CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-473

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Department of Health and Human Services
Food and Drug Administration

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

Form Approved: OMB No. 0910-0513
Expiration Date: 04/30/10
See OMB Statement on Page 3.

NDA NUMBER
22-473

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)	STRENGTH(S)
sildenafil citrate	0.8 mg/mL

DOSAGE FORM
Injectable

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	b. Issue Date of Patent	c. Expiration Date of Patent
5250534	10/5/1993	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	FAX Number *(if available)*
10017	
Telephone Number	**E-Mail Address *(if available)***
(212) 733-2323	

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

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

City/State

ZIP Code	FAX Number *(if available)*
Telephone Number	**E-Mail Address *(if available)***

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☑ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ No

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

2. Drug Substance (Active Ingredient)

2.1	Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☑ Yes	☐ No
2.2	Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☑ No
2.3	If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4	Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3**.		
2.5	Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) ?	☐ Yes	☑ No
2.6	Does the patent claim only an intermediate?	☐ Yes	☑ No
2.7	If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1	Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☑ Yes	☐ No
3.2	Does the patent claim only an intermediate?	☐ Yes	☑ No
3.3	If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 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?	☐ Yes	☑ 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?	☐ Yes ☐ No
4.2a	If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)*	

5. No Relevant Patents

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

6. Declaration Certification

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

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

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
Bruce A. Pokras	11/5/2008

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

Check applicable box and provide information below.

☐ NDA Applicant/Holder	☑ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Bruce A. Pokras	
Address 150 East 42nd Street	City/State New York, NY
ZIP Code 10017	Telephone Number (212) 733-6422
FAX Number *(if available)* (646) 563-9571	E-Mail Address *(if available)* bruce.a.pokras@pfizer.com

EXCLUSIVITY SUMMARY

NDA # 22-473 SUPPL # HFD # 110

Trade Name Revatio Injection

Generic Name sildenafil

Applicant Name Pfizer

Approval Date, If Known 11/20/09

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:

d) Did the applicant request exclusivity?

YES ☒ NO ☐

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

3 years

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

YES ☐ NO ☒

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

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# 21-845 Revatio (sildenafil) Tablets

NDA# 20-895 Viagra Tablets

NDA#

2. Combination product.

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

YES ☐ NO ☒

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

NDA#

NDA#

NDA#

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

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

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

summary for that investigation.

YES ☒ NO ☐

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

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

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

YES ☒ NO ☐

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

(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:

A1481024: Safety and efficacy of IV in subjects (85) with pulmonary hypertension

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"):

148-203: Phase I single blind, 4 way cross-over, escalating dose IV (8 volunteers)
148-208: Phase 1, open, randomized, 2 way cross over to investigate PK after oral and IV single dose (12 volunteers)
148-215: Phase 1 open, parallel group to investigate ADME radiolabelled oral and IV (6 volunteers)
A148-301: Phase 1 IV single dose open label in subjects with ischemic heart disease (8 volunteers)
A1481024: Safety and efficacy of IV in subjects (85) with pulmonary hypertension
A1481134: Phase II/III, randomized double blind multicentrestudy to assess IV sildenafil citrate as treatment of PH post corrective heart surgery for CHD (18 subjects. Terminated early, lack of recruitment)
A1481157 (part 1): Multicentre randomized, placebo controlled, dose ranging study, IV sildenafil citrate for PPHN (36 subjects. Terminated early, lack of recruitment)

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

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

Investigation #1		!
		!
IND # 64,924	YES ☒	! NO ☐
		! Explain:
Investigation #2		!
		!

IND # 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: Dan Brum, PharmD, MBA, RAC
Title: Senior Regulatory Project Manager
Date: 11/17/09

Name of Office/Division Director signing form: Norman Stockbridge, M.D., Ph.D.
Title: Director, Division of Cardiovascular and Renal Products

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

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

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

/s/

DANIEL BRUM
11/17/2009

NORMAN L STOCKBRIDGE
11/17/2009

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 22-473 Supplement Number: _____ NDA Supplement Type (e.g. SE5): _____

Division Name: DCRP PDUFA Goal Date: 11/21/09 Stamp Date: 1/21/2009

Proprietary Name: Revatio

Established/Generic Name: sildenafil citrate

Dosage Form: Injection

Applicant/Sponsor: Pfizer

Indication(s) *previously approved* (please complete this question for supplements and Type 6 NDAs only):
(1) _____
(2) _____
(3) _____
(4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 1
(Attach a completed Pediatric Page for each indication in current application.)

Indication: Treatment of pulmonary arterial hypertension (WHO Group I) to improve exercise ability and delay clinical worsening.

Q1: Is this application in response to a PREA PMR? Yes ☐ Continue
No ☒ Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #: _____ PMR #: _____

Does the division agree that this is a complete response to the PMR?

☐ Yes. Please proceed to Section D.

☐ No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW ☐ active ingredient(s) (includes new combination); ☐ indication(s); ☒ dosage form; ☐ dosing regimen; or ☐ route of administration?*

(b) ☐ No. PREA does not apply. **Skip to signature block.**

**** Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.***

Q3: Does this indication have orphan designation?

☐ Yes. PREA does not apply. **Skip to signature block.**

☒ No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

☒ Yes: (Complete Section A.)

☐ No: Please check all that apply:

- ☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)
- ☐ Deferred for some or all pediatric subpopulations (Complete Sections C)
- ☐ Completed for some or all pediatric subpopulations (Complete Sections D)
- ☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
- ☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

☒ Necessary studies would be impossible or highly impracticable because:

- ☐ Disease/condition does not exist in children
- ☒ Too few children with disease/condition to study
- ☐ Other (e.g., patients geographically dispersed): _____

☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.

☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☒ Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible#	Not meaningful therapeutic benefit*	Ineffective or unsafe†	Formulation failedΔ
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

\# Not feasible:

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____

* Not meaningful therapeutic benefit:

- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

- ☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)*

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4)

additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification †**
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): _____						

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:			
Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as

pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:					
Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

Pediatric Research and Equity Act Waivers

NDA #: **22-473** Supplement Type: n/a Supplement Number: n/a

Product name and active ingredient/dosage form: **Revatio (sildenafil citrate) Injection**

Sponsor: **Pfizer**

Indications(s): **Treatment of pulmonary arterial hypertension (WHO Group I) to improve exercise ability and delay clinical worsening.**

1. Pediatric age group(s) to be waived. **Ages 0-16 years**

2. Reason(s) for waiving pediatric assessment requirements (choose all that apply **and provide justification**):

   a. **Studies are impossible or highly impractical (e.g., the number of pediatric patients is so small or is geographically dispersed). If applicable, choose from adult-related conditions in Attachment I**

Justification: The sponsor is conducting studies under a pediatric Written Request, originally issued in 2001 and last amended in May 2007.

[ ] b(4)

however, after some discussion, the sponsor convinced the Agency that studies using the intravenous formulation would be highly impractical largely because of extremely low enrollment.

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

/s/

DANIEL BRUM
11/02/2009

NDA 22-473

Revatio® (sildenafil citrate)

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.

DMKay for Robert Clarke
Signature of Company Representative

December 16, 2008
Date

REVATIO® (sildenafil citrate) ——— Injection b(4)

NDA 22-473

FINANCIAL DISCLOSURE COVER NOTE

Module 1.3.4, Section 1.3.4.1

There are 7 covered studies for this NDA. The covered studies were not funded via variable compensation and none of the investigators in the study hold any form of propriety interest in **Revatio®**.

Financial Disclosure information for one of the studies, A1481140 was submitted in the original NDA 21-845 submitted in late 2004 and is not provided again.

Study	Study Title	FD Submitted
A1481140	**A Multinational, Multi-Centre, Randomised, Double-Blind, Double-Dummy, Placebo-Controlled Study to Assess the Efficacy and Safety Of 20, 40, and 80 mg Sildenafil Three Times A Day (TID) in the Treatment of Pulmonary Arterial Hypertension (PAH) in Subjects Aged 18 Years and Over.**	**NDA 21-845 Late 2004**

One of the covered studies, A148-208 was conducted at Pfizer Clinical Research Unit in Brussels, Belgium.

Study	Study Title	End date plus one year
A148-208	**An Open, Randomised, Two-Way Crossover Study To Investigate The Pharmacokinetics Of UK-92,480 After Oral Administration And Intravenous Administration In The Fasted State**	**October 97**

The clinical investigator(s) participating in the study A148-208, were employee(s) of Pfizer. Therefore, as defined in 21 CFR Part 54, certification regarding the financial interests of these investigators is not required. We have included a list of the investigators and a bias statement for A148-208. There were no independent investigators participating in A148-208.

The remaining five covered studies spanned a number of years including studies commencing before and ending prior to February 2nd 1999. Information regarding Pfizer's efforts to eliminate bias for the five studies in addition to A148-208 are described in the attached bias statements in Module 1, Section 1.3.4.

We have categorized the studies into 2 groups depending on the end of study plus one year date.

Group 1: Study end date plus one year is prior to February 2nd 1999.

There are three covered studies conducted prior to February 2nd 1999. The studies are:

Study	Study Title	End date plus one year
A148-203	**A Single Blind, Four-Way Crossover Study to Investigate The Pharmacokinetics of and Assess The Safety and Tolerance of UK-92,480 after Administration of Escalating Intravenous Doses in The Fasted State**	October 97
A148-215	**An Open, Parallel Group Study To Investigate The Absorption, Metabolism And Excretion Of A Single Oral And A Single Intravenous Dose Of Radiolabelled [14c]-Uk 92,480.**	August 98
A148-301	**An Open Single Intravenous Dose Study Of The Haemodynamic Effects Of Uk-92,480 (Sildenafil) In Patients With Stable Ischaemic Heart Disease**	March 97

Therefore consistent with the December 31, 1998 revisions to the Rule as it applies to publicly traded sponsors, it is only with respect to studies ongoing as of February 2, 1999 that equity interests information need be compiled and reported and only payments made on or after February 2, 1999 must be tracked. There are no disclosures in this category, the covered studies were not funded via variable compensation and none of the investigators in the studies hold any form of propriety interest in **Revatio®**.

- **Compensation potentially affected by the outcome of the covered study (21 CFR 54.4(a)(3)(i), 54.2(a))**
  Pfizer did not compensate clinical investigators in such a way as the total amount could vary with the outcome of the study. This is now formally stated in an organization-wide policy statement. Consequently, there are no disclosures in this category.
- **Significant payments of other sorts from the sponsor of the covered study (21 CFR 54.4(a)(3)(ii), 54.2(f))**
  Consistent with the December 31, 1998 revisions to the Rule, only payments made on or after February 2, 1999 must be tracked; therefore, there are no disclosures in this category.
- **Proprietary interest in the tested product (21 CFR 54.4(a)(3)(iii),54.2(c))**
  No Clinical Investigator participating in the "covered study" has a proprietary interest in **Revatio®**.
- **Significant equity interest in the sponsor of the covered study product (21 CFR 54.4(a)(3)(iv), 54.2(b))**
  Consistent with the December 31, 1998 revisions to the Rule, as it applies to publicly traded sponsors, it is only with respect to studies ongoing as of February 2, 1999 that equity interests information need be compiled and reported; therefore, there are no disclosures in this category.

Group 2 Studies started after February 2, 1999.

Two of the covered clinical studies started after February 2nd 1999. Pfizer has examined its financial data regarding significant payments of other sorts made to all investigators in the study and equity information as provided by the investigators, as defined in 21 CFR 54.2. Disclosure: Financial Interests and Arrangements of Clinical Investigators.

