

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203109Orig1s000

CHEMISTRY REVIEW(S)

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: August 29, 2012

TO: File

THROUGH: Ramesh K. Sood, Ph.D., Branch Chief, ONDQA

FROM: Mohan K. Sapru, Ph.D., Sr. Regulatory Review Chemist, ONDQA

SUBJECT: Chemistry, Manufacturing and Controls (CMC) Approval Recommendation for Use of Proposed Modified Oral Dosing Syringe for Dispensing Sildenafil Suspension (NDA 203-109)

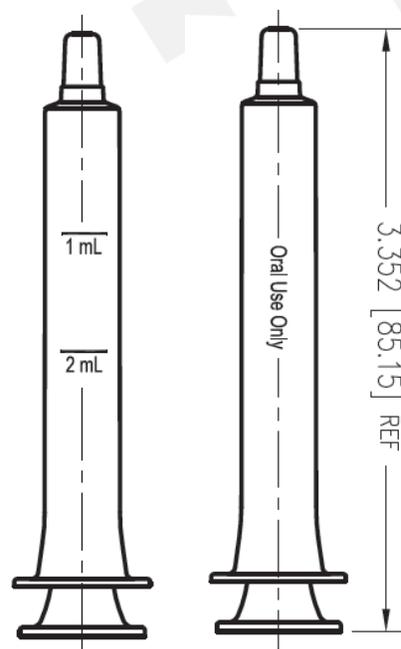
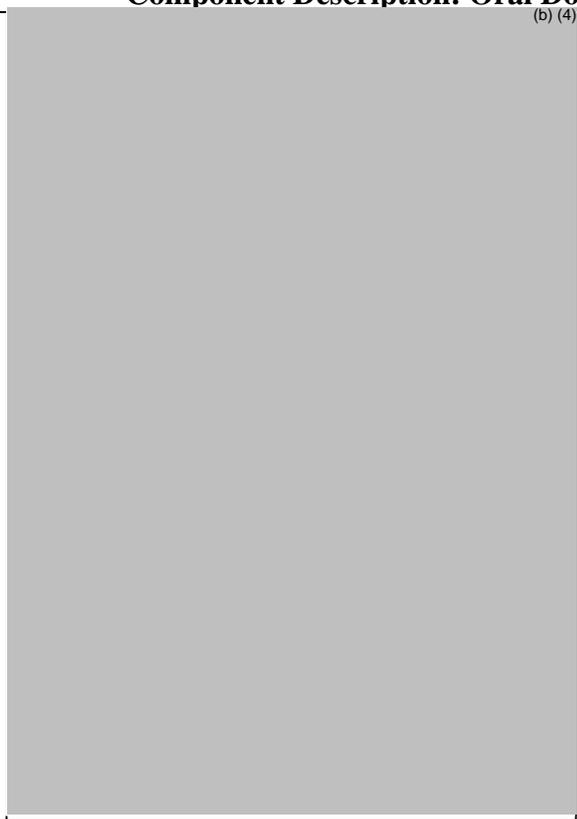
Following the previous CMC approval recommendation for the NDA 203-109 (Sildenafil for Oral Suspension), the applicant, Pfizer, Inc., in response to concerns raised by DMEPA pertaining to syringe barrel markings, has proposed to use modified oral dosing syringe with altered markings. Specifically, the originally proposed syringe (referred to as original syringe with product code (b)(4)) in addition to (b)(4) and (b)(4) markings had the (b)(4) statement printed on the syringe barrel. To avoid the possibility of (b)(4) statement giving the wrong impression that the syringe can be used for (b)(4) and avoid possible dosing errors due to (b)(4) and (b)(4) markings, DMEPA advised the applicant to change syringe barrel markings. The applicant agreed to make the recommended changes and proposed the use of modified oral dosing syringe (referred to as modified syringe with product code (b)(4)). From CMC perspective, the details concerning original syringe have been previously reviewed and found to be adequate (see CMC review for NDA 203-109). To review the CMC aspects concerning modified syringe, the applicant was asked to submit a side-by-side comparative CMC details concerning the original and the modified syringes, which are tabulated below.

