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RESEARCH**

APPLICATION NUMBER:

203109Orig1s000

OTHER REVIEW(S)

Project Manager Overview

NDA 203109 for REVATIO® (sildenafil) for oral suspension, 10 mg/mL

proposed indication: pediatric pulmonary arterial hypertension

PDUFA goal date: August 30, 2012 (includes 3-month extension for major amendment)

Pharmacologic Class: PDE-5 Inhibitor

Type 3 NDA: New Dosage Form

RPM: Daniel Brum, PharmD, MBA, BCPS, RAC

Priority Review

Regulatory Background

NDA 21845 Revatio Tablets

On June 3, 2005, DCRP approved Pfizer's NDA 21845 for 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, DCRP approved sNDA 21845/S-006 for the treatment of pulmonary arterial hypertension to improve exercise capacity and *delay clinical worsening*. Again, the recommended dosage was 20 mg three times a day approximately 4-6 hours apart (no change from previously approved regimen).

NDA 22473 Revatio Injection

On November 18, 2009, DCRP approved NDA 22473 for Revatio 0.8 mg/mL injection (20 mL single use vial containing a sterile solution) to be administered three times daily for patients unable to take Revatio via the oral route of administration.

NDA 203109 Revatio for Oral Suspension

On November 30, 2011, NDA 203109 was submitted to market a *new dosage form* (powder for oral suspension) and expand the indication to *pediatrics* (treatment of pediatric PAH was orphan designated on July 28, 2011). Under the auspices of a WR (see RPM Filing Review dated 1/5/12 pp. 11-12 for WR history) Pfizer conducted study 1131 (blinded) and 1156 (open-label) to evaluate sildenafil in pediatric PAH.

An advisory committee meeting was held July 29, 2010, in part, to discuss use of endpoints other than those traditionally used to seek marketing approval in the U.S. i.e., hemodynamic endpoints rather than exercise. Although the primary endpoint for study 1131 was exercise capacity (cycle ergometry in children able to perform the test), the study did not reach statistical significance; however, some FDA reviewers suggested that there might be a correlation between 6MWD and PVRI based on a databased of clinical trial results from several drug programs. The June 2011 amendment to the WR reflects incorporation of PVRI as the primary endpoint.

Pediatric exclusivity was granted for studies conducted on sildenafil and went into effect on February 9, 2012.

203109 REVATIO® (sildenafil) for oral suspension

The sponsor's intention is to market all dosage forms for Revatio for PAH using a single package insert. The pediatric NDA received a Priority review (as do all submissions for pediatrics submitted in response to Written Requests).

NDA 203109 safety concerns related to the dose-response increase in mortality

See reviews including Dr. Mary Ross Southworth's memo dated April 20, 2012.

Pfizer sent a Dear Health Care Provider letter in the fall of 2011 informing providers that in study A1481156, a higher risk of mortality was observed among patients in the higher compared to lower study-specific dose groups. An independent Data Monitoring Committee (DMC) had been following mortality trends since the completion of the pivotal trial in 2008. The DHCP letter is appended to this review.

PDUFA goal-date 3-month extension

On May 24, 2012, Pfizer notified me that data was inadvertently omitted from the NDA and that they were planning to submit the information by May 30, 2012. On May 24, 2012, we received a cover letter explaining what information was omitted from the NDA; the actual data was received on May 30, 2012. A letter notifying Pfizer that the goal date had been extended is dated May 30, 2012.

NDA Reviews and Memos

Office Director's Memo

See sNDA 21845/S-008 for Dr. Ellis Unger's office memo.

Division Director's Memo

Dr. Norman Stockbridge; May 24, 2012

Dr. Stockbridge recommends approval of the dosage form only. With regards to labeling, he recommends adding a new warning about the long-term mortality findings in children.

CDTL Memo

Dr. Abraham Karkowsky: May 15, 2012

Dr. Karkowsky recommends *against* approval for *pediatric* use; he is unopposed to approval of the new dosage form but for *adults* only. He suggests that labeling for adults be revised to reflect uncertainty (and potential harm) for longer-term use (e.g., beyond 16 weeks). Dr. Karkowsky also recommends Pfizer conduct a long-term, controlled trial of Revatio in adults. Lastly, deaths related to the right heart catheterization procedure in this trial (in addition to literature reports) raise serious concerns regarding the ethics of using invasive hemodynamic measurements as an endpoint in future pediatric PAH trials (see CDTL memo for details).

Clinical Reviews

Dr. Maryann Gordon: April 18, 2012 and August 27, 2012

Dr. Gordon recommends against approval for both the pediatric indication *and* the new dosage form (see review for details). Given the serious safety signal in pediatrics and

paucity of controlled, long-term data in the adult population, she also suggests issuing a PMR for a controlled, randomized, long-term safety study in adults with PAH.

Statistical Review

Dr. John Lawrence: April 30, 2012

Dr. Lawrence recommends against approval for both the pediatric indication *and* the new dosage form (see review for details). Given the serious safety signal in pediatrics and paucity of controlled, long-term data in the adult population, he suggests issuing a PMR for a controlled, randomized, dose-response study in adults with PAH.

Pharmacometrics and Clinical Pharmacology

Dr. Satjit Brar: April 27, 2012

Dr. Brar recommends approval of the lower doses studied and the new dosage form (see review for details).

Pharmacology

Dr. Donald Jensen: May 1, 2012

Dr. Jensen has no approvability issues from a nonclinical standpoint; however, he notes that the lack of nonclinical safety signals does not ameliorate the adverse clinical outcomes observed in the clinical studies (see review for details).

Biopharmaceutics

Dr. Arzu Selen: April 25, 2012; May 16, 2012; August 27, 2012 (PMC development template)

Dr. Selen has no approvability issues related to the new dosage form. She notes that the dissolution method and acceptance criterion are acceptable on an *interim* basis as the final method is expected to be developed and implemented within 14 months from the action date (see review for details).

CMC

Dr. Mohan Sapru: April 27, 2012; May 17, 2012; August 29, 2012

Dr. Sapru has no approvability issues related to the new dosage form (see review for details). Exclusion from environmental assessment acceptable; facility inspections acceptable.

DMEPA

Mr. Forest (Ray) Ford: May 2, 2012 (review), May 29, 2012 (email), August 30, 2012 (email)

A discipline review letter that included comments from the May 2, 2012 review was sent to the sponsor on May 4, 2012. The sponsor responded to the DR letter on May 18, 2012 and again on May 25, 2012 (the sponsor did not implement all of the changes on May 18, 2012, hence the May 25, 2012 submission); Mr. Ford agreed that the sponsor implemented the recommended changes in the May 4, 2012 DR letter (email communication from Ray Ford to Dan Brum dated May 29, 2012). DMEPA reviewed the sponsor's May 25, 2012 submission and DCRP issued a DR letter on August 28,

203109 REVATIO® (sildenafil) for oral suspension

2012. The sponsor responded to all deficiencies on August 29, 2012 and DMEPA concurred with the changes (email dated August 29, 2012).