Pfizer Inc. is submitting financial disclosure information in the sNDA on the following covered studies

Study	Study Title	FD Start Date	FD End date plus one year or submission date
A1481024	**A Pilot, Multicentre Trial to Assess the Safety, Efficacy and Toleration of Intravenous Sildenafil in Subjects With Pulmonary Hypertension**	November 1999	November 17th 2008
A1481141	**A multinational, multi-centre, randomised, double-blind, placebo controlled, parallel group study to assess the safety and efficacy of a subject optimised dose of sildenafil (20, 40 or 80mg sildenafil TID) based on toleration, when used in combination with intravenous prostacyclin (epoprostenol) in the treatment of pulmonary arterial hypertension**	January 2000	November 17th 2008

With a total of 258 investigators listed as participating in the 2 covered studies which were initiated after February 2nd 1999, 21 of the listed investigators had financial information to disclose. Specifically, 19 investigators have significant payments of other sorts greater than $25K and 2 investigator disclosed equity greater than $50K. One investigator [redacted] participated in both studies [redacted] and [redacted] and had significant payments of other sorts [redacted] signed a financial disclosure form for [redacted] but could not be located to complete a Financial disclosure form for [redacted] even after Pfizer conducted due diligence process. Therefore [redacted] is listed as due diligence on the 3454 for [redacted] and also on two 3455's for [redacted] and [redacted] to reflect payments of other sorts. This information is listed in the 3455 Forms in Module 1, Section 1.3.4. b(6) b(6)

It is important to note that the investigator list for the studies determined by 1572s is not necessarily the same as that for financial disclosure. The FDA criteria for the two lists are not equivalent. Personnel involved with the studies, but not necessarily with the data, are listed on FDA Form 1572.

The individual investigators listed on the two covered studies identified in group 2 were sent the Financial Disclosure Form directly or via the principal investigator for their center. In addition, if necessary, we contacted the center by telephone and/or sent 2 separate follow-up letters to those individuals who did not return the Financial Disclosure Form. Although Pfizer was unable to obtain financial disclosure information specific to Equity in Pfizer for 22 of the investigators, Pfizer has examined it's financial data regarding the other categories of financial arrangements including significant payments of other sorts for all investigators. Additionally, all investigators are contacted at the time of the submission to remind them of the obligation to disclose financial information for Pfizer Inc and affiliated companies, including Warner-Lambert, Agouron, Pharmacia, Pharmacia & Upjohn, Searle/Monsanto and Sugen, which are wholly owned by Pfizer.

CERTIFICATION

A total of 264 studies participated in the studies listed in groups one and two.

Per Form 3454, certification is provided for 244 of the investigators indicating:

- Certified investigators. A total of 222 of the investigators are certified as having no Financial Arrangement as defined in 21 CFR 54.2.
- Due diligence in collecting the information on Equity. A total of 22 of the investigators did not respond or could not be reached by our due diligence effort.

With the exception of Equity, all other financial arrangements are checked via internal Pfizer procedures.

DISCLOSURE

In the covered studies, 21 of the investigators listed had financial information to disclose. A completed Form 3455 is attached for each of the 21 investigators. [redacted] could not be located and appears in due diligence on 3454 but did have significant payments of other sorts and therefore is listed in 3455. b(6

All Investigator Initiated Research Grants associated with investigators are paid directly to the Institution rather than to the individual investigator.

22-473 REVATIO® (sildenafil) Injection

Project Manager Overview

NDA 22-473 (pulmonary arterial hypertension)
REVATIO® (sildenafil) Injection T.I.D. Regimen
Pharmacologic Class: PDE-5 Inhibitor
Type 3 NDA: New Dosage Form
RPM: Daniel Brum, PharmD, RAC

Background

On June 3, 2005, DCRP approved Revatio (sildenafil) 20 mg oral tablets taken three times a day for the treatment of pulmonary arterial hypertension (WHO Group I) to improve exercise ability.

On May 22, 2009, FDA approved Pfizer's sNDA 21-845/S-006 for the treatment of pulmonary arterial hypertension to improve exercise capacity and delay clinical worsening. The recommended dosage is 20 mg three times a day approximately 4-6 hours apart (no change from previously approved regimen).

The sponsor submitted a new NDA for Revatio 0.8 mg/mL injectable solution [redacted] single use vial) to be administered three times daily for those patients unable to take Revatio orally. b(4)

All studies in support of this application were conducted under IND 64,924 or are cross-referenced to the original NDA. The Division reviewed this NDA under the Good Review Management Principles and Practices (21st Century Review)—the NDA was assigned a Standard review (10-month clock).

NDA Reviews and Memos

Division Director's Memo
Dr. Norman Stockbridge; November 16, 2009
Recommends approval.

CDTL Memo
Dr. Mehul Mehta: November 13, 2009
Recommends approval and is in agreement with the primary reviewers.

Pediatric age group(s) to be waived. Ages 0-16 years
Reason for waiving pediatric assessment requirements:
Studies are impossible or highly impractical (e.g., the number of pediatric patients is so small or is geographically dispersed).

The CDTL review thoroughly covers the Division's review of this application; therefore, I shall reference the CDTL memo for further detail.

Clinical Review
Dr. Maryann Gordon: October 28, 2009
Recommends approval (see review for details).

Pharmacometrics and Clinical Pharmacology
Dr. Satjit Brar: October 16, 2009
Recommends approval (see review for details).

Chemistry
Dr. Mohan Sapru: October 23, 2009 and November 16, 2009
Recommends approval (see review for details). Exclusion from environmental assessment acceptable; facility inspections acceptable.

Microbiology
Dr. Stephen Langille: October 23, 2009
Recommends approval (see review for details).

Pharmacology
Dr. Tom Papoian: February 24, 2009
Recommends approval (see review for details).

DRISK review of patient labeling, patient package insert
Mr. Steve Morin: October 1, 2009
A PPI was not felt to be needed for Revatio Injection; therefore, no formal review was conducted.

DDMAC review of patient labeling, patient package insert
Mr. Mike Sauers: October 2, 2009
DDMAC made several labeling recommendations for the Division to consider.

Action Items: Labeling is being finalized and an approval letter will be drafted for Dr. Stockbridge's signature.