Table 3.2.P.7.1-1. Associated Component Description: Oral Dosing Syringe Comparison of Initial Syringe and Proposed Modified Syringe:

Component Description: Oral Dosing Syringe		
Submission Date	November 2011	May 2012 (with FDA requested changes)
Product Code	(b)(4)	
Color	Barrel: Natural Plunger: White	Barrel: Natural Plunger: White
Materials of Construction	(b)(4)	
Manufacturer	(b)(4)	
DMF References	(b)(4)	

Component Description: Oral Dosing Syringe

Drawing
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ILLUSTRATIVE
PURPOSES
ONLY



As is clearly indicated in Table 3.2.P.7.1-2, with the exception of changes in barrel markings, there is no difference between the original oral dosing syringe (product code (b) (4)) and the proposed modified oral dosing syringe (product code (b) (4)) with regard to color, materials of construction, manufacturer of syringe barrel and plunger, and DMF references. Specifically, the applicant has agreed to make DMEPA-recommended changes, which include the change in graduation marks on the syringe barrel and the statement change from “(b) (4)” to “Oral Use Only.”

Given that there are no CMC-related approvability issues regarding the proposed modified syringe, from the CMC perspective, the use of oral dosing modified syringe (product code (b) (4)) is recommended for approval for dispensing sildenafil oral suspension under NDA 203-109.

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/s/

MOHAN K SAPRU
08/29/2012

RAMESH K SOOD
08/29/2012

MEMORANDUMDEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**DATE:** May 17, 2012**TO:** File**THROUGH:** Ramesh K. Sood, Ph.D., Branch Chief, ONDQA**FROM:** Mohan K. Sapru, Ph.D., Sr. Regulatory Review Chemist, ONDQA**SUBJECT: Final Chemistry, Manufacturing and Controls (CMC) Approval Recommendation for NDA 203-109 (Sildenafil for Oral Suspension)**

The applicant, Pfizer, Inc., has sought U.S. marketing approval for Revatio® (Sildenafil) for Oral Suspension under the provisions of Section 505(b)(1) of the Federal Food Drug and Cosmetic Act and 21 CFR §314.50. The proposed formulation of Revatio® (sildenafil) for oral suspension is for the treatment of pulmonary arterial hypertension in pediatric patients in the age group of 1 to 17 years. The amber glass bottle with a (b) (4) closure will be filled with 32.27 g of dry powder blend, and subsequently constituted by a Pharmacist with the addition of 90 mL of water. The constituted suspension, 10 mg/mL, is sufficient for 30 days when given at a dose of 10 mg t.i.d or (b) (4) at a dose of 20 mg t.i.d.

As indicated in the previously submitted CMC review for NDA 203-109 (dated April-27-2012), all the identified CMC deficiencies have been satisfactorily addressed by the applicant. Specifically, to justify the acceptance limit for specified (b) (4), the applicant has confirmed that this impurity is (b) (4) for sildenafil citrate drug substance intended for use in oral dosage forms. In compliance with the ICH Q6A, the applicant has agreed to add a second identification technique to the drug product specification. In addition, the drug product specification has been revised to include routine testing of the (b) (4) (sodium benzoate) content as a release test for all the drug product batches. The applicant has provided drug product challenge studies data, which include dose-delivery robustness studies over the in-use period and evaluation of dose uniformity over a range of viscosity values and varying degrees of agitation. These data show that potency values remain within dose uniformity targets of (b) (4) of label claim for all viscosity values, regardless of hold time, suggesting product robustness of the suspension formulation. Furthermore, the in-use stability data and in-use dose accuracy and viscosity studies support a 30-day in-use shelf life for suspension formulation when stored below 30°C (86°F). The post-approval stability protocol has been modified by the applicant to include the commitment to perform stability studies on the first three commercial lots under both accelerated storage conditions as well as long-term storage conditions.

Although there were no pending CMC deficiencies, at the time of submission of the CMC review in DARTS, however, there were a few pending Biopharmaceutics-related deficiencies that were identified by the Biopharmaceutics review team. To address these deficiencies, the applicant has revised the drug product specification by including the modified (interim) dissolution method and dissolution acceptance criteria (*see Updated Regulatory Specification for the Drug Product at the end of this memo*). In addition, the applicant has provided dissolution profile data (using the modified 'interim' dissolution method), for the following:

- The bio-batch (product used in the BE Study A1481293, lot number: 10-082576).
- Two sets of drug product samples with viscosities at the mid and the upper end of the range of typical viscosities observed during stability testing.

Following review of the Biopharmaceutics data in the original submission and the applicant's additional dissolution data provided on May-7-2012, the Biopharmaceutics review team has recommended approval for this NDA from the Biopharmaceutics perspective (for details refer to the Biopharmaceutics review addendum by Dr. Arzu Selen, dated May 16-2012).

Lastly, Office of Compliance (OC) has previously made an overall "acceptable" recommendation for all the listed manufacturing and testing facilities.

In view of the fact that all the identified chemistry, manufacturing and controls (CMC) and Biopharmaceutics-related deficiencies have been satisfactorily addressed by the applicant, from the CMC perspective, this new drug application (NDA 203109) for Revatio® (Sildenafil) for Oral Suspension is recommended for approval.

