DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

WRITTEN REQUEST - AMENDMENT #6

NDA 21845

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

Dear Ms. McKay:

Please refer to your correspondence dated August 18, 2010, requesting changes to the amended Written Request dated May 30, 2007, for pediatric studies with sildenafil. We also make reference to the FDA Center for Drug Evaluation and Research Cardiovascular and Renal Drugs Advisory Committee meeting held on July 29, 2010. Based on these discussions and our analysis of data for drugs approved to treat pulmonary arterial hypertension, using a clinically relevant endpoint of pulmonary vascular resistance index (PVRI) is acceptable.

We have reviewed your proposed changes and are amending the below-listed sections of the Written Request. All other terms stated in our Written Request issued on December 17, 2001, and as amended on June 24, 2002, December 20, 2002, November 3, 2005, September 15, 2006, and May 30, 2007, remain the same.

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. (Text added is underlined. Text deleted is ~~strikethrough~~.)

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~~ hemodynamics or exercise when feasible in which oral sildenafil and placebo are each

added to standard therapy in pediatric patients ages 1 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.

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~~ measure of effectiveness must be ~~clinically relevant, such as exercise tolerance, need for rescue therapy, or global assessment by a parent, guardian, or physician~~ change from baseline in pulmonary vascular resistance index (PVRI). Exercise, as a secondary endpoint, must be measured in patients able to perform the test. ~~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~~ Effectiveness must be assessed over a period of at least 16 weeks, with no fewer than 35 subjects per treatment group evaluable for the analysis of PVRI, of whom ~~overall~~ no less than 25% of the overall population are to be <7 years old at enrollment. Patients must be given the option of enrollment in an open-label ~~follow-on~~ safety 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 (consisting of external examination, assessment of visual acuity, assessment of color vision, and funduscopy – as age appropriate) 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

The observed effect on the primary endpoint, significant at $p<0.05$ would support the approval for use in children on the basis of a single study.

PVRI expressed as percentage of baseline should be used to contrast the individual sildenafil dose groups (low, medium, and high groups) and the sildenafil combined group with the placebo treatment group. The analysis should explore the covariates of PAH etiology, weight groups, and capability of performing the exercise capacity test (yes/no) and treatment. For those subjects who did not complete the trial, an informative missing imputation method should be used and explicitly described.

Other efficacy endpoints (e.g., including exercise capacity, WHO Functional class, and hemodynamics) and safety, should be analyzed descriptively on the All-Randomized analysis set.

The submitted report must include an analysis to describe the relationship between change from baseline in PVRI and change from baseline in exercise capacity for both adult and pediatric patients who are able to exercise.

~~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

[1] Up to age of 3 years.

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.

~~**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.~~

Additional requirements

Please note that, as detailed below, and in accordance with the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007, certain additional requirements now apply to this Written Request. These additional requirements are as follows:

- In accordance with section 505A(e)(2), if:

  1) you develop an age-appropriate formulation that is found to be safe and effective in the pediatric population(s) studied (i.e., receives approval);
  2) the Agency grants pediatric exclusivity, including publishing the exclusivity determination notice required under section 505A(e)(1) of the Act; and
  3) you have not marketed the formulation within one year after the Agency publishes such notice,

  the Agency will publish a second notice indicating you have not marketed the new pediatric formulation.

- Under section 505A(j) of the Act, regardless of whether the study(ies) demonstrate that sildenafil is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the study(ies).

- In accordance with section 505A(k)(1) of the Act, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following:

  - the type of response to the Written Request (i.e., complete or partial response);
  - the status of the application (i.e., withdrawn after the NDA or supplement has been filed or pending);
  - the action taken (i.e., approval or complete response); or
  - the exclusivity determination (i.e., granted or denied).

If your trial is considered an "applicable clinical trial" under section 402(j)(1)(A)(i) of the Public Health Service Act (PHS Act), you may be required to comply with the provisions of section 402(j) of the PHS Act with regard to registration of your trial and submission of trial results. Additional

information on these requirements and the submission of this information can be found at www.ClinicalTrials.gov.

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.

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.~~

~~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 or as a new 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 (240-276-9327) or messenger to:

Director
Office of Generic Drugs
HFD-600, Metro Park North II
7519 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.

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

Sincerely,

{See appended electronic signature page}

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Attachment (Complete Clean Copy of Written Request as amended)

NDA 21845 **WRITTEN REQUEST - AMENDMENT #6**

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

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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.

Requested Clinical Trials
We are requesting two clinical studies:

1. A controlled trial measuring hemodynamics or exercise when feasible in which oral sildenafil and placebo are each added to standard therapy in pediatric patients ages 1 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, 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 measure of effectiveness must be change from baseline in pulmonary vascular resistance index (PVRI). Exercise, as a secondary endpoint, must be measured in patients able to perform the test. Effectiveness must be assessed over a period of at least 16 weeks, with no fewer than 35 subjects per treatment group evaluable for the analysis of PVRI, of whom no less than 25% of the overall population are to be <7 years old at enrollment. Patients must be given the option of enrollment in an open-label safety study.

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 (consisting of external examination, assessment of visual acuity, assessment of color vision, and funduscopy – as age appropriate) 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

Long-term safety
Patients enrolled in the open-label follow-on study must have safety (adverse events), growth (change in head circumference[2], 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
The observed effect on the primary endpoint, significant at $p<0.05$ would support the approval for use in children on the basis of a single study.

PVRI expressed as percentage of baseline should be used to contrast the individual sildenafil dose groups (low, medium, and high groups) and the sildenafil combined group with the placebo treatment group. The analysis should explore the covariates of PAH etiology, weight groups, and capability of performing the exercise capacity test (yes/no) and treatment. For those subjects who did not complete the trial, an informative missing imputation method should be used and explicitly described.

Other efficacy endpoints (e.g., including exercise capacity, WHO Functional class, and hemodynamics) and safety, should be analyzed descriptively on the All-Randomized analysis set.

The submitted report must include an analysis to describe the relationship between change from baseline in PVRI and change from baseline in exercise capacity for both adult and pediatric patients who are able to exercise.

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 weight 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
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.

[2] Up to age of 3 years.

Additional requirements
Please note that, as detailed below, and in accordance with the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007, certain additional requirements now apply to this Written Request. These additional requirements are as follows:

- In accordance with section 505A(e)(2), if:

  4) you develop an age-appropriate formulation that is found to be safe and effective in the pediatric population(s) studied (i.e., receives approval);
  5) the Agency grants pediatric exclusivity, including publishing the exclusivity determination notice required under section 505A(e)(1) of the Act; and
  6) you have not marketed the formulation within one year after the Agency publishes such notice,

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- Under section 505A(j) of the Act, regardless of whether the study(ies) demonstrate that sildenafil is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the study(ies).

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If your trial is considered an "applicable clinical trial" under section 402(j)(1)(A)(i) of the Public Health Service Act (PHS Act), you may be required to comply with the provisions of section 402(j) of the PHS Act with regard to registration of your trial and submission of trial results. Additional information on these requirements and the submission of this information can be found at www.ClinicalTrials.gov.

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.

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

Sincerely,

{See appended electronic signature page}

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
06/07/2011