CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

201739Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA:	201739
Type:	Original NDA
Generic Name:	Epinephrine
Proposed Trade Name	TBD
Proposed Indication:	Emergency treatment of allergic reactions (Type 1) including anaphylaxis to stinging insects and biting insects, allergen immunotherapy, foods, vaccines, drugs, diagnostic testing substances and other allergens, as well as idiopathic anaphylaxis or exercise induced anaphylaxis
Dosage Form:	Auto-injector
Strength:	0.15 mg and 0.3 mg
Route of Administration:	Subcutaneous or Intramuscular
Proposed Dosing regimen:	0.15 mg for patients who weigh 15 to 30 kg and 0.3 mg for patients who weigh 30 kg or more. Prescriber should assess each patient to determine the most appropriate dose of epinephrine, recognizing the life-threatening nature of the reactions for which the drug is indicated. With severe persistent anaphylaxis, repeat injections with an additional dose may be necessary
Applicant:	Intellijject, Inc
OCP Division:	Division of Clinical Pharmacology 2
Clinical Division:	Division of Pulmonary, Allergy, and Rheumatology Products
Submission Date:	September 29, 2010
Reviewer:	Liang Zhao, Ph.D.
Team Leader (Acting):	Suresh Doddapaneni, Ph. D.

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1 EXECUTIVE SUMMARY

1.1 Recommendations

This NDA is acceptable from a clinical pharmacology perspective.

1.2 Phase IV commitments

None.

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Sponsor's objective of the program for this product is to assess comparative bioavailability of their product with respect to the reference autoinjector product, EpiPen (NDA 19430). As such, study INT0802 is the only clinical pharmacology study submitted to this NDA. In addition, data from three design and human factors-related studies were included in the submission (INT0801, INT0803, and INT0901).

Study INT0802 was a randomized, single dose, single-blind, 2-treatment, 3-period, 3-sequence crossover study to document the bioavailability of epinephrine delivered by this product and EpiPen. The study design employed is a replicated design with the Test product administered once and EpiPen administered twice in a random sequence (TRR, RTR, RRT) as epinephrine (endogenous drug substance) is a highly variable drug substance. In addition, a scaled bioequivalence (BE) approach was used for the BE analysis. A total of 67 subjects were recruited into the study. The primary Pharmacokinetic (PK) parameters for assessment of BE were Cmax and AUC. Mr. Donald Schuirmann (Mathematical Statistician) in the Office of Biostatistics was consulted on the statistical analysis.

Similar epinephrine Cmax (peak drug concentration) and total AUC0-t exposure (area under the concentration-time curve from baseline to the last measurable concentration) were obtained between the Test product (TBD) and EpiPen®. Cmax, AUC0-t, and AUCinf met the equivalence criteria using the baseline corrected data set. Cmax and AUC0-t met the equivalence criteria using the base uncorrected data set (see section 2.2.2 for additional details on this). Overall, it can be concluded that the exposure of the two products is equivalent.

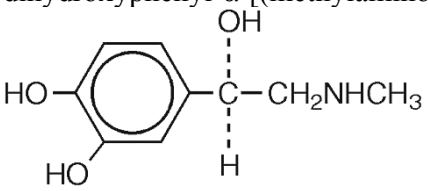
Division of Scientific Investigation (DSI) audit of the study did not reveal any significant issues that precluded acceptance of the data. Per the review of Dr. Sandra Suarez of ONDQA Biopharmaceutics group dated 27 May 2011, a biowaiver for the 0.15 mg strength was granted by the Agency.

Overall, there are no issues precluding the acceptance of this NDA from a clinical pharmacology perspective.

2 QUESTION BASED REVIEW

2.1 General Attributes/Background

Epinephrine is a sympathomimetic catecholamine. Chemically, epinephrine is (-)-3, 4-dihydroxyphenyl-α-[(methylamino)methyl]benzyl alcohol, with the following structure:



Intellijject, Inc. (Intellijject) has developed Epinephrine Auto-Injector 0.15 mg (epinephrine injection USP 1:1000) and Epinephrine Auto-Injector 0.3 mg (epinephrine injection USP 1:1000), collectively referred to as TBD, or individually referred to as TBD 0.15 mg and TBD 0.3 mg.

TBD is a compact, patient-actuated, auto-injection system that delivers a single dose of either 0.3 mg (0.3 mL) or 0.15 mg (0.15 mL) epinephrine injection, USP 1:1000 (or 1 mg/mL) intramuscularly or subcutaneously. Selection of the appropriate dosage strength is determined according to patient body weight. TBD 0.3 mg is intended for patients weighing 30 kg or more (approximately 66 pounds or more) and TBD 0.15 mg is intended for patients who weigh 15 to 30 kg (33 to 66 pounds). TBD is to be used as emergency supportive therapy only and is not a substitute for immediate medical care.

TBD 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. TBD 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.

2.1.1 What pertinent regulatory background or history precedes the current assessment of the NDA submission for epinephrine auto-injector?

EpiPen 0.15 mg and 0.3 mg Autoinjector (NDA 19430) was originally approved on 12 December 1987. Twinject 0.15 mg and 0.3 mg Autoinjector (NDA 20800) was approved on 5 May 2003. No PK data was submitted in support of approval of Twinject. Instead, the approval of Twinject relied on previous findings of safety and efficacy of the approved EpiPen NDA and on literature data.

In the pre-IND meeting package submitted on 1 February 1, 2007, Intellijject proposed a comparative bioavailability/bioequivalence study in support of their product and did not request a biowaiver for 0.3 mg strength. On 05 March 2009 (Serial No. 0005 Submission to IND 76,367), Intellijject submitted a request for Type B meeting to obtain feedback from FDA regarding Intellijject's proposal to change the objective of the Bioavailability/Bioequivalence Study INT0802 from demonstrating bioequivalence of Epinephrine AutoInjector (EAI) and EpiPen to documenting the bioavailability of EAI and EpiPen. On 27 April 2009, FDA sent a written correspondence stating:

"Changing the primary objective of the Protocol INT0802 from bioequivalence (BE) to comparative bioavailability assessment is acceptable. However, we still recommend that you conduct the statistical data analysis using the BE approach appropriate for the proposed replicated crossover study design and submit the results as part of the study report."

In the Meeting Package dated 25 September, 2009, the sponsor asked the following Clinical Pharmacology question related to the results of Study INT0802:
"Does FDA agree that the bioavailability results from Clinical Study INT0802 (see Study Report Synopsis in Appendix 1.A) are sufficient to demonstrate the bioavailability of epinephrine injected using (b) (4) is comparable to EpiPen?" In the response dated 23 October, 2009, FDA responded that "we recognize that you have adopted the novel reference replicated-treatment study design and the statistical data analysis using reference-scaling average BE approach that has been proposed in recent literature by the Agency. Provide justification either from published literature or study data to support your conclusion that epinephrine is a highly variable drug, especially the within-subject variability. Realize that this new method has not yet been part of any published FDA Guidance for Industry. The assessment of comparative bioavailability study results between your product and EpiPen will be part of the ensuing NDA review."

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical trials?

