CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-473

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

Original NDA:	**22-473**
Submission Dates:	**12/16/2008**
Brand Name:	**Revatio® Injection**
Generic Name:	**Sildenafil citrate injection**
Dosage Form & Strength:	**Injection, 10 mg (0.8 mg/mL in 12.5 mL)**
Indication:	For the continued treatment of patients with pulmonary arterial hypertension (PAH) who are currently prescribed oral REVATIO and who are temporarily unable to take oral medication.
Applicant:	Pfizer
Submission:	Original NDA
Clinical Division:	Cardiovascular-Renal Drug Products, HFD-110
OCP Divisions:	Clinical Pharmacology 1 and Pharmacometrics
Primary Reviewer:	Satjit Brar, Pharm.D., Ph.D.
Review of DDI Simulations:	Ping Zhao, Ph.D.
OCP Team Leader:	Rajanikanth Madabushi, Ph.D.
Pharmacometrics Team Leader:	Pravin Jadhav, Ph.D.

Table of Contents

List of Tables

List of Figures

1 EXECUTIVE SUMMARY

Pfizer Incorporated is seeking the approval of Original NDA 22-473 for Revatio® Injection (sildenafil citrate, intravenous injection) for patients with *pulmonary arterial hypertension (PAH) who are unable to take oral sildenafil therapy during hospitalization.* Sildenafil citrate is currently approved under NDA 21-845 as an oral formulation (Revatio®) for the treatment of pulmonary arterial hypertension (WHO Group I) to improve exercise ability and delay clinical worsening. The delay in clinical worsening was demonstrated when Revatio® was added to background epoprostenol therapy.

Revatio® Injection is intended to be marketed as a solution for intravenous (IV) injection and it is proposed to be administered as an IV bolus injection of 10 mg of sildenafil citrate three times a day. The approved dosage regimen for oral Revatio® tablets is 20 mg three times daily (TID).

The clinical pharmacology studies referenced in this application were originally submitted under NDA 20-895 [Viagra®] and NDA 21-845 [Revatio®]. The original packages included characterization of single dose and multiple dose pharmacokinetics, ADME characteristics, bioavailability and bioequivalence studies, potential interactions with other medications, and studies in special populations, including pharmacokinetic evaluation of sildenafil citrate in patients with PAH. The current package includes resubmission of relevant data to justify a dosing recommendation for IV sildenafil citrate.

No new clinical studies have been submitted. The clinical pharmacology program for NDA 22-473 references a total of 5 clinical studies incorporating the use of IV and oral formulations of sildenafil citrate in healthy volunteers and PAH patients (study 148-203, 148-208, 148-215, 148-301, and A1481024). The package includes a population pharmacokinetic study which evaluates the absolute bioavailability of oral sildenafil citrate. It also includes simulations along with external validation to justify dosing.

The following are the major findings:

1. The absolute bioavailability of sildenafil is approximately 40%. Therefore, 8 mg IV dose of sildenafil is reasonable to match AUC (of parent drug only) after IV and 20 mg oral dose.
2. The 10 mg IV dose has been selected to yield similar total PDE5 inhibition from sildenafil and the major active metabolite, UK-103,320, to that observed with a 20 mg oral dose.
3. The drug interaction potential with CYP inhibitors is likely to be lower. Therefore, the sponsor's labeling claim is acceptable.

1.1 RECOMMENDATION:

The Office of Clinical Pharmacology has reviewed the information submitted under NDA 22-473 for sildenafil (Revatio® Injection) and finds the sponsor's dosing rationale acceptable. We recommend approval of Revatio® Injection *for patients with pulmonary arterial hypertension (PAH) who are unable to take oral sildenafil therapy during hospitalization.*

1.2 PHASE IV COMMITMENTS:

Not Applicable

_____ Date_____

Satjit Brar, Pharm.D., Ph. D.
Pharmacometrics Fellow
(Clinical Pharmacology and Pharmacometrics Reviewer)

_____

Ping Zhao, Ph.D.
Clinical Pharmacology Reviewer

_____

Rajanikanth Madabushi, Ph.D.
Cardio-Renal Team Leader

_____

Pravin Jadhav, Ph.D.
Pharmacometrics Team Leader

OCPB Briefing was held on September 25, 2009

cc list: NDA 22-473, HFD 110.

2 Summary of OCP Findings

The proposed dose for sildenafil citrate IV injection is 10 mg three times a day (TID) given as a bolus injection. This dose is expected to yield similar total PDE5 inhibition from the plasma concentration of sildenafil plus the major active metabolite, UK- 103,320, to that observed with a 20 mg TID oral dose (the current recommended oral therapeutic dose for patients with PAH).

Sildenafil PK parameters were obtained from a combined population analysis of pharmacokinetic data from healthy volunteers in three studies (study 148-203, 148-208 and 148-215, oral and IV formulation). In these studies sildenafil IV and oral doses were studied (see Table 1). The PK profile of a 10 mg intravenous bolus dose of sildenafil was simulated based on healthy patient PK parameters. It is important to note that a study involving administration of a 10 mg IV bolus has not be performed in healthy or PAH patients.

The clinical pharmacology review focused on the following key questions:

Does a 10 mg IV bolus dose of sildenafil provide an equivalent exposure to 20 mg PO dose?

The 10 mg IV bolus does not provide an equivalent exposure to 20 mg oral dose (PO) for the parent compound, sildenafil. The Cmax observed after 10 mg IV administration is >2 fold higher than that from 20 mg PO. The AUC after 10 mg IV bolus is 1.4-fold higher than that from 20 mg PO dose yielding an exposure of 338 and 240 h·ng/ml, respectively. To achieve a similar plasma sildenafil exposure (AUC) as observed for 20 mg sildenafil administered orally, the required IV dose is calculated to be 8 mg (~40% bioavailability estimated from two sources).

Is the strategy used to derive dosing recommendation, accounting for the active metabolite, appropriate for PAH patients?

Yes, the strategy accounting for active metabolite is acceptable. The strategy used for dosing recommendation matches total (parent + active metabolite) PDE5 inhibition after oral and IV administration. The circulating concentration of the major metabolite, UK-103,320, observed following IV administration is lower than for oral dosing (14.4% of parent vs. 54% of parent; taken from study 148-215). This active metabolite has been shown to have PDE5 inhibitory activity, with 50% of the potency of sildenafil. (see section 5- APPENDIX: Pharmacometrics Review)

Do the PK characteristics of sildenafil translate from healthy volunteers to PAH pateients?

Yes. External validation was performed with a population PK model (generated from healthy individuals), and compared to observed concentrations in PAH patients for the oral and IV formulations. The population model that accounts for 30% difference in clearance between healthy volunteer and PAH patients predicts exposures in PAH patients (by ~30%).

Is the dose of 10 mg TID approriate for PAH patients?

Yes. The plasma concentrations of parent drug will be higher by 2.0 fold after the proposed IV dose compared to the approved oral dose. The efficacy of 10 mg IV is expected to yield a similar PDE5 inhibition to 20 mg PO, accounting for sildenafil and active metabolite. Moreover, there is sufficient safety experience for sildenafil at exposures significantly higher than that of

the proposed IV dose. The expected exposures after 10 mg IV bolus is much lower than that observed in both healthy volunteers and PAH patients receiving higher doses as an infusion or oral preparation, which were well tolerated.

Is the sponsor's labeling claim [redacted] reasonable? b(4)

Yes, from mechanistic viewpoint the sponsor's claim is reasonable. Further, drug interaction potential with the IV sildenafil formulation was assessed via simulation with SimCYP©. The pharmacokinetics of sildenafil after IV (50mg or 80mg) or PO (50 mg or 100mg) administration was assessed after co-administration with ketoconazole or ritonavir (CYP3A inhibitors) using simulations. There were some limitations identified (see Dr. Ping Zhao's review on DDI Interaction Simulations with SimCYP®) in the sponsor's analysis. Therefore, while the claim is acceptable, we are not recommending any quantitative information in the label.

3 QUESTION BASED REVIEW

3.1 General Attributes

History of Regulatory Development

Revatio® (sildenafil citrate) is a potent and specific inhibitor of phosphodiesterase (PDE5). Sildenafil was originally approved in the US for the treatment of male erectile dysfunction under NDA 20-895 (Viagra®) in 1998. Revatio® 20mg tablets were approved in the US for the treatment of pulmonary arterial hypertension (WHO Group I) to improve exercise ability under NDA 21-845 in 2005.

A type B meeting was held on 17 March 2008 to discuss a filing strategy for the intravenous formulation of Revatio®. The Agency advised that if Pfizer had a progression claim for oral Revatio, this would support the use of IV sildenafil to cover interruption of oral therapy. Resultant of this meeting, an efficacy supplemental application (NDA 21-845, supplement 006) was submitted for priority review to expand the current Revatio® indication of pulmonary arterial hypertension (WHO Group I) to include a "delay clinical worsening" claim with the currently approved dose and dosing regimen (20 mg three times a day). The Agency concurred that the clinical worsening data from the submission supported the supplemental application for a progression claim and justified an application for an IV sildenafil formulation. It was subsequently approved 7 May 2009 for the delay in clinical worsening claim.

In this submission, Pfizer Incorporated is seeking the approval of Revatio® Injection for those patients with PAH who are unable to take oral sildenafil therapy during hospitalization. Revatio® Injection is intended to be marketed as a solution for intravenous (IV) injection and it is proposed to be administered as an IV bolus injection of 10 mg of sildenafil citrate TID.

The detailed information regarding the Clinical Pharmacology of sildenafil citrate was provided and reviewed under NDA 20-895 and NDA 21-845. This review will use the abbreviated QBR with the questions pertaining only to this submission.

What are the proposed dosages and route of administration?

The sponsor recommends that a 10 mg dose of sildenafil citrate be administered as an IV bolus three times a day.

3.2 General Clinical Pharmacology

Pharmacokinetics

Sildenafil citrate is currently approved in oral formulations (Revatio®) for the treatment of pulmonary arterial hypertension (WHO Group I) to improve exercise ability and delay clinical worsening of PAH. The detailed information regarding the Clinical Pharmacology of sildenafil citrate was provided and reviewed under NDA 20-895 and NDA 21-845. It is summarized in the section below.

Absorption, Distribution, Metabolism, Excretion

In healthy volunteers, Revatio® is rapidly absorbed after oral administration, with a mean absolute bioavailability of 41% (range 25-63%). Maximum observed plasma concentrations are reached within 60 minutes (median) with a range of 30 to 120 minutes. The rate of absorption is reduced when taken with a high-fat meal (average delay in tmax of 60 minutes and reduction in Cmax of ~29%). Average steady state volume of distribution (Vss) for sildenafil is 105 L, indicating distribution into the tissues. Sildenafil and its major circulating N-desmethyl metabolite are both approximately 96% bound to plasma proteins.

