

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-007

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY REVIEW

NDA:	22-007
Type:	505(b)(2); original
Generic Name:	Formoterol Fumarate Inhalation Solution
Trade Name:	Perforomist™
Indication:	Maintenance treatment of bronchoconstriction in COPD patients, including chronic bronchitis and emphysema.
Dosage Form:	Inhalation solution
Strength:	20 mcg/2 mL
Route of Administration:	Oral inhalation via nebulizer
Dosing regimen:	Nebulized 20 mcg/2 mL for long-term, twice daily dosing (morning and evening)
Applicant:	Dey, LP
Clinical Division:	DPAP (OND-570)
OCP Division:	DCP2
Submission Date:	June 28, 2006
Reviewer:	Partha Roy, Ph.D.
Team Leader:	Emmanuel Fadiran, Ph. D.

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1 EXECUTIVE SUMMARY

1.1 RECOMMENDATIONS

The Office of Clinical Pharmacology / Division of Clinical Pharmacology-2 (OCP / DCP-2) has reviewed NDA 22-007 submitted on June 28, 2006. The clinical pharmacology information submitted to NDA 22-007 is acceptable provided that satisfactory agreement is reached between the sponsor and the Agency regarding language in the package insert.

1.2 PHASE IV COMMITMENTS

None

1.3 SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

The sponsor, Dey, LP, is developing a nebulized Formoterol Fumarate Inhalation Solution (FFIS) 20 mcg/2 mL for long-term, twice daily (morning and evening) administration in the maintenance treatment of bronchoconstriction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. Formoterol fumarate, the active ingredient of (FFIS), is a selective, long-acting beta₂-adrenergic receptor agonist (LABA) that, when inhaled, acts locally in the lung as a bronchodilator. Approval for this product was sought based on the filing of a 505(b)(2) New Drug Application (NDA) for which, Dey would cross reference Foradil® Aerolizer® 12 mcg (NDA 21-279 and NDA 20-831, Novartis), approved for the same indication.

The sponsor has conducted one pharmacokinetic (PK) study (study DL-056) for this program. In addition, the sponsor has conducted 3 randomized, double-blind studies to support the efficacy claim for use in COPD patients; 1 phase III pivotal safety and efficacy trial (study 201-065), 2 phase II dose-finding studies (studies DL-057 and DL-052). None of these 3 efficacy studies had PK blood sampling.

Study DL-056 used a randomized, open-label, 4-way crossover design to compare the pharmacokinetics of FFIS (10 mcg, 20 mcg, 244 mcg), delivered via a nebulizer (Pari LC Plus®), and Foradil® (12 mcg), delivered via dry powder inhaler (Aerolizer®). This study enrolled 13 mild-to-moderate COPD patients 50 years of age or older, out of which 12 completed the study. The FFIS 20 mcg dose was selected because it is the intended therapeutic dose for twice daily administration of FFIS based on the results of two dose-finding studies (DL-052 and DL-057) conducted in COPD patients. The 10-mcg dose, i.e., one-half the proposed therapeutic dose, was selected to investigate linear pharmacokinetics. The FFIS 244-mcg dose was chosen because this dose was expected to be high enough for formoterol to be consistently detected in plasma using a LC/MS assay, and therefore to provide valid estimates of pharmacokinetic parameters. Foradil® Aerolizer®, the active comparator, was given at the marketed therapeutic dose of 12 mcg.

The primary objective of this PK study was to demonstrate that systemic exposure from the 20 mcg dose of FFIS would not exceed the systemic exposure from the marketed reference drug Foradil® Aerolizer® 12 mcg. It was critical to link systemic exposure of FFIS 20 mcg to that of Foradil® Aerolizer® 12 mcg for the following reasons: 1) this is a 505(b)(2) NDA application that cross-referenced marketed Foradil® Aerolizer® 12 mcg for its intended approval; 2) a higher dose of 24 mcg Foradil® Aerolizer® was not approved for marketing primarily due to more serious adverse events and withdrawals associated with this dose compared to the 12 mcg BID dose.

Plasma and urine formoterol fumarate concentrations were assessed using a LC/MS method with a lower limit of quantitation (LLOQ) of 2.5 pg/mL. Following bioanalysis of plasma samples, it was apparent that the bioanalytical method was not sensitive enough to measure the majority of the drug concentrations in plasma, which were mostly near or below the LLOQ, following single-dose inhalation administration of therapeutic doses (10 mcg and 20 mcg) of FFIS. A review of the urine data showed that formoterol fumarate concentrations in urine were reliably measured for all three FFIS doses. Therefore, excretion of unchanged formoterol in urine was used as an indirect measure of systemic exposure. Limited plasma PK data was only used as supportive in reaching study conclusions.

Plasma and urine PK parameters were summarized in Table 1 below. The mean amount of formoterol excreted in urine over 24 hrs following administration of FFIS 20 mcg was 14% lower compared to Foradil® Aerolizer® 12 mcg (Table 1). The mean percentage of dose excreted in urine was found to be consistent across all 3 FFIS groups suggesting linear pharmacokinetics. The mean percent dose excreted unchanged in urine over 24 hours was approximately 2-fold higher after patients were dosed with Foradil® Aerolizer® 12 mcg relative to the 20 mcg FFIS dose, indicating possibly lower bioavailability for FFIS compared to Foradil® Aerolizer®. These data, taken together, support the conclusion that formoterol systemic exposure after the administration of 20 mcg FFIS via nebulizer Pari LC Plus® was slightly lower compared to that from Foradil® Aerolizer® 12 mcg.

