CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-473

CHEMISTRY REVIEW(S)

Revatio
(sildenafil) Injection
NDA 22-473

Summary Basis for Recommended Action
From Chemistry, Manufacturing, and Controls

Applicant: Pfizer Inc.
New York, NY 10017

Indication: Indicated for the treatment of pulmonary arterial hypertension in patients currently on oral Revatio who are temporarily unable to take oral medication

Presentation: Revatio (sildenafil) injection, 10 mg/12.5 ml will be available in ——— b(4)
———glass, single use vials.

EER Status: Acceptable, 3-Mar-09

Consults: Methods Validation – Revalidation by Agency was not requested.
EA – categorical exclusion granted
Microbiology: acceptable (23-Oct-09)

II. Summary of Chemistry Assessments

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 currently approved NDAs 20-895 and 21-845. Since the proposed drug product is a parenteral formulation, Pfizer uses ——— in b(4)
the ——— step during the drug substance——— The proposed drug substance specification includes all previously approved test parameters with additional tests and limits for bacterial endotoxins. The specification also includes some tightening of an individual impurity and total impurities.

Conclusion: Acceptable.

Drug product: The drug product is a sterile, single-use, ready-to-use injectable solution containing 0.8 mg/mL sildenafil. The drug product formulation is a simple solution of API with dextrose being used as a——— b(4)
manufacturing process includes———

The drug product quality is assured through appropriate product specification which includes tests and limits for appearance, identity (IR and HPLC), assay (HPLC), degradation products, visible and sub-visible particulate matter, sterility, endotoxins, pH and extractable volume. All analytical procedures used for the product analysis are validated for their intended use.

The microbiological quality of the product was found to be acceptable by the microbiology reviewer as of 23-Oct-09.

Based on the available data a shelf life of 36 months may be granted for the product when stored under controlled room temperature.

Overall conclusion: The application is recommended for approval from CMC perspective.

Additional Items: None

Ramesh Sood, Ph.D.
Branch Chief/DPA1/Branch 1/ONDQA

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/

RAMESH K SOOD
11/17/2009

NDA 22-473

Revatio® (Sildenafil Citrate) [redacted] Injection

b(4)

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

Table of Contents

Chemistry Review Data Sheet

1. NDA: 22-473

2. REVIEW #: 2

3. REVIEW DATE: 09-Nov-2009

4. REVIEWER: Mohan K. Sapru, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
N/A	N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission	15-Dec-2008/Revised 01-Jan-2009
Amendment-01	07-Jan-2009
Amendment-03	27-April-2009
Amendment-04	29-April-2009
Amendment-05	08-May-2009
Amendment-06	14-May-2009
Amendment-07	03-Aug-2009
Amendment-08	01-Oct-2009
Amendment-09	05-Oct-2009
Amendment-10	23-Oct-2009
Amendment-11	27-Oct-2009

7. NAME & ADDRESS OF APPLICANT:

Name: Pfizer, Inc.

Address: 235 East 42nd Street, New York, NY 10017, USA

Representative: Nancy S. McKay, Director, US Regulatory, Pfizer, Inc.

Telephone: 212-733-4611

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Revatio®

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

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

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

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: The application was submitted under Section 505(b) (1) of the FD & C Act.

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

11. DOSAGE FORM: Sterile solution (injection)

12. STRENGTH/POTENCY: 0.8 mg/mL

13. ROUTE OF ADMINISTRATION: Intravenous

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:

Chemical 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

Molecular Formula: $C_{22}H_{30}N_6O_4S \cdot C_6H_8O_7$

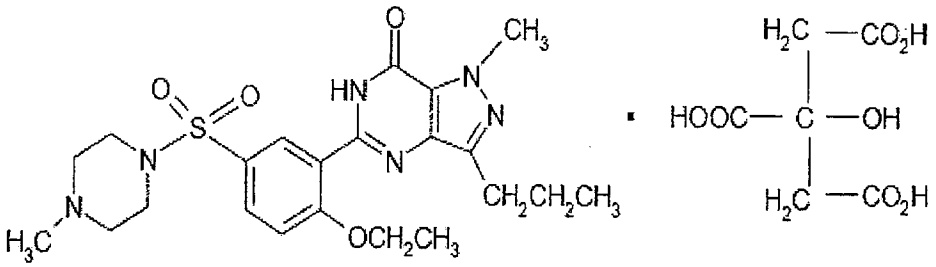
Chemistry Review Data Sheet

Molecular Weight: 666.71

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-5-yl)-4-ethoxyphenyl] sulfonyl]-4-methylpiperazine citrate.

