

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**203109Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

**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

203109

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)

10 mg/ml

DOSAGE FORM

For suspension

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.

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?	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> 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?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> 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).	<input type="checkbox"/> Yes	<input type="checkbox"/> 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.)	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.6	Does the patent claim only an intermediate?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> 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.)	<input type="checkbox"/> Yes	<input type="checkbox"/> 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?	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
3.2	Does the patent claim only an intermediate?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> 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.)	<input type="checkbox"/> Yes	<input type="checkbox"/> No

**4. Method of Use**

Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, 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?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
4.2	Patent Claim Number(s) (as listed in the patent)	Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	
		<input type="checkbox"/> Yes	<input type="checkbox"/> 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.)
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**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* 7/20/2011

**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.**

<input type="checkbox"/> NDA Applicant/Holder	<input checked="" type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
<b>Name</b> Bruce A. Pokras	
<b>Address</b> 5 Giralda Farms	<b>City/State</b> Madison, NJ
<b>ZIP Code</b> 07940	<b>Telephone Number</b> (973) 660-6583
<b>FAX Number (if available)</b> (646) 563-9571	<b>E-Mail Address (if available)</b> bruce.a.pokras@pfizer.com

The public reporting burden for this collection of information has been estimated to average 20 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:

Department of Health and Human Services  
 Food and Drug Administration  
 Office of Chief Information Officer  
 1350 Piccard Drive, Room 400  
 Rockville, MD 20850

*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*

## EXCLUSIVITY SUMMARY

NDA # 203109

SUPPL #

HFD # 110

Trade Name Revatio

Generic Name sildenafil

Applicant Name Pfizer

Approval Date, If Known 8/30/12

### 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.

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

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?

Yes

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# 20895

Viagra (sildenafil)

NDA# 21845 Revatio (sildenafil)

NDA# 22473 Revatio (sildenafil)

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:

(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:

A1481131: A Randomized, Double-Blind, Placebo Controlled, Dose Ranging, Parallel Group Study of Oral Sildenafil in the Treatment of Children, Aged 1-17 Years with Pulmonary Arterial Hypertension

A1481156: A Multicenter, Long-Term Extension Study to Assess Safety of Oral Sildenafil in the Treatment of Subjects Who Have Completed Study A1481131

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:

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:

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"):

A1481131: A Randomized, Double-Blind, Placebo Controlled, Dose Ranging, Parallel Group Study of Oral Sildenafil in the Treatment of Children, Aged 1-17 Years with Pulmonary Arterial Hypertension

A1481156: A Multicenter, Long-Term Extension Study to Assess Safety of Oral Sildenafil in the Treatment of Subjects Who Have Completed Study A1481131

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 # 63175            YES             ! NO   
! Explain:

Investigation #2  
IND # 63175            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

! NO

Explain:

! Explain:

Investigation #2

!  
!

YES

! NO

Explain:

! 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: Daniel Brum

Title: Regulatory Project Manager

Date: 8/30/12

Name of Office/Division Director signing form: Stephen Grant on behalf of Norman Stockbridge

Title: Deputy Division Director (Stephen Grant)

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

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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DANIEL BRUM  
08/30/2012

STEPHEN M GRANT  
08/30/2012

NDA 203109

Revatio® Oral Suspension  
(sildenafil)

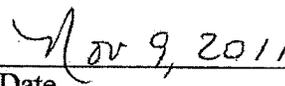
DEBARMENT CERTIFICATION

[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



\_\_\_\_\_  
Date

15:18

090177e182875f26\Final\Final On: 10-Nov-2

PFIZER CONFIDENTIAL

# ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # 203109 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: Revatio Established/Proper Name: sildenafil Dosage Form: (powder) for oral suspension		Applicant: Pfizer Agent for Applicant (if applicable):
RPM: Dan Brum		Division: DCRP
<p><b><u>NDA and NDA Efficacy Supplements:</u></b></p> <p>NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1)   <input type="checkbox"/> 505(b)(2)            Efficacy Supplement:   <input type="checkbox"/> 505(b)(1)   <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>	<p><b><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u></b></p> <p>Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> This application does not rely upon a listed drug.  <input type="checkbox"/> This application relies on literature.  <input type="checkbox"/> This application relies on a final OTC monograph.  <input type="checkbox"/> This application relies on (explain)</p> <p><b><u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft<sup>2</sup> to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></b></p> <p><b><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></b></p> <p><input type="checkbox"/> No changes   <input type="checkbox"/> Updated   Date of check:</p> <p><b>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</b></p>	
<b>❖ Actions</b>		
<ul style="list-style-type: none"> <li>• Proposed action</li> <li>• User Fee Goal Date is <u>August 30, 2012</u></li> </ul>		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> <li>• Previous actions (<i>specify type and date for each action taken</i>)</li> </ul>		<input checked="" type="checkbox"/> None

<sup>1</sup> The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.

<sup>2</sup> For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

<p>❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a>). If not submitted, explain _____</p>	<input type="checkbox"/> Received
<p>❖ Application Characteristics <sup>3</sup></p>	
<p>Review priority: <input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority Chemical classification (new NDAs only): 3</p> <p> <input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch  <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch  <input checked="" type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC         </p> <p>           NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510)  <input type="checkbox"/> Restricted distribution (21 CFR 314.520)            Subpart I <input type="checkbox"/> Approval based on animal studies  <input checked="" type="checkbox"/> Submitted in response to a PMR  <input type="checkbox"/> Submitted in response to a PMC  <input checked="" type="checkbox"/> Submitted in response to a Pediatric Written Request         </p> <p>           BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41)  <input type="checkbox"/> Restricted distribution (21 CFR 601.42)            Subpart H <input type="checkbox"/> Approval based on animal studies            REMS: <input type="checkbox"/> MedGuide  <input type="checkbox"/> Communication Plan  <input type="checkbox"/> ETASU  <input type="checkbox"/> MedGuide w/o REMS  <input type="checkbox"/> REMS not required         </p> <p>Comments: PMR under PREA</p>	
<p>❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)</p>	<input type="checkbox"/> Yes, dates
<p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
<p>❖ Public communications (<i>approvals only</i>)</p>	
<ul style="list-style-type: none"> <li>Office of Executive Programs (OEP) liaison has been notified of action</li> </ul>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> <li>Press Office notified of action (by OEP)</li> </ul>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> <li>Indicate what types (if any) of information dissemination are anticipated</li> </ul>	<input type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input checked="" type="checkbox"/> Other Drug Safety Communication (DSC)

<sup>3</sup> Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
<ul style="list-style-type: none"> <li>Is approval of this application blocked by any type of exclusivity?</li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> <li>NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>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.</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA #                      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #                      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #                      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #                      and date exclusivity expires:
<ul style="list-style-type: none"> <li>NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #                      and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> <li>Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.</li> </ul>	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> <li>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.</li> </ul>	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified  21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> <li>[505(b)(2) applications] If the application includes a <b>paragraph III</b> 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).</li> </ul>	<input type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> <li>[505(b)(2) applications] For <b>each paragraph IV</b> 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 section below (Summary Reviews)).</i></li> </ul>	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [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.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes     No

(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)).

*If "Yes," skip to question (4) below. If "No," continue with question (2).*

- (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)?

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 the rest of the patent questions.*

*If "No," continue with question (3).*

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes     No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) 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," 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 section below (Summary Reviews).*

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

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) 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).</p> <p><i>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 section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<p><input type="checkbox"/> Yes    <input type="checkbox"/> No</p>
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**CONTENTS OF ACTION PACKAGE**

❖ Copy of this Action Package Checklist <sup>4</sup>	Included
<b>Officer/Employee List</b>	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list ( <i>approvals only</i> )	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included
<b>Action Letters</b>	
❖ Copies of all action letters ( <i>including approval letter with final labeling</i> )	Action(s) and date(s) AP; 8/30/12
<b>Labeling</b>	
❖ Package Insert ( <i>write submission/communication date at upper right of first page of PI</i> )	
<ul style="list-style-type: none"> <li>• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> </ul>	8/29/12
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	11/30/11
<ul style="list-style-type: none"> <li>• Example of class labeling, if applicable</li> </ul>	

<sup>4</sup> Fill in blanks with dates of reviews, letters, etc.

<ul style="list-style-type: none"> <li>❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)</li> </ul>	<input type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input checked="" type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> <li>• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> </ul>	8/29/12
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	11/30/11
<ul style="list-style-type: none"> <li>• Example of class labeling, if applicable</li> </ul>	
<ul style="list-style-type: none"> <li>❖ Labels (<b>full color</b> carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)</li> </ul>	
<ul style="list-style-type: none"> <li>• Most-recent draft labeling</li> </ul>	8/29/12
<ul style="list-style-type: none"> <li>❖ Proprietary Name               <ul style="list-style-type: none"> <li>• Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>)</li> <li>• Review(s) (<i>indicate date(s)</i>)</li> <li>• Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.</li> </ul> </li> </ul>	N/A
<ul style="list-style-type: none"> <li>❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)</li> </ul>	<input checked="" type="checkbox"/> RPM 1/17/12 (see filing letter) <input checked="" type="checkbox"/> DMEPA 5/2/12 <input checked="" type="checkbox"/> DMPP/PLT (DRISK) 8/10/12 <input checked="" type="checkbox"/> ODPD (DDMAC) 8/9/12 <input checked="" type="checkbox"/> SEALD 8/24/12 <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
<b>Administrative / Regulatory Documents</b>	
<ul style="list-style-type: none"> <li>❖ Administrative Reviews (<i>e.g., RPM Filing Review<sup>5</sup>/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)</li> <li>❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte</li> <li>❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>)</li> </ul>	filing review 1/12/12; RPM overview 8/30/12  <input type="checkbox"/> Not a (b)(2) <input type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> <li>❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)</li> </ul>	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> <li>❖ Application Integrity Policy (AIP) Status and Related Documents  <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a> </li> </ul>	
<ul style="list-style-type: none"> <li>• Applicant is on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>• This application is on the AIP               <ul style="list-style-type: none"> <li>○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>)</li> <li>○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No  <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> <li>❖ Pediatrics (<i>approvals only</i>)               <ul style="list-style-type: none"> <li>• Date reviewed by PeRC <u>PMR (PREA) under NDA 21845 reviewed 3/14/12</u>                    If PeRC review not necessary, explain: <u>NDA 203109 orphan (PREA exempt)</u></li> <li>• Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Included

<sup>5</sup> Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent <i>(include certification)</i>	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Outgoing communications <i>(letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons)</i>	Included
❖ Internal memoranda, telecons, etc.	Included
❖ Minutes of Meetings	
• Regulatory Briefing <i>(indicate date of mtg)</i>	<input checked="" type="checkbox"/> No mtg
• If not the first review cycle, any end-of-review meeting <i>(indicate date of mtg)</i>	<input checked="" type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting <i>(indicate date of mtg)</i>	<input type="checkbox"/> No mtg 7/2/2009
• EOP2 meeting <i>(indicate date of mtg)</i>	<input checked="" type="checkbox"/> No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) <i>(indicate dates of mtgs)</i>	
❖ Advisory Committee Meeting(s)	<input type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	July 29, 2010 (IND 63175) - AC meeting was not specifically about NDA 203109 but related issues concerning efficacy (e.g., hemodynamic endpoints).
• 48-hour alert or minutes, if available <i>(do not include transcript)</i>	
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo <i>(indicate date for each review)</i>	<input type="checkbox"/> None see sNDA 21845/s-008
Division Director Summary Review <i>(indicate date for each review)</i>	<input type="checkbox"/> None May 24, 2012
Cross-Discipline Team Leader Review <i>(indicate date for each review)</i>	<input type="checkbox"/> None May 15, 2012
PMR/PMC Development Templates <i>(indicate total number)</i>	<input type="checkbox"/> None One PMC under NDA 203109 and one PMR under sNDA 21845/S008
<b>Clinical Information<sup>6</sup></b>	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) <i>(indicate date for each review)</i>	See CDTL memo
• Clinical review(s) <i>(indicate date for each review)</i>	4/18/12; 8/27/12
• Social scientist review(s) (if OTC drug) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not <i>(indicate date of review/memo)</i>	4/18/12
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> Not applicable

<sup>6</sup> Filing reviews should be filed with the discipline reviews.

❖ Risk Management <ul style="list-style-type: none"> <li>REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>)</li> <li>REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)</li> <li>Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)</li> </ul>	<input checked="" type="checkbox"/> None
❖ DSI Clinical Inspection Review Summary(ies) ( <i>include copies of DSI letters to investigators</i> )	<input checked="" type="checkbox"/> None requested
<b>Clinical Microbiology</b> <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
Clinical Microbiology Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
<b>Biostatistics</b> <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 4/30/12
Statistical Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Statistical Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 4/30/12
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 4/27/12
Clinical Pharmacology review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 4/27/12
❖ DSI Clinical Pharmacology Inspection Review Summary ( <i>include copies of DSI letters</i> )	<input type="checkbox"/> None 5/1/12
<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
• Supervisory Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 5/1/12
• Pharm/tox review(s), including referenced IND reviews ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 5/1/12
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary ( <i>include copies of DSI letters</i> )	<input checked="" type="checkbox"/> None requested

<b>Product Quality</b>		<input type="checkbox"/> None
❖ Product Quality Discipline Reviews		
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>		<input type="checkbox"/> None
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>		<input type="checkbox"/> None 4/27/12; 5/17/12
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>		<input type="checkbox"/> None 4/27/12; 5/17/12; 8/29/12
❖ Microbiology Reviews		<input checked="" type="checkbox"/> Not needed
<input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i>		
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>		
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>		<input type="checkbox"/> None Biopharm: 4/25/12 and 5/16/12; 8/27/12
❖ Environmental Assessment (check one) (original and supplemental applications)		
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>		See CMC review
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>		
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>		
❖ Facilities Review/Inspection		
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout) <i>(date completed must be within 2 years of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites<sup>7</sup>)</i>		Date completed: See CMC review <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER <i>(date of most recent TB-EER must be within 30 days of action date) (original and supplemental BLAs)</i>		Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>		<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed (per review)

<sup>7</sup> I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

## Appendix to Action Package Checklist

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

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** 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.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

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/s/  
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DANIEL BRUM  
08/30/2012



NDA 203109

**DISCIPLINE REVIEW LETTER**

Pfizer, Inc.  
Attention: Ms. Nancy McKay  
235 East 42nd St.  
New York, NY 10017

Dear Ms. McKay:

Please refer to your New Drug Application (NDA) dated November 30, 2011, received November 30, 2011, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act, for Revatio (sildenafil) for oral suspension 10 mg/mL.

The Division of Medication Error Prevention and Analysis (DMEPA) review of the proposed label and labeling section of your submission is complete, and we have identified the following deficiencies:

The proposed label and labeling introduce vulnerability that can lead to medication errors. We advise the following recommendations be implemented:

**A. Carton Labeling**

1. The back display panel refers to a (b) (4). This may cause confusion for patients since the enclosed syringe only contains markings of 1 mL and 2 mL. Revise (b) (4) to read 'An oral dosing syringe' on the back display panel of the carton labeling.
2. The net quantity statement detracts from the statement of strength. Move the net quantity statement to the lower third of the principle display panel.

**B. Oral Dosing Syringe**

1. The oral dosing syringe should include the statement "For use only with Revatio oral suspension." This statement should be located directly above the "Oral use only" statement and should not interfere with the graduation markings.

If you have any questions, please call Dan Brum, Pharm.D., RAC, Regulatory Project Manager, at (301)796-0578.

Sincerely,

*{See appended electronic signature page}*

Abraham Karkowsky, M.D., Ph.D.  
Cross Discipline Team Leader  
Division of Cardiovascular and Renal Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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/s/  
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ABRAHAM M KARKOWSKY  
08/28/2012

**Brum, Dan**

---

**From:** McKay, Nancy [Nancy.McKay@pfizer.com]  
**Sent:** Thursday, August 23, 2012 3:39 PM  
**To:** Brum, Dan  
**Subject:** RE: NDA 203109 PMC agreement verification (dissolution method development)  
**Sensitivity:** Confidential

Hi Dan,

I can confirm agreement with the proposed dates.

