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APPLICATION NUMBER:

205920Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA	205920
Submission Date	6/28/2016
Brand Name	Primatene®
Generic Name	(b) (4) 125 mcg/inhalation (Epinephrine Inhalation Aerosol USP)
Clinical Pharmacology Reviewer	Jianmeng Chen, M.D., Ph.D.
Clinical Pharmacology Team Leader	Bhawana Saluja, Ph.D.
OCP Division	Clinical Pharmacology II
OND Division	Nonprescription Drug Products, and Pulmonary, Allergy, and Rheumatology Products
Sponsor/Authorized Applicant	Armstrong Pharmaceuticals INC
Submission Type; Code	NDA resubmission
Formulation; Strength(s)	125 mcg/inhalation
Indication	Temporary relief of mild symptoms of intermittent asthma (as an OTC product) in adults and children 12 years of age and older.
Dosage Regimen	1 to 2 inhalations for each dose. Start with 1 inhalation, wait at least 1 minute. If not relieved, use once more. Wait at least 4 hours between doses. Do not use more than 8 inhalations in 24 hours. Children under 12 years of age: Do not use.

This is an amendment for the clinical pharmacology review (DARRTS date 12/9/2016) for NDA 205920.

While we considered that the assessment of PK profile may not be feasible for this product at the proposed therapeutic dose in patients 4-11 years old, the medical officers Dr. Sofia Chaudhry (DPARP) and Dr. Ryan Raffaelli (DNDP) suggested that some pediatric PK be collected at the therapeutic dose for this age group, to make sure that the systemic epinephrine exposure post-dose in patients 4-11 years old is not unexpectedly higher as compared to other populations. Below is our revised recommendation for PK assessment in 4-11 years old:

Assess epinephrine exposure around Tmax at the proposed test dose strengths in the

safety and efficacy trial. (b) (4) [redacted]

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/s/

JIANMENG CHEN
12/22/2016

BHAWANA SALUJA
12/23/2016

CLINICAL PHARMACOLOGY REVIEW

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Background

This is an NDA resubmission for epinephrine inhalation aerosol bronchodilator MDI product formulated with epinephrine free base as the active ingredient and HFA as the propellant. The proposed indication is for over-the-counter (OTC) use in the temporary relief of mild symptoms of intermittent asthma, including wheezing, tightness of chest, and shortness of breath in patients 12 years and older.

The proposed drug product is intended to be a replacement for "Primatene Mist" which was an epinephrine MDI that contained CFC as the propellant. Primatene Mist was approved by the FDA in 1967 and was distributed in the OTC market until December 31, 2011, when it was removed from the U.S. market as required by the Montreal Protocol of the United Nations, and not due to safety reasons. The initial submission of the NDA

205920 was on 7/22/13, and the clinical pharmacology components was reviewed by Dr. Arun Agrawal (DARRT date 04/09/2014). A CR (complete response) action was taken due to reasons unrelated to clinical pharmacology. The current submission is to address deficiencies identified by the FDA in a complete response letter (CRL) on 5/22/2014 and does not contain additional clinical pharmacology information.

This product triggers PREA as a new dosing regimen. This product did not have an iPSP because the original application was submitted before 2012. A study (E004-D) in children 4-11 years of age was submitted in the initial submission, but the study failed to meet its primary endpoint. (b) (4) The PeRC discussed the potential pediatric studies and related potential PMR (meeting minutes DARRT date 12/2/2016 by Dr. Gettie Audain). PeRC recommended (b) (4) that the PK information can be obtained as part of the clinical trial in the PMR. After the PeRC meeting, Clinical pharmacology was consulted about the pharmacokinetic (PK) assessment plan in these pediatric patients (4-11 yrs).

PK assessment in pediatric patients

First, the PK of this product in the pediatric population would not be useful for efficacy and safety extrapolation. This is a locally (lung) acting product and therefore, the systemic exposure will not be an indicator of efficacy and local safety. For this product, the efficacy in pediatric patients cannot be extrapolated from adults based on PK matching; and in general, the safety assessment in pediatric population should be based on the study in pediatric patients, not extrapolation from adults.

Secondly, it is very challenging, or infeasible to assess PK in patients 4-11 years old with the proposed therapeutic dose of epinephrine. In the previous submission, the sponsor conducted three PK studies, all in healthy adult volunteers. Due to low concentrations of epinephrine in plasma at the proposed therapeutic epinephrine dose (2 x 125 mcg /inhalation), all PK studies were conducted using a dose (1.08-1.60 mg) 4 to 6 times of the proposed therapeutic dose. Also, in order to eliminate the interference from endogenous epinephrine, stable isotope-labeled epinephrine (epinephrine-d3) was used for exogenous epinephrine administration. Of note, the exogenous epinephrine concentrations in the plasma declined to an undetectable level within an hour post-dose in all the PK studies, despite the supra-therapeutic dose and the isotope labeled epinephrine. Due to these issues, no PK data were collected in the efficacy study in asthma patients, and no PK data were collected for patients 12-17 years old in the current submission.

Clinical pharmacology recommendation for PK assessment in pediatric patients

For reasons stated above, we agree that PK assessment in pediatric patients 4-11 years old should be optional, and we recommend that the PK assessment not be included in the PMR (post marketing requirement).

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/s/

JIANMENG CHEN
12/09/2016

BHAWANA SALUJA
12/09/2016

CLINICAL PHARMACOLOGY REVIEW

NDA Number:	205-920 (Related IND 074,286)
Submissions Date:	07/22/2013 (SDN 1)
Submission Type:	505(b)(2)
Proposed Brand Name:	(b) (4)
Generic Name:	Epinephrine Inhalation Aerosol Bronchodilator
Sponsor:	Armstrong Pharmaceuticals, Inc.
Route of Administration:	Oral Inhalation
Dosage Form:	Aerosol
Dosage Strength:	Each inhalation of the aerosol delivers 125 mcg of epinephrine
OND Divisions:	Nonprescription Clinical Evaluation, and Pulmonary, Allergy, and Rheumatology Products
OCP Division:	Clinical Pharmacology II
Reviewer:	Arun Agrawal, Ph.D.
Team Leader:	Satjit Brar, Pharm.D., Ph.D.
Indication:	Non-prescription (b) (4) for temporary relief of mild symptoms of intermittent asthma in adults and children 12 years of age and older.
Dosage Administration:	1 to 2 inhalations for each dose. Start with 1 inhalation, wait at least 1 minute. If not relieved, use once more. Wait at least 4 hours between doses. Do not use more than 8 inhalations in 24 hours. Children under 12 years of age: (b) (4)

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1.0 EXECUTIVE SUMMARY

1.1 Recommendation

From the viewpoint of the Office of Clinical Pharmacology, NDA 205-920 is acceptable.