Revatio® is hepatically cleared by the CYP3A (major route) and CYP2C9 (minor route) isoenzymes. The major circulating metabolite results from N-desmethylation of sildenafil, and is, itself, further metabolized. This metabolite has a phosphodiesterase selectivity profile similar to sildenafil and an in vitro potency for PDE5 approximately 50% of the parent drug. In healthy volunteers, plasma concentrations of this metabolite are approximately 40% of those seen for sildenafil, so that the metabolite accounts for about 20% of sildenafil's pharmacologic effects. Both parent sildenafil and the active metabolite have terminal half-lives of ~4 hours. After oral or intravenous administration, sildenafil is excreted as metabolites predominantly in the feces (approximately 80% of the administered oral dose) and, to a lesser extent, in the urine (approximately 13% of the administered oral dose). In PAH patients, the ratio of metabolite to sildenafil plasma levels are, on average, 72% at steady state (using the approved dosage of 20 mg TID). Although the average ratio differs from healthy volunteers considerably, the inter-individual variability of the ratio in PAH patient's was large ~77.5% (n = 329, range: 0.09 to 5.31).

Based on population pharmacokinetics, age, gender, race, and renal and hepatic function does not have a significant impact on sildenafil pharmacokinetics in patients with PAH. In patients with PAH, the average steady-state concentrations were 30% higher when compared to those of healthy volunteers. These findings suggest a lower clearance and/or a higher oral bioavailability of sildenafil in patients with pulmonary hypertension compared to healthy volunteers.

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

For this current submission, no new clinical pharmacology or clinical studies were performed. Throughout the overall clinical development program for adults, a total of five (5) clinical

studies incorporated the use of an intravenous formulation of sildenafil citrate, providing relevant pharmacokinetic data in 26 healthy volunteers (148-203, 148-208 and 148-215) and 93 patients (148-301 and A1481024). The majority of patients had PAH (N = 85, study A1481024). The remaining eight patients had stable Ischemic Heart Disease (N = 8, study 148-301). A list of the pertinent studies along with a brief trial design description may be seen in the table below.

Table 1: Studies involving intravenous sildenafil administration in healthy volunteers and patients.

Study title and design (N)	Dose	Endpoints
Study 148-203 – Phase 1, single-blind, placebo-controlled, 4-way cross-over, escalating IV doses (8 healthy volunteers)	IV: 20, 40, 80 mg in 80mL infusion at 2 ml/min	PK/PD parameters
Study 148-208 – Phase 1, open, randomized, 2-way cross-over to investigate pharmacokinetics after oral and IV single dose (12 healthy volunteers)	IV: 50 mL infusion given at 1/mg/mL/min, Oral: 50 mg (2 x 25 mg capsules)	PK and safety parameters
Study 148-215 – Phase 1, open, parallel group study to investigate ADME using radiolabelled oral and IV doses (6 healthy volunteers)	IV: 25 mL [14C] sildenafil infusion given at 1/mg/ml/min, Oral: 50 mg solution	PK and safety parameters
Study 148-301 – Phase 1, open, IV single dose study in patients with ischemic heart disease (8 patients)	IV: 5, 10, 20, 40 mg total doses given cumulatively over 60 minutes	PK, hemodynamics and safety parameters
Study A1481024 – Phase 2, safety and efficacy of IV sildenafil in patients with pulmonary hypertension (85 patients)	IV: target plasma concentration of 10-500 ng/mL (given as 20 min infusion)	Pulmonary hemodynamics and safety

Data from IV Studies 148-203 and 148-208 were compared with oral pharmacokinetic data from Study 148-215 and were used to estimate the total plasma concentrations of PDE5 inhibitors (sildenafil + UK-103,320) in order to predict IV doses that would achieve a therapeutic equivalent to the recommended oral dose of 20 mg TID.

Concentration data from 3 studies were pooled for population PK analysis, incorporating data from 148-203, 148-208 and study 148-211. Study 148-211 is a study with repeated oral administration, in which subjects received sildenafil 40mg TID, sildenafil 20mg six times daily or placebo for eight days. The goal of this population analysis was to build a model to describe sildenafil PK following intravenous and oral administration in healthy volunteers and to ultimately compare with PAH patients. The model was used to simulate sildenafil PK profile after intravenous and oral administrations to ascertain a dose that yields similar exposure when switching from oral to intravenous administration. Two reports were submitted summarizing results of the PK modeling efforts (one population PK analysis pooling data from studies 148-203, 148-208 and 148-215 and one two-stage analysis for study 148-203). Study A148-301,

involving patients with ischemic heart disease, is included in this application to provide further supporting clinical pharmacology data for the use of IV sildenafil citrate.

With respect to investigations involving PAH patients, study A1481024 is considered to be the pivotal study presenting IV sildenafil PK/PD data for the target indication. PK parameters obtained from this study were compared to that found in the healthy patients. The population model was also subjected to external validation with other studies involving healthy patients and PAH patients, further supporting the utility of the population model. Further description may be viewed in the Pharmacometrics report below.

Further characterization of sildenafil metabolism was conducted via *in-vitro* recombinant DNA and human liver microsome studies. Three reports have been submitted with the current submission characterizing the *in-vitro* metabolism of sildenafil by CYP3A4, 3A7, 2B6 and 2C8. *In-vivo* clinical studies incorporating IV sildenafil drug-drug interactions (DDI) have not been performed. In lieu of the PK information that would be obtained from these studies, an *in-silico* report describing sildenafil pharmacokinetic drug-drug interactions was supplied by the sponsor. Modeling using SimCYP© following either IV or PO sildenafil administration are compared with clinical data obtained after administration via the two routes. Data from a clinical sildenafil (PO) – ritonavir DDI study was compared to SimCYP© simulations. In addition, ritonavir and ketoconazole interactions with sildenafil as substrate are simulated using SimCYP to compare the magnitude of the interaction seen with either IV or PO sildenafil. See Dr. Ping Zhao's review (see section 5- APPENDIX:DDI Interaction Simulations with SimCYP®) of sponsor's simulations for sildenafil PK and DDI.

What is the inter- and intra-subject variability of the PK parameters, and what are the major causes of variability?

In healthy patients, sildenafil has a moderately variable pharmacokinetics. From the population PK analysis of study 148-203, 148-208 and 148-211 (combining oral and IV data), the typical clearance value in healthy volunteers was estimated at 29.5 L/h and the interindividual variability was estimated at 31.2 CV%. For the two-compartment model that was employed to fit the data, the typical Vc (volume of central compartment) and Vp (volume of peripheral compartment) were estimated as 73.2 L (CV% 28.8) and 33.3 L (CV% 55.6), respectively. The typical F1 (bioavailability) at 20 mg was estimated to be 35.5% with a CV% of 23.6%. As the data for the analysis were from healthy, fasting patients, the sponsor did not conduct further covariate analysis to explain the variability in the sildenafil PK. For the two-stage analysis (study 148-203, n=8 patients, IV sildenafil 20 mg) the average clearance (geometric mean) in healthy volunteers was estimated as 26.9 L/h (CV% 19.5) which is comparable with the population analysis.

3.3 Intrinsic Factors

What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure?

From the review of the original submission, age, gender, race, and renal and hepatic function were included as factors assessed to evaluate variability in sildenafil pharmacokinetics in patients with PAH. None of these factors had a significant impact.

It is known that, in PAH patients dosed with oral sildenafil (20 mg), the average steady-state concentrations are 30% higher when compared to those of healthy volunteers. There is a doubling of Cmin levels compared to that of healthy volunteers. Both findings suggest a lower clearance and/or a higher oral bioavailability of sildenafil in patients with PAH compared to healthy volunteers.

Is there any the pharmacogenomic data submitted with this NDA?

No, this submission does not include pharmacogenomic information.

3.4 Extrinsic Factors

Is there any in-vitro basis to suspect in-vivo drug-drug interactions?

Yes. *In-vitro* metabolism of sildenafil has been studied extensively and is reflected in the original reviews and label.

Were any drug-drug interactions (DDI) studied in this NDA?

No formal DDI clinical studies have been performed with intravenous sildenafil. The DDI potential of sildenafil following IV administration was assessed *in-silico*. A SimCYP© model for sildenafil was developed utilizing physicochemical and *in-vitro* data. The PK of sildenafil after IV (50mg or 80mg) or PO (50 mg or 100mg) administration generated in the clinic was compared with simulations for external validation purposes. The magnitude of the sildenafil AUC change in the presence of CYP3A inhibitors was markedly reduced when the drug was given by the IV route compared with the PO route. Based on simulations, concomitant ketoconazole administration with sildenafil 50 mg IV or 50 mg PO is expected to increase exposure (AUC) by 3.1 and 8.3 fold, respectively. Further evaluation for the *in-silico* evaluation may be viewed in the appendix below (see section 5- APPENDIX: DDI Interaction Simulations with SimCYP®).

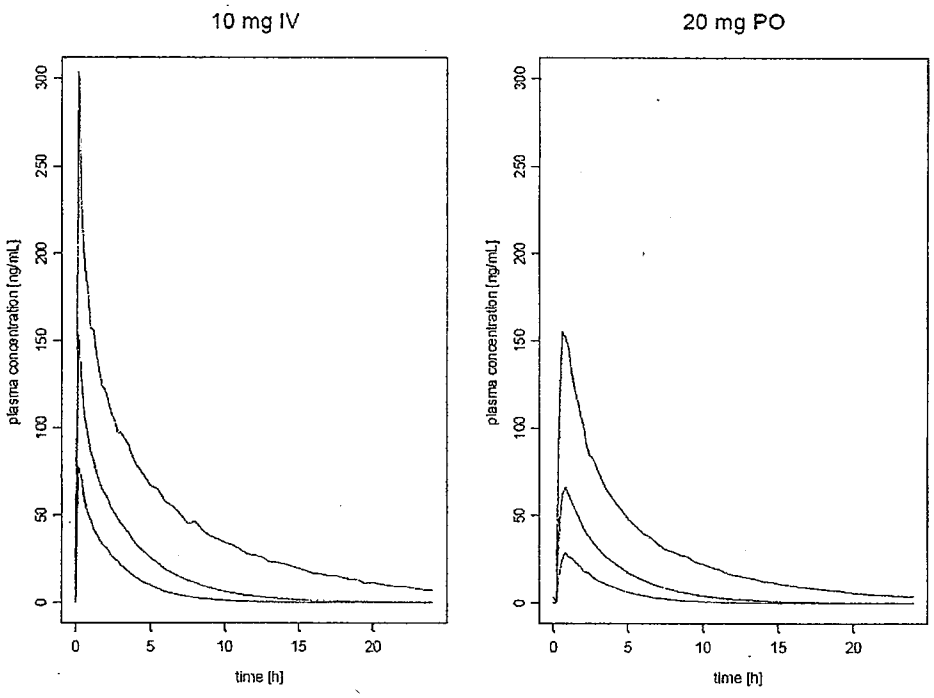
3.5 General Biopharmaceutics

What are the significant, unresolved issues related to in vivo BA and BE?

There are no unresolved issues related to *in-vivo* BA and BE. The pharmacokinetics after oral and IV sildenafil have been evaluated in two separate studies with healthy patients. The estimated bioavailability (~41%) of the oral formulation has been assessed at the 50 mg oral dose

(similar to that found in the Muirhead reference[1], ~38%). According to population PK analysis of healthy patients, the typical bioavailability, at the approved 20 mg dose level, is approximately 35.5%. The simulation results comparing 20 mg PO and 10 mg IV dose (single dose) are illustrated in Figure 1 below.