Thanks

Nancy

---

**From:** Brum, Dan [mailto:Dan.Brum@fda.hhs.gov]  
**Sent:** Thursday, August 23, 2012 3:26 PM  
**To:** McKay, Nancy  
**Subject:** RE: NDA 203109 PMC agreement verification (dissolution method development)

Nancy,  
 It should be 2/28/2013.  
 --Dan

---

**From:** Brum, Dan  
**Sent:** Wednesday, August 22, 2012 3:58 PM  
**To:** McKay, Nancy  
**Cc:** Brum, Dan  
**Subject:** NDA 203109 PMC agreement verification (dissolution method development)

Hi Nancy,

Can you please confirm whether Pfizer agrees to the following CMC-related PMC:

PMR/PMC Schedule Milestones:	The Applicant will submit a dissolution method development report with supportive data within 6 months of the action date.	02/30/2013
	The Applicant will submit the final dissolution method development report including proposed dissolution acceptance criterion with the supportive data within 14 months of the action date.	10/30/2013

Thanks,  
 --Dan

Dan Brum, Pharm.D., MBA, BCPS, RAC  
 Commander, US Public Health Service

Senior Regulatory Project Manager  
Division of Cardiovascular and Renal Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
p: (301)796-0578  
f: (301)796-9841  
[dan.brum@fda.hhs.gov](mailto:dan.brum@fda.hhs.gov)

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/s/  
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DANIEL BRUM  
08/25/2012

## Internal Minutes (teleconference)

**Meeting Date:** August 20, 2012  
**Application:** TSI #1311, NDAs 203109  
**Drug:** Revatio (sildenafil)  
**Sponsor:** Pfizer  
**Purpose:** To discuss a potential Post-Marketing Requirement (PMR)

### FDA Attendees:

Ellis Unger (ODE I director)  
Stephen Grant (deputy division director)  
Mary Ross Southworth (deputy division director of safety)  
Abraham Karkowsky (clinical team leader)  
John Lawrence (biometrics reviewer)  
Raj Madabushi (clinical pharmacology TL)  
Satjit Brar (pharmacometrics reviewer)  
Dan Brum (RPM)  
Lori Wachter (safety RPM)  
Amy Taylor (pediatric and maternal health staff)

### Sponsor Attendees:

Raj Aggarwal (Safety and Risk Lead)  
Cecile Balagtas (Medicines Development Lead)  
Bruce Behounek (Clinical Lead)  
Tom D'Eletto (Medical Lead)  
Xiang Gao (Clinical Pharmacology Lead)  
Lutz Harnisch (Pharmacometrics)  
Nancy McKay (Regulatory Lead)  
Eric Yan (Statistical Lead)  
Min Zhang (Statistician)  
Brian Harvey (VP, US Regulatory Strategy)  
Clare Kahn (VP, Worldwide Regulatory Strategy, Lead Specialty Care)

### **BACKGROUND**

The following discussion points reflect summary points made during the face-to-face meeting between Pfizer and FDA on July 26, 2012:

On July 25, 2012, Dr. Brum emailed draft labeling for NDA 203109 Revatio (sildenafil) to the sponsor. During the meeting the sponsor stated that they generally agreed with the draft labeling and in particular agreed with the language describing a new warning in section 5.1 and the results of STARTS-1 and STARTS-2 in section 8.4. The Office informed the sponsor that it intends to require them to conduct a postmarketing study to evaluate whether doses of Revatio above which there is no demonstrated increase in efficacy increase mortality.

The sponsor gave a presentation based on the attached slide deck. During the presentation, several issues were discussed, and the following items were agreed upon:

- there are no long-term controlled safety or efficacy data for Revatio in adults with PAH, only *12- and 16-week* controlled data are available
- there was dose-related mortality observed in STARTS-2 (long term extension of the STARTS-1 pediatric PAH trial)
- In the 16-week PACES trial (adult PAH leading to the approval of Revatio for delay in clinical worsening) there were fewer deaths in the subjects administered Revatio compared to placebo subjects. This outcome is at variance with the STARTS-2 trial (pediatric PAH), but several important limitations were discussed (e.g., small number of events in PACES, duration of therapy, severity of PAH)
- it is unknown how the dose-related mortality observed in children with PAH applies to adults with PAH
- the minimum effective dose of sildenafil is not known (i.e., it is unknown whether doses lower than 20 mg thrice daily, the approved dose, might be similarly effective and relatively safer)
- DCRP requested that the sponsor submit a prematurely discontinued dose exploration study of the effect of administering 1, 5, or 20 mg of sildenafil three times daily to adults on 6MWD at 12 weeks
- a *controlled* trial appears to be a critical design feature (vs. epidemiological data) for the required post-marketing study
- a placebo arm would not be part of the study design
- mortality would be the key outcome measure (versus combined morbidity and mortality)
- an additional meeting focusing on trial design and feasibility will be arranged upon request
- the population to be studied and endpoint of interest will have a significant impact on patient enrollment and study timelines

Prior to the August 20, 2012 teleconference, Pfizer submitted a document dated August 15, 2012 (see NDA 203109 supporting document #30) entitled “Revatio Post-Marketing Requirement Assessment”. Pfizer’s submission included potential study designs, statistical considerations, factors affecting subject recruitment rate, and factors affecting trial conduct and interpretation.

### **Discussion Points (August 20, 2012)**

- Pfizer proposed two different two-arm trial designs using sildenafil 5 and 20 mg thrice daily. Dr. Southworth suggested including an 80 mg TID dosing arm. Pfizer expressed concern about the advisability of administering an 80 mg TID dose in the safety study because it was higher than the recommended dose in the label. Furthermore, it would lead to approximately the same exposure as the highest dose in STARTS-2, the dose associated with the highest mortality. Dr. Grant pointed out that the label does not contraindicate a dose of 80 mg, and that Pfizer is aware that some adult patients with PAH in the USA are prescribed a dose of 80 mg. He then asked Pfizer if they believed that the 80 mg dose was unsafe and if the label should state it is unsafe. Pfizer replied they did not believe that there were sufficient data to indicate a dose of 80 mg was deleterious relative to the 20 mg dose in adult patients. Dr. Grant observed if Pfizer's belief was true, it was ethical to administer an 80 mg dose in clinical trials.
- The company’s representatives were cautiously receptive to a 3-arm study design with doses of 5, 20, and 80 mg TID, but noted that the sample size would need to be increased by possibly 40%, and that the time needed to enroll the study would be increased correspondingly.

- Dr. Southworth said that, in general, Pfizer's proposals seemed reasonable (e.g., sildenafil-naïve population, use of concomitant PAH therapies, ruling out a doubling of mortality between the lowest and highest doses (e.g., 5 mg and 80 mg)).
- Pfizer emphasized that based on their experience with the low-dose study in adults (Protocol A1481244) that enrolling the proposed safety study in adults quickly (in a matter of 4-5 years as in SERAPHIN) is likely impossible.
- The Division acknowledged that enrolling and conducting such a study would be challenging; however, Dr. Southworth said that the information is critical to better understand the risk profile of long-term sildenafil use in adults. Pfizer said they typically conduct a formal feasibility assessment prior to conducting clinical trials and that they had not done so for this potential PMR.
- Dr. Grant noted that the results of the low-dose study in adults with PAH indicated that a dose of 5 mg TID has a similar effect on functional capacity (as measured by 6-minute walk test) as 20 mg TID. He went on to suggest that publishing the results of that study and STARTS-2 (which demonstrated a dose-related increase in mortality in children with PAH) may make investigators less reluctant to randomize adult PAH patients to doses lower than 20 mg thrice daily. The company noted that they have submitted the results of the low-dose study in a manuscript that is now under review at *Circulation*.
- Dr. Karkowsky added that the Division would be interested in data investigating whether there is a persistence of benefit (e.g., on functional capacity as measured by 6-minute walk test at one year), given the apparent lack of improvement in functional capacity at one year in the pediatric trial.
- There was some discussion of revising the label at this time to reflect the uncertain effects of long-term use in adults; however, no specific labeling recommendations were agreed-upon.
- Dr. Southworth asked Pfizer if they were aware of the number of new prescriptions for Revatio for PAH. Pfizer said they would follow-up on this item.

Minutes preparation: {See appended electronic signature page}  
Dan Brum, Pharm.D., RAC

Concurrence, Chair: {See appended electronic signature page}  
Mary Ross Southworth, Pharm.D.

Edited by:

D. Brum 8/23/12 (drafted)

A. Karkowsky 8/24/12

S. Grant 8/26/12

M. Southworth 8/27/12

E. Unger 8/28/12

D. Brum 8/29/12 (finalized)

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/s/  
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DANIEL BRUM  
08/29/2012

MARY R SOUTHWORTH  
08/29/2012



NDA 203109

**MEETING MINUTES**

Pfizer, Inc.  
Attention: Ms. Nancy McKay  
235 East 42nd St.  
New York, NY 10017

Dear Ms. McKay:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Revatio (sildenafil).

We also refer to the meeting between representatives of your firm and the FDA on July 26, 2012.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call Dan Brum, Pharm.D., BCPS, RAC, Regulatory Project Manager, at 301-796-0578.

Sincerely,

*{See appended electronic signature page}*

Ellis F. Unger, M.D.  
Director  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Enclosures:

- meeting minutes
- sponsor's slides (emailed to Dan Brum on 7/25/12)

## MEMORANDUM OF MEETING MINUTES

**Meeting Type:** C  
**Meeting Category:** Safety Issues

**Meeting Date and Time:** July 26, 2012 @ 9 a.m.  
**Meeting Location:** White Oak Bldg 22 Room 1315

**Application Number:** NDA 203109  
**Product Name:** Revatio (sildenafil) tablets and oral suspension  
**Indication:** pulmonary arterial hypertension  
**Sponsor/Applicant Name:** Pfizer

**Meeting Chair:** Ellis Unger  
**Meeting Recorder:** Dan Brum

### **FDA ATTENDEES**

Office of Drug Evaluation 1  
Ellis F. Unger, Director

#### Division of Cardiovascular and Renal Products

Norman Stockbridge, Director  
Stephen Grant, Deputy Director  
Mary Ross Southworth, Deputy Director for Safety  
Abraham Karkowsky, Clinical team leader  
Maryann Gordon, Clinical Reviewer  
Ed Fromm, Chief Project Management Staff  
Dan Brum, RPM  
Lori Wachter, Safety RPM

#### Office of Biostatistics, Division of Biometrics I

Jim Hung, Director  
John Lawrence, Statistical Reviewer

#### Office of Clinical Pharmacology

Raj Madabushi, Team Leader  
Satjit Brar, Pharmacometrics Reviewer

#### Office of New Drugs, Pediatric and Maternal Health Staff

Amy Taylor  
Matt Bacho

### **PFIZER ATTENDEES**

Raj Aggarwal (Safety and Risk Lead)  
Cecile Balagtas (Medicines Development Lead)  
Bruce Behounek (Clinical Lead)

Tom D'Eletto (Medical Lead)  
Xiang Gao (Clinical Pharmacology Lead)  
Lutz Harnisch (Pharmacometrics)  
Nancy McKay (Regulatory Lead)  
Eric Yan (Statistical Lead)  
Min Zhang (Statistician)  
Brian Harvey (VP, US Regulatory Strategy)  
Clare Kahn (VP, Worldwide Regulatory Strategy, Lead Specialty Care)

(b) (4)

## BACKGROUND

The following discussion points reflect summary points made during the teleconference between Pfizer and FDA on April 11, 2012:

### Discussion points

- Dr. Southworth said the review of this safety issue is ongoing and no regulatory decisions had been made. The Division wanted to communicate to the sponsor its assessment that the dose-related increase in mortality in children with PAH may have implications for the safe use of the drug in adults with PAH.
- Dr. Southworth said the Division is considering the need for long-term, controlled data on mortality and other outcomes in adults with PAH treated with sildenafil because of the dose-related mortality observed in the STARTS-1 trial. She noted that there are no long-term controlled data for sildenafil in adults with PAH.
- The sponsor offered to work with the Division to help resolve outstanding questions.

Background documents: The sponsor submitted background documents on July 11 and July 23, 2012. The sponsor did not pose any questions in either background document and we did not provide preliminary responses. **Bold, green font** reflects the main discussion points during the meeting. Note the sponsor emailed slides to Dan Brum on July 25, 2012 (enclosed).

**On July 25, 2012, Dr. Brum emailed draft labeling for NDA 203109 Revatio (sildenafil) to the sponsor. During the meeting the sponsor stated that they generally agreed with the draft labeling and in particular agreed with the language describing a new warning in section 5.1 and the results of STARTS-1 and STARTS-2 in section 8.4. The Office informed the sponsor that it intends to require them to conduct a postmarketing study to evaluate whether doses of Revatio above which there is no demonstrated increase in efficacy increase mortality.**

**The sponsor gave a presentation based on the attached slide deck. During the presentation, several issues were discussed, and the following items were agreed upon:**

- **there are no long-term controlled safety or efficacy data for Revatio in adults with PAH, only 12- and 16-week controlled data are available**
- **there was dose-related mortality observed in STARTS-2 (long term extension of the STARTS-1 pediatric PAH trial)**

- **In the 16-week PACES trial (adult PAH leading to the approval of Revatio for delay in clinical worsening) there were fewer deaths in the subjects administered Revatio compared to placebo subjects. This outcome is at variance with the STARTS-2 trial (pediatric PAH), but several important limitations were discussed (e.g., small number of events in PACES, duration of therapy, severity of PAH)**
- **it is unknown how the dose-related mortality observed in children with PAH applies to adults with PAH**
- **the minimum effective dose of sildenafil is not known (i.e., it is unknown whether doses lower than 20 mg thrice daily, the approved dose, might be similarly effective and relatively safer)**
- **DCRP requested that the sponsor submit a prematurely discontinued dose exploration study of the effect of administering 1, 5, or 20 mg of sildenafil three times daily to adults on 6MWD at 12 weeks**
- **a *controlled* trial appears to be a critical design feature (vs. epidemiological data) for the required post-marketing study**
- **a placebo arm would not be part of the study design**
- **mortality would be the key outcome measure (versus combined morbidity and mortality)**
- **an additional meeting focusing on trial design and feasibility will be arranged upon request**
- **the population to be studied and endpoint of interest will have a significant impact on patient enrollment and study timelines**

### **3.0 ISSUES REQUIRING FURTHER DISCUSSION**

Trial design and timelines will be discussed at an upcoming (to-be-scheduled) meeting.

### **4.0 ACTION ITEMS**

Pfizer plans to submit the above mentioned dose-ranging study using sildenafil 1, 5, and 20 mg thrice daily in adults with PAH.

Post-meeting note: Pfizer submitted the study report of the above mentioned dose-ranging study on 08/01/2012.

### **5.0 ATTACHMENTS AND HANDOUTS**

There was a slide presentation.

# Finding of Relation of Dose and Mortality in Children (20-45 Kg) With Pulmonary Hypertension Treated With Sildenafil

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- True drug effect (? mechanism; opposite the effect seen in adults)
- Play of chance (small number of events)
- Imbalance between groups in measured or unmeasured variables at baseline or following randomization

# Challenges in Carrying Out a Definitive Mortality Trial in Pulmonary Hypertension

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- Very uncommon disease
- If target population includes patients with mild disease, event rates are not high.
- Need for very long follow-up to discern potential drug effect and accumulate events
- Difficulties in maintaining randomized assignment for long periods of time
- High likelihood of differential intensification of concomitant treatments during follow-up
- Current pediatric trial struggled with recruitment for approximately 5 years

# Does Mortality Finding With Sildenafil in Children Have Implications for Adults?

## *PACES Trial*

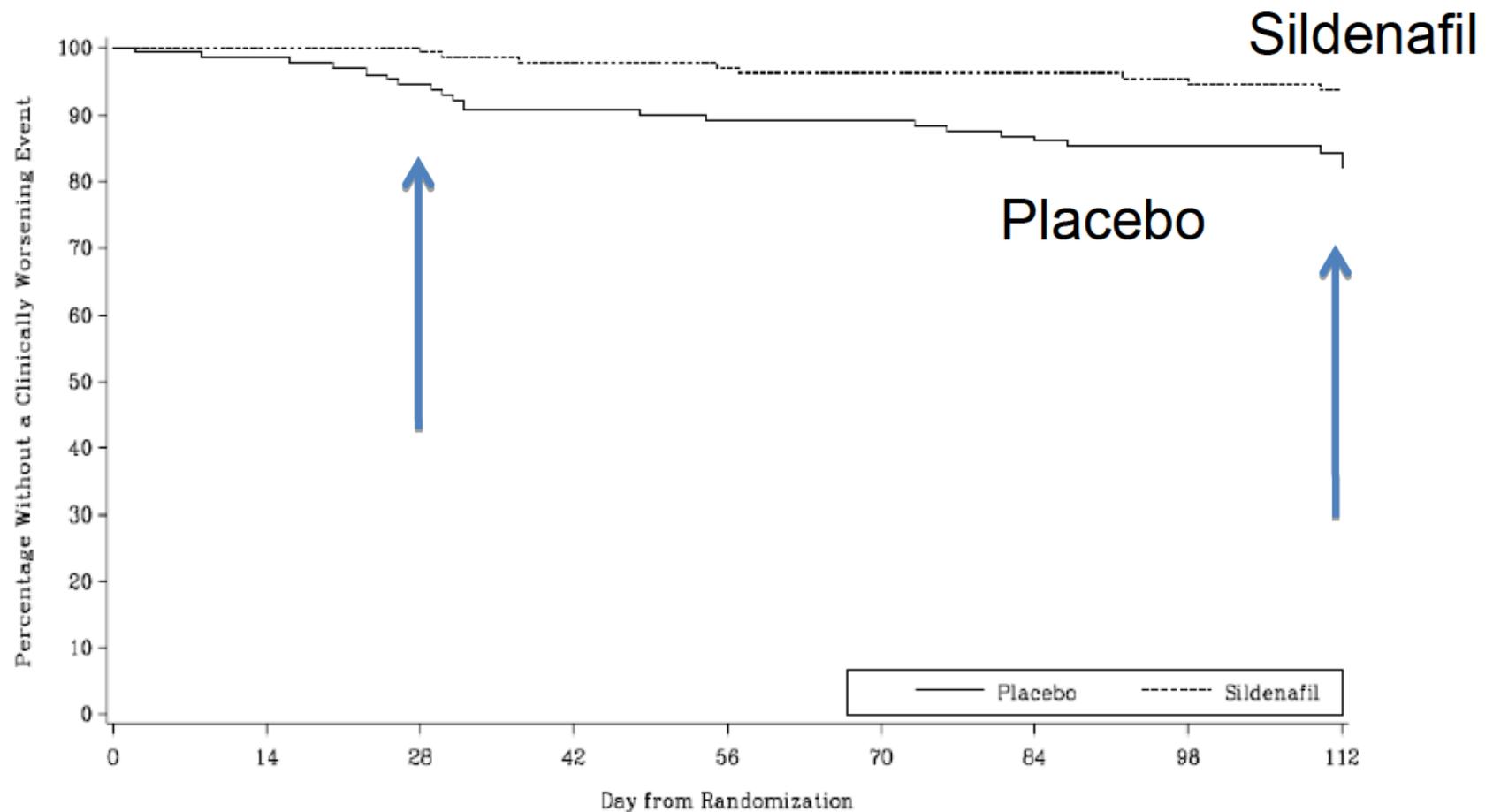
*Table 2. Incidence of Clinical Worsening Event\**

