

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-845

ADMINISTRATIVE
DOCUMENTS/CORRESPONDENCE

**PATENT INFORMATION SUBMITTED WITH THE
FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT**

**For Each Patent That Claims a Drug Substance
(Active Ingredient), Drug Product (Formulation and
Composition) and/or Method of Use**

NDA NUMBER

To be assigned

NAME OF APPLICANT / NDA HOLDER

Pfizer Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)

REVATIO

ACTIVE INGREDIENT(S)

sildenafil citrate

STRENGTH(S)

20mg

DOSAGE FORM

Tablet

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number

5250534

b. Issue Date of Patent

10/5/1993

c. Expiration Date of Patent

3/27/2012

d. Name of Patent Owner

Pfizer Inc.

General Patent Counsel

Address (of Patent Owner)

235 East 42nd Street

City/State

New York, NY

ZIP Code

10017

FAX Number (if available)

Telephone Number

(212) 733-2323

E-Mail Address (if available)

e. **Name of agent or representative** who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address (of agent or representative named in 1.e.)

City/State

ZIP Code

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b)? Yes No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)? Yes No

2.6 Does the patent claim only an intermediate? Yes No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)? Yes No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No

3.2 Does the patent claim only an intermediate? Yes No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)? Yes No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2 Patent Claim Number (as listed in the patent) Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the approved labeling.)

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

6. Declaration Certification

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

Date Signed

Bruce A. Pokras

9/21/2004

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name
Bruce A. Pokras

Address
201 Tabor Road

City/State
Morris Plains, NJ

ZIP Code
07950

Telephone Number
(973) 385-5399

FAX Number (if available)
(973) 385-7330

E-Mail Address (if available)
bruce.a.pokras@pfizer.com

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send

comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

REVATIO™ (sildenafil citrate)
Pulmonary Arterial Hypertension
NDA 21-845

Module 1.4.10 NOTICE OF CLAIMED EXCLUSIVITY
[21CFR314.108(b)(4)]

Pfizer Inc hereby claims three (3) years of marketing exclusivity from the date of approval of sildenafil citrate (REVATIO) for the treatment of pulmonary arterial hypertension (PAH) in adults pursuant to 21 CFR § 314.108 ¶ (b) (4).

Pfizer Inc certifies hereby that the application contains new clinical investigations that were conducted or sponsored by Pfizer under IND 64,924, are essential to approval of the application and, to the best of Pfizer's knowledge, meet the definition of "new clinical investigation" set forth in Sec. 314.108(a).

A list of all published studies or publicly available reports of clinical investigations known to Pfizer through a literature search that are relevant to the conditions for which the Pfizer is seeking approval is attached (Module 1.4.9 of this application). Pfizer Inc further certifies hereby that Pfizer has thoroughly searched the scientific literature and, to the best of Pfizer's knowledge, the list is complete and accurate. In Pfizer's opinion, such published studies or publicly available reports do not provide sufficient basis for the approval of the conditions for which Pfizer is seeking approval without reference to the new clinical investigations in the application, as none of the published studies or reports satisfies the requirements for adequate and well-controlled studies as defined in 21CFR314.126, and required under section 505 (b) of the Act.

010000044838631.01.Approved119-Nov-2004 11:37

EXCLUSIVITY SUMMARY

NDA # 21-845

SUPPL #

HFD # 110

Trade Name Revatio

Generic Name Sildenafil citrate

Applicant Name Pfizer

Approval Date, If Known

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

N/A

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

N/A

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 Years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

N/A

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 20-895

Viagra (sildenafil citrate)

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

N/A

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

A1481140, A1481142

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

N/A

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

N/A

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

A1481140, A1481142

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1
IND # 64,924 YES ! NO
! Explain:

Investigation #2
IND # 64,924 YES ! NO
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES

Explain:

!

!

! NO

! Explain:

Investigation #2

YES

Explain:

!

!

! NO

! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES

NO

If yes, explain:

Name of person completing form: Russell Fortney

Title: RHPM

Date: 5/31/05

Name of Office/Division Director signing form: Norman Stockbridge

Title: Acting Director, Division of Cardio-Renal Drug Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 21-845 Supplement Type (e.g. SE5): _____ Supplement Number: _____

Stamp Date: 12/3/05 Action Date: 6/3/05

HFD-110 Trade and generic names/dosage form: Revatio (sildenafil citrate) Tablets 20 mg

Applicant: Pfizer Therapeutic Class: _____

Indication(s) previously approved: _____

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: Treatment of Pulmonary Arterial Hypertension

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.
- No: Please check all that apply: Partial Waiver Deferred Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
 Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is

complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. 0 Tanner Stage _____
 Max _____ kg _____ mo. _____ yr. 16 Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: Pediatric studies are ongoing under a Written Request under NDA 20-895 Viagra (sildenafil citrate)

Date studies are due (mm/dd/yy): June 19, 2007

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
 Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

 Russell Fortney
 Regulatory Project Manager

cc: NDA 21-845
 HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

NDA
Sildenafil Tablets

DEBARMENT CERTIFICATION
[FD&C Act 306(k)(1)]

Pfizer hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.



Signature of Company Representative

10/19/04

Date

JAMAN MARONI

REVATIO™ (sildenafil citrate)
NDA 21-845
FINANCIAL DISCLOSURE COVER NOTE
Module 1, Section 1.3.6.1

There are two (2) covered studies for this NDA. The covered studies were not funded via variable compensation and none of the investigators in the studies hold any form of propriety interest in REVATIO™.

Information regarding Pfizer's efforts to eliminate bias for each study is described in Module 1, Section 1.3.6.3. Pfizer has examined its financial data regarding significant payments of other sorts made to all investigators in the studies and equity information as provided by the investigators, as defined in 21 CFR 54.2. Disclosure: Financial Interests and Arrangements of Clinical Investigators described in Module 1, Sections 1.3.6.4 & 1.3.6.5.

With a total of 791 investigators listed in the multi-centered studies, 8 of the listed investigators had financial information to disclose. Specifically, 8 investigators have significant payments of other sorts. Four investigators participated in both protocols and therefore have multiple FDA forms 3455. This information is listed in the 3455 Forms in Module 1, Section 1.3.6.5.

It is important to note that the investigator list for the studies determined by 1572s, is not necessarily the same as that for financial disclosure. The FDA criteria for the two lists are not equivalent. Personnel involved with the studies, but not necessarily with the data, are listed on FDA Form 1572. There is a complete investigator population list for the covered studies attached to this cover note (Module 1, Section 1.3.6.2).

Pfizer Inc is submitting financial disclosure information on the following covered studies:

Protocol # A1481140

A Multinational, Multi-Centre, Randomised, Double-Blind, Double-Dummy, Placebo-Controlled Study to Assess the Efficacy and Safety Of 20, 40, and 80 mg Sildenafil Three Times A Day (TID) in the Treatment of Pulmonary Arterial Hypertension (PAH) in Subjects Aged 18 Years and Over.

Protocol # A1481142

A Multicentre, Multinational, Long Term Extension Study, to Assess the Safety and Toleration of Subject Optimised Treatment Regimens of Oral Sildenafil for Pulmonary Arterial Hypertension in Subjects Who Have Completed Study A1481140

Please note that Protocol #A1481142 is an ongoing study.

A complete list of the 791 investigators who participated in the two (2) covered studies is attached. Each of the individual investigators listed was sent the Financial Disclosure Form directly or via the principal investigator for their site. In addition, if necessary, we contacted the site by telephone and/or sent 2 separate follow-up letters to those individuals who did not return

the Financial Disclosure Form. Additionally, all investigators are contacted at the time of the submission to remind them of the obligation to disclose financial information for Pfizer Inc and affiliated companies, including Warner-Lambert, Agouron, Pharmacia, Pharmacia & Upjohn, Searle/Monsanto and Sugem, which are wholly owned by Pfizer.

CERTIFICATION

Per Form 3454, certification is provided for 783 of the 791 investigators indicating:

- Certified investigators. A total of 781 of the 791 investigators are certified as having no Financial Arrangement as defined in 21 CFR 54.2.
- Due diligence. A total of 2 of the 791 investigators did not respond or could not be reached by our due diligence effort.

Note that all investigators are assessed for Equity, Significant Payments of Other Sorts, Variable Compensation, & Propriety Interest. With the exception of Equity, all other financial arrangements are checked via internal Pfizer procedures.

DISCLOSURE

In the covered studies, 8 of the 791 investigators listed had financial information to disclose. A completed Form 3455 is attached for the 8 investigators. Please note that four of the investigators participated in multiple protocols; therefore, there are multiple 3455 Forms for these investigators.

All Independent Grants associated with our investigators are paid directly to the Institution rather than to the individual investigator.

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA 21-845	Efficacy Supplement Type SE-	Supplement Number	
Drug: Revatio (sildenafil citrate) Tablets 20 mg		Applicant: Pfizer	
RPM: Russell Fortney		HFD-110	Phone # 301-594-5311
<p>Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p> <p>If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.</p> <p><input type="checkbox"/> Confirmed and/or corrected</p>		Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):	
❖ Application Classifications:			
• Review priority		<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority	
• Chem class (NDAs only)		5P	
• Other (e.g., orphan, OTC)			
❖ User Fee Goal Dates		June 3, 2005	
❖ Special programs (indicate all that apply)		<input type="checkbox"/> None Subpart H: <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2	
❖ User Fee Information			
• User Fee		<input checked="" type="checkbox"/> Paid UF ID number	
• User Fee waiver		<input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other (specify)	
• User Fee exception		<input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) <input type="checkbox"/> Other (specify)	
❖ Application Integrity Policy (AIP)			
• Applicant is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	

<ul style="list-style-type: none"> • This application is on the AIP 	() Yes (X) No
<ul style="list-style-type: none"> • Exception for review (Center Director's memo) 	
<ul style="list-style-type: none"> • OC clearance for approval 	
<ul style="list-style-type: none"> ❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent. 	(X) Verified
<ul style="list-style-type: none"> ❖ Patent 	
<ul style="list-style-type: none"> • Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. 	(X) Verified
<ul style="list-style-type: none"> • Patent certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. 	(X) N/A (not a 505(b)(2) application).
<ul style="list-style-type: none"> • [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	(X) N/A
<ul style="list-style-type: none"> • [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next box below (Exclusivity)).</i> • [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. <p>Answer the following questions for each paragraph IV certification:</p> <p>(1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).</p> <p><i>If "Yes," skip to question (4) below. If "No," continue with question (2).</i></p> <p>(2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?</p> <p><i>If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).</i></p> <p><i>If "No," continue with question (3).</i></p> <p>(3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its</p>	<p>(X) N/A (no paragraph IV certification) () Verified</p> <p>() Yes () No</p> <p>() Yes () No</p> <p>() Yes () No</p>

❖ Actions	
• Proposed action	(X) AP () TA () AE () NA
• Previous actions (specify type and date for each action taken)	N/A
• Status of advertising (approvals only)	(X) Materials requested in AP letter () Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	(X) Yes () Not applicable
• Indicate what types (if any) of information dissemination are anticipated	() None (X) Press Release () Talk Paper () Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	N/A
• Most recent applicant-proposed labeling	Included in package
• Original applicant-proposed labeling	Included in package
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings (indicate dates of reviews and meetings)	DDMAC Review: 5/2/05 DMETS Review: 5/23/05
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	Viagra (sildenafil citrate), Tracleer (bosentan), Ventavis (iloprost)
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	N/A
• Applicant proposed	Included in package
• Reviews	DMETS Review: 5/23/05
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	N/A
• Documentation of discussions and/or agreements relating to post-marketing commitments	N/A
• Outgoing correspondence (i.e., letters, E-mails, faxes)	Acknowledgment Letter: 12/15/04
• Memoranda and Telecons	T-con minutes: 5/13/05
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	Included in package: 4/3/02
• Pre-NDA meeting (indicate date)	Included in package: 7/14/04
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other	N/A
❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
• Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A

representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

(4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).