Figure 1: Comparison of Simulated Mean Sildenafil Plasma Concentrations (Plus 90% Prediction Intervals) in Healthy Volunteers for 10 mg IV vs. 20 mg Oral (PO)



From sponsor report "Population Pharmacokinetics Analysis and Simulation After Oral and Intravenous Sildenafil Administration", Figure 1, pg 29.

The proposed 10 mg IV bolus does not provide an equivalent exposure to 20 mg oral dose (PO) for the parent compound, sildenafil. The Cmax observed after 10 mg IV administration is ~2 fold higher than that from 20 mg PO. The AUC after 10 mg IV bolus is ~1.4-fold higher than that from 20 mg PO dose yielding an exposure of 338 and 248 h·ng/ml, respectively (obtained from reviewer simulation in Pharmacometrics review below). The 8 mg IV bolus dose yields sildenafil AUC similar to that of 20 mg PO.

The sponsor substantiates the choice of 10 mg dose via accounting for circulating active metabolite. The circulating concentration of the major metabolite, UK-103,320, observed following IV administration is lower than for oral dosing (14.4% of parent vs. 54% of parent;

[1] Muirhead GJ, Rance DJ, Walker DK, and Philip Wastall. Comparative human pharmacokinetics and metabolism of single-dose oral and intravenous sildenafil citrate. Br J Clin Pharmacol. 2002 February; 53(S1): 13S–20S.

taken from study 148-215). This active metabolite has been shown to have PDE5 inhibitory activity, with 50% of the potency of sildenafil. Considering the relative PDE5 inhibitory potency, the exposure differences of parent and metabolite after PO and IV administration, and the plasma protein binding of each active moiety the following calculation was performed:

$$\text{Relative IV sildenafil dose (mg)} = \frac{So(1 + Mo \bullet R \bullet Ur)}{Si(1 + Mi \bullet R \bullet Ur)}$$

where,
So = plasma sildenafil AUC following oral dose
Mo = (oral plasma UK-103,320 AUC) /So (=0.54)
Si = plasma sildenafil AUC following IV dose
Mi = (IV plasma UK-103,320 AUC)/Si (=0.144)
R = relative PDE5 inhibitory potency, UK-103,320/sildenafil (=0.5)
Ur = free fraction ratio UK-103,320/sildenafil (= 0.05/0.04 = 1.25)

Hence the oral/IV ratio for [sildenafil + UK-103,320] concentrations, adjusting for relative potency and protein binding, assuming the same dose administered by either route = 1.227 So/Si. Specifically, the IV dose calculated to yield similar total plasma concentrations of [sildenafil + UK-103,320] for an oral 20 mg dose is 9.82 mg, rounded to 10 mg for use in clinical practice.

According to the Clinical Pharmacology reviewer, this approach is deemed appropriate for dose selection. Further evaluation of the dose calculation is provided in the Pharmacometrics review.

3.6 Analytical section

How the active moieties are identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

Sildenafil and its corresponding active metabolites have been identified and measured appropriately in all clinical pharmacology and biopharmaceutics studies to date. Assay characteristics, extraction procedure and bioanalytical validation has been previously reviewed.

What is the overall conclusion regarding NDA 22-473?

Overall, the provided data supports the approval of 10 mg IV sildenafil given as an IV bolus three times a day.

4 DETAILED LABELING RECOMMENDATIONS

GENERAL

b(4)

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CLINICAL PHARMACOLOGY COMMENTS

Labeling Comments:

The sponsor's labeling changes are acceptable.

5 APPENDIX

5.1 Individual Study Reviews

A148203: TWO COMPARTMENTAL ANALYSIS OF PHARMACOKINETICS IN STUDY 148-203
Sponsor: Pfizer, Inc.
Report: a148203
Protocol number: 148-203
Study Dates: 11/08/1991 - 12/31/1991
Phase of Development: Phase I

Objective	To estimate pharmacokinetic parameters for two compartment with first order elimination model and to predict Cmax after bolus administration of 10 mg of sildenafil.
Investigational compound (s)	Sildenafil citrate
Study design	Single blind, 4-way crossover, dose escalation study of three single doses of UK-92,480 (20, 40, 80 mg) with a randomly inserted dose of placebo. Each dose was separated by a washout period of 7 days and escalation was dependent on toleration of the previous dose.
Data analysis and Statistics	Plasma concentration-time data obtained from 8 healthy male subjects, after IV infusion administration of a single dose of 20 mg sildenafil over 40 minutes were utilized for this analysis (using WinNonlin version 5.0). The CL/F, V1, V2 and CLD2 were estimated for each subject and the results were descriptively summarized (two-stage analysis).

Sponsors Results and Discussion

Table 2: The individual estimated PK parameters for 20 mg IV bolus (n=8)

	Parameter			
Sub ID	CL	CLD2	V1	V2
1	[redacted]			
2				
3				
4				
5				
6				
7				
8				
Mean	27.36	15.13	49.36	33.39
SD	5.34	33.31	11.46	28.58
Min	[redacted]			
Median	25.82	3.57	53.18	33.16
Max				

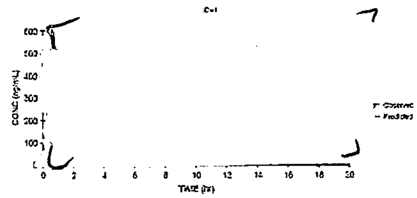
b(4)

b(4)

CV%	19.5	220.1	23.2	85.6
Geometric mean	26.92	3.50	48.11	15.94

The individual plasma concentrations of sildenafil after one administration of 20 mg (40-minute IV infusion) is shown below.

Figure 2: Individual observed plasma concentration-time data and model-predicted concentrations (from sponsor)



X vs. Observed Y and Predicted Y
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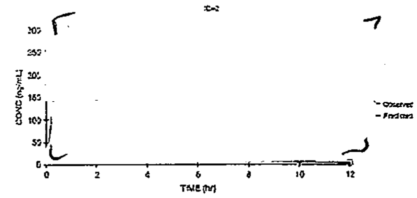

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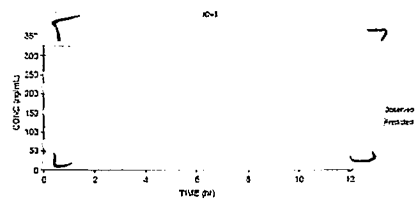

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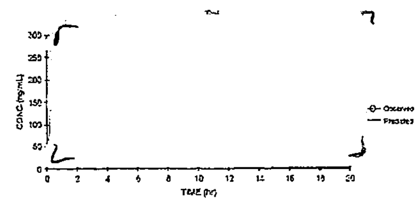

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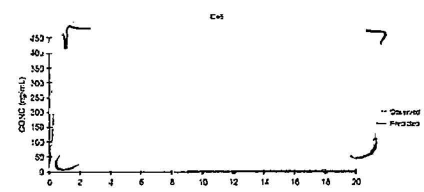

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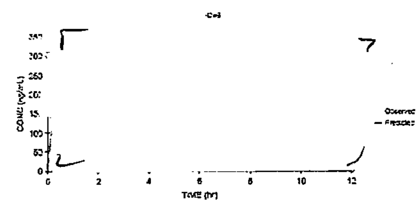

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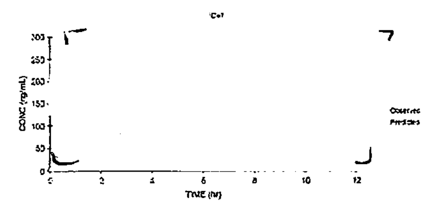

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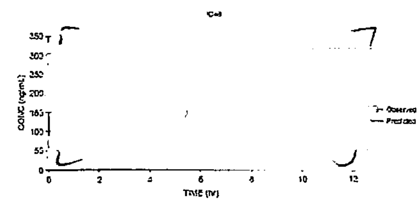

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The mean value of V1 was 49.4 L. Therefore, the mean Cmax after 10 mg of bolus sildenafil administration was predicted at 203 ng/mL.

Reviewer Comments

- The sildenafil parameter variability after the IV administration was ~23.2% and 19.5% for V1 and CL, respectively. The average projected Cmax in the healthy population was 203 ng/ml (range 155.8 to 297.8 ng/ml). Within the small sample size the projected range of Cmax covers a two-fold range of concentrations. As there is no safety concern at this concentration, this variability is not suspected to cause unwarranted effects.

- The two-compartment body model was appropriate for PK parameter estimation.

5.2 Pharmacometrics Review

Key Review Questions

The purpose of this review is to address the following key questions.

Does a 10 mg IV bolus dose of sildenafil provide an equivalent exposure to 20 mg PO dose?
The 10 mg IV bolus dose does not provide an equivalent exposure to 20 mg oral dose (PO) for the parent compound, sildenafil. From simulations, the Cmax observed after 10 mg IV administration is >2 fold higher that that from 20 mg PO. A 1.4-fold difference in AUC is observed between 10 mg IV and 20 mg PO, yielding exposures of 338.9 and 240.6 h*ng/ml, respectively. To achieve a similar plasma sildenafil exposure (AUC) to 20 mg PO, the required IV dose is 8 mg (assuming 40% bioavailability). To justify the use of a 10 mg IV dose, the sponsor includes active metabolite exposure into the dosing.

Is the strategy used to derive dosing recommendation, accounting for the active metabolite, appropriate for PAH patients?
Yes, the strategy accounting for active metabolite is acceptable. The strategy used for dosing recommendation matches total (parent + active metabolite) PDE5 inhibition after oral and IV administration. The circulating concentration of the major metabolite, UK-103,320, observed following IV administration is lower than for oral dosing (14.4% of parent vs. 54% of parent; taken from study 148-215). This active metabolite has been shown to have PDE5 inhibitory activity, with 50% of the potency of sildenafil.

Do the PK characteristics of sildenafil translate from healthy volunteers to PAH pateients?
Yes. External validation was performed with a population PK model (generated from healthy individuals), and compared to observed concentrations in PAH patients for the oral and IV formulations. The population model that accounts for 30% difference in clearance between healthy volunteer and PAH patients predicts exposures in PAH patients (by ~30%).

Is the dose of 10 mg TID appropriate for PAH patients?
Yes. The plasma concentrations of parent drug will be higher by 2.0 fold (Cmax) after the proposed IV dose compared to the approved oral dose. There is sufficient safety experience for sildenafil at exposures significantly higher than that of the proposed IV dose. The expected exposures after 10 mg IV bolus is much lower than that observed in both healthy volunteers and PAH patients receiving higher doses as an infusion or oral preparation, which were well tolerated.

Pharmacometrics analysis

Does a 10 mg IV bolus dose of sildenafil provide an equivalent exposure to 20 mg PO dose?
In order to evaluate an exposure comparison between 10 mg IV bolus and 20 mg PO administration, simulations were performed using the model generated by the sponsor (from healthy patients). Parameter estimate averages from the population model were used to simulate

both IV and PO and exposure metrics (i.e., Cmax and AUC) were calculated. The model was a 2-compartment model with first-order absorption and lag-time. F1 shows a dose dependency (expressed by a power model) and F2 (bioavailability after IV administration) is fixed at 1 when IV dosage is $\leq$ 20 mg. The parameters used for the simulations are denoted in the table below.

Table 3: Population parameter estimates used for simulation of 10 mg IV and 20 mg PO, single dose.