Clinical Worsening Event	Patients with Event, n (%)	
	Placebo (n = 131)	Sildenafil (n = 134)
Any reason	24 (18.3)	8 (6.0)
Death	7 (5.3)†	0 (0)
Lung transplantation	1 (0.8)	0 (0)
Hospitalization due to pulmonary arterial hypertension	11 (8.4)	8 (6.0)
Change in epoprostenol dose because of clinical deterioration	16 (12.2)	2 (1.5)
Initiation of bosentan therapy	1 (0.8)	0 (0)



Most patients in the sildenafil group received 80 mg TID for up to 16 weeks, but event curves diverged significantly at 4 weeks, when dose was only 20 mg TID

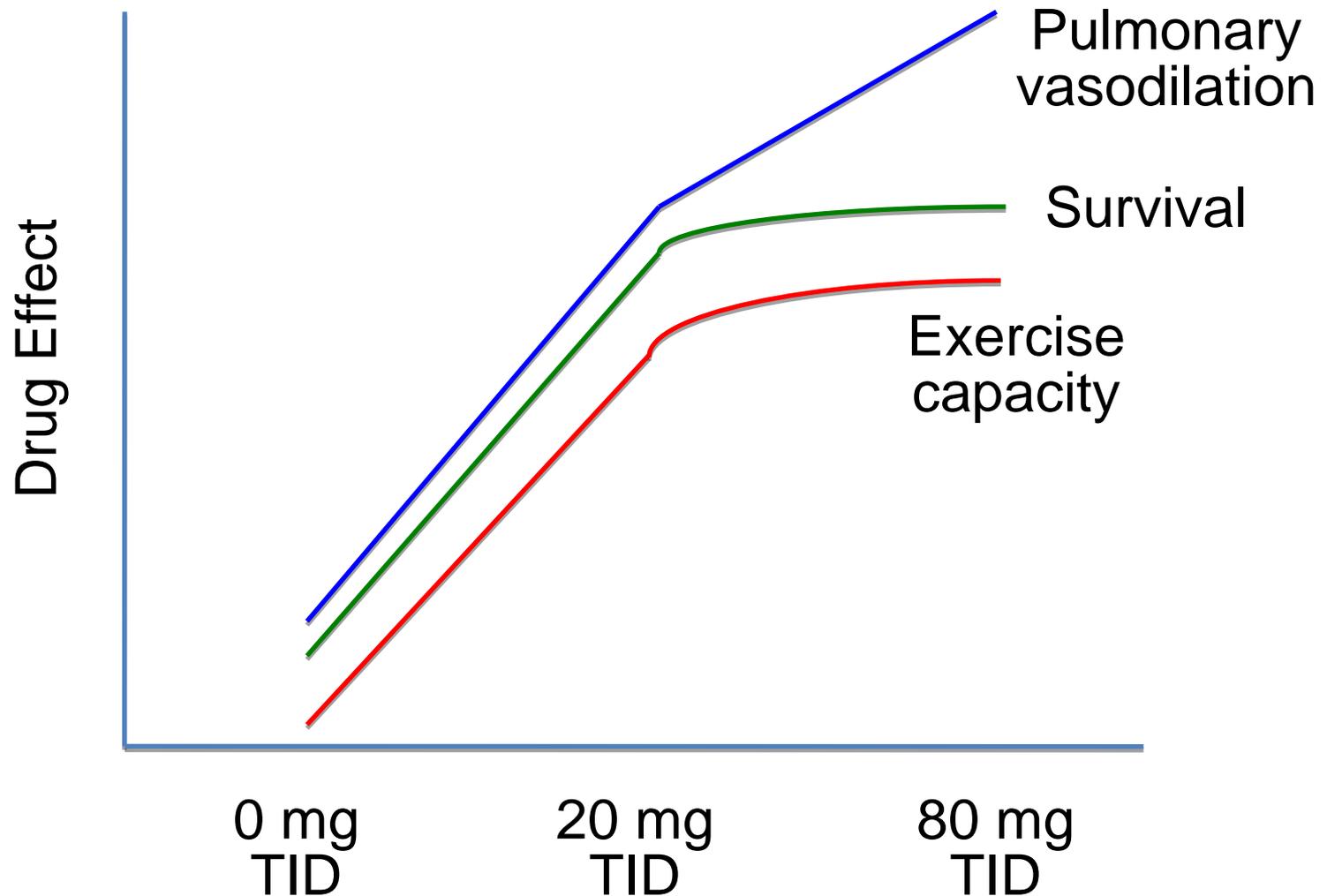
# PACES: Time to Clinical Worsening



Number at Risk (number censored)	Day 0	(a) Day 28	(b) Day 56	(c) Day 84	(d) Day 112
Placebo	131	(1) 123	(0) 116	(2) 111	(38) 70
Sildenafil	134	(0) 134	(2) 128	(2) 125	(44) 78

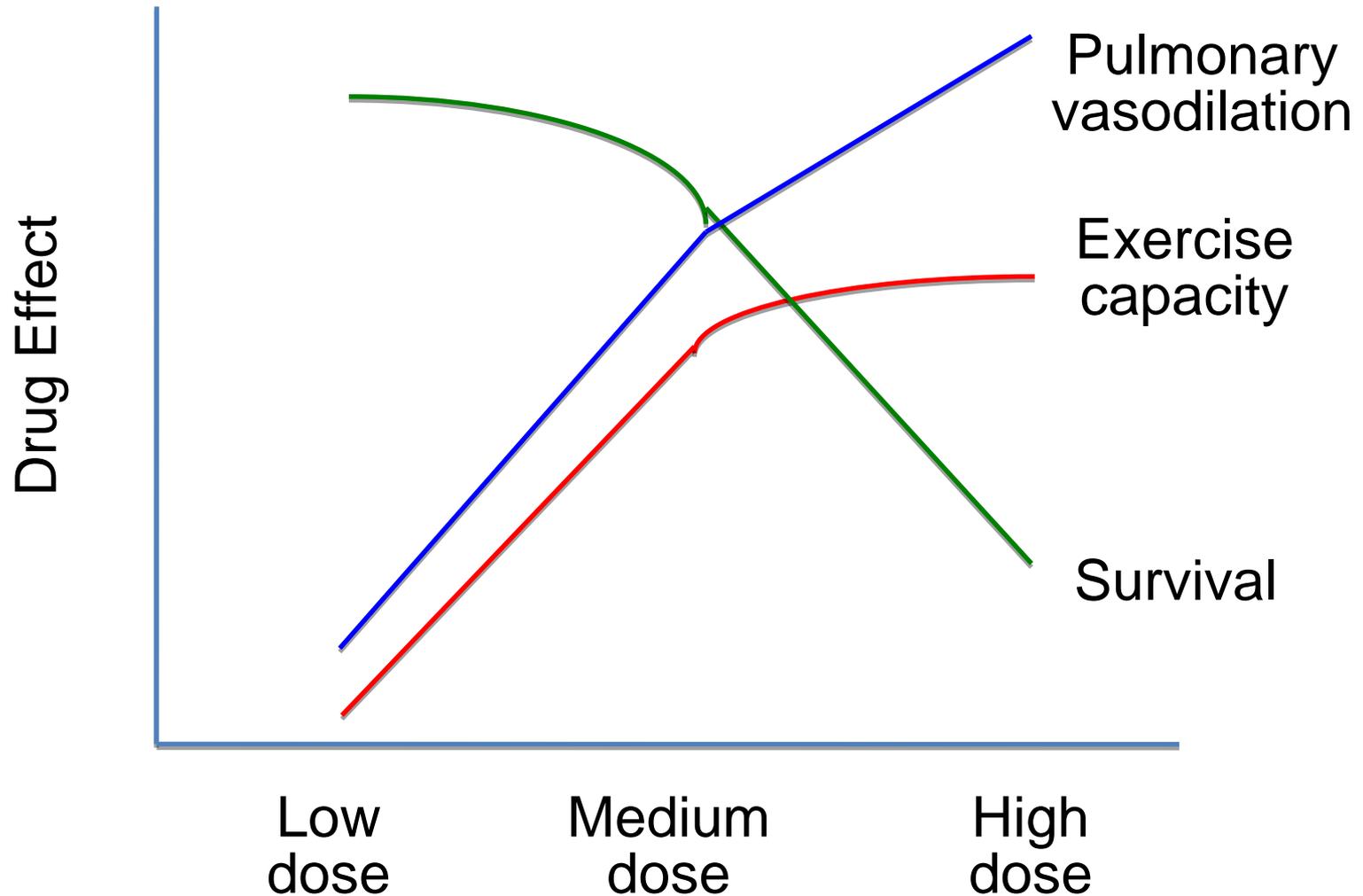
# Presumed Dose-Response Relation For Sildenafil in PAH in Adults

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# Presumed Dose-Response Relation For Sildenafil in PAH in Children

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/s/  
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DANIEL BRUM  
08/09/2012

ELLIS F UNGER  
08/09/2012



NDA 203109

**INFORMATION REQUEST**

Pfizer, Inc.  
Attention: Ms. Nancy McKay  
235 East 42nd St.  
New York, NY 10017

Dear Ms. McKay:

Please refer to your New Drug Application (NDA) dated November 30, 2011, received November 30, 2011, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act, for Revatio (sildenafil) for oral suspension 10 mg/mL.

The following is abstracted from my review memo:

The primary end point of A1481131 was change in pVO<sub>2</sub> in the ~50% of subjects able to perform cycle ergometry. FDA was also interested in the secondary end point of change in PVRI, and the sildenafil Pediatric Written Request was modified post-study to reflect this interest.

The pVO<sub>2</sub> end point was analyzed by LOCF with all doses pooled and showed an ~10% increase above baseline and placebo with p=0.056. pVO<sub>2</sub> was reassessed at 1 year in A1481156, at which time the effects were of similar magnitude to the values at the end of A1481131 and not distinguishable across doses<sup>1</sup>.

Modest dose-related reductions were seen in PVRI at 16 weeks (p=0.041 for pooled doses vs. placebo). Not surprisingly, exclusion of a handful of subjects with the largest observed changes renders the p-value no longer statistically significant.

While Dr. Lawrence demonstrates there is poor correlation between PVRI and pVO<sub>2</sub> in these data, the relationship is not very strong across studies of *all* drugs approved to treat PAH in adults. The nominal effect on pVO<sub>2</sub> in A1481131 is about what one would expect from the nominal effect on PVRI if the relationship were the same in adults and children.

I conclude that the evidence of an effect of sildenafil on exercise or a surrogate thereof is weak.

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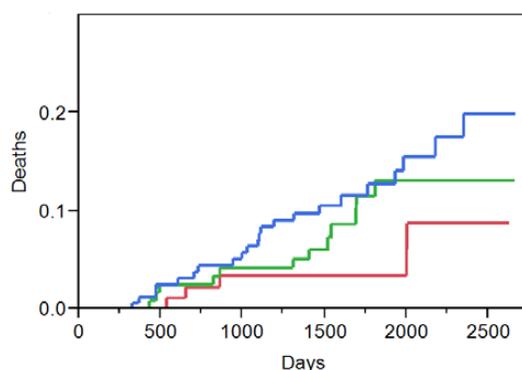
<sup>1</sup> This result is described as either no effect or preservation of effect in various reviews.

Other indices of clinical benefit in this program trended favorably—WHO functional class, global assessments by subjects/parents, and global assessments by investigators.

On the whole, one might reasonably conclude there was adequate evidence of net benefit of sildenafil in children, were it not for the mortality data.

There were no deaths among randomized subjects in A1481131. There were 35 deaths reported for A1481156. The majority of these deaths (77%) occurred among the minority (33%) of subjects with primary pulmonary hypertension.

K-M curves are shown below<sup>2</sup>:



Dr. Lawrence provides several p-values associated with the mortality observations by randomized treatment. If one assumes a linear relationship by dose, he gets  $p=0.008$ . If one makes no linearity assumption, then he gets non-significant p-values (not given) for comparisons of low and middle doses and for middle and high doses, and  $p=0.015$  for comparison of low to high. Dr. Karkowsky concludes that the true relationship must lie somewhere between  $p=0.008$  and  $p=0.015$ .

Of the 35 deaths, 26 occurred within 7 days off treatment. I cannot identify the 9 subjects with deaths more than 7 days off treatment, do not know how long off treatment they were, and do not have a K-M curve excluding them.

I also do not have a K-M analysis by actual treatment. Five subjects in A1481156 underwent down-titration (original groups not described), and 28 underwent up-titration in the low-dose group, 11 in the middle-dose group, and 13 in the high-dose group. I do not know the bounds for reasonable p-values to ascribe to these mortality observations.

Causes of death (described in Dr. Gordon's review) bear no obvious hallmark of a specific drug-related cause. There are a few sudden deaths,

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<sup>2</sup> From Dr. Karkowsky's review. Red=low dose, green=middle dose, and blue=high dose.

but most represent progression of disease to heart failure. Considered individually, none is unexpected among patients with PAH.

Noteworthy, too, are the lack of any mortality during the first 16 weeks (A1481131)<sup>3</sup> and the first year in A1481156.

There are several analyses of serious adverse events. Dr. Gordon tabulates treatment-emergent SAEs (p. 50) in A1481131—2 on placebo and middle dose, 1 on low dose, and 7 on high dose—representing a wide range of events, only one of which (stridor) was ascribed any likely relationship to treatment. In study A1481156, 2 subjects discontinued with AEs from low dose, and 5 each from middle and high doses, with no predominant cause. Overall, she reports 24% of subjects in the two studies had an SAE in the low-dose group, 62% in the middle-dose group, and 44% in the high-dose group<sup>4</sup>. Dr. Karkowsky's list (p. 6) also covers both studies, excludes deaths, and includes discontinuations and events "[of] concern"—7% on low dose, 19% on middle dose, and 19% on high dose. His list includes 5 cases of pneumonia on the middle dose and 8 cases of pneumonia on the high dose. Dr. Karkowsky interprets the SAE data as being consistent with there being some adverse dose-related effect of sildenafil, but the lack of any plausibly treatment-related finding makes me think the SAE data are equally consistent with some differences in underlying risk that were not handled by randomization.

One then looks at data for all adverse events and for trends by dose for events that might be expected to underlie the mortality findings. And there are no trends with respect to bleeding, hypotension, heart failure, or dyspnea. There are no trends for laboratory findings, for ECG findings, for vital signs, for discontinuations, for cognitive development, or for motor development—none of which is integrated into the reviewers' assessments of the mortality findings.

Please attempt to fill in some of the gaps that my memo cites. Specifically,

1. Please provide a listing of the 35 deaths including randomized dose in A1481156, actual dose, time of last dose, and briefly the events leading up to the mortal event.
2. Please analyze mortality by dose in A1481156 with all permutations of the following:
  - a. Including/excluding deaths more than 7 days off treatment.
  - b. Assuming or not, linearity across doses.
  - c. For subjects on active treatment in A1481131, including or excluding their time in A1481131.

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<sup>3</sup> Data from A1481131 appears to be omitted from all analyses of mortality.

<sup>4</sup> I assume these are not necessarily treatment-emergent. These events are not otherwise described.

- d. By randomized dose in A1481156 or by actual last dose in A1481156.

I recognize that some of what I request is available in your submission, but it would be helpful if this information was assembled in one place. You may also wish to provide other information related to these matters as you see fit.

If you have any questions, please call Dan Brum, Pharm.D., RAC, Regulatory Project Manager, at (301)796-0578.

Sincerely,

*{See appended electronic signature page}*

Norman Stockbridge, M.D., Ph.D.  
Director  
Division of Cardiovascular and Renal  
Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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/s/  
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NORMAN L STOCKBRIDGE  
05/31/2012



NDA 203109

**REVIEW EXTENSION –  
MAJOR AMENDMENT**

Pfizer, Inc.  
Attention: Ms. Nancy McKay  
235 East 42nd St.  
New York, NY 10017

Dear Ms. McKay:

Please refer to your New Drug Application (NDA) dated November 30, 2011, received November 30, 2011, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act, for Revatio (sildenafil) for oral suspension 10 mg/mL.