Patient Labeling Team review of patient labeling

Ms. Latonia Ford: August 10, 2012

FDA and the sponsor reached agreement on labeling for both the PPI and IFU.

OPDP review of patient labeling

Dr. Zarna Patel: August 9, 2012

SEALD labeling review

Dr. Eric Brodsky: August 24, 2012

Action Items:

Because the sponsor's intention is to market all dosage forms for Revatio for PAH using a single package insert, sNDA 21845/s-008 and sNDA 22473/s-003 will be approved at the same time as NDA 203109 (powder for oral suspension).

The PMR for Revatio is included in the sNDA 21845/S-008 (tablets) approval letter and Dr. Unger will sign that letter for this reason.

On behalf of Dr. Norman Stockbridge, Dr. Stephen Grant (Deputy Director for DCRP) will sign the approval letters for NDA 203109 and sNDA 22473/S-003. There is one PMC (biopharm) described in the approval letter for NDA 203109. The approval letters with postmarketing studies were cleared by SRT/SWAT.

*Overview by Daniel Brum, PharmD, RAC
August 30, 2012*

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/s/

DANIEL BRUM
08/30/2012

**PMR/PMC Development Template Completed for
ONDQA/Biopharmaceutics Review for NDA 203-109**

NDA/BLA # Product Name:	NDA 203-109 Revatio® (sildenafil citrate) 10 mg/mL Powder for Oral suspension	
PMR/PMC Description:	In vitro dissolution test method and dissolution acceptance criterion for sildenafil from Revatio® (sildenafil citrate) 10 mg/mL Powder for Oral suspension	
PMR/PMC Schedule Milestones:	The Applicant will submit a dissolution method development report with supportive data within 6 months of the action date.	<u>02/28/2013</u>
	The Applicant will submit the final dissolution method development report including proposed dissolution acceptance criterion with the supportive data within 14 months of the action date.	<u>10/30/2013</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

In the NDA, the Applicant proposed [REDACTED] (b) (4) during the review cycle, the Applicant responded to our information requests and generated limited but adequate data for establishing an interim dissolution method. As agreed (April 2012), the interim dissolution method is temporary and the Applicant will continue their efforts to develop a more informative dissolution method for this product.

The interim dissolution method is considered suitable to enable patient access to the drug product for a short-time window immediately after approval while a more informative dissolution method can be developed for continued long-term characterization of the product. The final dissolution method and dissolution acceptance criterion will serve as a life-cycle product quality tool at release and stability testing of the Revatio (sildenafil citrate) 10 mg/mL Powder for Oral Suspension.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The data requested in this PMC request are *in vitro* dissolution data. There are no clinical studies.

The reason we need this PMC:

Dissolution testing and dissolution acceptance criterion are critical for product quality assessment. Data collected from *in vitro* dissolution testing could alert to significant changes in release characteristics which could result in dosing errors and undesired clinical outcomes.

The availability of a reliable and robust *in vitro* dissolution test method will bridge the newly manufactured batches with the batches studied in clinical trials and will enable assessment of the impact of manufacturing changes and site transfers and possibly, some modifications in the formulation.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study:** all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial:** any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The data generated in response to this PMC will be in vitro dissolution data as detailed in the 5/1/2012 Meeting Minutes (written by Ms. Teshara Bouie.)

At the time of this meeting when the following agreement was reached, the multidisciplinary review was ongoing and the references are made with respect to the action date. The agreement was not prepared in the PMC format at that time.

Specifically, the following items were discussed and agreed (cut/paste from the meeting minutes):

- Pfizer agreed to provide the dissolution method development report with complete data within 6 months of the NDA action as an amendment to the IND. Pfizer will indicate in the cover page of their submission a request for review of the proposed dissolution method. The Agency will review the report and provide feedback in a timely manner.

- Based on the Agency's feedback on the acceptability of the final dissolution method, Pfizer will collect additional dissolution profile data (using the final dissolution method) from the batches manufactured during the first year post-action date. These data will be used to set the final acceptance criterion

- Within 14 months of action date, Pfizer will submit a prior approval supplement (PAS) to their NDA with their proposal for the final acceptance criterion and the supportive dissolution data.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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/s/

ARZU SELEN
08/24/2012

RICHARD T LOSTRITTO
08/27/2012

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label and Labeling Review

Date: August 27, 2012

Reviewer: Ray Ford, RPh, Safety Evaluator
Division of Medication Error Prevention and Analysis

Team Leader: Irene Z. Chan, PharmD, BCPS, Team Leader
Division of Medication Error Prevention and Analysis

Drug Name: Revatio (Sildenafil) Powder for Oral suspension, 10 mg/mL

Application Type/Number: NDA 203109

Applicant/sponsor: Pfizer

OSE RCM #: 2011-4482

*** This document contains proprietary and confidential information that should not be released to the public.***

1 INTRODUCTION

This review responds to a request from the Division of Cardiology Products (DCRP) for a review of the revised carton labeling, and container label for Revatio (Sildenafil) Powder for Oral Suspension, 10 mg/mL, received on May 25, 2012 (Appendix A). The sponsor also submitted a diagram of the revised oral syringe on May 18, 2012 (Appendix A). DMEPA previously reviewed the proposed labeling, container label, constitution cup, and oral dosing syringe under OSE RCM #2011-4482 dated March 22, 2012.

2 MATERIAL REVIEWED

DMEPA reviewed the revised carton labeling and container label submitted on May 25, 2012 and compared them against the recommendations contained in OSE review # 2011-4482 dated March 22, 2012. The Applicant, per DMEPA's previous recommendation, has removed the (b) (4)

DMEPA also reviewed the revised oral dosing syringe diagram submitted on May 18, 2012. In an email from the CMC reviewer dated August 24, 2012, CMC recommends approval of the proposed oral syringe since the proposed oral syringe is identical to the previously submitted oral syringe except for the (b) (4). We compared the revised oral dosing syringe against the recommendations contained in OSE review # 2011-4482 dated March 22, 2012. The Applicant was unable to provide a sample at this time.

3 CONCLUSIONS AND RECOMMENDATIONS

Review of the revised label and labeling show that the Applicant implemented the majority of DMEPA's recommendations under OSE review #2011-4482 dated March 22, 2012. However, we have identified additional areas of vulnerability that may lead to medication error and provide additional recommendations below. We recommend these be implemented prior to approval of this product.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications on this review, please contact the OSE Regulatory Project Manager, Cheryle Milburn at 301-796-2048.