Structure:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE [1]	STATUS[2]	DATE REVIEW COMPLETED
[redacted]					Adequate	26-Oct-2000
					Adequate	06-April-2006
					Adequate	21-March-2005

b(4)

[1] 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
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	20-895	Viagra® tablets for erectile dysfunction
NDA	21-845	Revatio® tablets for pulmonary arterial hypertension

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	03-March-09	S. Adams
Methods Validation	Not requested. The methods are conventional and don't qualify for internal validation by FDA laboratories.		Mohan Sapru, Ph.D.
EA	Categorical Exclusion		Mohan Sapru, Ph.D.
Microbiology	Pending		Stephen Langille, Ph.D.

The Chemistry Review for NDA 22-473

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing and controls (CMC) perspective, this NDA for Revatio® (Sildenafil) Injection (for intravenous use) is recommended for approval.

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

Not applicable.

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 that functions as a selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type-5 (PDE5). For detailed description of this compound and related CMC information, the applicant has referred to Pfizer's previously approved NDA 20-895 (Viagra® tablets for erectile dysfunction) and NDA 21-845 (Revatio® tablets for pulmonary arterial hypertension). The identity of the drug substance is confirmed using Fourier Transform Infrared Spectroscopy (FT-IR) and High Performance Thin Layer Chromatography (HPTLC) analyses. The specifications for sildenafil citrate drug substance for parenteral use are identical to those for sildenafil citrate drug substance previously approved for oral dosage under NDA 21-845 except for a) tightening of the limit for the specified impurity——— from —— to the ICH Q3A(R) qualification threshold of 0.15%, b) tightening of the acceptance criteria for total impurities from ——to ——;and c) inclusion of a bacterial endotoxin test to control for bacterial endotoxins. b(4)

Drug Product: The sildenafil citrate drug product is a sterile, single-use, ready-to-use injectable solution containing 0.8 mg/mL sildenafil. This injection formulation uses USP-grade water as a——— and contains compendial excipient dextrose. No novel excipents or excipients of animal origin are used. Since the formulation is a single-use sterile product, no antimicrobial agent is used. The drug product manufacturing process employs standard methods of ——————— and ——————— The b(4) b(4)

suitability of sildenafil citrate injection for intended use is supported by purity profiles of tested batches of the drug product. The individual unspecified degradation products or the total degradation products are [redacted] in any of the clinical or stability batches tested. The endotoxin levels, in the range of [redacted] have been maintained within specification limits. In addition, in all the tested drug product batches, levels of [redacted] are in the range of [redacted] which is within the specification limits of [redacted] b(4)

The commercial container closure system, originally proposed by Pfizer, consisted of [redacted] However, since, only a total volume of 12.5 mL, equivalent to 10 mg dosage, is to be used for patient administration, [redacted] The proposed packaging thus raised safety concerns, which included potential for possible misuse [redacted] This major deficiency was brought to the notice of the applicant in the 3rd month of PDUFA clock. Following several telephone conferences, Pfizer agreed to the recommendation of using a [redacted] glass vial with a USP-compliant fill volume of 12.5 mL nominal volume [redacted] b(4)