1.2 Phase 4 Commitments

None

1.3. Summary of Clinical Pharmacology Findings

Three pharmacokinetic (PK) studies were conducted that measured the systemic exposure of epinephrine following oral inhalation of epinephrine HFA (E004) and Primatene Mist. Due to low concentrations of epinephrine in plasma at the proposed therapeutic E004 dose (2 x 125 mcg/inhalation) all PK studies were conducted using a dose 4 to 6 times of the proposed therapeutic dose. Of note, the exogenous epinephrine concentrations in the plasma declined to an undetectable level within an hour post-dose in all the PK studies. Summary of PK studies is provided below:

Study API-E004-CL-B (Study B):

This exploratory study evaluated the pharmacokinetics of epinephrine following oral inhalation of E004 (125 and 160 mcg/inhalation) and Primatene Mist (220 mcg/inhalation). The Cmax for epinephrine was observed around 5 min which was the first time point post-dose (Table 1). Both the AUC and Cmax increased in an approximately dose-proportional manner when E004 was administered at 1.25 mg and 1.60 mg doses. For total epinephrine (exogenous + endogenous), E004 demonstrated 10% and 31% higher AUC, respectively for the 1.25 mg and 1.60 mg doses, than that for Primatene Mist at 2.20 mg dose. Further, the Cmax for E004 was 2.5 to 3.2 times higher than that for Primatene Mist for total epinephrine.

Study API-E004-CL-B2 (Study B2):

This study evaluated a more accurate PK profile for E004 (125 mcg/inhalation) and Primatene Mist (220 mcg/inhalation). The Cmax for epinephrine was observed around 2 min post-dose (Table 1). The Cmax for E004 was 4.5 times higher than that for Primatene Mist for total epinephrine. The relative bioavailability of total epinephrine for E004 (1.25 mg) was 37% higher than for Primatene Mist (2.20 mg).

Study API-E004-CL-B3 (Study B3):

This study evaluated the PK profile for E004 (90 and 100 mcg/inhalation) and Primatene Mist (220 mcg/inhalation). The Cmax for epinephrine was observed around 2 min post-dose (Table 1). The Cmax for E004 doses was 2.4 to 2.6 times higher than that for Primatene Mist for total epinephrine. The AUCs of E004 at 1.08 mg and 1.20 mg were 7% and 6% lower than that for Primatene Mist at 2.64 mg, respectively.

Overall, the relative bioavailability of epinephrine HFA at 125 mcg/inhalation was 37% higher as compared to Primatene Mist (220 mcg/inhalation) for total epinephrine. Further, the Cmax for epinephrine HFA was 4.5 times higher than that for Primatene Mist for total epinephrine. Clinical safety relevance of the higher exposure and higher Cmax

for epinephrine HFA as compared to Primatene Mist will be evaluated and discussed in Clinical review by Dr. Jennifer Pippins. In summary, adequate clinical pharmacology information was provided in support of this NDA.

Table 1 Summary of PK Results for Total Epinephrine (exogenous + endogenous) in Healthy Volunteers

Study Code	Study Design	Dosage Form, Dose	PK Parameters (Total Epinephrine)			Conclusions
			tmax min*	Cmax** ratio	AUC** ratio	(versus Primatene Mist)
		E004, **1.25 mg**	5	2.45	1.10	2.5x higher Cmax
	Randomized	(10 x 125 mcg/inh)				10% higher exposure
Study B	Evaluater-blinded	E004, **1.60 mg**	5	3.19	1.31	3.2x higher Cmax
	Single dose	(10 x 160 mcg/inh)				31% higher exposure
	Crossover	Primatene Mist, **2.20 mg**	5			
		(10 x 220 mcg/inh)				
	Randomized	E004, **1.25 mg**	2	4.53	1.37	4.5x higher Cmax
Study B2	Evaluater-blinded	(10 x 125 mcg/inh)				37% higher exposure
	Single dose	Primatene Mist, **2.20 mg**	2			
	Crossover	(10 x 220 mcg/inh)				
		E004, **1.08 mg**	2	2.38	0.93	2.4x higher Cmax
	Randomized	(12 x 90 mcg/inh)				7% lower exposure
Study B3	Evaluater-blinded	E004, **1.20 mg**	2	2.57	0.94	2.6x higher Cmax
	Single dose	(12 x 100 mcg/inh)				6% lower exposure
	Crossover	Primatene Mist, **2.64 mg**	2			
		(12 x 220 mcg/inh)				

* Observed from the average PK curves
** Cmax and AUC ratios as compared to Primatene Mist treatment

2.0 QUESTION BASED REVIEW

2.1 General Attributes of the Drug

2.1.1 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

Proposed product is an epinephrine inhalation aerosol bronchodilator MDI product formulated with epinephrine free base as the active ingredient and HFA as the propellant. The proposed drug product is intended to be a replacement for "Primatene Mist" which was an epinephrine MDI that contained CFC as the propellant. Primatene Mist was approved by the FDA in 1967 and was distributed in the OTC market until December 31, 2011, when it was removed from the U.S. market as required by the Montreal Protocol of the United Nations. Primatene Mist was also manufactured and distributed by the sponsor of the current submission.

2.1.2 What are the highlights of the chemistry and physicochemical properties of the drug substance, and the formulation of the drug product?