3.1 COMMENTS TO THE APPLICANT

A. Carton Labeling

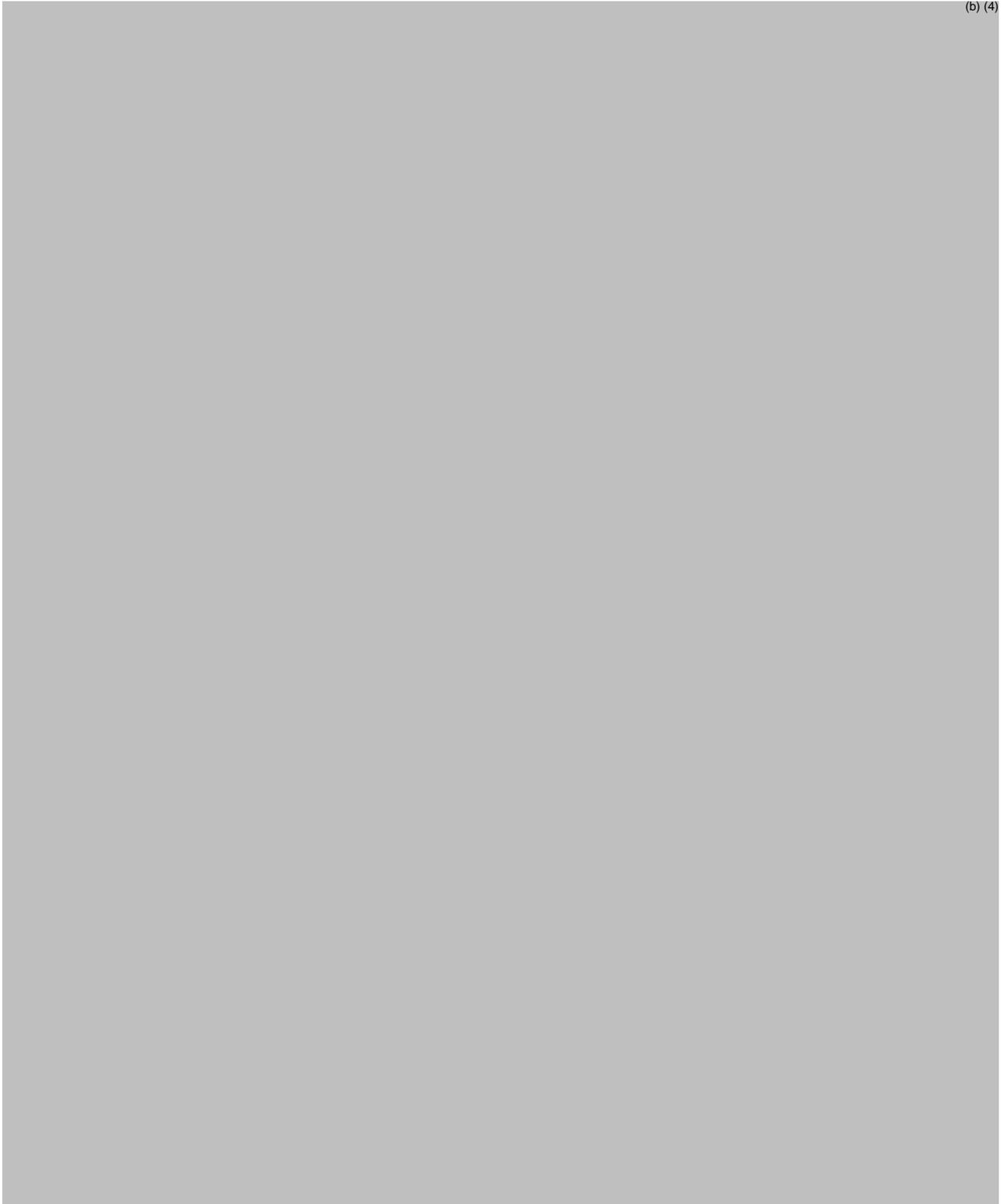
1. The back display panel refers to a (b) (4). This may cause confusion for patients since the enclosed syringe only contains markings of 1 mL and 2 mL. Revise (b) (4) to read 'An oral dosing syringe' on the back display panel of the carton labeling.
2. The net quantity statement detracts from the statement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

B. Oral Dosing Syringe

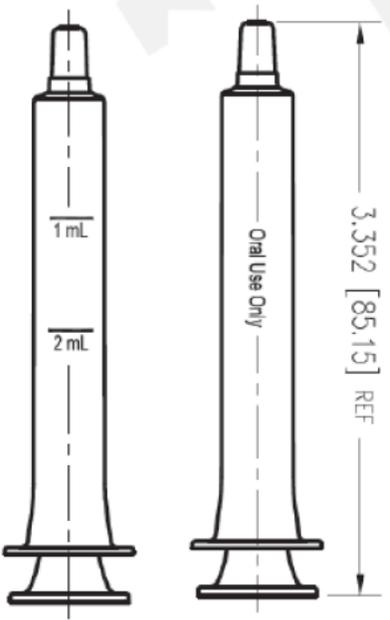
1. The oral dosing syringe should include the statement “For use only with Revatio oral suspension. This statement should be located directly above the “Oral use only” statement and should not interfere with the graduation markings.

Appendix A: Revised Carton Labeling, Container Labels, and Syringe Diagram

(b) (4)



Associated Component Description: Oral Dosing Syringe

Component Description: Oral Dosing Syringe	
Product Code	(b) (4)
Color	Barrel: Natural Plunger: White
Materials of Construction	(b) (4)
Manufacturer	(b) (4)
DMF References	(b) (4)
Drawing PROVIDED FOR ILLUSTRATIVE PURPOSES ONLY	

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/s/

FOREST R FORD
08/27/2012

IRENE Z CHAN
08/27/2012

SEALD Director Sign-Off Review of the End-of-Cycle Prescribing Information: Outstanding Format Deficiencies

Product Title	REVATIO (sildenafil) tablets, for oral use REVATIO (sildenafil) for oral suspension REVATIO (sildenafil) injection, for intravenous use
Applicant	Pfizer
Applications/Supplement Numbers	NDA 203109/S-1 (oral suspension), NDA 21,845/S-8 (tablets), and NDA 22,473/S-3 (intravenous)
Type of Applications	Original NDA for new dosage form (oral suspension) and efficacy supplements (new population – pediatric patients)
Indication	Treatment of pulmonary arterial hypertension
Established Pharmacologic Class ¹	phosphodiesterase 5 (PDE5) inhibitor
Office/Division	ODEI/DCRP
Division Project Manager	Dan Brum
Date FDA Received Applications	November 30, 2011
Goal Dates	August 30, 2012 for original NDA and September 30, 2012 for efficacy supplements
Date PI Received by SEALD	August 23, 2012
SEALD Review Date	August 24, 2012
SEALD Labeling Reviewer	Eric Brodsky
SEALD Division Director	Laurie Burke

PI = prescribing information

¹ The established pharmacologic class (EPC) that appears in the final draft PI.