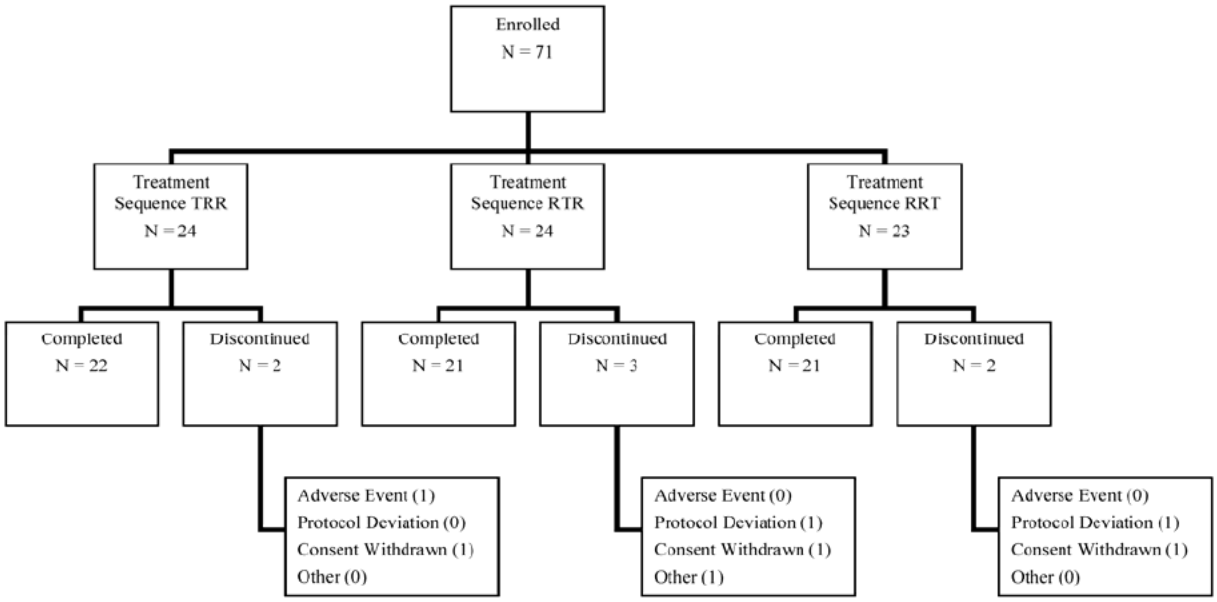
Since sponsor's objective of the program for this product was to assess bioavailability with respect to the reference autoinjector product, study INT0802 is the only clinical pharmacology study submitted in this NDA. In addition, data from three design and human factors-related studies are included in the submission (INT0801, INT0803, and INT0901). This review will focus on study INT0802 only.

Study INT0802 was a randomized, single dose, single-blind, 2-treatment, 3-period, 3-sequence crossover study to document the bioavailability of epinephrine delivered by TBD and reference listed epinephrine product, EpiPen (NDA 19430), marketed by Meridian Medical Technologies.

The 3-period, 3-sequence crossover design with the Test product (TBD) administered once and Reference product (EpiPen) administered twice in a random sequence (TRR, RTR, RRT) was selected based on FDA issued BA/BE guidance (FDA Guidance for Industry: Statistical Approaches to Establishing Bioequivalence, 2001; FDA Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products-General Considerations, 2003) for drugs with a high expected within subject variability (i.e. a percentage coefficient of variation [%CV] of one or more natural logarithm-transformed PK parameters that is ≥ 30%). In addition to allowing comparisons of the PK profiles of epinephrine administered using TBD versus EpiPen, this design allowed for calculation of within subject variability for the Reference product.

Sixty-six eligible subjects were planned for enrollment and randomization to one of 3 treatment sequences predose on Day 1 of Period 1, according to a randomization schedule prepared by (b) (4) before the start of the study. Subjects were randomized to a treatment sequence; TRR, RTR or RRT, as described in Figure 1, below.

Figure 1. Treatment groups (INT0802)



N = number of subjects; T= Test ((b) (4) R = Reference (EpiPen)

During Screening (Day -30 to Day -1), subjects signed informed consent and underwent procedures to determine eligibility. Eligible subjects reported to the CPRU on Day 0 (for all treatment periods), the evening prior to dose administration, and underwent predose procedures. On Day 1 of each treatment period, subjects received a single injection of investigational product in the thigh, administered by trained medical personnel. Subjects were discharged from the CPRU after the 6-hour postdose blood sample was collected (Periods 1 and 2). After the third treatment period, subjects remained in the CPRU at least until the 6-hour postdose blood sample was collected and the end-of-study discharge procedures were completed. Blood was collected for PK samples at the following time points: predose and 5, 10, 15, 20, 30, 40, and 50 minutes and 1, 1.25, 1.5, 2, 3, 4, and 6 hours postdose for each treatment period. Subjects may have remained at the CPRU overnight after dosing during any period at the discretion of the Investigator. There was a wash-out period of at least 24 hours between treatment periods.

The PK of epinephrine delivered by TBD and EpiPen was determined by plasma concentrations collected through 6 hours postdose. Intensive sampling was conducted during the first hour postdose to fully characterize the early PK profile after investigational product administration.

All subjects were required to fast for a minimum of 10 hours before dosing. A washout period of at least 24 hours was considered sufficient to prevent carryover effects of the Test product and the Reference product; the duration of this washout was greater than 5 half lives as determined in a previous study in individuals who received a 0.3 mL (0.3 mg) IM epinephrine injection using the EpiPen Auto-Injector (Simons FE, Roberts JR, Gu, X, Simons KJ. Epinephrine absorption in children with a history of anaphylaxis. J Allergy Clin Immunol. 1998 Jan;101(1):33-37).

In order to avoid variations in endogenous epinephrine levels, subjects were not allowed to view the injection devices before or during the injection process. Subjects were also blinded to study treatment to minimize bias based on subjective expectations. Serial blood sampling from predose to 6 hours postdose was considered sufficient to determine epinephrine PK profiles following an injection using either test product or EpiPen.

Primary PK parameters, such as peak drug concentration (Cmax), time at maximum plasma concentration (Tmax), area under the concentration-time curve from baseline to the last measurable concentration (AUC0-t), AUC from baseline extrapolated to infinity (AUCinf), and terminal-phase elimination half life (T1/2), were estimated using non-compartmental analysis (NCA). Secondary partial AUC parameters were determined for each subject's concentration-time profiles by calculating the AUC from time zero to the time of the maximum plasma concentration (Tmax) after injection with the Reference product (i.e., EpiPen).

Epinephrine is a highly variable endogenous compound. Therefore, the reference scaled bioequivalence evaluation approach, as recommended by Haidar et al (Haidar SH, Davit B, Chen ML, Conner D, Lee L, Li QH, et al Bioequivalence approaches for highly variable drugs and drug products. Pharm Res. 2008 Jan;25(1):237-41), was used to determine bioequivalence. There are two criteria to pass based on this method:
1. The upper 95% confidence limit for $(\mu_T - \mu_R)^2/\sigma_{WR}^2$ should be less than or equal to 0.8
2. The point estimate of $(\mu_T - \mu_R)$ must lie within the interval $(\log_e(0.8), \log_e(1.25))$.

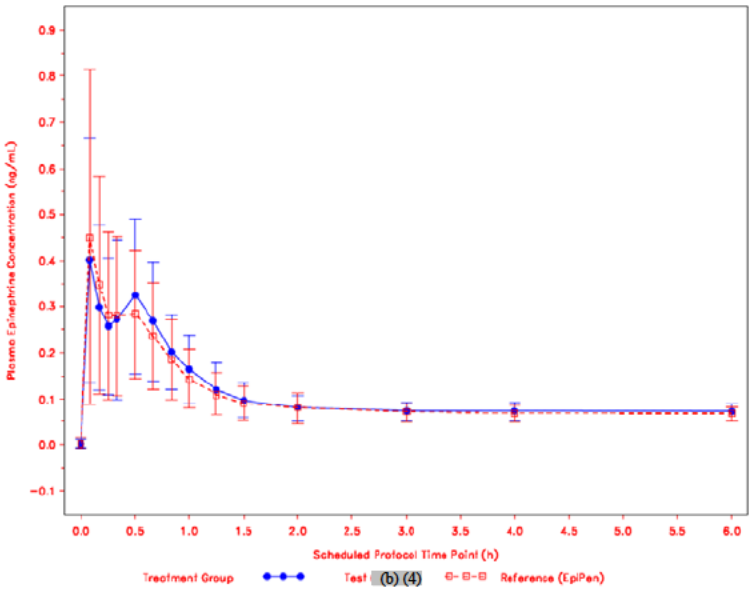
The Haidar et al approach was used for PK parameters such as Cmax, AUC0-t, and AUCinf. The actual calculation of the 95% upper confidence limit for $(\mu_T - \mu_R)^2/\sigma_{WR}^2$ was adapted from the method described by Hyslop et al (Hyslop T, Hsuan F, Holder DJ. A small sample confidence interval approach to assess individual bioequivalence. Stat Med. 2000 Oct 30;19(20):2885-97).

