DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-895

Pfizer
Attention: Ms. Melinda Rudnicki
235 East 42nd Street
New York, NY 10017

Dear Ms. Rudnicki:

The Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug and Cosmetic Act (the Act), to obtain needed pediatric information for sildenafil. We request that you submit information from trials in pediatric patients as described below.

Reference is made to your original submission to 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 April 24, 2002, to the amended Written Request of June 24, 2002, to minutes of the meeting with you on September 26, 2002, and to your request to amend the Written Request October 11, 2002. This amended Written Request supercedes the one of June 24, 2002.

At present there is no indication for use of sildenafil in any pediatric population nor is there an indication for any form of pulmonary hypertension, pediatric or adult. There is certainly rationale that suggests sildenafil might be useful in managing pulmonary hypertension in pediatric populations. Thus, the Food and Drug Administration (FDA) is hereby making a formal Written Request that you conduct studies (as outlined below).

Pediatric age grouping that we have previously suggested for age categorization are:

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

Formal pharmacokinetic studies in each age group are not necessary since population pharmacokinetic analyses of blood samples from the trials outlined below can suffice, if appropriately designed and executed.

Strategy of Clinical Trials

The requested data will provide guidance for the use of sildenafil to treat pulmonary hypertension in pediatric patients. These data will be derived from

- an outcome trial in which intravenous sildenafil and placebo are each added to standard therapy in young pediatric patients with post-surgical pulmonary hypertension,

- an outcome trial in which oral sildenafil and placebo are each added to standard therapy in pediatric patients with persistent pulmonary hypertension of the newborn (PPHN),

- an outcome trial in which oral or intravenous sildenafil and placebo are each added to standard

therapy in older pediatric patients with primary or secondary pulmonary hypertension, and

- safety data derived from the controlled trials and open treatment phases following the trials, with a summary and analysis of available information, published or unpublished, on the safety of the drug in pediatric patients. Unpublished safety data should be sought from institutions that collect such data as part of pediatric healthcare delivery.

Pediatric Subgroups

The study in PPHN should be conducted with term or near-term newborns, and the study of primary and secondary pulmonary hypertension should include at least 30% of patients under the age of 6 years, at least 20% of patients age 6 years to Tanner stage 2, and at least 20% of patients Tanner stage 3 to 16 years.

The study of post-surgical pulmonary hypertension should be conducted among patients under one year of age. You may, at your discretion, include patients between 1 year and 17 years old, and the interpretability decision will be based on the full population. However, no more than 25% of patients should be >1 year old.

Formulation Issues

Formulations should be well characterized and appropriate to the age and clinical setting. Any unapproved formulation will need to be supported by a study of the relative bioavailability of sildenafil; these studies may be conducted in adults. If you cannot develop a potentially marketable formulation, you will need to document the attempt to do so, and you will need to obtain an agreement with the Agency regarding the adequacy of the formulation you use. Full study reports of any relative bioavailability studies should be submitted to the Agency.

Controlled Outcome Trials

Trial designs

Post-surgical pulmonary hypertension. The aim of this trial should be to provide data on the safety and effectiveness of intravenous sildenafil in the treatment or prevention of pulmonary hypertension following corrective cardiac surgery for congenital defects. This trial could enroll an at-risk population to study prevention of pulmonary hypertension (prophylaxis), or it could enroll a population manifesting pulmonary hypertension at the time of randomization (treatment), but prophylaxis and treatment populations should not be included in the same study. The study should be double-blind. The primary end point should be clinically relevant, such as need for rescue therapy or time on ventilator.

Persistent pulmonary hypertension of the newborn. The aim of this trial should be to provide data on the safety and effectiveness of intravenous sildenafil in the treatment of PPHN. If the study permits use of inhaled nitric oxide, randomization should be stratified based on its use. The study should be double-blind. The primary end point should be clinically relevant, such as need for rescue therapy.