On May 30, 2012, we received your May 29, 2012, unsolicited major amendment to this application. The receipt date is within three months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is August 30, 2012.

In addition, in accordance with the “PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2008 THROUGH 2012,” the timeline for communicating labeling changes and/or postmarketing requirements/commitments, provided in our January 17, 2012, filing communication letter, no longer applies and no new timeline will be provided.

If you have any questions, please call Dan Brum, Pharm.D., RAC, Regulatory Project Manager, at (301)796-0578.

Sincerely,

*{See appended electronic signature page}*

Norman Stockbridge, M.D., Ph.D.  
Director  
Division of Cardiovascular and Renal Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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NORMAN L STOCKBRIDGE  
05/30/2012

**Brum, Dan**

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**From:** Brum, Dan  
**Sent:** Tuesday, May 22, 2012 1:21 PM  
**To:** 'McKay, Nancy'  
**Subject:** RE: packaging and labeling--discipline review letter -- NDA 203109 sildenafil -- additional comments  
**Sensitivity:** Confidential

Nancy,

In response to your submission dated May 18, 2012, DMEPA has the following comments:

**Oral Dosing Syringe:**

- 1) The syringe depicted in the IFU is a 2 mL syringe. However, section 16 How Supplied/Storage and Handling states "A (b) (4) oral dosing syringe and a press-in bottle adapter are also provided." Revise this statement to read "A 2 mL oral dosing syringe and a press-in bottle adapter are also provided."
- 2) In the IFU under figures labeled #3 through #7, the syringe in these figures show multiple graduation marks, which differ from those in figure #1. Revise the figures so they accurately reflect the actual dosing syringe that will be co-packaged with the medicine and are consistent from figure to figure.

**Carton Labeling:**

- 1) The Pfizer logo above the proprietary name distracts from the proprietary name. Move this logo to the bottom third of the principle display panel and select a color for the logo that is consistent with the currently marketed oral and injection Revatio products.

**Container Label:**

- 1) The Pfizer logo competes for prominence with the proprietary name, established name, and strength statement. Minimize and relocate the Pfizer logo away from the proprietary name, established name, and strength statement, and select a color for the logo that consistent with the currently marketed oral and injection Revatio products.

--Dan

---

**From:** McKay, Nancy [mailto:Nancy.McKay@pfizer.com]  
**Sent:** Thursday, May 17, 2012 11:46 AM  
**To:** Brum, Dan  
**Subject:** RE: packaging and labeling--discipline review letter -- NDA 203109 sildenafil  
**Sensitivity:** Confidential

Thanks, Dan.

We will make this change with tomorrow's submission with responses to the other labeling comments.

Nancy

---

**From:** Brum, Dan [mailto:Dan.Brum@fda.hhs.gov]  
**Sent:** Thursday, May 17, 2012 8:11 AM  
**To:** McKay, Nancy  
**Subject:** RE: packaging and labeling--discipline review letter -- NDA 203109 sildenafil  
**Sensitivity:** Confidential

Nancy,

Yes, to avoid a user fee, include the following verbiage:

REVATIO is indicated for the treatment of **pediatric** pulmonary arterial hypertension (WHO Group I) to improve exercise ability [REDACTED] <sup>(b) (4)</sup>. [see *Clinical Studies (14)*].

Studies establishing effectiveness included predominately patients with WHO Functional Class I-III symptoms and etiologies of idiopathic pulmonary arterial hypertension (33%) or PAH associated with congenital heart disease (systemic to pulmonary shunt 36%, surgical repair 30%).

--Dan

---

**From:** McKay, Nancy [mailto:Nancy.McKay@pfizer.com]  
**Sent:** Thursday, May 17, 2012 8:02 AM  
**To:** Brum, Dan  
**Subject:** RE: packaging and labeling--discipline review letter -- NDA 203109 sildenafil  
**Sensitivity:** Confidential

Thanks, Dan.

Will this also apply to the change to the indication for the Orphan comment? If you agree with the insertion of the header I suggested, I could potentially include this change with this week's submission, as well.

Thanks

Nancy

---

**From:** Brum, Dan [mailto:Dan.Brum@fda.hhs.gov]  
**Sent:** Thursday, May 17, 2012 7:03 AM  
**To:** McKay, Nancy  
**Subject:** RE: packaging and labeling--discipline review letter -- NDA 203109 sildenafil  
**Sensitivity:** Confidential

Nancy,  
Yes, we don't expect that you send SPL at this point.  
Thanks,  
--Dan

---

**From:** McKay, Nancy [mailto:Nancy.McKay@pfizer.com]  
**Sent:** Wednesday, May 16, 2012 7:09 PM  
**To:** Brum, Dan  
**Subject:** RE: packaging and labeling--discipline review letter -- NDA 203109 sildenafil  
**Sensitivity:** Confidential

Dan,

We plan to submit our responses to this discipline review letter and proposed labeling changes this week. Given the stage of the review process, we would propose providing the USPI in Word format with track changes marked. We would prefer to wait until all labeling comments are addressed for the NDA prior to providing a revised SPL. Would this proposal be acceptable?

Regards

Nancy

---

**From:** Brum, Dan [mailto:Dan.Brum@fda.hhs.gov]  
**Sent:** Friday, May 04, 2012 3:29 PM  
**To:** McKay, Nancy  
**Subject:** RE: packaging and labeling--discipline review letter -- NDA 203109 sildenafil

Nancy,

I guess I recommend revising and submitting rather waiting for further comments.

--Dan

---

**From:** McKay, Nancy [mailto:Nancy.McKay@pfizer.com]  
**Sent:** Friday, May 04, 2012 2:51 PM  
**To:** Brum, Dan  
**Subject:** RE: packaging and labeling--discipline review letter -- NDA 203109 sildenafil

Hi Dan,

Thank you for sending the attached labeling comments. Is it your preference that we provide revised proposed labeling in the next few days or await further labeling comments?

Thanks

Nancy

---

**From:** Brum, Dan [mailto:Dan.Brum@fda.hhs.gov]  
**Sent:** Friday, May 04, 2012 10:26 AM  
**To:** McKay, Nancy  
**Subject:** packaging and labeling--discipline review letter -- NDA 203109 sildenafil

Hi Nancy,  
Please review the attached letter and let me know if you have any questions.  
Thanks,  
--Dan

Dan Brum, Pharm.D., MBA, BCPS, RAC  
Commander, US Public Health Service  
Senior Regulatory Project Manager  
Division of Cardiovascular and Renal Products  
Center for Drug Evaluation and Research  
Food and Drug Administration

p: (301)796-0578  
f: (301)796-9841  
[dan.brum@fda.hhs.gov](mailto:dan.brum@fda.hhs.gov)

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/s/  
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DANIEL BRUM  
05/22/2012



NDA 203109

**DISCIPLINE REVIEW LETTER**

Pfizer, Inc.  
Attention: Ms. Nancy McKay  
235 East 42nd St.  
New York, NY 10017

Dear Ms. McKay:

Please refer to your New Drug Application (NDA) dated November 30, 2011, received November 30, 2011, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act, for Revatio (sildenafil) for oral suspension 10 mg/mL.

The Division of Medication Error Prevention and Analysis (DMEPA) review of the proposed label and labeling section of your submission is complete, and we have identified the following deficiencies:

The proposed label and labeling introduce vulnerability that can lead to medication errors. We advise the following recommendations be implemented:



**B. ORAL DOSING SYRINGE** (b) (4)

1. Include an oral dosing device (e.g., oral syringe) that bears markings consistent with the labeled dosage directions of 1 mL or 2 mL. Ensure the 1 mL and 2 mL measurements do not include trailing zeros. Trailing zeros have been noted to result in a 10-fold error by the Institute for Safe Medication Practices (ISMP) and lead to confusion. For additional guidance, refer to the Guidance for Industry titled "Dosage Delivery Devices for Orally Ingested OTC Liquid Drug Products" published May 2011, since this information is also pertinent to prescription dosing devices.

2. The barrel of the syringe has printed “(b) (4)” which indicates (b) (4). Revise the syringe barrel route of administration text to read “Oral Use Only” to minimize the risk of (b) (4) confusion in the marketplace.
3. When obtaining a dose of medication from the reconstituted suspension, the user must insert the oral dosing syringe into the bottle adapter opening, invert the bottle with inserted syringe simultaneously, and then pull back the syringe plunger to the graduation mark corresponding to the dose that has been ordered by the prescriber. With the proposed syringe inverted, the graduation numbers would have to be read upside down. This may lead to confusion. Include an oral dosing syringe for use with this suspension whose graduation numbers can be read right side up when obtaining a dose from the amber glass bottle. For additional guidance, refer to the Guidance for Industry titled “Dosage Delivery Devices for Orally Ingested OTC Liquid Drug Products” published May 2011, since this information is also pertinent to prescription dosing devices.

### C. CARTON LABEL

1. The Pfizer logo above the proprietary name distracts from the proprietary name. Move this logo to the bottom third of the principle display panel and select a color for the logo that is consistent with the currently marketed oral and injection Revatio products.
2. Debold and move the “Rx Only” statement to the bottom third portion of the principle display panel.
3. The statement “FOR ORAL USE ONLY” has decreased readability due to all uppercase font, and its placement can be made more prominent by moving the “Grape Flavored” statement to the bottom third of the principle display panel and replacing it with this statement instead. Revise the statement to title case: “For Oral Use Only” and move the statement so it is directly below the statement of strength.
4. The statement “SHAKE WELL BEFORE EACH USE” has decreased readability due to all uppercase font and is inadequately prominent due to its placement on the side panel. Revise the statement to title case: “Shake Well Before Each Use” for improved readability and move to the principle display panel so it is more prominent.
5. There is currently no net quantity statement on the principle display panel. Add the statement “112 mL following Constitution” to the primary display panel.
6. The top half of the side display panel is bolded and cluttered making it difficult to read. To minimize clutter, we recommend revising the statement (b) (4) to “Discard any unused portion 30 days after constitution.” Additionally, remove the statement (b) (4) since there is already an expiration date included on the carton labeling.
7. The side display panel does not currently contain any directions for constitution of the oral suspension for the pharmacist. Add this information to the side panel.

#### **D. CONTAINER LABEL**

1. The Pfizer logo competes for prominence with the proprietary name, established name, and strength statement. Minimize and relocate the Pfizer logo away from the proprietary name, established name, and strength statement, and select a color for the logo that is consistent with the currently marketed oral and injection Revatio products.
2. Debold the “Rx only” statement to decrease its prominence and move it to the side panel.
3. The statement “FOR ORAL USE ONLY” has decreased readability due to all uppercase font, and its placement can be made more prominent by moving it to the principle display panel, replacing the “(b) (4)” statement. Revise the statement to title case: “For Oral Use Only” and move the statement so it is directly below the statement of strength.
4. The statement “SHAKE WELL BEFORE EACH USE” has decreased readability due to all uppercase font and is inadequately prominent due to its placement on the side panel. Revise the statement to title case: “Shake Well Before Each Use” for improved readability and move to the principle display panel so it is more prominent.
5. In the After Constitution section, revise (b) (4) to “Discard unused portion 30 days after constitution” to maintain consistency with the carton labeling.

#### **E. INSERT LABELING**

1. You have used in the HIGHLIGHTS OF PRESCRIBING INFORMATION, and FULL PRESCRIBING INFORMATION error prone abbreviations. The symbols  $<$ ,  $\leq$ ,  $>$ ,  $\geq$  were utilized in the insert labeling to represent “less than,” “less than or equal to,” “greater than,” or “greater than or equal to,” respectively. These symbols can be misinterpreted as the opposite of the intended symbol or mistakenly used as the incorrect symbol. As part of a national campaign to decrease the use of dangerous symbols<sup>1</sup>, the FDA agreed not to use such error prone symbols in the approved labeling of products because these abbreviations can be carried over to prescribing. Therefore, we recommend that  $<$  be replaced with “less than,”  $\leq$  be replaced with “less than or equal to,”  $>$  be replaced with “greater than,” and  $\geq$  be replaced with “greater than or equal to.”
2. The Dosage and Administration section of the insert labeling, the patient counseling information section of the insert labeling, as well as the instructions for use do not clearly indicate that the suspension should be shaken before each use. Revise “Shake the closed bottle of constituted suspension (b) (4)” to read “Shake the closed bottle of constituted suspension for a minimum of 10 seconds before Each use” in the Dosage and Administration section of the insert

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<sup>1</sup> Institute for Safe Medication Practices (ISMP). ISMP’s List of Error-Prone Abbreviations, Symbols, and Dose Designations. ISMP: 2010

labeling, the patient counseling information section of the insert labeling, as well as the instructions for use section.

3. You have included instructions for use intended for the patient in the Dosage and Administration section titled "Instructions for Use." This information is inappropriately placed and unnecessary since there are separate instructions for use already. We recommend removal of the instructions intended for patient use from the Dosage and Administration section since this is a duplication of the instruction for use in the patient package insert section.
4. The Instructions For Use (IFU) do not include a clear diagram of the oral dosing syringe that shows the graduation marks that patients will use to accurately draw up a dose. Insert a labeled diagram of the oral dosage syringe indicating the individual components and graduation marks.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, please call Dan Brum, Pharm.D., RAC, Regulatory Project Manager, at (301)796-0578.

Sincerely,

*{See appended electronic signature page}*

Abraham Karkowsky, M.D., Ph.D.  
Cross Discipline Team Leader  
Division of Cardiovascular and Renal Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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/s/  
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ABRAHAM M KARKOWSKY  
05/04/2012



# Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH  
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: April 20, 2012

From: Mary Ross Southworth, PharmD  
Deputy Director for Safety  
Division of Cardiovascular and Renal Products /CDER

To: File

Subject: Opening Memo  
TSI # 1311: Sildenafil and increased mortality (pulmonary hypertension indication) NDA 203109, 22473. 21845

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Materials reviewed:

1. Clinical/Statistical Review, NDA 203109, Maryann Gordon, April 11, 2012
2. Barst R., et al. A randomized, double-blind, placebo-controlled, dose-ranging study of oral sildenafil citrate in treatment-naïve children with pulmonary arterial hypertension. *Circulation*. 2012; 125:324-334.
3. Response to FDA Proposed Discussion Points for April 11, 2012 Teleconference, Pfizer (to be submitted officially).
4. Drug Utilization Review, TSI 1311, Kusum Mistry, April 13, 2012.

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Sildenafil, a phosphodiesterase-5 inhibitor, is approved to improve exercise ability and delay clinical worsening in patients with pulmonary arterial hypertension (PAH) WHO Group I. The sponsor recently submitted data to support a pediatric PAH indication (age 1-17 years). The study (A1481131) is a randomized, double-blind, placebo controlled parallel group dose ranging study. Pediatric patients with primary PAH, PAH secondary to congenital heart disease or collagen vascular disease were

randomized to placebo or 3 dose levels of sildenafil to achieve steady state concentrations of 47 (low) , 140 (medium) , or 373 (high) ng/ml; depending on body doses were 10mg, 20mg, 40mg, or 80 mg TID. They were followed for 16 weeks and the primary endpoint was percent change in PVO<sub>2</sub> (oxygen consumption-a measure of exercise tolerance) from baseline to week 16. At the end of the study, patients could continue into a long term extension study (A1481156). With the exception of the placebo subjects, subjects remained in the same treatment group as the previous study. The subjects on placebo were randomized to 1 of the 3 dose groups. Treatment in the extension study remained blinded until the last subject completed the 16 week study; then the study became open label. The primary objective of the extension study was to assess safety and tolerability of long-term treatment.

For A1481131, the study failed to show a significant effect of sildenafil on the primary endpoint. The combined doses (low, medium, and high) produced a statistically insignificant 8% increase in peak VO<sub>2</sub> compared to placebo. (p=0.056). There were no major safety findings during this 16 week study and no deaths were reported.