Since epinephrine is an endogenous compound, pharmacokinetic parameters and the associated statistical analyses were also done for baseline-corrected concentrations.

2.2.2 What is known about the pharmacokinetics of Epinephrine?

The drug concentration profile is shown in Figure 2 for the observed data. The mean values of the observed concentrations between the two treatments were comparable. As showed by error bars indicating standard deviations, the measured epinephrine concentrations were highly variable.

Figure 2. Mean+/-SD plasma epinephrine concentration-time profiles (observed) in linear scale



Summary of plasma epinephrine PK parameters is shown in Table 1.

Table 1. PK parameters summary for observed data

TRT	Statistic	Cmax (ng/mL)	T1/2 (h)	AUC0-t (ng.h/mL)	AUCinf (ng.h/mL)	Tmax (h)	AUC0_MED (ng.h/mL)	R1acotmx (ng.h/mL)	R2acotmx (ng.h/mL)
Test	n	67	59	67	59	67	67	65	64
	Mean	0.486	1.656	0.536	0.724	0.330*	0.042	0.075	0.063
	CV%	50.8	137.7	36.6	52.8	0.08-1.00*	69.7	110.6	112
Reference	n	135	131	135	131	135	135	135	132
	Mean	0.52	1.139	0.466	0.583	0.170*	0.05	0.077	0.07
	CV%	63.1	100.3	42.2	47.9	0.07-1.00*	79.7	115.4	104.3

n	Number of observations
CV%	Coefficient of Variation in %
Reference	Epipen®
Test	TBD
Cmax	Peak drug concentration
T1/2	Terminal-phase elimination half-life
AUC0-t	Area under the concentration-time curve from baseline to the last measurable concentration
AUCinf	Area under the concentration-time curve from baseline extrapolated to infinity
Tmax	Time at maximum plasma concentration
AUC0_MED	AUC t_0 to median Tmax
R1ACOTMX	AUC t_0 to Tmax 1ST receipt of Reference
R2ACOTMX	AUC t_0 to Tmax 2ND receipt of Reference

*: For Tmax, the table reports the median and the range (minimum - maximum).

Epinephrine Cmax (ng/mL) and total AUC0-t exposure were similar between the Test product (TBD) and the Reference product (EpiPen®). For the observed dataset, the mean Cmax was 0.486 ng/mL for the test product and 0.520 ng/ml for the reference product; the mean AUC0-t

was 0.536 ng.h/mL for the test product and 0.466 ng.h/mL for the reference product. For the baseline corrected dataset, the means of Cmax was 0.484 ng/mL for the test product and 0.518 ng/ml for the reference product; the mean AUC0-t was 0.526 ng.h/mL for the test product and 0.56 ng.h/mL for the reference product.

Tmax, the time to reach Cmax after Epinephrine auto-injection, was short with a median of approximately 10 minutes for the test and 20 minutes for EpiPen and ranging widely from 5 to 60 minutes for both treatments. Due to the high and overlapping variability associated with Tmax, strict evaluation of similarity in Tmax is not meaningful.

The use and acceptability of scaled bioequivalence approach in IND/NDAs was discussed in an Office of Clinical Pharmacology Scientific Rounds on 15 February 2011. It was agreed that acceptance on a case by case basis will be allowed if adequate justification is available that the variability is not coming from a poor formulation. In this case, epinephrine is an endogenous drug substance with varying baseline levels and the formulation is a simple solution. As such, use of scaled BE approach in this instance is reasonable.

Since the statistical analysis employed in this study was novel, Mr. Donald Schuirmann, Mathematical Statistician, in the Office of Biostatistics was consulted on the bioequivalence analysis.

The evaluation outcome of the bioequivalence analyses is shown in Table 2. Primary parameters of interest are Cmax and AUC. Partial AUC parameters R1ACOTMX and R2ACOTMX are presented here for completion.

Table 2a. Bioequivalence analysis results for PK parameters derived from observed dataset

PK Parameters	Ratio	90% Confidence Interaval Lower	Upper	μ_T-μ_R	σ_{WR}^2	Upper 95% Conf Limit for $(\mu_T-\mu_R)^2$-0.8 σ_{WR}^2	CV_{WR} (%)	Criterion 1: Confidence Limit *	Criterion 2: Point Estimate **	Bioequivalent (yes or no)
Cmax	0.9448	0.8439	1.0842	-0.0568	0.1888	-0.1019	43.45	Pass	Pass	Yes
AUC0-t	1.1586	1.0602	1.2776	0.1472	0.1091	-0.0231	33.03	Pass	Pass	Yes
AUCinf	1.1864	1.1035	1.3790	0.1709	0.1003	0,0034	31.68	Fail	Pass	No
R1ACOTMX	0.7924	0.6552	0.9225	-0.2327	0.3410	-0.0628	66.49	Pass	Fail	No
R2ACOTMX	0.7874	0.6569	0.9504	-0.2390	0.3030	-0.0559	55.04	Pass	Fail	No

Table 2b. Bioequivalence analysis results for PK parameters derived from baseline corrected dataset

PK Parameters	Ratio	90% Confidence Interaval Lower	Upper	μ_T-μ_R	σ_{WR}^2	Upper 95% Conf Limit for $(\mu_T-\mu_R)^2$-0.8 σ_{WR}^2	CV_{WR} (%)	Criterion 1: Confidence Limit *	Criterion 2: Point Estimate **	Bioequivalent (yes or no)
Cmax	0.9446	0.8439	1.0844	-0.0570	0.1931	-0.1046	43.94	Pass	Pass	Yes
AUC0-t	1.1544	1.0575	1.2774	0.1436	0.1279	-0.0373	35.76	Pass	Pass	Yes
AUCinf	1.1747	1.0915	1.3693	0.1610	0.1250	-0.0179	35.36	Pass	Pass	Yes
R1ACOTMX	0.7635	0.6549	0.9219	-0.2698	0.3494	-0.0686	59.11	Pass	Fail	No
R2ACOTMX	0.7896	0.6585	0.9532	-0.2362	0.3154	-0.0670	56.16	Pass	Fail	No

*: The upper 95% confidence limit for $(\mu_T - \mu_R)^2/\sigma_{WR}^2$ should be less than or equal to 0.8, or $(\mu_T - \mu_R)^2$-0.8σ_{WR}^2 must be negative
**: The point estimate of $(\mu_T - \mu_R)$ must lie within the interval ($\log_e(0.8)$, $\log_e(1.25)$) or the ratio must be with (0.8, 1.25)

Based on Table 2, primary PK parameter such as Cmax and AUC0-t passed the reference scaled bioequivalence evaluation based on both observed and baseline corrected datasets. In addition, AUCinf passed for the baseline corrected data set.

See attachment 1 for additional details on Mr. Schuirmann's analysis.

