DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

WRITTEN REQUEST – AMENDMENT 160

NDA 21-845
IND 63,175

Pfizer Inc.
Attention: Peter Aprile
235 East 42nd Street
New York, NY 10017

Dear Mr. Aprile:

Please refer to your correspondence dated May 3, 2007, requesting changes to the original Written Request dated December 17, 2001, for pediatric studies with sildenafil citrate.

Reference is made to your original submission, IND 63,175, dated August 31, 2001, to the minutes of a meeting between Pfizer and the Agency on July 24, 2001, to the Written Request issued December 17, 2001, to your request to amend the Written Request dated April 24, 2002, to the amended Written Request of June 24, 2002, to minutes of the meeting with you on September 26, 2002, to your request to amend the Written Request dated October 11, 2002, to the amended Written Request of December 20, 2002, to the minutes of a teleconference with you on October 12, 2004, to the minutes of a meeting with you on February 3, 2005, to the minutes of the teleconference with you on August 17, 2005, to the amended Written Request dated November 3, 2005, to your request to amend the Written Request dated December 15, 2005, and to the amended Written Request of September 15, 2006. This amended Written Request supersedes the one of September 15, 2006.

We have accepted your proposed changes and are amending the Written Request. This Written Request contains a mixture of requirements (failure to fulfill these would result in denial of exclusivity) *and* advice. We have highlighted formal requirements to make this distinction clear.

The Food and Drug Administration (FDA) is making a formal Written Request that you conduct the studies outlined below to provide guidance for the use of sildenafil to treat pulmonary arterial hypertension in pediatric patients.

The pediatric age groupings that we have previously suggested for age categorization are:

- Neonates (age less than 1 month)
- Infants and toddlers (age 1 to <24 months)
- Preschool children (age 2 to <6 years)
- School age children (age 6 to Tanner stage 2)
- Adolescents (Tanner stage 3 to 16 years)

Requested Clinical Trials

We are requesting two clinical studies:

1. A controlled trial measuring either clinical events or functional improvement in which oral sildenafil and placebo are each added to standard therapy in pediatric patients age birth to 16 years (infants to adolescents) with primary or secondary pulmonary hypertension. Pharmacokinetic data must also be collected in this study

2. A safety study based on an open treatment phase following the controlled trial.

We also request a summary and analysis of available information, published or unpublished, on the safety of the drug in pediatric patients. Unpublished safety data must be sought from institutions that collect such data as part of pediatric healthcare delivery.

Formulation Issues

Use an age-appropriate formulation in the studies described above. This requirement can be fulfilled by developing and testing a new dosage form for which you will seek approval for commercial marketing. Any new commercially marketable formulation that you develop for use in children must meet Agency standards for marketing. If you demonstrate that reasonable attempts to develop a commercially marketable formulation have failed, then you must develop and test an age-appropriate formulation that can be compounded by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients. Development of a commercially marketable formulation is preferable.

If you cannot develop a commercially marketable formulation age-appropriate formulation, you must provide the Agency with documentation of your attempts to develop such a formulation and the reasons such attempts failed. If we agree that you have valid reasons for not developing a commercially marketable age-appropriate formulation, you must submit instructions for compounding an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using a compounded formulation, the following information must be provided and will appear in the product label upon approval: active ingredients, diluents, suspending and sweetening agents, detailed step-by-step compounding instructions, packaging and storage requirements, and formulation stability information.

Bioavailability of any novel formulation used in the studies must be characterized and, as needed, a relative bioavailability study comparing the approved drug to the age-appropriate formulation can be conducted in adults.

Trial in primary or secondary pulmonary arterial hypertension

The aim of this trial is to provide data on the safety and effectiveness of oral sildenafil when it is added to standard care in the treatment of chronic, symptomatic, primary or secondary pulmonary hypertension. The study must be double-blind. The primary end point must be clinically relevant, such as exercise tolerance, need for rescue therapy, or global assessment by a parent, guardian, or physician. You might consider different end points by age cohort. There would need to be an overall statistical plan that deals, among other things, with the different end points. The primary end point must be assessed over a period of at least 16 weeks. Patients must be given the option of enrollment in an open-label follow-on study with a placebo-controlled withdrawal study after 1 year, again assessing exercise tolerance or need for rescue therapy. As an alternative, you may provide information on the durability of the effects of treatment from a study of pulmonary hypertension in adults, but such a study would need to meet statistical considerations criteria described in this Written Request. If you believe that even a short placebo withdrawal study is unethical because of the potential for rapid and irreversible harm that cannot be reliably prevented by close monitoring, you should provide all available evidence of such potential harm and seek to have this requirement removed from the Written Request.