If "No," continue with question (5).

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).

If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).

If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.

❖ Exclusivity (approvals only)	
<ul style="list-style-type: none"> Exclusivity summary Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.) 	-Included in package -No
<ul style="list-style-type: none"> Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification. 	<input type="checkbox"/> Yes, Application # _____ <input checked="" type="checkbox"/> No
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	

❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review)	Medical Team Leader: 5/23/05
❖ Clinical review(s) (indicate date for each review)	Included in package: 5/3/05
❖ Microbiology (efficacy) review(s) (indicate date for each review)	N/A
❖ Safety Update review(s) (indicate date or location if incorporated in another review)	See page 97 of clinical review
❖ Risk Management Plan review(s) (indicate date/location if incorporated in another rev)	N/A
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	Included in package
❖ Demographic Worksheet (NME approvals only)	N/A
❖ Statistical review(s) (indicate date for each review)	Included in package 5/4/05
❖ Biopharmaceutical review(s) (indicate date for each review)	Included in package 5/20/05
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	Included in package
• Bioequivalence studies	N/A
CMC Information	
❖ CMC review(s) (indicate date for each review)	Included in package: 5/26/05
❖ Environmental Assessment	
• Categorical Exclusion (indicate review date)	5/26/05
• Review & FONSI (indicate date of review)	5/26/05
• Review & Environmental Impact Statement (indicate date of each review)	5/26/05
❖ Microbiology (validation of sterilization & product sterility) review(s) (indicate date for each review)	N/A
❖ Facilities inspection (provide EER report)	Date completed: January 3, 2005 (X) Acceptable () Withhold recommendation
❖ Methods validation	() Completed (X) Requested () Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	Included in package: 5/20/05
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	N/A
❖ CAC/ECAC report	N/A

Appendix A to NDA/Efficacy Supplement Action Package Checklist

An application is likely to be a 505(b)(2) application if:

- (1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
- (2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
- (4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

RHPM NDA Overview
May 31, 2005

Application: NDA 21-845
Drug Name: Revatio (sildenafil citrate) Tablets 20 mg
Sponsor: Pfizer
Classification: 5P
Date of Application: December 3, 2005
User Fee Goal Dates: June 6, 2005

Background:

Sildenafil citrate (Viagra) was originally approved for use in male erectile dysfunction in 1998 under NDA 20-895. That NDA now resides in the Division of Reproductive and Urologic Drug Products (HFD-580). Pfizer has submitted this new NDA to the Division of Cardio-Renal Drug Products for sildenafil citrate for use in the treatment of pulmonary arterial hypertension. This application was submitted as a new NDA, rather than a supplement, as Pfizer will be using a new label and a new name (Revatio) for the PAH indication.

Review

Postmarketing
Commitments:

1. To investigate the therapeutic effect of Revatio when administered below the proposed recommended dose of 20mg t.i.d.
2. To generate data describing the safety and efficacy of Revatio when used clinically in combination with bosentan.

Safety Update: Submitted April 8, 2005. Safety Update Review included in primary Medical Review.

Patent Information: Included in package.

Pediatric Information: A deferral will be granted.

Exclusivity: Included in package.

DSI: DSI inspected two clinical sites. No deficiencies were noted at the sites inspected that could compromise the integrity of the data. Thus, the data reviewed is acceptable.

Debarment

Certification: Included in package

Tradename Review: The tradename was reviewed by DMETS on May23, 2005. DMETS recommended against using a second proprietary name for sildenafil citrate Tablets (The Viagra product is currently being used for use in male erectile dysfunction). DMETS discourages the use of two tradenames for products with the same active ingredient from the same

Advisory Committee

Meeting: No meeting held.

Medical Review

Reviewer: Maryann Gordon, M.D.

Labeling: Dr. Gordon's labeling recommendations have been incorporated into the labeling during negotiations with the sponsor.

Conclusion: The efficacy of sildenafil in subjects with PAH was demonstrated in one well-controlled study (A1481140). All doses of sildenafil tested prolonged walking distance compared to baseline by up to 50 m ($p < 0.0001$). Limited information indicates that there is no dose response, i.e., sildenafil 20 mg tid was as efficacious as 80 mg tid. There was very little change in walk distance beyond 12 weeks despite continuation of sildenafil in an open label, uncontrolled extension study. Sildenafil also significantly decreased the mean pulmonary artery pressure from baseline compared to placebo.

The review of safety of sildenafil doses 20, 40, and 80 mg tid for 12 weeks in subjects with PAH did not raise major concerns. Reports of serious safety events including deaths were similar across treatment groups. More adverse events and discontinuations for adverse events were reported for subjects receiving sildenafil 80 mg tid.

Adverse events with the largest placebo subtracted incidence rates included headache (7%), flushing (7%), and epistaxis (5%). Other adverse events that were reported with greater frequency in the sildenafil treated groups included visual disturbance, diarrhea, dyspepsia, gastritis, and myalgia. Ocular testing did not reveal serious eye adverse events. Bleeding events, particularly epistaxis, were more frequent in the sildenafil plus vitamin K antagonists compared to sildenafil alone. For those taking vitamin K antagonists (74% of all subjects), the incidence rate for sildenafil groups reporting any bleeding was 20% compared to 13% for placebo. In addition, those sildenafil subjects with PAH secondary to connective tissue disease were more likely to report epistaxis (13%) compared to those on placebo (0%) and those with primary PAH (2%). In conjunction with this finding, there were minor decreases in mean hemoglobin/hematocrit.

After reviewing both adverse events and laboratory values, there was no convincing evidence that sildenafil has an adverse effect on the liver, kidney, or bone marrow.

Approvable.

Statistical Review

Reviewer: Valeria Freidlin, Ph.D.

Labeling: None

Conclusion:

Dr. Freidlin's analysis of the primary efficacy endpoint of the single pivotal Phase 3 Study A1481140 showed that all sildenafil doses (20 mg, 40 mg, and 80 mg) were statistically significantly ($p < 0.0001$) better than placebo relative to 6-minute walk test at 12 weeks.

The secondary efficacy analysis showed that all sildenafil doses (20 mg, 40 mg, and 80 mg) were statistically significantly ($p \leq 0.021$) better than placebo relative to mean pulmonary artery pressure (PAP) at 12 weeks. Relative to time to clinical worsening, the comparison of sildenafil 80 mg to placebo showed no statistically significant reduction. Therefore, according to the pre-specified sequential step-down testing procedure, no further secondary endpoints and doses were evaluated. Safety results showed that proportion of subjects with treatment related adverse events was higher in the sildenafil 80 mg group. All five subjects who permanently discontinued from the study due to adverse events were in the sildenafil 80 mg group. For one of the subjects, adverse events were classified as treatment related.

Chemistry Review

Reviewer:

William Timmer, Ph.D.

Labeling:

Add "Rx Only" statement under product name at top of labeling.

Methods Validation:

Pending

Environmental

Assessment:

Categorical Exclusion has been submitted.

Conclusion:

Approvable.

Pharmacology Review

Reviewer:

Tom Papoian, Ph.D.

Labeling:

The following labeling issues should be addressed:

1. Under the section "Carcinogenesis, Mutagenesis, Impairment of Fertility", the applicant uses

Levels of parent drug plus major metabolite should be used in estimating drug exposure for both male and female rats.

2. Under the sections: (a) "Carcinogenesis, Mutagenesis, Impairment of Fertility" and (b) "Pregnancy", the applicant estimates human exposure levels from a 20 mg t.i.d. (3X/day) dosing regimen by

The expected human exposure should be based on AUCs determined in studies in which subjects received 20 mg t.i.d.

3. Under the section "Pregnancy", doses in rats and rabbits are expressed as surface area-based multiples of the human dose. It is preferable to compare animal to human exposures on the basis of AUCs when that data is available.

4. Although comparisons of animal and human exposures should be made on the basis of AUCs or body surface area, animal doses expressed in mg/kg should be included whenever animal studies are described. This information was not provided for the rat carcinogenicity study.

Because the sponsor may not be able to provide revised dose multiples prior to the PDUFA goal date, the Division may allow the information from the Viagra labeling to be used in the Revatio label, with a commitment from the sponsor to revise the label in a post-approval supplement.

Conclusion: Based on: (1) the extensive clinical experience with sildenafil for the treatment of erectile dysfunction at doses comparable to those proposed for the new indication, (2) the extensive pharmacology and toxicology studies conducted for both indications (i.e., erectile dysfunction and pulmonary arterial hypertension), and (3) the lack of any significant safety concerns for the indicated patient population at the recommended dosing regimen of 20 mg t.i.d. (3X/day), NDA #21-845 is approvable from a pharmacology and toxicology perspective.

Biopharmaceutics Review

Reviewer: Elena Mishina, Ph.D.
Labeling: The Biopharmaceutics' team's labeling recommendations have been incorporated into the labeling during negotiations with the sponsor.
Conclusion: The Office of Clinical Pharmacology and Biopharmaceutics has reviewed NDA 21-845 and finds the clinical pharmacology and biopharmaceutics sections acceptable.

A 20 mg tablet has been developed for the PAH indication. These tablets are manufactured from — which is qualitatively and quantitatively similar to the commercial Viagra ® formulation. The minor differences in the tablet presentations for each indication are a change in tablet shape and the color of the film coat which are Level I changes. The in vitro dissolution method and specifications for sildenafil citrate tablets, 20 mg, are identical to the same of VIAGRA tablets and are shown below.

Condition	Recommendation
Dissolution Medium	0.01N HCL
Basket Speed	100 rpm
USP Apparatus I	
Volume	900 mL
Specifications	— in 15 minutes

Secondary Medical Review

Reviewer: Tom Marciniak, M.D.
Labeling: Dr. Marciniak's labeling recommendations have been incorporated into the labeling during negotiations with the sponsor.
Conclusion: Dr. Marciniak recommends approval of sildenafil for the treatment of pulmonary arterial hypertension (PAH). The single pivotal study shows convincingly and highly statistically significantly that sildenafil use improves function, i.e., walking distance, in patients with PAH. The

lowest dose tested, 20 mg TID, appears to be as effective as the higher doses tested. The adverse effect profile seems acceptable relative to the benefit and compared to adverse event profiles of other approved drugs. I do recommend that a post-marketing study be performed testing lower doses of sildenafil and a sildenafil- warfarin interaction study be done.