Parameter	Estimates (mean)	
	20 mg PO	10 mg IV
CL (L/h)	29.5	
Vc (L)	73.2	
Vp (L)	33.3	
Q (L/h)	5.32	
Ka (/h)	25.6	
Lag time (h)	0.485	0
Typical F1 (@ 20 mg)	0.355	1.0
F1 dose dependency	0.289	0.289

In addition, 8 mg IV dose was also simulated using the above parameters. The figure below represents concentration vs. time profiles, after a single dose of 20 mg PO, 10 mg IV and 8 mg IV sildenafil.

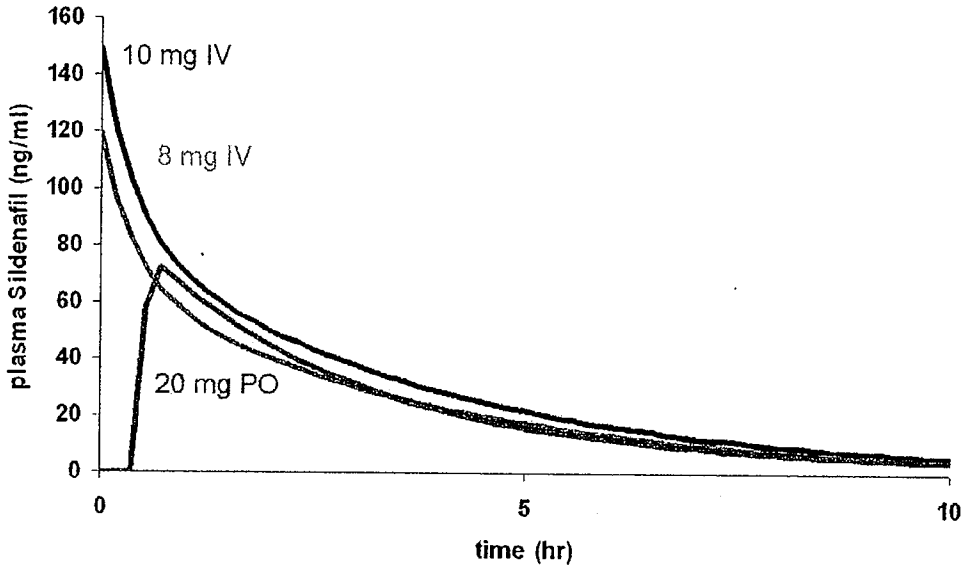


Figure 3: Simulated sildenafil concentration-time profiles for 20 mg PO, 10 mg IV, and 8 mg IV.

Table 4: Population predicted C_{max} and AUC following different PO and IV doses.

sildenafil	Cmax (ng/ml)	AUC (h*ng/ml)
20 mg PO	73.2	247.9
10 mg IV	149.3	338.9
8 mg IV	119.4	271.2

From the simulation, the Cmax observed after 10 mg IV administration is ~2.0 fold higher than 20 mg PO. A 1.4-fold difference in AUC is observed between 10 mg IV and 20 mg PO, yielding exposures of 338.9 and 247.9 h*ng/ml, respectively.. To achieve a similar 20 mg PO sildenafil exposure (AUC), the required IV dose is 8 mg (assuming a 40% bioavailability). To justify the use of a 10 mg IV dose, the sponsor includes active metabolite exposure into the dosing.

Is the strategy used to derive dosing recommendation, accounting for the active metabolite, appropriate for PAH patients?

Yes, the strategy accounting for active metabolite is acceptable. The strategy used for dosing recommendation matches total (parent + active metabolite) PDE5 inhibition after oral and IV administration. The circulating concentration of the major metabolite, UK-103,320, observed following IV administration is lower than for oral dosing (14.4% of parent vs. 54% of parent; taken from healthy patients in study 148-215). This active metabolite has been shown to have PDE5 inhibitory activity, with 50% of the potency of sildenafil.

In healthy volunteers, the circulating concentration of the major metabolite, UK-103,320, following IV administration is lower than for oral dosing. To obtain a relative IV sildenafil dose, the following calculation was performed:

$$\text{Relative IV sildenafil dose} = \frac{So(1 + Mo \bullet R \bullet Ur)}{Si(1 + Mi \bullet R \bullet Ur)}$$

where,
So = plasma sildenafil AUC following oral dose
Mo = (oral plasma UK-103,320 AUC) /So (=0.54)
Si = plasma sildenafil AUC following IV dose
Mi = (IV plasma UK-103,320 AUC)/Si (=0.144)
R = relative PDE5 inhibitory potency, UK-103,320/sildenafil (=0.5)
Ur = free fraction ratio UK-103,320/sildenafil (= 0.05/0.04 = 1.25)

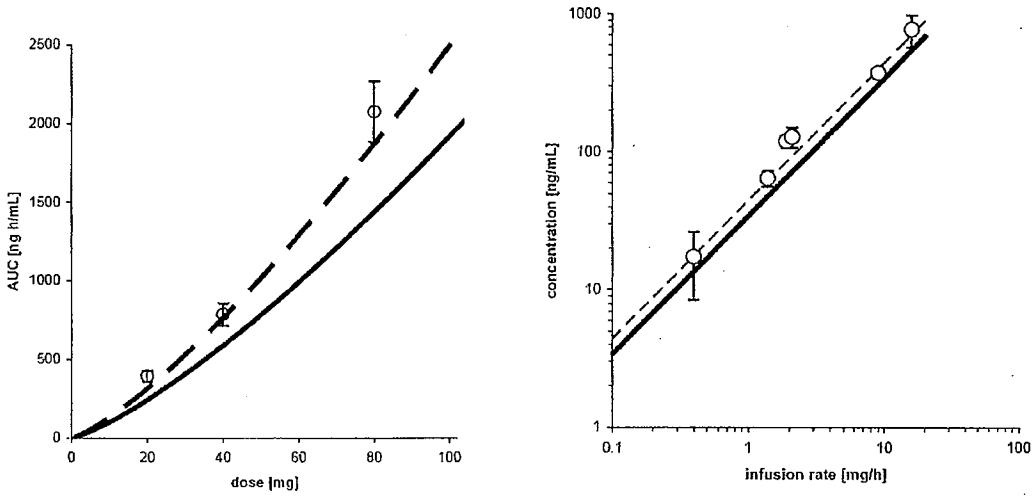
The oral/IV ratio for [sildenafil + UK-103,320] concentrations, adjusting for relative potency and protein binding, assuming the same dose administered by either route = 1.227 So/Si. In healthy volunteers, the So/Si ratio is reported to be 0.4. Therefore, the IV dose calculated to yield similar total plasma concentrations of [sildenafil + UK-103,320] for an oral 20 mg dose is 9.82 mg, rounded to 10 mg for clinical use.

In PAH patients, the ratio of metabolite to sildenafil plasma levels are, on average, 72% at steady state (using the approved 20 mg dose, from original Revatio® submission). The contribution of metabolite to the pharmacological effect of sildenafil would therefore increase to about 36%. Assuming *Mo* ~ 0.72 and *Mi* ~ 0.19 (*Mi* = 0.144 in healthy volunteers is changed by the factor of 1.3 (0.72/0.54) assuming similar shift in metabolite after IV administration), the IV dose calculated for PAH patients would be 10.4 mg to yield similar exposure of parent and metabolite.

The dosing required for PAH patients, using this approach, approximates dosing derived from healthy volunteer data (10.4 mg vs. 9.8 mg). This strategy used to derive the dosing recommendation is appropriate for dose selection in PAH patients.

Do the PK characteristics of sildenafil translate from healthy volunteers to PAH patients?

Yes. Sildenafil PK has been characterized and reviewed in the original Viagra® and Revatio® submissions. The lower clearance and/or a higher oral bioavailability of sildenafil in patients with PAH compared to healthy volunteers is known. External validation was performed with a population PK model using observed concentrations in PAH patients for the oral and IV formulations (see figure below). Study A1481140 (left plot) was a study involving PAH patients randomized to 20, 40, or 80 mg of oral sildenafil over a twelve-week period.



O: A1481140 O: A1481024

(the broken line shows 30% higher value from model prediction)

Figure 4: Comparison between Model Predicted AUC and Observed AUC (mean and 90% CI) in the Other PO Studies (left plot) and IV studies (PAH patients)

In the external validation, the population model consistently under predicts what is observed in PAH patients. Both plots suggest PAH patient have a lower systemic clearance of sildenafil compared to that of healthy patients. The population model that accounts for 30% difference in clearance between healthy volunteer and PAH patients predicts exposures in PAH patients (by ~30%). To further evaluate the comparison between healthy volunteers and PAH patients, population parameters are tabulated from three different population analyses below.

Table 5: Population parameters gained from three different population analyses with healthy volunteers and PAH patients.

Parameter (SE%)	Healthy Volunteers 148-203, 148-208, 148-211 (PO and IV)	PAH Patients 1140/1141* (PO)	PAH Patients 1024** (IV)
Number of observations	1479	1849	160
Subjects	45	337	62
CL (L/h)	29.5	*CL/F*= 55.1	CL = 24.7
IIV(CV%)	31.2	NA	24.4
Vc (L)	73.2	*V/F* = 352	
IIV(CV%)	28.8	61.2	
Vp (L)	33.3		
IIV(CV%)	55.6		
Q (L/h)	5.32		
IIV(CV%)	75.0		
Ka (/h)	25.6		
IIV(CV%)	155.6		
Lag time (h)	0.485		
Typical F1 (@20mg)	0.355		
IIV(CV%)	23.6		
F1 dose dep	0.289		
Residual Var (%)	30.3		

* Study 1140/1141 used a 1-cmpt model with zero-order abs, no lag-time and increased F after 80 mg TID

** Study 1024 used a R = Css* CL for the structural model where R= rate of administration, Css is conc at steady-state and CL is the total systemic clearance. Volume of distribution was not assessed.

Assuming a 40% bioavailability at 20 mg, study 1140/1141 (PO study) yields a total systemic clearance of 22.1 L/hr, which is comparable to that seen in study 1024 (IV). Upon comparison with healthy patients, the systemic clearance for 1140/1141 and 1024 is 33% and 19.4% lower than that observed is healthy patients, respectively. These results offer evidence to support 30% adjustment in CL for the external validation.

Is the dose of 10 mg TID appropriate for PAH patients?

Yes. The plasma concentrations (Cmax) of parent drug will be higher by ~2.0 fold after the proposed IV dose compared to the approved oral dose. Due to the short half life of both sildenafil and the active metabolite UK-103,320 (~4 hours for both) no accumulation of either sildenafil or its metabolites is expected during TID intravenous dosing. There is sufficient safety experience for sildenafil at exposures significantly higher than that being currently proposed of the approval of IV formulation.

The oral formulation of sildenafil has been studied to a maximum of 800 mg in healthy volunteers and 80 mg three times a day (TID) in patients with PAH. Single oral doses of up to 800 mg have been tolerated by healthy volunteers where the average maximum concentration (C_{max}) achieved was 5834 ng/mL. The IV formulation as a single dose has been studied up to the 80 mg dose level in healthy volunteers and 40 mg as a single dose in patients with ischemic heart disease with no significant or unexpected adverse events.