For the study, background therapy should conform to local standards of care.

Safety data must include assessment of possible relationship of observed hypotension to use of concomitant medication. Comprehensive vision testing must be performed after 16 weeks and 1 year of study.

There must be an independent data monitoring committee (DMC) that assesses ongoing trial results. Except in cases where immediate action is required to protect the health of subjects, DMC recommendations to stop or to modify the study must be discussed with FDA prior to your making any final decision to stop or modify the

study.

Dose groups
The appropriate dose range in children probably cannot be predicted without better characterization of the dose-response relationship in adults. Your study must include at least 3 sildenafil treatment arms with doses separated by factors of about 3. The lowest dose in the pediatric study must be one that, on a weight-adjusted basis, would be expected to produce half or less of the maximal effect in adults.

Long-term safety
Patients enrolled in the open-label follow-on study must have safety (adverse events), growth (change in head circumference[1], weight, and length or height), and development (milestones, school performance, or neurocognitive testing) assessed at baseline and at one year. Measurements must be standardized across centers.

Statistical considerations
Since there is now an approved use of sildenafil to treat pulmonary arterial hypertension in adults, an observed effect on the primary end point significant at $p<0.05$ would support approval for use in children on the basis of a single study. Analysis should be pairwise with an analysis plan to control alpha error rate at $\alpha=0.05$ (two-sided). The study must be powered to be able to detect a "clinically meaningful" treatment benefit on the primary end point. For the purpose of satisfying the Written Request, a clinically meaningful treatment benefit is considered to be a 10% reduction in event rate or a 10% increase in exercise ability.

This requires you to show that if the true treatment effect for one of the treatment groups were minimally "clinically meaningful", the pre-planned analysis would have at least 90% power to infer that at least one dose or the high dose is significantly different from placebo. You may wish to obtain an estimate of variability to use in power calculations from a preliminary study. However, to ensure that the study is adequately powered, you must obtain an estimate of variability from an interim analysis and then follow a pre-specified rule to adjust the sample size to achieve the specified target power. This interim analysis must be performed at >90% of initially planned enrollment. Options for estimating variability are (1) a blinded, pooled analysis of all groups, (2) a blinded analysis of one group, or (3) a partially unblinded analysis of variability within each group (performed by an independent third party). No alpha-spending adjustment is required for this interim analysis to assess the variability, but if you want to perform an efficacy assessment at this or some other interim analysis, an appropriate alpha adjustment is required.

In the course of conducting these studies, you may discover evidence to indicate that there are unexpected safety concerns, unexpected benefits, or other unexpected, useful results. In the event of such findings, it may be possible to revise the requirements of the Written Request. If you believe this to be the case, you must contact the Agency to seek an amendment. It is solely the Agency's discretion whether it is appropriate to issue an amendment under these circumstances.

Pharmacokinetic Studies
Data must be collected with respect to sildenafil and any metabolites that make substantial contributions to its efficacy or toxicity. For the parent and each metabolite followed, the data collected must provide estimates of the exposure (AUC), half-life, clearance, volume of distribution, C_{max}, and t_{max} in not fewer than 6 pediatric patients in each of the age groups covered by the clinical trial.

Some or all of the pharmacokinetic data may be obtained from patients in the effectiveness trial or from safety studies, using traditional or sparse sampling to estimate pharmacokinetic parameters.

Safety Data
Independent of considerations relating to the establishment of effectiveness, your study must enroll no fewer

[1] Up to age of 3 years.

than 200 patients (including placebo) to provide safety data. In addition, the safety evaluation in children must include formal analyses of available published and unpublished safety data. Unpublished safety data may come from institutions or organizations that collect such data in the course of delivering healthcare to children.