E004 (125 mcg/inhalation) and Primatene Mist (220 mcg/inhalation) have:

- the same active moiety -- epinephrine
- the same administration route -- oral inhalation
- the same delivery device -- pressurized MDI

The major differences between the formulations of E004 and Primatene Mist are:

- the propellant is changed from CFC (Primatene Mist) to HFA (E004)
- the type of formulation is changed from true solution (Primatene Mist) to suspension (E004)
- the pH of the solution is changed from acidic (Primatene Mist, pH 3.5 - 4.5) to neutral (E004, pH 7)
- the amount of alcohol in E004 (b) (4) compared to Primatene Mist

The formulation of E004 includes the active ingredient, epinephrine as free base, and the excipients: HFA, alcohol, polysorbate-80, and thymol.

2.1.3 What are the proposed mechanism(s) of action and therapeutic indication(s)?

Epinephrine (adrenaline) is reportedly a stimulant of both α- and β-adrenergic receptors. The orally inhaled, pulmonary-delivered epinephrine binds to the β2-adrenergic receptors on airway smooth muscles, leading to dilation of the tracheal bronchial lumen and increase in air passage. Epinephrine acts as a functional antagonist to relax the airway smooth muscles and thus protects against bronchoconstrictor challenges. Epinephrine HFA is indicated for the temporary relief of mild symptoms of intermittent asthma in adults and children 12 years of age and older.

2.1.4 What are the proposed dosage(s) and route(s) of administration?

Adults and children 12 years of age and over: One to two inhalations for each dose. Start with 1 inhalation, wait at least 1 minute. If not relieved, use once more. Wait at least 4 hours between doses. Do not use more than 8 inhalations in 24 hours.

Children under 12 years of age: (b) (4)

2.1.5 What is the to-be-marketed formulation?

Formulation information for E004 and Primatene Mist is given in Table 2:

Table 2: Formulation Information of E004 and Primatene Mist

Items	Primatene® Mist	E004
Product Status	Previously Marketed OTC Drug, which was phase out 12/31/2011	Proposed Replacement of Primatene® Mist
Regulatory Status	NDA 016-120 (1967) and ANDA 087-907 (1984)	IND 74,286
Indications	Temporary Relief of Mild Symptoms of Intermittent Asthma	*ibid*
Delivery Path	Oral Inhalation	*ibid*
Delivery Device	Pressured MDI	*ibid*
Active Moiety	Epinephrine	*ibid*
Active Ingredient	Epinephrine (b) (4)	Epinephrine (free base)
Dose Strength, mcg base /inh	220 mcg	125 mcg
Normal Dose (2 inhalations)	440 mcg	250 mcg
Formulation: Type	Solution	Suspension
Propellant	CFC-12 and CFC-114	HFA-134a
(b) (4)	None	Polysorbate-80
	Ethanol (34%)	Ethanol (1%)
	Ascorbic acid	Thymol
Others inactive ingredients	Nitric acid and Hydrochloric Acid	None
pH	3.5 - 4.5	Neutral
Container of the Products	Plastic-coated glass bottles	Aluminum Canister

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

Design features of the clinical and clinical pharmacology studies that were conducted in support of this product are given the Table 3.

Table 3: List of Clinical and Clinical Pharmacology Studies for E004

#	Study Code	Phase	Purpose of the Study	Population	Study Design	Dose	# of Subjects*				
							E004	Placebo	Primatene CFC	Total Treated	Studied but Untreated
1	A	I	Efficacy, Dose Response & Initial Safety	Adult Asthma Patients	Crossover	Single Dose	26	24	25	26	-
2	A2	II	Efficacy, Dose Response & Initial Safety (Lower Dose)	Adult Asthma Patients	ibid	ibid	29	30	30	30	-
3	B	II	PK and Safety at High Dose	Healthy Volunteers	ibid	ibid	24	-	22	24	-
4	B2	II	ibid	Ibid	ibid	ibid	23	-	23	23	-
5	B3	II	ibid	ibid	ibid	ibid	23	-	22	23	-
6	C	III	Efficacy and Safety	Adult Asthma Patients	Parallel	2 puffs, QID, 12 weeks	248	61	64	373	-
7	C2	III	Safety	Adult Asthma Patients	Parallel	2 puffs, QID, additional 3 months	134	38	35	207	-
8	D	III	Pediatric Efficacy and Safety	Pediatric 4-11 y	Parallel	2 puffs, QID, 4 weeks	35	35	-	70	-
9	F	III	Label Comprehension	Adult Volunteers (≥16 yr old)	-	-	-	-	-	-	1,345
10	G	III	Label Behavior	Adult and Adolescent Volunteers (≥12 yr old)	-	-	-	-	-	-	61
Total							542	188	221	776	1406

2.2.2 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Exogenous and endogenous epinephrine was measured in the plasma. This is a locally (lung) acting product and therefore, no exposure response relationship was evaluated as systemic exposure will not be an indicator of local efficacy and safety.

2.2.3 What efficacy and safety information (e.g., biomarkers, surrogate endpoints, and clinical endpoints) contribute to the assessment of clinical pharmacology study data? How was it measured?

The primary efficacy endpoint for clinical studies was the AUC0-t of Δ% FEV1, which was defined as the area under the curve of post-dose FEV1 percentage changes (Δ%) from the pre-dose baseline FEV1 (FEV10) versus time (Table 4). Please see Clinical review by Dr. Jennifer Pippins for details on efficacy and safety evaluations.