Updated Regulatory Specification for the Drug Product

 PFIZER GLOBAL MANUFACTURING	REGULATORY SPECIFICATION DRUG PRODUCT FINISHED	PAGE 1 OF 1
DOCUMENT NO.:		RP-01-83707-02
MATERIAL NAME:		SILDENAFIL CITRATE POWDER FOR SUSPENSION- ORAL 10 mg/mL
TEST NAME	TEST METHOD	ACCEPTANCE CRITERIA
Appearance of powder	Visual	White to (b)(4) powder
Fill weight [^]	W 5.974	Each bottle contains (b)(4) grams of powder
(b)(4)	(b)(4)	(b)(4)
Appearance of suspension	Visual	(b)(4)
Identification (HPLC) [^]	TM-0390A	Retention time conforms to reference standard
Identification (UV) [^]	TM-0390A	The UV spectrum of the sildenafil peak in the sample chromatogram conforms with the spectrum of the reference standard
Assay (HPLC)	TM-0390A	(b)(4) of label claim
Purity (HPLC)		
Unspecified degradation product	TM-0390A	Not more than (b)(4) each
Total degradation products	TM-0390A	Not more than (b)(4)
Sodium benzoate	TM-0389A	(b)(4)
pH	Potentiometric	3.0 – 4.0
Dissolution (HPLC)	TM-1490A	Not less than (b)(4) of the label claim is dissolved in (b)(4) minutes
Microbial Limits*		
Total aerobic microbial count	USP <61>	Not more than 10 ² cfu/g
Total combined yeast and mould count	USP <61>	Not more than 10 ¹ cfu/g
E. coli [^]	USP <62>	Absent in 1 g
(b)(4)		
[^] Will not be tested on stability.		
PFIZER CONFIDENTIAL		

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/s/

MOHAN K SAPRU
05/17/2012

RAMESH K SOOD
05/17/2012

NDA 203109
Revatio® (Sildenafil) for Oral Suspension

Pfizer, Inc.

Mohan K. Sapru, Ph.D.
Office of New Drug Quality Assessment
Pre-Marketing Assessment Division I/Branch I Cardiovascular
and Renal Products, HFD-110

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Chemistry Review Data Sheet

1. NDA: 203109
2. REVIEW #: 1
3. REVIEW COMPLETION DATE: 20-April-2012
4. REVIEWER: Mohan K. Sapru, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous DocumentsDocument Date

N/A

N/A

6. SUBMISSION(S) REVIEWED:

Submission (s) Reviewed	Document Date
<u>Original Submission</u>	30-November-2011
Amendment-07	03-February-2012
Biopharmaceutics Amendment-14	29-February-2012
Amendment-16	05-April-2012

7. NAME & ADDRESS OF APPLICANT:

Name: Pfizer, Inc.
Address: 235 East 42nd Street,
New York, NY 10017-5755 (USA).

Representative: Nancy McKay, Director.
Worldwide Regulatory Strategy,
Pfizer, Inc.

Telephone: 212-733-4755

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: REVATIO® (Sildenafil) for Oral Suspension.

b) Non-Proprietary Name (USAN): Sildenafil citrate.

Chemistry Review Data Sheet

c) Code Name/ # (ONDQA only): N/A

d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 3
- Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: The application was submitted under Section 505(b)(1) of the Federal Food Drug and Cosmetic Act and 21 CFR §314.50.

10. PHARMACOL. CATEGORY/INDICATION: Phosphodiesterase type 5 inhibitor for the treatment of pulmonary arterial hypertension in pediatric patient population.

11. DOSAGE FORM: Powder for oral suspension.

12. STRENGTH/POTENCY: 10 mg/mL

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: X Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

 SPOTS product – Form Completed
 X Not a SPOTS product

16. CHEMICAL NAME, MOLECULAR FORMULA, MOLECULAR WEIGHT, STRUCTURAL FORMULA:

IUPAC name: 1-[[3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1*H*-pyrazolo [4,3-*d*] pyrimidin-5yl)-4-ethoxyphenyl] sulfonyl]-4-methylpiperazine citrate.

Molecular Formula: C₂₂H₃₀N₆O₄S • C₆H₈O₇

Molecular Weight: 666.71

Chemistry Review Data Sheet

CAS No.: 171599-83-0

Chemical Name: 1-[[3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1*H*-pyrazolo [4,3-*d*] pyrimidin-5yl)-4-ethoxyphenyl] sulfonyl]-4-methylpiperazine citrate.