DSI audited study INT0802 and recommended acceptance of the data as no significant issues were found during the inspection (for additional details, see review dated 6 April 2011 by Dr. Abhijit Raha of DSI) .

For the 0.15 mg strength, biowaiver was granted by the Agency (for additional details on this see review dated 27 May 2011 by Dr. Sandra Suarez of Biopharmaceutics group in ONDQA).

2.2.3 What are the characteristics of the dose-response relationships for efficacy?

No dose-response relationship has been established historically.

2.2.4 What are the safety issues attributed to epinephrine auto-injector?

No new safety issues were identified in study INT0802 from a clinical pharmacology perspective

2.2.5 What is the composition of the new Epinephrine auto-injector and how does it differ from the currently marketed product Twinject® or EpiPen®?

Formulation composition of both products is shown in the table below.

Component	Amount (mg)[a]			
	EAI 0.3 mg (0.3 mL)	EAI 0.15 mg (0.15 mL)	EpiPen (0.3 mg)[b] (0.3 mL)	EpiPen Jr. (0.15 mg)[b] (0.3 mL)
Epinephrine	0.3	0.15	0.3	0.15
Sodium Bisulfite	(b) (4)			
Sodium Metabisulfite			(b) (4)	
Sodium Chloride	(b) (4)			
Hydrochloric Acid (0.5 N)	*qs ad* pH 2.5 ± 0.2	*qs ad* pH 2.5 ± 0.2	pH 2.2–5	pH 2.2–5
Water for Injection	*qs ad* 1.0 mL	*qs ad* 1.0 mL	*qs ad* 1.0 mL	*qs ad* 1.0 mL

[a] Amounts rounded consistent with EpiPen package insert (Section 1.14.3.2).
[b] Amounts based on information from EpiPen package insert and analysis of epinephrine in EpiPen lots. EpiPen Jr. uses a 1:2000 solution of epinephrine to deliver 0.15 mg in a 0.3 mL injection.

2.2.6 What was the relative bioavailability of epinephrine delivered from the auto-injector? Was bioequivalence demonstrated between the two formulations?

As shown in Table 2, Both Cmax and AUC met the criteria to demonstrate equivalence between the test and reference products for the baseline corrected dataset and observed data set (except for AUCinf for the observed dataset) indicating that the two products have similar exposure, overall.

2.3 Intrinsic and extrinsic factors

2.3.1 Are there any significant intrinsic or extrinsic factors that affect the PK of epinephrine?

Data in patients with renal impairment, hepatic impairment, or elderly were not required supporting this product. Sponsor is relying on the information in the package insert of the reference product related to all intrinsic and extrinsic factors.

2.3.2 Did the sponsor use to-be-marketed formulation in the bioequivalence trial INT0802?

Yes.

2.4 Analytical Section

2.4.1 Were the analytical procedures used to determine drug concentrations in this NDA acceptable?

All bioanalytical assays fulfilled the regulatory criterion [refer to the FDA guidance for industry "Bioanalytical Method Validation (Final-May 2001)] of not exceeding 15% (20% for the lowest QC samples) for precision and accuracy. The accuracy and inter-day precision were acceptable for all the studies (<15% bias or %CV). Study samples were analyzed in runs containing calibrators and quality control samples, as recommended in the FDA guidance.

Project samples were analyzed according to (b) (4) Method P981.00, entitled "Quantitation of Epinephrine in Human Plasma via HPLC with Fluorescence Detection". The current method developed by (b) (4) was validated to quantitation within a nominal range of 0.0500 to 8.00 ng/mL. The lower limit of quantitation was nominally 0.0500 ng/mL.
Precision and accuracy were evaluated by analyzing quality control pools prepared at five levels. Precision was expressed as the percent coefficient of variation (%CV) of each pool. Accuracy was measured as the difference from theoretical in %.

The intra-assay precision and accuracy for different run IDs are shown in Table 3.

Table 3a. Intra-Assay Precision and Accuracy.

Run ID	QC 1 (ng/mL)	QC 2 (ng/mL)	QC 3 (ng/mL)	QC 4 (ng/mL)	QC 5 (ng/mL)
14AFGF	0.0508	0.125	0.330	1.11	5.94
	0.0473	0.124	0.333	1.08	5.81
	0.0521	0.121	0.338	1.09	6.06
	0.0466	0.122	0.320	1.06	5.72
	0.0486	0.125	0.324	1.06	5.85
	0.0492	0.113	0.294	0.993	6.04
N	6	6	6	6	6
Theoretical Concentration	0.0500	0.120	0.360	1.25	6.00
Mean	0.0491	0.122	0.323	1.06	5.90
S.D.	0.00207	0.00456	0.0156	0.0398	0.136
%C.V.	4.22	3.75	4.82	3.74	2.31
% Difference from Theoretical	-1.80	1.37	-10.2	-14.9	-1.60
Low Limit	0.0400	0.102	0.306	1.06	5.10
High Limit	0.0600	0.138	0.414	1.44	6.90

Table 3b. Intra-Assay Precision and Accuracy.

Run ID	QC 1 (ng/mL)	QC 2 (ng/mL)	QC 3 (ng/mL)	QC 4 (ng/mL)	QC 5 (ng/mL)
15AFGF	0.0449	0.121	0.358	1.29	5.23
	0.0462	0.121	0.346	1.22	6.05
	0.0493	0.116	0.352	1.25	5.79
	0.0482	0.124	0.369	1.24	5.93
	0.0447	0.121	0.357	1.26	5.93
	0.0456	0.117	0.353	1.28	6.07
N	6	6	6	6	6
Theoretical Concentration	0.0500	0.120	0.360	1.25	6.00
Mean	0.0465	0.120	0.356	1.26	5.83
S.D.	0.00188	0.00300	0.00771	0.0270	0.310
%C.V.	4.04	2.49	2.17	2.15	5.32
% Difference from Theoretical	-7.03	0.133	-1.17	0.524	-2.77
Low Limit	0.0400	0.102	0.306	1.06	5.10
High Limit	0.0600	0.138	0.414	1.44	6.90

Table 3c. Intra-Assay Precision and Accuracy.

Run ID	QC 1 (ng/mL)	QC 2 (ng/mL)	QC 3 (ng/mL)	QC 4 (ng/mL)	QC 5 (ng/mL)
17AFGF	0.0472	0.132	0.374	1.35	6.46
	0.0504	0.124	0.417	1.37	6.13
	0.0465	0.125	0.390	1.32	6.25
	0.0438	0.120	0.348	1.22	5.90
	0.0456	0.117	0.363	1.25	5.96
	0.0471	0.120	0.359	1.23	5.68
N	6	6	6	6	6
Theoretical Concentration	0.0500	0.120	0.360	1.25	6.00
Mean	0.0468	0.123	0.375	1.29	6.06
S.D.	0.00217	0.00517	0.0250	0.0626	0.274
%C.V.	4.64	4.20	6.66	4.86	4.52
% Difference from Theoretical	-6.45	2.45	4.22	3.04	1.07
Low Limit	0.0400	0.102	0.306	1.06	5.10
High Limit	0.0600	0.138	0.414	1.44	6.90

Inter-assay precision and accuracy were evaluated by analyzing at least two replicates of the QC levels in at least three runs. A summary of the results is shown by Table 4.

Table 4. Inter-Assay Precision and Accuracy.

N	20	32	28	28	32
Theoretical Concentration	0.0500	0.120	0.360	1.25	6.00
Mean	0.0470	0.120	0.354	1.20	6.00
S.D.	0.00257	0.0663	0.0233	0.175	0.309
%C.V.	5.46	5.53	6.57	14.6	5.15
% Difference from Theoretical	-6.00	0.00	-1.59	-4.12	0.00
Low Limit	0.0400	0.102	0.306	1.06	5.10
High Limit	0.0600	0.138	0.414	1.44	6.90

LEGEND:
a Analyzed at n = 6 to validate new QC preparation.
* Statistical calculations performed in Excel using truncated values.