Plasma PK data, though limited, further supported these conclusions. The mean formoterol C_{max} and AUC_t from FFIS 20 mcg were found to be 29% and 46% lower compared to that obtained from Foradil® Aerolizer®, respectively (Table 1). The systemic exposure from 244 mcg FFIS (i.e. 12-fold the intended therapeutic dose of FFIS) was comparable to that from 120 mcg Foradil® Aerolizer® (i.e. 10-fold the approved dose of Foradil® Aerolizer®). The study did not reveal any unexpected PK characteristics that differ significantly from what were known for Foradil® Aerolizer®.

Table 1. Summary of mean (SD) urine and plasma PK parameters of formoterol after single dose inhalation administration of FFIS and Foradil® Aerolizer®.

	Treatment				
	FFIS 10 mcg	FFIS 20 mcg	FFIS 244 mcg	Foradil® 12 mcg	Ratio (FFIS 20 mcg: Foradil® 12 mcg)
Urine PK data					
A _{e(0-24h)} (ng)	109.7 (56.0)	349.6 (190.3)	3317.5 (1733.0)	406.3 (116.5)	0.86
CL _R (mL/min)	NR	NR	157.0 (66.4)	NR	—
% dose	1.1 (0.6)	1.7 (1.0)	1.4 (0.7)	3.4 (1.0)	0.5
Plasma PK data					
C _{max} (pg/mL)	5.7 (8.1)	8.7 (9.3)	72.5 (35.3)	12.3 (4.2)	0.71
AUC _t (pg.hr/mL)	23.1 (30.2)	28.7 (38.3)	388.9 (173.8)	53.4 (44.6)	0.54
AUC _{inf} (pg.hr/mL)	NR	NR	449.8 (190.9)	NR	—
T _{max} * (hr)	7.5 (0.1-24.1)	0.6 (0.1-35.9)	0.2 (0.1-0.5)	0.5 (0.1-24.0)	1.2
T _{1/2} (hr)	NR	NR	7.0 (2.6)	NR	—

* Median (range); NR = Not reliably quantified; A_{e(0-24h)} = Amount of drug excreted from time 0 to 24 hrs post-dose; CL_R = renal clearance; % dose = percent dose excreted in urine over 24 hrs.

1.4 COMMENTS TO THE MEDICAL OFFICER

The following comments were discussed with the medical officer:

The single-dose pharmacokinetics of FFIS did not significantly differ from that of Foradil® Aerolizer®. The systemic exposure obtained following single-dose inhalation of 20 mcg FFIS was slightly less than that obtained from 12 mcg Foradil® Aerolizer®. Although unavailability of the multiple-dose data in this application prevents direct evaluation of time-dependency of FFIS pharmacokinetics, assumption of linear PK allows a reasonable prediction of minimal accumulation following chronic dosing, consistent with Foradil® Aerolizer®.

Reviewer

Partha Roy, Ph.D.

Office of Clinical Pharmacology

Division of Clinical Pharmacology 2

Concurrence:

Emmanuel Fadiran, Ph.D., Team leader

2 QUESTION BASED REVIEW

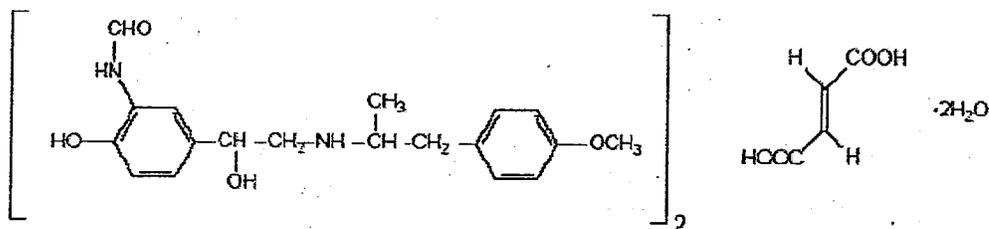
2.1 General Attributes

Q1. What are the general attributes of Formoterol Fumarate Inhalation Solution?

Formoterol Fumarate Inhalation Solution 20 mcg/2 mL is a sterile, clear, colorless, _____ free solution that contains the active ingredient of dihydrate form of formoterol fumarate, a racemic mixture of (R, R)- and (S, S)-enantiomers. Formoterol fumarate is a selective beta₂-adrenergic bronchodilator. Its chemical name is (±)-2-hydroxy-5-[(1R)-1-hydroxy-2-[[[(1R)-2-(4-methoxyphenyl)-1-methylethyl]-amino]ethyl]formanilide fumarate dihydrate.

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STRUCTURAL FORMULA:



Molecular formula: (C₁₉H₂₄N₂O₄)₂C₄H₄O₄·2H₂O

Molecular weight: 840.92

Solubility: Formoterol fumarate dihydrate is a practically odorless, white to yellowish white powder. It is freely soluble in glacial acetic acid and methanol, slightly soluble in water and ethanol, and practically insoluble in ether.

FORMULATION

Formoterol Fumarate Inhalation Solution 20 mcg/2 mL is in ready to use unit-dose vials that requires no dilution before administration by nebulization. Each 2 mL unit-dose vial contains 20 mcg of formoterol fumarate (anhydrous basis), sodium chloride to _____ citric acid, _____ and sodium citrate dihydrate as buffering agents to a target pH 5.0, and _____ as the vehicle. Each unit dose vial is overwrapped in a pre-printed foil- _____ pouch and is packaged in cartons of _____ and 60 pouches.

b(4)

INDICATION (as per proposed label)

FFIS is indicated for long-term, twice daily administration in the maintenance treatment of bronchoconstriction in patients with COPD including chronic bronchitis and emphysema.

DOSAGE AND ADMINISTRATION (as per proposed label)

Intended for oral inhalation only:

- One 20 mcg/2 mL vial every 12 hours,
- For use with a nebulizer (with a facemask or mouthpiece) connected to

an air compressor.

2.2 General Clinical Pharmacology

Q2. What is known about the pharmacokinetics of FFIS?