Labeling Changes
The results of the completed study may be used in the labeling of your drug products to add a new indication for use of sildenafil in the treatment of pulmonary arterial hypertension in pediatric patients and to provide information on appropriate dosing for this use. The decision to grant a new indication will depend on the overall risk-benefit assessment, and other labeling changes might be appropriate even if no new indication is granted.

Reports
Full study reports of the requested trials not previously submitted to the Agency addressing the issues outlined in this request, including full analysis, assessment, and interpretation, must be submitted according to applicable guidance. In addition, the reports are to include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients should be categorized according to the following designations for race: American Indian or Alaskan Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, or White. For ethnicity, one of the following designations should be used: Hispanic/Latino or Not Hispanic/Latino.

Notice of Intent
In accordance with the Best Pharmaceuticals for Children Act, section 4(a), within 180 days of receipt of this Written Request, you must notify the Agency of your intention to act on the Written Request. If you agree to the request, you must indicate when you expect the studies will be initiated.

Submit the protocol for the above study to an investigational new drug application (IND) and clearly mark your submission, "**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY**" in large font, bolded type at the beginning of the cover letter of the submission. You should identify any discrepancies between your proposed protocol and the Written Request. If there are differences, it is your responsibility to seek an amendment to the Written Request.

Notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Clearly mark such a submission "**PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES"** in large-font, bolded type at the beginning of the cover letter of the submission.

Dissemination of Pediatric Information
In accordance with the Best Pharmaceuticals for Children Act, Section 9, if a pediatric supplement is submitted in response to a Written Request and is filed by FDA, FDA will make public a summary of the medical and clinical pharmacology reviews of the studies conducted. This disclosure will occur within 180 days of submission and will apply to all supplements submitted in response to a Written Request and filed by FDA, regardless of:

- whether or not the response to the Written Request is complete,
- whether the supplement is pending or withdrawn,
- whether the supplement is approved, approvable, or not approvable, and
- whether or not exclusivity is granted.

FDA will post these review summaries on the FDA website at http://www.fda.gov/cder/pediatric/summaryreview.htm and it will publish in the Federal Register a notice of availability.

As required by the Food and Drug Modernization Act and the Best Pharmaceuticals for Children Act, you must register certain clinical trials involving your drug product in the Clinical Trials Data Bank (http://clinicaltrials.gov). If your drug is intended for the treatment of a serious or life-threatening disease or condition and you are conducting trials to test its effectiveness, then you must register these trials in the Data

Bank. Although not required, we encourage you to register effectiveness trials for non-serious diseases or conditions as well as non-effectiveness trials for all diseases or conditions, whether or not they are serious or life-threatening. Additional information on registering your clinical trials, including the required and optional data elements, can be found in the FDA Draft Guidance for Industry, "Information Program on Trials for Serious or Life-Threatening Diseases or Conditions", available at the Protocol Registration System (PRS) Information Site (http://prsinfo.clinicaltrials.gov).

Timeframe

Reports on these studies must be submitted to the Agency on or before December 28, 2011. Remember that pediatric exclusivity attaches only to existing patent protection or exclusivity that has not expired at the time you submit your reports of the studies in response to this Written Request.

Reports on these studies must be submitted as a supplement to your approved NDA with the proposed labeling changes you believe would be warranted based on the data derived from this study. When submitting the reports, clearly mark your submission "**SUBMISSION OF PEDIATRIC STUDY REPORT – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED"** in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Also send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger to:

Director
Office of Generic Drugs
HFD-600, Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked "**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

None of the following can be construed to alter the terms of this Written Request or to establish that your activities meet the terms of the Written Request:

- Verbal communications,
- Informal written communications (including e-mail), or
- The lack of comment by the Agency regarding any of the your verbal or written communications.

Although not currently required, we request that study data be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the document "Study Data Specifications," which is posted on the FDA website at http://www.fda.gov/cder/regulatory/ersr/studydata-v1.1.pdf and referenced in the FDA Guidance for Industry, Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications http://www.fda.gov/cder/guidance/7087rev.pdf.

We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits to the pediatric population.

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

Sincerely,

{See appended electronic signature page}

Robert Temple, M.D.
Director
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/

Robert Temple

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