RHPM Comments:

An approval-on-draft-labeling letter will be drafted for Dr. Stockbridge's signature.

**APPEARS THIS WAY
ON ORIGINAL**

MEMORANDUM OF TELECON

DATE: May 13, 2005

APPLICATION NUMBER: NDA 21-845, Sildenafil

BETWEEN: Pfizer

AND Division of Cardio-Renal Drug Products, Pharmacology Team
 B. Nhi Beasley, Pharm. D., Pharmacometrics
 Joga Gobburu, Ph. D., Team Leader, Pharmacometrics
 Elena Mishina, Ph.D., Clinical Pharmacology
 Dianne Paraoan, Regulatory Health Project Manager

PURPOSE: To discuss the population PK/PD model developed by the sponsor for sildenafil in the treatment of pulmonary hypertension to aid in justifying the dose selection. This application has a goal date of June 3, 2005.

BACKGROUND: In preparation for this teleconference, Pfizer was provided with an agenda, focusing on two questions to be discussed on May 11, 2005. Pfizer in turn, provided the group, this morning, a draft response to question 1.

DISCUSSION:

Pfizer began the discussion by explaining Figure 2 (PVRi Change from Baseline vs. Sildenafil Plasma Concentrations: Full Concentration Range) of their response. The sponsor stated that there was no general trend change of higher PVRI from baseline with increasing sildenafil plasma levels. They added that the low population mean estimate is accurate. The sponsor referenced Figure 4 (Study 1140- Placebo-Corrected Treatment Effects- Mean and 95% Confidence Intervals) to support their conclusion. Pfizer will send the data on the outliers to the Division on Monday.

Dr. Gobburu informed the sponsor that the reason for this teleconference was to allow the sponsor to provide justification as to why the 20 mg dose is recommended given the flat dose-6MWD relationship. He then commented that indeed, Figure 4 provides for some evidence supporting a 20 mg dose, but one must exclude the outliers to come to that conclusion.

The sponsor justified the 20 mg TID dose from the data available from study 1024 and the data from Viagra to make their dosage plan. They believe that their dose is efficacious, well tolerated, and provides for a good benefit to risk relation. Since pulmonary hypertension is a progressive disease in which patients deteriorate rapidly, Pfizer stated that a lower dose would be potentially detrimental. They added that they do not have the data to support the lower dose.

Dr. Gobburu informed the sponsor that there is a considerable difference in the design and PK/PD effects between study 1140 and 1024. Study 1024 provides much more controlled

measurement of PK/PD. Pfizer concurred that there is a difference between both trials. One specific difference is the concentration effect relationship. Because of the risks of right heart catheterization, further catheterization was not possible. They acknowledged that they would have liked to have had more data on the concentration effect relationship.

The sponsor provided the Division with a partial response to question 2 for study 1140. They stated that although, it is routinely done, they intentionally did not account for placebo effect when they estimated the drug effect. They commented that they did attempt to run them together, but because they got large standard errors, they had less confidence in the model when together. Therefore, the models were done separately. Dr. Gobburu informed the sponsor that the Division tested the models as required, and concluded that it did not make a significant difference.

Dr. Gobburu offered the sponsor to contact the Division if they need further clarification on the questions.

ACTION ITEMS:

1. Pfizer will submit an official response to the questions discussed in this teleconference next week to include data on the outliers.

Joga Gobburu, Ph. D.
Team Leader, Pharmacometrics

Attached:

1. Agenda
2. Sponsor response to Question 1

Draft: 13May05 Final: 23May05

RD:

Gobburu: 5/20/05

Beasley: 5/19/05

Mishina: 5/19/05

Attachment 1

**Agenda for Discussion Between
Cardio-Renal Clinical Pharmacology Group and Pfizer
NDA 21-845 N 000**

Subj: Discuss the population PK/PD model developed by the sponsor for sildenafil in the treatment of pulmonary hypertension to aid in justifying the dose selection

Date: Friday, May 13, 2005

Time: 11 am - 12 noon, EST

Location: Conf Rm F

Attendees: Patrick Marroum, Team Leader Clinical Pharmacology
Joga Gobburu, Team Leader Pharmacometrics
Nhi Beasley, Pharmacometrics Reviewer
Atul Bhattaram, Pharmacometrics Reviewer
Elena Mishina, Clinical Pharmacology Reviewer
Dianne Paraoan, project manager covering for Russell Fortney

The t-con will primarily focus on the following question.

1. What are the potential reasons for the discrepancy between the low EC50 (2.92 ng/mL) values derived using the concentration-PVRI relationship (model 217) and the non-saturating dose response (Figure 1)?

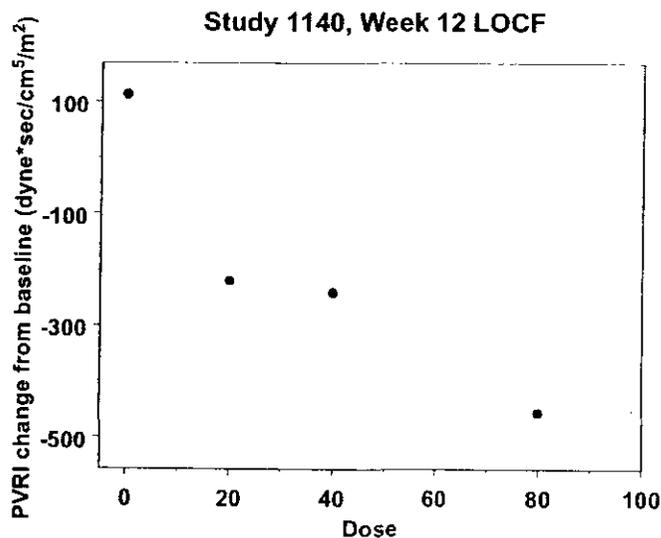


Figure 1. Change in PVRI from baseline versus dose, obtained from page 62 of study 1140 clinical report.

If time permits FDA pharmacometricians would like clarification on the following:

2. We would like to obtain clarification on the pharmacodynamic models used to describe the concentration-PVRI relationship for the studies 1024 and 1140 (models 2133 and 217, respectively).

a. The equations for PLA and ACT, in our opinion, do not account for placebo effect when estimating the drug effect. For example, consider the run217 model (study 1140):

$$\begin{aligned} \text{BASE} &= \text{BLA} * \text{ISA} + 0.01 \\ \text{EMAX} &= \text{EMA} * \text{ISA} + 0.01 \\ \text{P50} &= \text{EC50} * \text{ISA} + 0.01 \\ \text{INT} &= \text{BLP} * \text{ISP} + 0.01 \\ \text{SLOP} &= \text{SL} * \text{ISP} + 0.01 \end{aligned}$$

$$\text{ACT} = \text{BASE} * (1 - \text{EMAX} * \text{CONC} / (\text{P50} + \text{CONC})) \quad (1)$$

$$\text{PLA} = \text{INT} + (\text{SLOP} * \text{TIME}) \quad (2)$$

$$\text{F} = \text{PLA} + \text{ACT} \quad (3)$$

Consider a patient receiving the active drug. The equations 1, 2 and 3 can be represented as:

$$\begin{aligned} \text{ACT} &= \text{BLA} * (1 - \text{EMA} * \text{CONC} / (\text{EC50} + \text{CONC})) \\ \text{PLA} &= 0 \text{ (as it is } 0 + (0 * \text{TIME})) \\ \text{F} &= 0 + \text{ACT} \end{aligned}$$

Hence, our interpretation is that the model does not account for placebo effect when estimating the drug effect. A similar derivation for the model2133 (study 1024) showed that the placebo effect, in fact, uses the same parameters as the drug effect, as shown below:

$$\begin{aligned} \text{BASE} &= \text{BLP} * \text{ISP} + \text{BLA} * \text{ISA} \\ \text{EMAX} &= \text{EMP} * \text{ISP} + \text{EMA} * \text{ISA} \\ \text{P50} &= \text{TE50} * \text{ISP} + \text{EC50} * \text{ISA} \end{aligned}$$

$$\text{PLA} = \text{BASE} * (1 - \text{EMAX} * \text{TIME} / (\text{P50} + \text{TIME})) \quad (4)$$

$$\text{ACT} = \text{BASE} * (1 - \text{EMAX} * \text{CONC} / (\text{P50} + \text{CONC})) \quad (5)$$

$$\text{F} = \text{PLA} + \text{ACT} \quad (6)$$

Consider a patient receiving the active drug. The equations 4, 5 and 6 can be represented as:

$$\begin{aligned} \text{PLA} &= \text{BLA} * (1 - \text{EMA} * \text{TIME} / (\text{EC50} + \text{TIME})) \\ \text{ACT} &= \text{BLA} * (1 - \text{EMA} * \text{CONC} / (\text{EC50} + \text{TIME})) \end{aligned}$$

The parameters EMA and EC50 are used for both the placebo and drug effects. Similarly, the parameters for PLA are different for patients who receive placebo (ie., they will be EMP and TE50).

**APPEARS THIS WAY
ON ORIGINAL**

Attachment 2

Response to FDA question 1: Discrepancy between linear dose response for the change from BL of PVRI and low EC50 estimated in the population PK/PD analysis of study A148 1140.

Figure 1 and Figure 2 show the absolute change from baseline of PVRI data versus sildenafil plasma concentrations at the time of the PVRI measurements, which have been used in the population PK/PD analysis of study A148 1140. Figure 1 shows the concentration range up to 100 ng/ml, Figure 2 shows the full concentration range for each dose group.

Figure 2 shows that a few patients on 80 mg TID had high sildenafil plasma levels and high changes of PVRI from baseline. The higher mean change from baseline shown in the plot provided by the FDA reviewers at 80 mg TID compared to the lower doses is very likely due to these outliers. Figure 1 and Figure 2 also show that there is no overall trend of higher PVRI changes from baseline with increasing sildenafil plasma levels. Therefore, the low population mean estimate of the EC50 appears to be correct.