In conformity with the ICH guideline Q1A (R2), stability data following storage at 25^0C/60% RH and 30^0C/65% RH through 36 months and 40^0C/75% RH through 6 months of three commercial scale batches of sildenafil citrate solution [redacted] have been provided. The integrity of the container closure is maintained throughout the duration of the registration stability studies. In addition, photostability data from the [redacted] and 12.5 mL fill in [redacted] vial presentations have been provided. Together, the stability data supports a 36-month shelf life for the commercial product when stored at controlled room temperature i.e., 15°C to 30°C. However, it is important to point out that the stability data have been generated using the [redacted] vial presentation and not from the revised commercial presentation i.e., 12.5 mL fill in [redacted] vial. The contact surfaces, including the type of glass vial and [redacted] used in the originally proposed and revised commercial presentations are identical. The headspace relative to product volume is larger for 12.5 mL fill in [redacted] vial compared to the originally proposed presentation i.e. [redacted] However, the applicant's contention is that his difference will not impact long-term stability because the formulation is known to be insensitive to oxidation. In support of this argument, the applicant points out that there is no evidence of formation of any oxidation degradation products of sildenafil citrate in any of the stability samples evaluated for up to 36 months at 30°C/65% RH, 6 months at 40°C/75% RH, 3 months at 50°C/20% RH and on photostability. More importantly, the results from oxygen bubbling study demonstrate no significant effect of oxidation on sildenafil citrate stability, thereby, suggesting the validity of the stability data from the [redacted] vial presentation for the revised commercial presentation of 12.5 mL fill in [redacted] vial. The applicant has provided confirmatory three-month stability data from the revised commercial presentation i.e., 12.5 mL fill in b(4)

vial (Amendment # 10, dated 23-Oct-2009). Based on the existing stability data for sildenafil citrate injection and the purposeful degradation studies of sildenafil citrate drug substance, the applicant has provided experimental evidence to demonstrate that sildenafil citrate is insensitive to oxidation and, hence, increased headspace will not result in any significant oxidative degradation of sildenafil citrate injection in the commercial presentation. Together, the results from these studies lend support to applicant's contention that the stability of sildenafil citrate formulation is maintained despite change in the glass vial size, fill volume or headspace ratio, and hence, the stability data from the vial presentation and the vial presentation are representative of the commercial presentation i.e., 12.5 mL in vial. Viewed together, the stability data, would support a 36-month shelf life for sildenafil citrate injection presented as a 12.5 mL in a vial when stored at controlled room temperature e.g. 15°C to 30°C.

b(4)

b(4)

b(4)

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

Since sildenafil citrate has been shown to exert effects as a selective pulmonary vasodilator, the current NDA describes the development of sildenafil citrate formulation for intravenous administration to adult patients with pulmonary arterial hypertension (PAH) who are temporarily unable to take oral Revatio medication. The recommended dose of REVATIO (0.8 mg/mL sildenafil) Injection is 10 mg and is administered as a bolus injection. This is well within the range of intravenous doses examined in clinical studies.

C. Basis for Approvability or Not-Approval Recommendation

The CMC review comments and identified deficiencies, including the safety concerns about the container closure system, have been adequately addressed by the applicant. The revised commercial presentation consists of a glass vial with a USP-compliant fill volume of 12.5 mL nominal volume Based on initial CMC review and DMEPA's evaluation, several labeling-related changes have been incorporated in the revised labeling. Lastly, the manufacturing sites have been approved by the Office of Compliance. In response to CMC review comments, the firm submitted: a) additional stability data (amendment #10, dated 23-Oct-2009) concerning drug product in the commercial presentation, and b) labeling amendment (amendment #11, dated 27-Oct-2009). The stability data provided as amendment #10 demonstrate stability of the drug product in the commercial presentation. Pfizer, Inc. has satisfactorily addressed all the labeling-related deficiencies, including incorporation of recommended labeling correction to ensure that the product established name and the strength declaration match. In conclusion, from the CMC perspective, this NDA for Revatio® (Sildenafil) Injection (for intravenous use) is recommended for approval.

b(4)

III. Administrative

A. Reviewer's Signature

Mohan Sapru

B. Endorsement Block

Review Chemist:	Mohan K. Sapru, Ph.D.
Chemistry Team Leader:	Ramesh Sood, Ph.D.
Project Manager:	Dan Brum

C. CC Block

82 Page(s) Withheld

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

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Chemistry Assessment Section

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application:	NDA 22473/000	Sponsor:	PFIZER
Org. Code:	110		235 EAST 42ND ST
Priority:	3S		NEW YORK, NY 10017
Stamp Date:	16-DEC-2008	Brand Name:	REVATIO
PDUFA Date:	21-NOV-2009	Estab. Name:	
Action Goal:		Generic Name:	SILDENAFIL CITRATE , b(4)
District Goal:	17-AUG-2009	Product Number; Dosage Form; Ingredient; Strengths	001; SOLUTION, INJECTION; SILDENAFIL CITRATE; EQ .8MG BASE