3 LABELING RECOMMENDATIONS

Sponsor relied on all product non-specific labeling language in Epipen for constructing their label. With respect to the PK section, following information from study INT0802 specific to this product was included in section 12.3. At the time of writing this review, the following are the

suggested changes (denoted by strikethrough (for deletions) and underline (for additions)). Exact language will be finalized upon further discussion within the review team. Refer to the NDA action letter for the full text of the final labeling.

12.3 Pharmacokinetics

(b) (4)

(b) (4)

Attachment 1: Statistical Analyses

The following pertinent analysis results were provided by Mr. Donald Schuirmann

Summary Statistics
This table is for observed (i.e. not baseline corrected) data, as found in the sponsor's PKPARMOB dataset.

TRT	Statistic	Cmax	Thalf	AUCt	AUCinf
T	n	67	59	67	59
	Mean	0.486	1.656	0.536	0.724
	CV%	50.8	137.7	36.6	52.8
R	n	135	131	135	131
	Mean	0.520	1.139	0.466	0.583
	CV%	63.1	100.3	42.2	47.9

This agrees with the information in the sponsor's table. The corresponding table for baseline corrected data (obtained from the sponsor's PKPARMCH dataset) is:

TRT	Statistic	Cmax	Thalf	AUCt	AUCinf
T	n	67	59	67	59
	Mean	0.484	1.571	0.526	0.695
	CV%	51.1	139	37.2	50.9
R	n	135	135	131	135
	Mean	0.518	0.456	0.56	0.05
	CV%	63.1	40.9	44	79.8

For Tmax, the sponsor notes that they report the median Tmax and the range (minimum - maximum).

TRT	Statistic	Tmax
T	n	67
	Median	0.330*
	range	0.08-1.00*
R	n	135
	Median	0.170*
	range	0.07-1.00*

This agrees with the sponsor's table. The corresponding information for baseline corrected data is:

TRT	Statistic	Tmax
T	n	67
	Median	0.330*
	range	0.08-1.00*
R	n	135
	Median	0.170*
	range	0.07-1.00*

There are three partial area endpoints in the sponsor's PKPARMOB and PKPARMCH datasets. These are given as

AUC0_MED	AUC 0 – median Tmax
R1ACOTMX	AUC t_0 to Tmax 1ST receipt of Reference
R2ACOTMX	AUC t_0 to Tmax 2ND receipt of Reference

The number, mean, and CV% for these may be obtained from the m1p.sas SAS statements. These are the values for observed data:

TRT	Statistic	AUC0_MED	R1acotmx	R2acotmx
T	n	67	65	64
	Mean	0.042	0.075	0.063
	CV%	69.7	110.6	112
R	n	135	135	132
	Mean	0.05	0.077	0.07
	CV%	79.7	115.4	104.3

NDA 201739 - Summary of Scaled Average Bioequivalence (BE) analyses using the sponsor's PKPARMCH (baseline corrected) dataset

Analysis outputs using OGD's SAS code

```
Cmax          unscabe_ unscabe_                                    method_
```

```
Obs   lower    upper  pointest   s2wr    sWR   critbound   used   outcome
 1   0.84385  1.08442  0.94458 0.19311 0.43944  -0.10463 scaled/P  pass
AUCt         unscabe_ unscabe_                                    method_
Obs   lower    upper  pointest   s2wr    sWR   critbound   used   outcome
 1   1.05749  1.27743  1.15440 0.12787 0.35759 -0.037347 scaled/P  pass
AUCinf       unscabe_ unscabe_                                     method_
Obs   lower    upper  pointest   s2wr    sWR    critbound   used   outcome
 1   1.09149  1.36927  1.17466 0.12503 0.35359 -0.017882 scaled/P  pass
AUCmed       unscabe_ unscabe_                                    method_
Obs   lower    upper  pointest   s2wr    sWR   critbound   used   outcome
 1   0.68256  1.00898  0.79637 0.45627 0.67547  -0.16009 scaled/P  fail
AUCRtmx1     unscabe_ unscabe_                                    method_
Obs   lower    upper  pointest   s2wr    sWR   critbound   used   outcome
 1   0.65488  0.92185  0.76350 0.34937 0.59107 -0.068578 scaled/P  fail
AUCRtmx2     unscabe_ unscabe_                                    method_
Obs   lower    upper  pointest   s2wr    sWR   critbound   used   outcome
 1   0.65846  0.95323  0.78960 0.31543 0.56163 -0.067045 scaled/P  fail
```

Summary of outputs

```
            unscaled analysis
            90% conf. interval
endpoint    lower    upper                scaled analysis

Cmax        0.84385  1.08442 pass unsc    scaled/P  pass
AUCt        1.05749  1.27743 fail unsc    scaled/P  pass
AUCinf      1.09149  1.36927 fail unsc    scaled/P  pass
AUC0_med    0.68256  1.00898 fail unsc    scaled/P  fail (PE)
R1ACOtmx    0.65488  0.92185 fail unsc    scaled/P  fail (PE)
R2ACOtmx    0.65846  0.95323 fail unsc    scaled/P  fail (PE)
```

NDA 201739 - Summary of Scaled Average Bioequivalence (BE) analyses using the sponsor's PKPARMOB (observed) dataset

Analysis outputs using OGD's SAS code

```
Cmax        unscabe_ unscabe_                                    method_
      Obs   lower    upper  pointest   s2wr    sWR   critbound   used
outcome
       1   0.84394  1.08420  0.94475 0.18882 0.43454  -0.10187 scaled/P  pass
AUCt        unscabe_ unscabe_                                    method_
      Obs   lower    upper  pointest   s2wr    sWR   critbound   used
outcome
       1   1.06015  1.27761  1.15858 0.10911 0.33033 -0.023107 scaled/P  pass
AUCinf      unscabe_ unscabe_                                     method_
      Obs   lower    upper  pointest   s2wr    sWR    critbound   used
outcome
       1   1.10347  1.37896  1.18644 0.10034 0.31677 .003398619 scaled/P
fail
AUCmed      unscabe_ unscabe_                                    method_
      Obs   lower    upper  pointest   s2wr    sWR   critbound   used
outcome
       1   0.67946  1.00412  0.79239 0.44208 0.66489  -0.14639 scaled/P  fail
```

```
AUCRtmx1    unscabe_ unscabe_                                    method_
      Obs   lower    upper  pointest   s2wr    sWR   critbound   used
outcome
       1   0.65515  0.92251  0.76381 0.34096 0.58392 -0.062766 scaled/P  fail
AUCRtmx2    unscabe_ unscabe_                                    method_
      Obs   lower    upper  pointest   s2wr    sWR   critbound   used
outcome
       1   0.65689  0.95039  0.78738 0.30299 0.55044 -0.055911 scaled/P  fail
```

Summary of outputs

```
            unscaled analysis
            90% conf. interval
endpoint    lower    upper                scaled analysis

Cmax        0.84394  1.08420 pass unsc    scaled/P  pass
AUCt        1.06015  1.27761 fail unsc    scaled/P  pass
AUCinf      1.10347  1.37896 fail unsc    scaled/P  fail (criterion)
AUC0_med    0.67946  1.00412 fail unsc    scaled/P  fail (PE)
R1ACOtmx    0.65515  0.92251 fail unsc    scaled/P  fail (PE)
R2ACOtmx    0.65689  0.95039 fail unsc    scaled/P  fail (PE)
```