Figure 1: A148 1140 PVRI Change from Baseline vs Sildenafil Plasma Concentrations: Concentrations up to 100 ng/ml

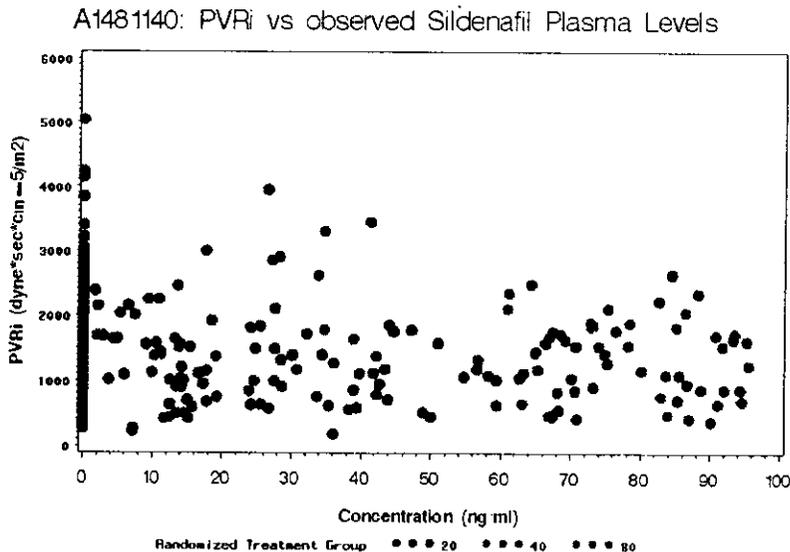


Figure 2: A1481140 PVRI Change from Baseline vs Sildenafil Plasma Concentrations: Full Concentration Range

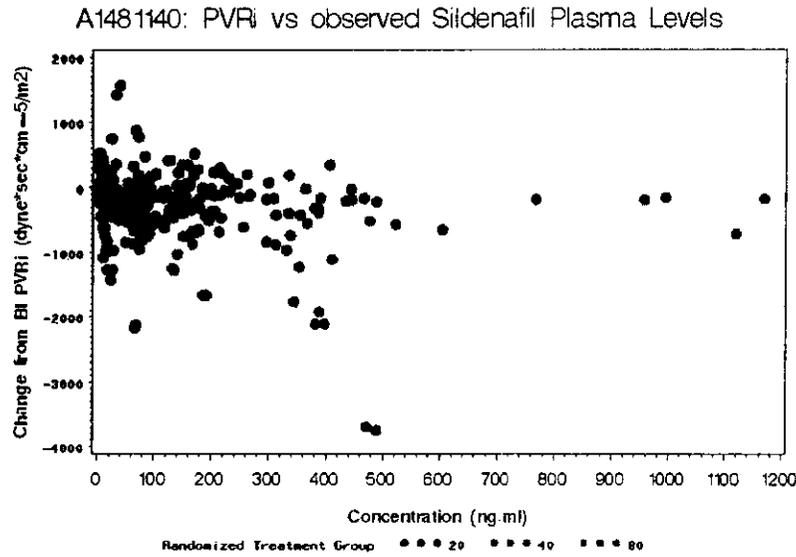


Figure 3 presents the mean changes from baseline to Week 12 LOCF in PVRI together with corresponding confidence intervals. This shows considerable overlap of the confidence intervals between the sildenafil dose groups and hence, supports the conclusion that there is no significant difference between the sildenafil dose groups in the changes from baseline to Week 12 in PVRI.

Figure 3: A1481140 Change from Baseline to Week 12 (LOCF) in PVRI – Mean and 95% confidence intervals

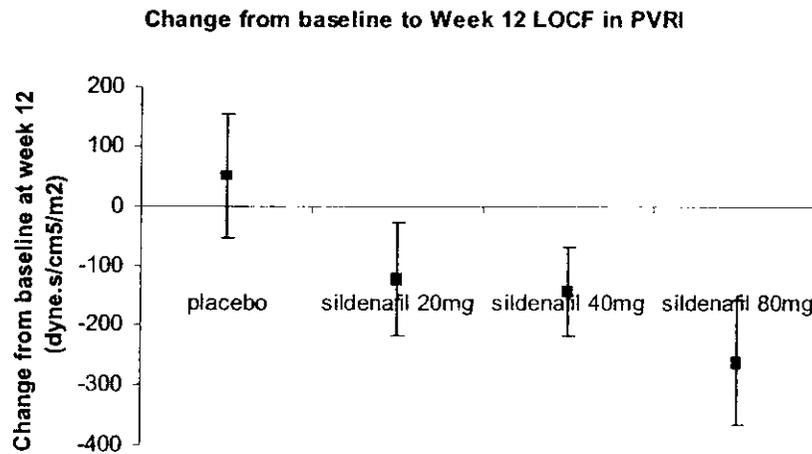
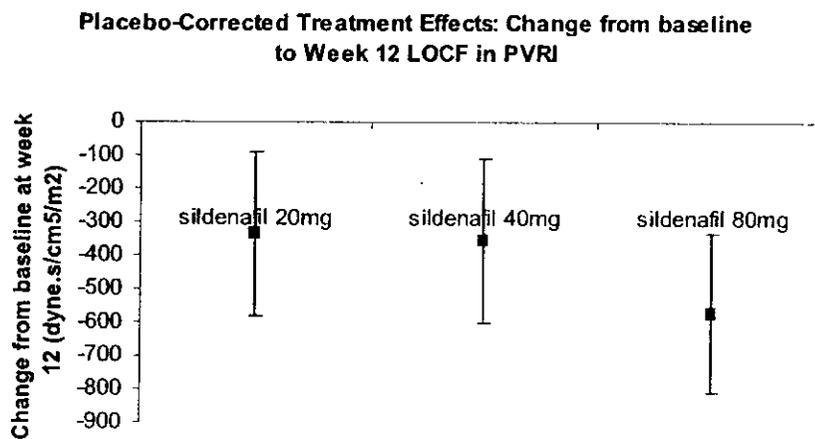


Figure 4 presents the mean placebo-corrected effects in changes from baseline to Week 12 LOCF in PVRI together with corresponding confidence intervals. This also shows considerable overlap of the confidence intervals between the sildenafil dose groups and provides further evidence that there is no significant difference between the sildenafil dose groups with respect to the treatment effects seen in PVRI.

Figure 4: A1481140 Placebo-Corrected Treatment Effects – Mean and 95% confidence intervals



Conclusions

The outliers highlighted in Figure 2 above appear to be influencing the mean change from baseline to Week 12 (LOCF) in the 80mg dose group. Assessing mean changes in the context of confidence intervals shows there is a substantial overlap in the confidence intervals among dose groups, providing evidence to support the lack of a significant difference between sildenafil dose groups in PVRI and hence, for the low population mean estimate of the EC50.

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/s/

Jogarao Gobburu
5/23/05 09:07:16 AM



APR 7 2005

Food and Drug Administration
Rockville MD 20857

Dianne Zwicke, M.D.
University of Wisconsin
2801 W KK River Parkway Suite 440
Milwaukee, Wisconsin 53215

Dear Dr. Zwicke:

Between February 16 and 22, 2005, Ms. Denise Burosh, representing the Food and Drug Administration (FDA), conducted an investigation to review your conduct of the following clinical study: Protocol A1481140, "A multinational, multi-centre, randomised, double-blind, double-dummy, placebo-controlled study to assess the efficacy and safety of 20, 40, and 80 mg sildenafil three times a day (TIC) in the treatment of pulmonary arterial hypertension (PAH) in subjects aged 18 years and over." This study of the investigational drug sildenafil was performed for Pfizer, Inc.

This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

From our review of the establishment inspection report, the documents submitted with that report, and your March 28, 2005 written response, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations. We are aware that at the conclusion of the inspection, Ms. Burosh presented and discussed with you the Form FDA 483, Inspectional Observations. We wish to emphasize the following:

You did not adhere to the investigational plan [21 CFR 312.60]. For example,

- a. The protocol required that all observed or volunteered events regardless of treatment group or suspected causal relationship to study drug be recorded on the adverse event page of the case report form. Subject 10251 had reported lens opacity at study visit 12 that was not noted at baseline, but this event was not recorded on the case report form.
- b. The protocol required that the 6-minute walk test be performed at screening, baseline, study week 4, 8, 12 and at follow-up (if withdrawn from the study). The protocol also required that the test be performed as close to trough levels of sildenafil as possible (i.e., just prior to dosing and at least 4 hours after the previous dose). The six minute walk test was performed at < 4 hours after the last dose for subject 10247 at study weeks 4 and 12. Similarly, subject 10264 had the six minute walk test performed at < 4 hours after the last dose at study week 4.
- c. The protocol required that a third pharmacokinetic (PK) blood sampling be collected > 6-8 hours post first dose of the day. The PK sample was obtained at 5 hours rather than at

Page 2 -- Dianne Zwicke, M.D.

> 6-8 hours post dose for subject 10264 at study week 12.

Please make appropriate corrections in your procedures to assure that the findings noted above are not repeated in any ongoing or future studies. Any response and all correspondence will be included as a permanent part of your file.

We appreciate the cooperation shown Investigator Burosh during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,



Leslie K. Ball, M.D.
Branch Chief
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

Page 3 -- Dianne Zwicke, M.D.

FEI: 3004972068

Field Classification: VAI

Headquarters Classification:

1)NAI

2)VAI- no response required

3)VAI- response requested

4)OAI

If Headquarters classification is a different classification, explain why:

cc:

HFA-224

HFD-110/Doc.Rm./NDA 21-845

HFD-110/Stockbridge/Director

HFD-570/Gordon/MO

HFD-570/Fortney/PM

HFD-46/47c/r/s/ GCP File #11445

HFD-47/Pratt/Ball

HFD-45/Salewski/Laddon

HFR-CE850/DIB/Bigham

HFR-CE850/BIMO/Matson

HFR-CE8590/FI/Burosh

GCF-1 Seth Ray

r/d: Pratt/3/31/2005

reviewed: LKB: 3/31/2005

f/t:eip: 4/4/05

o:/pratt/Zwicke-VAI.doc

Page 4 -- Dianne Zwicke, M.D.

Reviewer Note to Rev. Div. M.O.

Pfizer submitted a type 6P NDA 21-845 for sildenafil in support of a new indication for the treatment of pulmonary arterial hypertension. Dr. Zwicke has not been previously inspected.

The pivotal study, protocol A1481140, was audited. A total of 7 subjects were enrolled at this site. The inspection reviewed case report forms, data listings and source documents. Source documents included progress notes, IRB and sponsor correspondences, drug accountability records, lab reports, medical charts, ocular tests, 6-minute walk tests, subject diaries, ECGs, concomitant medications, informed consent documents and adverse event records. The data listings from the EDR were verified with on site documentation for selected subjects; no significant findings were identified.

The inspection found that Dr. Zwicke was not in compliance with applicable regulations and a 483 was issued on 2/22/05 for minor protocol violations, as noted herein. The inspection is classified VAI. Data at this site appear acceptable.

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/s/

Leslie Ball

4/11/05 06:27:01 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

APR - 4 2005

Food and Drug Administration
Rockville MD 20857

Adanni E. Frost, M.D.
Baylor College of Medicine
6550 Fannin, Suite 1236
Houston, Texas 77030

Dear Dr. Frost:

Between February 14 and 18, 2005, Ms. Jocelyn Turner, representing the Food and Drug Administration (FDA), conducted an investigation to review your conduct of the following clinical study: Protocol A1481140, "A multinational, multi-centre, randomised, double-blind, double-dummy, placebo-controlled study to assess the efficacy and safety of 20, 40, and 80 mg sildenafil three times a day (TIC) in the treatment of pulmonary arterial hypertension (PAH) in subjects aged 18 years and over." This study of the investigational drug sildenafil was performed for Pfizer, Inc.