This Study Endpoints and Labeling Development (SEALD) Director Sign-Off review of the end-of-cycle, draft prescribing information (PI) for critical format elements reveals **outstanding labeling format deficiencies that must be corrected** before the final PI is approved. After these outstanding labeling format deficiencies are corrected, the SEALD Director will have no objection to the approval of this PI.

The critical format elements include labeling regulation (21 CFR 201.56 and 201.57), labeling guidance, and best labeling practices (see list below). This review does not include every regulation or guidance that pertains to PI format.

Guide to the Selected Requirements for Prescribing Information (SRPI) Checklist: For each SRPI item, one of the following 3 response options is selected:

- **NO**: The PI **does not meet** the requirement for this item (**deficiency**).
- **YES**: The PI **meets** the requirement for this item (**not a deficiency**).
- **N/A** (not applicable): This item does not apply to the specific PI under review.

Selected Requirements of Prescribing Information

Highlights (HL)

GENERAL FORMAT

- YES** 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment:

- YES** 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period (for RPMs)**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of Cycle Period (for SEALD reviewers)**

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment:

- YES** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

- NO** 4. White space must be present before each major heading in HL.

Comment: Add white space above the following HL headings: *Recent Major Changes, Indications and Usage, Warnings and Precautions, Drug Interactions, Adverse Reactions, and Patient Information Counseling. Consider removing the extra white space above the Limitations of Use heading.*

- NO** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment: Add a reference to the last sentence in the Indications and Usage header (1).

- NO** 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required

Selected Requirements of Prescribing Information

• Initial U.S. Approval	Required
• Boxed Warning	Required if a Boxed Warning is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state “None.”)
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment: *Drug Interactions heading should appear after the Adverse Reactions heading.*

YES

7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES

8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: “**HIGHLIGHTS OF PRESCRIBING INFORMATION**”.

Comment:

Highlights Limitation Statement

YES

9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”

Comment:

Product Title

YES

10. Product title in HL must be **bolded**.

Comment:

Initial U.S. Approval

YES

11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment:

Boxed Warning

N/A

12. All text must be **bolded**.

Comment:

N/A

13. Must have a centered heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and

Selected Requirements of Prescribing Information

other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

- N/A** 14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” centered immediately beneath the heading.

Comment:

- N/A** 15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)

Comment:

- N/A** 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

- YES** 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

- YES** 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

- YES** 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Dosage and Administration, Coronary Stenting (2.2) --- 3/2012”.

Comment:

- YES** 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

- YES** 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment:

Dosage Forms and Strengths

- YES** 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

Selected Requirements of Prescribing Information

- NO** 23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.

Comment: *The HL contraindication for hypersensitivity states “(b) (4)” To be consistent with the FPI contraindications amend this sentence to “any component of the tablet, injection, or oral suspension.”*

- YES** 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

- YES** 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement

- NO** 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**”

Comment: *“FDA-approved patient labeling” is in sentence case; not uppercase.*

Revision Date

- NO** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

Comment: *Add the word “August”.*

Contents: Table of Contents (TOC)

GENERAL FORMAT

- YES** 28. A horizontal line must separate TOC from the FPI.

Comment:

- YES** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”.

Comment:

- YES** 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment:

Selected Requirements of Prescribing Information

- 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.
YES Comment:
- 32. All section headings must be **bolded** and in UPPER CASE.
YES Comment:
- 33. All subsection headings must be indented, not bolded, and in title case.
YES Comment:
- 34. When a section or subsection is omitted, the numbering does not change.
YES Comment:
- 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “**FULL PRESCRIBING INFORMATION: CONTENTS**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”
YES Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

- YES** 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: “**FULL PRESCRIBING INFORMATION**”.
Comment:
- YES** 37. All section and subsection headings and numbers must be **bolded**.
Comment:
- YES** 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse

Selected Requirements of Prescribing Information

9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- YES** 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

- YES** 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, “[see *Warnings and Precautions (5.2)*]”.

Comment:

- YES** 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

- N/A** 42. All text is **bolded**.

Comment:

- N/A** 43. Must have a heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

- N/A** 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

- N/A** 45. If no Contraindications are known, this section must state “None”.

Comment:

Adverse Reactions

Selected Requirements of Prescribing Information

- YES** 46. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”

Comment:

- YES** 47. When postmarketing adverse reaction data is included (typically in the “Postmarketing Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

Patient Counseling Information

- YES** 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

- “See FDA-approved patient labeling (Medication Guide)”
- “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information)”
- “See FDA-approved patient labeling (Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

Comment:

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/s/

ERIC R BRODSKY
08/24/2012

LAURIE B BURKE
08/24/2012

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
Division of Professional Drug Promotion
Division of Consumer Drug Promotion**

******Pre-decisional Agency Information******

Memorandum

Date: August 9, 2012

To: Daniel Brum
Regulatory Project Manager
Division of Cardio-Renal Products (DCRP)

From: Emily Baker, PharmD
Regulatory Review Officer
Division of Professional Drug Promotion (DPDP)
Office of Prescription Drug Promotion (OPDP)

Zarna Patel, PharmD
Regulatory Review Officer
Division of Consumer Drug Promotion (DCDP)
Office of Prescription Drug Promotion (OPDP)

Subject: **Revatio (sildenafil) powder for oral suspension
NDA 20319**

OPDP has reviewed the proposed Package Insert (PI), Patient Package Insert (PPI), Instructions for Use, and carton and container labeling submitted for consult on December 7, 2011, for Revatio (sildenafil) powder for oral suspension. OPDP's comments are based on the labeling at the following EDR location, \\CDSESUB1\EVSPROD\NDA203109\0000, as well as the version provided to us on August 9, 2012 (located on the shared drive at the following location, \\fdsfs01\ode2\DCRP\NDA203109 Revatio peds). Please note our comments have been added to the version located on the shared drive.

DPDP reviewed the carton and container labeling and we have no comments at this time.

DCDP reviewed the Instructions for Use and we have no comments at this time.

Thank you for the opportunity to comment on these proposed materials.

If you have any questions on the comments for the PI or carton and container labeling, please contact Emily Baker at 301.796.7524 or emily.baker@fda.hhs.gov.

If you have any questions on the comments for the PPI or Instructions for Use, please contact Zarna Patel at 301.796.3822 or zarna.patel@fda.hhs.gov.

Prescribing Information

Highlights of Prescribing Information

WARNINGS AND PRECAUTIONS

- Section 5.3 states that Revatio is not recommended in patients with PVOD. Please consider including this in the Highlights.

ADVERSE REACTIONS

- Epistaxis appears to have been omitted from this list.

5.2 Vasodilation

- According to Section 7, blood pressure should be monitored when co-administering blood pressure lowering drugs with Revatio. Please consider including this information in this section.

