmaceutics

The Applicant conducted a single comparative bioavailability trial, INT0802, to demonstrate the bioequivalence of EAI with the reference epinephrine product, EpiPen. As mentioned earlier, a BE trial was not a requirement for the clinical program, but given the relative lack of information available for the proposed device at the time of discussion, the Agency accepted the Applicant's proposal to conduct the BE trial. A total of 66 patients ages 18 to 45 years were randomized in a single dose, single blind, 2-treatment, 3-period, 3-sequence crossover trial comparing EAI with EpiPen. The reference product was administered twice in a random sequence given the expected, high within-subject variability (i.e. a percentage coefficient of variation [%CV] of one or more natural logarithm-transformed PK parameters that is ≥30%). The pharmacokinetics of epinephrine was determined by plasma concentrations collected through 6 hours post-dose.

Given the high intra-subject variability of the reference product, the Applicant applied a reference-scaling average BE approach (Haidar SH et al. *Pharm Res*. 2008 Jan; 25(1):237-41) to assess bioequivalence. Since epinephrine is an endogenous compound, analyses were conducted with and without correction for baseline concentrations. The main results of the bioequivalence analyses are summarized in **Table 1**.

Table 1 Bioequivalence analysis results

Parameter	Ratio	90% confidence interval		$\mu_T-\mu_R$	σ_{WR}^2	Upper 95% confidence limit for $(\mu_T-\mu_R)^2 - 0.8\,\sigma_{WR}^2$	CV_{WR}(%)	Criterion 1: Confidence limit	Criterion 2: Point estimate	BE
		Lower	Upper							
Observed dataset										
Cmax	0.9448	0.8349	1.0842	-0.0568	0.1888	-0.1019	43.45	Pass	Pass	Yes
AUC(0-t)	1.1586	1.0602	1.2776	0.1472	0.1091	-0.0231	33.03	Pass	Pass	Yes
AUC(inf)	1.1864	1.1035	1.3790	0.1709	0.1003	0.0034	31.68	Fail	Pass	No
Baseline-corrected dataset										
Cmax	0.9446	0.8439	1.0844	-0.0570	0.1931	-0.1046	43.94	Pass	Pass	Yes
AUC(0-t)	1.1544	1.0575	1.2774	0.1436	0.1279	-0.0373	35.76	Pass	Pass	Yes
AUC(inf)	1.1747	1.0915	1.3693	0.1610	0.1250	-0.0179	35.36	Pass	Pass	Yes

This analytical approach has limited regulatory precedent in the approval of new drug products. The applicability of this approach was discussed at an Office of Clinical Pharmacology Scientific Rounds on February 15, 2011. Based on the discussion at that meeting, the clinical pharmacology review team concluded that the scaled BE approach was acceptable for this specific application given the high variability of an endogenous drug substance and by virtue of the formulation being a simple solution. Using this approach, the clinical pharmacology review has concluded that exposure from EAI is equivalent to that from the reference product.

An audit of the study site conducted by the Division of Scientific Investigation (DSI) was found to be acceptable.

No trials were conducted for the proposed lower strength of EAI 0.15 mg. A biowaiver for the 0.15 mg strength was granted on the basis of the following: 1) results from the trial conducted

with the 0.3 mg strength; 2) proportionally similar composition between strengths; and 3) similarity of needle dimensions to the reference products.

Overall, the clinical pharmacology review concluded that there were adequate clinical pharmacology data to support the application.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

No efficacy trials were conducted for the application. As described earlier, the recommended dosing is based on the published literature and established clinical practice. Support for efficacy is based on the Agency's previous findings of efficacy for epinephrine in the treatment of allergic reactions and anaphylaxis.

8. Safety

Support for safety is based primarily on the Agency's previous findings of safety for epinephrine in the treatment of allergic reactions and anaphylaxis. Limited adverse event data from the BE trial INT0802 were also supportive of safety.

As a sympathomimetic catecholamine, epinephrine may induce effects attributable to overstimulation of both alpha and beta receptors. These effects are described in the Warnings and Precautions sections of the current package insert for the reference product and include hypertension, arrhythymias, and angina. Accidental injection into the extremities may cause local ischemia and pain. Other adverse reactions noted for epinephrine include palpitations, tachycardia, sweating, nausea and vomiting, respiratory difficulty, pallor, dizziness, weakness, tremor, headache, apprehension, nervousness, and anxiety.

In the BE trial, there were no deaths or serious adverse events (SAE) reported. One patient discontinued prematurely from the trial due to self-limited premature ventricular contractions that resolved within 2 minutes. The most common adverse event reported for EAI was local injection site reactions, consisting mainly of erythema. Other AEs reported included increased heart rate, dizziness, headache, tremor, and anxiety. Similar adverse events were reported for the reference arm, EpiPen, and the overall AE profile is consistent with the profile described in the EpiPen package insert. No new safety signals were identified.

The EpiPen label recommends caution when used in patients who may be predisposed to adverse effects from excess sympathomimetic stimulation, such as patients with underlying cardiovascular disease. However, epinephrine administration is still recommended for the treatment of anaphylaxis given its life-threatening potential. Similar recommendations apply

to the use of EAI, and there are no absolute contraindications to its use in a life-threatening situation.

9. Advisory Committee Meeting

Epinephrine is not a new molecular entity, and no new clinical issues were identified during the review. Therefore, no advisory committee meeting was held for the application. As noted above, the application was discussed at an Office of Clinical Pharmacology Scientific Rounds to assess the acceptability of the scaled BE analysis used in the application.

10. Pediatrics

The application does not include a pediatric plan, since EAI does not contain any new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration that would necessitate a pediatric assessment.

Although the Pediatric Research Equity Act (PREA) (21 U.S.C 355c) does not apply, the Agency has previously encouraged the Applicant to explore dosing in lower weight patients given an existing public health need (written response to pre-NDA briefing package; dated October 23, 2009). The Agency has also informed the Applicant that the Agency can issue a Written Request for pediatric studies if the product represents a potential health benefit in the pediatric population under the Best Pharmaceuticals for Children Act (BPCA).

11. Other Relevant Regulatory Issues

The appropriateness of a 505(b)(2) regulatory pathway for this application has not been confirmed by the Office of New Drugs and by the Office of Regulatory Policy. The Applicant will depend on the Agency's previous findings of safety and effectiveness for epinephrine for the proposed indication. The Applicant submitted certifications to each of the patents under section 505(b)(2)(A)(iv) of the Act stating that the patents are invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of, this drug product under this application. The Applicant submitted documents indicating that the patent holder for the referenced patents, (b) (4), was notified of the reference on December 8, 2010. Legal action against the Applicant was filed on January 19, 2011, in the US District Court, District of Delaware, claiming infringement of US Patent No. 7,794,432 B2. On May 19, 2011, during a teleconference between the Agency and the Applicant to discuss the proposed comparability protocol, the Applicant informed the Agency that Intellijject was under a 30-month stay due to the patent infringement suit.

Section 505(c)(3)(C) of the Act provides that approval of a new drug application submitted pursuant to section 505(b)(2) of the Act shall be made effective immediately, unless an action is brought for infringement of one or more of the patents that were the subject of the Paragraph IV certifications. Therefore, final approval cannot be granted until expiration of the 30-month

period or other court action, in addition to confirmation that there is no new information that would affect whether final approval should be granted. As of the time of this memorandum, the patient issue remains unresolved, and an Approval action would be a Tentative Approval dependent on the outcome of the patent infringement suit.

12. Labeling

Unlike the reference product, the labeling for EAI 0.3 and 0.15 mg is in the PLR format. Following discussion with the Applicant, the labeling was revised to include Warnings and Precautions statements regarding use in patients with various comorbid conditions and accidental injection into the extremities. Similar to other epinephrine auto-injector products, the proposed label notes that there are no absolute contraindications to the use of EAI. At the time of this memorandum, final labeling remains under negotiation.

In addition to physician and patient labeling for the active device, the Applicant also submitted a trainer device with corresponding patient labeling. The trainer has a similar automated auditory prompt system but lacks a needle and active medication. Trainer function and labeling were reviewed in conjunction with the active device. To support potential co-packaging of the trainer with EAI, the Applicant also submitted a human factors study during the review period, noting several safety features intended to minimize misuse of the trainer or accidental substitution of the trainer for the active device. The Division, in conjunction with consultants from the Office of Surveillance and Epidemiology, has concluded that co-packaging of the proposed trainer with the active combination product is acceptable.

The proposed tradename is "e-cue," which is currently under review by the Division of Medication Error Prevention and Analysis (DMEPA).

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

The recommended regulatory action is Approval pending final inspection results and resolution of the patent infringement suit.

- Risk Benefit Assessment

The efficacy and safety of EAI rely on the Agency's previous findings of efficacy and safety for epinephrine in the treatment of allergic reactions and anaphylaxis. The information provided in the application does not alter the known risk benefit profile of epinephrine for the proposed indication, thereby supporting approval of EAI pending final inspection results and resolution of the patent infringement suit.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

No postmarketing risk evaluation and management strategies (REMS) are recommended.

- Recommendation for other Postmarketing Requirements and Commitments

No postmarketing requirements (PMR) and commitments (PMC) are recommended at this time. Recommendations may be forthcoming, depending on the outcome of the ongoing inspections.

- Recommended Comments to Applicant

At the time of this memorandum, no deficiencies have been identified for communication to the Applicant. Comments may be forthcoming, depending on the outcome of the ongoing inspections.

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/s/

SUSAN L LIMB
07/08/2011

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	201-739
Priority or Standard	Standard
Submit Date(s)	September 29, 2010
Received Date(s)	September 29, 2010
PDUFA Goal Date	July 29, 2011
Division/Office	Division of Pulmonary, Allergy, and Rheumatology Products
Reviewer Name(s)	Brian Oscar Porter, M.D. Ph.D., M.P.H.
Review Completion Date	June 22, 2011
Established Name	Epinephrine Autoinjector
(Proposed) Trade Name	e-cue
Therapeutic Class	Sympathomimetic
Applicant	Intellijject
Formulation(s)	Injectable solution
Dosing Regimen	• 0.15 mg IM/SC • 0.30 mg IM/SC
Indication(s)	Acute anaphylaxis
Intended Population(s)	Patients 15-30 kg (0.15 mg) Patients ≥ 30 kg (0.30 mg)

Template Version: March 6, 2009

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List of Abbreviations

EAI	Epinephrine Autoinjector
RLD	Reference Listed Drug
IM	intramuscular
SC	subcutaneous
MAF	Master File
BMI	body mass index
SBP	systolic blood pressure
DBP	diastolic blood pressure
LDL	low-density lipoprotein
OTC	over-the-counter
%CV	percent coefficient of variation
TEAE	treatment-emergent adverse events
PIL	Patient Information Leaflet

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The recommended action is Approval. The 505(b)(2) application supports the approval of Epinephrine Autoinjector (EAI) for the emergency treatment of allergic reactions, including anaphylaxis. The Applicant has established the bioequivalence between EAI and the reference products, EpiPen and EpiPen, Jr. In addition, the simulated clinical use human factors evaluation program demonstrated that the final EAI device posed no significant residual risks associated with potential critical user errors. In addition, safety data from the single bioequivalence study of EAI and the reference listed drug device (EpiPen) revealed no new safety signals or increased risk associated with this novel epinephrine autoinjector, beyond that of the reference listed drug (RLD).

1.2 Risk Benefit Assessment

The safety and efficacy assessment of EAI in the treatment of acute anaphylaxis is based primarily on results generated from a randomized, single-blind, two-treatment, three-period (1 EAI and 2 RLD), single dose, three-sequence crossover trial, known as INT0802. This trial was conducted to demonstrate bioequivalence to a currently approved and marketed RLD (EpiPen) that is known to be safe and effective for this same indication, within the context of known risks and toxicities associated with systemic epinephrine formulated for delivery in an autoinjector device. Having established pharmacokinetic bioequivalence to the RLD using a novel scaled bioequivalency analytical approach, the current 505(b)(2) application relies on the established safety, efficacy, and extensive postmarketing experience with the RLD to support its approval, as well as an extensive human factors usability evaluation program, which assessed the unique design features of the EAI. Despite striking differences in device design from the RLD, the data submitted in this application support the safety, effectiveness, and usability of the EAI for the proposed indication.

In addition to the designated RLD (EpiPen), autoinjectable epinephrine is currently approved and marketed in several other combination drug devices for the treatment of acute anaphylaxis for both adult (0.3 mg dose) and pediatric (0.15 mg dose) use (e.g., TwinJect, Adrenaclick). Although the design features of the EAI (including its novel shape, retractable needle feature, and incorporation of electronic visual and auditory cues) distinguish it from these other devices, critical features such as the delivered drug dose, exposed needle length, and needle gauge fall within the range of these other currently marketed devices, further supporting the safety of EAI for its intended use. Likewise, the most common adverse events associated with epinephrine autoinjectors (e.g., local injection site reactions) and the known class effects of alpha- and beta-adrenergic agonists have been well-characterized for the RLD, as well as from

extensive postmarketing experience with other epinephrine autoinjectors. In turn, these risks are all acknowledged in the proposed EAI product label and were also assessed through the safety monitoring procedures of Study INT0802. Despite the serious nature of many of these potential adverse reactions (e.g., fatal ventricular arrhythmias, tissue ischemia related to incorrect injection site), the significant mortality associated with acute anaphylactic events makes the risk-benefit profile of EAI acceptable, given that no new safety signals were identified in the EAI development program and that bioequivalency to the RLD was adequately established.

Of note, however, the EAI development program did not fully characterize the potential risk of complications resulting from incorrect injection site episodes (e.g., digital injection), which is a relatively common adverse event of significant clinical concern with the RLD. This risk is difficult to assess in the premarketing stage, given the contrived nature of clinical trials. Moreover, the bioequivalence trial (INT0802) and simulated clinical use studies, which comprise the EAI clinical development program could not adequately address this potential complication, by the nature of their study designs. A formal postmarketing requirement or REMS to address this safety risk are not recommended at this time. However, such events may be captured in postmarketing surveillance data that reflect real-world use of the device in emergent, nonclinical settings, in which user anxiety and confusion are not artificially minimized. In turn, this issue is not sufficient to prevent approval of EAI, given the potential for its novel design features to mitigate the risk of user error-related complications.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No postmarketing risk evaluation and mitigation strategies are recommended.

1.4 Recommendations for Postmarket Requirements and Commitments

No postmarketing requirements or commitments are recommended.

2 Introduction and Regulatory Background

2.1 Product Information

Epinephrine Autoinjector (EAI) is a single dose combination drug device, designed for single use administration of intramuscular (IM) or subcutaneous (SC) injectable epinephrine USP 1:1000, a sympathomimetic catecholamine with the following proposed indication:

[redacted] *is indicated in the emergency treatment of allergic reactions (Type I) including anaphylaxis to stinging insects (e.g., order Hymenoptera, which include bees, wasps, hornets, yellow jackets and fire ants) and biting insects (e.g., triatoma, mosquitoes), allergen immunotherapy, foods, drugs (e.g., penicillin, omalizumab), diagnostic testing substances (e.g., radiocontrast media) and other allergens, as well as idiopathic anaphylaxis or exercise-induced anaphylaxis.*

[redacted] *is intended for immediate administration (following exposure to a potential allergen) in patients who are determined to be at increased risk for anaphylaxis, including individuals with a history of anaphylactic reactions.*

Anaphylactic reactions may occur within minutes after exposure and consist of flushing, apprehension, syncope, tachycardia, thready or unobtainable pulse associated with a fall in blood pressure, convulsions, vomiting, diarrhea and abdominal cramps, involuntary voiding, wheezing, dyspnea due to laryngeal spasm, pruritus, rashes, urticaria or angioedema.

[redacted] *is intended for immediate self or caregiver administration as emergency supportive therapy only and is not a substitute for immediate medical care."*

As a non-selective agonist of both alpha and beta adrenergic receptors, epinephrine mediates vasoconstriction, thereby counteracting the vasodilatory, hypotensive, and bronchoconstrictive processes associated with acute anaphylaxis. The Applicant has proposed the trade name of e-cue for this product, which is currently under review at the time of this Clinical Review. Thus, the device henceforth will be referred to as EAI in this document.

In the proposed indication, the Applicant has included the following elements, which differ from the RLD product (EpiPen) label. According to a communication from the Applicant dated January 28, 2011, in response to a request for information sent by the Agency on January 13, 2011, these changes in the Indications and Usage section of the product label are not intended to reflect new claims or indications for use:

- [redacted]

o (b) (4)

o

o

EAI has been developed as an autoinjector unit containing a total of 0.76 mL of epinephrine solution at a concentration of 1 mg/mL. The portable, palm-sized device is rectangular shaped (3.4" x 2.0" x 0.64") with an approximate weight of 64 gm and is contained in an outer plastic case. Both electronic battery-powered visual (LED prompts) and auditory (spoken language prompts) cues are incorporated into the device to facilitate its expedient use and minimize errors of administration and are both activated upon removal of the EAI from its outer case. A removable protective red-colored safety guard is initially in place to prevent premature activation of the device and to visually identify the end of the device that contains the self-retracting injection needle. This needle is attached to a retraction spring and is contained in a moveable black-colored base. The injection needle protrudes upon activation of the device by manually pressing the black base against the skin, thereby triggering the release of an (b) (4) gas-containing chamber (creating an audible hiss) that propels the needle forward and the plunger down through the epinephrine drug cartridge, allowing for delivery of the medication either subcutaneously or intramuscularly, depending on injection site and skin thickness (preferred site: outer thigh). Following delivery of the drug, the retraction spring attached to the needle recoils, thereby retracting the needle and its carrier assembly back into the device housing. Of note, the EpiPen reference product does not contain a retractable needle feature. The EAI device also contains a clear viewing window on the device housing that is visible through the external housing label, which allows direct visualization of the active drug component. Visualization of drug provides confirmation that the device has not already been activated (with release of the drug), as opposed to post-injection, when the needle hub is seen through the viewing window. In addition, following injection, the base of the device will lock against the housing, providing another indicator that the device has been activated and used.

Two separate autoinjectors of identical size but different color schemes have been developed to deliver one of two single use doses of the same formulation of epinephrine:

- 0.3 mg: 0.3 mg/0.3 mL epinephrine injection [USP 1:1000] pre-filled autoinjector for patients weighing ≥ 30 kg (66 lbs); red and green outer color scheme for housing

- 0.15 mg: 0.15 mg/0.15 mL epinephrine injection [USP 1:1000] pre-filled autoinjector for patients weighing 15-30 kg (33-66 lbs); blue and green outer color scheme for housing. EAI has not been studied in patients weighing < 15 kg.

In addition to the color scheme and appropriate dose-related text on the outer labels of the device housing, these two devices also differ in the epinephrine drug cartridge carrier and needle lengths utilized, which are designed to dispense the correct amount of active drug intramuscularly or subcutaneously from an identical drug cartridge, based on the respective dose level (a 0.3 mL dose versus a 0.15 mL dose). The two cartridge carriers are differently colored (0.3 mg is blue and 0.15 mg is green), as another method of differentiation during the manufacturing and assembly process.

2.2 Table of Currently Available Treatments for Proposed Indications

There are currently three other FDA-approved combination drug-device autoinjector products containing epinephrine which are indicated for the treatment of anaphylaxis, as summarized below.

Table 1: Alternative pharmacologic-device treatments currently available for the acute treatment of anaphylaxis.

Product Name	Trade Name	Approval Date	Indication and Age Group	Recommended Dose
NDA 19-430 Epinephrine autoinjector device	• EpiPen (0.3 mg) • EpiPen, Jr. (0.15 mg)	12/22/87	• Patients ≥ 30 kg • Patients 15-30 kg	Single dose devices • 0.30 mg IM/SC • 0.15 mg IM/SC
NDA 20-800 Epinephrine autoinjector device	• TwinJect 0.30 mg • TwinJect 0.15 mg	5/30/03	• Patients ≥ 30 kg • Patients 15-30 kg	Double dose devices • 0.30 mg IM/SC • 0.15 mg IM/SC
NDA 20-800 SCS-018 Epinephrine autoinjector device	• Adrenaclick 0.30 mg • Adrenaclick 0.15 mg	11/25/09	• Patients ≥ 30 kg • Patients 15-30 kg	Single dose devices • 0.30 mg IM/SC • 0.15 mg IM/SC

IM = intramuscular; SC = subcutaneous

In contrast to EAI, none of these three products has a needle retraction mechanism. However, while the total needle lengths of the EAI 0.3 mg and 0.15 mg devices are longer than those of EpiPen and EpiPen, Jr., respectively, as shown in the following table, the exposed needle lengths of the EAI devices (upon injection) and barrel size (gauge) are within the range of currently approved and marketed epinephrine autoinjectors (EpiPen and TwinJect).