This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

From our inspection of the establishment inspection report and the documents submitted with that report, we conclude you have adhered to the applicable statutory requirements and FDA regulations governing the conduct of the clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Investigator Turner during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

Leslie K. Ball, M.D.
Branch Chief
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

Page 2 -- Adanni E. Frost, M.D.

FEI: 3003231466

Field Classification: NAI

Headquarters Classification:

1)NAI

2)VAI- no response required

3)VAI- response requested

4)OAI

If Headquarters classification is a different classification, explain why:

cc:

HFA-224

HFD-110/Doc.Rm./NDA 21-845

HFD-110/Stockbridge/Director

HFD-570/Gordon/MO

HFD-570/Fortney/PM

HFD-46/47c/t/s/ GCP File #11438

HFD-47/Pratt/Ball

HFD-45/Salewski/Laddon

HFR-SW150/DIB/Thornburg

HFR-SW1540/BIMO/Martinez

HFR-CE650/Fl/Turner

GCF-1 Seth Ray

r/d: Pratt/3/28/2005

reviewed: LKB: 3/28/05

f/t:eip: 3/31/2005

o:/pratt/Frost-NAI.doc

Page 3 -- Adanni E. Frost, M.D.

Reviewer Note to Rev. Div. M.O.

Pfizer submitted a type 6P NDA 21-845 for sildenafil in support of a new indication for the treatment of pulmonary arterial hypertension. Dr. Frost was previously inspected in January 2001 and was classified NAI.

The pivotal study, protocol A1481140, was audited. A total of 11 subjects were screened at this site; 8 randomized and 7 completed the study. The inspection reviewed case report forms, data listings and source documents. Source documents included progress notes, IRB and sponsor correspondences, drug accountability records, lab reports, medical charts, ocular tests, 6-minute walk tests, subject diaries, ECGs, concomitant medications, informed consent documents and adverse event records. The data listings from the EDR were verified with on site documentation for selected subjects; no significant findings were identified.

The inspection found that Dr. Frost was in compliance with applicable regulations and no 483 was issued. The inspection is classified NAI. Data at this site appear acceptable.

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/s/

Leslie Ball
4/7/05 11:32:05 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-845

Pfizer, Inc.
Attention: Ms. Martha C. Brumfield
235 E. 42nd Street
New York, NY 10017

Dear Ms. Brumfield:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Revatio™ (sildenafil citrate) 20 mg Tablets
Review Priority Classification:	Priority (P)
Date of Application:	December 2, 2004
Date of Receipt:	December 3, 2004
Our Reference Number:	NDA 21-845

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 1, 2005, in accordance with 21 CFR 314.101(a). If we file the application, the user fee goal date will be June 3, 2005.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

U.S. Postal Service:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products, HFD-110
Attention: Division Document Room, 5002
5600 Fishers Lane
Rockville, Maryland 20857

NDA 21-845

Page 2

Courier/Overnight Mail:

Food and Drug Administration

Center for Drug Evaluation and Research

Division of Cardio-Renal Drug Products, HFD-110

Attention: Division Document Room, 5002

1451 Rockville Pike

Rockville, Maryland 20852

If you have any questions, please call:

Mr. Russell Fortney

Regulatory Health Project Manager

(301) 594-5311

Sincerely,

{See appended electronic signature page}

Edward Fromm

Chief, Project Management Staff

Division of Cardio-Renal Drug Products

Office of Drug Evaluation I

Center for Drug Evaluation and Research

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/s/

Edward Fromm
12/15/04 12:26:21 PM

PRESCRIPTION DRUG USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: <http://www.fda.gov/cder/pdufa/default.htm>

1. APPLICANT'S NAME AND ADDRESS Pfizer Inc 235 East 42 nd Street New York, NY 10017	4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER
2. TELEPHONE NUMBER (Include Area Code) (212) 733-5406	5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM IF RESPONSE IS "YES" CHECK THE APPROPRIATE RESPONSE BELOW <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO: _____ (APPLICATION NO. CONTAINING THE DATA)
3. PRODUCT NAME Sildenafil Citrate for the treatment of Pulmonary Arterial Hypertension (PAH)	6. USER FEE ID NUMBER 4844

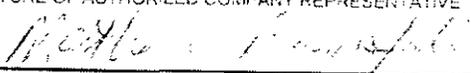
7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO CHECK THE APPLICABLE EXCLUSION.

<input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9-1-92 (Self Explanatory)	<input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE (See item 7, reverse side before checking box.)
<input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)	<input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (Self Explanatory)

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? YES NO
(See item 8, reverse side if answered YES)

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services Food and Drug Administration CBER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448	and	Food and Drug Administration CDER, HFD-94 12420 Parklawn Drive, Room 3046 Rockville, MD 20852	An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.
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SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE 	TITLE VP and Site Lead NY Worldwide Regulatory Affairs and Quality Assurance	DATE 12/20/06
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REVATIO™ (sildenafil citrate)
Pulmonary Arterial Hypertension
NDA 21-845

Module 1.3.8 CLAIM FOR CATEGORICAL EXCLUSION OF ENVIRONMENTAL ASSESSMENT
[21CFR314.50(d)(1)(iii)]

Pursuant to 21 CFR § 314.50 ¶ (d) (1) (iii) and 21 CFR § 25.31 ¶ (b), Pfizer Inc claims categorical exclusion from Environmental Assessment, as described in 21 CFR § 25.40, and Environmental Impact Statement, as described in 21 CFR § 25.42, for sildenafil citrate as the action on the NDA will increase the use of the active moiety, but the estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 part per billion.

Furthermore, Pfizer Inc is unaware of any extraordinary circumstances for which available data establish that, at the expected level of exposure, there is the potential for serious harm to the environment or that would adversely affect a species or the critical habitat of a species determined under the Endangered Species Act or the Convention on International Trade in Endangered Species of Wild Flora and Fauna to be endangered or threatened or wild flora or fauna that are entitled to special protection under some other Federal law.

The undersigned certifies that the information presented is true, accurate, and complete to the best knowledge of Pfizer Inc:


Richard T. Williams, Ph.D.
Senior Research Fellow
Pfizer Global Research and Development

10/25/04
Date

CONSULTATION RESPONSE
DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)

DATE RECEIVED: October 5, 2004	DESIRED COMPLETION DATE: December 5, 2004 PDUFA DATE: June 3, 2005	ODS CONSULT #: 04-0270
TO: Norman Stockbridge, M.D. Acting Director, Division of Cardio-Renal Drug Products HFD-110		
THROUGH: Russell Fortney Project Manager HFD-110		
PRODUCT NAME: Revatio (Sildenafil Citrate Tablets) 20 mg NDA # 21-845 (IND#: 64,924)		NDA SPONSOR: Pfizer
SAFETY EVALUATOR: Linda M. Wisniewski, RN		
RECOMMENDATIONS:		
<ol style="list-style-type: none"> 1. DMETS does not recommend the use of a second proprietary name for Sildenafil Citrate. We discourage the practice of the use of two tradenames from the same manufacturer for the same active ingredient for this product as described in section IID-1. However, we have not identified any proprietary names that would render the name objectionable from a look-alike or sound-alike perspective. If approved as Revatio, we recommend implementation of the Risk Management recommendations as described in section IID of this review. This is considered a final decision. However, if the approval of this application is delayed beyond 90 days from the signature date of this document, the name and its associated labels and labeling must be re-evaluated. A re-review of the name will rule out any objections based upon approval of other proprietary or established names from the signature date of this document. 2. DMETS recommends implementation of the label and labeling revisions outlined in section III of this review that might lead to safer use of the product. We would be willing to revisit these issues if the Division receives another draft of the labeling from the manufacturer. 3. DDMAC finds the proprietary name Revatio acceptable from a promotional perspective. 		
Denise Toyer, PharmD. Deputy Director Division of Medication Errors and Technical Support Office of Drug Safety Phone: (301) 827-3242 Fax: (301) 443-9664		Carol Holquist, RPh Director Division of Medication Errors and Technical Support Office of Drug Safety Phone: (301) 827-3242 Fax: (301) 443-9664

1 Page(s) Withheld

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

 § 552(b)(5) Deliberative Process

 § 552(b)(5) Draft Labeling

**Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; PKLN Rm. 6-34
Center for Drug Evaluation and Research**

PROPRIETARY NAME REVIEW

DATE OF REVIEW: October 21, 2004
NDA# 21-845 (IND # 64,924)
NAME OF DRUG: Revatio (Sildenafil Citrate Tablets) 20 mg
IND HOLDER: Pfizer

I. INTRODUCTION:

This consult was written in response to a request from the Division of Cardio-Renal Drug Products (HFD-110), for assessment of the proprietary name, "Revatio", regarding potential name confusion with other proprietary or established drug names. The sponsor proposes to market sildenafil citrate tablets with a new indication of use, pulmonary arterial hypertension, under the proprietary name Revatio. The sponsor currently markets sildenafil citrate tablets under the proprietary name Viagra, which has been marketed since its approval on March 27, 1998, for use in patients with erectile dysfunction (NDA 20-895). The firm submitted this name, Revatio, for review and comment. Draft container labels, carton and insert labeling were provided for review and comment at this time.

PRODUCT INFORMATION

Revatio is the proposed proprietary name for sildenafil citrate used for the treatment of pulmonary arterial hypertension. The recommended dose of Revatio is 20 mg three times a day and should be taken approximately six to eight hours apart, with or without food. It is supplied as 20 mg tablets in bottles of 90 tablets.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts^{1,2} as well as several FDA databases³ for existing drug names which sound-alike or look-alike to Revatio to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted⁴. The Saegis⁵ Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription

¹ MICROMEDEX Integrated Index, 2004, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

² Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

³ AMF Decision Support System [DSS], Drugs@FDA, the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, and the electronic online version of the FDA Orange Book.

⁴ WWW location <http://www.uspto.gov/tmdb/index.html>.

⁵ Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at www.thomson-thomson.com

study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name Revatio. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC finds the proprietary name Revatio acceptable from a promotional perspective.
2. The Expert Panel identified three proprietary names that were thought to have the potential for confusion with Revatio. These products are listed in Table 1 (see below), along with the dosage forms available and usual dosage.