The predicted upper 90% prediction interval of C_{max} for the commercial 10 mg IV bolus does not exceed 300 ng/mL. Therefore, the C_{max} after 10 mg IV bolus is much lower than concentrations observed in healthy volunteers and PAH patients receiving higher doses as an infusion or an oral preparation, which were well tolerated.

In study A1481140, PAH subjects were randomized to 20, 40, or 80mg oral doses TID over 12-weeks. In patients receiving 80 mg TID, the mean Cmax was ~ 1.5 fold higher than the upper 90% prediction interval of C_{max} for the 10 mg IV bolus (300 ng/mL). The mean Cmax after 20 and 80 mg TID PO were, 81.4 (range 33.3-182.2 ng/ml) and 439.5 (range 73.0 – 803.6 ng/ml). In study A1481024, 32 subjects achieved concentrations above 300 ng/mL after intravenous infusion, without significant or unexpected adverse events.

In addition, based on previous experience for sildenafil in patients with PAH, the efficacy is expected to be similar between 20 mg PO and the proposed 10 mg IV administration. Pharmacokinetic modeling of the available data and accounting for active metabolite has predicted that 10 mg IV sildenafil will provide the same level of PDE5 inhibition as 20 mg PO.

5.3 DDI Interaction Simulations with SimCYP®

Clinical Pharmacology and Biopharmaceutics NDA Review

Brand name: REVATIO Injection
Generic name: Sildenafil citrate
Type of dosage form and strength(s): 10 mg intravenous bolus injection three times a day
Indication(s): Indicated for the treatment of pulmonary arterial hypertension (WHO Group I) to improve exercise ability and delay clinical worsening.
NDA number, type: NDA 22-473
Applicant name: Pfizer Inc.
Submission date (letter date): Dec 16, 2008

Submission: Results of the study *"Study DM41: Simulation of CYP3A4 Inhibition on the Pharmacokinetics of PO and IV Sildenafil"*

OCP Division name:	Division of Clinical Pharmacology I
OND: Division name:	Division of Cardiovascular and Renal Products
OCP Reviewer name:	Ping Zhao, Ph.D.

Executive Summary

The current submission compared the relative extent of interaction with strong CYP3A inhibitors between intravenously administered (IV) and orally administered (PO) sildenafil using physiologically-based pharmacokinetic (PBPK) simulations. The sponsor concluded that the magnitude of sildenafil AUC change was markedly reduced when drug was given by the IV route compared with the PO route (Predicted AUCR with co-administration of ritonavir 3.5 and 9.8, respectively; observed AUCR was 11 for PO sildenafil).

The Office of Clinical Pharmacology has reviewed this information along with additional simulations and finds the sponsor's conclusions and labeling changes acceptable from a qualitative point of view.

Question-based Review:

1. Can physiologically-based pharmacokinetic (PBPK) modeling be used to predict the relative extent of interaction with strong CYP3A inhibitors between intravenously administered and orally administered sildenafil?

The current submission evaluated the relative extent of interaction with strong CYP3A inhibitors between intravenously administered (IV) and orally administered (PO) sildenafil using physiologically-based pharmacokinetic (PBPK) simulations. The key findings were as follows: The sponsor developed a PBPK model for sildenafil. The model was used to simulate pharmacokinetics of sildenafil after IV or PO administrations in the presence and in the absence of CYP3A4 inhibitors. Simulations of sildenafil pharmacokinetics and the degree of drug

interaction measured by AUC ratio (with and without co-administration of inhibitor, AUCR) were comparable to those observed in *in vivo* studies. The sponsor concluded that the magnitude of sildenafil AUC change was markedly reduced when drug was given by the IV route compared with the PO route (Predicted AUCR with co-administration of ritonavir 3.5 and 9.8, respectively; observed AUCR was 11 for PO sildenafil, Muirhead, Br. J Clin Pharmacol, 2000).

The reviewer performed PBPK simulations (SimCYP® version 8.2, SP2) using parameters estimated and reported in the submission for sildenafil (report table 1). The ritonavir data were provided by the sponsor on Aug 6, 2009. Table 1 shows that the simulations performed by the FDA reviewer agree with those performed by the sponsor. The FDA reviewer's Simulation predicted a lower magnitude of inhibition by co-administration of strong CYP3A inhibitor (e.g. ritonavir) with IV sildenafil than with PO sildenafil (AUCR of 2.7 and 7.2-9.6, respectively).

Table 6: PBPK simulations of sildenafil-ritonavir drug interactions

Simulation	sildenafil	Ritonavir	Number of Trials	Median AUCR	AUCR 5% CI	AUCR 95% CI
FDA	PO 100 mg on day 3	500 mg BID 7 days	3 (n=10/trial)	8.8	3.7	20.3
FDA	PO 100 mg on day 3	500 mg BID 7 days	10 (n=10/trial)	7.2	3.4	19.1
FDA	IV 100 mg on day 3	500 mg BID 7 days	3 (n=10/trial)	2.7	1.5	5.5
FDA	IV 100 mg on day 3	500 mg BID 7 days	10 (n=10/trial)	2.7	1.5	5.1
FDA	PO 100 mg on day 6	ref (2)	10 (n=10/trial)	9.6	3.0	29.4
Sponsor	PO 100 mg on day 3	500 mg BID 7 days	3 (n=10/trial)	9.8	4.1	30.0
Sponsor	IV 100 mg on day 3	500 mg BID 7 days	3 (n=10/trial)	3.5	2.1	6.4

(1). According to sponsor's data generated in SimCYP Version 7. Ritonavir does not have induction effect.
(2). Muirhead GJ, BJCP, 2000. RTV 300 mg BID on day 1, 400 mg BID on day 2, and 500 mg BID on day 3-7. Sildenafil on day 6/7

Decreased inhibition potential by strong CYP3A inhibitor for IV administration as compared to oral has been observed for other CYP3A substrates that undergo first-pass metabolism. For example, Table 2 shows that for midazolam, a sensitive CYP3A substrate with gut and hepatic first pass metabolism, a lower magnitude of inhibition by co-administration of a strong CYP3A inhibitor with IV midazolam than with PO midazolam was observed (AUCR of 2.7 and 7.0, respectively with clarithromycin; AUCR of 3.4-4.2 and 11.0-15.0, respectively with 200-400 mg ketoconazole). In addition to decreasing systemic clearance of a CYP3A substrate (CL_{iv}), an inhibitor can increase the bioavailability in both liver and small intestine (F_g and F_h).

Accordingly, one can expect a lower AUCR when IV sildenafil is co-administered with a strong CYP3A inhibitor than after oral administration.

Table 7: Summary of PK parameters of midazolam and sildenafil with and without co-administration of CYP3A inhibitor

	PK parameters				AUCR (+/- Inhibitor)		Ref
	CL_{iv}	F_{oral}	F_g	F_h	PO	IV	
Midazolam	27.8	0.31	0.42	0.74	-	-	Gorski, 2005 (1)
Midazolam+clarithromycin	10.1	0.75	0.83	0.90	7.0	2.7	Gorski, 2005
Midazolam+ketoconazole (200mg)	-	-	-	-	11.0	3.4	Lucksiri, 2005 (2)
Midazolam+ketoconazole (400mg)	-	-	-	-	15.0	4.2	Lucksiri, 2005
Sildenafil	40.8	0.38	0.69	0.55	NA	-	Muirhead, 2002a (3)
Sidenafil+ritonavir	-	-	-	-	11	-	Muirhead, 2000 (4)
Sildenafil+saquinavir	-	-	-	-	3.1	-	Muirhead, 2000
Sidenafil+erythromycin	-	-	-	-	2.6	-	Muirhead, 2002b (5)

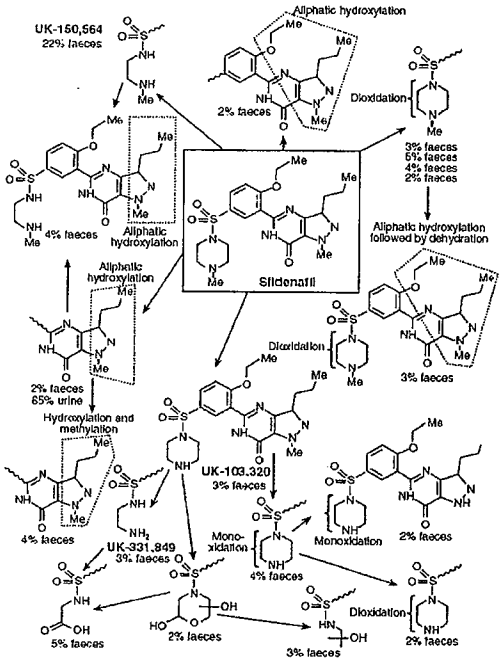
(1). Gorski 2005: IV and PO midazolam was given before and on day 7 of oral clarithromycin (500 mg BID day 1-7)
(2). Lucksiri 2005: IV and PO midazolam was given before and during 7-day oral ketoconazole (200 or 400 mg QD, IV midazolam on day 6, PO midazolam on day 7)
(3). Muirhead 2002(a):IV sidenafil 25 mg; PO sidenafil 50 mg. Blood pharmacokinetic parameters were calculated. Complete absorption and predominant liver metabolism after IV administration were assumed.
(4). Muirhead, 2000: PO sildenafil before and on day 6/7 of BID oral ritonavir (300 mg BID on day 1, 400 mg BID on day 2, and 500 mg BID on day 3-7), or PO sildenafil before and on day 6/7 of oral saquinavir (1200 mg TID)
(5). Muirhead, 2002(b): PO sildenafil before and on day 5 of BID oral erythromycin (500 mg)

In conclusion, the PBPK model was able to predict a lower magnitude of interaction with strong CYP3A inhibitors for IV sildenafil than for PO sildenafil.

2. What are limitations of the current PBPK model?

Two critical areas need to be considered.

First, *in vitro* parameters (CL'_{int}) of the formation of UK-103,320 were used to extrapolate the *in vivo* clearance of sildenafil, of which CYP3A4 and CYP2C9 were responsible for ~80% and ~20%, respectively (Sponsor's supporting document). Although comparable *in vivo* clearance was simulated, extrapolation using one pathway may be limited in its utility (see figure below, Muirhead, Br. J Clin Pharmacol, 2002). UK-103,320 is an active metabolite and its pharmacokinetics has been assessed in several pharmacokinetic and drug interaction studies (references in Table 1). If the formation of UK-103,320 is not the predominant route of sildenafil elimination, the current PBPK model will over predict the formation rate of this metabolite. In addition, if the formation of other primary metabolites are mainly contributed by CYP3A (e.g. >90%), the overall contribution of CYP3A for sildenafil elimination may actually be higher than 80% as used in this model, which was based only on UK-103,420 formation.



Second, ritonavir compound profile did not consider concurrent induction of CYP3A. If induction of CYP3A4 by multiple dose of ritonavir contributed significantly in addition to strong CYP3A inhibition, accurate prediction of drug interaction by ritonavir for IV sildenafil can be more complicated than the current model, which included only inhibition (Table 2).

Minor comments:

Sponsor used PBPK distribution module for IV PK study, whereas for the other scenarios, a one-compartment distribution model is used. In addition, sponsor has used MW 666.7 in all simulations, whereas the value of 474.3 was reported in the report table 1. These did not seem to impact PBPK simulations.