The sponsor has conducted one single dose oral inhalation PK study in mild-to-moderate COPD patients to support approval of this 505(b)(2) NDA for the sponsor's proposed 20 mcg dose of FFIS. Three FFIS doses of 10 mcg, 20 mcg, and 244 mcg along with 12 mcg Foradil® Aerolizer® were tested in this study. A summary of urine and plasma mean PK parameters is presented in Table 1 above (page 4). Foradil® Aerolizer® PI was referenced for additional PK information including ADME. Refer to Clinical Pharmacology and Biopharmaceutics (CPB) Reviews by Dr. Young Moon Choi (NDA 21-279 – July 17, 2001) and Dr. Shinja Kim (NDA 21-592 – September 24, 2003) for further details.

Urinary excretion of unchanged formoterol was used as an indirect measure of systemic exposure because the lower limit of quantitation of the bioanalytical method employed was not sensitive enough to measure the majority of the plasma drug concentrations following administration of therapeutic doses of formoterol, which were mostly near or below the lower level of quantitation. Plasma drug disposition data parallel urinary excretion, and the elimination half-lives calculated for urine and plasma were similar. This reviewer is of the opinion that this approach is acceptable from a clinical pharmacology perspective based on earlier CPB reviews by Dr. Young Moon Choi for NDA 21-279 (July 17, 2001) and Dr. Bradley K. Gillespie for NDA 20-831 (June 2, 1998).

Following single-dose inhalation of FFIS 244 mcg in COPD patients, formoterol was rapidly absorbed into plasma, reaching a maximum drug concentration of 72.5 pg/mL within 12 minutes of dosing. Nearly dose-proportional increase in plasma C_{max} and AUC_t as well as total drug excreted unchanged in urine ($A_{e(0-24)}$) was observed across FFIS doses of 10 mcg, 20 mcg and 244 mcg, suggesting linear pharmacokinetics. The mean percentage of dose excreted in urine was found to be consistent across all 3 FFIS groups. The mean terminal half-life of formoterol was estimated to be 6.1 hrs following FFIS single-dose of 244 mcg. The mean renal clearance (CLR) was estimated to be 157 mL/min that is comparable to the value of 150 mL/min reported in the Foradil® Aerolizer® label.

Q3. How does the systemic exposure from FFIS compare to that from Foradil® Aerolizer®?

The mean amount of formoterol excreted unchanged in urine over 24 hrs ($A_{e(0-24h)}$) following administration of FFIS 20 mcg was numerically less, i.e. about 14% lower, compared to Foradil® Aerolizer® 12 mcg (Table 1, page 4). In 7/10 subjects, $A_{e(0-24h)}$ following administration of 12 mcg Foradil® Aerolizer® was greater compared to that after FFIS 20 mcg dosing. The mean percent dose excreted unchanged in urine was found

to be approximately 2-fold higher after patients were dosed with Foradil® Aerolizer® 12 mcg relative to the FFIS 20 mcg, likely indicating lower bioavailability for the later.

Plasma PK data, though limited, further supported these conclusions. The mean formoterol C_{max} from Foradil® Aerolizer® 12 mcg and FFIS 20 mcg were 12.3 pg/mL and 8.7 pg.hr/mL, respectively. The corresponding AUC_t values were 53.4 pg.hr/mL and 28.7 pg.hr/mL, respectively. The mean formoterol C_{max} from 244 mcg FFIS was found to be 21% lower compared to that from 120 mcg Foradil® Aerolizer® [72.5 pg/mL (study DL-056) vs. 92 pg/mL (Foradil® Aerolizer® label)]. No multiple-dose PK data was available for comparison between the two drug products.

Q4. Is systemic exposure of formoterol fumarate proportional to increments of dose following administration of FFIS?

Urinary excretion of unchanged formoterol was used as an indirect measure of systemic exposure due to insensitivity of the bioanalytical method to detect and quantify plasma drug concentrations. The mean amount of formoterol excreted unchanged in 24 hours following single dose oral inhalation doses of 10, 20, and 244 mcg FFIS were found to be 109.7 ng, 349.6 ng, and 3317.5 ng, respectively. This indicated near dose proportional increase in systemic exposure within the dose range tested. The plasma formoterol C_{max} following 10 mcg, 20 mcg, and 244 mcg doses of FFIS were 5.7 pg/mL, 8.7 pg/mL, and 72.5 pg/mL, respectively, indicating less than dose-proportional increase. Though limited by lack of sufficient sensitivity at the lower limit of quantitation, plasma AUC_t of 23.1 pg.hr/mL, 28.7 pg.hr/mL, and 388.9 pg.hr/mL indicated dose-dependent increase in systemic exposure. Taken both plasma and urine PK data together, this reviewer concluded that there was some evidence to suggest nearly dose-proportional increase in systemic exposure in the dose range of 10 mcg to 244 mcg FFIS.

Q5. Based on dose-response data, is the selection of the intended therapeutic dose of FFIS appropriate?

The sponsor conducted two dose ranging studies, DL-052 and DL-057. The initial dose ranging study, DL-052, was conducted with single treatments of FFIS at doses of 40 mcg and 80 mcg and Foradil® Aerolizer® at doses of 12 mcg and 24 mcg. Based on a subsequent discussion with the FDA, the sponsor conducted an additional dose-ranging study, DL-057, to more adequately define the dose-response curve using doses that were anticipated to be therapeutically sub-optimal as well as doses that were expected to demonstrate equivalent or slightly better efficacy than Foradil® Aerolizer® 12 mcg (i.e. to bracket the marketed Foradil® Aerolizer® 12 mcg formulation). The study DL-057 proved to be the critical dose-ranging study that identified the 20 mcg dose of FFIS as the dose to be further studied in the pivotal safety and efficacy trial (study 201-065).