Table 4: List of Clinical Efficacy and Safety Studies for E004

No.	Phase	Study Reference No.	Study Objectives	Number of Study Sites	Study Design, Control Type	Study Start Enrollment status Date Total Enroll./ Enroll. Goal	Duration & Diagnosis Inclusion Criteria	Primary Endpoint(s)	Arm	Treatment	
										Drug	Dose, mcg
1	I	API-E004-CL-A, (Simplified as **E004-A**)	(1) Efficacy Evaluation; (2) Initial Safety Evaluation; (3). Identify the optimum dose	**4** sites in the US	Randomized, double-blinded or evaluator blinded, placebo- and active- controlled, five arm, crossover, single dose study in asthma patients	Started: 3/25/2010, Completed: 6/30/2010, 26/24	Single Dose adult patients with mild-to-moderate persistent asthma	AUC of Δ%FEV1, relative to the same day baseline	T1	E004	250
									T2	E004	320
									T3	E004	440
									P	Placebo	0
									A	Primatene®	440
2	II	API-E004-CL-A2, (Simplified as **E004-A2**)	(1) Efficacy Evaluation; (2) Initial Safety Evaluation; (3). Identify the optimum dose	**5** sites in the US	Randomized, double-blinded or evaluator blinded, placebo- and active- controlled, five arm, crossover, single dose study in asthma patients	Started: 11/22/2010, Completed: 2/10/2011, 30/24	Single Dose adult patients with mild-to-moderate persistent asthma	AUC of Δ%FEV1, relative to the same day baseline	T1	E004	90
									T2	E004	125
									T3	E004	180
									T4	E004	200
									T5	E004	250
									P	Placebo	0
									A1	Primatene®	220
									A2	Primatene®	440
3	III	API-E004-CL-C, (Simplified as **E004-C**)	(1) Efficacy (2) Safety Evaluation for adolescent & adult asthma patients	34 sites in the US	12-week, randomized, double- & evaluator-blinded, placebo- & active-controlled, parallel, multiple dose study in patients	Started: 5/5/2011, Completed: 11/16/2011, 373/300	12 weeks adolescent and adult patients with mild to moderate asthma	AUC of Δ%FEV1, relative to the same day baseline for Week-12	T	E004	250, QID
									P	Placebo	0, QID
									A	Primatene®	440, QID
4	III	API-E004-CL-C2, (Simplified as **E004-C2**)	(1) Safety Evaluation for adolescent & adult asthma patients	27 sites in the US	Additional 3-month extension safety study, randomized, double- & evaluator-blinded, placebo- & active-controlled, parallel, study in patients	Started: 11/9/2011, Completed: 4/5/2012, 207/180	additional 3 months, adolescent and adult patients with mild to moderate asthma	AUC of Δ%FEV1, relative to the same day baseline for Week-12	T	E004	250, QID
									P	Placebo	0, QID
									A	Primatene®	440, QID
5	III	API-E004-CL-D, (Simplified as **E004-D**)	(1) Efficacy (2) Safety for Pediatric patients	8 sites in the US	4-week, randomized, double-blinded, placebo controlled, two-arm, parallel, multiple dose study in pediatric patients	Started: 10/08/2011, Completed: 3/14/2012, 70/60	4 weeks Pediatric patients with mild to moderate asthma	AUC of Δ%FEV1, relative to the same day baseline for Week-4	T	E004	250, QID
									P	Placebo	0, QID

2.2.4 Exposure Response

No formal PK/PD studies were conducted to establish the relationship between systemic exposure and response as this is a locally (lung) acting product and systemic exposure will not be an indicator of local efficacy and safety. Single dose studies A and A2, demonstrated the E004 efficacy profile in the dose range of 90 to 440 mcg. These studies showed that E004 efficacy:

- rapidly increased from the lowest dose studied, 90 mcg
- became statistically significant for the dose of 125 mcg
- reached a stable range with reliable efficacy near 250 mcg (2 x 125 mcg/inhalation)
- converged for higher doses up to the highest studied dose, 440 mcg

The selection of the final dose of 2 x 125 = 250 mcg/inhalation for Phase 3 studies was agreed with the Agency (for details, please see Clinical review by Dr. Jennifer Pippins).

2.2.5 Does this drug prolong the QT or QTc interval?

No formal QTc study was conducted for E004. Based on the long-term use of E004 in adults and adolescent patients the impact of E004 on QT or QTc was reportedly similar to

that of placebo or Primatene Mist (for details, please see Clinical review by Dr. Jennifer Pippins).

2.2.6 What are the general PK characteristics of the drug and its major metabolite?

No distribution, metabolism, or elimination studies were conducted for epinephrine HFA inhalation aerosol. The following PK information is provided from the current epinephrine HFA NDA.

2.2.6.1 What are the single dose PK parameters?

The current submission included information on CMC, clinical and clinical pharmacology studies conducted in subjects ≥12 years. The following three single-dose PK studies were conducted that measured the systemic exposure of epinephrine following oral inhalation of E004 and Primatene Mist:

- Study API-E004-CL-B (Study B)
- Study API-E004-CL-B2 (Study B2)
- Study API-E004-CL-B3 (Study B3)

Due to low concentrations of epinephrine in plasma at the proposed therapeutic E004 dose (2 x 125 mcg/inhalation) all PK studies were performed using a dose 4 to 6 times of the proposed therapeutic dose. In order to eliminate the interference from endogenous epinephrine, stable-labeled epinephrine (epinephrine-d3) was used for exogenous epinephrine administration. Both epinephrine-d3 (exogenous) and epinephrine-h3 (endogenous) were analyzed in each PK study. All PK studies were conducted as randomized, evaluator-blinded, single-dose, two or three-arm, crossover designs with approximately 20-24 healthy male and female volunteers per study. Results of these studies are briefly described below:

Study API-E004-CL-B (Study B):

This study evaluated the PK profiles for E004 (125 mcg and 160 mcg/inhalation) and Primatene Mist (220 mcg/inhalation). As no PK data was available for inhaled epinephrine, this exploratory study was designed to assess the PK profile prior to thorough assessment in subsequent studies (Studies B2 and B3). Following 3 treatment arms were evaluated in this study:

- T1: 1.25 mg of E004 (10 x 125 mcg/inhalation)
- T2: 1.60 mg of E004 (10 x 160 mcg/ inhalation)
- C: 2.20 mg of Primatene Mist (10 x 220 mcg/ inhalation)

The Cmax for epinephrine was observed at 5 min which was the first time point post-dose (Table 5 and Figures 1-3). This study helped in selecting time points around the Cmax for subsequent PK studies. The exogenous epinephrine concentration in plasma declined to an undetectable level in 60 minutes post-dose. Both the AUC and Cmax increased in an approximately dose proportional manner for exogenous epinephrine when E004 was administered at 1.25 and 1.60 mg doses. For total epinephrine, E004 at 125 mcg/inhalation demonstrated 10% higher AUC as compared to Primatene Mist at 220 mcg/inhalation. Further, Cmax for E004 was 2.5 times (Arm T1) and 3.2 times (Arm T2)

higher than that for Primatene Mist (Arm C) for total epinephrine. Five to six hours after drug inhalation, endogenous epinephrine concentration in the plasma, increased 3 times to a level of approximately 30 pg/mL. This observation may likely be due to the circadian rhythm of the endogenous epinephrine.