5.5 Visual Loss and 5.6 Hearing Loss

- The highlights section states that Revatio should be discontinued if sudden decrease or loss of vision or hearing occurs. If appropriate, please consider including this information in sections 5.5 and 5.6

Patient Package Insert (PPI)

What is Revatio?

- The following context, “Your heart has to work hard to pump blood into your lungs”, sounds promotional in tone and misleadingly suggests overstatement of efficacy. We recommend deletion.
- According to the Indications and Usage section of the PI, “REVATIO is indicated for the treatment of pulmonary arterial hypertension (WHO Group I) in adults to improve exercise ability and delay clinical worsening....” Please revise the indication statement in this section so that it is consistent with the PI. For example, including the context, “help lessen symptoms”, misleadingly overstates the efficacy of the product (especially when included in promotional pieces) by implying that Revatio helps lessen all symptoms associated with PAH, when such is not the case. We recommend deleting this context.
- The Indications and Usage section also includes the following additional context, “...The delay in clinical worsening was demonstrated when REVATIO was added to background epoprostenol therapy. Studies establishing effectiveness were short-term (12 to 16 weeks), and included predominately patients with New York Heart Association (NYHA) Functional

Class II-III symptoms....” We recommend including this important material fact regarding the efficacy of the product.

What are the possible side effects of REVATIO?

- The highlights section states that Revatio should be discontinued if sudden decrease or loss of vision or hearing occurs. If appropriate, please consider including this information in this section.

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/s/

ZARNA PATEL
08/09/2012

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs**

PATIENT LABELING REVIEW

Date: **August 09, 2012**

To: Norman Stockbridge, MD
Director
Division of Cardiovascular and Renal Products (DCRP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)
Barbara Fuller, RN, MSN, CWOCN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Latonia M. Ford, RN, BSN, MBA
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Subject: DMPP Review of Patient Labeling: Patient Package Insert
(PPI) and Instructions for Use (IFU)

Drug Name (established name): REVATIO (sildenafil)

Dosage Form and Route: for oral suspension

Application Type/Number: NDA 203109

Applicant: Pfizer Inc.

1 INTRODUCTION

On November 30, 2011, Pfizer Inc. submitted an Original New Drug Application (NDA) 203109, for REVATIO (sildenafil) for oral suspension with the proposed indication to treat pulmonary arterial hypertension (WHO Group I) and to improve exercise ability [REDACTED] (b) (4) for pediatric patients' age 1 to 17 years. REVATIO (sildenafil) Tablets (NDA 21845) was originally approved on June 3, 2005, for the treatment of pulmonary arterial hypertension (WHO Group I) to improve exercise ability. REVATIO (sildenafil) Injection (NDA 22473) was approved on November 18, 2009, for the treatment of pulmonary arterial hypertension (WHO Group 1) to improve exercise ability and delay clinical worsening.

On December 2, 2011, the Division of Cardiovascular and Renal Products (DCRP) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for REVATIO (sildenafil) for oral suspension.

This review is written in response to a request by Division of Cardiovascular and Renal Products (DCRP) for Division of Medical Policy Programs (DMPP) to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for REVATIO (sildenafil) for oral suspension.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFU was completed on May 2, 2012.

2 MATERIAL REVIEWED

- Draft REVATIO (sildenafil) for oral suspension PPI and IFU received on November 30, 2011, revised by the Review Division throughout the review cycle, and received by DMPP on July 25, 2012.
- Draft REVATIO (sildenafil) for oral suspension Prescribing Information (PI) received on November 30, 2011, revised by the Review Division throughout the review cycle, and received by DMPP on July 25, 2012.

Approved ADCIRCA (tadalafil) tablets for oral administration comparator labeling dated April 5, 2011.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI and IFU the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using

fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the PPI and IFU document using the Verdana font, size 11.

In our review of the PPI and IFU we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI and IFU are consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The PPI and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our review of the PPI and IFU is appended to this memorandum. Consult DMPP regarding any additional revisions made to the Package Insert (PI) to determine if corresponding revisions need to be made to the PPI and IFU.

Please let us know if you have any questions.

18 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS)
immediately following this page

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/s/

LATONIA M FORD
08/09/2012

BARBARA A FULLER
08/09/2012

LASHAWN M GRIFFITHS
08/10/2012

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label and Labeling Review

Date: May 2, 2012

Reviewer(s): Ray Ford, RPh
Division of Medication Error Prevention and Analysis

Team Leader Irene Z Chan, PharmD, BCPS
Division of Medication Error Prevention and Analysis

Associate Director Scott Dallas, RPh
Division of Medication Error Prevention and Analysis

Drug Name and Strengths: Revatio (Sildenafil) Powder for Oral suspension, 10 mg/mL

Application Type/Number: NDA 203109

Applicant/sponsor: Pfizer

OSE RCM #: 2011-4482

*** This document contains proprietary and confidential information that should not be released to the public.***

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1 INTRODUCTION

This review evaluates the proposed packaging, labels, and labeling for Revatio (Sildenafil) Oral Suspension, 10 mg/mL, for areas of vulnerability that could lead to medication errors, in response to a request from the Division of Cardiovascular and Renal Products (DCRP). Pfizer submitted this NDA to add a new dosing formulation, powder for oral suspension, to the currently marketed dosing formulations.

1.1 REGULATORY HISTORY

Revatio (Sildenafil) Tablets, 20 mg, was approved on June 3, 2005, for the treatment of pulmonary arterial hypertension (PAH) under NDA 024145. Revatio (Sildenafil) Injection, 10 mg per 12.5 mL, was approved on November 18, 2009, for treatment of pulmonary arterial hypertension (World Health Organization Group I) to improve exercise ability and delay clinical worsening under NDA 022473.

1.2 PRODUCT INFORMATION

The following product information is provided in the November 30, 2011 submission:

- **Active Ingredient:** Sildenafil
- **Indication of Use:** PAH (WHO Group I) to improve exercise ability (b) (4) in pediatric patients age 1 year to 17 years.
- **Route of administration:** Oral
- **Dosage form:** Powder for Oral Suspension (POS)
- **Strength:** 10 mg/mL after reconstitution
- **Constitution:** 90 mL of water is added in three increments of 30 mL to achieve a final concentration of 10 mg/mL, with a total volume of 112 mL.
- **Dosage and Frequency of Administration:** (b) (4)
- **How Supplied:** Revatio for oral suspension is supplied in 125 mL amber glass bottles. Each bottle contains 32.27 grams of powder for oral suspension. Following reconstitution, the volume of the suspension is 112 mL (10 mg/mL). A 3 mL oral dosing syringe, (b) (4) a press in bottle adaptor are also provided.
- **Storage:** Recommended storage for REVATIO powder for oral suspension: Store below 30°C (86°F) in the original package in order to protect from moisture. The shelf life of the powder for oral suspension is 24 months. Constituted Suspension: Store below 30°C (86°F) or in refrigerator at 2°C to 8°C (36°F to 46°F). Do not freeze. The shelf life of the constituted suspension is 30 days. Any remaining suspension should be discarded 30 days after constitution.