Study DL-057 was a dose-ranging study that used a randomized, double-blind, double-dummy, placebo- and active-controlled, 7-treatment (FFIS 2.5, 5, 10, 20, and 40 mcg, Foradil® Aerolizer® 12 mcg, and placebo), crossover design to determine the lowest dose of FFIS that was comparable to Foradil® Aerolizer® 12 mcg. The primary

efficacy variable in the study was the FEV₁ AUC₀₋₁₂ for each treatment following single-dose administration of study medication.

Equivalency of efficacy was measured using a step-down procedure comparing successive (highest to lowest) FFIS mean changes in FEV₁ AUC₀₋₁₂ to the Foradil® Aerolizer® (FA) mean change (see Table below). Equivalency was defined as a 90% CI that fell within a range of 80% to 125%. In this study, patients administered FFIS 40 mcg had the greatest mean for FEV₁ followed in descending order by FFIS 10, 2.5 and 5 mcg. Although the 90% CIs for all FFIS doses fell within the range of 80% to 125%, the 90% CI for FFIS 20 mcg most closely bracketed 100% equivalence (CI: 99.6, 104.6). Based on the step-down procedure, the FFIS 20 mcg dose was the first dose to demonstrate a non-significant p-value (p = 0.1721).

Transformed FEV₁ AUC_(0-12h): Completer Population

COMPARATOR	TREATMENT	EQUIVALENCY RESULTS		
		EXPONENTIATED MEAN RATIO (%)	90% CI*	P-VALUE**
FA 12 mcg	FFIS 40 mcg	105.1	102.5, 107.7	0.0011
FA 12 mcg	FFIS 20 mcg	102.1	99.6, 104.6	0.1721
FA 12 mcg	FFIS 10 mcg	99.5	97.1, 102.0	NA
FA 12 mcg	FFIS 5 mcg	98.6	94.2, 99.0	NA
FA 12 mcg	FFIS 2.5 mcg	95.7	93.4, 98.1	NA

* Equivalency was established if the 90% CIs fell within the range of 80% to 125%.

**P-values were based on a step-down procedure comparing successive mean changes between treatment.

FA=Foradil Aerolizer, FFIS=Formoterol Fumarate Inhalation Solution

Refer to the medical officer's and/or Statistical reviews for additional details on the dose-ranging studies in this NDA.

2.3 Intrinsic Factors

No studies were submitted to the present NDA that investigated the effect of intrinsic factors on the pharmacokinetics of formoterol following administration of FFIS. Reference is made to Foradil® Aerolizer® 12 mcg (NDA 21-279 and NDA 20-831) from Novartis.

2.4 Extrinsic Factors

No studies were submitted to the present NDA that investigated the effect of extrinsic factors on the pharmacokinetics of formoterol following administration of FFIS. Reference is made to Foradil® Aerolizer® 12 mcg (NDA 21-279 and NDA 20-831) from Novartis.

2.5 General Biopharmaceutics

Q6. Was the to-be-marketed formulation used in the only pharmacokinetic study DL-056?

Yes. The following batch number was used in the only PK study (DL-056) submitted as part of this NDA: Formoterol Fumarate Inhalation Solution 20 mcg, Lot number C054. The batch number used in study 201-065 (pivotal safety and efficacy study) was C062A.

These batch numbers correspond to the to-be-marketed inhalation solution formulation delivered via nebulizer (Pari LC Plus®).

2.6 Analytical Section

Q7. Was the suitability of the analytical method supported by the submitted information?

Yes, the sponsor submitted all the appropriate information that supports the bioanalytical method (LC/MS) used in NDA 22-007 as accurate, precise, sensitive and specific.

Recovery:

The recoveries of formoterol at 7.5 pg/mL (low), 80 pg/mL (medium) and 160 pg/mL (high) were _____, respectively with the overall recovery being ____%. The recovery of internal standard was found to be _____. Though recovery estimates across the range of formoterol concentrations varied considerably and certainly not optimum, the overall recovery between the analyte and the internal standard was comparable and hence acceptable.

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Assay Specificity:

No major interference was detected at the retention times of formoterol and _____ (internal standard).

b(4)

Assay Sensitivity:

The lower limit of quantitation of formoterol in human plasma was 2.5 pg/mL. The LLOQ samples had a precision (%CV) and accuracy (%nominal) of _____ respectively, i.e. well below $\pm 20\%$ requirement for a validated bioanalytical method.

Linearity:

The standard curve is linear from _____ pg/mL. Linearity of the analytical method is demonstrated by correlation coefficients that calculate greater than _____ for each standard.

b(4)

Inter-Assay Precision and Accuracy:

Between batch accuracy and precision were investigated over a course of three days. Between-batch precision (%CV) for quality control samples in human plasma at 7.5 pg/mL (low), 80 pg/mL (medium) and 160 pg/mL (high) for formoterol were found to be _____ respectively. Between-batch accuracy (%nominal) for quality control samples in human plasma at 7.5 pg/mL (low), 80 pg/mL (medium) and 160 pg/mL (high) for formoterol were found to be _____, and ____%, respectively. These results meet the regulatory criterion [refer to the guidance for industry "Bioanalytical Method Validation (Final-May 2001)] of not exceeding 15% (20% for the lowest QC samples) for precision and accuracy.

b(4)