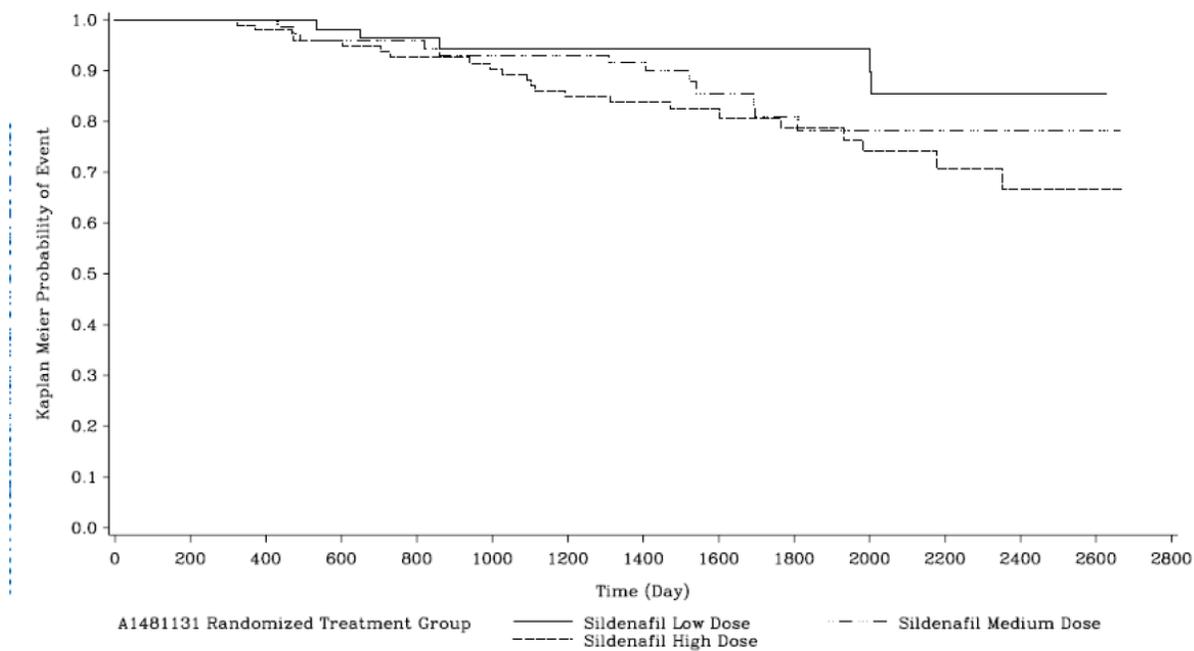
Unexpectedly, in the extension study, a higher risk of mortality was found in patients randomized to the high dose group compared to the low dose group (HR 3.5; CI 1.29, 9.51) and in the medium dose vs. the low dose (HR 1.85). The Data Monitoring Committee concluded that high dose sildenafil is associated with increased risk of mortality and halted both the high and medium dose arms of the study as well as the low dose arm in children with a body weight of <20kg. At the time of the DMC decision, all subjects were > 3 years post randomization. Although dose titrations were permitted in the extension portion of the study, an analysis by modal dose per subject revealed that randomization was relatively preserved throughout the extension study.

Most deaths occurred years after the start of therapy (during the extension) and in most cases appear to be deaths from the underlying disease or its consequences. A dose response relationship to mortality is observed.

The number of deaths in each of the treatment groups was

- 20/100 (20%) in the high dose treatment group (sildenafil high/high dose and placebo/high dose),
- 10/74 (13.5%) in the medium dose treatment group (sildenafil medium/medium dose and placebo/medium dose), and
- 5/55 (9%) in the low dose treatment group (sildenafil low/low dose and placebo/low dose), respectively.

Figure 1.2  
Sildenafil Protocol A1481131 and A1481156  
Kaplan Meier Survival Plot by Sildenafil Treatment Group (Relative to start of Sildenafil) As of 04Aug2011



Sildenafil is approved for adults on the basis of short term (~16 weeks) studies that demonstrated a beneficial effect on exercise tolerability and clinical worsening (largely driven by the need to add parenteral therapy for PAH). There are no long term controlled outcome studies for sildenafil (or any other PAH drug approved to date). Although the currently approved labeling for sildenafil for PAH contains a recommendation to avoid doses higher than 20 mg TID, higher doses are commonly used in clinical practice (about 19% of prescriptions are for doses higher than 20 mg TID according to sponsor response). Therefore, there is concern that the mortality finding seen in pediatrics could be extrapolated to adults and should be studied further.

A discussion was held with the sponsor about the study findings and implications for adults on April 11, 2012 (minutes under TSI). The sponsor agreed to work with the division to help resolve outstanding questions once reviews are completed.

Clin Pharm, Stats, and CDTL reviews for the NDA are still pending. The following issues need to be addressed:

Safety/Efficacy determination in Pediatrics

Minimal efficacy (as measured by PV02) in the low dose groups and increased risk of mortality in the high dose groups has major implications for approvability. The results of the study will be included in labeling along with recommendations for use/avoidance of use) in children. If the risk/benefit determination is negative, a drug safety communication seems warranted since a substantial number of pediatric patients are receiving this therapy (~21,250 from 2005-2011; age 0-17).

### Implications for Adults

Although the sponsor has proffered a favorable survival rate for long term sildenafil (open label, uncontrolled) as compared to historical controls, these comparisons are not reliable given the biases introduced by heterogeneity of patient types and therapy approaches. Virtually all drugs for PAH have been approved based on short term hemodynamic studies and one may be concerned whether beneficial effects on hemodynamics do not translate into beneficial outcomes (as was observed in some heart failure therapy programs and the CAST trials). This study may be one of the only long-term, controlled explorations of mortality effects of a pulmonary hypertension drug available. Given its concerning safety signal, potential study designs for further *controlled* examination should be pursued.

It should be noted that sildenafil is also marketed as Viagra (NDA 20895), a drug for erectile dysfunction. However, there is no indication that this safety signal applies to use of that product given the differences in patient population and dosing regimen. We will keep the Division of Reproductive and Urologic Products informed as we move forward with the review.

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/s/  
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MARY R SOUTHWORTH  
04/20/2012

# MEMORANDUM OF TELECON

DATE: April 12, 2012

APPLICATION NUMBER: NDA 203109

**BETWEEN:**

Name: Pfizer, Inc.

**AND**

Name: Office of New Drug Quality Assessment  
Ramesh Sood, Branch Chief  
Angelica Dorantes, Biopharmaceutics Team Leader  
Arzu Selen, Biopharmaceutics Research Lead  
Kasturi Srinivasachar, CMC Lead  
Mohan Sapru, CMC Reviewer  
Teshara G. Bouie, Project Manager

**SUBJECT:** Interim Dissolution Method and Acceptance Criterion for Sildenafil Citrate Powder for Oral Suspension

**Background:**

Since currently there are very limited data to make a recommendation on the acceptability of the final dissolution method and acceptance criterion, the Agency recommended the following method and criterion on an interim basis:

**Dissolution Method**

USP Apparatus 2 with 50 rpm paddle speed

Medium:

900 mL pH 5 buffer (as provided in the Pfizer response dated xxx) at 37° C

**Dissolution Acceptance Criterion**

Q = (b) (4) in 20 minutes

**The Call:**

- During the teleconference Pfizer agreed to implement the proposed interim dissolution method and the dissolution acceptance criterion and will update the specification table for the drug product accordingly.
- Pfizer agreed to generate and provide dissolution profile data using the agreed interim method not later than May 7, 2012, for the following:
  - Drug products with viscosities covering the top, middle and bottom of the

viscosity range observed in the stability studies (approximately from (b) (4) and product with the viscosity value observed on Day 30 of the in-use stability testing (approximately (b) (4)

- Pfizer agreed in principle to provide dissolution profile data for the bio-batch (product used in the BE Study A1481293, lot number: 10-082576), and requested time to confirm whether they can access the material within the discussed time-frame.
- The Agency emphasized the value of getting dissolution profile data from the bio-batch to further support the interim dissolution acceptance criterion for this application.
- As alternate approaches for dissolution method development, the Agency suggested Pfizer to explore lower paddle speeds, lower dissolution medium volume and pH values of 5 or higher.
- Pfizer agreed to provide the dissolution method development report with complete data within 6 months of the NDA action as an amendment to the IND. Pfizer will indicate in the cover page of their submission a request for review of the proposed dissolution method. The Agency will review the report and provide feedback in a timely manner.
- Based on the Agency's feedback on the acceptability of the final dissolution method, Pfizer will collect additional dissolution profile data (using the final dissolution method) from the batches manufactured during the first year post-action date. These data will be used to set the final acceptance criterion
- Within 14 months of action date, Pfizer will submit a prior approval supplement (PAS) to their NDA with their proposal for the final acceptance criterion and the supportive dissolution data.

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Teshara G. Bouie  
Regulatory Health Project Manager

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/s/  
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TESHARA G BOUIE  
05/01/2012

## Internal Minutes (teleconference)

**Meeting Date:** April 11, 2012  
**Application:** TSI #1311, NDAs 203109, 21845, 22473  
**Drug:** Revatio (sildenafil)  
**Sponsor:** Pfizer  
**Purpose:** FDA concerns about dose-related increases in mortality in pediatric PAH patients observed in the STARTS-1 study

### FDA Attendees:

Ellis Unger (ODE I director, acting)  
Norman Stockbridge (director)  
Stephen Grant (deputy director)  
Mary Ross Southworth (deputy director of safety)  
Abraham Karkowsky (clinical team leader)  
Maryann Gordon (medical officer)  
Jim Hung (director, office of biometrics I)  
Raj Madabushi (clinical pharmacology TL)  
Satjit Brar (pharmacometrics reviewer)  
Ed Fromm (CPMS)  
Dan Brum (RPM)

### Sponsor Attendees:

Rajesh Aggarwal (Safety & Risk Management)  
Cecile Balagtas (Medical Development Lead)  
Tom D'Eletto (Medical Lead)  
Gwyn D'Souza (Clinical Lead)  
Xiang Gao (Pharmacokinetics)  
Lutz Harnisch (Pharmacometrics)  
Irina Konourina (Clinical)  
Gary Layton (Statistics)  
Nancy McKay (Regulatory Lead)

### Background

FDA sent Pfizer the following information request via email on March 8, 2012:

*We would like to explore further with you the mortality finding in the high-dose versus low-dose groups observed in the STARTS-1 trial. We are concerned about these findings, and their potential implication for adult patients taking Revatio, where there is, to our knowledge, little controlled long-term experience.*

*Please be prepared to discuss:*

1. *whether you believe Revatio causes dose-related death in children;*
2. *if so, whether you believe the effect is unique to children, i.e., the extent to which these findings can be extrapolated to adults;*
3. *the prevalence of use of Revatio at doses greater than 20 mg TID in adult patients with pulmonary arterial hypertension (PAH) (although 20 mg TID is the only dose approved for the treatment of adults with PAH, it is our understanding that doses up to 80 mg TID are frequently used);*
4. *the mortality rate in adult PAH patients overall, by WHO functional class, and PAH etiology*
5. *consideration of potential study designs to explore mortality in adult patients with PAH. In our internal discussions, we have outlined some potential characteristics of such a study:*
  - *enroll patients who have been on sildenafil for less than 1 year (or who are sildenafil naïve);*
  - *enroll patients who are WHO Group 1 functional class II or worse;*
  - *a dose-ranging study design of 2 or 3 doses with at least one dose much less than 20 mg TID;*
  - *power the study to rule out a doubling of mortality between the high and low dose group; and*
  - *consideration of a large, simple study design.*

Prior to the teleconference, Pfizer sent FDA the attached responses via email on April 5, 2012. In the document, Pfizer concludes as follows:

*Based on the previous responses, we conclude that the pediatric data should not be extrapolated to the adult population. Additional analyses of the pediatric data do not support the conclusion that Revatio causes dose-related death in children. Furthermore, data from the adult studies and ongoing post-marketing safety review provide no evidence that higher doses are associated with a lower survival benefit or increased safety risk.*

*Pfizer acknowledges FDA's creation of a Trackable Safety Issue (TSI) to monitor high dose mortality and welcomes the opportunity to partner with FDA in carefully following post marketing events to better understand this safety topic. Pfizer will continue its rigorous pharmacovigilance activities monitoring for any potential safety concerns with Revatio.*

*Consistent with the approved labeling, the overall Revatio development program supports the use of 20 mg tid as a safe and effective dose in the adult PAH population.*

The following discussion points reflect summary points made during the teleconference between Pfizer and FDA on April 11, 2012:

#### **Discussion points**

- Dr. Southworth said the review of this safety issue is ongoing and no regulatory decisions had been made. The Division wanted to communicate to the sponsor its assessment that the dose-

related increase in mortality in children with PAH may have implications for the safe use of the drug in adults with PAH.

- Dr. Southworth said the Division is considering the need for long-term, controlled data on mortality and other outcomes in adults with PAH treated with sildenafil because of the dose-related mortality observed in the STARTS-1 trial. She noted that there are no long-term controlled data for sildenafil in adults with PAH.
- The sponsor offered to work with the Division to help resolve outstanding questions.

Minutes preparation: *{See appended electronic signature page}*  
Dan Brum, Pharm.D., RAC

Concurrence, Chair: *{See appended electronic signature page}*  
Mary Ross Southworth, Pharm.D.

Edited by:

- D. Brum 4/11/12 (drafted)
- A. Karkowsky 4/12/12
- S. Grant 4/12/12
- M. Southworth 4/13/12
- N. Stockbridge 4/13/12
- D. Brum 4/13/12 (finalized)

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/s/  
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DANIEL BRUM  
04/13/2012

MARY R SOUTHWORTH  
04/16/2012



NDA 203109

**INFORMATION REQUEST**

Pfizer, Inc.  
Attention: Nancy McKay, Director, WW Regulatory Strategy  
235 East 42nd Street  
New York, NY 10017

Dear Ms. McKay:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Revatio (sildenafil) Oral Suspension.

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Your proposed drug product specification, (b) (4), is not acceptable. As specified in ICH Q6A, identity tests should be specific for the drug substance, e.g., infrared spectroscopy. (b) (4)  
However, the use of two chromatographic procedures, where the separation is based on different principles, or combination of tests into a single procedure, such as HPLC/UV diode array, HPLC/MS, or GC/MS, is generally acceptable. Revise drug product specification to comply with ICH Q6A for establishing the identity of the API.
2. Your (b) (4) is not acceptable. Revise drug product specification to include routine testing of (b) (4) (sodium benzoate) content as a release test for all the drug product batches.
3. Since drug product dispensing involves direct contact of the constituted sildenafil citrate suspension with the syringe and press-in bottle adapter, provide relevant extraction studies data on the packaging system as specified in USP <661>.
4. Regarding proposed (b) (4) is not acceptable. Modify post-approval stability protocol to include commitment to perform stability studies on the first three commercial lots both under accelerated storage conditions as well as long-term storage conditions.

If you have any questions, contact Teshara G. Bouie, Regulatory Project Manager, at (301) 796-1649.

Sincerely,

*{See appended electronic signature page}*

Ramesh Sood, Ph.D.  
Branch Chief  
Division of New Drug Quality Assessment I  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

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/s/  
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RAMESH K SOOD  
03/15/2012

**Brum, Dan**

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**From:** Brum, Dan

**Sent:** Thursday, March 08, 2012 11:19 AM

**To:** 'McKay, Nancy'

**Subject:** sildenafil -- mortality finding in the high-dose versus low-dose groups -- STARTS-1 trial

Nancy,

We would like to explore further with you the mortality finding in the high-dose versus low-dose groups observed in the STARTS-1 trial. We are concerned about these findings, and their potential implication for adult patients taking Revatio, where there is, to our knowledge, little controlled long-term experience.

Please be prepared to discuss:

1. whether you believe Revatio causes dose-related death in children;
2. if so, whether you believe the effect is unique to children, i.e., the extent to which these findings can be extrapolated to adults;
3. the prevalence of use of Revatio at doses greater than 20 mg TID in adult patients with pulmonary arterial hypertension (PAH) (although 20 mg TID is the only dose approved for the treatment of adults with PAH, it is our understanding that doses up to 80 mg TID are frequently used);
4. the mortality rate in adult PAH patients overall, by WHO functional class, and PAH etiology
5. consideration of potential study designs to explore mortality in adult patients with PAH. In our internal discussions, we have outlined some potential characteristics of such a study:
  - o enroll patients who have been on sildenafil for less than 1 year (or who are sildenafil naïve);
  - o enroll patients who are WHO Group 1 functional class II or worse;
  - o a dose-ranging study design of 2 or 3 doses with at least one dose much less than 20 mg TID;
  - o power the study to rule out a doubling of mortality between the high and low dose group; and
  - o consideration of a large, simple study design.

We look forward to discussing this issue with your team.

Regards,  
--Dan

Dan Brum, Pharm.D., MBA, BCPS, RAC  
Commander, U.S. Public Health Service  
Senior Regulatory Project Manager  
Division of Cardiovascular and Renal Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
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[dan.brum@fda.hhs.gov](mailto:dan.brum@fda.hhs.gov)

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/s/  
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DANIEL BRUM  
03/08/2012

# Pediatric Exclusivity Board Minutes

February 7, 2012

## Voting Board Members

John Jenkins, Chair  
Charles Ganley  
Sally Loewke

## Advisors

Kim Dettelbach  
Martha Nguyen  
Dianne Murphy

## Review Division/Office

John Lawrence  
Maryann Gordon  
Satjit Brar  
Norman Stockbridge  
Dan Brum  
Abraham Karkowsky  
Ed Fromm

## Others

Matthew Bacho, Board RPM  
Erica Radden  
Rosemary Addy  
Courtney Suggs  
Nadia Hejazi  
William Rodriguez  
Robert Nelson  
Hari Sachs  
Amy Taylor  
Yeruk Mulugeta

## Determination for Sildenafil (NDA 203109/S-000)

Original Written Request:

12/17/01

Amended Written Requests:

6/24/02; 12/20/02; 11/3/05;  
9/15/06; 5/30/07; 6/7/11

Timeframe for submission of studies:

12/28/11

Date report of studies received:

11/30/11

Due Date for Pediatric Exclusivity Determination:

2/28/12

The Written Request (WR), as amended, described two (2) studies to provide data on the use of sildenafil for the treatment of pulmonary arterial hypertension (PAH) in pediatric patients.