Structure:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETE D
(b) (4)	IV	(b) (4)	(b) (4)	3	Adequate	14-Nov-2011
	III			4		
	III			3	Adequate	04-July-2000
	III			3	Adequate	15-August-2011
	III			3	Adequate	12-Jan-2009

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Chemistry Review Data Sheet

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	21,845	Revatio® tablets for pulmonary arterial hypertension.

18. STATUS:

ONDQA:

CONSULTS/ CMC-RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	22-Jan-2012	D. Smith
Methods Validation	Not requested. The methods are conventional and don't qualify for internal validation by the FDA laboratories.	20-April-2012	Mohan Sapru, Ph.D.
Environmental Assessment	Categorical Exclusion	20-April-2012	Mohan Sapru, Ph.D.
Biopharmaceutics	Though the Biopharmaceutics reviewer has currently recommended a complete response action due to pending issues, a final recommendation from Biopharmaceutics is still awaited.	26-April-2012	Arzu Selen, Ph.D.

Executive Summary Section

The Executive Summary (NDA 203109)**I. Recommendations.****A. Recommendation and Conclusion on Approvability**

From the chemistry, manufacturing and controls (CMC) perspective, this NDA for Revatio® (Sildenafil) for Oral Suspension will be recommended for approval provided the applicant satisfactorily addresses the pending deficiencies that have been identified by the Biopharmaceutics review team. Specifically, the applicant's originally proposed dissolution method and acceptance criteria have been found to be inadequate. The Biopharmaceutics review team has recommended to accept the applicant's modified dissolution method and acceptance criteria on an interim basis. Furthermore, the applicant has agreed to update the specification table for the drug product and provide dissolution profile data (using the modified interim method), by May 7, 2012, for the following:

- The bio-batch (originally used in the BE Study A1481293).
- Drug product suspensions with viscosities covering the top, middle and bottom of the viscosity range observed in the stability studies.

A follow up memorandum, which specifies the final CMC recommendation, will be submitted after the Biopharmaceutics reviewer completes review of the above-specified dissolution profile data.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Not applicable at this stage.

II. Summary of Chemistry Assessments.**A. Description of the Drug Substance (s) and Drug Product (s)**

Drug Substance: The drug substance, sildenafil citrate, is a thermodynamically stable, white to off-white crystalline powder that exhibits pH-dependent solubility. Sildenafil citrate is an achiral, amphoteric synthetic compound with pKa's of 6.53 and 9.17. It functions as a selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type-5 (PDE5), and has been shown to exert effects as a selective pulmonary vasodilator. For detailed description of this compound, including elucidation of its structure, and manufacturing process, impurity and stability profiles, the applicant has referred to Pfizer's previous NDA 21-845 (Revatio® tablets for pulmonary arterial hypertension), which has been previously reviewed and approved by the Agency. The current drug substance specification is identical to the previously approved specification for sildenafil citrate under the NDA 21-845.

Executive Summary Section

Drug Product: Sildenafil citrate Powder for Oral Suspension (POS), provided as a dry powder blend for constitution, is packaged in an amber glass bottle with a (b) (4) closure. Upon constitution by a Pharmacist with the addition of water, 10 mg/mL suspension is achieved. The suspension formulation, which is (b) (4) contains (b) (4) (sucralose and sorbitol) and flavor (grape) (u) (4). The multidose suspension also includes sodium benzoate (b) (4). (b) (4) xanthan gum, is included to (b) (4). In addition, a (b) (4) (silicon dioxide) and (b) (4) (titanium dioxide) are included in the formulation. With the exception of grape flavor (b) (4) all excipients in the sildenafil citrate POS are of pharmacopoeial or food grade, and have been included at precedented levels for oral liquid products. Although grape flavor has not been used in an FDA approved drug product, it is a component of Lipitor chewable tablets for pediatrics approved in the EU. For proprietary CMC information concerning the grape flavor (b) (4) the applicant has referred to the DMF (b) (4), which has been previously reviewed and found to be adequate by the Agency. The proposed process for manufacture of commercial drug product is a standard manufacturing process involving (b) (4) which is followed by (u) (4) and (b) (4). (b) (4) are the two product attributes that are evaluated as a part of in process monitoring during routine commercial manufacture. The data concerning blend uniformity, content uniformity for all three commercial scale batches and the bottle processing results suggest that the manufacturing process for sildenafil citrate POS is robust. Container/closure system consists of an amber glass bottle with a (b) (4) plastic closure. The associated components include a (b) (4), a (u) (4) oral dosing syringe and a press-in bottle adapter (PIBA). The applicant contends that the glass bottle and the closure liner, and the associated components (b) (4), oral syringe, and PIBA) meet the requirements of 21 CFR 177.1520. The analytical procedures for sildenafil citrate POS have been validated to meet the general requirements of the ICH Q2B. Specifically, validated HPLC assays have been developed for the determination of a) sildenafil citrate in sildenafil citrate POS and b) impurities and degradation products of sildenafil citrate POS. Microbial limits i.e., total viable aerobic, yeast and mold counts are determined in accordance with USP <61>. Absence of Escherichia Coli is determined in conformity with the USP <62>. Regarding drug product batch analysis, the three tested batches, which have been manufactured at the proposed commercial scale, have complied with the relevant drug product release specification. It is important to note that (b) (4) a potential degradation product, has not been detected in any of the release or stability samples tested. The unspecified degradation products are not present at levels of more than (b) (4) in any of the tested batches. The (b) (4) sodium benzoate, is present in all the three batches at an acceptable level of (u) (4). In accordance with ICH guideline Q1A (R2), a registration stability program consisting of three batches of sildenafil citrate POS has been completed through 18 months at 25°C/60% RH or 30°C/75% RH storage conditions, and 6 months at the accelerated (40°C/75% RH) or refrigerated (5°C) conditions. Based on stability data for three registration stability batches of sildenafil citrate powder, which show no significant trends for a storage period of 18 months at 25°C/60% RH or 30°C/75% RH, the applicant's proposed expiration period of 24 months for sildenafil citrate powder packaged in 125 mL (b) (4) amber bottles with (b) (4) plastic closure and stored below 30°C (86°F) is acceptable. Furthermore, the