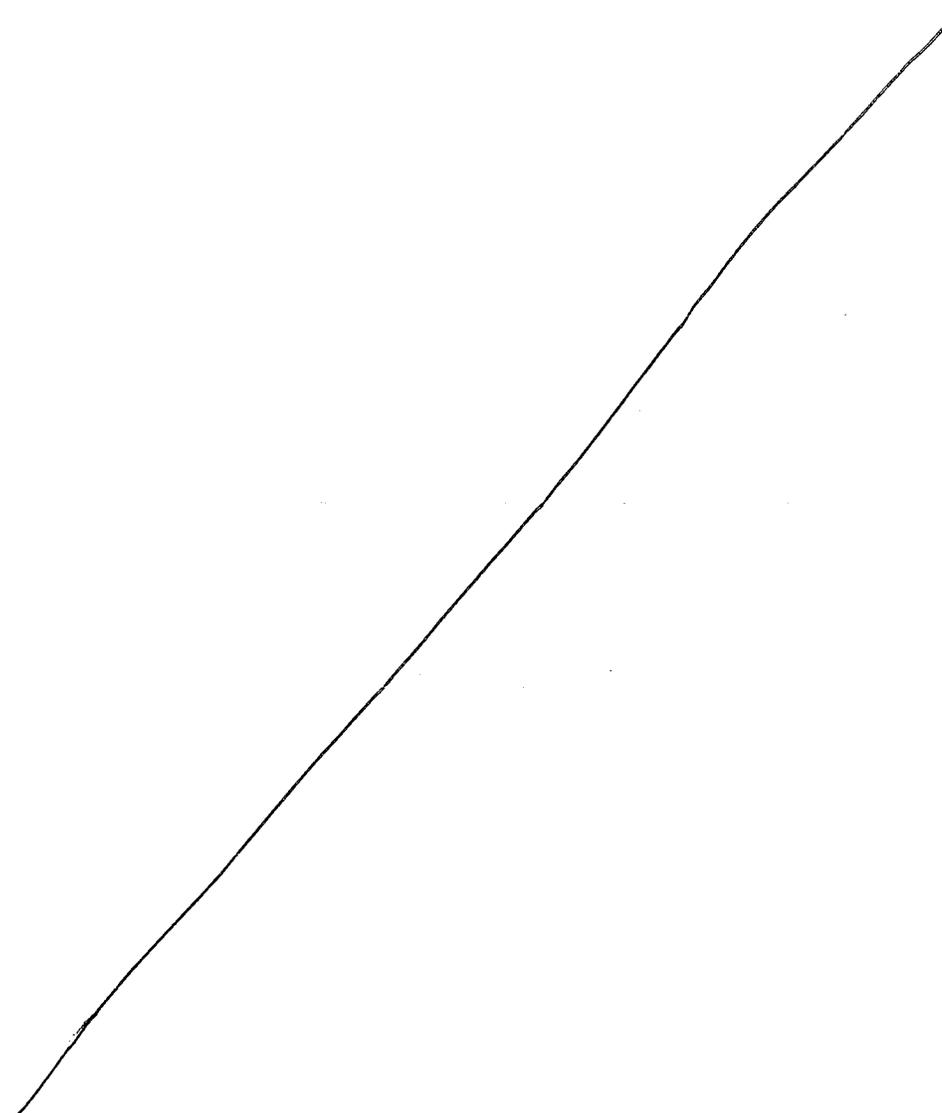
Intra-Assay Precision and Accuracy:

Within-batch precision (%CV) for quality control samples in human plasma at 7.5 pg/mL (low), 80 pg/mL (medium) and 160 pg/mL (high) for formoterol were found to be _____ respectively. Between-batch accuracy (%nominal) for quality control samples in human plasma at 7.5 pg/mL (low), 80 pg/mL (medium) and 160 pg/mL (high) for formoterol were found to be _____, respectively. These results were acceptable based on the regulatory criterion [refer to the guidance for industry "Bioanalytical Method Validation (Final-May 2001)] for precision and accuracy.

3 DETAILED LABELING RECOMMENDATIONS

The labeling texts are under negotiation at the time of completion of this review.

Initial labeling recommendations for Clinical Pharmacology sections are as follows:



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4 APPENDICES
4.1 PROPOSED PACKAGE INSERT

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ON ORIGINAL**

11 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

4.2. Individual Report: Study DL-056

AN OPEN-LABEL, FOUR-WAY CROSSOVER PHARMACOKINETIC STUDY OF FORMOTEROL FUMARATE INHALATION SOLUTION AND FORMOTEROL FUMARATE DRY POWDER INHALER IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Protocol No: DL-056
IND No: 68,782
Date of Final Report: 07 November 2005
Phase: I

OBJECTIVE

The primary objective of the study was to evaluate the pharmacokinetics of formoterol fumarate inhalation solution (FFIS) in mild to moderate COPD patients after single-dose administration of FFIS 10, 20, and 244 mcg compared to the marketed reference drug Foradil® Aerolizer® 12 mcg.

STUDY DESIGN AND TREATMENT ADMINISTRATION

This was a randomized, open-label, 4-way crossover phase I study to compare the pharmacokinetics of FFIS in mild-to-moderate COPD patients, delivered via PARI LC-PLUS® nebulizer and 12 mcg Foradil®, delivered via Aerolizer®. There were 4 treatments (FFIS 10 mcg, 20 mcg, and 244 mcg, and Foradil® 12 mcg) administered under fasted condition on 4 occasions separated by a washout period of at least 5 days (with a minimum of 48 hours of long-acting beta₂-agonist washout, 8 hours of short-acting beta₂ agonist washout, and caffeinated beverages washout of 8 hours after each study drug administration).

SUBJECTS

This study enrolled 13 adult patients 50 years of age or older (6 males and 7 females) who met the American Thoracic Society (ATS) definition of COPD, had a current or prior history of at least 10-pack years of cigarette smoking, and had an FEV₁ of at least 30% but less than 80% of predicted normal with an FEV₁/forced vital capacity (FVC) ratio less than 70%. Mean age was 58.5 years, and most patients (92.3%) were white. There were few protocol deviations or exceptions to the enrollment eligibility criteria (2 patients did not meet the age restriction of ≥50 years; 1 patient did not meet the FEV₁/FVC criterion of <70%), however none of these were expected to impact the interpretation of the pharmacokinetic study results.