Attachment 2: Filing Form

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**201,739**	**Brand Name**	(b) (4) **currently referred to as** (b) (4) **(brand name under review)**
OCP Division (I, II, III, IV, V)	**II**	**Generic Name**	**Epinephrine**
Medical Division	**570**	**Drug Class**	**Adrenergic**
OCP Reviewer	**Liang Zhao, Ph D.**	**Indication(s)**	**Emergency treatment of allergic reactions (Type 1)**
OCP Team Leader (Acting)	**Yun Xu, Ph.D.**	**Dosage Form**	**Auto-injector**
		Dosing Regimen	**Emergency supportive therapy only**
Date of Submission	**29 Sep. 10**	**Route of Administration**	**SC**
Estimated Due Date of OCP Review	**May 29th, 2011**	**Sponsor**	**INTELLIJECT INC**
PDUFA Due Date	**July 29th 2011**	**Priority Classification**	**Standard**
Division Due Date	**May 29th, 2011**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	**X**	4	1	**3 Human factor studies and 1 human PK study**
HPK Summary	**X**	1	1	
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				

Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -	X	1	1	**INT0802**
solution as reference:				**INT0802**
alternate formulation as reference:	X	1	1	
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**1**		

Filability and QBR comments		
	"X" if yes	Comments
Application filable ?	**X**	
Comments sent to firm ?	**X**	**<u>Comments to sponsor in 74 day letter:</u>** As we stated in the pre-NDA meeting comments, we recognize that you have adopted the novel reference replicated-treatment study design and the statistical data analysis using reference-scaling average BE approach that has been proposed in recent literature by the Agency. Based on the fact that this new method has not yet been part of any published FDA Guidance for Industry, the PK analysis results based on this method will be a review issue.
QBR questions (key issues to be considered)		
Other comments or information not included above	DSI inspection will be required on the bioavailability study INT0802.	
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

Reviewer's comments: NDA is filable from a Clin Pharm standpoint. DSI inspection will be required on the bioavailability study INT0802.

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/s/

LIANG ZHAO
06/24/2011

SURESH DODDAPANENI
06/24/2011

BIOPHARMACEUTICS REVIEW Office of New Drugs Quality Assessment			
Application No.:	NDA 201-739	**Reviewer:** Sandra Suarez Sharp, Ph.D	
Division:	DPARDP		
Sponsor:	Intellijject, Inc	**Team Leader:** Angelica Dorantes, Ph.D .	
Trade Name:	Epinephrine Auto-Injector (EAI)	**Supervisor:** Patrick J. Marroum, Ph.D	
Generic Name:	Epinephrine injection USP 1:1000	**Date Assigned:**	Jan 21, 2011
Indication:	Allergic reactions	**Date of Review:**	May 24, 2011
Formulation/strength	Solution, 0.15 mg and 0.3 mg		
Route of Administration	Subcutaneously or intramuscularly		

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Submission date	CDER Stamp Date	Date of informal/Formal Consult	PDUFA DATE (extended)
September 29, 2010	September 29, 2010	Oct 28, 2010	May 2011

Type of Submission:	Original NDA
Type of Consult:	Biowaiver for lower strength (0.15 mg epinephrine injection USP 1:1000)

REVIEW SUMMARY:

EpiPen and EpiPen Jr. autoinjectors were approved on December 22, 1987 under NDA 19-430. The Agency approved Twinject® auto-injector (NDA 20-800) as a 505(b)(2) application on May 30, 2003, with the reference drug being EpiPen.

The sponsor is seeking approval of Epinephrine Auto-Injector 0.15 mg (epinephrine injection USP 1:1000) and Epinephrine Auto-Injector 0.3 mg (epinephrine injection USP 1:1000), collectively referred to as EAI with the proposed indication for the emergency treatment of allergic reactions. Each EAI is intended for single patient use only via subcutaneous or intramuscular administration. In this 505(b)(2) application, the sponsor is referencing EpiPen® Auto- Injector 0.3 mg and EpiPen Jr Auto-Injector 0.15 mg in support of the clinical safety and efficacy of epinephrine in the emergency treatment of allergic reactions (Type I).

The clinical program for this NDA consists of one pivotal clinical study which, according to the sponsor, supports the 505(b)(2) marketing application with EpiPen as the listed drug. This trial was a Phase 1 comparative clinical bioavailability study in healthy volunteers at the higher dose (0.3 mg). The sponsor states that this study utilized only the 0.3 mg dose because the concentration of epinephrine is the same in both presentations of EAI. In addition to the pivotal study, Intellijject submitted the results of three studies to evaluate design and human factors-related aspects of EAI. These clinical studies are being reviewed by the OCP team.

The Biopharmaceutics review focused on the approvability of the lower strength (0.15 mg) based on the following biowaver requirements since no in vivo studies were conducted to support it:

- Results of the BA/BE study conducted with the highest strength
- Proportionally similar composition between strengths

- Similarity of needle dimensions

The pivotal BE study results submitted for the comparison of the EAI 0.3 mg vs. EpiPen 0.3 mg are being reviewed by the OCP. The formulations for the 0.15 mg and 0.3 mg of EAI are proportionally similar.

EAI needle's length between the 0.3 mg and 0.15 mg are not similar (0.616 in vs. 0.478 in, respectively). However, this also holds true for the two approved strengths of EpiPen, suggesting the lack of clinical relevance of needle dimensions similarities between strengths in this particular case. Nevertheless, the needle's most relevant dimensions (exposed length and gauge) comparing the 0.15 mg strength of EpiPen vs. the 0.15 mg strength of EAI and the 0.3 mg strength of EpiPen vs. the 0.3 mg strength of EAI are very similar. Therefore, the waiver of the in vivo BE/BA requirements for the 0.15 mg strength of EAI autoinjector is granted with the understanding that the OCP finds the bioequivalence study linking the 0.3 mg strength of EpiPen to the 0.3 mg strength of EAI acceptable.

RECOMMENDATION:
The ONDQA/Biopharmaceutics team has reviewed NDA 201-739 submitted on Sep 29, 2010. This NDA is acceptable from the Biopharmaceutics perspective. The waiver of the in vivo requirements for the 0. 15 mg strength of EAI autoinjector is granted pending the review outcome of the pivotal BE study being evaluated by OCP.

Sandra Suarez Sharp, Ph. D.
Biopharmaceutics Reviewer
Office of New Drugs Quality Assessment

Patrick J. Marroum, Ph. D.
Biopharmaceutics Supervisor
Office of New Drugs Quality Assessment

Cc: DHenry, ADorantes, Ywang, ASchroeder

Background
There are a number of products containing epinephrine that have been the subject of an NDA or ANDA. EpiPen and EpiPen Junior autoinjectors were approved on December 22, 1987 under NDA 19-430. The Agency approved Twinject® auto-injector (NDA 20-800) as a 505(b)(2) application on May 30, 2003, with the reference drug being EpiPen. The sponsor has developed an Epinephrine Auto-Injector 0.15 mg (epinephrine injection USP 1:1000) and Epinephrine Auto-Injector 0.3 mg (epinephrine injection USP 1:1000), collectively referred to as EAI. EAI is indicated in the emergency treatment of allergic reactions including anaphylaxis to stinging insects and biting insects, allergen immunotherapy, foods, drugs, diagnostic testing substances and other allergens. Each EAI is intended for single patient use only. Selection of the appropriate dosage strength is determined according to patient body weight. EAI 0.3 mg is intended for patients weighing 30 kg or more (approximately 66 pounds or more) and EAI 0.15 mg is intended for patients who weigh 15-30 kg (33-66 pounds).