Table 2: Comparative needle lengths of EAI versus other epinephrine autoinjector devices (range)

Autoinjector Device	0.15 mg Dose Device			0.3 mg Dose Device		
	Total Length (in)	Exposed Length (in)	Gauge	Total Length (in)	Exposed Length (in)	Gauge
EAI	0.65	0.478	23	0.78	0.618	23
EpiPen	0.56	0.4-0.6	22	0.56	0.5-0.7	22
TwinJect	0.625	0.5	25	0.625	0.5	25

Source: EAI-MAF (b) (4) Amendment 3, Volume 1; Epipen-Medical Officer Clinical Review of NDA 20-800 (May 28, 2004) and Meridian submission to NDA 19-430 (February 6, 1998); (b) (4)

2.3 Availability of Proposed Active Ingredient in the United States

The active ingredient in EAI, epinephrine, is currently available in the United States in combination with three different autoinjector devices as FDA-approved combination products indicated for the acute treatment of anaphylaxis in pediatric patients and adults, as detailed above in Table 1. EAI is not currently approved nor marketed in any country.

(b) (4) However, the proposed RLD was later changed to EpiPen epinephrine autoinjector (NDA 19-430; approved December 22, 1987) in October 2008. EpiPen is currently available by prescription at in two doses: 0.3 mg (EpiPen) and 0.15 mg (EpiPen, Jr.). An updated design was launched in October 2009, with Prescribing Information dated September 2008. The differences between the updated design and the previous version consist primarily of changes to the color and shape of specific components of the EpiPen device and incorporation of a needle cover with sharps protection, along with associated changes to the carton and container labels and the patient instructions for use. An EpiPen trainer autoinjector device containing no medication or needle component is also available with separate patient instructions. The Applicant has cited RLD prescribing information dated April 2009 as the reference Package Insert to which the proposed EAI Package Insert is annotated. However, the EpiPen label to which the Applicant is referring is for the older EpiPen product configuration. There are no substantive differences between the two labels with regard to the PI.

2.4 Important Safety Issues with Consideration to Related Drugs

Significant areas of concern related to this and other epinephrine-containing autoinjector devices cited in the product labels include the following:

1) Local injection site complications, including erythema, induration, pain, or hemorrhage

2) Failure of drug delivery due to improper autoinjector technique

3) Complications associated with of local vasoconstriction and tissue ischemia at inappropriate sites of injection due to improper autoinjector technique

4) Development of transient, moderate anxiety; apprehensiveness; restlessness; tremor; weakness; dizziness; sweating; palpitations; pallor; nausea and vomiting; headache; and/or respiratory difficulties

5) Increase in heart rate or other arrhythmias

6) Development of angina pectoris, fatal ventricular arrhythmias, rapid rises in blood pressure leading to cerebral hemorrhage in patients with heart disease, especially with elderly patients

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The Applicant developed EAI with the goal of creating an autoinjectable self-administered epinephrine delivery device with greater ease of use and a lower likelihood of dosing errors, by virtue of an electronic prompt system with both auditory and visual cues, including voice prompts. The following is a timeline of regulatory highlights of the EAI development program in the United States:

- **July 21, 2005:** Planning meeting with representatives from the Office of Combination Products, CDER, and CDRH, in which CDER was designated the lead review center for a future NDA, given that the action of epinephrine is considered the primary action of the combination product. Multiple CMC recommendations were also provided by the Agency. The Agency also indicated that clinical trial data would be needed to establish the safety and effectiveness of the product. The Applicant was instructed to submit a formal Pre-IND meeting request and briefing package to the Agency.

- **March 9, 2007:** The Agency provided feedback to the Applicant's Pre-IND briefing package (written communication dated February 1, 2007). (b) (4)

(b) (4)

- (b) (4)

- (b) (4)

- **August 7, 2008:** The Applicant submitted a device Master File (MAF) for the single-use EAI, with amendments to the MAF submitted on October 22, 2008, and December 12, 2008.

- **October 17, 2008:** The Applicant (b) (4) the EpiPen and EpiPen, Jr. Autoinjectors marketed at that time, which was deemed acceptable by the Agency.

- **December 19, 2008:** IND 76,367 submitted with the opening protocol for the bioequivalence Study INT0802 of EAI in healthy adults (protocol amendments submitted on February 17, 2009, and March 3, 2009), as well as descriptions of Study INT0801, a human factors usability study of EAI trainer devices, and Study INT0803, a human factors and sharps injury prevention study of EAI (full protocol submitted January 26, 2009).

- **March 25, 2009:** The Agency denied the Applicant's request for Fast Track designation for EAI (submitted February 27, 2009), stating that an unmet medical need had not been established.

- **April 27, 2009:** The Agency informed the Applicant that the plan to change the primary objective of Study INT0802 from bioequivalence to comparative bioavailability is acceptable, although a bioequivalence statistical approach was still recommended for the NDA.

- **October 22, 2009:** The Agency responded to the Applicant's request for a Deferral of Pediatric Studies (submitted September 21, 2009) stating that while it did not appear that pediatric assessment would be required for the proposed product, this decision would be made during the NDA submission.

- **October 23, 2009:** The Agency responded to a pre-NDA briefing package (submitted September 25, 2009), providing input on the planned 505(b)(2) NDA submission. Topics covered included multiple CMC specifications, bioequivalence and pharmacokinetic statistical methodology, electronic dataset submissions, affirmation of EpiPen as the planned RLD, dose accuracy studies for EAI, the designation of EAI software as of Moderate Level of Concern, the final report format for clinical use studies INT0803 and INT0801, the need for patient instructions for use in the proposed labeling, and the planned approach to pediatric product evaluation. The Agency suggested that a pediatric assessment of EAI may not be required, as none of the five PREA triggers apply to EAI (i.e., new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration). However, given the public health need, the Agency still encouraged the Applicant to evaluate EAI in all appropriate age ranges, indicating that a Written Request for pediatric trials could potentially be issued by the Agency under BPCA. The Applicant subsequently cancelled the Pre-NDA Meeting.

- **October 26, 2009:** The Applicant submitted additional questions to the Agency regarding CMC device specifications and to seek concurrence that nurses trained in TwinJect and EpiPen teaching were an appropriate population for clinical use-associated injury prevention studies.

2.6 Other Relevant Background Information

EAI is not currently approved nor marketed in the United States or any foreign country.

3 Ethics and Good Clinical Practices

A review of the ethical and clinical research practices utilized for Study INT0802 revealed no deficiencies which compromised the validity of the data collected.

3.1 Submission Quality and Integrity

Overall, the submission was organized in a manner consistent with Agency guidelines for electronic application submissions. A complete study report for INT0802 was provided and contained all the necessary components for review. Analysis datasets for this biocomparability trial were also provided, as well as a data definition file. Complete study reports were also provided in the EAI Master File for Device for all three human factors simulated clinical use studies INT0801, INT0803, and INT-FE-0901.

3.2 Compliance with Good Clinical Practices

The Applicant has certified that Study INT0802 was conducted in compliance with Good Clinical Practices. The trial was conducted at a single U.S. study center in Baltimore, Maryland. Study INT0802 was the only biocomparability trial submitted in this application. A DSI audit of this study site was requested by the Clinical Pharmacology Review Team. No other safety or efficacy trials conducted with EAI were submitted in this 505(b)(2) application.

3.3 Financial Disclosures

No clinical investigators involved in the clinical program were listed by the Applicant as having any relevant financial disclosures.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

As noted in the NDA CMC Review by Dr. Ying Wang, the designated RLD for EAI consists of a currently marketed formulation of epinephrine. Of note, however, stability testing with EAI revealed that the largest degradant of the active drug product is (b) (4) which accumulates over time to levels as high as (b) (4)% after 18 months in storage. In addition, the preservative used in the manufacturing process of the drug component of EAI is (b) (4), in contrast to the RLD, which uses (b) (4). As noted in the NDA CMC review, (b) (4) degrades to (b) (4) in aqueous solution. In addition, the CMC Review Team also noted that the epinephrine formulation storage specifications of EAI indicate a greater percentage of (b) (4) degradation, as compared to the RLD, from (b) (4)% for EpiPen to (b) (4)% for EAI. While this may not be expected to affect the bioavailability of EAI if used soon after its manufacture, in practical terms, epinephrine autoinjectors are often stored long-term by patients in anticipation of home use in an emergency situation. The submitted drug stability data support the proposed shelf-life of the earlier of 20 months from the manufacturing date for the drug component or 18 months from the date of final drug-device assembly.

At the mid-cycle review meeting for NDA 201-739 held on March 2, 2011, consultants from CDRH also addressed two potential deficiencies in the CMC product testing program: 1) biocompatibility testing should be conducted on the final finished materials for the device components that contact the patient or the drug product; 2) biocompatibility testing of the EAI needle should be conducted or data should be provided to demonstrate that the EAI needle is identical (other than in dimension) to that of the referenced (b) (4) product (b) (4)). These concerns were communicated to the Applicant in a request for information dated March 8, 2011, to which the Applicant responded on March 17, 2011.

A Quality Microbiology Review by Dr. Steven Fong of the (b) (4) manufacturing processes for EAI, which include (b) (4) exposure, indicated that these processes were adequate and well controlled. In addition, consultants from CDRH concurred that no concerns were identified with the sterilization procedures of the EAI manufacturing process.

4.2 Clinical Microbiology

Neither EAI nor the RLD contains an antimicrobial agent; thus, a clinical microbiology assessment has not been done for EAI.

4.3 Preclinical Pharmacology/Toxicology

As discussed in the Pharmacology/Toxicology NDA Review by Dr. Kathleen Young, no new non-clinical information was submitted for this efficacy supplement. The RLD is approved and currently marketed for the same route of administration, indication, and patient population.

4.4 Clinical Pharmacology

The Office of Clinical Pharmacology held a Scientific Rounds session on February 15, 2011, to discuss the scaled bioequivalence analytical approach utilized in the EAI development program, in relation to the RLD. It was agreed that this method of pharmacokinetic analysis could be considered acceptable on an individual case-by-case basis, if a drug demonstrated a sufficient degree of exposure variability (30% threshold), so as to make traditional methods of bioequivalence analysis less robust, and if adequate justification was provided to demonstrate that this variability was not due to poor formulation characteristics. From the epinephrine exposure data submitted, epinephrine meets these criteria, given that this is an endogenous substance, demonstrating highly variable baseline plasma levels from individual to individual, even in the absence of treatment with exogenous drug. In addition, the epinephrine formulation present in EAI is a simple formulation, which is unlikely to contribute to this significant exposure variability. In turn, the use of the scaled bioequivalence approach is acceptable for this submission.

4.4.1 Mechanism of Action

Anaphylaxis is a Type I immediate hypersensitivity reaction, which results in the systemic release of chemical mediators including histamine, prostaglandins, and tryptase from mast cells and basophils following the cross-linking of allergen-bound cell-surface IgE molecules. These mediators lead to vasodilation and capillary leakage, which may result in systemic life-threatening effects including hypotension, bronchoconstriction, and angioedema of the respiratory and gastrointestinal tracts, as well as urticaria and anxiety. As the active drug component of EAI, the mechanism of action of epinephrine in the treatment of anaphylaxis results from its agonist effects on both alpha- and beta-adrenergic receptors. When delivered intramuscularly or subcutaneously, epinephrine has a rapid but short duration of action.

Epinephrine counters the physiological effects of anaphylaxis in several ways. Via its action on alpha-adrenergic receptors, epinephrine causes vasoconstriction and reduces

vascular permeability. Through its action on beta-adrenergic receptors, epinephrine causes relaxation of bronchial smooth muscle cells, which counters the bronchospasm, wheezing, and dyspnea that are associated with anaphylaxis. Epinephrine also relieves pruritus, urticaria, and angioedema of the gastrointestinal and respiratory tracts. As a 505(b)(2) application, no new mechanism of action is presented for EAI, beyond that of the RLD EpiPen.

4.4.2 Pharmacodynamics

No pharmacodynamic trials were conducted in the EAI development program. Biomarkers, such as clinical laboratory tests, which reflect the pharmacodynamic effects of epinephrine, have not been established,

4.4.3 Pharmacokinetics

A single pharmacokinetic biocomparability trial (INT0802) was conducted for the EAI development program. The Applicant did not submit a biowaiver to request an exemption from conducting a bioequivalence trial for the EAI 0.30 mg dose device for this 505(b)(2) application. Study INT0802 was conducted voluntarily by the Applicant and not at the specific request of the Division.

Protocol Title: Study INT0802: A randomized, single-blind, two-treatment, three-period, three-sequence study of the bioavailability of two formulations/delivery devices for epinephrine in healthy human volunteers

Original Protocol Date: December 16, 2008

Amendment Dates: January 8, 2009 (Amendment 1)
February 13, 2009 (Amendment 2)
February 25, 2009 (Amendment 3)

Enrollment Initiation and Completion Dates: February 18, 2009 to March 25, 2009

Final Report Date: July 20, 2010

Study Sites: Single center trial (b) (4)

Primary Objective: To document bioavailability following a single injection of 0.3 mg epinephrine USP 1:1000 administered using EAI and EpiPen under fasted conditions

Secondary Objective: To assess the safety and tolerability of epinephrine injection by EAI compared to EpiPen

Study Rationale: Aqueous epinephrine is indicated for the acute treatment of anaphylaxis as soon as possible, upon manifestation of immediate hypersensitivity symptoms consistent with an anaphylactic reaction. Thus, it is recommended that patients at risk for anaphylaxis have epinephrine capable of self-administration on their person at all times. The Applicant has developed EAI to be portable, ergonomic, and to minimize user error with visual and audible cues. Thus, Study INT0802 is designed to evaluate the bioavailability of EAI 0.3 mg in comparison to the RLD EpiPen 0.3 mg, following intramuscular injection in healthy adults.

Study Design Overview: This bioavailability trial utilized a novel reference replicated-treatment period design as a randomized, single-blind, two-treatment, three-period (1 EAI and 2 RLD), single dose, three-sequence crossover trial to evaluate the bioavailability of epinephrine delivered by EAI versus EpiPen.

Study Population: Participants were healthy male and female young to middle-aged adults aged 18-45 years. The target sample size of 66 subjects was calculated to provide 80% power to establish bioequivalence, using variance estimates derived from the medical literature (Simons et al. Epinephrine absorption in adults: intramuscular versus subcutaneous injection. J Allergy Clin Immunol. 2001. Nov; 108(5):871-3).

Pertinent Inclusion Criteria

- Males or females aged 18 to 45 years, inclusive
- Willing and able to understand and provide written informed consent
- Willing and able to participate in all required study activities
- Body mass index (BMI) between 18.5 and 29.9 kg/m², inclusive, and a weight of $\geq$ 50 kg
- Female subjects of childbearing potential (not surgically sterile and premenopausal or < 2 years postmenopausal, who agrees to contraception from 3 months prior to dosing and throughout the study: hormonal (oral, transdermal, implant, or injection), barrier (condom, diaphragm with spermicide), intrauterine device, or vasectomized partner (6 months minimum)
- No clinically significant abnormal findings on the physical examination, medical history, or clinical laboratory results during Screening
- Blood pressure, pulse, and other vital signs within acceptable ranges prior to dosing

Pertinent Exclusion Criteria

- History of clinically significant gastrointestinal, renal, hepatic, neurologic, hematologic, endocrine, oncologic, pulmonary, immunologic, psychiatric, or

cardiovascular disease, or other condition which would jeopardize safety or impact validity of results (per investigator)

- History of diabetes or cardiac risk factors that would place subject at increased risk of cardiovascular events: family history, hypertension (SBP > 150 or DBP > 95), hypercholesterolemia (total > 300, triglycerides > 225, or LDL > 150)
- History of abnormal heart rhythm, e.g., supraventricular tachycardia or episodic disturbances
- History of conditions (e.g., hyperthyroidism, syncope, panic attacks, migraine) that might place subject at increased risk of adverse events from IM or SC epinephrine
- History of allergic or adverse responses to epinephrine or sulphite
- Subjects who (for whatever reason) have consumed xanthines (caffeine, theobromine) in coffee, colas, or tea during the 24 hours preceding Day 0 (Admission)
- Subjects who donated blood within 56 days or plasma within 14 days of Day 0
- Participation in a clinical trial within 30 days prior to Day 0
- Use of any over-the-counter (OTC) medication, including topical medications (eye drops or nose drops), vitamins, alternative and complementary medicines (including herbal formulations), within 7 days prior to Day 0 or during the study
- Use of any prescription medication within 14 days prior to Day 0 or during the study, with the exception of hormonal contraceptives for women of childbearing potential
- Use of monoamine oxidase inhibitors or tricyclic antidepressants within 30 days prior to Day 0 or during the study
- Treatment with any known CYP450 enzyme altering drugs (e.g., barbiturates, phenothiazines, cimetidine, carbamazepine, etc.) within 30 days prior to Day 0 or during the study
- Smoking or use of tobacco products within 6 months prior to Screening or during the study as determined by a urine cotinine concentration > 200 ng/mL
- Women who are trying to conceive, pregnant, or lactating at Screening or during the study
- Positive serum pregnancy test at Screening or positive urine pregnancy test prior to each drug administration for all women, regardless of childbearing potential

- Positive blood screen for HIV, HBsAg, or hepatitis C antibody at Screening
- Positive urine screen for drugs of abuse, urine cotinine (> 200 ng/mL), or positive breath alcohol test at Screening or during the study
- Subjects who have used alcohol within 72 hours of Day 0
- History of alcohol, cocaine, or any other substance abuse within 6 months prior to Day 0

Study Treatments:

Sixty-six subjects were randomized 1:1:1 to each of 3 treatment sequences of three treatment periods with a single dose each of epinephrine 0.3 mg administered via either EAI (Test Drug = T) or EpiPen (Reference Drug = R). During each treatment period, a single injection of 0.3 mg epinephrine USP 1:1000 was administered, either by EAI in 1 of the 3 treatment periods and EpiPen in the other 2 treatment periods, as shown in the following table:

Table 3: Treatment sequences for INT0802 bioequivalence trial

Treatment Sequence	# of Subjects	Period 1	Period 2	Period 3
1	22	T	R	R
2	22	R	T	R
3	22	R	R	T

T=Test Drug (EAI); R=Reference Listed Drug (EpiPen)
Source: Protocol INT0802, Appendix 16.1.1

In addition to the restricted medications listed in the Exclusion Criteria, alcohol use was also prohibited during the study.

Study Procedures: Following screening, subjects were randomized 1:1:1 to one of three treatment sequences (EAI-EpiPen-EpiPen; EpiPen-EAI-EpiPen; EpiPen-EpiPen-EAI). Single IM doses of epinephrine were administered following a fasting period of at least 10 hours, with at least a 24 hour wash-out period between doses, as specified. Serial pharmacokinetic blood sampling was done in each treatment period at pre-dose and throughout the first 6 hours post-dose at 5, 10, 15, 20, 30, 40, and 50 minutes and 1, 1.25, 1.5, 2, 3, 4, and 6 hours. Safety assessments done pre-dose and post-dose during each treatment period (unless otherwise specified) included adverse events monitoring, concomitant medications, physical examinations (pre-dose and at end-of-study), vital signs, 12-lead EKGs, 2-lead cardiac telemetry, and clinical laboratory tests (pre-dose and at end-of-study). Compliance was ensured by direct observation, as

injectable epinephrine was administered by trained study personnel. Additional subjects were enrolled as needed to ensure 66 completers.

A schedule of trial procedures and assessments is presented in the following table.

Table 4: Timetable of assessments for Study INT0802

Assessments	**Screening** Day -30 to Day -1	**Treatment Period 1**		**Treatment Period 2**		**Treatment Period 3**	
		Day 0 Pre-dose	**Day 1 Tx**	**Day 0 Pre-dose**	**Day 1 Tx**	**Day 0 Pre-dose**	**Day 1 Tx/ End-of-Study**
Informed Consent	X						
Eligibility Criteria	X	X		X		X	
Medical History	X						
HIV/Hepatitis B/C Screen	X						
Serum Pregnancy Test	X						
Urine Pregnancy Test		X		X		X	
Urine Drug Screen	X	X		X		X	
Alcohol Breath Test	X	X		X		X	
Physical Examination	X						X
Vital Signs	X		X		X		X
ECG (12-lead)	X		X		X		X
Telemetry (2-lead)			X		X		X
Clinical Laboratory Tests	X						X
Study Treatment			X		X		X
PK Blood Sampling			X		X		X
Adverse Events		X	X	X	X	X	X
Concomitant Medications		X	X	X	X	X	X

Tx = Treatment
Source: Protocol INT0802, Appendix 16.1.1

Safety Assessments:

- Clinical laboratory tests (hematology, chemistry with hepatorenal function tests and lipid profile, urinalysis with microscopy if abnormal) at baseline and end-of-study
- Physical examination at screening and end-of-study
- 12-lead ECG at baseline and each treatment day at 60 min pre-dose and 6 hours post-dose

- 2-lead cardiac telemetry from 30 min pre-dose to 1.5 hours post-dose
- Vital signs (supine BP, heart rate, oral temperature, and respiratory rate) at baseline and each treatment day at 60 min pre-dose and 6 hours post-dose
- Adverse events on all study days, coded using MedDRA v. 11.1 or higher
- Concomitant medications were assessed in conjunction with any adverse event

Pharmacokinetic Assessments:

Pharmacokinetic Bioavailability Parameters

- C_{max}: maximum plasma concentration
- T_{max}: time to maximum plasma concentration
- $AUC_{(0-t)}$: area under the concentration-time curve from baseline to last measurable concentration
- $AUC_{(inf)}$: area under the plasma concentration-time curve from baseline extrapolated to infinity
- $AUC_{(0-RTmax)}$: area under the concentration-time curve from time zero to time of T_{max} for RLD
- λz: elimination rate constant
- $T_{½}$: terminal elimination half-life

Statistical Analysis Plan: The Statistical Analysis Plan (originally dated May 26, 2009) was revised 3 times: August 10, 2009 (version 2); September 1, 2009 (version 3); March 14, 2010 (version 4). Data were analyzed descriptively, including differences from baseline, where applicable. In addition, pharmacokinetic parameters reflecting bioavailability were compared using a mixed-effects linear model repeated measures ANOVA for the 3-sequence 3-period crossover design. All data from discontinued subjects and completed subjects were included. Bioequivalence was determined using the approach of Haidar et al. (Bioequivalence approaches for highly variable drugs and drug products. Pharm Res. 2008 Jan; 25(1):237-41). Safety data were tabulated for all subjects who received at least 1 dose of study drug. Changes from baseline were summarized via descriptive statistics, as well as shift from baseline.