Overview by Daniel Brum, PharmD, RAC
11/17/09

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

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

/s/

DANIEL BRUM
11/17/2009

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]		
NDA # 22-473 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Revatio Established/Proper Name: sildenafil Dosage Form: Injection		Applicant: Pfizer Agent for Applicant (if applicable):
RPM: Dan Brum, PharmD, RAC		Division: Division of Cardiovascular and Renal Products

NDAs: NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2) (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 NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)	505(b)(2) Original NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)): Provide a brief explanation of how this product is different from the listed drug. ☐ If no listed drug, check here and explain: **Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review.** ☐ No changes ☐ Updated Date of check: **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.** **On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.**

❖ User Fee Goal Date Action Goal Date (if different)	11/21/09 11/20/09 (Friday)
❖ Actions	
• Proposed action	☒ AP ☐ TA ☐ AE ☐ NA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ Promotional Materials *(accelerated approvals only)* Note: If accelerated approval (21 CFR 314.510/601.41), promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see guidance http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received

[1] 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.

❖ Application Characteristics [2]	
Review priority: ☒ Standard ☐ Priority Chemical classification (new NDAs only): 3 ☐ Fast Track ☐ Rolling Review ☐ Orphan drug designation ☐ Rx-to-OTC full switch ☐ Rx-to-OTC partial switch ☐ Direct-to-OTC NDAs: Subpart H ☐ Accelerated approval (21 CFR 314.510) ☐ Restricted distribution (21 CFR 314.520) Subpart I ☐ Approval based on animal studies BLAs: Subpart E ☐ Accelerated approval (21 CFR 601.41) ☐ Restricted distribution (21 CFR 601.42) Subpart H ☐ Approval based on animal studies ☐ Submitted in response to a PMR ☐ Submitted in response to a PMC Comments: _____	
❖ Date reviewed by PeRC *(required for approvals only)* If PeRC review not necessary, explain: _____	9/23/09
❖ BLAs only: *RMS-BLA Product Information Sheet for TBP* has been completed and forwarded to OBPS/DRM *(approvals only)*	☐ Yes, date
❖ BLAs only: is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☒ No
• Press Office notified of action (by OEP)	☐ Yes ☒ No
• Indicate what types (if any) of information dissemination are anticipated	☒ None ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

[2] All questions in all sections pertain 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	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(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.)*	☒ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• 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.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• 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.	21 CFR 314.50(i)(1)(*i*)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☐ 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).*

(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? (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). *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*).* *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.*	☐ Yes ☐ No
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist[3]	11/17/09
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) AP 11/20/09
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	11/17/09
• Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling	12/16/08
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	Revatio tablets: 21-845/s-006 approved 5/7/09
❖ Medication Guide/Patient Package Insert/Instructions for Use *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☒ Patient Package Insert ☐ Instructions for Use ☐ None

[3] Fill in blanks with dates of reviews, letters, etc.

• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	11/16/09
• Original applicant-proposed labeling	12/16/08
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	Revatio tablets: 21-845/s-006 approved 5/7/09
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent division proposal for (only if generated after latest applicant submission)	
• Most recent applicant-proposed labeling	10/27/09
❖ Proprietary Name • Review(s) *(indicate date(s))* • Acceptability/non-acceptability letter(s) *(indicate date(s))*	N/A
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☐ RPM ☐ DMEDP ☒ DRISK 10/1/09 ☒ DDMAC 10/2/09 ☐ CSS ☐ Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[4]/Memo of Filing Meeting) (indicate date of each review)*	Filing Review/Memo 3/11/09
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant in on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatric Page *(approvals only, must be reviewed by PERC before finalized)*	☒ Included
❖ 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 *(include certification)*	☒ Verified, statement is acceptable
❖ Outgoing communications *(letters (except previous action letters), emails, faxes, telecons)*	10/22/09; 9/23/09; 9/2/09; 2/10/09; 1/26/09
❖ Internal memoranda, telecons, etc.	
❖ Minutes of Meetings	6/10/09
• PeRC *(indicate date of mtg; approvals only)*	☐ Not applicable 9/23/09
• Pre-Approval Safety Conference *(indicate date of mtg; approvals only)*	☐ Not applicable 9/21/09 combined with mid-cycle and wrap-up meeting

[4] Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

• Regulatory Briefing *(indicate date of mtg)*	☒ No mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg See September 22, 2008 pre-meeting responses under IND 64,924; also see meeting minutes from meeting held March 17, 2008 (under NDA 21-845), and June 17, 2008 pre-meeting responses (under NDA 21-845).
• EOP2 meeting *(indicate date of mtg)*	☒ No mtg
• Other (e.g., EOP2a, CMC pilot programs)	
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available *(do not include transcript)*	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☐ None 11/16/09
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None 11/13/09
PMR/PMC Development Templates *(indicate total number)*	☒ None
Clinical Information[5]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	10/28/09
• Clinical review(s) *(indicate date for each review)*	10/28/09
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Safety update review(s) *(indicate location/date if incorporated into another review)*	N/A
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, review/memo explaining why not	10/28/09
❖ Clinical reviews from other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ Not needed
❖ Risk Management • REMS Document and Supporting Statement *(indicate date(s) of submission(s))* • REMS Memo *(indicate date)* • Review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☒ None
❖ DSI Clinical Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☒ None requested
Clinical Microbiology ☐ None	

[5] Filing reviews should be filed with the discipline reviews.

❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☒ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☒ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ None
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ None
Statistical Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☐ None 10/16/09
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 10/16/09
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of DSI letters)*	☒ None
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ None
• Supervisory Review(s) *(indicate date for each review)*	☒ None
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 24/09
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary *(include copies of DSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☒ None
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☐ None 11/17/09
• Product quality review(s) *(indicate date for each review)*	☐ None 10/23/09; 11/16/09
• ONDQA Biopharmaceutics review *(indicate date for each review)*	
• BLAs only: Facility information review(s) *(indicate dates)*	☐ None
❖ Microbiology Reviews • NDAs: Microbiology reviews (sterility & pyrogenicity) *(indicate date of each review)* • BLAs: Sterility assurance, product quality microbiology *(indicate date of each review)*	10/23/09 ☐ Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	11/16/09

☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
• NDAs: Facilities inspections (include EER printout) *(date completed must be within 2 years of action date)*	Date completed: Feb-Mar 2009 ☒ Acceptable ☐ Withhold recommendation
• BLAs: o TBP-EER o Compliance Status Check (approvals only, both original and all supplemental applications except CBEs) *(date completed must be within 60 days prior to AP)*	Date completed: ☐ Acceptable ☐ Withhold recommendation Date completed: ☐ Requested ☐ Accepted ☐ Hold
❖ NDAs: Methods Validation	☐ Completed ☐ Requested ☐ Not yet requested ☒ Not needed

Appendix A 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.