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Proprietary Name	Dosage Form(s), Established name	Usual adult dose*	Other**
Revatio	Sildenafil Citrate Tablets 20 mg	20 mg three times a day	N/A
Rondec	Drops: Pseudoephedrine HCl and Carbinoxamine Maleate 15 mg/1 mg per mL. Syrup: Pseudoephedrine HCl and Brompheniramine Maleate 45 mg/4 mg per mL Tablets: Pseudoephedrine HCl and Carbinoxamine Maleate 60 mg/4 mg	Pediatric dosing: 1 to 3 months: 0.25 mL q.i.d. 3 to 6 months: 0.5 mL q.i.d. 6 to 12 months: 0.75 mL q.i.d. 12 to 24 months: 1 mL q.i.d. 5 mL q.i.d. 1 tablet q.i.d.	L/A
Rondec-DM	Drops: Pseudoephedrine HCl, Carbinoxamine Maleate and Dextromethorphan HBr 15 mg/1 mg/4 mg per mL Syrup: Pseudoephedrine HCl, Brompheniramine Maleate and Dextromethorphan HBr 45 mg/4 mg/15 mg per mL	Pediatric dosing: 1 to 3 months: 0.25 mL q.i.d. 3 to 6 months: 0.5 mL q.i.d. 6 to 12 months: 0.75 mL q.i.d. 12 to 24 months: 1 mL q.i.d. 5 mL q.i.d.	L/A
Rondec-TR	Pseudoephedrine Hydrochloride and Carbinoxamine Maleate Timed-Release Tablets: 120 mg/8 mg	1 tablet b.i.d.	L/A

*Frequently used, not all-inclusive.
**L/A (look-alike), S/A (sound-alike)

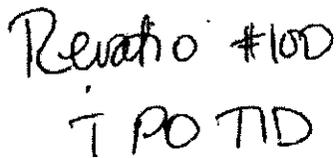
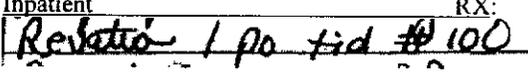
B. PHONETIC and ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. The phonetic search module returns a numeric score to the search engine based on the phonetic similarity to the input text. Likewise, an orthographic algorithm exists which operates in a similar fashion. All names considered to have significant phonetic or orthographic similarities to Revatio were discussed by the Expert Panel.

C. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of Revatio with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 122 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Revatio (see below). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
<p>Outpatient RX:</p> 	<p>Revatio: One three times a day. # 100</p>
<p>Inpatient RX:</p> 	

2. Results:

None of the interpretations of the proposed name overlap, sound similar, or look similar to any currently marketed U.S. product. See Appendix A for the complete listing of interpretations from the verbal and written studies.

D. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name Revatio, the primary concerns related to potential safety concerns that may arise from the use of dual tradenames (Revatio and Viagra) for the product Sildenafil Citrate. In addition, we identified the following possible look-alike and sound-alike names that have the potential for confusion with Revatio: Rondec, Rondec-DM, Rondec-TR, and Renotec.

Upon further review of the names gathered from EPD, the name Renotec will not be reviewed further. Renotec appears in the discontinued section of the Orange Book. Additionally, no dosing information or reference to the active ingredient in Renotec (Technetium TC-99M Ferpentate) can be found in commonly used references such as Drug Facts and Comparison, Physician's Desk Reference, DestinationRx.com, Rx.com, and the Red Book.

DMETS also conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that the proposed name could be confused with any of the aforementioned names. However, negative findings are not predicative as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to a small sample size. The majority of misinterpretations were misspelled/phonetic variations of the proposed name, Revatio.

1. Dual Tradename Concerns:

The sponsor proposes to market sildenafil citrate tablets under two proprietary names, Viagra and the pending application Revatio. In essence, if approved, sildenafil citrate will be available from the same manufacturer with two different names (Viagra and Revatio). Confusion may arise if practitioners are not aware that Viagra and Revatio are the same drug product. Viagra is a name that is associated with a very publicized adverse event profile. Additionally, we are concerned that the use of the name Revatio may result in concomitant administration of both products or be administered to a patient with a documented allergy, hypersensitivity, or intolerance to the active ingredient not knowing both products contain the same active ingredient.

a. Safety Concerns Discussed with Cardio-renal and Reproductive/Urologic Drug Products

DMETS discussed their dual trade name safety concerns with representatives of the Cardio-renal Revatio review team and Dr. Mark Hirsch (Team Leader, Division of Reproductive and Urologic Drug Products) at a telecon held on May 6, 2005. The following issues were addressed during this telecon.

- i. Viagra's adverse event profile is well known by prescribers, emergency medical personnel, patients, and consumers. Since the safety profile is so well known, healthcare providers (e.g., pharmacists, paramedics, E.R. physicians, etc) will ask patients before treating/dispensing about their previous use of Viagra. Thus preventing concomitant administration of nitrates in these patients. One of DMETS' concerns is that healthcare practitioners, (paramedics, emergency room physicians, etc), other than cardiologists/pulmonologists, are unlikely to know that Revatio contains the same active ingredient as Viagra. These healthcare practitioners and emergency personnel may not be aware that sildenafil is being

used for indications of use other than erectile dysfunction. Additionally, it is unlikely that patients taking Revatio would positively respond to a question concerning the use of Viagra (sildenafil). Therefore, the potential for adverse outcomes may exist if any of these patients are treated with nitrates while concomitantly taking Revatio.

- ii. DMETS is generally concerned with the co-administration of Revatio and Viagra and the potential resultant adverse events. The sponsor conducted a study to determine if the adverse event profile would change with an increased dose of sildenafil. The sponsor used individual doses of 20 mg t.i.d., 40 mg t.i.d., and 80 mg t.i.d. (total daily doses of 60 mg/day, 120 mg/day, and 240 mg/day, respectively). These dosing regimens would include the total daily dose that a patient on Viagra (maximum 100 mg/day) and Revatio (maximum 60 mg/day) could concurrently be prescribed. DMETS notes that the three treatment groups included similar numbers of participants (n=69, n=67, and n=71 for the 20 mg t.i.d., 40 mg t.i.d., and 80 mg t.i.d., respectively). Based on the study results, patients who received two times and four times the recommended daily dose of Revatio experienced similar adverse events as those in the 60 mg/day group. Table 2 below lists the adverse events seen in the different treatment groups. The adverse events seen, appear to be comparable across all treatment groups except for myalgia, pyrexia, and visual disturbances. For these three events, the number of cases seen in the 240 mg group appear substantially larger than those seen in the lower treatment groups or in the placebo group. The sponsor states in the package insert that 'patients across WHO functional classes I-IV participated in the study', and that the study population consisted of 25% male and 75% women. This is consistent with the most likely targeted patient population as indicated in the literature, where the condition exists more often in women with a 1:1.7 ratio and with the World Health Organization (WHO) classification of pulmonary hypertension as four functional classes⁶. DMETS does not know if this is a statistically significant difference. However, during discussions with the Revatio review team, they indicated that if a patient takes Viagra 100 mg and Revatio 20 mg the potential adverse events are not significant.

Table 2. Sildenafil Adverse Events More Frequent than Placebo in 23% of Patients.

ADVERSE EVENT (%)	Placebo (N=70)	SILDENAFIL TREATMENT GROUPS			
		20 mg (N=69)	40 mg (N=67)	80 mg (N=71)	Total (N=207)
Headache	39	46	42	49	46
Flushing	4	10	9	16	12
Dyspepsia	7	13	6	13	11
Back pain	11	13	13	9	12
Diarrhea	6	9	12	19	19
Limb pain	6	7	13	9	10
Myalgia	4	7	6	14	9
Cough	6	7	5	9	7
Epistaxis	1	9	9	4	7
Pyrexia	3	6	3	10	6
Influenza	3	6	5	2	5
Vertigo	1	1	5	3	3
Gastritis	0	3	3	2	3
Erythema	0	6	2	1	3
Insomnia	1	7	5	2	6
Visual disturbance*	0	0	5	7	2
Dyspnea (exacerbated)	3	7	2	1	3
Sinusitis	0	3	5	1	3
Paresthesia	0	3	5	1	3
Rhinitis	0	4	2	3	3

*Visual disturbances: Mild and transient, predominantly color tinge changes, but also increased sensitivity to light or blurred vision.

⁶ Nauser, T. & Stites, S. (2001). *Diagnosis and Treatment of Pulmonary Hypertension*. American Family Physician, 63, 9, 1789-1798.

- iii. Despite the sponsor's study, DMETS is more concerned with the co-administration of Revatio and Viagra in the HIV infected population. A large majority of these patients will be taking a protease inhibitor. The following interactions were noted in the Revatio insert labeling:

'In a study performed in healthy volunteers, co-administration of the HIV protease inhibitor saquinavir, a CYP3A4 inhibitor, at steady state (1200 mg t.i.d.) with sildenafil (100 mg single dose) resulted in a 140% increase in sildenafil C_{max} and a 210% increase in sildenafil AUC. Stronger CYP3A4 inhibitors will have still greater effects on plasma levels of sildenafil (see **DOSAGE AND ADMINISTRATION**).

In another study in healthy volunteers, co-administration with the HIV protease inhibitor ritonavir, a potent CYP3A4 inhibitor, at steady state (500 mg b.i.d.) with sildenafil (100 mg single dose) resulted in a 300% (4-fold) increase in sildenafil C_{max} and a 1000% (11-fold) increase in sildenafil plasma AUC. At 24 hours, the plasma levels of sildenafil were still approximately 200 ng/mL, compared to approximately 5 ng/mL when sildenafil was dosed alone. This is consistent with ritonavir's marked effects on a broad range of P450 substrates (see **WARNINGS and DOSAGE AND ADMINISTRATION**). Although the interaction between other protease inhibitors and REVATIO has not been studied, their concomitant use is expected to increase sildenafil levels.'

Moreover, these patients may also be using Viagra for erectile dysfunction. Co-administration of Revatio, Viagra, and protease inhibitors may result in adverse outcomes as a result of this known drug interaction. We note that the insert labeling for Viagra states that the AUC is increased 11 fold when 100 mg of Viagra is co-administered with ritonavir in healthy adults. Patients and prescribers need to be aware of the potential adverse outcome when these drugs are co-administered.

- iv. Currently, third-party payors may not reimburse patients for Viagra prescriptions, and the patients pay cash. Thus, it may be difficult to track concomitant administration post-marketing. Additionally, you may see an increased use of Revatio because healthcare providers will switch patients to Revatio so they can be reimbursed for the drug purchase.

b. Risk Minimization Recommendations

It appeared from the discussion with Cardio-Renal Drug Products that this NDA may be approved during this review cycle. In light of the aforementioned safety concerns identified with the use of dual tradenames, DMETS would like to suggest consideration of the following methods to minimize the risk associated with using both the names Viagra and Revatio for the same product.

- i. The sponsor should devise a plan that would monitor concomitant administration of these products and the adverse events associated with the concomitant use of both drug products postmarketing.