FORMULATIONS

The following formulations and lot numbers were used in this study:
Formoterol Fumarate Inhalation Solution 10 mcg: Lot number C053
Formoterol Fumarate Inhalation Solution 20 mcg: Lot number C054
Formoterol Fumarate Inhalation Solution 244 mcg: Lot number C043
Foradil® Aerolizer™ 12 mcg: Lot numbers 022G7030, 006H0421

RATIONALE

The FFIS 20 mcg dose was selected because it is the intended therapeutic dose for twice daily administration of FFIS. The 10 mcg dose, i.e., one-half the recommended therapeutic dose, was selected to investigate linear pharmacokinetics. The FFIS 244 mcg dose (~12-fold the intended therapeutic dose) was chosen because this dose was expected to be high enough for formoterol to be consistently detected in plasma using the most sensitive assay available, and therefore to provide valid estimates of pharmacokinetic parameters. Foradil® Aerolizer®, the active comparator, was given at the recommended therapeutic dose of 12 mcg as a comparator.

PHARMACOKINETIC MEASUREMENTS

Blood and urine sampling

Blood samples for PK analysis were taken just prior to dosing and at the following post-dose time points: 5, 10, and 30 minutes and 1, 3, 6, 12, 16, 24, and 36 hours. All urine voided was collected as follows: 0-3, 3-6, 6-12, and 12-24 hours post-dose; a pre-dose urine sample also was collected immediately prior to administration of study drug.

Analytical method

Plasma and urine formoterol fumarate concentrations following administration of FFIS and Foradil® Aerolizer® were measured using a LC/MS method with a lower limit of quantitation of 2.5 pg/mL. The sponsor submitted all the appropriate information that supports that the analytical methods used in NDA 22-007 as accurate, precise, sensitive and specific.

DATA ANALYSIS

Pharmacokinetic Analysis

Pharmacokinetic parameters were estimated following non-compartmental analysis of plasma concentration-time data. Plasma concentration results below the LOQ were assigned a value of zero in the absorption phase and treated as missing in the terminal phase. Pharmacokinetic parameters for most plasma and urine data were summarized descriptively. A general linear model procedure, with treatment, sequence, period, and patient nested within sequence, was used to analyze the percent of the dose excreted in urine over 24 hours post-dose. Ninety percent confidence intervals (CIs) were provided for a ratio of FFIS versus Foradil® for percent dose excreted in urine.

Safety

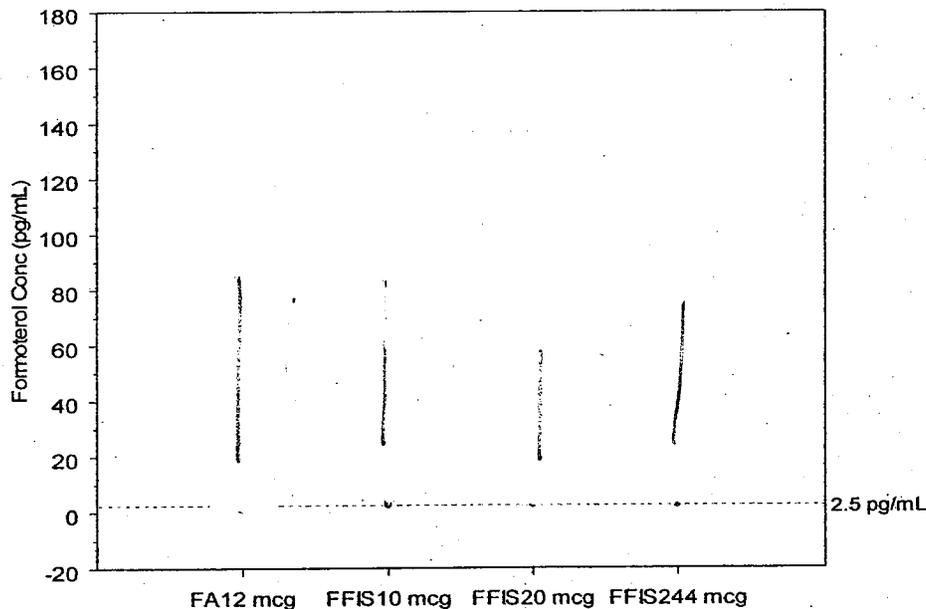
Safety population includes all randomized patients who took at least 1 dose of study medication and had at least 1 safety evaluation during treatment. The safety of the drug regimen was assessed by evaluation of non-serious AEs, SAEs, laboratory evaluations, vital signs, physical examination findings, heart rate, ECG findings, and prior and concomitant medication use.

PHARMACOKINETIC RESULTS

Plasma Formoterol Concentrations

Majority of the formoterol concentrations in plasma samples collected following administration of FFIS 10 and 20 mcg and Foradil® Aerolizer® 12 mcg were at or near the lower level of quantitation (2.5 pg/mL) of the bioanalytical method, hence limiting the reliability of the evaluation of plasma PK parameters (Figure 1). By 6 to 12 hrs post-dose, plasma concentrations in almost all subjects were below the level of quantitation. There were eight occasions when plasma concentrations of all post-dose samples in a total of 6 patients following FFIS dosing of either 10 or 20 mcg were below the limit of quantitation.

Figure 1. Plasma formoterol concentrations following single dose administration of Foradil® Aerolizer® (FA) 12 mcg, FFIS 10 mcg, 20 mcg and 244 mcg in all subjects.