Executive Summary Section

in-use stability data and in-use dose accuracy and viscosity studies support a 30 day in-use shelf life for suspension formulation stored below 30°C (86°F).

B. Description of How the Drug Product is Intended to be Used

The proposed formulation of Revatio® (sildenafil) for oral suspension is for the treatment of pulmonary arterial hypertension in pediatric patients in the age group of 1 to 17 years. The amber glass bottle with a (b)(4) closure will be filled with 32.27 g of dry powder blend, and subsequently constituted by a Pharmacist with the addition of 90 mL of water. The constituted suspension, 10 mg/mL, is sufficient for 30 days when given at a dose of 10 mg t.i.d or for (b)(4) at a dose of 20 mg t.i.d. In addition to the bottle, a (b)(4) of the formulation will be provided, along with a press-in bottle adapter (PIBA) and syringe to ensure accurate dosing of either strength.

C. Basis for Approvability or Not-Approval Recommendation

It is important to note that all the identified CMC deficiencies have been satisfactorily addressed by the applicant. Specifically, to justify the acceptance limit for specified impurity (b)(4), the applicant has confirmed that this impurity is qualified at the level of (b)(4) for sildenafil citrate drug substance intended for use in oral dosage forms. In compliance with the ICH Q6A, the applicant has agreed to add a second identification technique to the drug product specification. In addition, the drug product specification has been revised to include routine testing of (b)(4) (sodium benzoate) content as a release test for all the drug product batches. The applicant has provided drug product challenge studies data, which include dose-delivery robustness studies over the in-use period and evaluation of dose uniformity over a range of viscosity values and varying degrees of agitation. These data show that potency values remain within dose uniformity targets of (b)(4) of label claim for all viscosity values, regardless of hold time, suggesting product robustness of the suspension formulation. Furthermore, the in-use stability data and in-use dose accuracy and viscosity studies support a 30-day in-use shelf life for suspension formulation when stored below 30°C (86°F). The post-approval stability protocol has been modified by the applicant to include the commitment to perform stability studies on the first three commercial lots under both accelerated storage conditions as well as long-term storage conditions.

Although there are no pending CMC issues, however, several deficiencies identified by Biopharmaceutics review team still remain unresolved. In view of these pending deficiencies, the Biopharmaceutics reviewer has recommended a complete response action (for details refer to Biopharmaceutics review by Dr. Selen Arzu). The major issue concerns the applicant's originally proposed dissolution method and dissolution acceptance criteria, which based on Biopharmaceutics review, are inadequate. The applicant has recently proposed (b)(4)

Since there are currently very limited dissolution data to make a recommendation on the acceptability of the

Executive Summary Section

final dissolution method, the Biopharmaceutics review has recommended to accept the modified dissolution method with revised acceptance criteria on an interim basis. Pfizer has agreed to revise the drug product specification by including the modified dissolution method and revised dissolution acceptance criteria, and provide dissolution profile data (using the modified interim method), by May 7, 2012, for the following:

- The bio-batch (product used in the BE Study A1481293, lot number: 10-082576).
- Drug product suspensions with viscosities in the top, middle and bottom of the viscosity range as observed in the stability studies, including the 30-day in-use stability study.