FDA Contacts:	D. HENRY	Project Manager	301-796-4227
	K. SRINIVASACHAR	Team Leader	301-796-1760

Overall Recommendation: ACCEPTABLE on 03-MAR-2009 by S. ADAMS () 301-827-2443

Establishment:	CFN: 9611016 FEI: 3002807852		
	PFIZER IRELAND PHARMACEUTICALS INC. RINGASKIDDY API PLANT		
	RINGASKIDDY, COUNTY CORK, , IRELAND		
DMF No:		AADA:	
Responsibilities:	DRUG SUBSTANCE MANUFACTURER		
	DRUG SUBSTANCE RELEASE TESTER		
Profile:	[redacted]	OAI Status:	NONE b(4)
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	10-FEB-2009		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

Establishment:	CFN: 9610715 FEI: 3000234005		
	PFIZER SA ZONE IND. 29, ROUTE DES INDUSTRIES		
	AMBOISE CEDEX, , FRANCE		
DMF No:		AADA:	
Responsibilities:	FINISHED DOSAGE LABELER		
	FINISHED DOSAGE MANUFACTURER		
	FINISHED DOSAGE PACKAGER		
	FINISHED DOSAGE RELEASE TESTER		
	FINISHED DOSAGE STABILITY TESTER		b(4)
Profile:	[redacted]	OAI Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	03-MAR-2009		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

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

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/s/

MOHAN K SAPRU
11/16/2009

RAMESH K SOOD
11/16/2009

NDA 22-473

Revatio® (Sildenafil Citrate)
——— Injection b(4)

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

Table of Contents

Chemistry Review Data Sheet

1. NDA: 22-473

2. REVIEW #: 1

3. REVIEW DATE: 09-Oct-2009

4. REVIEWER: Mohan K. Sapru, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
N/A	N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission	15-Dec-2008/Revised 01-Jan-2009
Ammendment-01	07-Jan-2009
Ammendment-03	27-April-2009
Ammendment-04	29-April-2009
Ammendment-05	08-May-2009
Ammendment-06	14-May-2009
Ammendment-07	03-Aug-2009
Ammendment-08	01-Oct-2009
Ammendment-09	05-Oct-2009

7. NAME & ADDRESS OF APPLICANT:

Name: Pfizer, Inc.

Address: 235 East 42nd Street, New York, NY 10017, USA

Representative: Nancy S. McKay, Director, US Regulatory, Pfizer, Inc.

Telephone: 212-733-4611

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Revatio®

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

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

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

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: The application was submitted under Section 505(b) (1) of the FD & C Act.

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

11. DOSAGE FORM: Sterile solution (injection)

12. STRENGTH/POTENCY: 0.8 mg/mL

13. ROUTE OF ADMINISTRATION: Intravenous

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:

Chemical 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

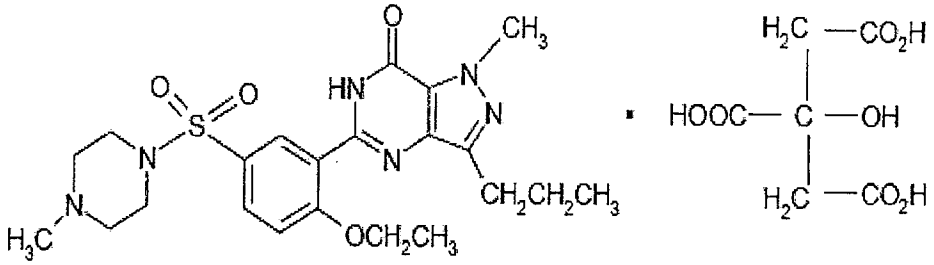
Molecular Formula: $C_{22}H_{30}N_6O_4S \cdot C_6H_8O_7$

Molecular Weight: 666.71

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-5-yl)-4-ethoxyphenyl] sulfonyl]-4-methylpiperazine citrate.

Structure:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE [1]	STATUS[2]	DATE REVIEW COMPLETED
					Adequate	26-Oct-2000
					Adequate	06-April-2006
					Adequate	21-March-2005

b(4)

[1] 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
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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	20-895	Viagra® tablets for erectile dysfunction
NDA	21-845	Revatio® tablets for pulmonary arterial hypertension

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	03-March-09	S. Adams
Methods Validation	Not requested. The methods are conventional and don't qualify for internal validation by FDA laboratories.		Mohan Sapru, Ph.D.
EA	Categorical Exclusion		Mohan Sapru, Ph.D.
Microbiology	Pending		Stephen Langille, Ph.D.