Table 5: Summary of PK Results in Healthy Volunteers

	Arm T1	Arm T2	Arm C	T2/T1
Study Drug	E004-d3	E004-d3	Primatene Mist	-
Dose, mg (10 inhalation)	1.25	1.60	2.20	1.3
Exogenous Data (per Epinephrine-d3)				
AUC0-6h, pg/mL*min	3381 ± 2787	4760 ± 3650	-	1.4
Cmax, pg/mL	337 ± 297	438 ± 332	-	1.3
tmax, min	5.0 ± 0.0	5.0 ± 0.0	-	1.0
Endogneous Data (per Epinephrine-h3)				
AUC0-6h, pg/mL*min	4557 ± 4525	4678 ± 4356	-	1.0
Cmax, pg/mL	34 ± 25	33 ± 25	-	1.0
tmax, min	306 ± 115	297 ± 123	-	1.0
Total Epinephrine				
AUC0-6h, pg/mL*min	7938 ± 5023	9438 ± 4819	7218 ± 6489	1.2
Cmax, pg/mL	340 ± 294	444 ± 328	139 ± 98	1.3
tmax, min#	5	5	5	1.0

observed from the average PK curves

Figure 1: Plasma Epinephrine Concentration-Time Curves for Arm T1 (E004 1.25 mg)

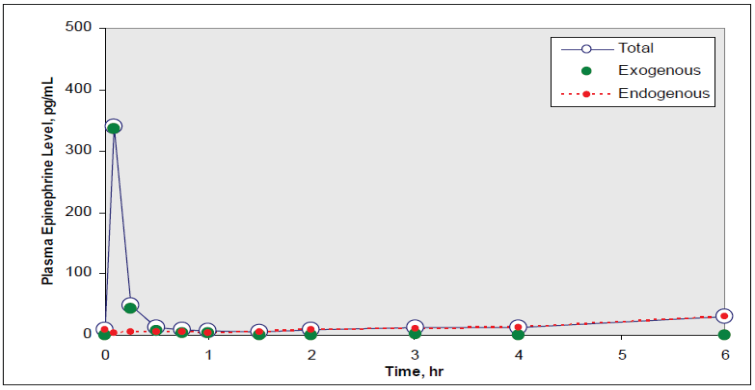


Figure 2: Plasma Epinephrine Concentration-Time Curves for Arm T2 (E004 1.60 mg)

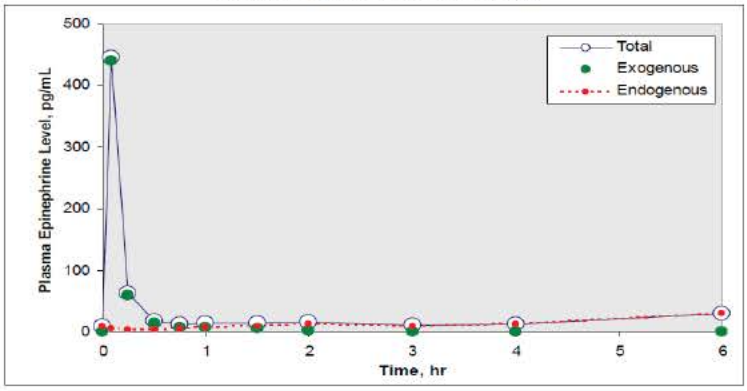
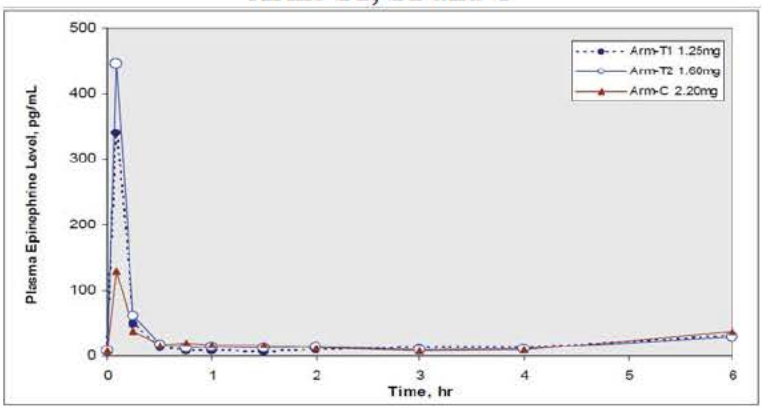


Figure 3: Total Plasma Epinephrine Concentration-Time Curves for Arms T1, T2 and C



Study API-E004-CL-B2 (Study B2):

Study B2 was designed to obtain a more accurate PK profile for E004 at 125 mcg/inhalation by collecting more blood samples 0-60 min post-dose. The following 2 treatment arms were evaluated:

- T1: 1.25 mg of E004 (10 x 125 mcg/inhalation)
- C: 2.20 mg of Primatene Mist (10 x 220 mcg/inhalation)

The Cmax for epinephrine was observed around 2 min post-dose (Table 6 and Figures 4-5). The exogenous epinephrine concentration in plasma declined to an undetectable level in 60 minutes post-dose. The relative bioavailability of total epinephrine for E004 (1.25 mg) was 37% higher as compared to Primatene Mist (2.20 mg). Further, the Cmax for E004 was 4.5 times higher than that for Primatene Mist for total epinephrine. The plasma epinephrine levels for E004 and Primatene Mist were similar around 20 minutes post-inhalation.