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

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/s/

DANIEL BRUM
11/17/2009

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22-473

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 December 16, 2008, received January 21, 2009 (user fee receipt date), submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act, for Revatio (sildenafil citrate) Injection.

There is a mismatch between the product's established name i.e., "sildenafil citrate" and the strength declaration i.e., "10 mg/12.5 mL (0.8 mg/mL)", which actually reflects the concentration of *sildenafil* and not sildenafil citrate. To ensure that the product name and the strength declaration match, please make the following revisions to the labels and labeling:

1. Change the product name

   FROM

   [redacted] b(4)

   TO

   Revatio (sildenafil) Injection

2. Revise statements describing the composition of the drug product on the container labels and in the **DESCRIPTION** section of the Package Insert by changing the text

   FROM

   [redacted] b(4)

   TO

   Each mL of solution contains 1.124 mg sildenafil citrate, 50.5 mg dextrose and Water for Injection

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}

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

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

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/s/

NORMAN L STOCKBRIDGE
10/22/2009

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22-473

INFORMATION REQUEST

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

Dear Ms. McKay:

Please refer to your December 16, 2008 new drug application submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Sildenafil Citrate ——— injection. b(4)

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. Regarding the FT-IR spectroscopy method validation, it is not clear how the characteristics of FT-IR spectrum of sildenafil, the active pharmaceutical ingredient, in the presence of the excipient dextrose and ———— ———— ·, differ from those of sildenafil standard, and placebo solution for injection. Provide the details of actual data generated, including the FT-IR spectra of placebo, and sildenafil citrate solution. b(4)

2. Regarding the batch analysis data (Stability Batches), provide discrete numbers for quantitative attributes such as sub-visible particles rather than stating "conforms to compendia".

3. Regarding labeling, the quantitative amounts of excipients need to be stated on container label, carton label and in the Description section of the Package Insert.

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

Sincerely,

{See appended electronic signature page}

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

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

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/s/

RAMESH K SOOD
09/23/2009

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22-473

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 December 16, 2008, received January 21, 2009 (user fee receipt date), submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act, for Revatio (sildenafil citrate) Injection.

The Division of Medication Error Prevention and Analysis' review of the labels and labeling sections of your submission are complete, and the following deficiencies have been identified:

A. General Comments (All Labels and Labeling)
   1. The presentation of the dosage form in conjunction with the established name should be revised to read (Sildenafil Citrate) Injection in accordance with the recommendations made by the reviewing chemist. This change should be made to all product labels and labeling, including the package insert.
   2. Revise the presentation of the strength of the vial to be expressed in terms of total drug content followed by the concentration, for example:

b(4)

B. Container Label and Carton Labeling
   1. Revise the statement "[redacted] to read "Sterile Single-use Vial, Discard Unused Portion". b(4)
   2. Revise the '[redacted] statement to read "For Intravenous Use". Additionally, relocate the statement so that it is presented below the strength to ensure that there is no intervening matter between the proprietary name and strength.

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}

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/

NORMAN L STOCKBRIDGE
09/02/2009

Minutes of a Teleconference—June 5, 2009

Application:	**NDA 22-473**
Drug:	**Revatio (sildenafil) I.V.**
Sponsor:	**Pfizer, Inc.**
Purpose:	**Follow-up t-con to discuss vial size**
Meeting Type:	**A**
Date:	**June 5, 2009**

FDA Attendees:

Norman Stockbridge, M.D., Ph.D.	Director, DCRP
Tsvi Aranoff, M.D.	Medical Officer (fellowship), DCRP
Dan Brum, Pharm.D., RAC	Regulatory Project Manager, DCRP
Ramesh Sood, Ph.D.	Branch Chief, ONDQA
Mohan Sapru, Ph.D.	Chemist, ONDQA
Stephen Langille, Ph.D.	Microbiologist, ONDQA
Don Henry, Ph.D.	Regulatory Project Manager, ONDQA
Anne Crandall, Pharm.D.	Safety Evaluator, OSE/DMEPA

Pfizer

CMC / Pharm Sci: Nancy Harper, Lynsey Hesmondhalgh, Zena Smith
Regulatory: Nancy McKay (US), Helen Spain (global)
Development Team Lead: Colin Ewen
Clinical / Safety: Hunter Gillies (Clinical), Sandip Chaudhuri (Safety)

Background:

b(4)

- Original submission for Revatio I.V. included ——— Revatio solution (0.8 mg sildenafil/mL) in a ——— single use vial—proposed dosage is 12.5 mL (10 mg) sildenafil three times daily
- March 31, 2009 – FDA requested teleconference with sponsor to discuss development of a ——— vial size/fill
- April 9, 2009 – Teleconference
- April 27, 2009 – Sponsor submitted rationale for developing ——— vial with ——— fill as interim solution with plans to develop ——— vial size/fill (e.g., 12.5 ml ———
- May 8, 2009 – Sponsor provided proposal for ——— vial size/fill and requested a teleconference (submission also included sponsor's version of teleconference minutes that Dr. Stockbridge and I reviewed and concurred with)
- June 5, 2009 – Teleconference (see meeting discussion points listed below)

Meeting Discussion Points:

- FDA agreed that the sponsor's proposal to develop a 12.5 mL ——— , in a ——— vial (herein referred to as 12.5 in ——— vial) was a good approach from a safety viewpoint and that 3 months of stability data would be an adequate basis upon which to make a regulatory decision. b(4)
- In support of this application, FDA asked the sponsor to submit the following information:
  - Experimental conditions used and the data from the hydrogen peroxide degradation study and from the forced degradation studies conducted on drug substance solution mentioned in their May 7, 2009 submission (sponsor will submit) b(4)
  - Structure of the ——— impurity, assay method, and limits of detection (sponsor plans to submit data from original Viagra dossier)
  - To conduct and submit the results of an oxygen bubbling experiment because the head space in the proposed 12.5 in ——— vial would be relatively larger than that in the original proposal (sponsor will discuss internally) b(4)
- FDA encouraged the sponsor to submit the sterile process validation package (SPVP) on the proposed 12.5 in ——— vial "as early as possible". The agency agreed that submission of the SPVP package in December 2009 (as suggested by the sponsor) would be a reasonable timeframe. b(4)
- [redacted] b(4)
- When the sponsor submits the 12.5 in ——— vial package, they will also revise the Revatio I.V. labels and labeling.
- Sponsor's planned submission timeline as discussed:
  - July/August 2009 – 12.5 in ——— vial package (will include hydrogen peroxide degradation study ——— data as described above, and revised labels and labeling) b(4)
  - November 1, 2009 – 3-month stability package
  - Oxygen bubbling experiment results – sponsor will discuss timing of submission internally

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

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

Drafted—6/7/09

Reviewed:

Sapru 6/9/09
Langille 6/9/09
Sood 6/9/09
Henry 6/9/09
Crandall 6/9/09
Stockbridge 6/9/09

Finalized—6/10/09

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/s/

Dan Brum
6/10/2009 07:08:38 AM

Norman Stockbridge
6/10/2009 07:35:40 AM

NDA/BLA REGULATORY FILING REVIEW

(Including Memo of Filing Meeting)

Application Information		
NDA # 22-473 BLA#	NDA Supplement #: BLA STN #	New Dosage Form with clinical data
Proprietary Name: Revatio Established/Proper Name: sildenafil citrate Dosage Form: Intravenous ~~injection~~) b(4) Strengths: 10 mg TID [0.8 mg/mL]		
Applicant: Pfizer Inc. Agent for Applicant (if applicable): N/A		
Date of Application: December 16, 2008 (no user fee) Date of Receipt: December 16, 2008 Date clock started after UN: **January 21, 2009 (user fee paid)**		
PDUFA Goal Date: November 21, 2009	Action Goal Date (if different):	
Filing Date: March 22, 2009 Date of Filing Meeting: January 22, 2008	Pre-filing mtg 1/15/09	
Chemical Classification: 3		
Proposed Indication(s): Treatment of pulmonary arterial hypertension (WHO Group 1) to improve exercise ability and delay clinical worsening (the addition of "delay clinical worsening" to the indication is being evaluated concurrently and separately under NDA 21-845/S-006).		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***Refer to Appendix A for further information.***	☒ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)	
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease Priority review voucher was submitted, review classification defaults to Priority.***	☒ Standard ☐ Priority ☐ Tropical disease Priority review voucher submitted	
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐		
Part 3 Combination Product? ☐	☐ Drug/Biologic ☐ Drug/Device ☐ Biologic/Device	
☐ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other: Orphan disease but sildenafil does not have orphan designation.	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ 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): 64,924	
PDUFA and Action Goal dates correct in tracking system? ***If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒ YES ☐ NO
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established name to the supporting IND(s) if not already entered into tracking system.***	☒ YES ☐ NO
Are all classification codes/flags (e.g. orphan, OTC drug, pediatric data) entered into tracking system? ***If not, ask the document room staff to make the appropriate entries.***	☒ YES ☐ NO
Application Integrity Policy	
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at: http://www.fda.gov/ora/compliance_ref/aiplist.html*** **If yes**, explain: **If yes**, has OC/DMPQ been notified of the submission? **Comments**:	☐ YES ☒ NO ☐ YES ☐ NO
User Fees	
Form 3397 (User Fee Cover Sheet) submitted	☒ YES ☐ NO
User Fee Status **Comments:** User fee paid late – some kind of misunderstanding between Pfizer's Revatio staff and Pfizer's financial staff.	☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
Note: *505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. It is expected that all 505(b) applications, whether 505(b)(1) or 505(b)(2), will require user fees unless otherwise waived or exempted (e.g., business waiver, orphan exemption).*	
Exclusivity	

Does another product have orphan exclusivity for the same indication? ***Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm***	☒ YES ☐ NO
If yes, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)*** **Comments**: Pfizer never requested orphan designation for sildenafil in PAH; now it's too late to request it since NDA 21-845 was previously approved.	☐ YES ☒ NO
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.* **Comments:**	☒ YES # years requested: 3 ☐ NO
If the proposed product is a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***): 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)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***	☒ Not applicable ☐ YES ☐ NO
505(b)(2) (NDAs/NDA Efficacy Supplements only)	☒ **Not applicable**
1. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐ YES ☐ NO
2. 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 less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).	☐ YES ☐ NO
3. 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	☐ YES ☐ NO

available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))? ***Note:*** *If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).*	

4. Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.fda.gov/cder/ob/default.htm***	☐ YES ☒ NO

If yes, please list below:

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

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.

Format and Content	
Do not check mixed submission if the only electronic component is the content of labeling (COL). **Comments:**	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?	N/A
If electronic submission: paper forms and certifications signed (non-CTD) or electronic forms and certifications signed (scanned or digital signature)(CTD)? ***Forms** include: 356h, patent information (3542a), financial disclosure (3454/3455), user fee cover sheet (3542a), and clinical trials (3674); **Certifications** include: debarment certification, patent certification(s), field copy certification, and pediatric certification.* **Comments:**	☒ YES ☐ NO
If electronic submission, does it follow the eCTD guidance? (*http://www.fda.gov/cder/guidance/7087rev.pdf*) **If not,** explain (e.g., waiver granted): The sponsor's submission is not organized as well as it could be. See filing meeting comments.	☒ YES ☐ NO