Plasma Pharmacokinetics

Analyses of the formoterol pharmacokinetics data revealed that 7 plasma concentration values were possible outliers and according to the sponsor most of these values were either the sole concentration value within the sequence, and were usually extreme in magnitude and temporally out of place. Upon review of these apparent outliers, this reviewer determined that the 3-hr plasma sample for patient 208 at visit 3 is the only concentration (85.743 pg/mL) that can be unambiguously judged an outlier as it was the only nonzero concentration (34-fold the LLOQ) in that particular concentration-time profile. Based on this criterion, plasma PK parameters were re-summarized that included

all the other 6 apparent outlier data except the above sample data from patient 208 and presented below in Table 2.

Table 2. Mean (SD) plasma formoterol PK parameters following single-dose administration in COPD patients excluding one outlier (patient 208, 3-hr sample at visit 3) as judged by this reviewer.

	Treatment				
	FFIS 10 mcg	FFIS 20 mcg	FFIS 244 mcg	FA 12 mcg	FA 120 mcg* (Foradil® label)
C_{max} (pg/mL) <i>N</i>	5.7 (8.1) 12	8.7 (9.3) 12	72.5 (35.3) 12	12.3 (4.2) 12	92
AUC_t (pg.hr/mL) <i>N</i>	23.1 (30.2) 12	28.7 (38.3) 12	388.9 (173.8) 12	53.4 (44.6) 12	365
AUC_{inf} (pg.hr/mL) <i>N</i>	NR	NR	449.8 (190.9) 12	NR	458
T_{max}^{**} (hr) <i>N</i>	7.5 (0.1-24.1) 8	0.6 (0.1-35.9) 9	0.2 (0.1-0.5) 12	0.5 (0.1-24.0) 12	0.083
$T_{1/2}$ (hr) <i>N</i>	NR	NR	7.0 (2.6) 12	NR	10

* Mean plasma formoterol PK parameters following single-dose inhalation administration in healthy subjects (data obtained from Foradil® label) are presented for comparison

** Median data

NR = Not Reliable

For patients receiving FFIS 10 mg and FFIS 20 mcg, the mean C_{max} was 5.7 pg/mL and 8.7 pg/mL, respectively, and the mean AUC_t estimates were 23.1 pg-hr/mL and 28.7 pg-hr/mL, respectively indicating dose-dependent increase in systemic exposure of formoterol. Dose-proportionality could not be reliably judged due to very low (near LLOQ) plasma concentrations measured following administration of these doses. For the same reason, half-life and $AUC_{0-\infty}$ could not be accurately determined for most patients following administration of therapeutic doses of FFIS and Foradil® Aerolizer® 12 mcg. Formoterol was rapidly absorbed into plasma following single inhalation of 20 mcg FFIS with a median T_{max} of 0.6 hour. The formoterol mean C_{max} and AUC_t from Foradil® Aerolizer® 12 mcg were found to be 12.3 pg/mL and 53.4 pg.hr/mL, respectively. Hence, on average, the systemic exposure from FFIS 20 mcg was found to be generally lower compared to that from the marketed Foradil® Aerolizer® 12 mcg. Following treatment with FFIS 244 mcg, the mean C_{max} and AUC_{inf} were 72.5 pg/mL and 467.4 pg hr/mL, respectively. The median T_{max} was 0.2 hours with a mean $T_{1/2}$ of 7 hours. These pharmacokinetic data are generally comparable to that obtained with 120 mcg dose of Foradil® Aerolizer® (10-fold the therapeutic dose) described in its published label.

Urine Pharmacokinetic Results

Only a few urine samples were either missing or not quantifiable for FFIS concentrations using the same bioanalytical method as used for plasma analysis with LLOQ of 2.5 pg/mL. Pharmacokinetic urine parameters are summarized by treatment in Table 3. The total amount of unchanged drug excreted in urine exhibited dose-dependent increase across the doses of 10 mcg, 20 mcg and 244 mcg FFIS. The amount excreted in urine following FFIS 20 mcg appeared to be less than that for Foradil® Aerolizer® 12 mcg, suggesting numerically lower systemic exposure for the inhalation solution. The mean percentage of dose excreted in urine was found to be consistent across all 3 FFIS doses suggesting linear pharmacokinetics. The ninety percent (90%) confidence intervals for the ratios of percent of dose of formoterol fumarate excreted unchanged in urine after dosing with FFIS 10 mcg, FFIS 20 mcg, and FFIS 244 mcg versus percent of dose excreted unchanged after dosing with Foradil® Aerolizer® 12 mcg were 0.24 to 0.39, 0.37 to 0.61, and 0.30 to 0.48, respectively. Thus, the mean percent dose excreted in urine over 24 hours was approximately 2 to 3 times higher in the Foradil® Aerolizer® 12 mcg group relative to the FFIS groups, likely suggesting higher bioavailability from FFIS compared to Foradil® Aerolizer®. Renal clearance (CL_R) results for FFIS 10 mcg and 20 mcg provided limited information because CL_R could only be calculated for a limited number of profiles due to very few quantifiable plasma concentrations. The CL_R value estimated for FFIS 244 mcg compares well with that found with 120 mcg Foradil® Aerolizer® reported in its label as shown in Table 3.

Table 3. Mean (SD) urine formoterol PK parameters following single-dose administration in COPD patients.

	Treatment				
	FFIS 10 mcg	FFIS 20 mcg	FFIS 244 mcg	FA 12 mcg	FA 120 mcg* (Foradil® label)
$A_{e(0-24h)}$ (ng) N	109.7 (56.0) 11	349.6 (190.3) 10	3317.5 (1733.0) 12	406.3 (116.5) 11	NA
CL_R (mL/hr) N	NR	NR	157 7	NR	150
% dose N	1.1 (0.6) 11	1.7 (1.0) 10	1.4 (0.7) 12	3.4 (1.0) 11	4
90% CI FFIS:FA	0.24 - 0.39	0.37 - 0.61	0.30 - 0.48		

FFIS = Formoterol Fumarate Inhalation Solution;

FA = Foradil® Aerolizer®;

$A_{e(0-24h)}$ = amount of drug excreted from time 0 to 24 hours post-dose;

CL_R = renal clearance; % dose = percent dose excreted in urine over 24 hours post-dose.