In conclusion, from CMC perspective, this NDA will be recommended for approval provided the applicant satisfactorily addresses the above-specified pending deficiencies that have been identified by the Biopharmaceutics review team.

III. Administrative.**A. Reviewer's Signature**

Mohan Sapru, Ph.D.

B. Endorsement Block

Review Chemist:	Mohan Sapru, Ph.D.
Branch Chief:	Ramesh Sood, Ph.D.

C. CC Block

Project Manager:	Dan Brum
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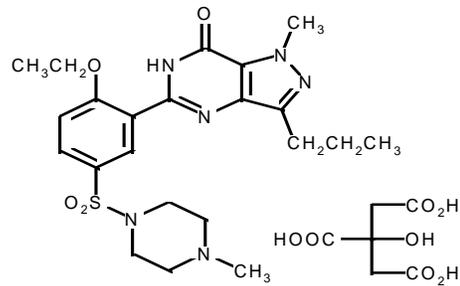
/s/

MOHAN K SAPRU
04/27/2012

RAMESH K SOOD
04/27/2012

Initial Quality Assessment
Branch I

OND Division: Division of Cardiovascular and Renal Products
NDA: 203109
Applicant: Pfizer Inc.
Letter Date: Nov. 30, 2011
Stamp Date: Nov. 30, 2011
PDUFA Date: May 30, 2012 (priority)
Tradename: Revatio
Established Name: Sildenafil
Dosage Form: Powder for oral suspension, 10 mg/mL
Route of Administration: Oral
Indication: Treatment of Pediatric Pulmonary Arterial Hypertension
Assessed by: Kasturi Srinivasachar
ONDQA Fileability: Yes



Sildenafil Citrate

Summary

This is an e-CTD 505(b)(1) Type 3 NDA application for sildenafil powder for oral suspension to treat pulmonary arterial hypertension (PAH) in the pediatric population. Clinical development of this drug was carried out under IND 63,175 in response to a Pediatric Written Request. The NDA contains clinical efficacy and safety data in pediatric patients. In addition, bioequivalence studies have been performed to bridge the to-be-marketed powder for oral suspension formulation with both intact sildenafil immediate release tablets (10, 20, 40 and 80 mg) and crushed tablets mixed with soft food which were administered in the clinical studies.

There were no CMC specific meetings with the Applicant. In multi-discipline meetings over many years no significant CMC questions were posed by Pfizer and the only CMC information provided was updates on their progress towards a marketable formulation and the difficulties encountered in this endeavor. In a correspondence dated Sep. 24, 2010, the Division agreed to Pfizer's proposal to submit the NDA with 6 months' long term stability data and provide an additional 6 months of data during the review period.

Pfizer has two approved NDAs for treatment of PAH in adults: Revatio (NDA 21-845) 20 mg tablets and Revatio (NDA 22-473) injection.

Drug Substance

The drug substance is a white to off-white crystalline powder which exhibits pH dependent solubility. Sildenafil citrate is an achiral synthetic molecule and all CMC information is cross referenced to NDA 21-845. The specification for sildenafil citrate, although not provided in the submission, (b) (4)

Drug Product

The dosage form is 32.27 g of a dry powder blend filled into an amber glass bottle with a (b) (4). The powder blend is constituted with 90 mL water yielding approximately 112 mL of suspension which has a strength of 10 mg/mL of sildenafil. The powder blend contains the (b) (4), sorbitol and sucralose, a citric acid/sodium citrate (b) (4), xanthan gum as a (b) (4), sodium benzoate (b) (4), colloidal silicon dioxide, grape flavor and titanium dioxide as a (b) (4). Titanium dioxide (b) (4). (b) (4) silicon dioxide is an (b) (4).

All excipients are compendial grade except the grape flavor. It is stated that grape flavor is food grade and is comprised of GRAS ingredients. Although this has not been used in an FDA approved drug product it is a component of Lipitor chewable tablets for pediatrics approved in the EU.

The constituted suspension, 10 mg/mL, is sufficient for 30 days when given at a dose of 10 mg t.i.d or (b) (4) at a dose of 20 mg t.i.d. The product is supplied as a kit with a (b) (4) (b) (4) a press-in bottle adapter and an oral dosing syringe. The powder for oral suspension is constituted by the pharmacist who then inserts the bottle adapter and dispenses the suspension with a 30 day expiration date.