Form 356h: Is a signed form 356h included? ***If foreign applicant, <u>both</u> the applicant and the U.S. agent must sign the form.*** Are all establishments and their registration numbers listed on the form? **Comments**: None listed on 356h.	☒ YES ☐ NO ☐ YES ☒ NO
Index: Does the submission contain an accurate comprehensive index? **Comments**:	☒ YES ☐ NO
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain:	☒ YES ☐ NO
Controlled substance/Product with abuse potential: Abuse Liability Assessment, including a proposal for scheduling, submitted? Consult sent to the Controlled Substance Staff? **Comments**:	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
BLAs/BLA efficacy supplements only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	 ☐ YES ☐ NO
Patent Information (NDAs/NDA efficacy supplements only)	
Patent information submitted on form FDA 3542a? **Comments**:	☒ YES ☐ NO
Debarment Certification	
Correctly worded Debarment Certification with authorized signature? ***If foreign applicant, <u>both</u> the applicant and the U.S. Agent must***	☒ YES ☐ NO

sign the certification. ***Note:*** *Debarment Certification should use wording in FD&C Act section 306(k)(l) 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..."* **Comments**:	
Field Copy Certification (NDAs/NDA efficacy supplements only)	
Field Copy Certification: that it is a true copy of the CMC technical section (***applies to paper submissions only***) ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☒ Not Applicable (*electronic submission or no CMC technical section*) ☐ YES ☐ NO
Financial Disclosure	
Financial Disclosure forms included with authorized signature? ***Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an Agent.*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.* **Comments**:	☒ YES ☐ NO
Pediatrics	
PREA ***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 & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.* Are the required pediatric assessment studies or a full waiver of pediatric studies included? **If no,** is a request for full waiver of pediatric studies OR a request for partial waiver/deferral and a pediatric plan included? • ***If no, request in 74-day letter.*** • **If yes**, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3) **Comments**: The sponsor has been issued a Written Request	☐ Not Applicable ☐ YES ☒ NO ☐ YES ☒ NO ☐ YES ☐ NO

(last amended May 2007).	
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, contact PMHS (pediatric exclusivity determination by the Pediatric Exclusivity Board is needed).*** **Comments:**	☐ YES ☒ NO
Prescription Labeling	
Check all types of labeling submitted. **Comments:**	☐ **Not applicable** ☒ Package Insert (PI) ☒ Patient Package Insert (PPI) ☐ Instructions for Use ☐ MedGuide ☒ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)
Is electronic Content of Labeling submitted in SPL format? ***If no, request in 74-day letter.*** **Comments:** I'm asking the sponsor to send SPL.	☒ YES ☐ NO
Package insert (PI) submitted in PLR format? **If no**, was a waiver or deferral requested before the application was received or in the submission? **If before**, what is the status of the request? ***If no, request in 74-day letter.*** **Comments:**	☒ YES ☐ NO ☐ YES ☐ NO
All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? **Comments:**	☒ YES ☐ NO
MedGuide or PPI (plus PI) consulted to OSE/DRISK? (*send WORD version if available*) **Comments:** Sponsor is making very few changes to PPI which may not warrant a consult, however, I've submitted one to be safe.	☐ Not Applicable ☒ YES ☐ NO
REMS consulted to OSE/DRISK? **Comments:**	☒ Not Applicable ☐ YES ☐ NO
Carton and immediate container labels, PI, PPI, and proprietary name (if any) sent to OSE/DMEPA?	☐ Not Applicable ☒ YES

Comments:	☐ NO

OTC Labeling	
Check all types of labeling submitted. **Comments:**	☒ **Not Applicable** ☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)
Is electronic content of labeling submitted? ***If no, request in 74-day letter.***	☒ YES ☐ NO
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.*** **Comments:**	☐ YES ☐ NO
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.*** **Comments:**	☐ YES ☐ NO
Proprietary name, all labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEDP? **Comments:**	☐ YES ☐ NO
Meeting Minutes/SPA Agreements	
End-of Phase 2 meeting(s)? ***If yes, distribute minutes before filing meeting.*** **Comments:**	☐ YES Date(s): ☒ NO
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? ***If yes, distribute minutes before filing meeting.*** **Comments**: See September 22, 2008 pre-meeting responses under IND 64,924; also see meeting minutes from meeting held March 17, 2008 (under NDA 21-845), and June 17, 2008 pre-meeting responses (under NDA 21-845).	☒ YES Date(s): ☐ NO
Any Special Protocol Assessment (SPA) agreements? ***If yes, distribute letter and/or relevant minutes before filing***	☐ YES Date(s):

meeting. **Comments:**	☒ NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: January 22, 2009

NDA/BLA #: 22-473

PROPRIETARY/ESTABLISHED NAMES: Revatio (sildenafil) 10 mg Intravenous TID

APPLICANT: Pfizer, Inc.

BACKGROUND: Revatio (sildenafil citrate) was approved under NDA 21-845 for treatment of pulmonary arterial hypertension (WHO Group I) in patients to improve exercise ability. The sponsor submitted NDA 21-845/s-006 as a means to expand the indication to include "delay in clinical worsening" based on a placebo-controlled randomized trial with epoprostenol as background therapy—the efficacy supplement references a significant portion of data in the parent NDA (e.g., CMC, pharmtox, and clinical pharmacology), but also provides new clinical information including a population PK study report.

The sponsor submitted a new NDA for Revatio 0.8 mg/mL solution for injection to be administered three times daily for those patients unable to take oral Revatio. The basis for approvability of Revatio IV depends partly on whether FDA approves the expanded indication for "delay clinical worsening". The sponsor proposes to market a [redacted] vial even though only 12.5 mL is to be administered as a bolus injection [redacted] b(4)
Pfizer did not pay a user fee in December; once we received the fee, we sent Pfizer a combination Unfileable/Acknowledgement letter.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Dan Brum	Y
	CPMS/TL:	Ed Fromm	Y
Cross-Discipline Team Leader (CDTL)	Tom Marciniak **Changed to Mehul Mehta in February**		Y
Clinical	Reviewer:	Maryann Gordon	Y
	TL:	Tom Marciniak	Y
Social Scientist Review (*for OTC products*)	Reviewer:		
	TL:		

Labeling Review (*for OTC products*)	Reviewer:		
	TL:		
OSE	Reviewer:		
	TL:		
Clinical Microbiology (*for antimicrobial products*)	Reviewer:		
	TL:		
Clinical Pharmacology	Reviewer:	Islam Younis	Y
	TL:	Elena Mishina	N
Biostatistics	Reviewer:	Fanhui Kong	Y
	TL:	Jim Hung	N
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Tom Papoian	Y
	TL:	Al DeFelice	N
Statistics, carcinogenicity	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Mohan Sapru	Y
	TL:	Kasturi Srinivasachar	Y
Facility (*for BLAs/BLA supplements*)	Reviewer:		
	TL:		
Microbiology, sterility (*for NDAs/NDA efficacy supplements*)	Reviewer:	Stephen Langille	N
	TL:	James Vidra	N
Bioresearch Monitoring (DSI)	Reviewer:	Sharon Gershon	N
	TL:		
Pharmacometrics	Satjit Brar		Y

OTHER ATTENDEES: Norman Stockbridge.