Of note, the analytical methodology used to assess bioavailability in this trial utilizes a reference-scaling average bioequivalence approach, which is less stringent than the standard requirement of having 95% confidence intervals for test product exposure fall within 80-125% of the RLD. The Applicant justified this alternative approach based on

the high exposure variability seen with EAI (e.g., T_{max} occurring as late as 1 hour post-dose in some patients).

Sample Size Calculation: The required sample size to document bioavailability was considered no higher than that required to evaluate bioequivalence. Estimates of between-subject variability in pharmacokinetic parameters (%CV = 1.13 for Cmax) were drawn from the medical literature (Simons et al. Epinephrine absorption in adults: intramuscular versus subcutaneous injection. *J Allergy Clin Immunol*. 2001. 108(5):871-3). Sample size was estimated using a Monte Carlo computer simulation under various scenarios for high within-subject variability to achieve 80% statistical power with a sample size of 66 subjects, as described by Haidar et al. (Bioequivalence approaches for highly variable drugs and drug products. *Pharm Res*. 2008. 25(1):237-41) and Hyslop et al. (A small sample confidence interval approach to assess individual bioequivalence. *Stat Med*. 2000. 19(20):2885-97).

Summary of Amendment Changes: Amendment 1 (dated December 16, 2008) corrected the weight requirement in the inclusion criteria to ≥ 50 kg and expanded the screening window from 21 to 30 days. Amendment 2 (dated February 13, 2009) clarified the focus of the trial as an assessment of bioavailability, rather than bioequivalence. In addition, the exclusion criteria for subjects at cardiovascular risk were clarified, the trial duration was increased to 44 days per participant, the randomization technique was clarified, the adverse event data collection and vital signs/ECG methodology were clarified, and thigh circumference at end-of-study and methadone levels were removed as assessments. In addition, phlebotomy record-keeping practices and the description regarding sample size determination were clarified. Amendment 3 (dated February 25, 2009) allowed for the enrollment of additional subjects to meet the goal sample size of 66 subjects, as well as clarified the timing of vital signs and ECG/telemetry assessments and the entry criteria prior to treatment periods 2 and 3. In addition, a Note to File dated April 17, 2009, also clarified the use of sodium metabisulfite, rather than sodium bisulfite, as the preservative used in sample processing. None of these amendments significantly impacted the validity of the trial results.

Demographic Results:

A total of 132 subjects were screened, with 66 subjects randomized to the study and 5 more enrolled as replacement subjects. Of these, 64 subjects completed the trial and 7 discontinued early. Baseline demographics of the sample are summarized in the following table.

Table 5: Patient demographics at baseline for Study INT0802

Demographic Variable	Treatment Sequence			Overall N = 71
	TRR N = 24	RTR N = 24	RRT N = 23	
Gender: n (%)				
Male	17 (70.8)	19 (79.2)	17 (73.9)	53 (74.6)
Female	7 (29.2)	5 (20.8)	6 (26.1)	18 (25.4)
Age in years mean (SD)	35.5 (6.3)	33.6 (6.7)	30.2 (5.0)	33.2 (6.3)
Ethnicity: n (%)				
Hisp/Latino	5 (20.8)	4 (16.7)	7 (30.4)	16 (22.5)
Not Hisp/Latino	19 (79.2)	20 (83.3)	16 (69.6)	55 (77.5)
Race: n (%)				
Black/Afr Amer	16 (66.7)	13 (54.2)	7 (30.4)	36 (50.7)
Asian	1 (4.2)	2 (8.3)	0	3 (4.2)
White	7 (29.2)	8 (33.3)	16 (69.6)	31 (43.7)
Amer Ind	0	1 (4.2)	0	1 (1.4)
Height in cm mean (SD)	172.1 (8.6)	174.0 (8.53)	175.2 (10.0)	173.7 (9.0)
Weight in kg mean (SD)	75.5 (9.9)	77.9 (11.6)	77.6 (13.0)	77.0 (11.5)
BMI in kg/m^2 mean (SD)	25.5 (2.6)	25.6 (2.4)	25.2 (3.1)	25.4 (2.7)
Thigh Circ in cm mean (SD)	51.5 (6.9)	49.6 (6.0)	50.0 (6.0)	50.3 (6.3)
Skin-fold thickness in mm: mean (SD)	27.8 (15.5)	30.0 (17.0)	29.2 (12.4)	29 (14.9)
Ex-smoker: n (%)				
Yes	3 (12.5)	5 (20.8)	4 (17.4)	12 (16.9)
No	21 (87.5)	19 (79.2)	19 (82.6)	59 (83.1)

T=Test Drug (EAI); R=Reference Listed Drug (EpiPen); SD = standard deviation; Hisp = Hispanic; Afr Amer = African-American; Amer Ind = American Indian; Circ = circumference

Source: Clinical Study Report for INT0802, Appendix 16.2, Listing 16.2.4.1, Table 14.1.2, Table 14.1.3

An imbalance in the proportion of female versus male subjects is evident across all three randomized treatment sequence arms. In addition, with regard to the racial composition of the sample, although Latino and Black/African-American subjects were well represented in the trial (i.e., at levels greater than in the general population), other ethnic minority groups are minimally represented. However, although certain IgE-mediated allergic diseases (such as asthma) have been shown to disproportionately affect certain ethnic minority groups, there is no evidence that gender or ethnic

differences affect the pathophysiology or treatment of acute anaphylaxis. Moreover, while an imbalance in the racial composition of the RRT treatment sequence arm is evident, compared to the other two treatment sequences, individual subjects served as their own controls in this crossover trial. Thus, this imbalance is unlikely to have had a significant impact on the overall conclusions of the trial, regarding pharmacokinetic comparisons between EAI and the RLD.

Subject Disposition:

A total of 132 subjects underwent screening. Of the 66 subjects who were randomized to the trial and 5 more who served as replacement subjects, 64 subjects completed the trial, with 7 discontinuing prematurely for the following reasons: withdrawn consent (n = 3), protocol deviation from positive urine drug screen (n = 2), adverse event of ventricular extrasystoles (n = 1), and noncompliance with unit regulations (n = 1).

Subject disposition is summarized in the following table:

Table 6: Subject Disposition for Study INT0802

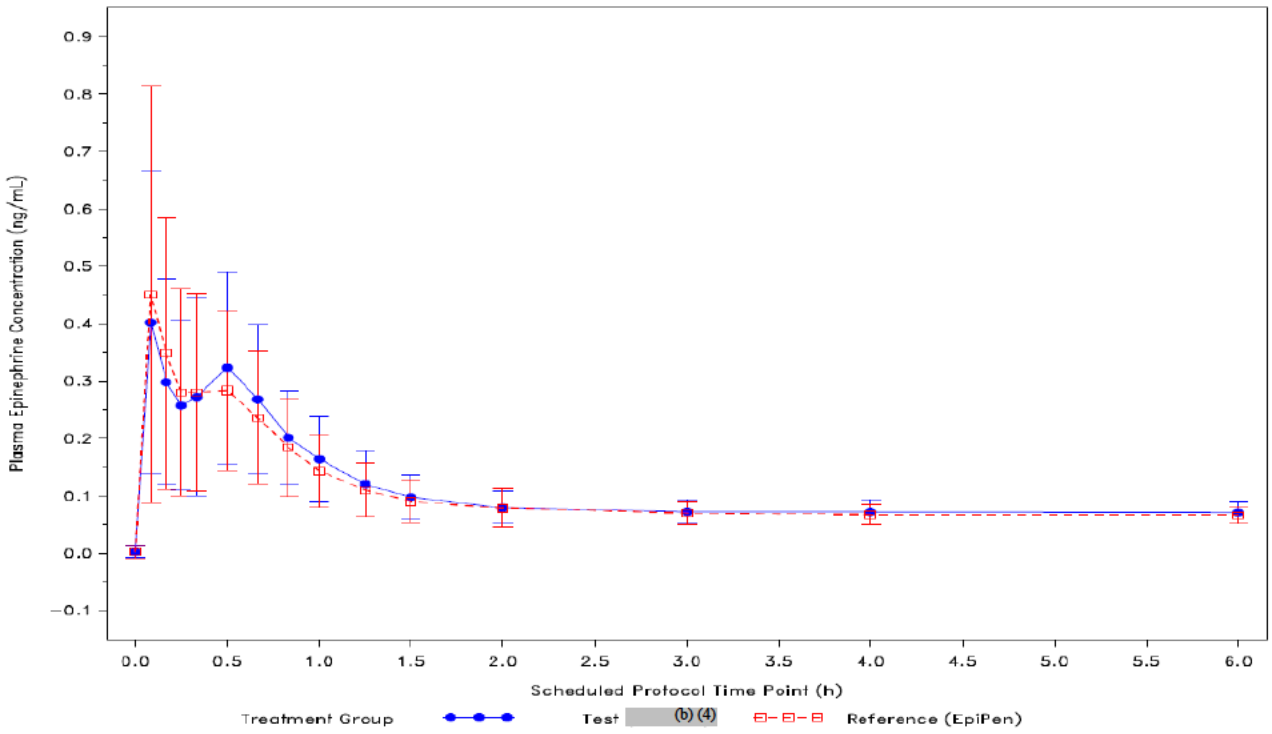
	Treatment Sequence			
	TRR n = 24	**RTR n = 24**	**RRT n = 23**	**Total N = 71**
Enrolled	24 (100%)	24 (100%)	23 (100%)	71 (100%)
Completed Study	22 (91.7%)	21 (87.5%)	21 (91.3%)	64 (90.1%)
Discontinued Study	2 (8.3%)	3 (12.5%)	2 (8.7%)	7 (9.9%)
Timing of Discontinuation				
Prior to Period 1 Tx	0	0	0	0
Prior to Period 2 Tx	2 (8.3%)	2 (8.3%)	0	4 (5.6%)
Prior to Period 3 Tx	0	1 (4.2%)	2 (8.7%)	3 (4.2%)
Reason for Discontinuation				
Adverse Event	1 (4.2%)	0	0	1 (1.4%)
Protocol Deviation	0	1 (4.2%)	1 (4.3%)	2 (2.8%)
Withdrawn Consent	1 (4.2%)	1 (4.2%)	1 (4.3%)	3 (4.2%)
Lost to Follow-up	0	0	0	0
Death	0	0	0	0
Other	0	1 (4.2%)	0	1 (1.4%)

T = Test Treatment (EAI); R = Reference Listed Drug (EpiPen), Tx = Treatment
Source: Clinical Study Report for INT0802, Table 14.1.1

Analysis of Primary Bioequivalence Endpoints:

As the primary measure of bioavailability, plasma epinephrine concentration was quantified for each treatment period, combining data from the two RLD treatment periods in comparison to the single EAI period, as shown in the following figure, in which closed circles represent EAI and open squares represent EpiPen. A total of 71 subjects were included in the pharmacokinetic data analysis set. As indicated in the figure, the plasma-time concentration curves (mean and standard deviation) of these two treatments largely overlapped, with slightly higher epinephrine bioavailability conferred by EAI after 30 minutes post-dose.

Figure 1: Mean and standard deviation of epinephrine concentration over time by treatment group



Source: Clinical Study Report for INT0802, Section 14, Figure 14.2.4.5

A descriptive analysis of the main pharmacokinetic parameters reflective of this overlap is shown in the following table. A comparison of these mean values demonstrates that epinephrine administered via EAI has greater bioavailability and a longer half-life than that of the RLD, although C_{max} was slightly lower for EAI compared to EpiPen.

Table 7: Study INT0802: Main pharmacokinetic parameters by epinephrine delivery system

Treatment		C_{max}	T_{max}	$T_{1/2}$	$AUC_{(0-t)}$	$AUC_{(inf)}$	$AUC_{(0-Rtmax)}$
EAI	N	67	67	59	67	59	49
	Mean	0.486	0.330	1.656	0.536	0.724	0.139
EpiPen	N	135	135	131	135	131	52
	Mean	0.520	0.170	1.139	0.466	0.583	0.119

Source: Clinical Study Report for INT0802, Table 14.2.3, Table 14.2.5

The Applicant analyzed these data for bioequivalence using a mixed-effects linear model via the Haidar method (2008). Similar epinephrine Cmax (peak drug concentration) and total $AUC_{(0-t)}$ exposure (area under the concentration-time curve from baseline to the last measurable concentration) values were obtained between EAI and the RLD. Cmax, $AUC_{(0-t)}$, and $AUC_{(inf)}$ met the equivalence criteria using the baseline corrected dataset, while Cmax and $AUC_{(0-t)}$ met the equivalence criteria using the baseline uncorrected dataset. Therefore, overall it can be concluded that the exposure of the two products is equivalent.

Analysis of Secondary Endpoints:

Safety endpoints were considered secondary in this trial and are reported in Section 7 Review of Safety.

Subpopulations:

Subgroup analysis for INT0802 is not presented by the Applicant.

Analysis of Clinical Information Relevant to Dosing Recommendations:

The proposed dosing is based on the approved dosing for the reference product. In a communication to the Applicant dated March 9, 2007, the Agency agreed that a single bioequivalence study of the higher 0.3 mg EAI dose may support a 505(b)(2) NDA for both the 0.3 mg and 0.15 mg dose levels.

Discussion of Persistence of Effects:

Persistence of effect was not assessed in this biocomparability trial. Epinephrine is known to have a short duration of action. EAI and the RLD are indicated for the acute treatment of anaphylaxis with a single administration of drug that may be repeated if symptoms are severe and persistent. However, proposed EAI labeling indicates that more than two sequential doses of EAI should only be administered under direct

medical supervision. Thus, although dosing with EAI may be repeated over a patient's lifetime if anaphylactic attacks recur, EAI is not meant to be used regularly or chronically. Therefore, the potential for treatment tolerance (a decline in therapeutic effectiveness over time) over time was not assessed beyond this treatment period.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The development program for EAI was based on a single comparative bioavailability trial originally proposed by the Applicant (INT0802) that was submitted to IND 76,367, as shown in the following table.

Table 8: Clinical development program for EAI

Trial	Subjects	Design	Dose	Duration	Relevance
INT0802	69 healthy adults: 23-45 yrs, males and females on birth control	R, AC, 3-sequence, 3-period XO study	0.3 mg IM delivered by EpiPen (2 periods) or EAI (1 period)	Single injection in each of 3 periods	Comparative Bioavailability Study, operationalized as bioequivalence study

R=randomized, AC=active-controlled, XO=crossover; IM=intramuscular

The Applicant also conducted three simulated clinical use studies to evaluate human factors in which no active drug was injected into human subjects (INT0801, INT0803, INT-FE-0901), as summarized in the following table.

Table 9: Human Factors Simulated Clinical Use Studies for EAI

Trial	Subjects	Design	Dose	Duration	Relevance
INT0801	48 non-healthcare workers	OL, summative design simulated clinical use validation study: EAI with and without electronic interactive prompt system compared to two marketed epinephrine autoinjectors	N/A—no active drug given	Single injection	Multiple design changes recommended based on usability findings
INT0803	28 healthcare workers	OL, simulated clinical use study, utilizing injection model (orange) for 18 separate injections with 18 different EAI devices per subject (9 with wet hands and 9 with dry hands)	N/A—no active drug given	Single injection	Incorporated CDRH guidelines on sharps injury prevention and human factor evaluation; no needle retraction failures among 505 EAI model injections
INT-FE-0901	20 adult and 20 pediatric non-healthcare workers	OL, simulated clinical use validation and effectiveness study of Patient Information Leaflet and design changes (safety guard and electronic voice prompt system)	N/A—no active drug given	Single injection	Validation of design changes generated from INT0801

OL=open-label

5.2 Review Strategy

This Clinical Review presents a review of pharmacokinetic and safety data for the single comparative pharmacokinetic trial (INT0802) submitted in support of this 505(b)(2) application to establish the bioequivalency of EAI to the RLD EpiPen (0.3 mg) in adults aged 18-45 years). Trial methodology (including study design and inclusion/exclusion criteria), demographic data, and pharmacokinetic results are described in Section 4.4.3 Pharmacokinetics, whereas safety findings from this trial are presented in Section 7 Review of Safety. In addition, summaries of three human factors simulated clinical use studies designed to optimize the safe use of EAI are also presented in Section 7.4.5 Special Safety Studies/Clinical Trials, including descriptions of the study design, target population, methodology, results, and safety conclusions for each study. A comprehensive literature review was provided by the Applicant of recent drug-related

safety data for subcutaneous and intramuscular epinephrine injection used for the treatment of anaphylaxis, as discussed in Section 9.1 Literature Review/References.

5.3 Discussion of Individual Studies/Clinical Trials

As indicated above, a description of the methodology and pharmacokinetic results of the bioequivalence pharmacokinetic trial INT0802 is found in Section 4.4.3 Pharmacokinetics, with safety results from this trial described in Section 7 Review of Safety. A description of the methodology and findings of the three human factors simulated clinical use studies is found in Section 7.4.5 Special Safety Studies/Clinical Trials.

6 Review of Efficacy

Efficacy Summary

No separate clinical efficacy trials were conducted in the EAI development program.

6.1 Indication

The proposed indication for EAI is the emergency treatment of allergic reactions (Type I) including anaphylaxis to stinging insects, biting insects, allergen immunotherapy, foods, drugs, diagnostic testing substances, and other allergens, as well as idiopathic anaphylaxis or exercise-induced anaphylaxis.

6.1.1 Methods

No clinical efficacy trials were conducted for this application. Therefore, Sections 6.1.2 through 6.1.10 of the Clinical Review template have been omitted.

7 Review of Safety

Safety Summary

Safety of the drug component of EAI, injectable epinephrine solution, has been established for the RLD. In addition, a review of safety data from Study INT0802 and the three simulated clinical use human factors studies revealed no new safety signals with EAI compared to the RLD, major safety issues, or critical concerns that would affect approval of EAI. Treatment adherence in INT0802 was assessed by direct observation of EAI and RLD administration during this clinic-based bioequivalence study. No more than 2 subjects assigned to each treatment sequence failed to complete all 3 treatment periods, resulting in similar exposure to EAI (≥ 91%) and the

RLD (≥ 88%) throughout all 3 treatment periods. Study INT0802 adequately assessed the most common adverse events associated with EAI, which were local injection site reactions (erythema, bleeding, bruising, swelling, and pain). In addition, the main class effects of alpha- and beta-adrenergic agonists (transient anxiety, apprehensiveness, restlessness, tremor, weakness, dizziness, diaphoresis, palpitations, tachycardia, angina, arrhythmias, increases in blood pressure, pallor, nausea, vomiting, headache, respiratory difficulties) were also adequately addressed by the safety monitoring program.

Of note, potential complications arising from incorrect injection site locations (e.g., tissue ischemia of digits) were not addressed in Study INT0802, however, as injections were delivered under direct observation in a controlled setting, rather than as acute therapy in an emergency setting, when usage errors are most likely. However, the theoretical risk of this complication was assessed collectively through the three human factors simulated clinical use studies, as discussed in Section 7.4.5 Special Safety Studies/Clinical Trials. In addition, the extent of this adverse event has most commonly been assessed in the postmarketing phase of autoinjector use, given that this critical use error is largely related to user anxiety and confusion during its use in emergency situations outside of the clinical setting.

Despite being the most common adverse events noted with EAI, local injection site reactions did not differ markedly in type or frequency from those associated with the RLD, as discussed in Section 7.3.5 Submission Specific Primary Safety Concerns. Only injection site pruritus was observed at a greater frequency and in more than one patient following EAI injection than with the RLD (3% versus 0%). However, nearly all localized adverse events were reported as mild, other than one episode of moderate injection site pain reported following injection with each device. Although no severe or serious adverse events were reported, other moderate TEAEs associated with EAI included tachycardia and with the RLD included tachycardia (2 events), nausea, and increased excitability. Heart Rate Increased (17.9% versus 17.8%) and Anxiety (10.4% versus 7.4%) were the most commonly reported Preferred Term adverse events occurring after > 2 doses out of 67 total EAI doses and in a greater percentage than in RLD-recipients, as discussed in Section 7.4.1 Common Adverse Events.