In summary, if the quantitative fold change caused by ritonavir is to be confirmed using PBPK simulations, the sponsors should further define metabolic pathways for sildenafil. In addition, the sponsor may consider using ritonavir profile with CYP3A induction built-in to investigate the impact of concurrent inhibition/induction on drug interaction potential by ritonavir.

Comments to the Division of Cardiovascular and Renal Products Project Manager

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 1 has reviewed the information contained in this submission (Report DM41). The additional comments in section 1.1 need to be sent to the applicant.

5.4 Results of Sponsor's Population PK Analysis

a148203-a148208-a148211: POPULATION PHARMACOKINETICS ANALYSIS AND SIMULATION AFTER ORAL AND INTRAVENOUS SILDENAFIL ADMINISTRATION

Sponsor: Pfizer, Inc.
Report: a148203-a148208-a148211-clin pk report
Protocol number: 148-203, 148-208, 148-211 (all used for population analysis)
Phase of Development: Phase I

Objective: The investigation was designed to build a model to describe sildenafil PK following IV and PO administration in healthy volunteers. This information was then utilized to understand the PK profile of sildenafil in healthy volunteers in comparison to PAH patients. Ultimately, the model was used to simulate sildenafil PK profile after IV (10 mg) and PO administration (20 mg) to achieve similar exposure.

Data: Data from 3 studies (148-203, 148-208 and 148-211) were pooled for the population PK analysis. These studies were an IV study, an IV/PO cross over study and a PO study with healthy volunteers. Internal validation was performed using diagnostic plots and visual predictive checks. External validations were also performed using data obtained from with the other studies in healthy volunteers and patients with PAH. The studies that were used for the analysis are supplied in the table below.

Table 8: Summary of studies used for the population PK analysis.

Study title and design (N)	Dose	Endpoints
Study 148-203 – Phase 1, single-blind, placebo-controlled, 4-way cross-over, escalating IV doses (8 healthy volunteers)	IV: 20, 40, 80 mg in 80mL infusion at 2 ml/min	PK/PD parameters
Study 148-208 – Phase 1, open, randomized, 2-way cross-over to investigate pharmacokinetics after oral and IV single dose (12 healthy volunteers)	IV: 50 mL infusion given at 1/mg/mL/min, Oral: 50 mg (2 x 25 mg capsules)	PK and safety parameters
Study 148-211 – Phase 1, double-blind, randomized study to investigate PK/PD/safety after 8 day multiple dose (24 healthy volunteers)	Oral: 40 mg TID, 20 mg six times a day or placebo.	PK/PD, tolerability and safety

Modeling strategy: Visual inspection of the data suggested bi-phasic elimination after intravenous sildenafil administration, based on Study 203. A two-compartment model with first-order absorption (subroutine ADVAN4 TRANS4) was used for the fitting. The estimated PK parameters were CL (clearance), V1 (central volume), Q (intercompartmental clearance), V2

(peripheral volume), F1 (oral bioavailability) and lag-time. The F2 (bioavailability after IV administration) is fixed at 1 when IV dosage is 20 mg but allowed an empirical dose dependency using a power model. Regarding PO, F2 does not influence the time course after oral administration. FOCEI was used to estimate all the parameters. The inter-individual variability in the pharmacokinetic parameters was modeled using multiplicative exponential random effects. The within-subject variability was modeled with an additive error on the log-transformed concentration. Residual variability was modeled using the log-transformed error model. To select the final model, the difference in the objective function (-2LL) was used, and a difference over 7.879 with one degree of freedom was used as being statistically significant ($p<0.005$). The dose dependency on F was described using a power model.

Goodness of Fit: Goodness of fit of the final model to the data was evaluated using visual inspection of diagnostic plots and precision of the parameter estimates. For each dose and dose route, the Visual Predictive Check was performed. Based on the final model results, the time courses of the virtual 1000 subjects were generated, and 90% CI was calculated. This 90% CI and the observed values were plotted together to assess the model's predictive performance. External validation of the model was performed by calculation of AUC or concentrations based on the final model PK parameters and compared with the observed values in healthy volunteers, and modeled values with PAH patients.

Results: For the population analysis, the total number of subjects was 45 with a total of 1479 available plasma concentration values. The final model was a 2-compartment model with first-order absorption with lag-time F1 showing a dose dependency and expressed by a power model. The F2 (bioavailability after IV administration) is fixed at 1 when IV dosage is 20 mg but allowed dose dependency. Regarding PK profile after PO, the F2 does not influence on anything. The PK parameter estimates for the final model are given in the table below (Mean and 95%CI).

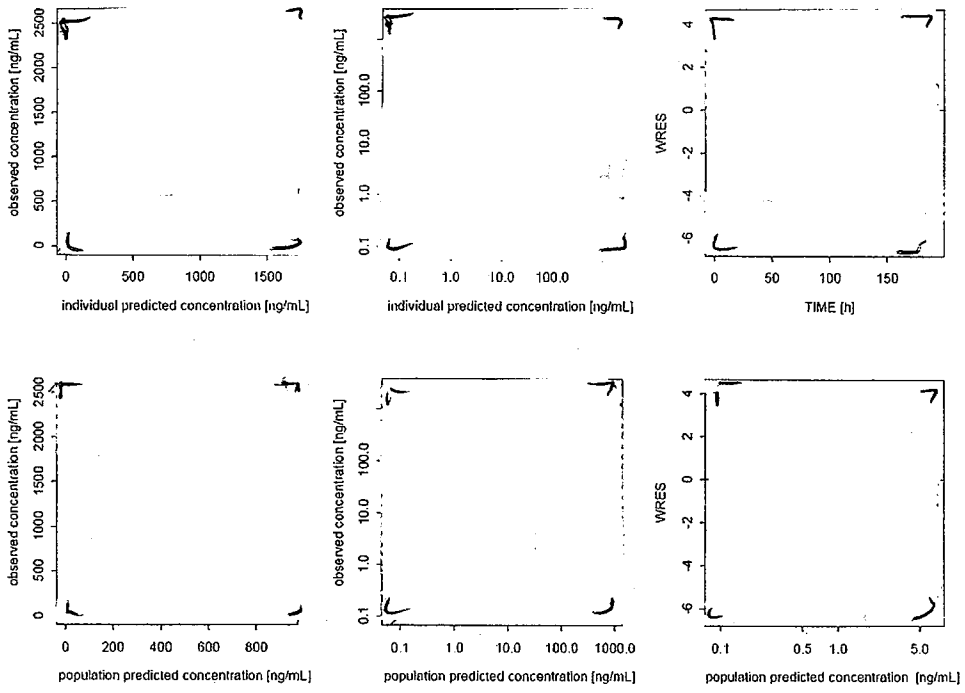
Table 9: Pharmacokinetic Parameter Estimates (Mean and 95%CI) for Final Model

OFV=-1404.042 (run 6)		
Parameters	mean	95%CI
CL (L/h)	29.5	(24.5-34.5)
IIV(CV%)	31.2	(22.4-38.0)
V_C (L)	73.2	(61.0-85.4)
IIV(CV%)	28.8	(20.3-35.3)
V_P (L)	33.3	(22.8-43.8)
IIV(CV%)	55.6	(36.2-69.8)
Q (L/h)	5.32	(3.49-7.15)
IIV(CV%)	75.0	(52.2-92.3)
Ka (/h)	25.6	(9.5-41.7)
IIV(CV%)	155.6	(101.7-195.2)
Lag-time (h)	0.485	(0.478-0.492)
Typical F1 (at 20 mg)	0.355	(0.295-0.415)
IIV(CV%)	23.6	(14.1-30.3)
F1 dose dependency	0.289	(0.107-0.471)
Residual Variability (%)	30.3	(28.3-32.2)

With this model, F1 = 0.355*(Dose/20)$^{0.289}$. The BA does not change after IV among dose range between 20 mg and 80 mg. Based on these results, the sponsors conclude:

- The typical clearance value in healthy volunteers was estimated at 29.5 L/h and the IIV was estimated at 31.2 CV%.
- The clearance after IV administration did not show a significant deviation from linearity after the range of doses given, therefore the observed non-linear increase in exposure after PO administration is likely to be linked to a non-linear absorption or first pass process (captured through the empirical power model in the fit).
- The almost half hour of lag-time was highly significant and the very rapid absorption was estimated, i.e. Ka was 25.6/h (95%CI: 9.5-41.7).
- The typical Vc and Vp were estimated at 73.2 (95%CI: 61.0-85.4) and 33.3 L (95%CI: 22.8-43.8), respectively.
- Based on the obtained values above, the bioavailability at 50 mg PO was calculated as 46% (= 0.355*(50/20)$^{0.289}$) and are inline with the actually observed BA value (~41%).

Diagnostic Plots: The sponsor's diagnostic plots along with the model predicted distributions for the PK parameters are shown in the figures below. In addition, the observed and model predicted individual time courses are shown. As a result, a good model fit was suggested from these diagnostic plots.



b(4)

b(4)

Figure 5: Sponsor diagnostic plots

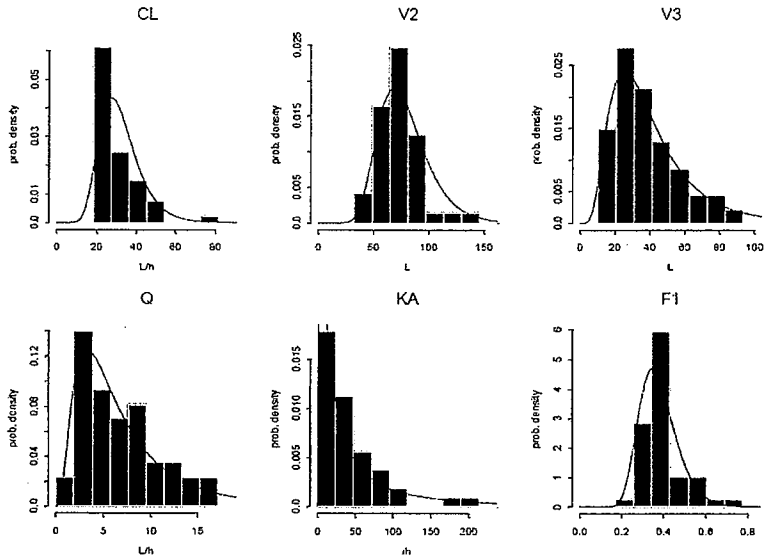
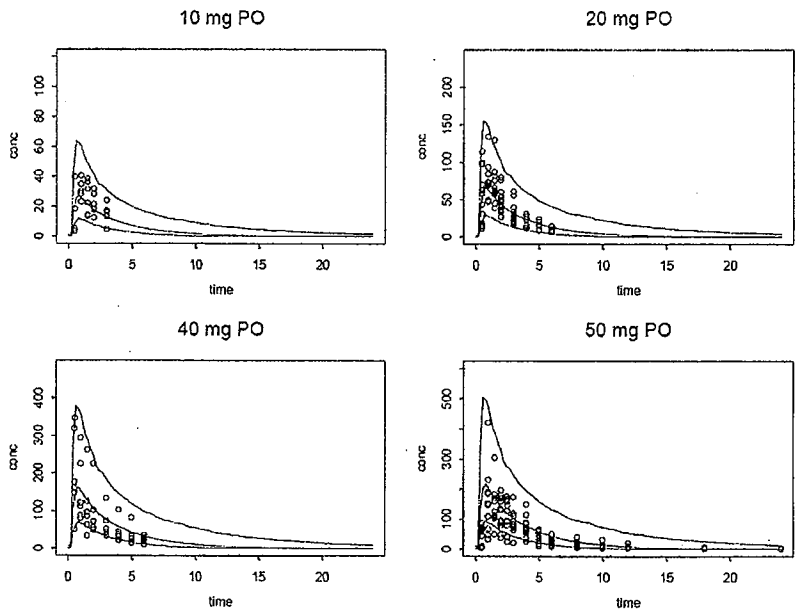