The formulation development (b) (4)

The test attributes in the drug product specification include appearance of both powder and suspension, identification, assay, impurities, (b) (4) pH, (b) (4) fill weight and microbial limits. Batch analysis data for the three (b) (4) registration batches have been submitted. Stability data have also been generated on these 3 batches of the powder for oral suspension stored in the container closures proposed for marketing. 12 months' data at 25°C/60% RH and 30°C/75% RH as well as 6 months' data at 40°C/75% RH and 5°C (refrigeration) have been provided. Photostability has been evaluated on one batch. The stability samples were evaluated for appearance, assay, degradation products, (b) (4), pH, viscosity, (b) (4) and microbial limits. Based on these data a 24 month expiration dating period is proposed.

Since this is a multidose product in-use stability testing has been performed after constituting the powder with 90 mL water to yield a suspension with final concentration of 10 mg/mL. These studies were carried out at day 0 and day 30 after constitution and storage of the suspension at 25°C/60% RH, 30°C/75% RH and 5°C in the inverted and upright configurations using the same tests and acceptance criteria as for the powder. In-use stability was also monitored at day 0 and day 30 for the suspension constituted from powder aged up to 12 months. Based on the data from these studies, the Applicant has concluded that once constituted, sildenafil citrate powder for suspension should be kept below 30°C and may be stored in a refrigerator between 2-8°C for no more than 30 days.

Critical Review Issues

Drug Substance

- No information has been submitted to this NDA regarding the drug substance sildenafil citrate and only a cross reference to Pfizer's NDA 21-845 is given. The reviewer should consider whether at least the current specifications and representative drug substance batch data from batches used in the manufacture of the product registration batches should be submitted.

- If the drug substance batches routinely meet the (b) (4) impurity limits implemented in NDA 22-473, these should be recommended for this NDA as well keeping in mind the high risk pediatric population.

Drug Product

- Has the compatibility of the excipients with the drug substance been adequately established?
- The Grape Flavor used in the formulation is a novel excipient and consequently the section of DMF (b) (4) that pertains to this component should be reviewed.
- The Applicant states (b) (4)

Pfizer proposes (b) (4)

These claims and proposals should be evaluated by the Biopharmaceutics reviewer.

- It is stated that particle size of the drug substance used in this formulation (b) (4) is appropriate. Have satisfactory data been generated to support this statement?
- It is stated that it is important to maintain the citrate salt form of sildenafil in the formulation in order to (b) (4). Since the citrate salt is mostly present as a suspension why should this matter? How sensitive is the PXRD method to detect changes in salt form since it is claimed that no conversion to free base was observed over the 30 day in use period for constituted product that had been aged for 6 months at 30°C/75% RH. Is it expected that the same would be true for product aged up to 2 years, the proposed shelf-life?
- How critical is viscosity in this formulation? Challenge studies to demonstrate robustness of this product were done with samples with viscosity ranges of (b) (4).
Although the lower end of this range seems to represent a worst case scenario, the upper end is (b) (4) viscosity values observed at release and on stability (b) (4). Is there a reason for this? Is accuracy of dose delivered not affected by these high viscosity values?
- Is the drug product manufacturing process described in sufficient detail? Are the proposed in-process controls acceptable?
- Has (b) (4) effectiveness been shown at the lowest specified level?
- Regarding finished product specifications:
 - It is stated that (b) (4) and the microbial limits tests will not be performed routinely (b) (4).
 - The proposed identification test relies solely on HPLC retention time which is not in accordance with ICH Q6A.

- Is the justification for excluding the viscosity test from the specification acceptable?
- As mentioned above, the Biopharmaceutics reviewer should decide whether a dissolution test is needed for release and stability testing of this product.
- Is Fill Weight an adequate substitute for Content Uniformity?
- Should reconstitution time and redispersibility tests be included in the specification?
- Are the calibration marks on the oral dosing syringe appropriate for the accurate delivery of the required doses?
- Can a 24 month expiration date be granted based on 12 months of long term and 6 months of accelerated stability data?
- The stability commitment for the first 3 commercial batches does not include the 3 and 9 month time points or testing under accelerated conditions (40°C/75% RH). Is this acceptable? **It should be noted that the registration batches were manufactured at (b) (4) scale which is claimed to be the commercial scale.**
- Is the 30 day in use shelf life of the constituted product justified on the basis of testing only at day 0 and day 30? Is testing beyond 30 days necessary?

Comments and Recommendations

The application is fileable -- see attached Filing Check List. Facilities have been entered into EES and the overall recommendation is currently "Pending"; the reviewer should confirm the completeness and accuracy of the entries. A categorical exclusion from environmental assessment has been requested. A single CMC reviewer is recommended since the drug substance has been previously reviewed and the drug product section is not very extensive or complex.