In terms of additional clinical safety monitoring, no clinically relevant changes in laboratory parameters (complete blood count, clinical chemistry with hepatorenal function tests), vital sign assessments, or 12-lead EKG parameters were noted between the randomized treatment sequences in Study INT0802 from baseline to end-of-study, other than a small number of decreased hemoglobin/hematocrit/RBC count values, which appeared related to phlebotomy-induced anemia. In addition, one episode of mild, transient ventricular extrasystoles resulted in the early withdrawal of one subject from Study INT0802. Benign to potentially fatal cardiac arrhythmias are cited in both the proposed EAI and referenced RLD product labels.

As this novel autoinjector device differs markedly in design from the RLD in terms of its shape and incorporation of electronic visual and auditory cues (including voice prompts), collectively, the three simulated clinical use human factors studies conducted with EAI adequately assessed these design features and suggested that they facilitated its appropriate usage and avoidance of critical use errors in adults, children, and healthcare professionals. However, direct conclusions regarding EAI usage in real-life settings cannot be drawn from these simulated use studies, as they utilized sham devices that did not include administration of active drug or contact with needle-based injection mechanisms. Nonetheless, the human factors evaluation program systematically evaluated use-related risks and validated user-performance of the highest priority tasks, noting no outstanding deficiencies that would impact approval of the to-be-marketed device.

In summary, the EAI development program supports the safety of this device for its intended use. Of note, the program was not designed to determine the extent to which the novel electronic user prompts and design features of EAI may minimize complications arising from incorrect injection site episodes (e.g., digital injection), as have been reported in the postmarketing setting for the RLD. While reviews by OSE/DRISK (dated March 21, 2011) and DPARP indicate that a formal postmarketing requirement or REMS is not recommended at this time, the risk of incorrect injection site location is difficult to assess at the premarketing stage, given the contrived nature of clinical trials. Moreover, the bioequivalence trial (INT0802) and simulated clinical use studies that comprise the EAI clinical development program could not adequately address this potential complication, by the nature of their study designs.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The safety profile of EAI is based on Study INT0802, which comprised the primary source data for the safety review. Adverse events and other safety outcomes were assessed for all 71 patients enrolled in Study INT0802, which is adequate in scope for the proposed indication. The safety database for INT0802 consisted of all subjects who received at least one dose of study medication. Overall, 67 subjects received EAI, while 69 subjects received at least one dose of RLD (EpiPen). Secondary data sources included three human factors simulated clinical use studies, which utilized sham devices (without active drug) to inject into inanimate objects, in order to identify safety issues related to administration technique. No additional safety data were reported in the Safety Update submitted by the Applicant during the review process of this submission.

7.1.2 Categorization of Adverse Events

Adverse events were categorized using terminology specified in MedDRA version 11.1, and adverse event data are coded in an acceptable manner.

7.1.3 Pooling of Data across Studies/Clinical Trials to Estimate and Compare Incidence

All safety data are derived from Study INT0802. No other clinical trials were conducted in the EAI development program.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Treatment adherence was assessed by direct observation during administration of study medications within a clinical research unit. No more than 2 subjects assigned to each treatment sequence failed to complete all 3 treatment periods. Overall, there appears to have been similar exposure to EAI (≥ 91%) and the RLD (≥ 88%) throughout all 3 treatment periods, as shown in the following table.

Table 10: Study INT0802: Treatment exposure by sequence

	Treatment Sequence		
Treatment Period	**TRR N = 24**	**RTR N = 24**	**RRT N = 23**
1	24 (100)	24 (100)	23 (100)
2	22 (91.7)	22 (91.7)	23 (100)
3	22 (91.7)	21 (87.5)	21 (91.3)

T=Test Drug (EAI); R=Reference Drug (EpiPen)
Source: Clinical Study Report INT0802, Table 14.1.4

The baseline demographics of the safety population were described previously in Section 4.4.3 Pharmacokinetics. The randomized, active-controlled trial design of Study INT0802 was appropriate to assess safety signals due to EAI in this healthy adult target population. The most common adverse reactions related to local injection site complications (erythema, bleeding, bruising, swelling, and pain) were sufficiently assessed by direct clinical assessment (i.e., interview and physical examination) in Study INT0802. In general, this trial also adequately assessed the major class effects of epinephrine, as an alpha and beta adrenergic receptor agonist, including transient anxiety, apprehensiveness, restlessness, tremor, weakness, dizziness, diaphoresis, palpitations, tachycardia, angina, arrhythmias (including potentially fatal ventricular fibrillation), increases in blood pressure, pallor, nausea, vomiting, headache, and respiratory difficulties. Of note, epinephrine-related increases in blood pressure may potentially lead to fatal cerebral hemorrhage in elderly patients with underlying cardiovascular disease—a safety risk which was not addressed by this trial in healthy adults, but which is included in the proposed EAI class effects labeling.

Similarly, potential complications arising from incorrect injection site locations (e.g., tissue ischemia of digits) were not addressed in Study INT0802, however, as injections were delivered under direct observation in a controlled setting, rather than as acute therapy in an emergency setting, when usage errors are most likely. Given the life-threatening nature of acute anaphylaxis, it would be difficult to design a randomized trial of an experimental therapy that would conform with current standards of medical practice. Incorrect injection site locations are usually observed in the postmarketing period. However, the theoretical risk of this complication was assessed collectively through the three human factors simulated clinical use studies, as discussed in Section 7.4.5 Special Safety Studies/Clinical Trials.

7.2.2 Explorations for Dose Response

Only one dose was evaluated in the bioavailability trial INT0802.

7.2.3 Special Animal and/or In Vitro Testing

No animal or in vitro testing data were submitted with this application.

7.2.4 Routine Clinical Testing

Routine clinical testing consisted of screening laboratory tests including hematology (complete blood count with leukocyte differential count: RBC, hematocrit, hemoglobin, platelets, white blood cells, eosinophils, neutrophils, lymphocytes, monocytes, and basophils), clinical chemistry (serum electrolytes and hepatorenal function tests: glucose, calcium, potassium, sodium, chloride, total bilirubin, alkaline phosphatase, AST, ALT, BUN, creatinine), cholesterol panel (total cholesterol, HDL, LDL, triglycerides), and urinalysis (pH, specific gravity, protein, occult blood, bilirubin, glucose, ketones, macroscopy, and microscopy if indicated), and signs (supine blood pressure, heart rate, oral temperature, and respiratory rate). The schedule of safety assessments, including clinical laboratory tests, is shown in Table 4.

7.2.5 Metabolic, Clearance, and Interaction Workup

Metabolic and pharmacokinetic analyses are discussed in Section 4.4.3 Pharmacokinetics. While no drug interaction data were submitted with this application, potential drug interactions cited in the RLD product label are discussed in Section 7.5.5 Drug-Drug Interactions.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Assessment of the major alpha- and beta-adrenergic receptor agonist class-specific adverse effects in Study INT0802 was described earlier in Section 7.2.1. Given this list of sympathomimetic class-associated adverse effects, as with all epinephrine autoinjectors, EAI should be used cautiously in elderly or debilitated patients and those with pre-existent hypertension, diabetes mellitus, hyperthyroidism, Parkinson's disease, tuberculosis, bronchial asthma, emphysema and degenerative heart disease. While subjects with these comorbidities were not included in the INT0802 study sample, these

conditions are listed in both the proposed EAI label and that of the RLD, as underlying conditions in which EAI should be used with increased caution. Of note, however, given the life-threatening nature of anaphylaxis, no concurrent medical conditions are listed in the product label as contraindications to the emergency use of EAI.

7.3 Major Safety Results

No deaths, serious adverse events, or severe treatment-emergent adverse events (TEAE) occurred in this trial, although one mild TEAE resulted in treatment discontinuation and trial withdrawal.

7.3.1 Deaths

No deaths were reported in Study INT0802.

7.3.2 Nonfatal Serious Adverse Events

No serious adverse events were reported in Study INT0802.

7.3.3 Dropouts and/or Discontinuations

One mild TEAE (as graded by the Applicant) resulted in treatment discontinuation and trial withdrawal (ventricular extrasystoles that occurred in a 44 year-old African-American man approximately 5 minutes after EAI dosing, which resolved spontaneously after 2 minutes).

7.3.4 Significant Adverse Events

No severe adverse events or other significant adverse events consistent with the ICH E3 Guidance for Industry: Structure and Content of Clinical Study Reports (July 1996) were reported for Study INT0802.

7.3.5 Submission Specific Primary Safety Concerns

Multiple types of local injection site reactions were documented following both EAI and RLD administration, although only injection site pruritus occurred at a greater rate after EAI dosing than after RLD and in more than one patient (3% in EAI and 0% in RLD), as shown Table 10. No other injection site reaction occurred at a greater rate following EAI dosing, other than injection site discomfort (1.5% in EAI and 0.7% in RLD), although the clinical significance of this difference is questionable, given that this finding was reported in only one subject in each group. All these localized reactions were considered mild adverse events, except for cases of injection site pain (one subject in each group), which were categorized as moderate. Case report forms or narratives were not provided for these moderate adverse events. Thus, it is not reported whether these reactions required medical intervention, although the Applicant reports that all injection site-related events resolved by end-of-study.

Table 11: Local injection site reactions following EAI and EpiPen Administration

Preferred Term	EAI Doses = 67 N (%)	EpiPen Doses = 135 N (%)
Injection site pruritus	2 (3.0)	0
Injection site discomfort	1 (1.5)	1 (0.7)
Injection site erythema	21 (31.3)	44 (32.6)
Injection site pain	9 (13.4)	33 (24.4)
Injection site hemorrhage	3 (4.5)	13 (9.6)
Application site induration	3 (4.5)	9 (6.7)
Injury, poisoning, and procedural complications	1 (1.5)	3 (2.2)
Procedural pain	0	3 (2.2)
Injection site paresthesia	0	2 (1.5)
Injection site warmth	0	2 (1.5)
Injection site injury	0	1 (0.7)
Injection site induration	0	1 (0.7)

Source: Clinical Study Report INT0802, Table 14.3.1.5

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Adverse events were elicited through open-ended, non-leading questions by the clinician at each patient visit, e.g., "How do you feel?" Resulting responses, as well as spontaneously reported adverse events were classified using MedDRA v.11.1 search terminology. Overall, more TEAEs occurred with EpiPen (87.0% of 196 total doses) compared to EAI (68.7% of 92 total doses). Most (97.6%) TEAE's were classified as mild. Moderate TEAEs associated with EAI included tachycardia and injection site pain, while moderate TEAEs associated with the RLD included tachycardia (2 events), injection site pain, nausea, and increased excitability.

The following table summarizes all Preferred Term adverse events that occurred at a greater rate with EAI-dosing compared to EpiPen-dosing. System Organ Class terms are included for reference.

Table 12: Common adverse events observed in Study INT0802

System Organ Class Preferred Term	Treatment Group	
	EAI Doses=67 N (%)	EpiPen Doses=135 N (%)
Cardiac Disorders	2 (3.0)	3 (2.2)
Ventricular Extrasystoles	1 (1.5)	0
General Disorders and Administration Site Conditions	34 (50.7)	79 (58.5)
Asthenia	1 (1.5)	0
Chest Discomfort	1 (1.5)	0
Chest Pain	1 (1.5)	0
Feeling Hot	1 (1.5)	1 (0.7)
Injection Site Discomfort	1 (1.5)	1 (0.7)
Injection Site Pruritus	2 (3.0)	0
Injury, Poisoning, and Procedural Complications	1 (1.5)	3 (2.2)
Procedural Site Reaction	1 (1.5)	0
Investigations	13 (19.4)	26 (19.3)
Heart Rate Increased	12 (17.9)	24 (17.8)
Musculoskeletal and Connective Tissue Disorders	4 (6.0)	1 (0.7)
Arthralgia	1 (1.5)	0
Back Pain	1 (1.5)	0
Limb Discomfort	1 (1.5)	0
Neck Pain	1 (1.5)	0
Nervous System Disorders	12 (17.9)	23 (17.0)
Dizziness	2 (3.0)	3 (2.2)
Headache	2 (3.0)	2 (1.5)
Somnolence	1 (1.5)	0

Psychiatric Disorders Anxiety Euphoric Mood	8 (11.9) 7 (10.4) 1 (1.5)	14 (10.4) 10 (7.4) 1 (0.7)
Reproductive System and Breast Disorders Spontaneous Penile Erection	1 (1.5) 1 (1.5)	0 0
Respiratory, Thoracic and Mediastinal Disorders Dyspnea	1 (1.5) 1 (1.5)	3 (2.2) 0

Source: Clinical Study Report INT0802, Section 14, Table 14.3.1.5

The only adverse events that were experienced after more than 2 EAI doses and at a greater rate with EAI-dosing were Heart Rate Increased (17.9%), which occurred at nearly an equal rate as with EpiPen (17.8%), and Anxiety (EAI: 10.4% versus EpiPen: 7.4%). Except for Injection Site Pruritus that developed after 2 EAI doses, all adverse events that were disproportionately observed with EAI-dosing and after more than 1 EAI dose are included in the proposed EAI Prescribing Information, which lists all the adverse events from Study INT0802 that occurred at greater than 5% in either treatment group. However, the following unlisted adverse events were observed disproportionately with EAI-dosing and after only a single EAI dose (1.5%): Chest Discomfort, Chest Pain, Feeling Hot, Arthralgia, Back Pain, Limb Discomfort, Neck Pain, Somnolence, Euphoric Mood, and Spontaneous Penile Erection. If chest pain events are pooled (Chest Pain, Chest Discomfort, Musculoskeletal Chest Pain), these events occurred after 3.0% of EAI doses and 0.7% (n = 1) of EpiPen doses. Similarly, if musculoskeletal pain adverse events are pooled (Arthralgia, Back Pain, Limb Discomfort, Neck Pain, Musculoskeletal Chest Pain), these events were observed after 6.0% of EAI doses and 0.7% of EpiPen doses. Given these limited numbers and the difficulty in determining whether a common etiology underlies these grouped adverse event terms, these findings do not appear to represent new safety signals for EAI.

Of note, as clarified by the Applicant in a communication dated March 3, 2011, two tachycardic adverse events occurred in a single patient during one RLD treatment period, but these two events are counted only once in the table above, as they both occurred following the same RLD injection. An additional class-related adverse event that is not included in the table above was palpitations, which occurred in 1 EIA-recipient and 3 RLD-recipients. Mild to moderate injection site pain (EAI: n = 9 or 13.4%; RLD: n = 33 or 24.4%) and injection site erythema (EAI: n = 21 or 31.3%; RLD: n = 44 or 32.6%) were also commonly experienced, but at lower rates in EAI-recipients, compared to RLD-recipients.

7.4.2 Laboratory Findings

No clinically relevant changes in laboratory parameters (complete blood count, clinical chemistry with hepatorenal function tests) from baseline to end-of-study were noted between the randomized groups based on treatment sequence in Study INT0802. That is, although scattered abnormal results were observed in the laboratory test database, there was no evidence of clustering of related abnormalities that would indicate an underlying pathology, other than decreases in hemoglobin/hematocrit/RBC count measures, which the Applicant suggests related to phlebotomy-induced anemia. Given that INT0802 required repeated pharmacokinetic blood draws (total blood volume collected per subject = 324 mL), this explanation reasonably accounts for the clinically significant low hemoglobin values observed in three subjects at end-of-study, ranging from 9-9.5 g/dL, which were reported as mild adverse events.

No patterns of persistent treatment-emergent laboratory abnormalities were observed, as most out-of-range values were preceded by baseline values that were similarly out-of-range in the same direction. Separate analyses of unscheduled laboratory tests were not provided, and no unscheduled hospitalizations were reported.

The following table summarizes the median shifts from baseline (screening) values in individual laboratory parameters (hematology, hepatorenal function tests, cholesterol panel, urine specific gravity) for each randomized treatment sequence. The sample sizes indicated are the number of subjects with baseline values. Sample sizes at follow-up were within 19-24 subjects, across the three treatment sequences.

Table 13: Median screening (baseline) and end-of-study values for selected safety laboratory parameters in epinephrine-treated subjects by randomized treatment sequence

	Treatment Sequence					
	TRR N = 24		RTR N = 24		RRT N = 23	
Laboratory Parameter	**Screening**	**End-of-Study**	**Screening**	**End-of-Study**	**Screening**	**End-of-Study**
Hgb (g/dL)	13.8	13.2	14.0	13.5	14.0	13.1
Hct (%)	41.3	39.5	42.4	40.6	42.0	38.3
RBC (10^6/mcL)	4.8	4.4	5.0	4.7	4.9	4.5
WBC (10^3/mcL)	5.6	5.9	6.2	6.2	6.2	5.6
Platelets (10^3/mcL)	262.5	252.0	233.0	247.0	247.0	236.0

Neutrophils (10^3/mcL)	2.8	3.8	3.4	3.6	3.2	3.5
Lymphocytes (10^3/mcL)	1.9	1.7	2.1	1.6	2.1	1.7
Monocytes (10^3/mcL)	0.4	0.4	0.4	0.4	0.5	0.4
Eosinophils (10^3/mcL)	0.1	0.1	0.1	0.1	0.1	0.1
Basophils (10^3/mcL)	0	0	0	0	0	0
BUN (mg/dL)	12.0	11.0	10.0	10.0	13.0	11.0
Creatinine (mg/dL)	0.90	0.85	0.90	0.90	0.90	0.80
Glucose (mg/dL)	80.0	90.0	83.0	84.0	79.0	92.0
Calcium (mg/dL)	9.7	9.6	9.6	9.3	9.7	9.3
Chloride (mmol/L)	105.0	105.0	105.0	104.0	105.0	105.0
Potassium (mmol/L)	4.5	4.2	4.4	4.1	4.3	4.1
Sodium (mmol/L)	142.5	140.0	141.0	141.0	142.0	141.0
AST (U/L)	27.5	27.0	27.0	28.0	25.0	24.0
ALT (U/L)	30.0	28.0	29.0	25.0	27.0	26.0
Alk Phos (U/L)	72.0	63.5	68.5	65.0	66.0	64.0
Tot Bili (mg/dL)	0.30	0.40	0.45	0.40	0.40	0.40
Cholesterol (mg/dL)	175.5	166.0	170.0	174.0	174.0	163.0
HDL (mg/dL)	50.5	49.0	51.0	46.0	52.0	42.0
LDL (mg/dL)	101.5	100.0	100.0	101.0	99.0	96.0
Triglycerides (mg/dL)	62.5	116.5	75.5	95.0	70.0	80.0

T = Test Drug (EAI); R = Reference Listed Drug (RLD)
Source: Clinical Study Report INT0802, Table 14.3.2.1, Table 14.3.2.2

The following table summarizes the number and percentage of subjects whose laboratory values shifted from normal at baseline (screening) to either above or below normal limits at end-of-study. Only those subjects with baseline values within the normal range are listed, and laboratory tests with no shifts from normal to abnormal in any subjects across all three treatment sequences are not shown.

Table 14: Frequency and percent of subjects with normal clinical laboratory values at baseline who shifted to abnormal values (H = high; L = low) at end-of-study by randomized treatment sequence

	Treatment Sequence								
	TRR N = 24			RTR N = 24			RRT N = 23		
Laboratory Parameter	**Total N**	**Freq**	%	**Total N**	**Freq**	%	**Total N**	**Freq**	%
Hgb-L > 12 g/dL in F > 13 g/dL in M	21	7	33.3	18	3	16.7	19	7	36.8
Hct-L < 37% in F < 42% in M	10	6	60	15	9	60	16	13	81.3
RBC-L < 4.1 x10^6/mcL in F < 4.6 x10^6/mcL in M	19	6	31.6	19	3	15.8	18	10	55.6
WBC-H > 10.8 x10^3/mcL in F > 10.8 x10^3/mcL in M	16	0	0	19	0	0	20	1	5.0
WBC-L < 4.8 x10^3/mcL in F < 4.8 x10^3/mcL in M	16	2	12.5	19	2	10.5	20	4	20.0
Neutrophils-H > 8 x10^3/mcL in F > 8 x10^3/mcL in M	20	0	0	22	0	0	22	1	4.5
Neutrophils-L < 2 x10^3/mcL in F < 2 x10^3/mcL in M	20	2	20.0	22	1	4.5	22	1	4.5
Monocytes-H > 0.7 x10^3/mcL in F > 0.7 x10^3/mcL in M	24	0	0	23	3	13	22	1	4.5
BUN-L < 7 mg/dL in F < 9 mg/dL in M	23	0	0	18	2	11.1	21	1	4.8
Glucose-H > 106 mg/dL in F > 106 mg/dL in M	18	2	11.1	19	3	15.8	17	0	0

Glucose-L < 74 mg/dL in F < 74 mg/dL in M	18	1	5.6	19	2	10.5	17	1	5.9
Calcium-L < 8.4 mg/dL in F < 8.4 mg/dL in M	23	0	0	23	0	0	22	1	4.5
Chloride-H > 107 mmol/L in F > 107 mmol/L in M	19	2	10.5	23	2	8.7	21	1	4.8
Potassium-H > 5.1 mmol/L in F > 5.1 mmol/L in M	24	4	16.7	23	2	8.7	23	1	4.3
Potassium-H < 3.5 mmol/L in F < 3.5 mmol/L in M	24	0	0	23	0	0	23	1	4.3
Sodium-L < 137 mmol/L in F < 137 mmol/L in M	21	1	4.8	23	1	4.3	22	0	0
AST-H > 36 U/L in F > 59 U/L in M	24	3	12.5	23	1	4.3	23	0	0
ALT-H > 52 U/L in F > 72 U/L in M	24	0	0	23	0	0	21	1	4.8
ALT-L < 9 U/L in F < 21 U/L in M	24	2	8.3	23	1	4.3	21	1	4.8
Alk Phos-L < 38 U/L in F < 38 U/L in M	24	0	0	23	0	0	23	1	4.3
Tot Bili-H > 1.3 mg/dL in F > 1.3 mg/dL in M	21	1	4.8	16	1	6.3	22	0	0
Tot Bili-L < 0.2 mg/dL in F < 0.2 mg/dL in M	21	2	9.5	16	0	0	22	3	13.6
Cholesterol-H > 200 mg/dL in F > 200 mg/dL in M	18	2	11.1	19	1	5.3	20	1	5.0
Cholesterol-L < 120 mg/dL in F < 120 mg/dL in M	18	0	0	19	2	10.5	20	3	15.0
HDL-H > 60 mg/dL in F > 60 mg/dL in M	15	1	6.7	11	0	0	14	0	0

HDL-L < 40 mg/dL in F < 40 mg/dL in M	15	1	6.7	11	1	9.1	14	2	14.3
LDL-H > 99 U/L in F > 99 U/L in M	10	2	20.0	10	1	10.0	13	2	15.4
Triglycerides-H > 149 mg/dL in F > 149 mg/dL in M	20	3	15.0	22	0	0	19	2	10.5

T = Test Drug (EAI); R = Reference Listed Drug (RLD)
Source: Clinical Study Report INT0802, Table 14.3.2.3, Table 14.3.2.4

There were only a small number of subjects with laboratory values outside of normal limits at baseline, which shifted to the opposite extreme at end-of study (versus remaining at the same extreme or shifting to within normal limits): glucose from low to high (TRR = 2 subjects, RTR = 1 subjects, RRT = 3 subjects); HDL from high to low (TRR = 1 subject). A shift from low to high glucose in these patients was consistent with known sympathomimetic class effects, but following a review of patient level data listings, none of these changes were clinically significant.