Figure 6: Model Predicted Distributions for each PK parameter (Sponsors)



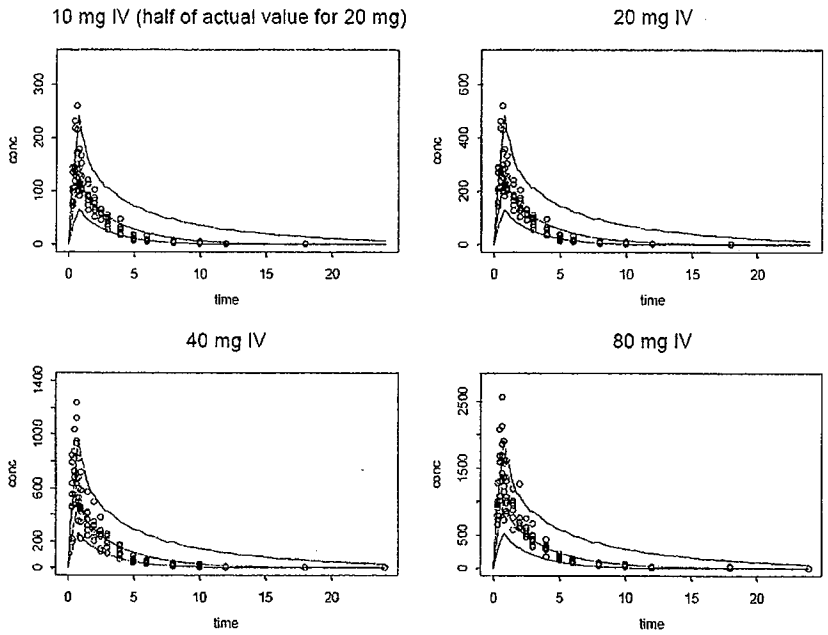


Figure 7: Visual Predictive Check for PO and IV Sildenafil (90% CI and the observed data from Study 203, 208 and 211)

External Validation (healthy patients): The observed AUC after single PO dose in the two additional studies, 148-207 and 148-228 (healthy patients), were compared with the model prediction. The results are shown in the figures below. Lower than 80 mg, the prediction fits to the observed values in these studies. This model was built through the dose ranges of 10 to 50 mg PO and 20 to 80 IV. After PO administration, dose over-proportional increase in AUC is observed lower than 50 mg. This model cannot predict the AUC after PO administration for doses over 50 mg. The observed AUC after single IV dose in the other studies, 148-215 was compared with the model prediction. The data are limited but the model prediction of clearance after IV dose was confirmed.

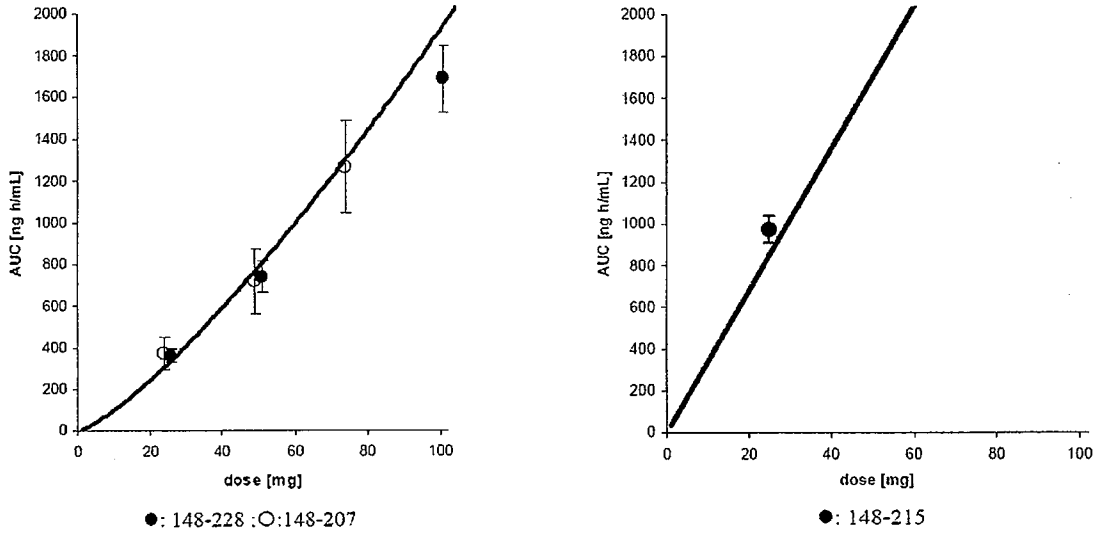
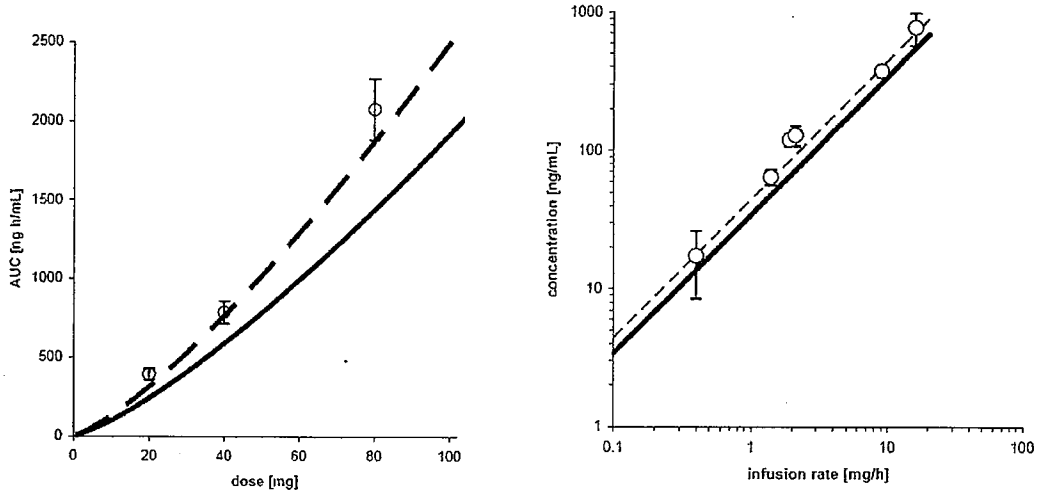


Figure 8: Comparison between Model Predicted AUC and Observed AUC (mean and 90% CI) in the Other PO Studies (left plot) and IV studies (healthy patients)

External Validation (PAH patients): The AUC after single PO and IV dose in PAH patients were calculated from the model analysis results for Study 1140 (PO) and study 1024 (IV). The results are shown in the figures below. These results show some extend of discrepancy and the exposure after PO administration in PAH patients seems 30% higher than the healthy volunteers (the clearance is 30% lower than that of healthy volunteers). Results show a good fitting to the prediction from this analysis. In addition, the nonlinearity of PK after IV administration is suggested to be very limited, i.e. the disposition of sildenafil is effectively linear over a wider range of doses.



O: A1481140 O: A1481024

(the broken line shows 30% higher value from model prediction)

Figure 9: Comparison between Model Predicted AUC and Observed AUC (mean and 90% CI) in the Other PO Studies (left plot) and IV studies (PAH patients)

Simulation after IV Bolus: The time courses of plasma sildenafil concentration were simulated for 10 mg IV bolus vs. 20 mg PO, and the results are shown in the figure below.

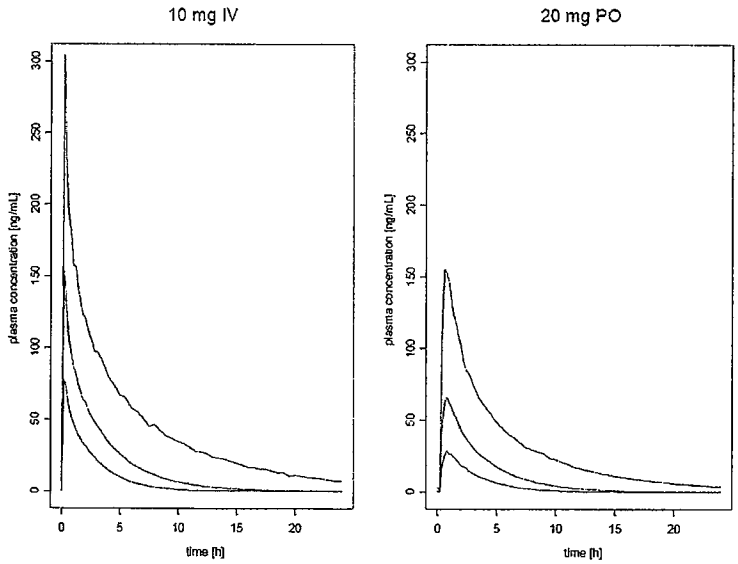


Figure 10: Comparison of Mean Sildenafil Plasma Concentrations (Plus 90% Prediction Intervals) in Healthy Volunteers for 10 mg IV bolus vs. 20 mg Oral

Discussion and Conclusion: In this analysis, the population PK analysis was performed with the data from 3 healthy volunteers' studies. All diagnostic plots and visual predictive check suggested this model showing a good fit to the observed values. The bioavailability increases through the dose escalation. The external validation showed the PK properties are consistent across number of studies in healthy volunteers. However, the exposure in PAH patients after PO and IV administration is approximately 30% higher than healthy volunteers. In this report, the time course of sildenafil plasma concentration after a bolus administration was simulated.

5.5 Reviewer's Population PK Analysis

Introduction

The reviewer reproduced the population analysis conducted by the sponsor to corroborate results and conclusions gained from the analysis.

Objectives
The objectives for reviewer's analysis are described below:

1. To estimate population PK parameters for the analyzed studies.

Methods

5.5.1 Data Sets

Data sets used are summarized in the table below.

Table :Analysis Data Sets

Study Number	Name	Link to EDR
148-203, 148-208, 148-211	473.csv	\\Cdsesub1\EVSPROD\NDA022473\0002\m5\datasets
	run473.ctl	

5.5.2 Software

NONMEM with PsN and S-PLUS were used for reviewer's analysis.