Table 6: Summary of PK Results in Healthy Volunteers

	Arm T1	Arm C
Study Drug	E004-d3	Primatene Mist
Dose, mg (10 inhalation)	1.25	2.20
Exogenous Data (per Epinephrine-d3)		
AUC0-6h, ng/mL*min	4.49 ± 2.51	-
Cmax, ng/mL	0.86 ± 0.53	-
tmax, min	2.0 ± 0.0	-
Endogenous Data (per Epinephrine-h3)		
AUC0-6h, ng/mL*min	4.01 ± 4.68	-
Cmax, ng/mL	0.037 ± 0.037	-
tmax, min	180 ± 143	-
Total Epinephrine		
AUC0-t, ng/mL*min	8.50 ± 5.21	6.19 ± 4.11
Cmax, ng/mL	0.86 ± 0.53	0.19 ± 0.12
tmax, min#	2	2

observed from the average PK curves

Figure 4: Plasma Epinephrine Concentration-Time Curves for Arm T1 (E004 1.25 mg)

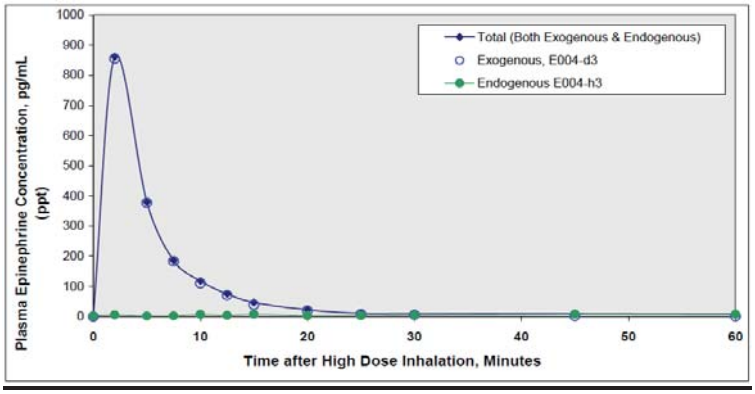
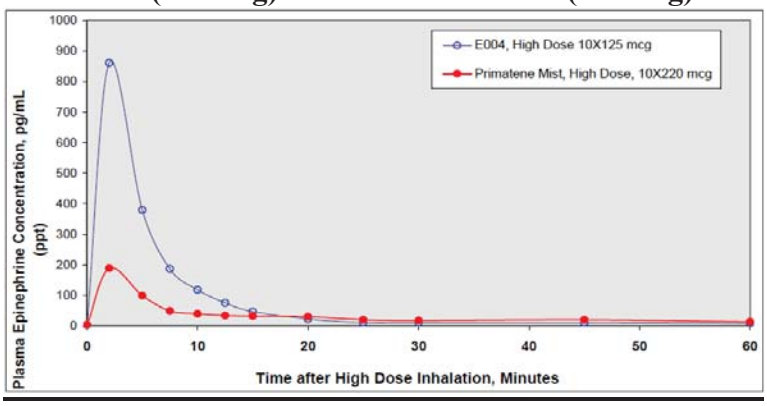


Figure 5: Total Plasma Epinephrine Concentration-Time Curves For E004 (1.25 mg) and Primatene Mist (2.20 mg)



Study API-E004-CL-B3 (Study B3):

This study evaluated the PK profile for E004 (90 mcg and 100 mcg/inhalation) and Primatene Mist (220 mcg/inhalation). The following 3 treatment arms were evaluated:

- T1: 1.08 mg of E004 (12 x 90 mcg/inhalation)
- T2: 1.20 mg of E004 (12 x 100 mcg/ inhalation)
- C: 2.64 mg of Primatene Mist (12 x 220 mcg/ inhalation)

The Cmax for epinephrine was observed at 2 min post-dose (Table 7 and Figures 6-8). The Cmax for exogenous epinephrine increased in a dose-proportional manner while the AUCs were similar for the two doses of E004. The exogenous epinephrine concentration in plasma declined to an undetectable level in 60 minutes post-dose. Plasma epinephrine concentrations of E004 and Primatene Mist were similar by 15 min post-dose. The total epinephrine Cmax for E004 arms was 2.4 to 2.6 times higher than that for Primatene Mist. The AUCs of E004 1.08 mg and 1.20 mg were 7% and 6% lower than that of Primatene Mist 2.64 mg, respectively.

Table 7: Summary of PK Results in Healthy Volunteers

	Arm T1	Arm T2	Arm C	T2/T1
Study Drug	E004-d3	E004-d3	Primatene Mist	-
Dose, mg (12 inhalation)	1.08	1.20	2.64	1.1
Exogenous Data (per Epinephrine-d3)				
AUC0-6h, pg/mL*min	3578 ± 2771	3665 ± 2110	-	1.0
Cmax, pg/mL	561 ± 336	606 ± 377	-	1.1
tmax, min	2.3 ± 0.9	2.2 ± 0.7	-	1.0
Endogenous Data (per Epinephrine-h3)				
AUC0-6h, pg/mL*min	7700 ± 7114	7709 ± 6072	-	1.0
Cmax, pg/mL	40 ± 28	45 ± 30	-	1.1
tmax, min	224 ± 144	222 ± 128	-	1.0
Total Epinephrine				
AUC0-6h, pg/mL*min	11279 ± 8376	11374 ± 6863	12142 ± 7450	1.0
Cmax, pg/mL	566 ± 337	612 ± 372	238 ± 196	1.1
tmax, min#	2	2	2	1.0

observed from the average PK curves

Figure 6: Plasma Epinephrine Concentration-Time Curves for Arm T1 (E004 1.08 mg)