7.4.3 Vital Signs

Line listings of vital signs data for blood pressure, heart rate, respiratory rate, and oral temperature were provided. However, descriptive statistics and shift change data were only provided for heart rate and blood pressure. A review of line listing data for all patients revealed no extreme abnormal values for respiratory rate (12 to 22 breaths per minute, inclusive) or temperature (36.2 to 37.3 ^{o}F, inclusive). In addition, no clinically relevant median changes in vital signs (blood pressure, heart rate) were noted between EAI and RLD groups in any treatment period, as shown in the following table of median shifts from baseline values.

Table 15: Baseline (pre-dose) vital sign values and post-dose change by treatment period for EAI versus EpiPen treatment groups

	Test = EAI						**RLD = EpiPen**					
	Period 1		**Period 2**		**Period 3**		**Period 1**		**Period 2**		**Period 3**	
	Pre	**Δ**	**Pre**	**Δ**	**Pre**	**Δ**	**Pre**	**Δ**	**Pre**	**Δ**	**Pre**	**Δ**
N	**24**	**24**	**22**	**22**	**22**	**22**	**47**	**47**	**45**	**45**	**43**	**43**
SBP	116.5	-2.5	112.5	1.5	116.0	3.0	114.0	2.0	110.0	2.0	110.0	3.0
DBP	71.0	-4.0	67.0	0	65.5	0	67.0	-2.0	65.0	1.0	66.0	-1.0
HR	67.0	10.5	61.5	10.0	63.5	12.0	62.0	12.0	62.0	13.0	66.0	9.0

Pre = pre-dose value; Δ = change in post-dose value; *N = number per treatment period by group; SBP = systolic blood pressure in mmHg; DBP = diastolic blood pressure in mmHg; HR = heart rate*
Source: Clinical Study Report INT0802, Table 14.3.3.1, Table 14.3.3.2

Several treatment-emergent adverse events related to heart rate were noted: 12 events of tachycardia in a total of 12 subjects after exposure to EAI and 25 events of tachycardia in a total of 17 subjects after exposure to the RLD. In addition, 1 report of palpitations was noted in 1 subject following injection with EAI, whereas 3 reports of palpitations were noted in 3 subjects following injection with the RLD. Specifically, one event of transient ventricular extrasystoles was noted in a 44 year-old African-American man 5 minutes after injection of 0.3 mg, which resulted in discontinuation from the trial, although the event resolved spontaneously within 2 minutes of onset without sequelae. Arrhythmias are a known potential adverse effect of epinephrine, which are listed in both the EAI and RLD product label.

7.4.4 Electrocardiograms (ECGs)

Individual patient line listings and descriptive statistics of QT interval data (QTcB and QTcF) from pre-dose and post-dose 12-lead ECGs done were provided. No post-treatment increases in QTcF from pretreatment of > 30 msec were noted, although 8 subjects had an increase of > 30 msec in QTcB: 4 following receipt of EAI ranging from 35-46 msec with a maximum value of 447 msec; 4 following receipt of the RLD ranging from 39-52 msec with a maximum of 440 msec. Three subjects were noted to have prolonged baseline QTcB values following receipt of the RLD, although only one of these subjects had a post-dose QTc prolongation as well (QTcB = 456 msec; QTcF = 450 msec). These individual ECG findings do not reflect clinically significant safety signals, and no clinically relevant changes in QT interval were noted between EAI and RLD groups in any treatment period, as shown in the following table of median shifts from baseline values.

Table 16: Baseline (pre-dose) QTcB/QTcF values and post-dose change by treatment period for EAI versus EpiPen treatment groups

	Test = EAI						RLD = EpiPen					
	Period 1		Period 2		Period 3		Period 1		Period 2		Period 3	
	Pre	Δ	Pre	Δ	Pre	Δ	Pre	Δ	Pre	Δ	Pre	Δ
N	**24**	**24**	**22**	**22**	**22**	**22**	**47**	**47**	**45**	**45**	**43**	**43**
QTcB	410.0	1.5	400.0	2.5	407.0	2.0	408.0	6.0	402.0	5.0	397.0	6.0
QTcF	406.0	-10.0	400.5	-9.5	401.5	-6.0	402.0	-6.0	407.0	-8.0	401.0	-6.0

Pre = pre-dose value; Δ = change in post-dose value; *N = number per treatment period by group*
Source: Clinical Study Report INT0802, Table 14.3.4.1, Table 14.3.4.2

Two-lead cardiac telemetry was also performed from 30 minutes pre-dose to at least 1.5 hours post-dose during all treatment periods, which identified the case of ventricular extrasystoles, which was categorized as a mild adverse event.

7.4.5 Special Safety Studies/Clinical Trials

Human Factors/Clinical Use Studies

Three simulated clinical use studies were completed for EAI. Collectively, these studies assessed usability factors of the EAI across several populations: adults and children, parents of food allergic children, health care professionals, and subjects with and without prior experience using an autoinjector device or familiarity with anaphylaxis. These three human factors studies were conducted sequentially (INT0801 → INT0803 → INT-FE-0901), although independently of the bioequivalence trial INT0802, which was conducted over approximately the same time frame as Study INT0803. Thus, INT0802 was not conducted with the final version of the EAI device. However, the device differences primarily involved aspects of the electronic prompt system, rather than mechanical aspects of drug delivery. Thus, given that Study INT0802 was conducted under direct clinical observation (thereby ensuring medication adherence and proper drug delivery), these design differences are unlikely to have affected the bioavailability results of INT0802.

The training components of the proposed EAI product evaluated through this human factors evaluation program included visual text and graphic stepwise labeling on the device surface, an electronic task-dependent voice instruction system with accompanying visual LED cues, patient- and healthcare-oriented leaflets to describe the EAI product and its use, and an EAI trainer device (without active drug or needle), which will be dispensed with each prescription of the active drug device for training purposes. Collectively, the findings from these studies support the role of various design features of the EAI device that facilitate its appropriate usage in self-administered or healthcare worker-administered settings. However, direct conclusions regarding EAI usage in real-life settings cannot be drawn from these simulated use studies, as they utilized sham devices that did not include administration of active drug or contact with needle-based injection mechanisms. Thus, while these studies do not provide direct safety data regarding the clinical use of EAI, they identified potential usability problems and design flaws (which was the primary objective of these simulated clinical use studies), allowing for subsequent modification of the EAI device to improve ease of use. In addition, an independent review by CDRH of the human factors testing program indicated the Applicant has systematically evaluated use-related risks and validated user-performance of the highest priority tasks, with no outstanding deficiencies noted.

Study INT0801: Summative Validation Study of EAI in Non-healthcare Workers

Enrollment Initiation Date: May 10, 2008

Enrollment Completion Date: June 12, 2008

Design and Methods

Study INT0801 was an open-label summative design validation study of EAI in 48 non-healthcare workers with varying levels of prior experience with autoinjector devices (evenly divided into 50% of sample with some level of prior experience with epinephrine autoinjector devices and 50% with no prior experience), who the Applicant felt adequately represented the projected target population for EAI use. The sample was stratified into 3 age categories with 16 subjects each: 7-10 year olds, 11-15 year-olds, and 16-55 year-olds. Subjects were required to be native English speakers with at least a second grade reading level and normal (with or without correction) vision and hearing.

This study evaluated the association of human factors with subject feedback on the usability and design of two versions of a modified EAI without active drug or needles--one with an interactive electronic voice prompt system and one without. Usability of these two investigational versions of EAI was also compared to that of two currently marketed products, the RLD EpiPen and the TwinJect epinephrine autoinjector. Subjects demonstrated use of the EAI devices, as well as the other two autoinjector devices, in randomized order under simulated stress conditions (increasing frequency and intensity of audible beeping, small study room, presence of study investigator). No formal training in the use of the devices or product labeling was offered, other than the instructions and graphics as they appeared on the devices themselves.

Data were collected via direct observation (via videotaping) by the investigator during simulated use on the outer thigh, as well as through subjective feedback from the participants in response to both open-ended and closed-ended structured questions. Correct adherence to the device's use protocol was defined as the absence of all of 13 predefined user errors. Use errors were classified as to whether they would have been likely to prevent adequate delivery of active drug during an actual use setting. Both descriptive and inferential statistics (95% confidence intervals for probability estimates and analysis of variance for multi-group comparisons) were used to compare use outcomes between the four autoinjector devices (EAI with electronic voice prompts, EAI without electronic voice prompts, EpiPen, and TwinJect). Overall, the design, target population, and execution of this trial were appropriate for identifying design flaws at this relatively early stage in the EAI development program.

Summary Results

Collectively, subjects experienced fewer use errors with EAI, with a greater likelihood of successful injection (defined as the absence of critical use errors, which would have

resulted in a failure of drug delivery in a real-use setting), even in the absence of prior device training (88% for EAI with electronic voice prompts, 91% for EAI without voice prompts; 74% for EpiPen; 68% for TwinJect). As might be expected, prior experience with epinephrine autoinjectors resulted in trends toward increased rates of successful injections with EAI (92% in experienced subjects versus 82% in inexperienced subjects). Of note, only 50% of younger pediatric subjects (7-10 years old) demonstrated successful injections, although this rate increased to 98% in older pediatric subjects (11-15 years old). The percentage of subjects successfully completing the entire protocol without committing any of the 13 predefined use errors (consisting of both critical and non-critical use errors) was much lower, although it was still highest in the group using the EAI with electronic voice prompts (45.8% for EAI with voice prompts, 27.1% for EAI without voice prompts, 12.5% for EpiPen, and 0% for TwinJect).

The complete EAI unit that included electronic voice prompts demonstrated fewer user errors than EAI without voice prompts, EpiPen, or TwinJect devices. Subjects also indicated a greater preference for EAI with the interactive prompt system with regard to size, shape, ease of use and ability to carry, instructions for use, and safety, compared to the three other devices. Given that all subjects used each of the four devices during the course of the study, the order in which subjects used each device (based on random assignment) was noted to impact their potential for a successful injection, as might be expected, given the potential for systemic bias related to recent use experience. In turn, critical use errors were more common with each device if it was used during the initial treatment period, while error rates were noted to decrease with each device in later treatment periods.

As with the other devices, critical use errors with the EAI device with electronic prompts were more commonly reported in pediatric than adult patients, including the following: incorrect injection sites other than muscle (n = 5), failure to inject at all (n = 3), did not remove safety caps (n = 3). In addition, use data for all four devices indicated that younger pediatric subjects aged 7-10 years were less likely to follow labeled device instructions and experience error-free use, as compared to older subjects.

Safety Conclusions

The findings from Study INT0801 supported further refinement of the EAI device, suggesting its potential role in achieving greater patient compliance and minimizing user error, as a novel epinephrine autoinjector for emergency self-administration in either adult or pediatric subjects. Although both adult and pediatric subjects demonstrated fewer use errors with the EAI device that contained the interactive electronic voice prompt system compared to the other 3 autoinjector devices, the Applicant states that post-hoc risk analysis identified several aspects of the device for potential improvement, which were later validated in Study INT-FE-0901:

1) Redesign of the red safety guard with increased tactile features and clarified use instructions in the product label to minimize difficulty with removal (particularly in pediatric patients) and premature removal
2) Redesign of voice prompts for the electronic prompt system and design updates to improve battery functionality and eliminate tear-through switch malfunctions, which were subsequently verified through *in vitro* testing
3) Revision of label to emphasize correct injection location
4) Revision of Prescribing Information and Patient Information Leaflet (PIL) to encourage training prior to use, with inclusion of a Trainer device and Trainer Information Leaflet with initial EAI prescriptions

Study INT0803: Sharps Prevention and Use Testing of EAI in Healthcare Workers

Enrollment Initiation Date: February 2, 2009

Enrollment Completion Date: February 27, 2009

Design and Methods

Study INT0803 was an open-label formative evaluation study of EAI in 28 healthcare workers (nurses) that utilized additional simulated clinical use testing per CDRH guidelines on Medical Devices with Sharps Injury Prevention Features and Human Factors Evaluations. Subjects were aged 18 to 65 years old and consisted of 25 male and 3 female healthcare workers (practicing nurses) familiar with the use of RLD, having either used or trained patients on the use of the EpiPen within the last 12 months of the study. All subjects were native English speakers with normal (with or without correction) vision and hearing.

This validation and formative study evaluated the effectiveness of an updated safety guard design, overall use of the device, and specifically the retractable needle feature through a simulated injection into an orange (to simulate human skin and muscle) 18 separate times with 18 different EAI devices per subject (9 with wet hands and 9 with dry hands). All subjects received training for the EAI with an EAI Trainer device before the simulated injection. Following simulated testing, subjects provided subjective feedback on multiple aspects of use, which included examining EpiPen and TwinJect devices that had been activated, although the study was not designed to directly compare use aspects of EAI versus EpiPen or TwinJect devices, which do not include retractable needle mechanisms. Descriptive statistics were used to describe use aspects, rather than inferential statistics. Overall, the design, target population, and execution of this trial were appropriate for evaluating the reliability of the retractable needle design system, as a total of 505 devices were tested (one more device than originally planned).

Summary Results

A total of 505 EAIs (0.3 mg dose) were tested, all of which demonstrated successful needle retractions with either wet or dry hands. In the use assessment, all 28 subjects used the device properly, while a majority of subjects indicated that they "agreed" or "strongly agreed" with the following statements regarding EAI use:

- Easy to use (79%)
- Worked well with hand size (86%)
- Did not require extensive training (89%)
- Designed to be used correctly (96%)
- Designed so as not to miss a crucial step in proper use of the device (100%)
- Did not require multiple uses to learn how to use EAI correctly (96%)
- Electronic voice instructions were a positive feature (93%)
- Audible prompts were loud enough (75%)
- Size preferred to EpiPen and TwinJect (79%)
- Shape preferred to EpiPen and TwinJect (68%)
- Ease of patient training greater than with EpiPen and TwinJect (93%)
- Perceived safety greater than for EpiPen and TwinJect (96%).

Additional comments indicated that some subjects found the device difficult to hold and indicated that it should be conveyed more clearly that the device can inject through clothing. These findings led to changes addressing these issues in the Instructions for Use portion of the EAI labeling, as well as in the PIL.

Safety Conclusions

Overall, this study demonstrated the reliability of the automatic needle retraction system, although the injection model (orange) cannot adequately replicate actual self-administration in an emergency setting, given that the attendant pain associated with medication delivery (i.e., injection) was not replicated in this scenario for obvious reasons. Thus, while this study supported the reliability of the automatic mechanism of the needle retraction system, it does not provide support that the device will be utilized correctly if administered to self or other patients (i.e., changes in positioning related to patient withdrawal from the injection site or user hesitancy during the process of needle triggering, related to pain, anxiety, and/or startle reaction by the injection recipient).

Study INT-FE-0901: Validation and Effectiveness Study of EAI PIL and Design Changes

Enrollment Initiation Date: April 8, 2010

Enrollment Completion Date: April 20, 2010

Design and Methods

Study INT-FE-0901 was an open-label labeling comprehension, validation, and effectiveness study of the EAI Patient Information Leaflet (PIL) in 40 participants (20 adult and 20 pediatric subjects) at a single community allergy clinic. A secondary objective of the study was to validate design changes to the safety guard and electronic voice prompt system, which were generated from the usability findings of device-related errors and residual risks from Study INT0801. Subjects completing the study ranged in age from 7 to 55 years, with 20 older subjects aged 16 to 55 years and 20 pediatric subjects aged 7 to 15 years. Subjects were required to be native English speakers with at least a second grade reading level and normal (with or without correction) vision and hearing. Eighty percent of adult participants and 35% of pediatric participants reported having had previous experience with an epinephrine autoinjector.

A modified version of EAI was used (without the gas cylinder, active drug, or needle) to simulate injection, relying solely on the Instructions for Use section of the PIL, written instructions for use in the device label, electronic voice prompts, and visual LED prompts on the outside of the EAI device itself, without any interactive training from the investigator or other study staff. Both the 0.3 mg and 0.15 mg dosing devices were used, depending on patient age and weight (i.e., 0.15 mg pediatric devices were used by pediatric subjects). Pediatric patients were instructed in the product's use by their parents only, and then demonstrated simulated use of the product on their own, without assistance from study investigators or parents.

Subjects were directly observed (and videotaped) to evaluate their use skills based on six defined instructions-for-use/injection steps. Critical user errors were defined as steps in this process that were not completed, and successful injection was defined as a subject who had completed all 6 steps, with or without accompanying use issues in one or more steps, as the Applicant states such issues would only cause a minor delay in medication delivery, but would not prevent the successful delivery of active medication in an actual use setting. Pediatric subjects were allowed two attempts to complete each step, with repeated parental training, if needed. In addition, detailed, probing post-test analysis was conducted on all subjects following the simulated injection, in order to obtain subjective feedback on participants' experiences with each of the defined injection steps, helpfulness of the electronic prompt system, as well as overall ease of use of the device. Of note, these patient-reported outcomes varied in format, including open-ended probing questions, closed-ended questions with evenly graded response scales (e.g., strongly disagree, disagree, agree, strongly agree), yes/no responses

questions, and closed-ended questions with arguably uneven response scales (e.g., Did not help at all; Helped a little; Helped me a lot). Overall, however, the design, target population, and execution of this trial were appropriate for validating design changes made to the EAI, based on findings from the earlier summative design validation study INT0801.

Summary Results

No adverse events were reported during the study. All adult subjects were able to successfully simulate clinical use of EAI without a critical user task error, based solely on the PIL and device label for prior use instructions, with 92.5% of all participants indicating the PIL was very easy/simple or easy to follow. When questioned post-test on aspects of EAI use using a graded response scale (strongly disagree, disagree, agree, strongly agree), all adult subjects (100%) answered either “agree” or “strongly agree” that the PIL was effective in training them to use the EAI, while 95% answered “agree” or “strongly agree” that the PIL provided all the key information needed to use the EAI safely and effectively. Of note, three subjects indicated that more force than expected was needed to trigger medication delivery by pressing the EAI against the outer thigh, with these subjects requiring repeated electronic voice prompts to complete this step of the injection process.

The Sponsor reports that only one pediatric subject relied on direct training from a parent during the simulated injection; although it is also stated that all pediatric patients received training from their parents prior to attempting to remove the EAI safety guard. In turn, all 20 pediatric subjects successfully removed the safety guard on their first attempt, although with 45% of subjects (n = 9) indicating that more force was needed to remove the cover than expected. In addition, all but one pediatric participant completed each use step (either with or without accompanying use issues) on their first attempt. Moreover, 95% of pediatric subjects stated they felt having their parents read the PIL made it easy for them to understand how to use the EAI, while 100% stated that the PIL contained all the information needed for their parents to teach them its proper use. Overall, 85% of pediatric subjects indicated that the electronic voice prompt system “helped them a lot,” while 15% indicated it “helped them a little bit.”

Safety Conclusions

The following design modifications generated by initial findings of INT0801 were also validated:

1) Redesign of the red safety guard with increased tactile features and clarified use instructions in the product label

2) Redesign of voice prompts for the electronic prompt system and design updates to improve battery functionality and eliminate switch malfunctions

3) Minor edits to the PIL and labeling revisions to more clearly emphasize correct injection location.