1. Pfizer (Sponsor) submitted reports for the following pivotal studies:
  - Study 1 (A1481131) – A Randomized, Double-Blind, Placebo Controlled, Dose Ranging, Parallel Group Study of Oral Sildenafil in the Treatment of Children, Aged 1-17 Years, With Pulmonary Arterial Hypertension; and
  - Study 2 (A1481156) – A Multicenter, Long-Term Extension Study to Assess Safety of Oral Sildenafil in the Treatment of Subjects Who Have Completed Study A1481131.
2. The Review Division (Division) made some preliminary comments and responded to inquiries from the Board regarding the Sponsor's clinical program:
  - The Sponsor encountered difficulties in enrolling a sufficient number of pediatric patients, which led the former to consider stopping this program;
  - FDA statisticians were able to pool the data to support an adequate efficacy analysis;
  - A hemodynamic measure, PVRI (pulmonary vascular resistance index), was discussed at an Advisory Committee meeting [7/29/10] as a surrogate marker for the 6-minute walk;

- The WR was eventually amended to include PVRI and used along with exercise tolerance to determine efficacy whenever the latter could not be measured (many of the patients in this program could not perform the 6-minute walk);
  - The Division amended the WR to fit the Sponsor's program and the latter decided they had enough interpretable data to submit an NDA and request a determination;
  - With respect to other safety data, the Sponsor had searched the relevant published literature, using major databases such as MEDLINE, Micromedex, and BIOSYS as well as abstracts of presentations and posters from professional society meetings and any clinical trials, unpublished safety data, and spontaneous reports from healthcare professionals/authorities;
  - As to formulation, the Sponsor used an extemporaneous oral suspension of crushed tablets, which proved to be bioequivalent (BE) to the intact tablets, in their clinical program;
  - The Sponsor had developed, and intended to market, an oral suspension for children that has not been studied in that population (BE was established with the tablet as well as 30-day stability);
  - The Division was comfortable with the pharmacokinetic (PK) data collected from 173 patients;
  - The studies did not show efficacy at the safer (low) dose while the higher doses indicated an adverse, dose-related trend in mortality, although the *p*-value was difficult to interpret;
  - The Sponsor pursued approval of the low dose (there is no other drug approved in children with PAH); and
  - The Division did not intend to approve this application although the studies will be described in the label.
3. The Division further described the outcome of the studies. The medium and high dose groups did show an effect on PVRI but, as discussed above, mortality was higher among these patients. The deaths only occurred during the long-term extension (Study 2). The Data Monitoring Committee stopped these doses. The Division also confirmed a correlation in the changes seen in both exercise tolerance and PVRI.
  4. When asked about the deaths, the Division stated that most of them were in India while relatively few were in the US (2 out of 39) and EU.
  5. The Division pointed out the bad outcomes in catheterized children and the uncertainty this created for future drug studies in such a setting. They had requested further information from the Sponsor on their catheter experience in this program. The Division added that a tadalafil study was being planned in the EU. (Sildenafil was approved for use in children in the EU.)
  6. The Board asked if the EU was aware of the mortality finding from this program and the Division responded that the Sponsor was responsible for communicating this outcome to the European Medicines Agency, although a letter was distributed to the investigators and the Sponsor probably informed the care centers.
  7. The Board Chair (Chair) acknowledged the Division's problem interpreting these data and suggested discussing these issues at a public Advisory Committee (AC) meeting. The Division was uncertain about the usefulness of such a discussion but perhaps a

written communication for public consumption could be done. In any event, they had not yet finished their review.

8. The Division noted that other marketed drugs used in this setting are less safe than sildenafil. They confirmed that the latter was used in children off-label at doses, in some cases, beyond what was approved in adults.
9. The Chair wondered whether the Agency should recommend against the use of sildenafil in children. And in this context, he also asked: 1) if such a decision should be made on a country-by-country basis depending on the standard of care and 2) if the new dosage form should be allowed on the market.
10. The Chair noted that FDA must take a position. The Division agreed that an AC meeting could be scheduled but the lack of data would make such a discussion unhelpful. The latter was exemplified by the lack of information from the long-term, high-dose group since most of the patients were moved to the low dose. And PAH may actually differ between adults and children.
11. Ultimately, the Chair stated that the Sponsor met the terms of the WR. However, in light of data interpretability issues and the fact that the Sponsor will receive 6 months of exclusivity, he strongly recommended that this matter be taken to an AC meeting.

#### Recommendations

1. The Board agreed that the Sponsor fairly responded to the WR.
2. Pediatric Exclusivity was granted effective February 9, 2012 (see Checklist signed into DARRTS).
3. The Division will inform the Sponsor via email, utilizing a notification script that Pediatric Exclusivity was granted. The fact that exclusivity was granted will be posted on the pediatric web site along with the WR and any amendments as required by FDAAA (2007), and the exclusivity will be reflected in the next monthly update to the Orange Book.

Prepared by: \_\_\_\_\_

Date: \_\_\_\_\_

Chair: \_\_\_\_\_

Date: \_\_\_\_\_

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/s/  
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MATTHEW A BACHO  
03/06/2012

JOHN K JENKINS  
03/08/2012



NDA 203109

**INFORMATION REQUEST**

Pfizer Inc.  
Attention: Ms. Nancy McKay  
Director, Worldwide Regulatory Strategy  
235 East 42<sup>nd</sup> Street  
New York, NY 10017

Dear Ms. McKay:

Please refer to your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Revatio (sildenafil) Oral Suspension, 10 mg/mL.

We reviewed your Chemistry, Manufacturing, and Controls information and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Regarding drug substance specification, you have referred to the NDA 21-845 (Revatio Tablets). However, compared to this specification, the acceptance limits for the specified impurity (b)(4) and total impurities have been tightened based on your most recently approved NDA 22-473 (Revatio Injection). Provide
  - a. A justification for (b)(4) the proposed pediatric formulation i.e., sildenafil citrate powder for oral suspension (POS)
  - b. Current specification for the drug substance to be used for the to-be-marketed sildenafil citrate POS.
2. Provide a representative certificate of analysis for the drug substance batch used for the manufacture of the pediatric clinical formulation.
3. Regarding the in-use stability studies, the stability of constituted suspension has been monitored only at day 0 and day 30, with no intermediate time points, and show changes in viscosity at day 30. To support the proposed 30-day in-use shelf life with inbuilt real world usage safety margins, provide in-use stability data for the constituted suspension (prepared using sildenafil citrate powder previously stored at 30°C/75% RH for 12 months) stored at 30°C for a period of beyond 30 days.
4. Considering that in the constituted suspension approximately (b)(4)% of sildenafil citrate is not dissolved, provide your rationale for (b)(4) from the product specification for Revatio Powder for Oral Suspension; and if you are considering

alternate parameter(s) as better indicators of its product quality and in vivo performance, provide your science- and risk-based recommendation for the alternate parameter(s).

5.

(b) (4)

If you have any questions, call Don Henry, Regulatory Project Manager, at (301) 796-4227.

Sincerely,

*{See appended electronic signature page}*

Ramesh K. Sood, Ph.D.  
Branch Chief  
Division of New Drug Quality Assessment I  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

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/s/  
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RAMESH K SOOD  
01/25/2012



NDA 203109

**INFORMATION REQUEST**

Pfizer, Inc.  
Attention: Ms. Nancy McKay  
235 East 42nd St.  
New York, NY 10017

Dear Ms. McKay:

Please refer to your New Drug Application (NDA) dated November 30, 2011, received November 30, 2011, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act, for Revatio (sildenafil) powder for oral suspension 10 mg/mL.

We also refer to the teleconference between representatives of your firm and FDA on January 18, 2012.

We are reviewing the clinical section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

In Study A1481131 we note there were five serious adverse events (SAEs) including two deaths that appear to be associated with the process of right heart catheterization (RHC). To gain some understanding of the possible relationship between the expertise of the investigators at the clinical sites and the poor outcomes from the RHCs, please provide the following information for each clinical site that enrolled patients in Study A1481131:

- How many RHCs in pediatric patients for either cardiac or PAH reasons had the site performed in the 18 months prior to or in the previous 100 subjects prior to conducting the RHC in the first patient enrolled in Study A1481131?
- How many RHCs in *pediatric PAH* patients had the site performed in the 18 months prior to conducting the RHC in the first patient enrolled in Study A1481131?
- Please include the following information by site for each RHC:
  - any SAEs associated with the RHCs and their associated outcomes
  - patient demographics
  - medications used to prepare for the RHCs (e.g., general anesthesia versus sedation alone)
  - concomitant medications
  - the number of clinician(s) performing the RHCs

- Please provide your rationale for selecting the clinical sites for Study A1481131 and any criteria you used to evaluate each site's qualifications.

If you have any questions, please call Dan Brum, Pharm.D., RAC, Regulatory Project Manager, at (301)796-0578.

Sincerely,

*{See appended electronic signature page}*

Norman Stockbridge, M.D., Ph.D.  
Director  
Division of Cardiovascular and Renal Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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/s/  
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NORMAN L STOCKBRIDGE  
01/23/2012



NDA 203109

**FILING COMMUNICATION**

Pfizer, Inc.  
Attention: Ms. Nancy McKay  
235 East 42nd St.  
New York, NY 10017

Dear Ms. McKay:

Please refer to your New Drug Application (NDA) dated November 30, 2011, received November 30, 2011, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act, for Revatio (sildenafil) powder for oral suspension 10 mg/mL.

We also refer to your amendment dated December 15, 2011.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. Therefore, the user fee goal date is May 30, 2012.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by May 9, 2012.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

We request that you submit the following information:

1. Please submit an analysis of the average dose level (i.e., low, medium, or high) assessed over the entirety of the long-term observation period and the relationship to mortal events. For example, if a patient randomized to the low dose received a dose increase to the high dose shortly after starting treatment in the long-term extension study, we would expect the average dose for that individual to approximate that of the high dose.
2. Please submit the CRFs for those individuals whose dose was increased during the long-term extension study to help us ascertain whether the dose increase was provoked by worsening of their status.
3. Please submit the CRFs and hospital records for the five subjects who had catheterization-related serious adverse events.

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

**Highlights (HL)**

- HL should be limited in length to one-half page. If it is longer than one-half page, please shorten to one-half page or request a waiver. Note that all Warnings and Precautions listed in the Full Prescribing Information (FPI) do not need to be included in Highlights. Therefore, clinical judgment should be used to ascertain which Warnings and Precautions to include in Highlights and which are not necessary.
- **Recent Major Changes (RMC)**
  - Applies only to supplements and is limited to substantive changes in five sections: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions. Please delete this section.
- **Indications and Usage**
  - If a product belongs to an established pharmacologic class, the following statement is required in HL: [Drug/Biologic Product) is a (name of class) indicated for (indication(s)].” Identify the established pharmacologic class for the drug at:  
<http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.htm>  
e.g., Revatio is a phosphodiesterase-5 (PDE-5) inhibitor indicated for the...
- **Patient Counseling Information Statement**
  - Must include the verbatim statement: “**See 17 for Patient Counseling Information**” or if the product has FDA-approved patient labeling: “**See 17 for Patient Counseling Information and (insert either “FDA-approved patient labeling” or “Medication Guide”)**”.  
e.g., **See 17 for Patient Counseling Information and FDA-approved patient labeling**

## **Full Prescribing Information (FPI)**

- **Adverse Reactions**

- Only “adverse reactions” as defined in 21 CFR 201.57(c)(7) should be included in labeling. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided.

- **Patient Counseling Information**

- Must reference any FDA-approved patient labeling, including the type of patient labeling. The statement “See FDA-approved patient labeling (insert type of patient labeling).” should appear at the beginning of Section 17 for prominence. For example:  
“See FDA-approved patient labeling (Patient Information)”

## **Patient Information Leaflet**

We will send you suggested revisions to the patient information leaflet in a separate document.

We request that you resubmit labeling that addresses these issues by February 3, 2012. The resubmitted labeling will be used for further labeling discussions. Per email correspondence dated November 7, 2011, we remind you to please revise the drug interactions information in the Revatio draft labeling to include a Forest Plot of the data in section 12.3 and only include drug interaction-related recommendations in section 7. Please refer to the publication by Menon-Andersen et al., in *Clinical Pharmacology & Therapeutics* (2011) 90 3, 471–474 for further details and sample SAS code to make the Forest Plot.

While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

## **REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. Because Revatio (sildenafil) for this indication has orphan drug designation, you are exempt from this requirement.

If you have any questions, please call Dan Brum, Pharm.D., RAC, Regulatory Project Manager, at (301)796-0578.

Sincerely,

*{See appended electronic signature page}*

Norman Stockbridge, M.D., Ph.D.  
Director  
Division of Cardiovascular and Renal Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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/s/  
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NORMAN L STOCKBRIDGE  
01/17/2012

## RPM FILING REVIEW

(Including Memo of Filing Meeting)

**To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]**

Application Information		
NDA # 203109 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: Revatio Established/Proper Name: sildenafil Dosage Form: powder for oral suspension (POS) Strengths: 10 mg/mL		
Applicant: Pfizer, Inc. Agent for Applicant (if applicable):		
Date of Application: November 30, 2011 Date of Receipt: November 30, 2011 Date clock started after UN:		
PDUFA Goal Date: May 30, 2012		Action Goal Date (if different):
Filing Date: January 29, 2012		Date of Filing Meeting: January 4, 2012
Chemical Classification: (1,2,3 etc.) (original NDAs only) Type 3		
Proposed indication(s)/Proposed change(s): pediatric pulmonary arterial hypertension and new dosage form (powder for oral suspension)		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i><b>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at: <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499</a> and refer to Appendix A for further information.</b></i>		
Review Classification:  <i><b>If the application includes a complete response to pediatric WR, review classification is Priority.</b></i>  <i><b>If a tropical disease priority review voucher was submitted, review classification is Priority.</b></i>	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority  <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
Resubmission after withdrawal? <input type="checkbox"/>		Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/>  <i><b>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</b></i>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system <input type="checkbox"/> Pre-filled biologic delivery device/system <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	

<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input checked="" type="checkbox"/> Orphan Designation  <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC  Other:	<input type="checkbox"/> PMC response <input checked="" type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input checked="" type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product):				
List referenced IND Number(s): IND 63175				
<b>Goal Dates/Product Names/Classification Properties</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
PDUFA and Action Goal dates correct in tracking system?  <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system?  <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at: <a href="http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm">http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm</a></i>  <i>If no, ask the document room staff to make the appropriate entries.</i>	X			
<b>Application Integrity Policy</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a></i>		X		
<i>If yes, explain in comment column.</i>				
<i>If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:</i>				
<b>User Fees</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input type="checkbox"/> Paid  <input checked="" type="checkbox"/> Exempt (orphan, government)  <input type="checkbox"/> Waived (e.g., small business, public health)  <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input type="checkbox"/> Not in arrears  <input type="checkbox"/> In arrears</p>																			
<p><b>505(b)(2)</b>  <b>(NDAs/NDA Efficacy Supplements only)</b></p>	<p><b>YES</b></p>	<p><b>NO</b></p>	<p><b>NA</b></p>	<p><b>Comment</b></p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>			<p>X</p>																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>																				
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs</i></p>																				
<p>Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)?  Check the <i>Electronic Orange Book</i> at:  <a href="http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm">http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</a></p> <p><b>If yes, please list below:</b></p> <table border="1" data-bbox="203 1451 1349 1587"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>																				
<p><b>Exclusivity</b></p>	<p><b>YES</b></p>	<p><b>NO</b></p>	<p><b>NA</b></p>	<p><b>Comment</b></p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at:</i>  <a href="http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm">http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm</a></p>		<p>X</p>																		

<p><b>If another product has orphan exclusivity</b>, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i></p>			X	
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p><b>If yes, # years requested: 3 years</b></p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>	X			
<p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?</p>		X		
<p><b>If yes</b>, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>			X	

Format and Content				
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)  <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<p><b>If mixed (paper/electronic) submission</b>, which parts of the application are submitted in electronic format?</p>				
<b>Overall Format/Content</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b>If electronic submission</b>, does it follow the eCTD guidance?<sup>1</sup>  <b>If not</b>, explain (e.g., waiver granted).</p>	X			
<p><b>Index:</b> Does the submission contain an accurate comprehensive index?</p>	X			
<p>Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:</p>	X			

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
<b>If no, explain.</b>				
<b>BLAs only:</b> Companion application received if a shared or divided manufacturing arrangement?				
<b>If yes, BLA #</b>				
<b>Forms and Certifications</b>				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, <b>paper</b> forms and certifications with hand-written signatures must be included. <b>Forms</b> include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); <b>Certifications</b> include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
<b>Application Form</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	X			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
<b>Patent Information (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
<b>Financial Disclosure</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	X			
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
<b>Clinical Trials Database</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 3674 included with authorized signature?	X			
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
<b>Debarment Certification</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a correctly worded Debarment Certification included with authorized signature?	X			

<p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <b>both</b> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FDCA Section 306(k)(1) i.e., “[Name of applicant] 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.” Applicant may not use wording such as, “To the best of my knowledge...”</i></p>				
<b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b>For paper submissions only:</b> Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>			X	

<b>Controlled Substance/Product with Abuse Potential</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>			X	

<b>Pediatrics</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b><u>PREA</u></b></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)<sup>2</sup></i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>		X		Although the application would trigger PREA because it is a new dosage form, the submission is in response to both PREA and a Written Request and it is orphan designated; therefore, this NDA is exempt from PREA. There is however a PeRC meeting scheduled

<sup>2</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

				for March 14, 2012 to discuss the pediatric assessment in response to a 2005 PREA PMR to study sildenafil in pediatric PAH.
<b>If the application triggers PREA</b> , are the required pediatric assessment studies or a full waiver of pediatric studies included?			X	The application has an orphan designation. Also see above.
<b>If studies or full waiver not included</b> , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?  <i>If no, request in 74-day letter</i>			X	
<b>If a request for full waiver/partial waiver/deferral is included</b> , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)?  <i>If no, request in 74-day letter</i>			X	
<b>BPCA (NDAs/NDA efficacy supplements only):</b>  Is this submission a complete response to a pediatric Written Request?  <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)<sup>3</sup></i>	X			Exclusivity board notified. Meeting with Division on February 7, 2012.
<b>Proprietary Name</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a proposed proprietary name submitted?  <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>		X		Sponsor plans to use the approved trade name "Revatio" and market all dosage forms in a single package insert.
<b>REMS</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a REMS submitted?  <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the DCRMSRMP mailbox</i>		X		No REMS needed.
<b>Prescription Labeling</b>	<input type="checkbox"/> <b>Not applicable</b>			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input checked="" type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>

<sup>3</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

Is Electronic Content of Labeling (COL) submitted in SPL format?	X			
<i>If no, request applicant to submit SPL before the filing date.</i>				
Is the PI submitted in PLR format? <sup>4</sup>	X			Will include labeling comments in filing letter.

