

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-845**

**CHEMISTRY REVIEW(S)**

**NDA 21-845**

**REVATIO® (sildenafil citrate) Tablets, 20 mg**

**Pfizer, Inc.**

**William C. Timmer, Ph.D.  
Division of Cardio-Renal Drug Products  
HFD-110**

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# Chemistry Review Data Sheet

1. NDA 21-845
2. REVIEW #1
3. REVIEW DATE: 10 May 2005
4. REVIEWER: William C. Timmer, Ph.D.
5. PREVIOUS DOCUMENTS:

<b>PREVIOUS DOCUMENTS</b>	<b>DOCUMENT DATE</b>
IND 64, 924	06-June-2002

6. SUBMISSION(S) BEING REVIEWED:

<b>SUBMISSION REVIEWED</b>	<b>DOCUMENT DATE</b>
NDA 21-845	02-December-2004

7. NAME & ADDRESS OF APPLICANT:

**NAME:** Pfizer, INC.

**ADDRESS:** 235 E. 42<sup>nd</sup> Street, New York, NY 10017

**REPRESENTATIVE:** Martha Brumfield

**TELEPHONE:** 212-733-5406

# CHEMISTRY REVIEW TEMPLATE

## Chemistry Assessment Section

**8. DRUG PRODUCT NAME/CODE/TYPE:**

<b>PROPRIETARY NAME</b>	Revatio
<b>NON-PROPRIETARY NAME (USAN)</b>	Sildenafil Citrate
<b>CODE NAME/# (ONDC ONLY)</b>	N/A
<b>CHEMISTRY TYPE/SUBMISSION PRIORITY</b>	6 P

9. LEGAL BASIS FOR SUBMISSION: 21 U.S.C. § 355

10. PHARMACOL. CATEGORY: Vasodilator for arterial hypertension

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 20 mg

13. ROUTE OF ADMINISTRATION: Oral

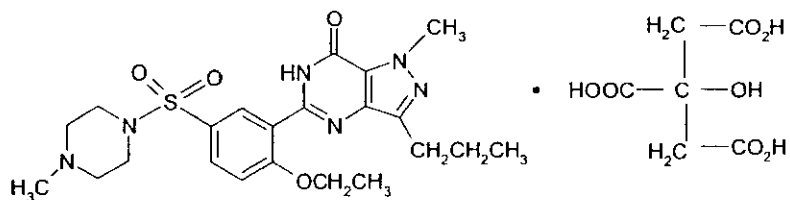
14. Rx/OTC DISPENSED:  Rx  OTC

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

SPOTS product – Form Completed

Not a SPOTS product

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



Molecular Formula:  $C_{22}H_{30}N_6O_4S \cdot C_6H_8O_7$   
Molecular Weight: 666.71 g/mol  
CAS No.: 171599-83-0  
CAS Name: 1-[[3-(6,7-Dihydro-1-methyl-7-oxo-3-propyl-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]-4-methylpiperazine citrate (1:1)

# CHEMISTRY REVIEW TEMPLATE

Chemistry Assessment Section

## 17. RELATED/SUPPORTING DOCUMENTS:

### A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED
/	III			4	N/A	
/	III			4	N/A	
/	III			4	N/A	
/	III III			4	N/A	
/	III III			4	N/A	
/	III			4	N/A	
/	III III			4	N/A	
/	IV			4	N/A	
/	IV			4	N/A	

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

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

# CHEMISTRY REVIEW TEMPLATE

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- 5 – Authority to reference not granted
- 6 – DMF not available
- 7 – Other (explain under "Comments")

<sup>2</sup> 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
IND	64, 924	Sildenafil Citrate
NDA	20-895	Sildenafil Citrate

### 18. STATUS:

CONSULTS & CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	03-JAN-2005	J. D'Ambrogio
EA	Categorical Exclusion	01-APR-2005	W.C. Timmer, Ph.D.
Methods Validation	-- to be initiated --	-----	W.C. Timmer, Ph.D.
ODS DMETS	-- pending --		

# The Chemistry Review for NDA 21-845

## Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

The drug product sildenafil citrate, 20-mg immediate release tablets, is recommended for approval from a CMC perspective.

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

There are no Phase 4 commitments.

### II. Summary of Chemistry Assessments

#### A. Description of the Drug Product(s) and Drug Substance(s)

##### 1. Drug Substance

The drug substance is sildenafil citrate.

Sildenafil citrate is the drug substance employed in the previously approved drug product Viagra®. Viagra® tablets consist of sildenafil citrate formulated into immediate release, turquoise-blue, diamond-shaped tablets in strengths of 25 mg, 50 mg, and 100 mg. Viagra® was approved in NDA 20-895 on 27 March 1998.

For reference, a very brief review of the properties of the DS sildenafil citrate will be presented.

Sildenafil citrate is a white to off-white crystalline powder.



# CHEMISTRY REVIEW TEMPLATE

## Chemistry Assessment Section

### 2. Drug Product

The drug product is sildenafil citrate 20 mg immediate release tablets.

Originally, three strengths (20 mg, 40 mg, 80 mg) were developed and studied; however, analysis of the clinical trial data warranted commercial presentation of the 20 mg strength only.

Composition of the sildenafil citrate film-coated 20 mg tablet is essentially the same as that of the commercially-available sildenafil citrate tablets, prescribed for the treatment of male erectile dysfunction and marketed as Viagra®<sup>2</sup> (refer to NDA 20-895). The only differences between the two formulations are 1) removal of the blue dye from the Viagra® film-coat formula, 2) a change in the shape of the tablet from diamond to oval, and 3) a new strength at 20 mg.