The Applicant states that residual risk analysis indicated no further design changes that could affect user interaction were needed, although several labeling changes to the PIL were recommended. Of note, the relevance of quantitative data indicating complete or near complete effectiveness of the PIL and product labeling based on subjective participant responses is of limited utility, given that the structured patient-reported outcome questionnaires utilized in the study were tailored specifically to this device and were not validated or standardized in terms of the scaling of responses. Overall, however, the findings from Study INT-FE-0901 validated the changes made to the EAI device at this later stage in the development program from a qualitative perspective and, along with INT0801 and INT0803, provided supportive data to sufficiently address usability issues identified in the EAI development program.

7.4.6 Immunogenicity

No immunogenicity data are presented in this submission. Anti-drug antibodies are not expected to be formed against this sympathomimetic catecholamine. Anti-drug antibody formation has not been reported for the RLD.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Dose-dependency was not assessed in Study INT0802, as all patients received a single dose within each treatment period of either EAI (T = Test; 1 treatment period) versus RLD (R = Reference Listed Drug; 2 treatment periods). No differences in the pattern of adverse events were apparent based on the ordering of these treatment periods (i.e., TRR, RTR, RRT.)

7.5.2 Time Dependency for Adverse Events

The Applicant did not provide summary adverse event tables, which describe the onset of timing or duration of common adverse events. An analysis of adverse event time dependency was not performed. No patterns with regard to time dependency were evident from the narrative descriptions of the reported serious adverse events.

7.5.3 Drug-Demographic Interactions

Demographic interactions with drug device safety or efficacy were not explored in the current submission. Given the current understanding of the pharmacologic effects of epinephrine, other than potential language barriers (as the vocal prompts for the EAI are scripted in English), the usability and potential safety profile of the active drug component are unlikely to be affected by gender or the racial/ethnic background of the

user. However, certain demographic traits capable of influencing physical dexterity, coordination, and cognitive abilities, such as age (both young and old extremes) or underlying neuromuscular comorbidities, would be likely to influence the successful use of EAI, as is also the case with the RLD. In addition, the mechanics of the autoinjector device itself are subject to the morphologic traits of the user, such as body fat and skin thickness. These potentially confounding characteristics were quantified for the sample and comparable between randomized treatment sequences, although a pharmacokinetic analysis was not specifically conducted on subsets of subjects based on these demographic traits.

7.5.4 Drug-Disease Interactions

Drug-disease interactions were not explored in the current submission, as the target sample for Study INT0802 consisted of healthy adults without significant comorbidities at the time of enrollment. As this trial was a bioavailability trial and not an efficacy trial, patients were not treated for the proposed indication (anaphylaxis). Thus, an assessment cannot be made from this trial regarding the potential efficacy of the EAI in the setting of anaphylactic symptoms of varying degrees of severity. In turn, by the nature of the trial design and target population, adverse event data could not be stratified by baseline disease severity in this sample of healthy adults.

7.5.5 Drug-Drug Interactions

Drug-drug interactions were not explored in the current submission, as systemic drug levels were only obtained for the same active drug product (epinephrine) delivered by two different autoinjector devices. Thus, although concurrent medications were elicited by history, the pharmacokinetic bioavailability design of this trial did not systemically evaluate the effects of any concurrently administered drugs. The RLD product label indicates that patients who receive epinephrine while also taking cardiac glycosides (e.g., digitalis) or diuretics are at risk for developing cardiac arrhythmias and require careful observation. In addition, specific drugs cited in the RLD label that may potentiate the effects of epinephrine include tricyclic antidepressants, monoamine oxidase inhibitors, levothyroxine sodium, and certain first-generation antihistamines, including chlorpheniramine, tripelennamine, and diphenhydramine. In contrast, the cardiostimulatory and bronchodilatory (beta-agonist) effects of epinephrine may be antagonized by beta-adrenergic blocking agents, such as propranolol, while the vasoconstrictive and hypertensive (alpha-agonist) effects of epinephrine may be antagonized by alpha-adrenergic blocking agents such as phentolamine, as well as ergot alkaloids.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

The human carcinogenicity potential of epinephrine was not specifically assessed in Study INT0802, but no tumor-related adverse events were identified. The RLD product

label states that epinephrine has been shown to have mutagenic potential in some in vitro assays (e.g., *WP2* bacterial reverse mutation assay; *B. subtilis* DNA repair test). However, neither nonclinical animal studies nor clinical trials have been conducted to assess this risk.

7.6.2 Human Reproduction and Pregnancy Data

No inadvertent drug exposure in pregnant subjects was reported in Study INT0802. Epinephrine is considered Pregnancy Category C, as its safe use during pregnancy and in nursing women is not established. Moreover, data are not presented in this submission, which address the potential effects of epinephrine on human reproduction or pregnancy outcomes. While some nonclinical animal reproduction studies have demonstrated adverse effects of epinephrine in general on fetal development, no human clinical trials have been conducted to assess the effects of epinephrine exposure on pregnancy and fertility. However, as a vasoconstrictor, epinephrine would be expected to have potential adverse effects on maternal to fetal blood blow, as well as lead to potential complications associated with elevated maternal blood pressure. Pregnancy is not listed as a contraindication to the use of EAI (or the RLD), however, given the significant maternal and fetal health risks of untreated hypotension associated with acute anaphylaxis.

7.6.3 Pediatrics and Assessment of Effects on Growth

Specific pediatric safety data were not submitted with this 505(b)(2) application. The proposed EAI label indicates that EAI has not been evaluated in pediatric patients who weigh less than 15 kg, although it may be safely administered to pediatric patients at a dosage appropriate to body weight. The RLD product label states that alternative injectable epinephrine formulations should be considered for patients weighing less than 15 kg, as patients in this weight group are at increased risk of complications, even if dosed with the 0.15 mg EpiPen, Jr. The Agency initially denied the Applicant a pediatric waiver to study EAI in patients weighing less than 15 kg, given the lack of approved autoinjectable regimens for this patient population. However, the Agency later indicated that pediatric assessment of EAI may not be required, as the EAI development program did not trigger PREA, although the Agency conveyed that it could still issue a Written Request for pediatric trials of EAI under BPCA. At present, no safety studies have been conducted with EAI in this patient population.

With regard to pediatric subjects weighing 15 to 30 kg, the 0.15 mg IM/SC dose of the RLD is approved for this population. In turn, the Applicant suggests that the 0.15 mg EAI product poses no greater risk to this patient population than EpiPen, Jr., referencing safety data from the RLD and the medical literature. Specific growth effects studies have not been conducted with self-administered epinephrine. However, given the rare frequency of expected EAI dosing (1-2 doses, given only during rare settings of acute anaphylaxis) and the short half-life of epinephrine, it is unlikely that this rare dosing would result in significant growth effects.

While the bioavailability trial INT0802 did not include subjects aged younger than 25 years, the Agency had previously agreed that a single bioequivalence trial with the higher 0.3 mg dose would support both the 0.3 mg and 0.15 mg dose levels. However, pediatric usability factors were assessed in the human factors simulated clinical use studies INT0801 and INT-FE-0901), which demonstrated equal or decreased rates of pediatric user errors (using a non-human injection model) versus other epinephrine autoinjectors, as discussed in Section 7.4.5 Special Safety Studies/Clinical Trials.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Overdose information is described in the proposed product labeling for EAI and is consistent with current labeling for the RLD. Primarily, cardiovascular complications are cited including elevated blood pressure potentially leading to fatal cerebral hemorrhage (particularly in the elderly), tachycardia, cardiac arrhythmias including transient bradycardia and potentially fatal ventricular tachycardia, pulmonary edema resulting from peripheral vasoconstriction, and possible atrioventricular block. In addition, symptoms of extreme pallor, coldness of the skin, metabolic acidosis, and renal failure are also cited in the product label.

Study INT0802 did not produce any episodes of accidental or purposeful overdosage. Given the intramuscular and/or subcutaneous route of administration of EAI in single doses, accidental overdosage is highly unlikely as individual injections are self-administered. Moreover, one EAI device contains only a single of active drug (either 0.15 mg or 0.30 mg, depending on the dose selected). Thus, the primary risk of EAI (epinephrine) overexposure appears to be related more to administration of the higher 0.3 mg dose to a patient weighing less than 30 kg). In these cases, the adverse effects described in the product label to epinephrine overdosage may be more likely to occur. In addition, although this submission does not include data to this effect, it may be possible that overdosage would be more likely to occur in poorly responsive patients who are unable to convey their level of subjective symptoms to health care workers or lay people administering rescue treatment in an acute setting. Thus, while the proposed EAI label does not address this scenario, patients who are poorly responsive at baseline (i.e., prior to the onset of anaphylaxis) may be more likely to receive unnecessary EAI re-dosing, as persistent altered mental status may also reflect the need for additional medical treatment during anaphylaxis (i.e., repeated epinephrine dosage),

EAI and epinephrine itself have no apparent addiction potential and do not appear to pose a recognizable risk related to addiction or dependency. Moreover, while rebound effects have been reported for topical sympathomimetics, such as intranasal oxymetazoline, these observations are less likely to apply to the use of a systemic beta-receptor agonist such as epinephrine. In turn, no data are reported regarding potential withdrawal or rebound effects of EAI.

7.7 Additional Submissions / Safety Issues

According to a 120-Day Clinical Safety Update submitted by the Applicant on January 27, 2011, there was one additional report of an accidental EAI injection in a 56 year-old man weighing 202 lbs, during a company-sponsored training event was noted. This subject delivered an accidental injection from the EAI 0.30 mg into his right upper thigh and subsequently underwent assessment by emergency medical personnel who noted injection site bleeding, tachycardia to 130 bpm, and elevated blood pressure to 170/100 mm Hg. No other complications were noted, and heart rate had decreased to 84 bpm at the time of his release from medical care. Upon follow-up assessment 5 hours after the initial event, the patient's blood pressure had decreased to 150/100 mm Hg, and he was recommended to resume his background antihypertensive regimen of irbesartan, along with a single dose of metoprolol 25 mg. Other than this event, no new adverse event patterns or safety concerns were noted in the safety update.

8 Postmarket Experience

There is no foreign postmarketing experience with EAI. Epinephrine is a known drug substance with extensive post-marketing experience. However, post-marketing adverse events are not currently included in the package insert for the RLD.

9 Appendices

9.1 Literature Review/References

A literature review was provided by the Applicant of recent drug-related safety data for subcutaneous and intramuscular epinephrine injection used for the treatment of anaphylaxis. Articles on alternative epinephrine administration routes, device-related safety issues, and clinical complications specific to anaphylaxis were not included in this review. The PubMed database was searched for all articles dealing with humans and dated from July 1, 2005, through May 31, 2010, utilizing the following key words: epinephrine, subcutaneous, intramuscular, injection, injury, adverse event, adverse effect, anaphylaxis, and allergy. This literature primarily describes the safety implications of epinephrine's sympathomimetic cardiovascular effects (e.g., increased blood pressure, tachycardia, arrhythmias, exacerbation of unstable angina, reversible left ventricular dysfunction) and potential local injection site reactions associated with accidental injection into the palm or digits of the hand (e.g., tissue ischemia, treatment ineffectiveness), which are all related to known pharmacologic effects of epinephrine and are cited in the current product label for the RLD and the proposed label for EAI. In addition, although ophthalmic adverse events are not typically associated with subcutaneous or intramuscular administration of epinephrine, one case of acute macular neuroretinopathy (i.e., acute paracentral scotomas with wedge-like macular lesions) in a 21 year-old woman following an epinephrine injection of unknown dose is cited.

A separate literature review of the PubMed database from January 1, 1977, through January 1, 2011, was performed to search for additional reports of complications or adverse events related to injectable epinephrine used for the treatment of anaphylaxis. For this search, the following terms were pooled into four separate searches:

1) epinephrine (120,343 citations)

2) subcutaneous OR intramuscular OR injection (602,911 citations)

3) anaphylaxis OR allergy OR hypersensitivity (310,392 citations)

3) injury OR adverse event OR adverse effect OR complication OR error OR sequela OR sequella OR sequelae OR sequellae (3,020,389 citations) [incorrect spelling variants included to capture additional citations]

These searches were then combined to identify overlapping citations in all four pools (#1 AND #2 AND #3 AND #4), which limited to references in humans, produced a final tally of 127 references.

Except for one case of myocardial infarction without underlying coronary artery disease, a review of the available abstracts for these citations identified no additional descriptions of adverse events associated with subcutaneous or intramuscular epinephrine for the treatment of anaphylaxis that were not already referenced in the Applicant's literature review, the safety data submitted for Study INT0802, or the proposed EAI product labeling. The complications discussed in these manuscripts that were associated with subcutaneous or intramuscular epinephrine administered as treatment for anaphylaxis are as follows:

1) Unintentional injection or incorrect injection site location with epinephrine autoinjectors: 9 citations

2) Inappropriate or inadequate use of epinephrine autoinjector due to insufficient training or knowledge: 7 citations

3) Epinephrine overdose: 2 citations

4) Unstable angina with underlying coronary artery disease: 1 citation

5) Transient left ventricular dysfunction (Takotsubo cardiomyopathy): 1 citation

6) Unlisted: Myocardial infarction without underlying coronary artery disease: 1 citation [Gikas, A., Lazaros, G., & Kontou-Fili, K. "Acute ST-segment elevation myocardial infarction after amoxicillin-induced anaphylactic shock in a young adult with normal coronary arteries: a case report." *BMC Cardiovasc Discord*. 2005. 5(1):6]

As noted, the risk of myocardial infarction without underlying coronary artery disease is not listed in the proposed EAI label or that of the RLD, only single case was identified in this literature search spanning 34 years. In addition, the etiology of this event and other ischemia-related cardiovascular adverse events is difficult to attribute to epinephrine dosing, anaphylaxis-associated hypotension, or both. Thus, the inclusion of this unlisted adverse event is not recommended in the proposed EAI labeling.

9.2 Labeling Recommendations

A review by the Division of Medication Error Prevention and Analysis (DMEPA) dated December 28, 2010, concluded that the proposed proprietary name for EAI, (b) (4), was misleading given its potential for being confused with the currently marketed product, (b) (4), due to its similarity in spelling. In addition, these two names appear similar when scripted, as the names share three letters, which are in the same position in each name. The Applicant submitted a Proprietary Name Reconsideration Request on January 20, 2011, in support of the proposed brand name (b) (4) and the alternate proposed brand name, (b) (4). In a teleconference with the Applicant held on February

2, 2011, the Agency conveyed its concerns with the spelling of (b) (4) and the orthographic similarity of (b) (4) with the currently marketed product, (b) (4). The Applicant subsequently withdrew both (b) (4) and (b) (4) as proposed proprietary names on February 8, 2011. On April 28, 2011, the Applicant submitted a new Request for Proprietary Name Review for the proposed trade name, e-cue. Review of this proposed brand name is pending at the time of this review.

The majority of the proposed label was taken from the approved product label for the RLD, EpiPen Autoinjector (Prescribing Information dated April 2009), including information on indications and usage, contraindications and adverse reactions, warnings and precautions, drug interactions, and use in specific populations. Information on dosage and administration, dosage forms and strengths, warnings and precautions, adverse reactions, use in specific populations, overdosage, general description, clinical pharmacology, clinical trials experience, storage and handling, patient counseling information, and general instructions have been revised to reflect information relevant to EAI.

At the time of this review, labeling discussions are pending. Unlike the RLD product label, the EAI label has been placed into PLR format. Key aspects of the proposed EAI product label, which differ from that of the RLD, are described below:

- **Highlights of Prescribing Information:** In contrast to the current EpiPen label, the proposed EAI label is in PLR format.

- **Indications and Usage:** (b) (4)

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

9.3 Advisory Committee Meeting

No Advisory Committee Meeting was held for this application, since epinephrine is a known molecular entity that is already FDA-approved for the RLD, as well as other autoinjectable epinephrine devices, for patients weighing ≥ 15 kg.

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/s/

BRIAN PORTER
06/24/2011

SUSAN L LIMB
06/24/2011

MEDICAL OFFICER REVIEW

Division of Pulmonary, Allergy, and Rheumatology Products

Application #:	NDA 201-739	**Application Type:**	505(b)(2) NDA
Applicant:	Intelliject	**Proprietary Name:**	(b) (4)
Clinical Reviewer:	Brian Oscar Porter, M.D., Ph.D., M.P.H.	**USAN Name:**	Epinephrine (USP 1:1000) Auto-Injector
Team Leader:	Susan Limb, M.D.	**Category:**	Sympathomimetic catecholamine
Review Date:	November 4, 2010	**Route:**	Intramuscular Injection

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	Submission Type	Comments
September 29, 2010	NDA 201-739 SD-1	Electronic submission

REVIEW SUMMARY: This is a 45-day filing and planning review of a 505(b)(2) new drug application submitted to NDA 201-739 for an epinephrine auto-injector (EAI) provisionally named (b) (4) (0.15 mg and 0.3 mg), delivered as an intramuscular injection. This application references the EpiPen® and EpiPen Jr® epinephrine auto-injector (NDA 19-430; Meridian Medical Technologies; approved December 22, 1987) as the reference listed combination drug device. EAI is being developed with the goal of decreased dosing errors by virtue of a unique self-actuated electronic injector device with interactive voice and visual prompts. The development program for EAI was based on three simulated clinical use studies to evaluate human factors in which no active drug was injected into human subjects (INT0801, INT0803, INT-FE-0901) and a single comparative bioavailability trial (INT0802), for which the complete study reports have been provided in support of a proposed indication for the emergency treatment of allergic reactions (Type I) including anaphylaxis in patients 15-30 kg (0.15 mg dose) and ≥ 30 kg (0.3 mg dose). The pivotal bioavailability trial was designed as a randomized, single-blind, two-treatment (EAI versus EpiPen), three-period (1 for EAI and 2 for EpiPen), three-sequence (randomized 1:1:1 to EAI-EpiPen-EpiPen; EpiPen-EAI-EpiPen; EpiPen-EpiPen-EAI) cross-over study to evaluate potential bioequivalence of a single dose of injectable epinephrine 0.3 mg delivered by one of two forms of auto-injectors to healthy adults aged 18-45 years.

The clinical review concludes that the 505(b)(2) NDA is fileable.

OUTSTANDING ISSUES: None

RECOMMENDED REGULATORY ACTION:

NDA, Efficacy/Label supplement: __X__ **Fileable** ____ **Not fileable**

I. General Information and Background

Epinephrine Auto-Injector (EAI) is a single dose combination drug device, designed for single use administration of intramuscular (IM) or subcutaneous (SC) injectable epinephrine USP 1:1000, a sympathomimetic catecholamine with the following proposed indication (bolded emphasis is not in the proposed label, but has been added to note changes from the RLD label):

> *"(b) (4) is indicated in the emergency treatment of allergic reactions (Type I) including anaphylaxis to stinging insects (e.g., order Hymenoptera, which include bees, wasps, hornets, yellow jackets and fire ants) and biting insects (e.g., triatoma, mosquitoes), allergen immunotherapy, foods,* ***vaccines,*** *drugs* ***(e.g., penicillin, omalizumab)****, diagnostic testing substances (e.g., radiocontrast media) and other allergens, as well as idiopathic anaphylaxis or exercise-induced anaphylaxis.*
>
> *(b) (4) is intended for immediate administration* ***(following exposure to a potential allergen)*** *in patients who are determined to be at increased risk for anaphylaxis, including individuals with a history of anaphylactic reactions.*
>
> ***Anaphylactic*** *reactions may occur within minutes after exposure and consist of flushing, apprehension, syncope, tachycardia, thready or unobtainable pulse associated with a fall in blood pressure, convulsions, vomiting, diarrhea and abdominal cramps, involuntary voiding, wheezing, dyspnea due to laryngeal spasm, pruritus, rashes, urticaria or angioedema.*
>
> *(b) (4) is intended for immediate self* ***or caregiver*** *administration as emergency supportive therapy only and is not a substitute for immediate medical care."*

As a non-selective agonist of both alpha and beta adrenergic receptors, epinephrine mediates vasoconstriction, thereby counteracting the vasodilatory, hypotensive, and bronchoconstrictive processes associated with acute anaphylaxis. The Applicant (Intelliject) has proposed the trade name of (b) (4) for this product, which will henceforth be referred to as EAI for the purposes of this filing review. EAI has been developed as an auto-injector unit containing a total of 0.76 mL of epinephrine solution at a concentration of 1 mg/mL. Two separate auto-injectors have been developed to deliver one of two single use doses:

- 0.3 mg: 0.3 mg/0.3 mL epinephrine injection [USP 1:1000] pre-filled auto-injector for patients weighing ≥ 30 kg (66 lbs)
- 0.15 mg: 0.15 mg/0.15 mL epinephrine injection [USP 1:1000] pre-filled auto-injector for patients weighing 15-30 kg (33-66 lbs); EAI has not been studied in patients weighing < 15 kg.

Several epinephrine auto-injectors are currently marketed, and the Applicant developed EAI with the goal of creating an auto-injectable self-administered epinephrine product with greater ease of use and a lower likelihood of dosing errors, by virtue of a unique self-actuated electronic injector device. The Applicant first sought Agency input on the EAI development program in July 2005, when it was established that CDER would be the primary review center for this combination product. (b) (4)

However, the proposed RLD was later changed to EpiPen epinephrine auto-injector (NDA 19-430; approved December 22, 1987) in October 2008, as indicated in the current submission. EpiPen is

currently available by prescription in two commercial versions at either the 0.3 mg or 0.15 mg doses: an updated design launched in 2010 with Prescribing Information dated September 2008, and an older pre-2010 version with more recent Prescribing Information dated April, 2009. A trainer auto-injector device containing no medication or needle component is also available with separate patient instructions. All labeling from both EpiPen versions is included in the current submission, but only the more recent April, 2009, Prescribing Information has been used to annotate the proposed EAI label.