In this 505(b)(2) application, Intelliject is referencing EpiPen® (i.e., EpiPen [epinephrine] Auto- Injector 0.3 mg and EpiPen Jr [epinephrine] Auto-Injector 0.15 mg)

NDA 019430 in support of the clinical safety and efficacy of epinephrine in the emergency treatment of allergic reactions (Type I).

The clinical program for this NDA consists of one pivotal clinical study under IND 76,367 (INT0802), which, according to the sponsor, supports the 505(b)(2) marketing application with EpiPen as the listed drug. This trial was a Phase 1 comparative clinical bioavailability study in healthy volunteers at the higher dose (0.3 mg). The sponsor states that this study utilized only the 0.3 mg dose because the concentration of epinephrine is the same in both presentations of EAI. The dose delivered (0.15 mg or 0.3 mg) by EAI is determined by the volume of drug delivered (0.15 mL or 0.3 mL) by the device constituent component of EAI. In addition to the pivotal study, Intellijet submitted the results of three studies to evaluate design and human factors-related aspects of EAI.

Chemistry

Drug Product

EAI is a drug-device combination product. The drug constituent component of EAI comprises 0.76 mL of epinephrine injection, USP 1:1000 (or 1 mg/mL) in a USP Type 1 (b) (4) glass cartridge, of which a single dose of 0.3 mg (0.3 mL) or 0.15 mg (0.15 mL) is delivered by autoinjection into the anterolateral aspect of the thigh, through clothing if necessary. The residual drug cannot be further administered and is discarded with the device. Each EAI is intended for single use only. The device constituent component of the combination product is an auto-injection device. The combination product is an epinephrine prefilled drug-device delivery system. The components and composition for this product are summarized in Table 1.

Table 1. Tablet Formulation for NOMAC + E2 film coated tablets

Component	Function	Amount (mg) per mL/%W/V	EAI 0.3 mg Amount per 0.3 mL	EAI 0.15 mg Amount per 0.15 mL
Epinephrine	Active ingredient	1.12/0.11%	0.300 mg	0.150 mg
Sodium Bisulfite	(b) (4)			
Sodium Chloride				
Hydrochloric Acid				
Water for Injection	(b) (4)	*qs ad* 1 mL/100%	*qs ad* 1 mL/100%	*qs ad* 1 mL/100%
(b) (4)				

Product Development Program

The sponsor conducted one pivotal clinical study under IND 076367 (INT0802) in support of the 505(b)(2) marketing application with EpiPen as the listed drug. This study was a randomized, single dose, single-blind, 2-treatment, 3-period, 3-sequence crossover

study to document the bioavailability of epinephrine delivered by (b) (4) and the reference listed epinephrine formulation/delivery device, EpiPen. This trial was a Phase 1 comparative clinical bioavailability study in healthy volunteers at the higher dose (0.3 mg) and it is being reviewed by OCP (refer to Dr. Liang Zhao's Review).

Data Supporting the Approval of the EAI Lower Strength (0.15 mg)

The BA/BE study described above utilized only the 0.3 mg dose because the concentration of epinephrine is the same in both presentations of EAI. The dose delivered (0.15 mg or 0.3 mg) by EAI is determined by the volume of drug delivered (0.15 mL or 0.3 mL) by the device constituent component of EAI. Therefore, the lower strength's approval is being supported by the following information:

- Results of the BA/BE study conducted with the highest strength: The outcome of this review is pending as of May 24, 2011.
- Proportionally similar composition between strengths: The 0.3 mg and the 0.15 mg strengths are proportionally similar in composition (see Table 1).
- Similarity of needle dimensions
    - Table 2 summarizes the needle dimensions for several formulations of epinephrine auto injectors approved.

Table 2. Characteristics of the epinephrine autoinjector products*

Product	Needle			Injection		Trigger Force*
	Total Length	Exposed Length	Gauge	Duration	Volume	
(b) (4)						
EpiPen[3]	9/16 (0.56) in[4] 14.3 mm	0.5-0.7 in[5] 14.2 (12.6-15.4) mm[6]	23[5] 22 (0.7mm)[8]	0.2 (0.17-0.3) sec[2]	0.3 mL	2-8 lb[3] ~85 N
EpiPen Jr	[?] 9/16 (0.56) in[4]	0.4-0.6 in[5] 10-15 mm[7]	23[5] 22 (0.7mm)[8]	0.2 (0.15-0.31) sec[2]	0.3 mL	2-8 lb[3] ~85 N
Twinject 0.3 mg[4]	5/8 in[8]	0.5 in	25[8]		0.3 mL	
Twinject 0.15 mg[4]	5/8 in[8]	0.5 in	25[8]		0.15 mL	
EpiEZPen[5]		0.5-0.7 & 0.4-0.6 in[5]	23[5]			2-8 lb[5]

EAI 0.3 mg	0.78 in	0.618 in	23[9]	5 sec	0.3 mL[11]	2-10 lb[10]
EAI 0.15 mg	0.65 in	0.478 in	23[9]	5 sec	0.15 mL[11]	2-10 lb[10]

(b) (4)

[redacted]

Reviewer's Comments

Table 2 shows that EAI needle's length between the 0.3 mg and 0.15 mg are not similar (0.616 in vs. 0.478 in, respectively). However, this also holds true for the two approved strengths of EpiPen, suggesting the lack of clinical relevance of needle dimensions similarities between strengths in this particular case. Nevertheless, the needle's most relevant dimensions (exposed length and gauge) comparing the 0.15 mg strength of EpiPen vs. the 0.15 mg strength of EAI and the 0.3 mg strength of EpiPen vs. the 0.3 mg strength of EAI are very similar. Therefore, the waiver of the in vivo BE/BA studies for the 0.15 mg is granted with the understanding that OCP founds the bioequivalence study linking the 0.3 mg strength of EpiPen to the 0.3 mg strength of EAI acceptable.

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/s/

SANDRA SUAREZ
05/27/2011

PATRICK J MARROUM
05/27/2011

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**201,739**	**Brand Name**	(b) (4) **currently referred to as** (b) (4) **(brand name under review)**
OCP Division (I, II, III, IV, V)	**II**	**Generic Name**	**Epinephrine**
Medical Division	**570**	**Drug Class**	**Adrenergic**
OCP Reviewer	**Liang Zhao, Ph.D.**	**Indication(s)**	**Emergency treatment of allergic reactions (Type 1)**
OCP Team Leader (Acting)	**Yun Xu, Ph.D.**	**Dosage Form**	**Auto-injector**
		Dosing Regimen	**Emergency supportive therapy only**
Date of Submission	**29 Sep. 10**	**Route of Administration**	**SC**
Estimated Due Date of OCP Review	**May 29th, 2011**	**Sponsor**	**INTELLIJECT INC**
PDUFA Due Date	**July 29th 2011**	**Priority Classification**	**Standard**
Division Due Date	**May 29th, 2011**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**	4	1	**3 Human factor studies and 1 human PK study**
HPK Summary	**X**	1	1	
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -	X	1	1	

solution as reference:				
alternate formulation as reference:	X	1	1	
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**2**		

Filability and QBR comments		
	"X" if yes	**Comments**
Application filable ?	**X**	
Comments sent to firm ?	**X**	**Comments to sponsor in 74 day letter:** As we stated in the pre-NDA meeting comments, we recognize that you have adopted the novel reference replicated-treatment study design and the statistical data analysis using reference-scaling average BE approach that has been proposed in recent literature by the Agency. Based on the fact that this new method has not yet been part of any published FDA Guidance for Industry, the PK analysis results based on this method will be a review issue.
QBR questions (key issues to be considered)		
Other comments or information not included above	DSI inspection will be required on the bioavailability study INT0802.	
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

Background: Please refer to the attached filing meeting slides

Reviewer's comments: NDA is filable from a Clin Pharm standpoint. DSI inspection will be required on the bioavailability study INT0802.