The drug product consist of tablet cores and a film coating. The tablet cores contain 20 mg of sildenafil citrate plus microcrystalline cellulose, dibasic calcium phosphate, croscarmellose sodium and magnesium stearate. The cores are film-coated

— tablets — round,

The tablet cores are manufactured from compendial materials.

Manufacturing process development studies, included in the original NDA 20-895 submission for Viagra® tablets, provide confidence in the robustness of the drug product manufacturing process. Moreover, the information gained from the process development studies and manufacturing experience of commercial Viagra® tablets underwrites the manufacture of the proposed sildenafil citrate tablets, which are prepared — which is qualitatively and quantitatively identical to that used for Viagra® tablets.

<sup>1</sup> A particularly useful reference is by Melnikov, et al., "Physicochemical Properties of Sildenafil Citrate (Viagra) and Sildenafil Base," in *J. Pharm. Sci.* 92, 2140(2003).

<sup>2</sup> Viagra® is marketed as 25 mg, 50 mg, and 100 mg immediate release tablets.

## CHEMISTRY REVIEW TEMPLATE

### Chemistry Assessment Section

The manufacturing process and equipment for the proposed product are identical to those used for Viagra®. The manufacturing process involves

Impurities in sildenafil citrate drug substance were previously discussed in NDA 20-895 as well as the CMC review of that NDA. It is worth noting that there are no additional impurities or degradation products seen in the drug product which are not seen in the drug substance. No other impurities, *e.g.*, solvents, are introduced during the tablet manufacturing process. Sildenafil citrate tablets showed no reportable degradation greater than under the recommended storage conditions. Consequently there are no specified impurities for the drug product.

Sildenafil citrate tablets are packaged in bottle/closure systems. The components of the two systems are of the same materials of construction as those approved for commercial Viagra® tablets (NDA 20-895).

A five year shelf life is proposed for sildenafil citrate tablets, 20 mg, when stored in the intended commercial packs at controlled room temperature, 15 to 30°C (59 to 86°F). The proposed shelf-life is based on the satisfactory results of the extensive stability evaluation of sildenafil citrate tablets.

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

The drug product is indicated for pulmonary hypertension. Pulmonary arterial hypertension (PAH) is a lung disorder in which the pressure in the pulmonary artery rises above normal levels. Patients with pulmonary hypertension have limited exercise tolerance, which can have a severe impact on their quality of life, and a reduced life expectancy (> 50% mortality over 5 years).

PAH is defined as a sustained elevation of pulmonary arterial pressure. Generally, the average blood pressure (BP) in a pulmonary artery is about 14 mmHg (at rest). In PAH, the average BP is usually greater than 25 mmHg.

The main vascular changes due to PAH are vasoconstriction, smooth-muscle cell and endothelial-cell proliferation, and thrombosis

Endothelial nitric oxide (NO) dilates pulmonary blood vessels by stimulating intracellular guanylate cyclase, thereby elevating intracellular cyclic guanosine monophosphate (cGMP) in pulmonary arterial vascular smooth muscle cells. Elevated cGMP reduces levels of intracellular calcium and thereby causes

## Chemistry Assessment Section

relaxation of the smooth muscle cells, which ultimately leads to reductions in the pulmonary artery pressure and the peripheral vascular resistance. Sildenafil citrate acts by specifically inhibiting phosphodiesterase type 5 (PDE5), an enzyme that metabolizes the breakdown of cGMP. Hence, inhibition of PDE5 by sildenafil enhances the effect of NO and the effects on vascular smooth muscle tone.

The recommended dosage is one 20 mg tablet three times daily.

C. Basis for Approvability or Not-Approval Recommendation

From a CMC perspective, Pfizer has submitted sufficient and appropriate information to support the approval of the drug product. The physical and chemical characteristics, impurity profile, and stability for sildenafil citrate 20 mg tablets are adequately demonstrated in this submission. The acceptance criteria are appropriate to ensure the identity, strength, quality, potency, and purity of the finished drug product. The criteria are also adequate to assure consistent quality so as to eliminate batch-to-batch variations. In particular, the HPLC assay provides an acceptable degree of separation of sildenafil citrate from its impurities and degradants. Based on analysis of the stability data, the approved shelf life for Revatio<sup>3</sup> (sildenafil citrate) Tablets, 20 mg is 60 months at room temperature when protected from light.

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<sup>3</sup> The tradename has not yet been approved.

**III. Administrative**

**A. Reviewer's Signature**

/s/ William C. Timmer, Ph.D.  
Review Chemist, HFD-150

/s/ Kasturi Srinivasacher, Ph.D.  
Team Leader, HFD-110  
Division of New Drug Chemistry I  
Office of New Drug Chemistry

**B. Endorsement Block**

HFD-110/WCTimmer/10-MAY-2004  
HFD-110/KSrinivasacher  
HFD-110/RFortney

**C. CC Block**

Original NDA 21-845

HFD-110/Division File  
HFD-110/RStockbridge

HFD-810/JSimmons  
HFD-810/HPatel

35 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

       § 552(b)(5) Deliberative Process

       § 552(b)(5) Draft Labeling

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

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William Timmer  
5/25/05 03:57:51 PM  
CHEMIST

Kasturi Srinivasachar  
5/26/05 02:18:48 PM  
CHEMIST