II. Clinical Development Program

The development program for EAI was based on three simulated clinical use studies to evaluate human factors in which no active drug was injected into human subjects (INT0801, INT0803, INT-FE-0901) and a single comparative bioavailability trial (INT0802) submitted to IND 76,367, as shown in the following table.

Clinical development program for EAI treatment of acute anaphylaxis

Trial	Subjects	Design	Dose	Focus
INT0801	*48 non-healthcare workers*	*OL, summative design simulated clinical use validation study: EAI with and without electronic interactive prompt system compared to two marketed epinephrine auto-injectors*	*N/A—no active drug administered*	*Multiple design changes recommended based on usability findings*
INT0803	*28 healthcare workers*	*OL, simulated clinical use study, utilizing injection model (orange) for 18 separate injections with 18 different EAI devices per subject (9 with wet hands and 9 with dry hands)*	*N/A—no active drug administered*	*Incorporated CDRH guidelines on sharps injury prevention and human factor evaluation; no needle retraction failures among 505 EAI model injections*
INT-FE-0901	*20 adult and 20 pediatric non-healthcare workers*	*OL, simulated clinical use validation and effectiveness study of Patient Information Leaflet and design changes (safety guard and electronic voice prompt system)*	*N/A—no active drug administered*	*Validation of design changes generated from INT0801*
INT0802 Phase I	69 healthy adults: 23-45 yrs, males and females on contraception	R, AC, 3-sequence, 3-period XO study	0.3 mg IM delivered by EpiPen (2 periods) or EAI (1 period)	Comparative Bioavailability Study, operationalized as bioequivalence study

OL=open-label, R=randomized, AC=active-controlled, XO=cross-over; IM=intramuscular;

Trials in italics did not involve administration of active drug to human subjects.

Reviewer's Comment: Completion of a bioequivalence trial is not an absolute requirement for product approval via the 505(b)(2) pathway. Completion of INT0802 was originally proposed by the Applicant.

III. Foreign Marketing and Regulatory History

The (b) (4) EAI is not currently approved or marketed in any country. The following is a summary of the regulatory interactions that have occurred between the Applicant and the Agency over the past five years.

- **July 21, 2005:** Planning meeting with representatives from the Office of Combination Products, CDER, and CDRH, in which CDER was designated the lead review center for a future NDA for this product, given that the action of epinephrine is considered the primary action of the combination product. Multiple CMC recommendations were also provided by the Agency. The Agency also indicated that some type of clinical trial would be needed to establish the safety and effectiveness of the product. The Applicant was instructed to develop a formal Pre-IND meeting request and briefing package for submission to the Agency.

Reviewer's Comment: As a combination drug-device product, the current NDA submission may require an independent review by CDRH. The Division will consult the Office of Combination Products to determine the appropriate review parties.

- **March 9, 2007:** The Agency provided feedback to the Applicant's Pre-IND briefing package (dated February 1, 2007). (b) (4)

- (b) (4)

- (b) (4)

[redacted] (b) (4)

- **August 7, 2008:** The Applicant submitted a device Master File (MAF) for the single-use EAI, with amendments to the MAF submitted on October 22, 2008, and December 12, 2008.

- **October 17, 2008:** Applicant [redacted] (b) (4) the EpiPen and EpiPen, Jr. Auto-Injectors marketed at that time, which was deemed acceptable by the Agency.

Reviewer's Comment: If the Applicant can demonstrate sufficient similarities between EAI and the RLD in terms of both the active drug component (epinephrine formulation and dosing) and physical specifications of the auto-injector device (e.g., needle length, needle gauge, drug volume, activation force, etc.), clinical data, i.e. the demonstration of bioequivalence between the two products through a standardized BE trial, may not be required.

- **December 19, 2008:** IND 76,367 is submitted for EAI, including the proposed protocol for the bioequivalence Study INT0802 of EAI in healthy adults (protocol amendments submitted on February 17, 2009, and March 3, 2009), as well as descriptions of Study INT0801, a human factors usability study of EAI trainer devices, and Study INT0803, a human factors and sharps injury prevention study of EAI (full protocol submitted January 26, 2009).

- **March 25, 2009:** The Agency denies the Applicant's request for Fast Track designation for EAI (submitted February 27, 2009), stating that an unmet medical need had not been established.

- **April 27, 2009:** The Agency informed the Applicant that the plan to change the primary objective of Study INT0802 from bioequivalence to comparative bioavailability is acceptable, although a bioequivalence statistical approach was still recommended as a key component of the NDA review.

- **October 22, 2009:** The Agency responded to the Applicant request for a Deferral of Pediatric Studies (submitted September 21, 2009) stating that while it did not appear that pediatric assessment would be required for the proposed product, this decision would be made during the NDA submission.

- **October 23, 2009:** The Agency responded to a pre-NDA briefing package (submitted September 25, 2009), providing input on the planned 505(b)(2) NDA submission. Topics covered included multiple CMC specifications, bioequivalence and pharmacokinetic statistical methodology, electronic dataset submissions, affirmation of EpiPen as the planned RLD, dose accuracy studies for EAI, the designation of EAI software as of Moderate Level of Concern, the final report format for clinical use studies INT0803 and INT0801, the need for patient instructions for use in the proposed labeling, and the planned approach to pediatric product evaluation, with the Agency suggesting that a pediatric assessment of EAI may not be required, as none of the five PREA triggers apply to EAI

(i.e., new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration). However, given the public health need, the Agency still encouraged the Applicant to evaluate EAI in all appropriate age ranges, indicating that a Written Request for pediatric trials could potentially be issued by the Agency under BPCA. The Applicant subsequently cancelled the Pre-NDA Meeting.

- **October 26, 2009:** The Applicant submitted additional questions to the Agency regarding CMC device specifications and to seek concurrence that nurses trained in TwinJect and EpiPen teaching were an appropriate population for clinical use-associated injury prevention studies.

IV. Items Required for Filing and Reviewer Comments (21 CFR 314.50)

The following items were included in this submission:

- Form FDA 356h [Vol 1.1.2]
- Debarment certification [Vol 1.3.3]
- Financial disclosure statement [Vol 1.3.4]
- Statement of Good Clinical Practice [Not provided as separate form, but indicated in Study Report for INT0802]
- Summary of Efficacy and Safety [Clinical Summary Vol 2.5, Summary of Clinical Efficacy Vol. 2.7.3, Summary of Clinical Safety Vol 2.7.4]
- Complete study report for INT0802 [Vol 5.3.1.2.3]
- Complete study reports for INT0801, INT0803, and INT-FE-0901 [Appendix I and Appendix J of MAF (b) (4)]

Reviewer's Comment: No human subjects received epinephrine in any of these three simulated clinical use trials.

- Literature review for safety information: [Vol 2.7.4; individual reference articles in Vol 5.4]
- Proposed labeling and annotated labeling [Vol 1.14.1]
- Overdose information provided in labeling [Vol 1.14.1.2, Full Prescribing Information Section 10]; no information on abuse potential is submitted

Reviewer's Comment: Auto-injectable epinephrine is an approved drug with extensive post-marketing experience and no apparent addiction potential.

- Environmental assessment [Vol 1.12.14]
- Summary data tabulations for primary and secondary outcome measures [Vol 5.3.1.2.3, Study Report INT0802; multiple locations throughout report]
- Individual subject level data listings [Vol 5.3.1.2.3, Study Report INT0802; multiple locations throughout report]
- Case report forms for patients with serious adverse events or discontinuing trial due to adverse events [Vol 5.3.1.2.2, Study Report INT0802, Appendix 16.3.1] (No deaths or SAEs occurred in

this trial, although 1 mild AE resulted in withdrawal, for which the CRF and case narrative are provided.)

- Electronic data sets [Vol 5.3.1.2.25.1]

Reviewer's Comment: In addition to a review by the Pharmacology/Toxicology Review Team to assess potential toxicity from components of either the EAI drug formulation or materials used in the auto-injector device, a review by the Microbiology Review Team will be required to assess the sterilization processes of the EAI combination product.

V. Clinical Trials/Studies

Human Factors/Clinical Use Studies

Three simulated clinical use studies were completed and are summarized below.

Study INT0801: Summative Validation Study of EAI in Non-healthcare Workers

Design and Methods

Study INT0801 was an open-label summative design validation study of EAI in 48 non-healthcare workers. This study evaluated the association of human factors with subject feedback on the usability and design of two versions of a modified EAI without active drug or needles--one with an interactive electronic prompt system and one without. Usability of these two investigational versions of EAI was also compared to that of two currently marketed products.

Results

Collectively, subjects experienced fewer use errors with the two EAI products, demonstrating a greater likelihood of successful injection in the absence of prior training, per the Applicant. Subjects also indicated a greater preference for EAI with the interactive prompt system with regard to size, shape, ease of use and ability to carry, instructions for use, and safety, compared to the three other devices. Use data for all four devices indicated that younger pediatric subjects aged 7-10 years were less likely to followed labeled device instructions and experience error-free use, compared to older subjects.

Safety Conclusions

Although both adult and pediatric subjects demonstrated fewer errors with the EAI device with an interactive prompt system, the Applicant states that post-hoc risk analysis identified several aspects of the device for potential improvement, which were later validated in Study INT-FE-0901:

1) Redesign of the red safety guard with increased tactile features and clarified use instructions in the product label
2) Redesign of voice prompts for the electronic prompt system and design updates to improve battery functionality and eliminate switch malfunctions

3) Revision of label to emphasize correct injection location
4) Revision of Prescribing Information and Patient Information Leaflet (PIL) to encourage training prior to use, with inclusion of a Trainer device and Trainer Information Leaflet with initial EAI prescriptions

Study INT0803: Sharps Prevention and Use Testing of EAI in Healthcare Workers

Design and Methods

Study INT0803 was an open-label study of EAI in 28 healthcare workers that utilized additional simulated clinical use testing per CDRH guidelines on Medical Devices with Sharps Injury Prevention Features and Human Factors Evaluations. This study evaluated the effectiveness of the retractable needle feature through a simulated injection into an orange 18 separate times with 18 different EAI devices per subject (9 with wet hands and 9 with dry hands).

Reviewer's Comment: In contrast to EAI, the RLD does not incorporate a retractable needle feature.

Results

A total of 505 EAIs (0.3 mg dose) were tested, all of which demonstrated successful needle retractions with either wet or dry hands. In the use assessment, all 28 subjects used the device properly, while a majority of subjects indicated that they "agreed" or "strongly agreed" with the following statements regarding EAI use:

- Easy to use (79%)
- Worked well with hand size (86%)
- Did not require extensive training (89%)
- Designed to be used correctly (96%)
- Designed so as not to miss a crucial step in proper use of the device (100%)
- Did not require multiple uses to learn how to use EAI correctly (96%)
- Electronic voice instructions were a positive feature (93%)
- Audible prompts were loud enough (75%)
- Size preferred to EpiPen and TwinJect (79%)
- Shape preferred to EpiPen and TwinJect (68%).

Study INT-FE-0901: Validation and Effectiveness Study of EAI PIL and Design Changes

Design and Methods

Study INT-FE-0901 was an open-label validation and effectiveness study of the EAI PIL in 40 participants (20 adult and 20 pediatric subjects), with a secondary objective of validating design changes to the safety guard and electronic voice prompt system, generated from the usability findings from Study INT0801 of device-related errors and residual risks. A modified version of EAI was used (without the gas cylinder, active drug, or needle) to simulate injection, relying solely on the PIL and device label for instruction prior to use.

Results

All adult subjects were able to successfully simulate clinical use of EAI without a critical user task error, based solely on the PIL and device label for prior use instructions, with 92.5% of all participants indicating the PIL was very easy/simple or easy to follow. After being trained by their parents, all 20 pediatric subjects successfully removed the safety guard on the first attempt, with some indicating more force was needed than expected. Of these patients, 85% indicated that the electronic voice prompt system "helped them a lot," while 15% indicated it "helped them a little bit."

Safety Conclusions

The following design modifications generated by initial findings of INT0801 were also validated:

1) Redesign of the red safety guard with increased tactile features and clarified use instructions in the product label
2) Redesign of voice prompts for the electronic prompt system and design updates to improve battery functionality and eliminate switch malfunctions
3) Revised labeling to more clearly emphasize correct injection location.

The Applicant states that residual risk analysis indicated no further design changes were needed, which could affect user interaction, although several labeling changes to the PIL were recommended.

Bioequivalence Trial

A single pivotal bioequivalence trial (Study INT0802) was conducted for the drug development program of EAI. The study report is appropriately indexed to allow for review. A summary follows:

A. Title

Study INT0802: A randomized, single-blind, two-treatment, three-period, three-sequence study of the bioavailability of two formulations/delivery devices for epinephrine in healthy human volunteers

B. Principal Investigator

(b) (4)

C. Objective

Primary: To document bioavailability following a single injection of 0.3 mg epinephrine USP 1:1000 administered using EAI (b) (4)) and EpiPen under fasting conditions

Secondary: To assess the safety and tolerability of epinephrine injection by EAI (b) (4) compared to EpiPen

D. Trial Design

Randomized, single-blind, two-treatment, three-period (1 EAI and 2 RLD), single dose, three-sequence cross-over study to document the bioavailability of epinephrine delivered by EAI (b) (4) versus EpiPen

Reviewer's Comment: This biocomparability trial utilized a novel replicate reference period design.

E. Dosing Schedule/Materials

During each treatment period, a single injection of 0.3 mg epinephrine USP 1:1000 will be administered, either by EAI in 1 of the 3 treatment periods and EpiPen in the other 2 treatment periods.

F. Trial Summary

1. Overview and Methodology

Study INT0802 was a single-blind, two-treatment (EAI versus EpiPen), three-period (1 for EAI and 2 for EpiPen), three-sequence cross-over trial to evaluate potential bioequivalence (comparative bioavailability) of a single dose of injectable epinephrine 0.3 mg delivered by one of two forms of auto-injectors to healthy adults aged 18-45 years. Following screening, subjects were randomized 1:1:1 to one of three treatment sequences (EAI-EpiPen-EpiPen; EpiPen-EAI-EpiPen; EpiPen-EpiPen-EAI). Single IM doses of epinephrine were administered following a fasting period of at least 10 hours, with at least a 24 hour wash-out period between doses, as specified. Serial pharmacokinetic blood sampling was done in each treatment period at pre-dose and throughout the first 6 hours post-dose at 5, 10, 15, 20, 30, 40, and 50 minutes and 1, 1.25, 1.5, 2, 3, 4, and 6 hours. Safety assessments done pre-dose and post-dose during each treatment period (unless otherwise specified) included adverse events monitoring, concomitant medications, physical examinations (pre-dose and at end-of-study), vital signs, 12-lead EKGs, 2-lead cardiac telemetry, and clinical laboratory tests (pre-dose and at end-of-study).

2. Population

Participants were healthy male and female young to middle-aged adults aged 18-45 years. The target sample size of 66 subjects was calculated to provide 80% power to establish bioequivalence, using variance estimates derived from Simons, et al. Epinephrine absorption in adults: intramuscular versus subcutaneous injection. JACI. 2001. Nov; 108(5):871-3.

3. Treatment Groups

Sixty-six subjects were randomized 1:1:1 to each of 3 treatment sequences of three treatment periods with a single dose each of epinephrine 0.3 mg administered via either EAI (Test Drug = T) or EpiPen (Reference Drug = R), as shown in the following table:

Treatment Sequence	# of Subjects	Period 1	Period 2	Period 3
1	22	T	R	R
2	22	R	T	R
3	22	R	R	T

T=Test Drug (EAI); R=Reference Drug (EpiPen)

Compliance was ensured by direct observation, as injectable epinephrine was administered by trained study personnel. Additional subjects were enrolled as needed to ensure 66 completers.

4. Inclusion/Exclusion

Pertinent Inclusion Criteria

- Males or females aged 18 to 45 years, inclusive
- Willing and able to understand and provide written informed consent
- Willing and able to participate in all required study activities
- Body mass index (BMI) between 18.5 and 29.9 kg/m², inclusive, and a weight of ≥ 50 kg
- Female subjects of childbearing potential **(**not surgically sterile and premenopausal or < 2 years postmenopausal, who agrees to contraception from 3 months prior to dosing and throughout the study: hormonal (oral, transdermal, implant, or injection), barrier (condom, diaphragm with spermicide), intrauterine device, or vasectomized partner (6 months minimum)
- No clinically significant abnormal findings on the physical examination, medical history, or clinical laboratory results during Screening
- Blood pressure, pulse, and other vital signs within acceptable ranges prior to dosing

Pertinent Exclusion Criteria

- History of clinically significant gastrointestinal, renal, hepatic, neurologic, hematologic, endocrine, oncologic, pulmonary, immunologic, psychiatric, or cardiovascular disease, or other condition which would jeopardize safety or impact validity of results (per investigator)
- History of diabetes or cardiac risk factors that would place subject at increased risk of cardiovascular events: family history, hypertension (SBP > 150 or DBP > 95), hypercholesterolemia (total > 300, triglycerides > 225, or LDL > 150)
- History of abnormal heart rhythm, e.g., supraventricular tachycardia or episodic disturbances
- History of conditions (e.g., hyperthyroidism, syncope, panic attacks, migraine) that might place subject at increased risk of AEs from IM or SC epinephrine
- History of allergic or adverse responses to epinephrine or sulphite
- Subjects who (for whatever reason) have consumed xanthines (caffeine, theobromine) in coffee, colas, or tea during the 24 hours preceding Day 0 (Admission)
- Subjects who donated blood within 56 days or plasma within 14 days of Day 0
- Participation in a clinical trial within 30 days prior to Day 0

- Use of any over-the-counter (OTC) medication, including topical medications (eye drops or nose drops), vitamins, alternative and complementary medicines (including herbal formulations), within 7 days prior to Day 0 or during the study

- Use of any prescription medication within 14 days prior to Day 0 or during the study, with the exception of hormonal contraceptives for women of childbearing potential

- Use of monoamine oxidase (MAO) inhibitors or tricyclic antidepressants within 30 days prior to Day 0 or during the study

- Treatment with any known CYP450 enzyme altering drugs (e.g., barbiturates, phenothiazines, cimetidine, carbamazepine, etc.) within 30 days prior to Day 0 or during the study

- Smoking or use of tobacco products within 6 months prior to Screening or during the study as determined by a urine cotinine concentration > 200 ng/mL

- Women who are trying to conceive, pregnant, or lactating at Screening or during the study

- Positive serum pregnancy test at Screening or positive urine pregnancy test prior to each drug administration for all women, regardless of childbearing potential

- Positive blood screen for HIV, HBsAg, or hepatitis C antibody at Screening

- Positive urine screen for drugs of abuse, urine cotinine (> 200 ng/mL), or positive breath alcohol test at Screening or during the study

- Subjects who have used alcohol within 72 hours of Day 0

- History of alcohol, cocaine, or any other substance abuse within 6 months prior to Day 0

5. Concomitant Medications

In addition to the restricted medications listed in the Exclusion Criteria, alcohol use was also prohibited during the study.

6. Outcome Measures

Pharmacokinetic Bioavailability Parameters

- C_{max}: maximum plasma concentration

- T_{max}: time to maximum plasma concentration

- $AUC_{(0-t)}$: area under the concentration-time curve from baseline to last measurable concentration

- $AUC_{(inf)}$: area under the plasma concentration-time curve from baseline extrapolated to infinity

- $AUC_{(0-RTmax)}$: area under the concentration-time curve from time zero to time of T_{max} for RLD

- λz: elimination rate constant
- T½: terminal elimination half-life

Safety parameters

- Clinical laboratory tests (hematology, chemistry with hepatorenal function tests and lipid profile, urinalysis with microscopy if abnormal) at baseline and end-of-study
- Physical examination at screening and end-of-study
- 12-lead ECG at baseline and each treatment day at 60 min pre-dose and 6 hours post-dose
- 2-lead cardiac telemetry from 30 min pre-dose to 1.5 hours post-dose
- Vital signs (supine BP, heart rate, oral temperature, and respiratory rate) at baseline and each treatment day at 60 min pre-dose and 6 hours post-dose
- Adverse events on all study days, coded using MedDRA v. 11.1 or higher
- Concomitant medications were assessed in conjunction with any AE

7. Statistical Considerations

Data were analyzed descriptively, including differences from baseline, where applicable. In addition, pharmacokinetic parameters reflecting bioavailability were compared using a mixed-effects linear model repeated measures ANOVA for the 3-sequence 3-period cross-over design. All data from discontinued subjects and completed subjects were included. Bioequivalence was determined using the approach of Haidar, et al. Bioequivalence approaches for highly variable drugs and drug products. Pharm Res. 2008 Jan; 25(1):237-41. Safety data were tabulated for all subjects who received at least 1 dose of study drug. Changes from baseline were summarized via descriptive statistics, as well as shift from baseline.