The Chemistry Review for NDA 22-473

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing and controls (CMC) perspective, this NDA for Revatio® (Sildenafil Citrate) Injection (for intravenous use) is approvable pending a): a satisfactory review of additional stability data concerning drug product in the commercial presentation that Pfizer, Inc. is committed to provide on November 2, 2009, and b): incorporation of a labeling correction to ensure that the product established name and the strength declaration match.

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

Not applicable.

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 that functions as a selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type-5 (PDE5). For detailed description of this compound and related CMC information, the applicant has referred to Pfizer's previously approved NDA 20-895 (Viagra® tablets for erectile dysfunction) and NDA 21-845 (Revatio® tablets for pulmonary arterial hypertension). The identity of the drug substance is confirmed using Fourier Transform Infrared Spectroscopy (FT-IR) and High Performance Thin Layer Chromatography (HPTLC) analyses. The specifications for sildenafil citrate drug substance for parenteral use are identical to those for sildenafil citrate drug substance previously approved for oral dosage under NDA 21-845 except for a) tightening of the limit for the specified impurity ——— from ——— to the ICH Q3A(R) qualification threshold of 0.15%, b) tightening of the acceptance criteria for total impurities from ——— to ———, and c) inclusion of a bacterial endotoxin test to control for bacterial endotoxins. b(4)

Drug Product: The sildenafil citrate drug product is a sterile, single-use, ready-to-use injectable solution containing 0.8 mg/mL sildenafil. This injection formulation uses USP-grade water as a ———, and contains compendial excipient dextrose. No novel b(4)

excipents or excipients of animal origin are used. Since the formulation is a single-use sterile product, no antimicrobial agent is used. The drug product manufacturing process employs standard methods of [redacted] b(4)
[redacted] The suitability of sildenafil citrate injection for intended use is supported by purity profiles of tested batches of the drug product. The individual unspecified degradation products or the total degradation products are [redacted] in any of the clinical or stability batches tested. The endotoxin levels, in the range of [redacted] b(4)
have been maintained within specification limits. In addition, in all the tested drug product batches, levels of [redacted] b(4)
[redacted] are in the range of [redacted] which is within the specification limits of [redacted]

The commercial container closure system, originally proposed by Pfizer, consisted of [redacted] b(4)
[redacted] .. However, since, only a total volume of 12.5 mL, equivalent to 10 mg dosage, is to be used for patient administration, [redacted] b(4)
[redacted] .. The proposed packaging thus raised safety concerns, which included [redacted] b(4)
[redacted] This major deficiency was brought to the notice of the applicant in the 3rd month of PDUFA clock. Following several telephone conferences, Pfizer agreed to the recommendation of using a [redacted] glass vial with a USP-compliant fill volume of 12.5 mL nominal volume [redacted] b(4)

In conformity with the ICH guideline Q1A (R2), stability data following storage at 25°C/60% RH and 30°C/65% RH through 36 months and 40°C/75% RH through 6 months of three commercial scale batches of sildenafil citrate solution [redacted] b(4)
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surfaces, including the type of glass vial and [redacted] used in the originally proposed and revised commercial presentations are identical. The headspace relative to product volume is larger for 12.5 mL fill in [redacted] vial compared to the originally proposed b(4)
presentation i.e., [redacted] However, the applicant's contention is that his difference will not impact long-term stability because the formulation is known to be insensitive to oxidation. In support of this argument, the applicant points out that there is no evidence of formation of any oxidation degradation products of sildenafil citrate in any of the stability samples evaluated for up to 36 months at 30°C/65% RH, 6 months at 40°C/75% RH, 3 months at 50°C/20% RH and on photostability. More importantly, the results from oxygen bubbling study demonstrate no significant effect

of oxidation on sildenafil citrate stability, thereby, suggesting the validity of the stability data from the [redacted] vial presentation for the revised commercial presentation of 12.5 mL fill i[redacted] vial. The applicant's confirmatory three-month stability data from the revised commercial presentation is awaited. b(4) b(4)

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

Since sildenafil citrate has been shown to exert effects as a selective pulmonary vasodilator, the current NDA describes the development of sildenafil citrate formulation for intravenous administration to adult patients with pulmonary arterial hypertension (PAH) who are temporarily unable to take oral Revatio medication. The recommended dose of REVATIO (0.8 mg/mL sildenafil) Injection is 10 mg and is administered as a bolus injection. This is well within the range of intravenous doses examined in clinical studies.