505(b)(2) filing issues? **If yes,** list issues:	☒ Not Applicable ☐ YES ☐ NO
Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
Electronic Submission comments **List comments:**	☐ Not Applicable
CLINICAL **Comments:**	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☐ YES ☒ NO
• Advisory Committee Meeting needed? **Comments:** ***If no, for an original NME or BLA application, include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***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***	☐ YES Date if known: ☒ NO ☐ To be determined Reason: Drug already approved and no extraordinary issues raised in this NDA.
• 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? **Comments:**	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY	☒ Not Applicable

Comments:	☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**: emailed Nancy McKay (sponsor) to submit PK datasets section 5.3.3.5 if haven't submitted already.	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**: No separate review required.	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**: Originally the reviewer was not going to do his review, however, the reviewer changed his mind and will do one.	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**: PM notified ONDQA that supplement was in-house.	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO ☒ YES ☐ NO
• Establishment(s) ready for inspection?	☐ Not Applicable ☒ YES ☐ NO

▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? **Comments:**	☐ Not Applicable ☒ YES ☐ NO
• Sterile product? **If yes**, was Microbiology Team consulted for validation of sterilization? **(NDAs/NDA supplements only)**	☒ YES ☐ NO ☒ YES ☐ NO
FACILITY (BLAs only) **Comments:**	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Norman Stockbridge, M.D., Ph.D.

GRMP Timeline Milestones: GRMP **Standard** Review Milestones will be adhered to.

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. ☒ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. List (optional): ☒ Standard Review ☐ Priority Review

ACTIONS ITEMS

☒	Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into tracking system.
☐	If RTF action, notify everybody who already received a consult request, OSE PM., and Product Quality PM. Cancel EER/TBP-EER.

☐	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.
☐	If BLA or priority review NDA, send 60-day letter.
☒	Send review issues/no review issues by day 74

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

/s/

Dan Brum
3/11/2009 01:38:18 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-473

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 December 16, 2008, received January 21, 2009 (user fee receipt date), submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act, for Revatio (sildenafil citrate) [redacted] injection. b(4)

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 **Standard**. Therefore, the user fee goal date is November 21, 2009.

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 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, mid-cycle, 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 commitment requests by November 1, 2009.

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

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

/s/

Norman Stockbridge
2/10/2009 07:50:34 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-473

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

Dear Ms. McKay:

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

Name of Drug Product:	Revatio (sildenafil citrate) [redacted] Injection (b(4))
Review Priority Classification:	Standard (S)
Date of Application:	December 16, 2008
Receipt Date of User Fees:	January 21, 2009
Our Reference Number:	NDA 22-473

This application was considered incomplete and was not accepted for filing because all fees owed for this application, products, establishments, or previous applications were not paid. Subsequently, we received on January 21, 2009 all fees due. The receipt date for fees due is considered the new receipt date for this application.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on March 22, 2009 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be November 21, 2009.

Please cite the NDA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardiovascular and Renal Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, please contact:

Dan Brum, PharmD, RAC
Regulatory Health Project Manager
(301) 796-0578

Sincerely,

{See appended electronic signature page}

Edward Fromm, R.Ph, RAC
Chief, Project Management Staff
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Edward Fromm
1/26/2009 01:36:38 PM

Form Approved: OMB No. 0910 - 0297 Expiration Date: January 31, 2010 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 CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS

PFIZER INC
Jessica Diaz
235 EAST 42ND STREET
NEW YORK NY 10017
US

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

22-473

2. TELEPHONE NUMBER
212-733 6560

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

[X] YES [ ] 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:

[X] THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION

[ ] THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

3. PRODUCT NAME
REVATIO (sildenafil citrate)

6. USER FEE I.D. NUMBER
PD3008919

7. 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)

[ ] A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE

[ ] THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) 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 COMMERCIALLY

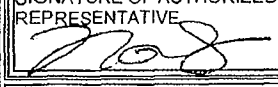
8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? [ ] YES [X] NO

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
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Drive, Room 3046
Rockville, MD 20852

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

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
	Director	16 December 2008

9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION
$1,247,200.00

Form FDA 3397 (03/07)

Close Print Cover sheet

Worldwide Regulatory Affairs & Quality Assurance
Pfizer Inc
235 East 42nd Street
New York, NY 10017

Global Research & Development

16 December 2008

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

RE: Original New Drug Application # 22-473 – REVATIO®(sildenafil) [redacted] Injection b(4)

Dear Mr. Woyshner

Pursuant to 21 C.F.R. § 11.2(b)(2) and the Office of Regulatory Affairs Memorandum dated 24 September 2003, Pfizer hereby certifies that an electronic version of the original New Drug Application identified above was submitted to the Center for Drug Evaluation and Research's Central Document Room on 16 December 2008. Chemistry Manufacturing and Controls (CMC) information provided with this submission includes a complete new drug product section and section addendums to the drug substance section, as appropriate for the solution for injection formulation, as well as an Environmental Assessment.

Should you have any questions please contact me at (212) 733-4755 (phone) or (212) 857-3558 (fax).

Sincerely,

N McKay

Nancy McKay
Director
Worldwide Regulatory Strategy
Worldwide Regulatory Affairs and Quality Assurance

Desk Copy: Mr. Dan Brum

NDA 22-473