Reviewer's Comment: The analytical approach used to assess bioequivalence in this trial is less stringent than the standard requirement of having 95% confidence intervals for test product exposure fall within 80-125% of the RLD. The Applicant justifies this alternative approach based on the high exposure variability seen with EAI (e.g., T_{max} occurring as late as 1 hour post-dose in some patients). The Clinical Pharmacology Review Team has indicated that the Applicant will need to support this claim with adequate data, which demonstrate this high variability (both interpatient and intrapatient, given the replicate reference period design). In addition to this alternative analytical approach, the Clinical Pharmacology Team will request that the Applicant submit a standard bioequivalency analysis of these data (based on 95% confidence intervals, as described above, focusing on $AUC_{(0-t)}$ and $AUC_{(inf)}$), which will be compared to the Agency's own analysis. In addition, the Statistical Review Team will evaluate this novel analytical method.

Given the regulatory significance of the Agency potentially accepting an alternative analytical method of determining bioequivalency, we will plan to present this issue internally within the Agency for further discussion at a Regulatory Briefing, in order to obtain the perspective of additional Agency stakeholders, such as the Office of Generic Drugs.

8. Results

8.1. Demographics and patient disposition

A total of 132 patients were screened, with 66 subjects randomized to the study and 5 more enrolled as replacement subjects. Of these, 64 subjects completed the trial and 7 discontinued early for the following reasons: withdrawn consent=3, protocol deviation (positive urine drug screen)=2, adverse event (ventricular extrasystoles)=1, and noncompliance with unit regulations=1. Baseline demographics are summarized in the following table.

Demographic Variable	Treatment Sequence			
	TRR N = 24	RTR N = 24	RRT N = 23	Overall N = 71
Gender: n (%)				
Male	17 (70.8)	19 (79.2)	17 (73.9)	53 (74.6)
Female	7 (29.2)	5 (20.8)	6 (26.1)	18 (25.4)
Age in years mean (SD)	35.5 (6.3)	33.6 (6.7)	30.2 (5.0)	33.2 (6.3)
Ethnicity: n (%)				
Hisp/Latino	5 (20.8)	4 (16.7)	7 (30.4)	16 (22.5)
Not Hisp/Latino	19 (79.2)	20 (83.3)	16 (69.6)	55 (77.5)
Race: n (%)				
Black/Afr Amer	16 (66.7)	13 (54.2)	7 (30.4)	36 (50.7)
Asian	1 (4.2)	2 (8.3)	0	3 (4.2)
White	7 (29.2)	8 (33.3)	16 (69.6)	31 (43.7)
Amer Ind	0	1 (4.2)	0	1 (1.4)
Height in cm mean (SD)	172.1 (8.6)	174.0 (8.53)	175.2 (10.0)	173.7 (9.0)
Weight in kg mean (SD)	75.5 (9.9)	77.9 (11.6)	77.6 (13.0)	77.0 (11.5)
BMI in kg/m^2 mean (SD)	25.5 (2.6)	25.6 (2.4)	25.2 (3.1)	25.4 (2.7)
Thigh Circ in cm mean (SD)	51.5 (6.9)	49.6 (6.0)	50.0 (6.0)	50.3 (6.3)
Skin-fold thickness in mm: mean (SD)	27.8 (15.5)	30.0 (17.0)	29.2 (12.4)	29 (14.9)
Ex-smoker: n (%)				
Yes	3 (12.5)	5 (20.8)	4 (17.4)	12 (16.9)
No	21 (87.5)	19 (79.2)	19 (82.6)	59 (83.1)

SD=standard deviation, Hisp=Hispanic, Afr Amer=African-American, Amer Ind=American Indian, Circ=circumference

Source: Clinical Study Report for INT0802, Appendix 16.2, Listing 16.2.4.1, Table 14.1.2, Table 14.1.3

8.2. Treatment Adherence and Exposure

Treatment adherence was assessed by direct observation during administration of study medications within a clinical research unit. No more than 2 subjects assigned to each treatment sequence failed to complete all 3 treatment periods. Overall, there appears to have been adequate exposure to EAI throughout all 3 treatment periods (≥ 88%), as shown in the following table.

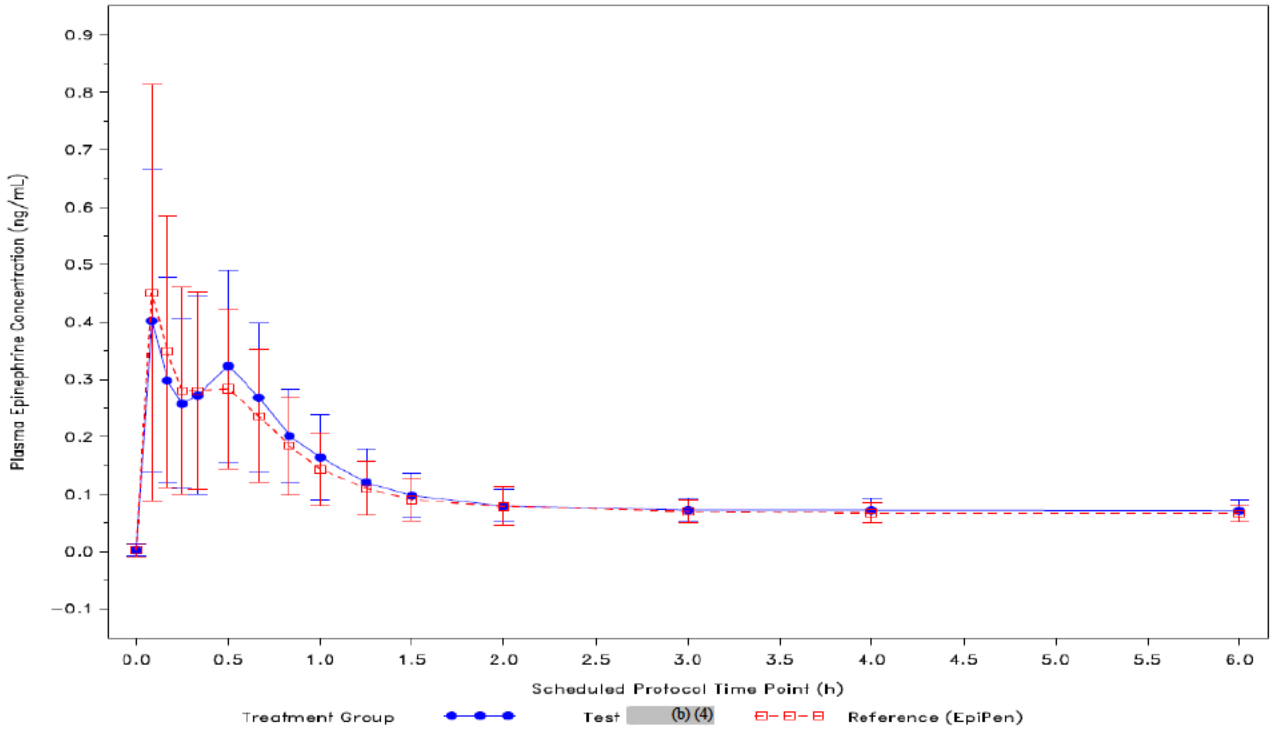
Treatment Period	Treatment Sequence		
	TRR N = 24	RTR N = 24	RRT N = 23
1	24 (100)	24 (100)	23 (100)
2	22 (91.7)	22 (91.7)	23 (100)
3	22 (91.7)	21 (87.5)	21 (91.3)

T=Test Drug (EAI); R=Reference Drug (EpiPen)

Source: Clinical Study Report INT0802, Table 14.1.4

8.3. Bioequivalence Results

As the primary measure of bioavailability, plasma epinephrine concentration was quantified for each treatment period, combining data from the two RLD treatment periods in comparison to the single EAI period, as shown in the following figure, in which closed circles represent EAI and open squares represent EpiPen. A total of 71 subjects were included in the pharmacokinetic data analysis set. As indicated in the figure, the plasma-time concentration curves (mean and standard deviation) of these two treatments largely overlapped, with slightly higher epinephrine bioavailability conferred by EAI after 30 minutes post-dose.



A descriptive analysis of the main pharmacokinetic parameters reflective of this overlap is shown in the following table. A comparison of these mean values demonstrates that epinephrine administered via EAI has greater bioavailability and a longer half-life that that of the RLD, although C_{max} was slightly lower for EAI compared to EpiPen.

Treatment		C_{max}	T_{max}	$T_{1/2}$	$AUC_{(0-t)}$	$AUC_{(inf)}$	$AUC_{(0-Rtmax)}$
EAI	N	67	67	59	67	59	49
	Mean	0.486	0.330	1.656	0.536	0.724	0.139
EpiPen	N	135	135	131	135	131	52
	Mean	0.520	0.170	1.139	0.466	0.583	0.119

An analysis of these data for bioequivalence via a mixed-effects linear model analysis using the Haidar method (2008) indicated that bioequivalence was established for both observed and change from baseline values in C_{max}, $AUC_{(0-t)}$, $AUC_{(inf)}$, and $AUC_{(0-Rtmax)}$.

Reviewer's Comment: The CMC Review Team noted that the epinephrine formulation storage specifications of EAI indicate a greater percentage of (b) (4) *degradation, as compared to the RLD, from* (b) (4) *% for EpiPen to* (b) (4) *% for EAI. While this may not be expected to affect the bioavailability of EAI if used soon after its manufacture, in practical terms, epinephrine auto-injectors are often stored long-term by patients in anticipation of home use in an emergency situation.*

8.4. Safety Results

The safety database consisted of all subjects who received at least 1 dose of study medication. Overall, 67 subjects received EAI, while 69 subjects received at least 1 dose of RLD (EpiPen).

Adverse Events

No deaths, serious adverse events, or severe treatment-emergent adverse events (TEAE) occurred in this trial, although one mild TEAE resulted in treatment discontinuation and study withdrawal (ventricular extrasystoles that occurred in a 44 year-old African-American man approximately 5 minutes after EAI dosing, which resolved spontaneously after 2 minutes). Overall, more TEAEs occurred with EpiPen (87.0% of 196 total doses) compared to EAI (68.7% of 92 total doses). Most (97.6%) TEAE's were classified as mild. Moderate TEAEs associated with EAI included tachycardia and injection site pain, while moderate TEAEs associated with the RLD included tachycardia (2 events), injection site pain, nausea, and increased excitability. The most commonly reported Preferred Term AEs occurring in ≥ 2 patients out of 67 total EAI doses and at a greater percentage than in EpiPen-recipients were Heart Rate Increased (which occurred at nearly an equal rate as with EpiPen: 17.9% versus 17.8%) and Anxiety (10.4% versus 7.4%), as shown in the following table. Based on MedDRA v. 11.1 search terminology, System Organ Class terms are shown alphabetically (regardless of rate), while Preferred Term headings, which meet the aforementioned criteria are also listed. The Preferred Term AEs are described in the current RLD product label, as well as the proposed product label for EAI. Thus, based on the reported AE profile for injectable epinephrine, a preliminary review suggests that no new safety signals emerged from Study INT0802.

System Organ Class Preferred Term	Treatment Group EAI Doses=67 N (%)	Treatment Group EpiPen Doses=135 N (%)
Cardiac Disorders	2 (3.0)	3 (2.2)
General Disorders and Administration Site Conditions **Injection Site Pruritus**	34 (50.7) 2 (3.0)	79 (58.5) 0
Investigations **Heart Rate Increased**	13 (19.4) 12 (17.9)	26 (19.3) 24 (17.8)
Musculoskeletal and Connective Tissue Disorders	4 (6.0)	1 (0.7)
Nervous System Disorders **Dizziness** **Headache**	12 (17.9) 2 (3.0) 2 (3.0)	23 (17.0) 3 (2.2) 2 (1.5)
Psychiatric Disorders **Anxiety**	8 (11.9) 7 (10.4)	14 (10.4) 10 (7.4)

Source: Clinical Study Report INT0802, Section 14, Table 14.3.1.5

An additional class-related adverse event that did not meet the prevalence criteria above was palpitations, which occurred in 1 EIA-recipient and 3 RLD-recipients. Mild to moderate injection site pain (EAI: n = 9 or 13.4%; RLD: n = 33 or 24.4%) and injection site erythema (EAI: n = 21 or 31.3%; RLD: n = 44 or 32.6%) were also commonly experienced, but at lower rates in EAI-recipients, compared to RLD-recipients.

Reviewer's Comment: With regard to reported tachycardic adverse events, a discrepancy was noted in the tabular AE data listed in Table 14.3.1.5 and summary data reported in the text, with tabular data indicating increased heart rate occurred after 24 RLD injections or 17.8% of all RLD doses, while the summary text in the Study Report for INT0802 indicated tachycardia occurred after 25 RLD injections or 18.5% of all injections. This is in comparison to the 12 events reported following EAI doses, which comprised 17.9% of all EAI doses. Thus, it is unclear whether tachycardia occurred at a greater or lower rate in the EAI versus RLD group.

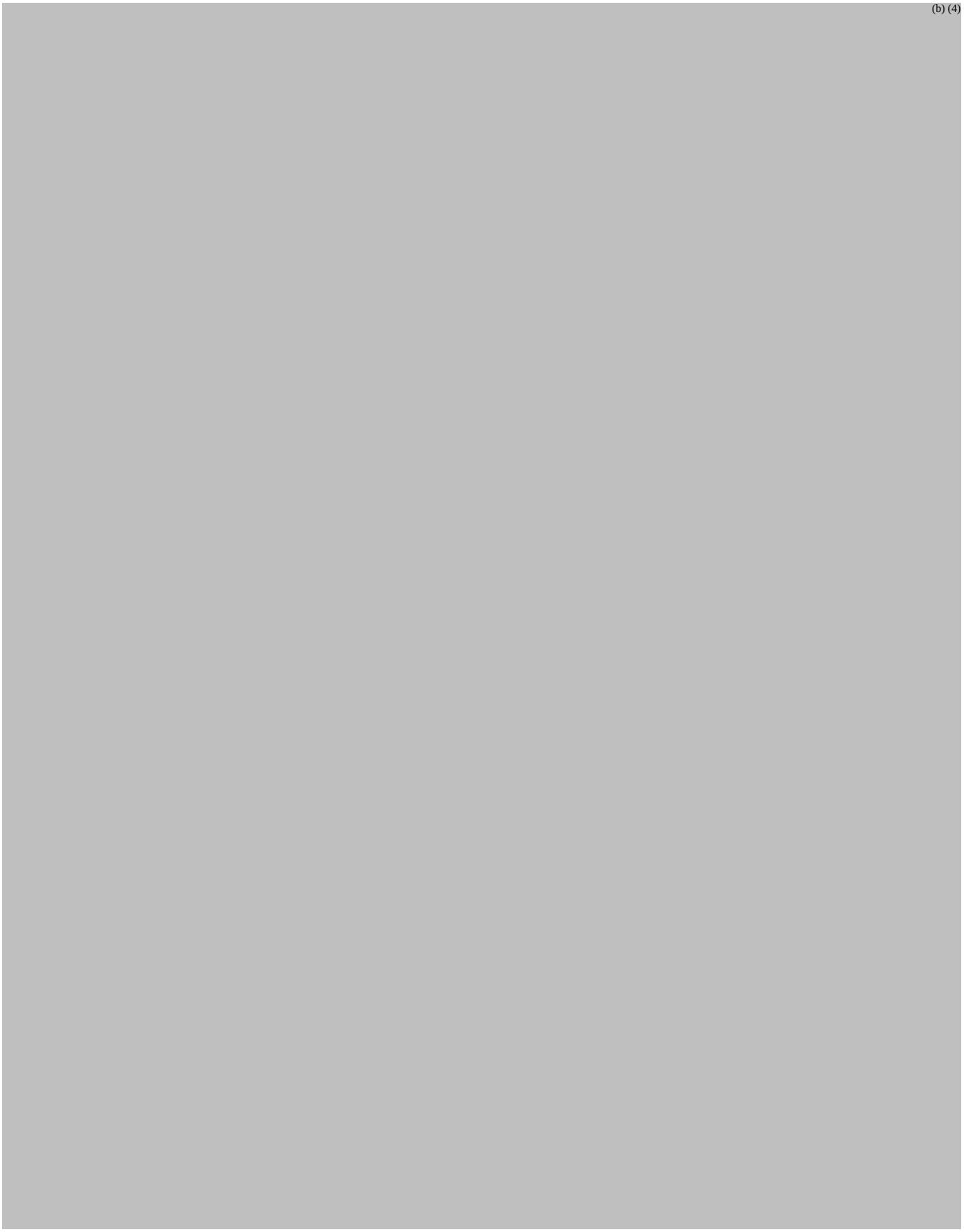
VI. Brief review of proposed labeling

Proposed product labeling with annotation has been submitted by the Applicant, which incorporates findings from Study INT0802. The Applicant has submitted the label in SPL format as well as in MSWord format to aid with the review process. A brief review of the proposed labeling was performed. The majority of the proposed label was taken from the approved product label for the RLD, EpiPen Auto-Injector (Prescribing Information dated April 2009), including information on indications and usage, contraindications and adverse reactions, warnings and precautions, drug interactions, and use in specific populations. Information on dosage and administration, dosage forms and strengths, warnings and precautions, adverse reactions, use in specific populations, overdosage, general description, clinical pharmacology, clinical trials experience, storage and handling, patient counseling information, and general instructions have been revised to reflect information relevant to EAI.

Key aspects of the proposed EAI product label, which differ from that of the RLD, are described below: do you want to mention how the indication is slightly different

(b) (4)

(b) (4)



(b) (4)

VII. DSI Review/Audit

Initial review of the application does not raise any data integrity concerns. Injectable epinephrine is a known drug substance with extensive post-marketing experience, including auto-injectable formulations. Data were obtained from a single U.S. study site. No investigators are listed as having relevant financial disclosures. Because of these reasons, the clinical team is not requesting a DSI audit for this application.

Reviewer's Comment: The Clinical Pharmacology Review Team feels that a DSI audit should be done.

VIII. Pediatric Plan

The Applicant has requested a waiver of pediatric studies for patients weighing less than 15 kg (less than 3 years and 6 months of age). The proposed labeling does not provide dosing recommendations for pediatric patients weighing less than 15 kg, as alternative epinephrine products are recommended for this population, given the fixed dosage of EAI. In Pre-NDA meeting comments dated October 23, 2009, the Agency previously informed the Applicant that a pediatric assessment of EAI may not be required, as PREA is not triggered by this proposed product. However, the Agency encouraged the Applicant to conduct trials in patients weighing < 15 kg. The Agency also stated that a decision regarding the deferral of pediatric assessment would be made during the NDA submission, and a Written Request asking for such trials may be issued by the Agency under BPCA, given pressing public health needs.

Reviewer's Comment: A formal waiver from the Office of Clinical Pharmacology and Biopharmaceutics will be required to exempt the Applicant from completing trials of the EAI 0.15 mg dose form, given that the current NDA submission only contains data from the EAI 0.3 mg dose form. This strategy was agreed to by the Agency in comments dated March 9, 2007, which were communicated to the Applicant following review of a Pre-IND briefing package dated February 1, 2007.

IX. Conclusions

The study reports for INT0801, INT0803, INT-FE-0901, and INT 0802 appear complete, and the information is appropriately indexed for review. No filing issues are identified.

X. Comments for the Applicant

The adequacy of the NDA for filing will be conveyed to the Applicant in the 74-day filing letter, along with the following comment from the Clinical Review Team:

1) We note that the proposed indication for EAI differs from the approved indication for the reference listed drug. Provide data to support the specific additional claims, or amend the proposed label to remove any unsupported claims.

XI. Review Timeline

November 4, 2010	Filing and planning meeting
December 12, 2010	74-Day Letter
March 2, 2011	Mid-Cycle Meeting
March 11, 2011	Regulatory Briefing
March 29, 2011	Labeling Meeting
June 22, 2011	Wrap-up Meeting
June 24, 2011	Primary reviews due
June 27, 2011	Wrap-up T-Con with Applicant
July 29, 2011	PDUFA goal date

XII. Clinical Filing Checklist

NDA/BLA Number: 201-739 **Applicant: Intellijject** **Stamp Date: 9/29/10**

Drug Name: Epinephrine Auto-Injector (EAI) **NDA/BLA Type: NDA standard review**

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

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			

	Content Parameter	Yes	No	NA	Comment
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			Summary of Clinical Safety
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			Summary of Clinical Efficacy
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	X			505(b)(2) NDA RLD: EpiPen and EpiPen Jr (NDA 19-430)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:			X	RLD dosing is referenced
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 Indication: Pivotal Study #2 Indication:			X	BE study with RLD
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?			X	BE study with RLD
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.			X	BE study with RLD
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	BE study with RLD
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			X	RLD

20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	X			RLD
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	X			BE Study
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			MedDRA v. 11.1
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.
[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			Separate form not included; statement in Clinical Study Report

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ___Yes___

If the Application is not fileable from the clinical 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.

Brian Oscar Porter, M.D. Ph.D., M.P.H. 11/4/10

Reviewing Medical Officer Date

Susan Limb, M.D. 11/4/10

Clinical Team Leader Date

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

/s/

BRIAN PORTER
11/08/2010

SUSAN L LIMB
11/09/2010