C. Basis for Approvability or Not-Approval Recommendation

The CMC review comments and identified deficiencies, including the safety concerns about the container closure system, have been adequately addressed by the applicant. The revised commercial presentation consists of a [redacted] glass vial with a USP-compliant fill volume of 12.5 mL nominal volume [redacted] Based on initial CMC review and DMEPA's evaluation, several labeling-related changes have been incorporated in the revised labeling. Lastly, the manufacturing sites have been approved by the Office of Compliance. In conclusion, from the CMC perspective, this NDA for Revatio® (Sildenafil Citrate) Injection (for intravenous use) is approvable pending a): a satisfactory review of additional stability data concerning drug product in the commercial presentation that Pfizer is committed to provide on November 2, 2009, and b): incorporation of a labeling correction to ensure that the drug product established name and the strength declaration match. b(4)

III. Administrative

A. Reviewer's Signature

Mohan Sapru

B. Endorsement Block

Review Chemist:	Mohan K. Sapru, Ph.D.
Chemistry Team Leader:	Ramesh Sood, Ph.D.
Project Manager:	Dan Brum

C. CC Block

72 Page(s) Withheld

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

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

CHEMISTRY REVIEW TEMPLATE

Chemistry Assessment Section

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application:	NDA 22473/000	Sponsor:	PFIZER
Org. Code:	110		235 EAST 42ND ST
Priority:	3S		NEW YORK, NY 10017
Stamp Date:	16-DEC-2008	Brand Name:	REVATIO
PDUFA Date:	21-NOV-2009	Estab. Name:	
Action Goal:		Generic Name:	SILDENAFIL CITRATE
District Goal:	17-AUG-2009	Product Number; Dosage Form; Ingredient; Strengths	001; SOLUTION, INJECTION; SILDENAFIL CITRATE; EQ .8MG BASE

FDA Contacts:	D. HENRY	Project Manager	301-796-4227
	K. SRINIVASACHAR	Team Leader	301-796-1760

Overall Recommendation: ACCEPTABLE on 03-MAR-2009 by S. ADAMS () 301-827-2443

Establishment:	CFN: 9611016 FEI: 3002807852
	PFIZER IRELAND PHARMACEUTICALS INC. RINGASKIDDY API PLANT
	RINGASKIDDY, COUNTY CORK, , IRELAND
DMF No:	AADA:
Responsibilities:	DRUG SUBSTANCE MANUFACTURER
	DRUG SUBSTANCE RELEASE TESTER
Profile:	[redacted] OAI Status: NONE b(4)
Last Milestone:	OC RECOMMENDATION
Milestone Date:	10-FEB-2009
Decision:	ACCEPTABLE
Reason:	DISTRICT RECOMMENDATION

Establishment:	CFN: 9610715 FEI: 3000234005
	PFIZER SA ZONE IND. 29, ROUTE DES INDUSTRIES
	AMBOISE CEDEX, , FRANCE
DMF No:	AADA:
Responsibilities:	FINISHED DOSAGE LABELER
	FINISHED DOSAGE MANUFACTURER
	FINISHED DOSAGE PACKAGER
	FINISHED DOSAGE RELEASE TESTER
	FINISHED DOSAGE STABILITY TESTER
Profile:	[redacted] OAI Status: NONE b(4)
Last Milestone:	OC RECOMMENDATION
Milestone Date:	03-MAR-2009
Decision:	ACCEPTABLE
Reason:	DISTRICT RECOMMENDATION