- **Container and Closure systems:** The commercial container closure system for Sildenafil citrate powder for oral suspension includes a 125 mL amber glass bottle, a (b) (4) closure, a (b) (4), a press in bottle adaptor (PIBA), and an oral dosing syringe.

2 METHODS AND MATERIALS REVIEWED

Using the principles of Failure Mode and Effects Analysis¹, principles of human factors, and postmarketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following, which were all submitted November 30, 2011, except where indicated:

- Carton Labeling (See Appendix A)
- Container Label (see Appendix B)
- (b) (4)
- Oral dosing syringe, (b) (4) (see Appendix D)
- Press in Bottle Adapter (PIBA) (see Appendix F)
- Insert Labeling (no image)
- Instructions for Use (no image)

We compared the proposed Revatio labels and labeling to the currently marketed Revatio labels and labeling to identify any potential safety concerns. Additionally, since Revatio is currently marketed, DMEPA searched the FDA Adverse Event Reporting System (AERS) database to identify medication errors involving Revatio.

2.1 SELECTION OF MEDICATION ERROR CASES

The January 9, 2012 AERS search used the following search terms: trade name “Revatio” and verbatim terms “Revatio%”. The reaction terms used were the MedDRA High Level Group Terms (HLGT) “Medication Errors” and “Product Quality Issues.”

The reports were manually reviewed to determine if a medication error occurred. Duplicate reports were combined into cases. The cases that described a medication error were categorized by type of error. We reviewed the cases within each category to identify factors that contributed to the medication errors. If a root cause was associated with the label or labeling of the product, the case was considered pertinent to this review.

Reports excluded from the case series include cases that did not describe a medication error (i.e., adverse events unrelated to a medication error, medication error due to another concomitant drug product). Additionally, medication error cases not applicable to this review (i.e., wrong strength, wrong drug, product quality issue, or wrong frequency of administration) were placed in Appendix H. See Appendices G for ISR #s and detailed narratives of all relevant cases.

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

3 MEDICATION ERROR RISK ASSESSMENT

The following sections describe the findings and analysis of our AERS search and labels and labeling risk assessment.

3.1 MEDICATION ERROR CASES

The Adverse Event Reporting System (AERS) database search retrieved 41 cases (see Appendix G and H for ISR numbers for all AERS cases). After individual review of the cases based on criteria stated in Section 2, two cases were found to be relevant to this review and are summarized below.

The first case of wrong drug error (ISR# 5664999) describes a patient was transferred from the hospital to a convalescent hospital. The patient was given Revia (naltrexone) 100 mg three times daily instead of Revatio (sildenafil) 100 mg three times daily January 02, 2008 until January 08, 2008. The error occurred during the transfer from the hospital to a convalescent hospital. Although not stated, based on the name similarity and similar product characteristics, this may be the result of the name confusion. We will continue to monitor for cases of name confusion with our routine post marketing surveillance.

We identified one case of wrong route of administration (ISR# 5124822). In this case, an 11 year old patient was being administered sildenafil as an oral solution. During hospitalization, a healthcare technician administered the sildenafil oral solution intravenously, rather than orally. After the intravenous administration, the patient's status worsened, he could not breathe and was taken to the intensive care unit, but he subsequently died. The case did not indicate if the healthcare technician prepared the dose of sildenafil oral solution. The exact root cause for error could not be determined. We reviewed the proposed bottle label and carton labeling for Revatio Oral Suspension to ensure the statement "For oral use only" is properly displayed. Upon review, it appears the statement needs to be displayed more prominently on the principle display panel (see section 4 below).

3.2 LABEL AND LABELING RISK ASSESSMENT

We compared the proposed Revatio Oral Suspension labels and labeling to the labels and labeling of the currently marketed Revatio (Sildenafil) 20 mg Tablet and Revatio (Sildenafil) 10 mg/12.5 mL Injection. There does appear to be adequate differences to minimize selection errors and prevent confusion within the product line.

Our review of the Revatio Oral Suspension label and labeling identified the following deficiencies:

A. PACKAGING COMPONENTS:



2. Oral dosing syringe (b) (4)
- The syringe numbers have trailing zeros which may lead to incorrect dosing and confusion.
 - The (b) (4) is not appropriate for the recommended dosage of 1 mL or 2 mL depending on weight. The dose of (b) (4) is not in the approved labeling.
 - The syringe has “(b) (4)” printed on the barrel which indicates that it can be used for two routes of administration which can lead to confusion.
 - The barrel of the syringe has printed (b) (4) but this dosing measurement is not reflected in the package insert and (b) (4)” may be misunderstood by patients. This may lead to dosing confusion.
 - When obtaining a dose of medication from the reconstituted suspension, the user must insert the oral dosing syringe into the bottle adapter opening, invert the bottle with inserted syringe simultaneously, and then pull back the syringe plunger to the graduation mark corresponding to the dose that has been ordered by the prescriber. With the proposed syringe inverted, the graduation numbers would have to be read upside down. This may lead to confusion. An example of an oral syringe is included in appendix E.

B. CARTON LABELING

1. The Pfizer logo and “Rx Only” statements are overly prominent and distract from the proprietary name, established name, and strength statements.
2. The statement “FOR ORAL USE ONLY” has decreased readability due to all uppercase font, and its placement can be made more prominent by moving the “Grape Flavored” statement to the bottom third of the principle display panel and replacing it with this statement instead.
3. The statement “SHAKE WELL BEFORE EACH USE” has decreased readability due to all uppercase font, and is inadequately prominent due to its placement on the side panel.
4. There are currently no directions for constitution for the pharmacist.
5. The principle display panel does not indicate the total volume following reconstitution.
6. The side display panel is cluttered and difficult to read.

C. CONTAINER LABEL

1. The Pfizer logo and “Rx Only” statements are overly prominent and distract from the proprietary name, established name, and strength statements.
2. The statement “FOR ORAL USE ONLY” has decreased readability due to all uppercase font, and its placement can be made more prominent by moving to the principle display panel and replacing the “Grape Flavored” statement.
3. The statement “SHAKE WELL BEFORE EACH USE” has decreased readability due to all uppercase font, and is inadequately prominent due to its placement on the side panel.

D. INSERT LABELING

1. The Dosage and administration section of the insert labeling, the patient counseling information section of the insert labeling, as well as the instructions for use do not clearly indicate that the suspension should be shaken before each use.
2. The Applicant has included Instructions For Use (IFU) in the Dosage and Administration section intended for the patient in the insert labeling. This information is inappropriately placed and unnecessary since there are separate instructions for use already.
3. Use of error prone abbreviations that may lead to medication errors such as “<, ≤, >, ≥” were found in the insert labeling.
4. The Instructions For Use (IFU) do not include a clear diagram of the oral dosing syringe that shows the graduation marks that patients will use to accurately draw up a dose .