- ii. Disseminate a Dear Healthcare Provider letter that informs all types of healthcare providers including emergency personnel, that Revatio and Viagra are the same drug product with the same adverse event profile. Additionally, the sponsor should institute an education campaign that includes professional journal ads.
- iii. Institute a public educational campaign to inform the public community that Revatio is the same drug as Viagra. This would provide a global information to the community that the same safety concerns that are seen with Viagra would expect to be seen with Revatio.
- iv. Ensure the Revatio package insert contains the same warning and precautions as Viagra. Additionally, the insert labeling should state “
- v. Ensure that the container labels and carton labeling include the statement “

2. Look-Alike Concerns:

Rondec may look similar to Revatio when scripted. The Rondec product line also includes Rondec DM and Rondec TR. However, the modifiers ‘DM and TR’ will help to distinguish between Rondec TR and Revatio or Rondec DM and Revatio. Therefore, only Rondec will be discussed. Both names begin with the same letter ‘R’. However, the rest of the name is orthographically different. Although both names contain an upstroke (t vs. d), the crossbar of the ‘t’ may help to differentiate these two names when scripted. There are differentiating product characteristics, such as dose and strength (20 mg vs. 60 mg/4 mg), frequency of administration (three times a day, approximately six to eight hours apart vs. four times a day), and indication of use (pulmonary arterial hypertension vs. nasal congestion). Although the doses and strengths of the tablets are different, each is supplied in only one strength, and as such may be ordered without a strength (e.g. Rondec tablets 1 QID and Revatio tablets 1 TID). Despite the potential for this similar prescribing scenario, the orthographic differences may help to minimize confusion between this name pair.

Revatio
Rondec

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In the review of the container labels, carton and insert labeling of Revatio, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified several areas of possible improvement, which might minimize potential user error.

A. GENERAL COMMENT

1. The graphic  DMETS recommends deleting this graphic
2. Ensure that the container labels and carton labeling include the statement 

B. CONTAINER LABEL (90 & 500 count, and

1. See GENERAL COMMENTS A1 and A2.
2. The 90-count  container appears to be unit-of-use. Please ensure that they have a Child Resistant Closure.

C. CARTON LABELING

See GENERAL COMMENTS A1 and A2.

D. CONTAINER LABEL

1. See GENERAL COMMENTS A1 and A2.
2. Ensure the established name is at least 1/2 the size of the proprietary name. We refer you to 21 CFR 201.10(g)(2).

E. CARTON LABELING (Institutional

1. See GENERAL COMMENTS A1 and A2.
2. Include a statement as to whether or not the unit-dose package is child resistant. If it is not child-resistant, we encourage the inclusion of a statement that if dispensed to outpatients, it should be with a child-resistant container. For example: this unit-dose package is not child-resistant. If dispensed for outpatient use, a child-resistant container should be utilized. (Note: The second sentence is optional).

Appendix A:

Outpatient	Voice	Inpatient
Revatio	Ravacio	Revatia
Revatio	Ravathio	Revatia
Revatio	Ravatio	Revatia
Revatio	ravatio	Revatia
Revatio	Revacio	Revatia
Revatio	Revacio	Revatia
Revatio	Revacio	Revatia
revatio	Revashio	Revatia
Revatio	Revatio	Revatia
Revatio	Revatio	Revatia
Revatio	Revatio	Revatia
Revatio	Revesio	Revatia
Revatio		Revatia
Revatio		Revatia
Revatio		Revatio
Revatio		Revatio
		Revatra
		Revatra
		Revetia

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

/s/

Linda Wisniewski
5/23/05 07:51:21 AM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
5/23/05 12:01:27 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
5/23/05 04:17:46 PM
DRUG SAFETY OFFICE REVIEWER

**DIVISION OF CARDIO-RENAL DRUG PRODUCTS
FOOD AND DRUG ADMINISTRATION**



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Transmitted to FAX Number: 734-622-2856

Attention: Dr. Deborah Ladenheim

Company Name: Pfizer

Phone: 734-622-1110

Subject: 7/14/04 Meeting Minutes

Date:

Pages including this sheet: 7

From: Melissa Robb

Phone: 301-594-5313
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PLEASE LET ME KNOW YOU RECEIVED THIS. THANKS!

Meeting Minutes
July 14, 2004

Drug: Viagra (sildenafil citrate) Tablets
IND: 64,924
Sponsor: Pfizer Global Research and Development

Date Requested: June 9, 2004
Date Confirmation Faxed: June 10, 2004

Type: Guidance
Classification: C

FDA Participants:

Robert Temple, M.D.	Director, Office of Drug Evaluation I, HFD-101
Norman Stockbridge, M.D., Ph.D.	Acting Director, Division of Cardio-Renal Drug Products, HFD-110
Abraham Karkowsky, M.D., Ph.D.	Acting Deputy Director, Division of Cardio-Renal Drug Products, HFD-110
Shari Targum, M.D.	Acting Team Leader, Clinical, HFD-110
Elena Mishina, Ph.D.	Pharmacokineticist, HFD-860
James Hung, Ph.D.	Team Leader, Statistics, HFD-710
Mehul Desai, M.D.	Medical Officer, HFD-110
Salma Lemtouni, M.D.	Medical Officer, HFD-110
Melissa Robb	Regulatory Health Project Manager, HFD-110

Pfizer Participants:

Gary Burgess, M.D.	Clinical R&D
Graham Delow, M.S.	Worldwide Regulatory Strategy
Mark Edwards, M.D.	Clinical R&D
Colin Ewen, Ph.D.	Full Development Team Leader
Dale Glasser, Ph.D.	Medical Director
Cheryl Graham, M.D., FCP	Worldwide Regulatory Affairs
Rochelle Hanley, M.D., FACP	Clinical R&D
Deborah Ladenheim, Ph.D.	Worldwide Regulatory Affairs
James Parker, MBA	Worldwide Regulatory Affairs
Tamiza Parpia, Ph.D.	Biostatistics
Stephen Watt, M.D.	Safety and Risk Management

Background:

Viagra (sildenafil citrate) has been approved for the treatment of male erectile dysfunction (NDA 20-895) since 1998. The sponsor has been conducting trials under IND 64,924 using sildenafil citrate for the treatment of pulmonary arterial hypertension. The sponsor met with the Agency on April 3, 2002 in an End of Phase 2 meeting to discuss their proposed clinical program for the development of sildenafil citrate for this indication. The sponsor requested this meeting to share the results of their pivotal study with the Agency and gain concurrence on their proposed NDA filing strategy.

Meeting:

Dr. Temple began by inquiring why the sponsor has changed their plan that they presented to the Agency at the April 3, 2002 End of Phase 2 (EOP2) Meeting. The sponsor stated they believed early discussion with the Agency was warranted due to the compelling nature of the data from the pivotal trial, the good safety profile of the drug and the

known off-label use of the drug in patients with PAH. Dr. Temple also noted that the sponsor has deviated from some of the agreements made at the EOP2 meeting. Specifically, the add-on trial is not yet completed, the sponsor plans to submit the supplement with a smaller safety database than discussed, and the pediatric data to augment the adult trial are not yet available. Dr. Temple inquired on the status of the pediatric trials. The sponsor stated the trials are currently ongoing and have been for approximately 1 year.

Questions:

1. Given the extent of efficacy data provided by Study A1481140 and the proposed safety package described in the briefing document, does the Agency agree that the application will provide sufficient information to allow for review of a sNDA?

The Agency believes the application would be filable. Dr. Temple inquired if the sponsor is able to obtain data from the published Sastry et al trial, which was a double-blind, randomized, placebo-controlled, cross-over trial of 22 patients. The sponsor stated this issue has been discussed and it looks as if they may be able to acquire the data. The Agency stated they would be interested in the protocol and raw data, including information about when the exercise testing was done in relation to dosing. Dr. Temple stated that the data the sponsor currently has may be sufficient on its own, but the data from the Sastry trial may assist in augmenting their single pivotal trial.

Efficacy

2. Highly statistically significant improvements were seen in the 6-Minute walk distance at all sildenafil doses when compared to placebo. Does the Agency concur that the magnitude of effects seen is clinically relevant?

The Agency agreed.

3. Does the Agency concur that the improvements seen in the 3 key secondary endpoints (change from baseline in mean pulmonary arterial pressure, BORG dyspnea score, and time to clinical worsening) provide supportive evidence of efficacy in this population?

These endpoints were to be assessed in a sequestered manner. Dr. Temple inquired about the significance the sponsor believes they showed in the BORG dyspnea score and the time to clinical worsening. The sponsor stated that the secondary endpoint, time to clinical worsening was not found to be statistically significant, although it trended in the correct direction. The secondary endpoint of BORG dyspnea score was not tested because time to clinical worsening was not found to be statistically significant and the sequential plan made testing of that endpoint inappropriate. However, it also trended in the correct direction. Therefore, the sponsor believes these two secondary endpoints show support as trends. The Agency agreed that the change in mean pulmonary arterial pressure appears to be a statistically significant secondary endpoint that would support efficacy in this population.

4. The submission will contain long-term efficacy data for approximately 250 patients at 6 months and approximately 150 patients at 1 year in the extension study. Does the Agency concur that this preliminary evidence of long-term efficacy will allow approval of this sNDA?

An issue for both long and short-term efficacy is the timing of the testing in relationship to doses. Dr. Temple inquired if exercise testing was performed in the extension trial, and when this was done. The sponsor stated that exercise testing was performed, and was performed at trough, approximately four hours after the last dose. The sponsor stated that the 12 week analyses was done only with patients who had exercise testing done at trough levels, which led to the exclusion of 34 patients. The sponsor stated they have data available for the timing of the drug administration and the timing of the exercise test in all patients. The sponsor added that they are also planning on doing population PK.

Dr. Temple stated that after reviewing the data presented in the briefing document, the Agency does not see much value in doses greater than 20 mg. The sponsor stated they looked at primary pulmonary hypertension and connective tissue patients independently and found that the drug behaved differently in these two populations. In the patients with primary pulmonary hypertension, the data revealed a linear increase in dose response from 20-80 mg doses. However, in patients with connective tissue disorders, the improvement was less apparent at doses greater than 40 mg.

Dr. Temple told the sponsor that they should address this issue in their submission. Dr. Temple suggested conducting a trial in patients who showed only modest improvements on 20 mg TID, randomizing them to either 20 or 80 mg to determine if improvements were then seen at the 80 mg dose. The sponsor agreed this may show some improved efficacy in the 80 mg dose.

Safety

5. The sNDA will provide safety information on 277 treated patients from Study A1481140. In order to fully understand the safety profile of sildenafil when used 3 times daily on a chronic basis, the submission will contain safety data from Study A1481140 pooled with the safety data from Study _____ a study _____ using the doses of 20, 40, 80 mg sildenafil TID for up to 28 days). In addition, long-term safety data will be provided from approximately 250 patients at 6 months and approximately 150 patients at 1 year in the extension Study A1481142. Serious adverse event information will also be provided from ongoing PAH oral studies. Does the Agency concur that the proposed safety package will adequately support the review of the pulmonary arterial hypertension indication in adults?

The Agency said this seemed to be adequate, but believes the sponsor should provide separate analyses in both populations, too.

6. The sNDA submission will also provide additional information relating to the safety of sildenafil from chronic dosing in other indications as described in Section 5.6.1 of the briefing document. Does the Agency consider that these data add useful additional information to support the safety of sildenafil?

The Agency agreed.