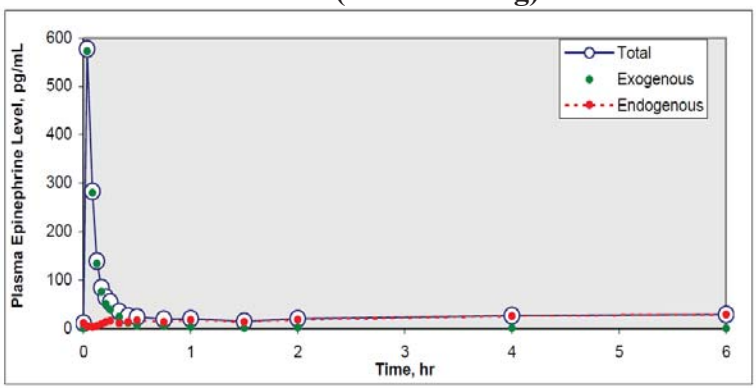


Figure 7: Plasma Epinephrine Concentration-Time Curves for Arm T2 (E004 1.20 mg)

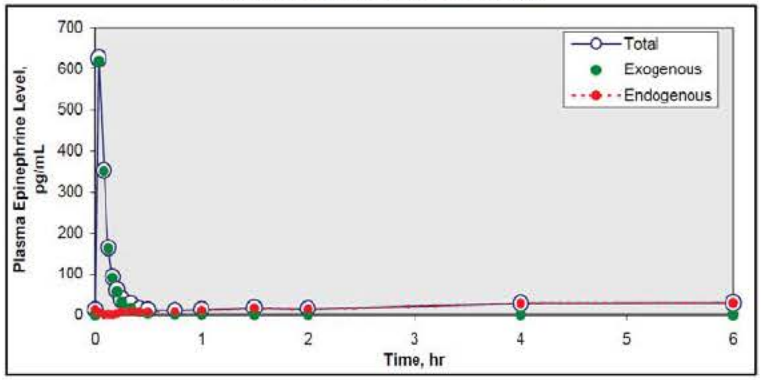
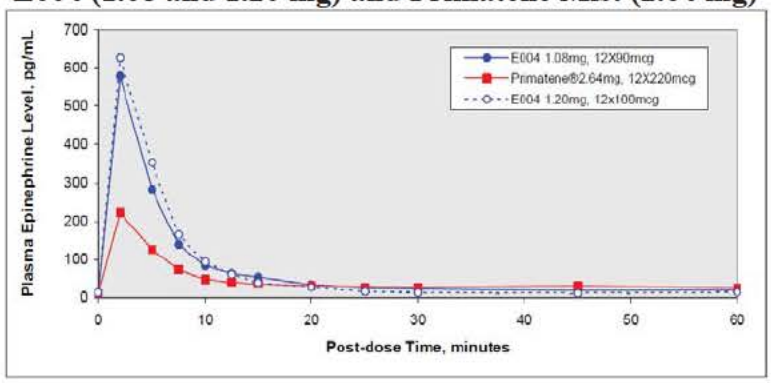


Figure 8: Total Plasma Epinephrine Concentration-Time Curves For E004 (1.08 and 1.20 mg) and Primatene Mist (2.64 mg)



Issue of higher Cmax for E004: Sponsor stated that at the proposed dose of E004 (2 x 125 mcg), the Cmax is calculated to be around 180 pg/mL, which is much less than the reported endogenous epinephrine levels after moderate exercise (as a 3 minutes running for 440 meters), 251 pg/mL for untrained subjects or 714 pg/mL for trained subjects (Table 8) and therefore, it should not be a safety concern. The clinical safety relevance of 37% higher exposure and 4.5 times higher Cmax for E004 as compared to Primatene Mist will be evaluated and discussed in Clinical review by Dr. Jennifer Pippins.

Table 8: Plasma Epinephrine Levels at Different Exercise Levels*

Exercise Level (V_{O2max})	Running Duration min	Running Speed		Running Distance	Plasma Epinephrine Level			
					Untrained Subject, n = 8		Trained Subject, n = 8	
		km/hr	sec./ 100m	m	nmol/L	pg/mL	nmol/L	pg/mL
60%	**7**	4.7	77	**548**	0.55 ± 0.16	**101** ± 29	0.90 ± 0.09	**165** ± 16
100%	3	8.8	41	440	1.37 ± 0.27	251 ± 49	3.9 ± 0.62	714 ± 112
110%	2	9.7	37	323	3.6 ± 1.1	660 ± 196	8.73 ± 1.51	1599 ± 272

* Reported by M. Kjaer *et. al*, Am. Physio. Soc. 1693-1700 (1986). The data shaded yellow were provided by this article; the other data were calculated based on the reported results.

2.2.6.2 What are the multiple dose PK parameters?
No formal multiple dose PK studies were conducted with epinephrine HFA.

2.2.6.3 What are the characteristics of drug absorption?
Tmax for epinephrine was approximately 2 minutes after oral inhalation indicating rapid absorption.

2.2.6.4 What are the characteristics of drug distribution?
No formal drug distribution studies were conducted with inhaled epinephrine HFA.

2.2.6.5 What are the characteristics of drug metabolism?
No formal drug metabolism studies were conducted with inhaled epinephrine HFA.

2.2.6.6 What are the characteristics of drug elimination?
The half-life for E004 was approximately 3 minutes after oral inhalation indicating rapid elimination from the systemic circulation.

2.2.6.7 Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?
Systemic exposure of inhaled E004 increased in an approximately dose dependent manner for the studied doses.

2.2.6.8 How do the PK parameters change with time following chronic dosing?
No formal chronic dose PK studies were conducted for inhaled epinephrine HFA.

2.3 Intrinsic Factors

2.3.1 Does weight, race, or disease state affect the PK of the drug? What dosage regimen adjustments are recommended for the subgroups?
No formal PK studies were conducted for inhaled epinephrine HFA in any special population.

2.3.1.1 Pediatrics
Sponsor is currently seeking approval for ≥12 year old asthma patients and has requested study deferral for patients 4-11 years of age. (b) (4) following approval of the currently proposed product for ≥12 year old asthma patients. Further, sponsor is seeking waiver for studies in children <4 years of age.

2.3.1.2 Geriatrics
Clinical studies with epinephrine HFA did not include sufficient number of subjects aged 65 years and over to determine whether they respond differently as compared to younger subjects.

2.3.1.3 Renal Impairment

No formal studies were conducted to assess the impact of renal impairment on PK.