Kasturi Srinivasachar
CMC Lead

Jan. 17, 2012
Date

Ramesh Sood
Branch Chief

Jan. 17, 2012
Date

**PRODUCT QUALITY -- CMC and BIOPHARMACEUTICS
FILING REVIEW FOR NDA**

NDA Number: 203-109 **NDA Type:** 3 **Established/Proper Name:** Sildenafil
Applicant: Pfizer Inc. **Letter Date:** Nov 30, 2011 **PDUFA Goal:** May 30, 2012
Stamp Date: Nov 30, 2011

CMC Reviewer: Mohan Sapru

Biopharmaceutics Reviewer: Arzu Selen

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	X		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X		
3.	Are all the pages in the CMC section legible?	X		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		

B. FACILITIES*				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	X		

6.	<p>For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? This question is not applicable for synthesized API.</p>			NA
7.	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		
8.	<p>Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		

9.	<p>Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 			NA
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X		

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
	Parameter	Yes	No	Comment
11.	Has an environmental assessment report or categorical exclusion been provided?	X		Categorical exclusion requested

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	Yes	No	Comment
12.	Does the section contain a description of the DS manufacturing process?		X	Cross reference to NDA 21-845
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?		X	Cross reference to NDA 21-845
14.	Does the section contain information regarding the characterization of the DS?		X	Cross reference to NDA 21-845
15.	Does the section contain controls for the DS?		X	Cross reference to NDA 21-845
16.	Has stability data and analysis been provided for the drug substance?		X	Cross reference to NDA 21-845
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		X	
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	

E. DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X		
21.	Is there a batch production record and a proposed master batch record?	X		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X		
23.	Have any Comparability Protocols been requested?		X	
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	X		
25.	Does the section contain controls of the final drug product?	X		
26.	Has stability data and analysis been provided to support the requested expiration date?	X		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		X	
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	

F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
29.	Is there a methods validation package?	X		

G. MASTER FILES (DMF/MAF)				
	Parameter	Yes	No	Comment
30.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X		

H. LABELING				
	Parameter	Yes	No	Comment
31.	Has the draft package insert been provided?	X		
32.	Have the immediate container and carton labels been provided?	X		

I. FILING CONCLUSION				
	Parameter	Yes	No	Comment
33.	IS THE PRODUCT QUALITY AND BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?	X		
34.	If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.			NA
35.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide filing comments to be sent to the Applicant.			NA
36.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?	X		Justification for not performing routine dissolution testing as part of the specification.

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

/s/

KASTURI SRINIVASACHAR
01/18/2012

RAMESH K SOOD
01/19/2012

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

NDA Number: 203109 Supplement Number and Type: **Established/Proper Name: Revatio®
Oral Suspension**

Applicant: Pfizer Inc. Letter Date: November 30, 2011 Stamp Date: November 30, 2011

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	X		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X		
3.	Are all the pages in the CMC section legible?	X		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?			N/A

B. FACILITIES*				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	X		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? This question is not applicable for synthesized API.		X	N/A
7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		
8.	Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

9.	Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 		X	N/A
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X		

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
	Parameter	Yes	No	Comment
11.	Has an environmental assessment report or categorical exclusion been provided?	X		

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	Yes	No	Comment
12.	Does the section contain a description of the DS manufacturing process?		X	N/A
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?		X	N/A
14.	Does the section contain information regarding the characterization of the DS?		X	N/A
15.	Does the section contain controls for the DS?		X	N/A
16.	Has stability data and analysis been provided for the drug substance?		X	N/A
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		X	N/A
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	N/A
E. Drug product (DP)				
	Parameter	Yes	No	Comment
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X		
21.	Is there a batch production record and a proposed master batch record?	X		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?			N/A
23.	Have any biowaivers been requested?		X	N/A
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	X		
25.	Does the section contain controls of the final drug product?	X		
26.	Has stability data and analysis been provided to support the requested expiration date?	X		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		X	N/A
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	N/A

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
29.	Is there a methods validation package?	X		

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?	X		

H. MASTER FILES (DMF/MAF)				
	Parameter	Yes	No	Comment
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?			N/A

I. LABELING				
	Parameter	Yes	No	Comment
32.	Has the draft package insert been provided?	X		
33.	Have the immediate container and carton labels been provided?	X		

J. FILING CONCLUSION				
	Parameter	Yes	No	Comment
34.	IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?	X		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.			N/A
36.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?			TBD

Mohan Sapru, Ph.D.

December 12, 2011

CMC Reviewer
Division of Pre-Marketing Assessment #1
Office of New Drug Quality Assessment

Date

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/s/

MOHAN K SAPRU
01/04/2012

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

/s/

DANIEL BRUM
01/11/2012

MOHAN K SAPRU
01/12/2012