7. Study _____

_____ will be ongoing at the time of sNDA submission and only serious adverse events from this study will be included in the application. It is intended that this study will be completed and the data will be submitted to the FDA for review for a labeling change, depending on the outcome of the study. Is this proposal acceptable?

The Agency agreed.

Strength of Evidence Based on a Single Pivotal Study

8. Does the Agency agree that Study A1481140 provides compelling evidence of efficacy based on the totality of the data and study quality (as discussed in Section 4.1.6 of the briefing document) to support an approval based on a single pivotal study?

The Agency stated that this is a review issue, but the submission would be fileable with one pivotal study.

Interaction Study

9. The interaction profile of sildenafil has been fully characterized in NDA 20-895. In addition, this sNDA submission will contain the bosentan interaction study (A 1481149) using 80 mg sildenafil and a population PK/PD analysis from Study A 481140. Does the Agency concur that these data will be adequate to demonstrate the interaction potential of sildenafil in PAH?

The Agency agreed. The Agency believes it will be important that data on warfarin be available for review. The sponsor stated 90% of patients in the trial were on warfarin. INR levels were collected and no change was noted in most patients. There were a few outliers and the sponsor is following up on specific warfarin doses in these cases.

Dr. Mishina advised the sponsor to pay specific attention to the interaction of sildenafil and warfarin in this patient population. Although there is information in the Label that "clinical trials showed no effect of warfarin on sildenafil pharmacokinetics", the statement does not describe the results of a drug-drug interaction study, and the sponsor should evaluate this interaction. The sponsor responded that they are going to include the assessment of warfarin-sildenafil interaction in the population data analysis from the clinical trials.

Label

10. The proposed indication will reflect the outcome of Study A 1481140 and will include the secondary endpoints that show statistically significant benefit over placebo as discussed previously with the Agency. Given the data described in this briefing document, the proposed indication will be:

Does the Agency concur that this is an acceptable target indication, pending review of the data?

The Agency stated that a statement _____ is not typically found in the indications section of the label. If this statement were found to be true, it would be more appropriately placed in the clinical pharmacology section.

Dr. Temple inquired about side effects noted in the trial. The sponsor stated that no adverse events with erection had been reported to date. In addition, the sponsor stated they have been doing intensive eye evaluation throughout the study and have found similar findings with chronic administration that were found with PRN dosing.

Dr. Temple inquired about the typical dose being administered to patients in the extension trial. The sponsor stated that they had believed _____. Therefore, the sponsor put all patients on placebo, 20 mg and 40 mg doses on the 40 mg dose at the beginning of the extension trial. Those on 80 mg remained on the 80 mg dose. At week 6, patients were uptitrated to 80 mg, but allowed to titrate down if they

were unable to tolerate the dose. Only 12 patients were down titrated due to tolerance. Therefore, most patients in the extension trial are taking 80 mg TID.

The sponsor asked whether the Agency would be taking this submission to the Advisory Committee for review. Dr. Temple stated that this had not been discussed, but most drugs for this indication that have gone in the past have been presented because of specific concerns.

The sponsor stated they would be requesting priority review status. The sponsor believes the trial reveals compelling evidence of efficacy and is for the treatment of a life threatening condition. Dr. Temple stated that priority review status is intended for products that are an improvement over available therapies. The sponsor believes sildenafil is an improvement over available therapies because of its increased safety and ease of administration. Dr. Temple stated this would be reviewed at the time of submission.

Signature, minutes preparer: *{See appended electronic signature page}*

Concurrence, Chair: *{See appended electronic signature page}*

Drafted: 7/15/04 Finaled: 8/12/04

RD:

Temple 8/11/04
Stockbridge 8/10/04
Karkowsky 8/9/04
Targum 8/9/04
Mishina 8/6/04
Hung 8/6/04
Desai 8/6/04
Lemtouni 8/6/04

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/s/

Russell Fortney
8/12/04 08:41:14 AM
On behalf of Melissa Robb

Robert Temple
8/12/04 05:31:14 PM

9 Page(s) Withheld

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

✓ § 552(b)(5) Deliberative Process

 § 552(b)(5) Draft Labeling

6 Page(s) Withheld

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 § 552(b)(5) Deliberative Process

 § 552(b)(5) Draft Labeling

**DIVISION OF CARDIO-RENAL DRUG PRODUCTS
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Transmitted to FAX Number: 734-622-3283
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Subject: Minutes of 4/3/02 Meeting
Date: 4/24/02
Pages including this sheet: 4

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Fax: 301-594-5494

You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes (as reflected in the minutes).

PLEASE LET ME KNOW YOU RECEIVED THIS. THANKS!

Meeting Minutes

Drug: Viagra (sildenafil citrate)
Sponsor: Pfizer
Date Requested: January 18, 2002
Date Confirmation Faxed: January 31, 2002
Date Briefing Doc. Received: March 1, 2002
Date of Meeting: April 3, 2002
Type: EOP2 – Adult Pulmonary Arterial Hypertension (PAH)
Classification: B

Meeting Chair: Robert Temple, M.D.
Meeting Recorder: Zelda McDonald
External Participant Lead: LaVonne Lang

FDA Participants:

Robert Temple, M.D.	Director, Office of Drug Evaluation I, HFD-101
Douglas C. Throckmorton, M.D.	Director, HFD-110
Norman Stockbridge, M.D., Ph.D.	Team Leader, Medical, HFD-110
Thomas Marciniak, M.D.	Medical Officer, HFD-110
Thomas Papoian, Ph.D.	Pharmacologist, HFD-110
James Hung, Ph.D.	Team Leader, Statistics, HFD-710
Valeria Freidlin, Ph.D.	Statistical Reviewer, HFD-710
Yong Cheng Wang, Ph.D.	Statistical Reviewer, HFD-710
Angelica Dorantes, Ph.D.	Team Leader, Biopharmaceutics, HFD-860
Robert Shibuya, Ph.D.	Pharmacologist, Division of Scientific Investigations, HFD-47
Zelda McDonald, B.S.	Regulatory Project Manager, HFD-110
Denise Hinton, R.N.	Regulatory Project Manager, HFD-110

Pfizer Participants:

Gary Burgess, M.D.	Clinical Development, Sandwich, UK
Mark Edwards, M.D.	Clinical Development, Sandwich, UK
Colin Ewen, Ph.D.	Project Management, Sandwich, UK
Neville Jackson, M.D.	Clinical Development, New London, CT
Deborah Ladenheim, Ph.D.,	Regulatory Affairs, Sandwich, UK
LaVonne Lang, RN, MPH.	Regulatory Affairs, Ann Arbor, MI
Harry Olson, Ph.D.	Toxicologist, Sandwich, UK
Tamiza Parpia, Ph.D.	Statistics, Development Operations, Sandwich, UK
Mike Sweeney, M.D.	Medical, New York, NY

Background:

Pfizer requested this meeting to discuss the specifics of their proposed clinical program and the adequacy of their completed toxicology program to support a marketing application for Viagra (sildenafil citrate) for the treatment of pulmonary arterial hypertension (PAH).

The current investigational plan is to study approximately 240 patients (180 on sildenafil) with PAH in a placebo-controlled study. All patients in the program will be given the opportunity of entering long-term extension studies. Consequently, at the time the NDA is submitted, approximately 600 patients will have been exposed to sildenafil in either concluded or on-going studies in PAH. Additional studies may include the investigation of the safety and efficacy of sildenafil as an adjunct to existing approved treatments for PAH and/or in special populations (e.g., HIV, thromboembolic PH).

Meeting:

The Agency had the following comments on the protocol:

1. A single trial, significant at 0.01, along with supporting data (assuming they trend in the same direction) from the pediatric program and the combination study are collectively acceptable. The Agency warned that if something untoward happened such as only winning on the primary end point, a single trial may not be enough to gain approval. The Agency noted that the pediatric program calls for four studies, and if the PAH studies turn out to be positive, Pfizer may propose a modification of the pediatric written request.
 2. The protocol should make a clear distinction between the primary statistical method and exploratory techniques. The protocol should pre-specify in detail the method to be used to assess the normality of the primary efficacy variable. The protocol should pre-specify the significance level at which the lack of normality would be declared and the Wilcoxon Rank Sum test would be used instead of the t-test.
 3. A precise form of the statistical model in the primary efficacy analysis should be pre-specified in the protocol with a detailed description of the covariates.
 4. An interaction term should not be included in the primary efficacy model. If the treatment effect is significant, then the heterogeneity of the treatment effect can be explored by graphical methods or by inclusion of the interaction term in the model.
 5. The protocol has too many secondary endpoints, some of which are safety end points. Mixing safety end points with efficacy end points is not uncommon, but unfortunately, it needs rethinking. The Agency suggested multiple primary end points followed by a sequential clinical progression approach, e.g., dividing the initial alpha between two primary endpoints, followed by sequential secondary end points. The Agency suggested that Pfizer submit a revised analysis plan, and the Agency would respond.
- The Agency asked whether Pfizer has considered stratifying by etiology of PAH. Pfizer stated that between the time the briefing document was submitted and this meeting, their expert consultants had advised them to stratify by PAH etiology.
 -
 -
 - The Agency asked when the hemodynamic measurements would be taken in relation to dosing and whether sildenafil is a 3A4 inhibitor. Pfizer stated that the exercise testing and any other measurements would be taken as close to trough as possible. The studies they had done with sildenafil showed minimal 3A4 and 2C9 inhibition (at a μ molar concentration).

- The Agency asked if carcinogenicity studies had been done. Pfizer stated that those studies were done in the original application and were negative. The Agency noted that if specific toxicology affects are seen in patients with PAH, more animal toxicity studies may have to be done.
- The Agency asked what Pfizer was finding with respect to patients' color perceptions. Pfizer stated that a change in color perceptions is seen in 11-12% of patients. They will be following all patients in the PAH studies.
- Pfizer asked if the dosing regimen (20-80 mg) and the length of the study were acceptable. The Agency stated that both were okay, but asked about follow-up, suggesting that Pfizer confirm that sildenafil's effect does not disappear. Pfizer may want to consider adding a randomized withdrawal study. Pfizer stated that they had discussed that but were worried about patients rebounding and never getting back to the same level of functionality. The Agency pointed out that it is important to find out what happens when a patient goes off sildenafil and to document long-term effects, i.e., is the patient still benefiting from the drug. It could be part of the open-label extension study.

In summary, the Agency agreed that a single study at 0.01 with a database of approximately 600 patients could support approval, provided the supporting studies and secondary efficacy endpoints trended in the same direction.

Signature minutes preparer: _____

Concurrence, Chair: _____

Drafted 4/9/02 Finaled 4/22/02

RD:

Temple	4/19/02
Throckmorton	4/16/02
Stockbridge	4/16/02
Hung	4/11/02
Dorantes	4/16/02
Papoian	4/12/02
Freidlin	4/16/02

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/s/

Zelda McDonald

4/25/02 10:49:15 AM

These minutes were signed-off by Dr. Temple on 4/24/02
and faxed to the Sponsor on 4/24/02.