2.3.1.4 Hepatic Impairment

No formal studies were conducted to assess the impact of hepatic impairment on PK.

2.4 Extrinsic Factors

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence exposure and/or response and what is the impact of any differences in exposure on pharmacodynamics?

No formal studies were conducted to assess the effect of other drugs, herbal products, diet, smoking, and alcohol use on the exposure and/or response of epinephrine HFA.

2.4.2 Drug-drug interactions

No formal drug-drug interaction studies were conducted for epinephrine HFA.

2.5 General Biopharmaceutics

2.5.1 What is the effect of food on the BA of the drug from the dosage form?

Not applicable as this is an oral inhalation product.

2.5.2 Was the to-be-marketed formulation used in the PK/Clinical trials?

The to-be-marketed formulation was used in the PK and clinical trials.

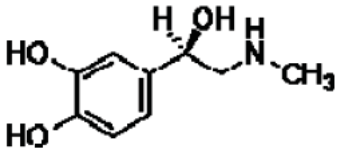
2.5.3 Is there a potential for dose dumping in the presence of alcohol?

Not applicable as this is an oral inhalation product.

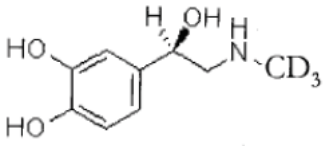
2.6 Analytical Section

2.6.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies? What is the QC sample plan? What are the accuracy, precision and selectivity of the method?

The active moiety of E004 is epinephrine, which also exists naturally in the human plasma. In order to differentiate the inhaled exogenous epinephrine from the endogenous epinephrine, a stable-isotope deuterium labeled epinephrine (epinephrine-d3 or E004-d3) was used to formulate E004 for PK studies. However, for Primatene Mist, total epinephrine (both exogenous + endogenous) was determined. The chemical structures of non-labeled epinephrine (epinephrine-h3) and epinephrine-d3, with the deuterated methyl group (-CD3), are shown below:



Epinephrine-h3, E004



Epinephrine–d3, E004-d3

The plasma concentrations of exogenous epinephrine following administration of the normal dose of E004 and Primatene Mist are very low. Therefore, for all PK studies, the treatment doses for E004-d3 and Primatene Mist were increased 4 to 6 times of their normal doses so that the plasma concentration of epinephrine-d3 and epinephrine-h3 can be quantified by LC/MS/MS method.

An LC/MS/MS method was developed and validated to simultaneously determine the epinephrine, epinephrine-d3 and the added internal standard, epinephrine-d6. Plasma samples and the internal standard were extracted by solid phase extraction. The extracts were then subjected to reverse phase HPLC. The analytes and internal standard were processed in positive ion electro-spray mode with multiple reaction monitoring. The chromatographic run time was 5 min per injection, with retention times of 1.8, 1.9, and 2.0 min for epinephrine, epinephrine-d3, and epinephrine-d6, respectively. The LC-MS/MS method met the validation acceptance criteria for specificity, linearity, precision and accuracy, sensitivity, recovery, and stability. The analytical method parameters are given below:

- Lower limit of quantitation (LLOQ) = 20 pg/mL
- Linearity range = 20 - 2,500 pg/mL
- Method precision CV = 5 - 9%
- Method recovery for 20 pg/mL = ±15%

3.0 DETAILED LABELING RECOMMENDATIONS

Epinephrine HFA is proposed as an OTC product and therefore, no clinical pharmacology information is included in the proposed "Drug Facts" label. Therefore, Clinical Pharmacology has no comments on the proposed Drug Facts label.

4.0 APPENDICES

4.1 Sponsor's Proposed Drug Facts Label

(b) (4)

4.2 Filing and Review Form

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	**205-920**	**Brand Name**	**TBD**
OCP Division (I, II, III, IV, V)	**II**	**Generic Name**	**Epinephrine HFA MDI**
Medical Division	**DNCE**	**Drug Class**	**Bronchodilator**
OCP Reviewer	**Arun Agrawal, Ph.D.**	**Indication(s)**	**Temporary relief of mild symptoms of intermittent asthma in adults and children 12 years of age and older**
OCP Team Leader	**Satjit Brar, Pharm.D., Ph.D.**	**Dosage Form**	**Aerosol (125 mcg/inhalation)**
Pharmacometrics Reviewer		**Dosing Regimen**	**1-2 inhalation/dose, wait at least 4 hours between doses, NTE 8 inhalation in 24 hour**
Date of Submission	**07/22/2013**	**Route of Administration**	**Oral inhalation**
Estimated Due Date of OCP Review		**Sponsor**	**Armstrong Pharmaceuticals**
Medical Division Due Date		**Priority Classification**	**Standard**
PDUFA Due Date	**05/22/2014**		

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**	**1**	**1**	
Tabular Listing of All Human Studies	**X**	**3**	**3**	**Study B, B2 and B3**
HPK Summary	**X**	**3**	**3**	**Study B, B2 and B3**
Labeling	**X**	**1**	**1**	
Reference Bioanalytical and Analytical Methods	**X**	**1**	**1**	**RD060910EP01R**
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -	**X**	**3**	**3**	**Study B, B2 and B3**
Healthy Volunteers-				
single dose:	**X**	**3**	**3**	**Study B, B2 and B3**
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:	**X**	**2**	**2**	**Study B and B3**
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**	**3**	**3**	**Study B, B2 and B3**
solution as reference:				
alternate formulation as reference:	**X**	**3**	**3**	**Study B, B2 and B3**
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies	**X**	**4**	**4**	

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

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			x	
2	Has the applicant provided metabolism and drug-drug interaction information?			x	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	x			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	x			
5	Has a rationale for dose selection been submitted?	x			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	x			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	x			

8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	x			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	x			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			x	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	x			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	x			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			x	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			x	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	(b) (6) [redacted]
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?			x	This is an OTC product and therefore, there is no separate clinical pharmacology section of the label.
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

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

/s/

ARUN AGRAWAL
04/09/2014

SATJIT S BRAR
04/09/2014