4 CONCLUSION AND RECCOMENDATIONS

DMEPA conluded that the proposed label and labeling introduce vulnerability that can lead to medication errors. We advise the following recommendations be implemented prior to approval of this NDA:

A.



B. ORAL DOSING SYRINGE (b) (4)

1. Include an oral dosing device (e. g. oral syringe) that bears markings consistent with the labeled dosage directions of 1 mL or 2 mL. Ensure the 1 mL and 2 mL measurements do not include trailing zeros. Trailing zeros have been noted to result in a 10 fold error by the Institute for Safe Medical practices and lead to confusion. For additional guidance, refer to the Guidance for Industry titled “Dosage Delivery Devices for Orally Ingested OTC Liquid Drug Products” published May 2011, since this information is also pertinent to prescription dosing devices.
2. The barrel of the syringe has printed “(b) (4)” which indicates (b) (4). Revise the syringe barrel route of administration to read “Oral Use Only” to minimize the risk of (b) (4) confusion in the marketplace.
3. When obtaining a dose of medication from the reconstituted suspension, the user must insert the oral dosing syringe into the bottle adapter opening, invert the bottle with inserted syringe simultaneously, and then pull back the syringe plunger to the graduation mark corresponding to the dose that has been ordered by the prescriber. With the proposed syringe inverted, the graduation numbers would have to be read upside down. This may lead to confusion. Include an oral dosing syringe for use with this suspension whose graduation numbers can be read right side up when obtaining a dose from the amber glass bottle. An example of an oral syringe is included in appendix E. For additional guidance, refer to the Guidance for Industry titled “Dosage Delivery Devices for Orally Ingested OTC Liquid Drug Products” published May 2011, since this information is also to prescription dosing devices.

C. CARTON LABEL

1. The Pfizer logo above the proprietary name distracts from the proprietary name. Move this logo to the bottom third of the principle display panel and select a color for the logo that is consistent with the currently marketed oral and injection Revatio products.
2. Debold and move the “Rx Only” statement to the bottom third portion of the principle display panel.
3. The statement “FOR ORAL USE ONLY” has decreased readability due to all uppercase font, and its placement can be made more prominent by moving the “Grape Flavored” statement to the bottom third of the principle display panel and replacing it with this statement instead. Revise the statement to title case: “For Oral Use Only” and move the statement so it is directly below the statement of strength.

4. The statement “SHAKE WELL BEFORE EACH USE” has decreased readability due to all uppercase font, and is inadequately prominent due to its placement on the side panel. Revise the statement to title case: “Shake Well Before Each Use” for improved readability and move to the principle display panel so it is more prominent.
5. There is currently no net quantity statement on the principle display panel. Add the statement “112 mL following Constitution” to the primary display panel.
6. The top half of the side display panel is bolded and cluttered making it difficult to read. To minimize clutter, we recommend revising the statement [REDACTED] (b) (4) to “Discard any unused portion 30 days after constitution.” Additionally, remove the statement [REDACTED] (b) (4) since there is already an expiration date included on the carton labeling.
7. The side display panel does not currently contain any directions for constitution of the oral suspension for the pharmacist. Add this information to the side panel.

D. CONTAINER LABEL

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

E. INSERT LABELING

1. The applicant has used in the HIGHLIGHTS OF PRESCRIBING INFORMATION, and FULL PRESCRIBING INFORMATION error prone abbreviations. The symbols $<$, \leq , $>$, \geq were utilized in the insert labeling to represent “less than,” “less than or equal to,” “greater than,” or “greater than or equal to,” respectively. These symbols can be misinterpreted as the opposite of the intended symbol or mistakenly used as the incorrect symbol. As part of a national campaign to decrease the use of dangerous symbols², the FDA agreed not to use such error prone symbols in the approved labeling of products because these abbreviations can be carried over to prescribing. Therefore, DMEPA recommends that $<$ be replaced with “less than,” \leq be replaced with “less than or equal to,” $>$ be replaced with “greater than,” and \geq be replaced with “greater than or equal to.”
2. The Dosage and Administration section of the insert labeling, the patient counseling information section of the insert labeling, as well as the instructions for use do not clearly indicate that the suspension should be shaken before each use. Revise “Shake the closed bottle of constituted suspension [REDACTED]” to read “Shake the closed bottle of constituted suspension for a minimum of 10 seconds before Each use” in the Dosage and Administration section of the insert labeling, the patient counseling information section of the insert labeling, as well as the instructions for use section.
3. The Applicant has included instructions for use intended for the patient in the Dosage and Administration section titled “Instructions for Use.” This information is inappropriately placed and unnecessary since there are separate instructions for use already. We recommend removal of the instructions intended for patient use from the Dosage and Administration section since this is a duplication of the instruction for use in the patient package insert section.
4. The Instructions For Use (IFU) do not include a clear diagram of the oral dosing syringe that shows the graduation marks that patients will use to accurately draw up a dose. Insert a labeled diagram of the oral dosage syringe indicating the individual components and graduation marks.

If you have further questions or need clarifications, please contact Nina Ton, OSE Project Manager, at 301-796-1648.

² Institute for Safe Medication Practices (ISMP). ISMP’s List of Error-Prone Abbreviations, Symbols, and Dose Designations. ISMP: 2010

Appendix G. AERS ISR Numbers

Relevant Cases:

ISR #5124822	<p>Narrative: This is a lay media report. An 11-year-old male patient with a history of a congenital heart defect (orifice) was brought to a hospital by his father last month, when his complaints of fatigue and easy exhaustion were increased. A committee of five physicians decided to perform an operation. The patient underwent the operation on (b) (6). The operation was successful and he stayed in the intensive care (b) (6) days. When he recovered and was able to walk, he was transferred to the service. Treatment with oral sildenafil was initiated to enhance blood circulation post operatively. He was being administered sildenafil as an oral solution. On (b) (6) a healthcare technician administered the sildenafil solution intravenously, rather than orally. After the intravenous administration, the patient's status worsened, he could not breathe, he was taken to intensive care unit, but he subsequently died. In the hospital report reason of death was documented as hypertension. A physician stated that this event was not confirmed, yet the patient's parents stated that the patient died because of IV sildenafil administration by mistake. The physician also stated that the case is legally under investigation and the event was not proven to be due to sildenafil. The exact reason of death will be determined following an autopsy.</p>
ISR #5664999	<p>Narrative: This is a report based on information reported to Pfizer by (b) (4). A distributor solicited and a representative reported that a 72-year-old female patient with primary pulmonary hypertension was hospitalized for internal bleeding on (b) (6) and was hospitalized for diarrhea and "was out it" on (b) (6). She had elevated liver function tests during the hospitalization on (b) (6) during the use of Tracleer (bosentan) therapy. It was reported that the patient resided in a convalescent hospital. Start date and stop dates of drug therapy reflected approximate dates of Tracleer use (26Sep2006 to (b) (6)). Tracleer was on hold until LFT's (liver function tests) returned to normal. A concomitant medication included Revatio (sildenafil). The prescribing cardiologist confirmed the events of internal bleeding, diarrhea and "was out of it", requiring hospitalization but described the internal bleeding as GI (gastrointestinal) bleed and assessed the events as not related to Tracleer. In accordance with our departmental convention regarding such cases, the event of elevated LFT's requiring hospitalization will be considered medically unconfirmed and possibly related to Tracleer until corroborated by a healthcare professional. The prescribing cardiologist confirmed that this 72-year-old female patient with primary pulmonary hypertension was hospitalized due to elevated (LFTs) and with associated hallucinations starting on (b) (6) that resulted in prolongation of hospitalization during the use of Tracleer therapy. Revia (naltrexone) was reported as a co-suspect. Additional concomitant medications included levothyroxine sodium, digoxin, calcium, risedronate sodium, warfarin sodium, colestyramine, atropine sulfite, diphenoxylate hydrochloride, ferrous sulfate,</p>

furosemide, kaolin pectin, tramadol hydrochloride, pantoprazole sodium, metronidazole, spironolactone, paracetamol and metolazone. Tracleer 62.5 mg twice daily was started on 30Sep2006, was uptitrated to 125 mg twice daily on 01Nov2006 and was discontinued on (b) (6). On (b) (6), the patient was transferred from the hospital to a convalescent hospital. The patient was given Revia (naltrexone) 100 mg three times daily instead of Revatio (sildenafil) 100 mg three times daily from (b) (6). On (b) (6), lab panels revealed AST (aspartate aminotransferase) 19.4xULN (582IU, 30 assumed), ALT (alanine aminotransferase) 10.3xULN (311 IU, 30 assumed), alkaline phosphatase (AP) normal (72, assumed 120), and total bilirubin 1.9xULN (1.9 1.0 assumed). On (b) (6), the patient experienced hallucinations and Tracleer was discontinued. Follow up LFT panel on 14Jan2008 revealed AST 2.7xULN (81 IU), ALT 5.6xULN (169) and total bilirubin 1.8xULN (1.8). LFT panel on 22Jan2008 revealed AST normal (28 IU), ALT 1.3xULN (39) and total bilirubin 1.6xULN (1.6). As of (b) (6) the patient was still in the hospital. The reporter considered the event of elevated LFTs resolved as of (b) (6). The reporter noted a positive de-challenge and assessed the event as serious and related to Tracleer and to naltrexone. Company Clinical Evaluation: Based on available information, the reported adverse events most likely related to Tracleer and naltrexone and are thus unrelated to Viagra.

Appendix H. Excluded AERS ISR Numbers

Excluded ISR Numbers that do not inform Revatio label, labeling, and packaging review:

4846927	6521361	6807198	7052323
4923437	6534507	6807390	7084238
4956348	6545533	6820209	7127415
5019683	6605184	6872121	7127430
5105127	6722584	6888189	7198941
5168524	6730968	6914767	7215827
5780952	6770412	6932130	7282340
6011710	6770472	7030449	7439306
6213469	6802214	7040264	7800536
6312215	6805717	7043622	

- Death reporting cause as unknown (n=4)
- Death reported cause as pulmonary hypertension (n=1)
- No medication error related to Revatio (n=4)
- Dose Omission due to cost of medication, outcome not reported or known (n=6)
- Improper dose with outcome not reported, not due to labels and labeling (n=10)
- Increased INR, patient taking bosentan and warfarin, no further outcome information provided (n=1)
- Drug interaction with no adverse event reported (n=1)
- Product quality issue, tested samples met specification (n=1)
- Off label use of Viagra to treat PAH, no outcome reported (n=1)
- Adverse drug event unrelated to medication error, no outcome known or reported (n=10)

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/s/

FOREST R FORD
05/02/2012

SCOTT M DALLAS on behalf of IRENE Z CHAN
05/02/2012

SCOTT M DALLAS
05/02/2012

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: April 27, 2012

TO: Norman Stockbridge, M.D.
Director,
Division of Cardiovascular and Renal Products

FROM: Xikui Chen, Ph.D.
Bioequivalence Investigations Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

THROUGH: Sam H. Haidar, Ph.D., RPh
Chief, Bioequivalence Investigations Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations
and
William H. Taylor, Ph.D., DABT
Director (Acting)
Division of Bioequivalence and GLP Compliance (DBGC)
Office of Scientific Investigations (OSI)

SUBJECT: Review of EIR Covering NDA 203-109, Revatio®
(sildenafil) Powder for Oral Suspension 10 mg/mL,
sponsored by Pfizer, Inc.

At the request of the Division of Cardiovascular and Renal Products (DCRP), the Division of Bioequivalence and GLP Compliance (DBGC) conducted an audit of the clinical portion of the following bioequivalence study:

Study A1481293: "A Pivotal Randomized, Open-Label 3-Way Crossover Study to Demonstrate Bioequivalence of the Sildenafil Citrate Powder for Oral Suspension (10 mg/mL) and the Sildenafil Citrate 10 mg Immediate Release (IR) Tablet Relative to the Revatio 20 mg IR Tablet in Healthy Volunteers Under Fasting Conditions"

Clinical Site: Pfizer Clinical Research Unit
Hopital Erasme
Bruxelles, BELGIUM

The inspection of the clinical portion of the study was conducted at Pfizer Clinical Research Unit, Hopital Erasme, Bruxelles, Belgium (March 19-21, 2012). Following the inspection, no Form FDA-483 was issued. Bioequivalence reserve samples were collected from an independent third party (b) (4)

Conclusion:

Following the inspection of the clinical site for study A1481293, no significant findings were observed. In the opinion of this reviewer, data from study A1481293 are acceptable for review.

Xikui Chen, Ph.D.
Bioequivalence Branch, DBGC, OSI

Final Classification:

NAI - Pfizer Clinical Research Unit, Hopital Erasme, Bruxelles,
Belgium
FEI 3007000232

cc:

OSI/Ball/Moreno
OSI/DBGC/Taylor/Haidar/Skelly/Dejernett/Chen
OND/ODE1/DCRP/Brum/Stockbridge
OTS/OCP/DPM/Brar
HFR-NE2530/Murphy
CDER OSI PM TRACK
Draft: XC 4/26/2012
Edit: MFS 4/26/2012
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/s/

XIKUI CHEN
04/27/2012

SAM H HAIDAR
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