DISCUSSION

This pharmacokinetic study was conducted primarily to demonstrate that systemic exposure from the 20 mcg dose of FFIS was either comparable to or lower than the systemic exposure from the marketed reference drug Foradil® Aerolizer® 12 mcg. The addition of a low (10 mcg) and a high dose (244 mcg) was to characterize the pharmacokinetics of formoterol delivered from FFIS. While the PK plasma data for

patients receiving clinically relevant doses did not yield useful information due to bioanalytical limitation, a review of the urine data showed that formoterol fumarate concentrations in urine were reliably measured for all 3 FFIS doses. Hence, urine data was primarily used to evaluate and compare formoterol systemic exposure from FFIS and Foradil® Aerolizer®.

The mean amount of formoterol excreted in urine over 24 hrs following administration of FFIS 20 mcg was 14% lower compared to Foradil® Aerolizer® 12 mcg, indicating slightly lower systemic exposure for the inhalation solution. The mean percentage of dose excreted in urine was found to be consistent across all 3 FFIS groups suggesting linear pharmacokinetics. The mean percent dose excreted unchanged in urine over 24 hours was approximately 2 to 3 times higher after patients were dosed with Foradil® Aerolizer® 12 mcg relative to the FFIS doses, likely indicating lower bioavailability for FFIS. Plasma PK data, though limited, also supported the conclusions from the urine data. Hence, on average, the rate of absorption from FFIS 20 mcg was found to be generally lower compared to that from the marketed Foradil® Aerolizer® 12 mcg product. In addition, systemic exposure from 12-fold the intended therapeutic dose of FFIS was comparable to 10-fold the marketed dose of Foradil® Aerolizer®. The study did not reveal any unexpected pharmacokinetic characteristics that differ from what were known with Foradil® Aerolizer®.

APPEARS THIS WAY
ON ORIGINAL

4.3. Consult Review

Not applicable.

**APPEARS THIS WAY
ON ORIGINAL**

4.4. OCP Filing/Review Form

Office of Clinical Pharmacology and Biopharmaceutics				
New Drug Application Filing and Review Form				
General Information About the Submission				
Information		Information		
NDA Number	22-007	Brand Name		
OCP Division	DCP2	Generic Name	Formoterol Fumarate	
Medical Division	DPADP	Drug Class	Long-acting Beta2 agonist	
OCP Reviewer	Partha Roy	Indication(s)	Maintenance treatment of bronchoconstriction in COPD patients including chronic bronchitis and emphysema	
OCP Team Leader	Emmanuel Fadiran	Dosage Form	Inhalation solution	
		Dosing Regimen	mcg/2 mL	
Date of Submission	28 June 2006	Route of Administration	Oral inhalation	
Estimated Due Date of OCPB Review	31 January 2007	Sponsor	Dey, L.P.	
PDUFA Due Date	29 April 2007	Priority Classification	Standard	
Division Due Date	28 February 2007			
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			
HPK Summary	x			
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:	x			
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:	x			
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 -				
solution as reference:				
alternate formulation as reference:				
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	1	
Filability and QBR comments				
	"X" if yes	Comments		
Application filable ?	x	Reasons if the application is <u>not</u> filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?		
Comments sent to firm ?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.		
QBR questions (key issues to be considered)	Is the systemic exposure of FFIS 20 mcg/2 mL equivalent or less than that of the approved product Foradil® Aerolizer® 12 mcg in order to reference the clinical safety of the approved product per 505(b)(2) requirement?			
Other comments or information not included above				
Primary reviewer Signature and Date	Partha Roy, Ph.D.			
Secondary reviewer Signature and Date	Emmanuel O. Fadiran, Ph.D.			

CC: NDA XX-XXX, HFD-850(Electronic Entry or Lee), HFD-XXX(CSO), HFD-8XX(TL, DD, DDD), CDR (B. Murphy)

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this page is the manifestation of the electronic signature.**

/s/

Partha Roy
2/21/2007 12:58:30 PM
PHARMACOLOGIST

Emmanuel Fadiran
2/21/2007 01:12:05 PM
BIOPHARMACEUTICS
I concur.

**Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form**

General Information About the Submission

	Information		Information
NDA Number	22-007	Brand Name	
OCP Division	DCP2	Generic Name	Formoterol Fumarate
Medical Division	DPADP	Drug Class	Long-acting Beta2 agonist
OCP Reviewer	Partha Roy	Indication(s)	Maintenance treatment of bronchoconstriction in COPD patients including chronic bronchitis and emphysema
OCP Team Leader	Emmanuel Fadiran	Dosage Form	Inhalation solution
		Dosing Regimen	mcg/2 mL
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Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
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Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	X			
Reference Bioanalytical and Analytical Methods	x			
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Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	x			
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:	x			
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:				

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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 -				
solution as reference:				
alternate formulation as reference:				
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				
Filability and QBR comments				
	"X" if yes	Comments		
Application filable ?	x	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?		
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Other comments or information not included above				
Primary reviewer Signature and Date	Partha Roy, Ph.D.			
Secondary reviewer Signature and Date	Emmanuel O. Fadiran, Ph.D.			

CC: NDA XX-XXX, HFD-850(Electronic Entry or Lee), HFD-XXX(CSO), HFD-8XX(TL, DD, DDD), CDR (B. Murphy)

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/s/

Partha Roy
8/28/2006 03:59:28 PM
PHARMACOLOGIST

Emmanuel Fadiran
8/28/2006 04:17:36 PM
BIOPHARMACEUTICS
I concur.