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4

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<b>If PI not submitted in PLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , what is the status of the request?  <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP (formerly DDMAC)?	X			
MedGuide, PPI, IFU (plus PI) consulted to OMP/Patient Labeling Team? ( <i>send WORD version if available</i> )	X			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
<b>OTC Labeling</b>	<input checked="" type="checkbox"/> <b>Not Applicable</b>			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is electronic content of labeling (COL) submitted?  <i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)?  <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?  <i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
<b>Other Consults</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)  <i>If yes, specify consult(s) and date(s) sent:</i>		X		DMEPA will handle review of oral dosing device and IFU; CDRH consult not needed.
<b>Meeting Minutes/SPAs</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
End-of Phase 2 meeting(s)? <b>Date(s):</b>  <i>If yes, distribute minutes before filing meeting</i>		X		

<p>Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)?  <b>Date(s):</b> July 2, 2009</p> <p><i>If yes, distribute minutes before filing meeting</i></p>	<p>X</p>			<p>Advisory Committee meeting held July 29, 2010. Note: the sponsor included a document in M1 summarizing the numerous meetings and teleconferences held over the past decade.</p>
<p>Any Special Protocol Assessments (SPAs)?  <b>Date(s):</b></p> <p><i>If yes, distribute letter and/or relevant minutes before filing meeting</i></p>		<p>X</p>		

ATTACHMENT

**MEMO OF FILING MEETING**

**DATE:** January 4, 2012

**BLA/NDA/Supp #:** NDA 203109

**PROPRIETARY NAME:** Revatio

**ESTABLISHED/PROPER NAME:** sildenafil

**DOSAGE FORM/STRENGTH:** powder for oral suspension

**APPLICANT:** Pfizer, Inc.

**PROPOSED INDICATION(S)/PROPOSED CHANGE(S):** expand indication to pediatric pulmonary arterial hypertension (PAH)

**BACKGROUND:** **NDA 21845** for Revatio (sildenafil) 20 mg tablets was approved in 2005 for treatment of adults with pulmonary arterial hypertension *to improve exercise ability*. In May 2009, NDA 21845/S-006 expanded the indication to include “delay in clinical worsening.” In November 2009, **NDA 22473** was approved for Revatio 0.8 mg/mL solution for injection to be administered three times daily for those patients unable to take Revatio orally.

On November 30, 2011, **NDA 203109** was submitted to market a new dosage form (oral suspension) and expand the indication to pediatrics. Under the auspices of a WR (see amendment history below), Pfizer conducted study 1131 (blinded) and 1156 (open-label) to evaluate sildenafil in pediatric PAH.

History of FDA Written Request Activities (per the sponsor’s submission):

- 17 Dec 2001 WR issued by FDA
- 24 June 2002 FDA amended WR (as a result of telecon)
- 20 Dec 2002 FDA amended WR following Pfizer’s comments on previous version submitted on 11 Oct 2002
- 03 Nov 2005 Removal of Cardiac Surgery and PPHN trials due to approval of adult PAH NDA and changes in treatment paradigm.
- 15 Sept 2006 Updated following FDA review and submission of 5 comments from Pfizer on previous version
- 30 May 2007 Minor updates including timing of submission of reports (at Pfizer’s request)
- 07 Jun 2011 WR Revised to reflect PVRI as a measure of effectiveness (following July 29, 2010 AC)

An advisory committee meeting was held July 29, 2010, in part, to discuss use of endpoints other than those traditionally used to seek marketing approval in the U.S. i.e., (b) (4) rather than exercise. Although the primary endpoint for study 1131 was exercise capacity (cycle ergometry in children able to perform the test), the study did not reach statistical significance; however, some reviewers at FDA suggested that there might be a correlation between 6MWD and

PVRI based on a databased of clinical trial results from several drug programs. The June 2011 amendment to the WR reflects incorporation of PVRI as the primary endpoint.

*Regulatory issues related to orphan designation that affects labeling:*

The adult PAH development program was never orphan designated (sponsor never requested orphan designation). This RPM suggested the sponsor request designation for pediatric PAH – the sponsor requested orphan designation and received it for “treatment of pediatric (defined as children less than 17 years of age) pulmonary arterial hypertension” on July 28, 2011.

The sponsor’s marketing plan is to include all dosage forms for PAH (adult and pediatric) in one label – but this presents a problem because to avoid a user fee the sponsor could not combine non-orphan indications (adult PAH) with the orphan indication (pediatric PAH); a solution was to submit pediatric PAH as a stand-alone label, however, the sponsor was required to also submit supplements to the tablet and injection NDAs. The supplements will receive Standard reviews and the pediatric NDA will receive a Priority review.

*RPM Comments: DCRP will need to review the pediatric PAH labeling for the pediatric NDA because, if approved, the labeling will be appended to the approval letter. But even if we don’t “approve” the supplement, DCRP will need to include information from the pediatric development program in the label. If approved, we will also work on a common label that includes all three dosage forms as well as information from the pediatric studies. If approved, the sponsor must finally submit a supplement to the pediatric NDA to combine all three dosage forms.*

**REVIEW TEAM:**

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Daniel Brum	Y
	CPMS/TL:	Edward Fromm	Y
Cross-Discipline Team Leader (CDTL)	Abraham “Avi” Karkowsky		Y
Clinical	Reviewer:	Maryann Gordon	Y
	TL:	Shari Targum	Y
Social Scientist Review (for OTC products)	Reviewer:		
	TL:		
OTC Labeling Review (for OTC products)	Reviewer:		
	TL:		
Clinical Microbiology (for antimicrobial products)	Reviewer:		

	TL:		
Clinical Pharmacology	Reviewer:	Satjit Brar	Y
	TL:	Pravin Jadhav	N
Biostatistics	Reviewer:	John Lawrence	Y
	TL:	Jim Hung	N
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Jensen “Nick” Donald	Y
	TL:	Tom Papoian	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) ( <i>for BLAs/BLA efficacy supplements</i> )	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Mohan Sapru	
	TL:	Kasturi Srinivasachar	
Quality Microbiology ( <i>for sterile products</i> )	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA	Reviewer:	Forest (Ray) Ford	Y
	TL:		
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (DSI)	Reviewer:	Sharon Gershon	N
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Pharmaceutics	Arzu Selen		Y
	Angelica Dorantes (TL)		N
Office of Prescription Drug Products (OPDP)	Emily Baker		N
	Zarna Patel		N
Patient Labeling Review (OMP)	Latonia Ford		Y
	Barbara Fuller (TL)		N
Other attendees	Norman Stockbridge (DD) Melinda McLawhorn (OSE/DPV) Amy Taylor (PMHS)		

**FILING MEETING DISCUSSION:**

<b>GENERAL</b>	
<ul style="list-style-type: none"> <li>505(b)(2) filing issues?</li> </ul> <p><b>If yes, list issues:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Per reviewers, are all parts in English or English translation?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Electronic Submission comments</li> </ul> <p><b>List comments:</b> Links are helpful and appear to be functioning appropriately.</p>	<input type="checkbox"/> Not Applicable
<b>CLINICAL</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Clinical study site(s) inspections(s) needed?</li> </ul> <p><b>If no, explain:</b></p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Advisory Committee Meeting needed?</li> </ul>	<input type="checkbox"/> YES

<p><b>Comments:</b> ACM July 29, 2010</p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> <li>○ <i>this drug/biologic is not the first in its class</i></li> <li>○ <i>the clinical study design was acceptable</i></li> <li>○ <i>the application did not raise significant safety or efficacy issues</i></li> <li>○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i></li> </ul>	<p>Date if known: See comments</p> <p><input checked="" type="checkbox"/> NO</p> <p><input type="checkbox"/> To be determined</p> <p>Reason:</p>
<ul style="list-style-type: none"> <li>• Abuse Liability/Potential</li> </ul> <p><b>Comments:</b></p>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> FILE</p> <p><input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<ul style="list-style-type: none"> <li>• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?</li> </ul> <p><b>Comments:</b></p>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<p><b>CLINICAL MICROBIOLOGY</b></p> <p><b>Comments:</b></p>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> FILE</p> <p><input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><b>CLINICAL PHARMACOLOGY</b></p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> FILE</p> <p><input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<ul style="list-style-type: none"> <li>• Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>	<p><input type="checkbox"/> YES</p> <p><input checked="" type="checkbox"/> NO</p>
<p><b>BIOSTATISTICS</b></p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> FILE</p> <p><input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><b>NONCLINICAL</b></p>	<p><input type="checkbox"/> Not Applicable</p>

<p><b>(PHARMACOLOGY/TOXICOLOGY)</b></p> <p>Comments:</p>	<input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</b></p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b>PRODUCT QUALITY (CMC)</b></p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b><u>Environmental Assessment</u></b></p> <ul style="list-style-type: none"> <li>• Categorical exclusion for environmental assessment (EA) requested?   <b>If no</b>, was a complete EA submitted?   <b>If EA submitted</b>, consulted to EA officer (OPS)?</li> </ul> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Quality Microbiology (for sterile products)</u></b></p> <ul style="list-style-type: none"> <li>• Was the Microbiology Team consulted for validation of sterilization? (<b>NDAs/NDA supplements only</b>)</li> </ul> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Facility Inspection</u></b></p> <ul style="list-style-type: none"> <li>• Establishment(s) ready for inspection?</li> <li>▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ?</li> </ul> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p><b><u>Facility/Microbiology Review (BLAs only)</u></b></p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b><u>CMC Labeling Review</u></b></p> <p>Comments:</p>	<input type="checkbox"/> Review issues for 74-day letter
<b>REGULATORY PROJECT MANAGEMENT</b>	
<p><b>Signatory Authority:</b> Norman Stockbridge, Division Director</p> <p><b>21<sup>st</sup> Century Review Milestones (see attached)</b> (listing review milestones in this document is optional):</p> <p>Comments:</p>	
<b>REGULATORY CONCLUSIONS/DEFICIENCIES</b>	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <input type="checkbox"/> No review issues have been identified for the 74-day letter. <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): <p><u>Review Classification:</u></p> <input type="checkbox"/> Standard Review <input checked="" type="checkbox"/> Priority Review
<b>ACTIONS ITEMS</b>	
<input type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.

<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input checked="" type="checkbox"/>	If priority review: <ul style="list-style-type: none"> <li>• notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices)</li> <li>• notify DMPQ (so facility inspections can be scheduled earlier)</li> </ul>
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found at: <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822</a> ]
<input type="checkbox"/>	Other

Daniel Brum

January 5, 2012

Regulatory Project Manager

Date

Chief, Project Management Staff

Date

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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DANIEL BRUM  
01/05/2012

Worldwide Regulatory Strategy  
Pfizer Inc  
235 East 42<sup>nd</sup> Street  
New York, NY 10017

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## Pfizer Medical

November 30, 2011

Jerome G. Woysner  
District Director  
Food and Drug Administration  
Office of Regulatory Affairs  
New York District Office  
158-15 Liberty Avenue  
Jamaica, New York 11433

THIS DOCUMENT CONTAINS  
CONFIDENTIAL AND/OR TRADE  
SECRET INFORMATION THAT IS  
DISCLOSED ONLY IN CONNECTION  
WITH THE LICENSING AND/OR  
REGISTRATION OF PRODUCTS FOR  
PFIZER INC OR ITS AFFILIATED  
COMPANIES. THIS DOCUMENT  
SHOULD NOT BE DISCLOSED OR USED,  
IN WHOLE OR IN PART, FOR ANY  
OTHER PURPOSE WITHOUT THE PRIOR  
WRITTEN CONSENT OF PFIZER INC.

**Re: New Drug Application # 203109**  
**Revatio® (sildenafil) Oral Suspension**  
**Serial No.: 0000**  
**eCTD Sequence No.: 0000**

Dear Mr. Woysner:

Persuant to 21 CFR § 11.2 (b)(2) and the Office of Regulatory Affairs Memorandum dated 24 September, 2003, Pfizer hereby certifies that an electronic version of the New Drug Application identified above was submitted to the Center for Drug Evaluation and Research Central Document Room on November 30, 2011. All relevant module information to support this submission has been provided for the appropriate assessment of this application.

Should you have any questions regarding this submission, do not hesitate to contact me at (212) 733 4755.

Sincerely,

A handwritten signature in black ink, appearing to read "Nancy McKay".

Nancy McKay  
Director  
Worldwide Regulatory Strategy

Form Approved: OMB No. 0910 - 0297 Expiration Date: January 31, 2013. See instructions for OMB Statement, below.

DEPARTMENT OF HEALTH AND HUMAN  
SERVICES  
FOOD AND DRUG ADMINISTRATION

## PRESCRIPTION DRUG USER FEE COVERSHEET

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 FDA's website:

<http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm>

1. APPLICANT'S NAME AND ADDRESS  PFIZER INC 235 E 42ND ST NEW YORK NY 10017-5755 US	4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER  203-109
2. NAME AND TELEPHONE NUMBER OF REPRESENTATIVE 212-733-6560	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 checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

3. PRODUCT NAME Revatio ( sildenafil )	6. USER FEE I.D. NUMBER PD3011846
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7. ARE YOU REDEEMING A PRIORITY REVIEW VOUCHER FOR THE TREATMENT OF TROPICAL DISEASES?  YES  NO  
PRIORITY REVIEW VOUCHER NUMBER:

8. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.  
 A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)  
 THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act  
 THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY

9. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?  YES  NO  
If a waiver has been granted, include a copy of the official FDA notification with your submission.

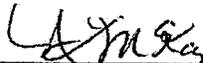
**OMB Statement:**

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  
Center for Biologics Evaluation and Research  
Office of Information Management (HFA-710)  
1350 Piccard Drive, 4th Floor  
Rockville, MD 20850

Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Information Management (HFA-710)  
1350 Piccard Drive, 4th Floor  
Rockville, MD 20850

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.

PRINTED NAME AND SIGNATURE OF AUTHORIZED REPRESENTATIVE  NANCY MCKAY 	TITLE DIRECTOR, WRS	DATE Nov 30, 2011
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9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION  
\$0.00

Form FDA 3397 (01/10)

## Meeting Minutes

**Date:** July 2, 2009  
**Application:** NDA 21-845 and IND 63,175  
**Drug:** Revatio (sildenafil)  
**Sponsor:** Pfizer  
**Purpose:** To determine if the pediatric data support submission of an sNDA and fulfill the requirements of the Written Request.  
**Meeting Type:** B

### **FDA Attendees:**

Norman Stockbridge, M.D., Ph.D.	Director, DCRP
Thomas Marciniak, M.D.	Medical Team Leader
Avi Karkowsky, M.D., Ph.D.	Medical Team Leader
John Lawrence, Ph.D.	Statistics
Edward Fromm, RPh, RAC	Chief, Project Management Staff
Michael Monteleone, M.S.	Regulatory Project Manager
Dan Brum, Pharm.D., MBA	Regulatory Project Manager
Tony Durmowicz, M.D.	Medical Team Leader, DPAP

### **Pfizer Attendees:**

Cassino, Cara; (VP Medical)  
Ewen, Colin; (Medical / Dev Team Lead)  
Gillies, Hunter; (Clinical)  
Harnisch, Lutz; (Clin PK)  
Kross, Kathryn; (US Regulatory – Sr. Dir PVD / Inflamm)  
Layton, Gary; (Stats)  
McKay, Nancy; (US Regulatory REVATIO)  
Serdarevic-Pehar, Marjana; (Clinical)  
Watt, Stephen; (Medical)  
Kobryn, Christine; (US Regulatory – REVATIO pediatric)  
Mychaskiw, Marko (Outcomes Research)

### **Background:**

On December 17, 2001, Pfizer was issued a Written Request to study Revatio (sildenafil) in children with pulmonary hypertension. After several amendments, the most recent Written Request was issued on May 30, 2007.