5.5.3 Models

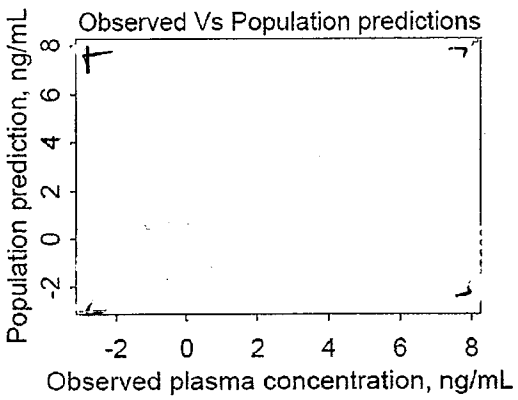
A two-compartment disposition model with first-order absorption (with lag time) and elimination was used to describe the sildenafil concentration-time profile following IV and PO administration (ADVAN 4 TRANS4 subroutine)

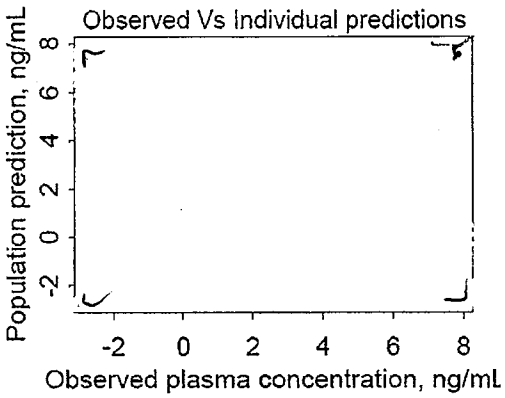
5.5.4 Results

The results of the reproduced population analysis are presented below.

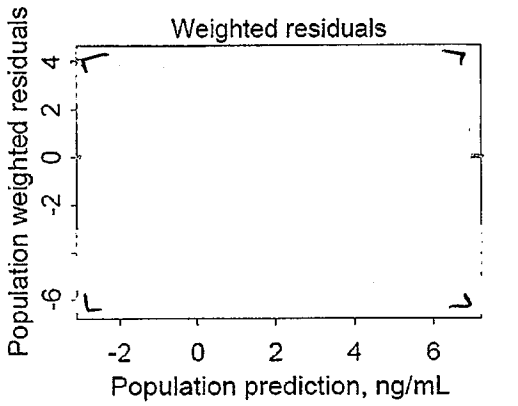
Table 10: Parameter comparison of sponsor and reviewer population PK analysis

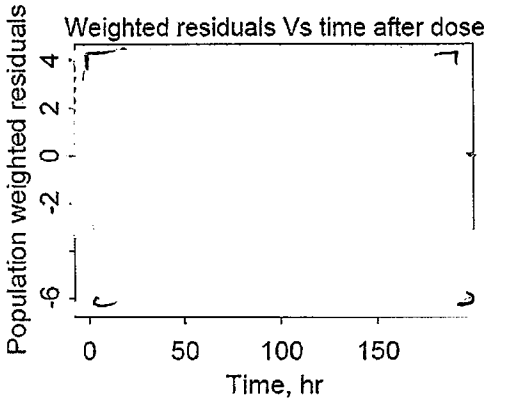
Parameter (SE%)	Sponsor		Reviewer	
	Mean	95% CI	Mean	95% CI
Number of observations	1479			
Subjects	45			
OFV	-1404.042		-1405.094	
CL/F (L/h)	29.5	(24.5-34.5)	29.5	(24.5 – 34.5)
IIV(CV%)	31.2	(22.4 – 38.0)	31.2	(22.4 – 38.0)
Vc (L)	73.2	(61.0-85.4)	73.1	(60.8 – 85.4)
IIV(CV%)	28.8	(20.3 – 35.3)	28.9	(20.5 – 35.7)
Vp (L)	33.3	(22.8 – 43.8)	33.3	(22.9 – 43.7)
IIV(CV%)	55.6	(36.2 – 69.8)	55.0	(35.9 – 68.2)
Q (L/h)	5.32	(3.49 – 7.15)	5.34	(3.52 – 7.16)
IIV(CV%)	75.0	(52.2 – 92.3)	74.6	(51.4 – 91.2)
Ka (/h)	25.6	(9.5 – 41.7)	25.6	(9.4 – 41.7)
IIV(CV%)	155.6	(101.7 – 195.2)	155.6	(101.7 – 195.2)
Lag time (h)	0.485	(0.478 – 0.492)	0.485	(0.478 – 0.492)
Typical F1 (@20mg)	0.355	(0.295 – 0.415)	0.355	(0.294 – 0.416)
IIV(CV%)	23.6	(14.1 – 30.3)	23.7	(14.2 – 30.5)
F1 dose dep	0.289	(0.107 – 0.471)	0.289	(0.104 – 0.474)
Residual Var (%)	30.3	(28.3 – 32.2)	30.3	(28.3 – 32.2)


Observed Vs Population predictions
Population prediction, ng/mL
-2
0
2
4
6
8
Observed plasma concentration, ng/mL

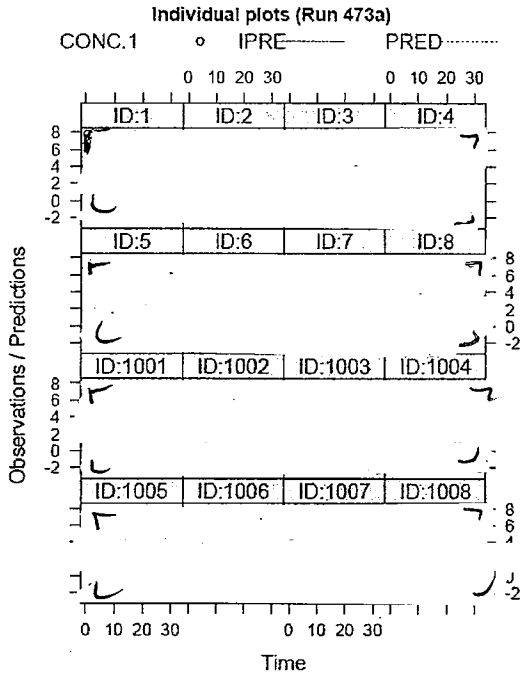

Observed Vs Individual predictions
Population prediction, ng/mL
-2
0
2
4
6
8
Observed plasma concentration, ng/mL

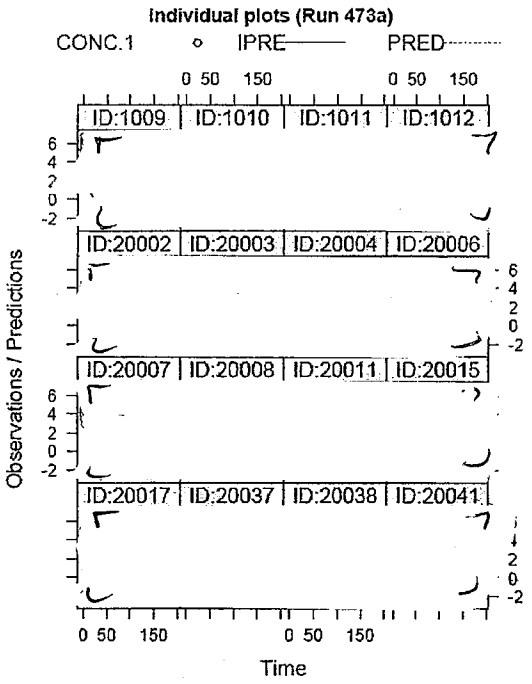
b(4)


Weighted residuals
Population weighted residuals
-6
-2
0
2
4
-2
0
2
4
6
Population prediction, ng/mL

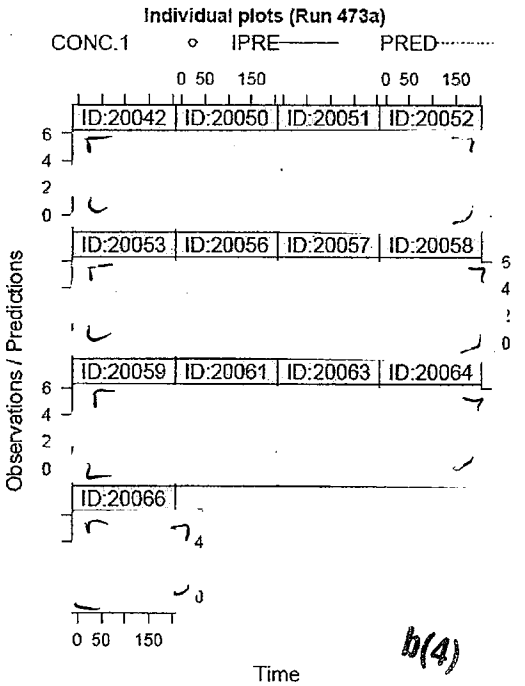

Weighted residuals Vs time after dose
Population weighted residuals
-6
-2
0
2
4
0
50
100
150
Time, hr

b(4)


Individual plots (Run 473a)
CONC.1 IPRE PRED
ID:1 ID:2 ID:3 ID:4
ID:5 ID:6 ID:7 ID:8
ID:1001 ID:1002 ID:1003 ID:1004
ID:1005 ID:1006 ID:1007 ID:1008
Observations / Predictions
Time


Individual plots (Run 473a)
CONC.1 IPRE PRED
ID:1009 ID:1010 ID:1011 ID:1012
ID:20002 ID:20003 ID:20004 ID:20006
ID:20007 ID:20008 ID:20011 ID:20015
ID:20017 ID:20037 ID:20038 ID:20041
Observations / Predictions
Time

b(4)


Individual plots (Run 473a)
CONC.1 IPRE PRED
ID:20042 ID:20050 ID:20051 ID:20052
ID:20053 ID:20056 ID:20057 ID:20058
ID:20059 ID:20061 ID:20063 ID:20064
ID:20066
Observations / Predictions
Time

b(4)

b(4)

5.6 APPENDIX III: OCP Filing Review Form

Office of Clinical Pharmacology
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	22-473	Brand Name	Revatio® for Injection
OCP Division (I, II, III)	DIV-1	Generic Name	Sildenafil citrate
Medical Division	Cardiovascular-Renal	Drug Class	PDE-5 Inhibitor
OCP Reviewer	Satjit Brar	Indication(s)	For patients with pulmonary hypertension who are unable to take oral sildenafil therapy
OCP Team Leader	Rajanikanth Madabushi	Dosage Form	Solution for intravenous bolus
		Dosing Regimen	10 mg TID
Date of Submission		Route of Administration	IV infusion
Estimated Due Date of OCP Review		Sponsor	Pfizer Inc.
PDUFA Due Date		Priority Classification	
Division Due Date			

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:				
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 -				
solution as reference:				
alternate formulation as reference:	X			
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				
Electrophysiology Study				
PK Simulated Data	X	1	1	
Total Number of Studies Reviewed				

Filability and QBR comments		
	"X" if yes	Comments
Application filable ?	X	
Comments sent to firm ?		
QBR questions (key issues to be considered)		
Other comments or information not included above		
Primary reviewer Signature and Date	DPM: Satjit Brar, Pharm.D., Ph.D. Date: Date:	
Secondary reviewer Signature and Date	DCP1 Team Leader: Rajanikanth Madabushi, Ph.D. Date: DPM Team Leader: Pravin Jadhav, Ph.D. Date:	

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22473	ORIG-1	PFIZER INC	REVATIO

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

/s/

PRAVIN R JADHAV
10/16/2009
The primary Clinical Pharmacology Reviewer for this application was Dr. Satjit Brar, PharmD, PhD.

PING ZHAO
10/16/2009

RAJANIKANTH MADABUSHI
10/16/2009