Primary or secondary pulmonary hypertension. The aim of this trial should be to provide data on the safety and effectiveness of oral or intravenous sildenafil in the treatment of chronic, symptomatic, primary or secondary pulmonary hypertension. The study should be double-blind. The primary end point should be clinically relevant, such as exercise tolerance, need for rescue therapy, or global assessment by a parent, guardian, or physician.. The sponsor might consider different end points by age cohort, with some overall statistical plan. The primary end point should be assessed over a period of at least 16 weeks. Patients should be enrolled in an open-label follow-on study with a placebo-controlled withdrawal 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 be expected to meet interpretability criteria

described in this Written Request.

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

Safety data should be collected in each study to enable analyses relating observed hypotension to use of concomitant medication. Comprehensive vision testing should be performed in the study of primary and secondary pulmonary hypertension after 16 weeks and 1 year of study.

If there is an independent data monitoring committee that assesses ongoing results, stopping rules for benefit and adverse effects should be developed.

Dose groups

All of the studies should be parallel and placebo-controlled. Each study should include at least three sildenafil treatment arms with doses separated by factors ≤3 and spanning at least the range expected to produce 50 to 90% PDE5 inhibition at peak.

Long-term safety

Patients in the trial(s) of clinical efficacy should be enrolled in an open-label follow-on study with 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.

Statistical considerations

A $p<0.01$ favoring sildenafil will be necessary to support approval of any of the three possible new indications for use in children on the basis of a single study. Alternatively, achieving a $p<0.05$ favoring sildenafil in two or three studies will be considered adequate support for those indications, because of the degree of overlapping pathophysiology. See *Interpretability* below for further statistical considerations. Please submit your proposed statistical analyses as an amendment to this request, following the procedure described at the end of this letter for submitting proposed changes.

Pharmacokinetic Trials

Data should be collected with respect to sildenafil and any metabolites that make substantial contributions to its efficacy and/or toxicity. For the parent and each metabolite followed, the data collected should 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 various age groups.

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

Safety Data

Independent of considerations relating to the establishment of effectiveness, the three studies together should enroll no fewer than 200 patients (including placebo) to provide safety data. In addition, the safety evaluation in children should 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.

[1] Up to age of 3 years.

Labeling Changes

The results of the completed studies may be used in the labeling of your drug products to add new indications for and information allowing proper dosing for the safe and effective use of sildenafil in the treatment of pulmonary hypertension in pediatric patients. 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.

Interpretability

You are being asked to perform studies adequate to obtain three new indications in children. The terms of the Written Request will be considered satisfied only if the data you obtain for each indication allows a clear determination whether or not sildenafil is effective. Thus, the results for each study must :

- favor sildenafil at $p<0.05$, or
- demonstrate that the study was powered to find a "clinically meaningful" treatment benefit on the primary end point.

The latter requires you to show by a post-hoc power analysis based on the observed variability, that if the true treatment effect were "clinically meaningful", the 95% confidence interval would have excluded zero treatment effect with ≥90% power. You may wish to obtain an estimate of variability from a preliminary study, or you may obtain a penalty-free estimate of variability from a pooled interim analysis (without unblinding) and then follow a pre-specified rule to adjust the sample size.

For the purpose of satisfying the interpretability criteria of this Written Request, a clinically meaningful treatment benefit is considered to be a 10% reduction in event rate or a 10% increase in exercise ability.

If the data from an ongoing study were to suggest that it should be discontinued for safety reasons, the sponsor should contact the Division to discuss the terms of the Written Request.

Reporting

Full study reports of the requested trials, including full analysis, assessment, and interpretation, should be submitted in the usual format. All data should be submitted in machine-readable form according to applicable guidance.

Reports of the above studies must be submitted to the Agency on or before 19 June 2007. Remember that pediatric exclusivity attaches only to existing patent protection or exclusivity that has not expired at the time you submit your reports of studies in response to this Written Request.

Submit protocols for the above studies 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 or to seek a Written Agreement.

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.

Reports of the studies should 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 these studies. When submitting the reports, clearly mark your submission "**SUBMISSION OF PEDIATRIC STUDY REPORTS – 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.

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 contact:

Ms. Melissa Robb
Regulatory Health Project Manager
(301) 594-5313

Sincerely yours,

Rachel Behrman, M.D., MPH
Deputy 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/

Rachel Behrman

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