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

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/s/

MOHAN K SAPRU
10/22/2009

RAMESH K SOOD
10/23/2009

Initial Quality Assessment
Branch I

OND Division:	Division of Cardiovascular and Renal Products
NDA:	22-473
Applicant:	Pfizer
Letter Date:	16 Dec 2008
Status Date:	16 Dec 2008
PDUFA Date:	16 Oct 2009
Tradename:	Revatio
Established Name:	Sildenafil citrate
Dosage Form:	Sterile solution (injection), 0.8 mg/mL
Route of Administration:	Intravenous
Indication:	Treatment of pulmonary arterial hypertension in patients currently on oral Revatio who are temporarily unable to take oral medication
Assessed by:	Kasturi Srinivasachar
ONDQA Fileability:	Yes

Summary
This NDA, in e-CTD format, is for a parenteral formulation of sildenafil citrate. Sildenafil citrate, a beta-adrenoreceptor blocker, is currently approved for oral administration under the tradenames Viagra (Pfizer's NDA 20-895) and Revatio (Pfizer's NDA 21-845) for the treatment of erectile dysfunction (Viagra) and pulmonary arterial hypertension (Revatio). This injection formulation for intravenous administration is indicated for patients who are temporarily unable to take oral medication for various reasons (e.g. surgery). Clinical development was carried out under IND 64,924. No CMC specific or interdisciplinary meetings with a significant CMC component were held with the sponsor.

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 NDAs 20-895 and 21-845. Since this drug substance will be used in a parenteral formulation Pfizer uses [redacted] in the [redacted] step. The specification for sildenafil citrate is the same as for the approved products except for 1) the addition of a bacterial endotoxin test, 2) tightening of the limit for impurity [redacted] from [redacted] to the ICH Q3A (R) qualification threshold of 0.15% and 3) tightening of the acceptance criterion for total impurities from [redacted] % to [redacted] b(4) b(4)

Drug Product
Sildenafil citrate injection is a sterile, single use solution [redacted] containing 0.8 mg/mL sildenafil in a [redacted] clear [redacted] glass vial [redacted] In addition to the active ingredient the formulation contains either dextrose [redacted] or dextrose [redacted] as [redacted] and water for injection. The excipients are compendial grade. Early clinical formulations contained sildenafil at a concentration of 1 mg/mL with [redacted] as b(4) b(4)

[redacted] Later, [redacted] was replaced by dextrose [redacted] b(4)

[redacted] No antimicrobial preservatives are added to the formulation since the product is labeled for single use only. It is stated that although the product is intended to be administered as a bolus injection, other administration scenarios such as low concentration dilution in an IV bag and slow infusion were studied to expand knowledge of product performance.

The manufacturing process is straightforward and employs standard methods of [redacted] b(4) [redacted] The specification proposed includes the standard test attributes for a parenteral product. [redacted] is the only impurity specified. An expiration dating period of 36 months is proposed for the drug product stored at controlled room temperature based on stability data on 3 batches manufactured and packaged at the commercial manufacturing site.

Critical Review Issues

Drug substance

- Is the Applicant's justification for not performing bioburden testing on the drug substance acceptable?

Drug Product

- Since this is a parenteral dosage form, the major critical issue is sterility assurance of the product after manufacture and maintenance of sterility over the shelf-life. These aspects are expected to be covered by the microbiology reviewer.
- Have appropriate tests been performed to show compatibility of the vial [redacted] with the drug product? b(4)
- Is the absence of osmolality testing in the drug product specification acceptable?

Labeling

- The established name and strength do not match and should be corrected in all labeling.
- The quantitative amounts of excipients should be stated on container labels and in the Description section of the Package Insert.
- "[redacted] is incorrect and should be changed to just "Injection" as per USP b(4)
- Each vial contains [redacted] of sildenafil and is for single use only. The D &A section of the labeling recommends 10 mg or 12.5 mL. This means that [redacted] b(4) Does Pfizer have a rationale for this presentation?

Comments and Recommendations

The application is fileable. Manufacturing, testing and packaging facilities are being entered into EES and the reviewer should verify the accuracy and completeness of the entries. A microbiology reviewer has been assigned to this NDA. A single CMC reviewer is recommended for this application.

Kasturi Srinivasachar	Jan.21, 2009
Pharmaceutical Assessment Lead	Date
Ramesh Sood, Ph.D.	Jan. 21, 2009
Branch Chief	Date

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/s/

Kasturi Srinivasachar
1/21/2009 05:29:08 PM
CHEMIST

Ramesh Sood
1/26/2009 03:48:42 PM
CHEMIST