The sponsor requested this meeting to gain insight into whether the studies performed in children would support submission of a pediatric supplemental New Drug Application, and whether the sponsor appears to have fulfilled the terms of the Written Request.

**Meeting:**

The sponsor requested responses to the following questions listed in the meeting briefing package. The questions are repeated below, and the Division's preliminary responses are in **bold**. Bold **green** text reflects discussion points during the meeting.

Question 1

Do the data from the pediatric Study A1481131 and the proposed safety data from A1481156 support a pediatric indication claim for REVATIO?

**FDA Response: A preliminary inspection of the results of Study A1481131 by us indicates that you have failed to demonstrate efficacy with any of the doses of sildenafil. Therefore, it is unlikely that you will have data to support the pediatric indication.**

**Major discussion points during the meeting**

- **The sponsor explained that in 2008, they modified the original Statistical Analysis Plan (SAP), but because the proposed changes were relatively close to data lock, the Division asked them to analyze the data using the *original* planned analysis in addition to the modified analysis plan.**
- **The Division asked how peak VO<sub>2</sub> had been measured in the study; the sponsor said that "children exercised until they couldn't any longer". The sponsor also said that lactic acid levels were not measured in the study. They commented that VO<sub>2</sub> levels in healthy children are generally around 40 mL/kg/min, whereas the levels in the "impaired" children in the study were around 20 mL/kg/min.**
- **The Division explained that the summary results provided in the briefing package and PowerPoint slides appeared to support a submission; however, the actual regulatory action would only be made after full review of the data.**
- **Regarding the study, the sponsor mentioned that 32 centers were involved, the study spanned a five-year period, extensive site monitoring and motivational visits were in place, and of 115 children capable of performing the exercise VO<sub>2</sub> measurements, 106 contributed to the analysis; those lost to follow-up were distributed among the treatment and placebo arms.**

Question 2

Do the data from the pediatric Study A1481131 and the proposed safety data from A1481156 fulfill the clinical requirements of the REVATIO Written Request when used in conjunction with the pediatric formulation activities?

**FDA Response: The final decision regarding the fulfillment of the requirements for the written request is not made by the Division. The Division suspects, based on the statement from the Written Request regarding sample size that is shown below, that analysis will show that you did not fulfill the request.**

The study must be powered to be able to detect a "clinically meaningful" treatment benefit on the primary endpoint. For the purpose of satisfying the Written Request, a clinically meaningful treatment benefit is considered to be a ... 10% increase in exercise ability. This requires you to show that if the true treatment effect for one of the treatment groups were minimally "clinically meaningful", the pre-planned analysis would have at least 90% power to infer that at least one dose or the high dose is significantly different from placebo. You may wish to obtain an estimate of variability to use in power calculations from a preliminary study. However, to ensure that the study is adequately powered, you must obtain an estimate of variability from an interim analysis and then follow a pre-specified rule to adjust the sample size to achieve the specified target power.

### Major discussion points during the meeting

- The Division reminded the sponsor that the Pediatric Exclusivity Board (PEB) determines whether sponsors meet the terms of Written Requests.
- The sponsor acknowledged that the sample size did not meet the terms of the Written Request; they provided a graphic highlighting the diminishing "half width of 95% confidence interval" as a function of "total sample size". Based on the sponsor's calculation, 180 patients (versus the 106 that were ultimately evaluated) would have been needed to achieve 90% power. The Division commented that the trial was approximately one-half as large as would have been needed to fulfill the terms of the Written Request based on the observed SD size.
- Additional discussion focused on the width of the confidence interval and power—the Division emphasized the importance that the result of the study be interpretable regardless of the outcome.
- The sponsor asserted that they made "a good faith effort" to meet the terms of the Written Request and opined that it seems unlikely that a study as large as they carried out could ever be repeated. In response, the Division made two points: 1) Had we known that the study could not result in a clinically meaningful effect, we would not have issued the Written Request in the first place, and 2) A "good faith effort" argument will not be the basis upon which the Division would consider an amendment to the Written Request, nor would such an argument persuade the PEB that the terms of the Written Request had somehow been fulfilled.
- Brainstorming possible options, the Division asked the sponsor to figure out if the chosen treatment effect (e.g., 10%) was inappropriate. If that is the case, the Division suggested that the sponsor provide data to support an amendment to the Written Request (prior to submission of the full study reports).

Minutes preparation: *{See appended electronic signature page}*  
Dan Brum, Pharm.D., MBA, RAC

Concurrence, Chair: *{See appended electronic signature page}*  
Norman Stockbridge, M.D., Ph.D.

Drafted – 7/02/09

Final – 7/08/09

Karkowsky 7/03/09

Durmowicz 7/02/09

Marciniak 7/06/09

Fromm 7/07/09

Lawrence 7/06/09

Stockbridge 7/07/09

*Cc: Sponsor's slides enclosed*

# REVATIO Pediatric Development Program

- Builds upon the adult program
  - Two large randomized placebo controlled studies conducted in the adult population (A1481140, A1481141)
  - Two long term extension studies (A1481142, A1481153)
- Generate data for prescribers for pediatric PAH
  - One large randomized placebo controlled study (A1481131)
  - One long term extension study (A1481156) providing additional safety and efficacy information
  - Supplemental data in PPHN and cardiac surgery (A1481157, A1481134)
- Comprehensive PK/PD dataset that spans patients from neonates to geriatrics

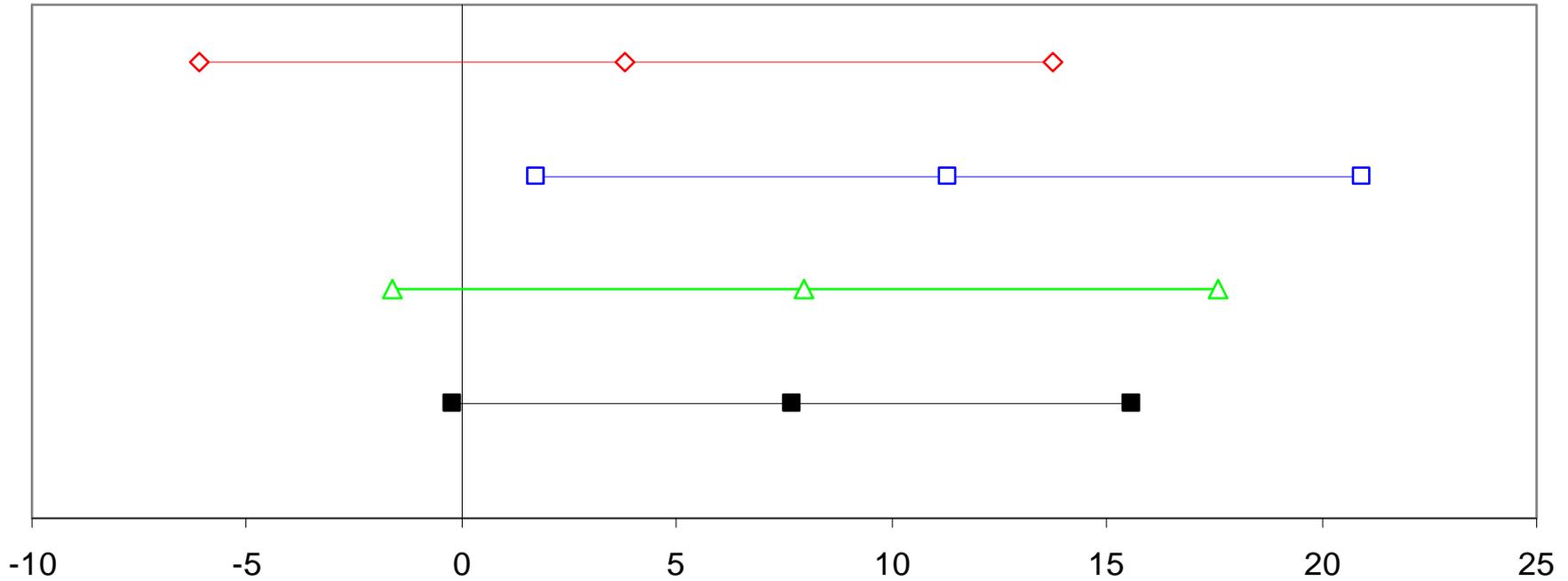
## Question 1

Do the data from the pediatric Study A1481131 and the proposed safety data from A1481156 support a pediatric indication claim for REVATIO?

***A1481131 : A randomized, double-blind, placebo controlled, dose ranging, parallel group study of oral sildenafil in the treatment of children, aged 1-17 years, with pulmonary arterial hypertension (PAH)***

- Phase 3 study
  - Definitive study to support safety and efficacy
  - Identified optimal dosing in children
- Consistent effects on primary and secondary endpoints
- Safety and efficacy consistent with data from two large randomized adult trials
- Provides meaningful information for treating physicians and patients

## % Change in Peak VO<sub>2</sub> from Baseline ITT Population

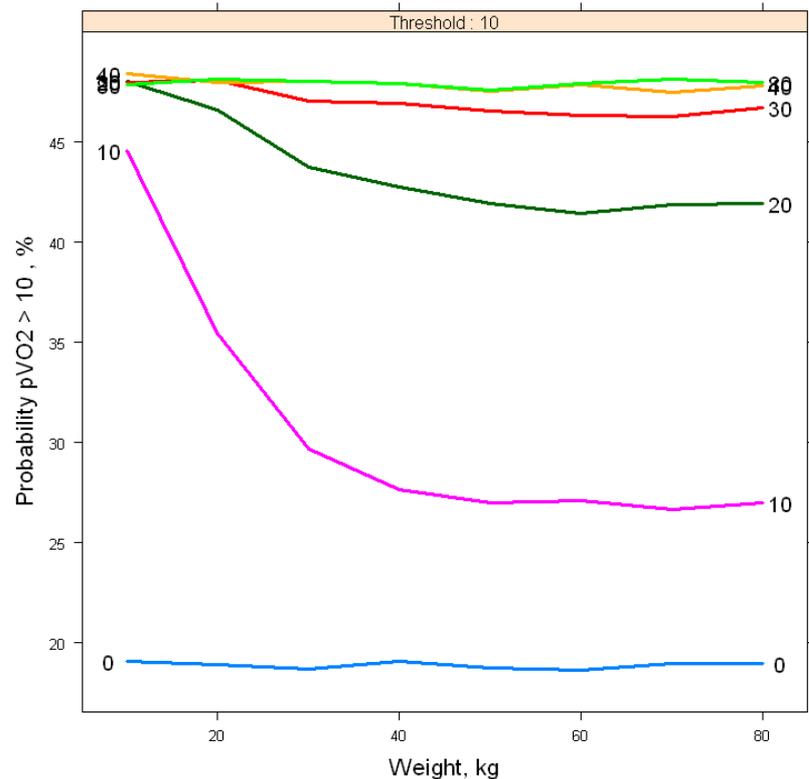


**Comparison to Placebo (n=29) with 95% CIs**

		% difference	95% CI
◇	Low Dose (n=24)	3.81	( -6.11 , 13.73 )
□	Medium Dose (n=26)	11.30	( 1.72 , 20.94 )
△	High Dose (n=27)	7.98	( -1.64 , 17.60 )
■	Combined	7.71	( -0.19 , 15.60 )

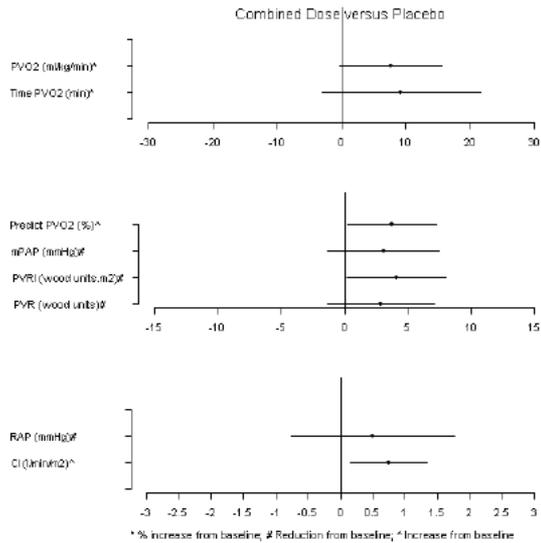
# PK/PD Modeling of Threshold Concentration

	MEAN	SEM	CV(%)	SD(%)	95% CI	
Baseline, pVO2	17.6	0.417	2.369	23.6	16.78	18.42
Emax, %	<b>9.09</b>	2.21	24.31		4.758	13.42
EC50, ng/mL	<b>23.7</b>	3.59	15.15		16.66	30.74
Hill	8					
res-err, %	11.9					
EC90	31.19	4.727	15.16		21.93	40.46

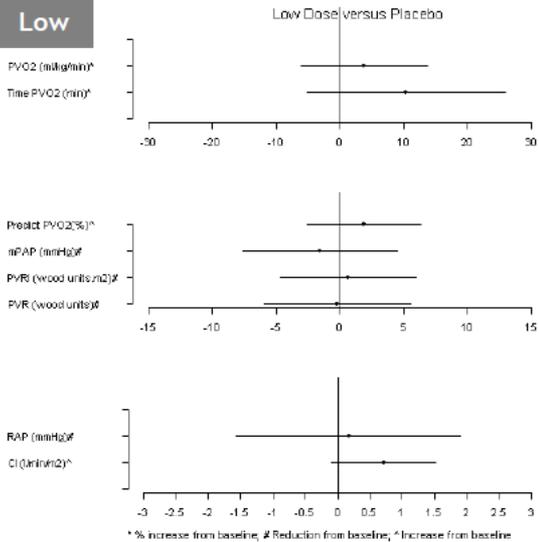


# In Study A1481131 pVO2 and HD 2ndry endpoints trend positively vs placebo

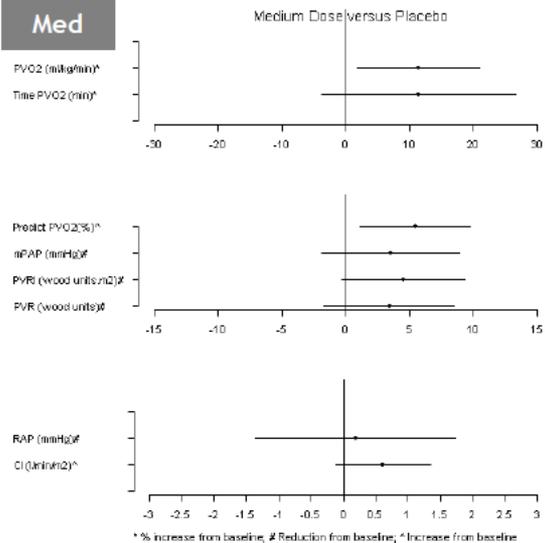
## Combined



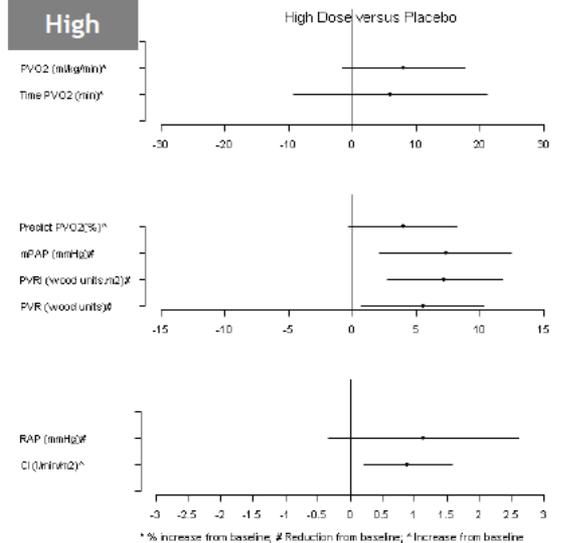
## Low



## Med



## High



# Key conclusions

- Positive benefit risk of sildenafil (b) (4)  
[REDACTED] in pediatric patients with PAH
- Inclusion of these data in the REVATIO labeling would provide important information for treating physicians and patients

## Question 2

Do the data from the pediatric Study A1481131 and the proposed safety data from A1481156 fulfill the clinical requirements of the REVATIO Written Request when used in conjunction with the pediatric formulation activities?

# A1481131 Feasibility Issues

- 234 subjects were treated in A1481131
  - 115 developmentally able subjects
  - 5 years duration
  - 16 countries
  - 32 centers
  - Larger study not possible

# Written Request Requirements (90% Power for 10% Effect Size)

- 204 developmentally able subjects for comparison of 'combined doses' versus placebo
- 388 developmentally able subjects for comparison of individual doses versus placebo (Hochberg approach)
- Study would have been in excess of 10 years duration
  - Interpretability issues (as highlighted by the Division)
  - Protracted length of time for subjects to be blinded to their treatment
  - Protracted length of time till the investigators/ PAH community are informed of the results

# REVATIO Pediatric Program

- Largest clinical program ever conducted in the pediatric PAH patient population
- Provides important information to inform prescribing physicians and patients
- Data consistent with the aims and objectives of the Written Request

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

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Dan Brum  
7/8/2009 07:36:19 AM

Norman Stockbridge  
7/8/2009 07:42:51 AM