Comments to sponsor in 74 day letter: As we stated in the pre-NDA meeting comments, we recognize that you have adopted the novel reference replicated-treatment study design and the statistical data analysis using reference-scaling average BE approach that has been proposed in recent literature by the Agency. Based on the fact that this new method has not yet been part of any published FDA Guidance for Industry, the PK analysis results based on this method will be a review issue.

NDA 201,739
Intellijject LLC

(b) (4)

NDA Filing

Liang Zhao/Yun Xu
Clinical Pharmacology

November 4th, 2010

Background

- Epinephrine Auto-Injector 0.15 mg (epinephrine injection USP 1:1000) and Epinephrine Auto-Injector 0.3 mg (epinephrine injection USP 1:1000)
- Selection of the appropriate dosage strength is determined according to patient body weight.
  - EAI 0.3 mg: patients weighing 30 kg+
  - EAI 0.15 mg: patients weighing 15-30 kg
- Referencing EpiPen® (0.3 mg)and EpiPen Jr (0.15 mg) NDA 019430 for clinical safety and efficacy of epinephrine
- For single dose use only

[redacted]

Regulatory History

- On **05 March 2009** (Serial No. 0005 Submission to IND 76,367), Intellijject submitted a Request for Type B meeting to obtain feedback from FDA regarding Intellijject's proposal to change the objective of Clinical Study INT0802 from showing bioequivalence of EAI and EpiPen to documenting the bioavailability of EAI and EpiPen (see Section 1.6.1). On **27 April 2009**, DPARP sent a written correspondence stating:
- *"Changing the primary objective of the Protocol INT0802 from bioequivalence (BE) to comparative bioavailability assessment is acceptable. However, we still recommend that you conduct the statistical data analysis using the BE approach appropriate for the proposed replicated crossover study design and submit the results as part of the study report"* Furthermore, FDA stated in their response:
- *"As you stated, establishing bioequivalence may not be a requirement, however, the BE assessment results will be considered as one of the key data in the NDA review."*

[redacted]

Clinical studies for the submission

- **Study INT0802:**
  - the 505(b)(2) marketing application with EpiPen as the listed drug. This trial was a Phase 1 comparative clinical bioavailability study in healthy volunteers at the higher dose (0.3 mg)
  - This study utilized only the 0.3 mg dose

- Three studies to evaluate design and human factors-related aspects
  - Study INT080:1 human factors engineering summative design validation study of EAI (no needle or drug) in a representative sample of 48 non-healthcare workers
  - Study INT0803: was a study of EAI in 28 healthcare workers that incorporated additional simulated clinical use testing per the FDA Center for Devices and Radiological Health (CDRH) guidelines on both Medical Devices with Sharps Injury Prevention Features and Human Factors Evaluations
  - Study INT-FE-0901: a human factors engineering formative usability study to validate the Patient Information Leaflet (PIL) in a representative sample of 40 (20 adult and 20 pediatric), non-healthcare workers

[redacted]

Summary of Study INT0802

Treatment Sequences (with A washout period of at least 24 hours)

Sequence	Number of Subjects[a]	Period 1 Treatment	Period 2 Treatment	Period 3 Treatment
1	22	T	R	R
2	22	R	T	R
3	22	R	R	T

[a]Additional subjects may have been enrolled as necessary to ensure that 66 subjects completed the study.
T= Test (b) (4)
R = Reference (EpiPen)
Source: Protocol INT0802, Appendix 16.1.1

This design allowed for calculation of within subject variability for the Reference product

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Epinephrine PK Parameters

Table 8: Summary of Plasma Epinephrine Pharmacokinetic Parameters

Treatment	Statistic	C_{max} (ng/mL)	T_{max}* (h)	$T_{½}$ (h)	$AUC_{(0-t)}$ (ng.h/mL)	$AUC_{(inf)}$ (ng.h/mL)	$AUC_{(0-Rtmax)}$ (ng.h/mL)
Test	n	67	67	59	67	59	49
	Mean	0.486	0.330	1.656	0.536	0.724	0.139
	CV%	50.8	0.08–1.00	137.7	36.6	52.8	59.0
Reference	n	135	135	131	135	131	52
	Mean	0.520	0.170	1.139	0.466	0.583	0.119
	CV%	63.1	0.07–1.00	100.3	42.2	47.9	55.7

n = Number of observations; CV% = Percent coefficient of variation; Reference = EpiPen; Test = (b) (4)
* T_{max} is summarized by median and range (minimum – maximum)
Observed data are presented
Source: Section 14, Table 14.2.3 and Table 14.2.5

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Assessment of Bioequivalence

Table 10: Bioequivalence Analysis Results for Observed Parameters

Pharmacokinetic Parameter*	μ_T (b) (4)	μ_R (EpiPen)	$\mu_T - \mu_R$**	σ_{WR}^2	Upper 95% Conf Limit for $(\mu_T - \mu_R)^2 - 0.8\ \sigma_{WR}^2$***	CV_{WR}	Bioequivalent (Yes or No)
C_{max}	-0.8637	-0.8141	-0.0496	0.1884	-0.1030	43.3%	Yes
$AUC_{(0-t)}$	-0.7127	-0.8621	0.1494	0.1082	-0.0223	32.9%	Yes
$AUC_{(inf)}$	-0.4518	-0.6585	0.2067	0.1354	-0.0013	32.2%	Yes
$AUC_{(0-RTmax)}$	-2.1382	-2.2836	0.1454	0.1920	-0.0558	43.8%	Yes

μ_T = Unbiased estimate of the Test product mean; μ_R = Unbiased estimate of the Reference product mean;
$\mu_T - \mu_R$ = Product difference; σ_{WR} = Within subject standard deviation for the Reference product;
Conf Limit = Confidence Limit; CV_{WR}= Within subject coefficient of variation for the Reference product
* Natural log (ln) scale
** Must lie within the natural log (ln) of 0.8 and 1.25 (-0.2231, +0.2231) to claim bioequivalence
*** Must be less than zero to claim bioequivalence

[redacted]

CONCLUSION

- NDA is filable from a ClinPharm standpoint
- DSI inspection will be required on the bioavailability study INT0802

[redacted]

Overview of Clinical Pharmacology

- Rapid onset and short duration of action on both alpha and beta adrenergic receptors
- PubMed database was searched for published clinical study data pertaining to the pharmacokinetics of SC and/or IM epinephrine in humans
  - Three Simons et al articles identified

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Inter-assay Precision and Accuracy Excluding Statistical Outliers

N	153	152	154	154	154
Theoretical Concentration	0.100	0.250	0.600	1.75	6.00
Mean	0.0980	0.242	0.582	1.70	5.79
S.D.	0.00760	0.0176	0.0360	0.101	0.359
%C.V.	7.76	7.28	6.19	5.94	6.20
% Difference from Theoretical	-2.04	-3.27	-3.07	-3.02	-3.44
Low Limit	0.0850	0.213	0.510	1.49	5.10
High Limit	0.115	0.288	0.690	2.01	6.90

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Intra-Assay Precision and Accuracy

N	6	6	6	6	6
Theoretical Concentration	0.0500	0.120	0.360	1.25	6.00
Mean	0.0491	0.122	0.323	1.06	5.90
S.D.	0.00207	0.00456	0.0156	0.0398	0.136
%C.V.	4.22	3.75	4.82	3.74	2.31
% Difference from Theoretical	-1.80	1.37	-10.2	-14.9	-1.60
Low Limit	0.0400	0.102	0.306	1.06	5.10
High Limit	0.0600	0.138	0.414	1.44	6.90

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/s/

LIANG ZHAO
11/22/2010

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