



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-895

Pfizer

Attention: Ms. Rita Wittich
235 East 42nd Street
New York, NY 10017

Dear Ms. Wittich:

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, and to the minutes of a meeting between Pfizer and the Agency on July 24, 2001.

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 primary pulmonary hypertension of the newborn (PPHN),
- an outcome trial in which oral 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 may be obtained from institutions that collect such data as part of pediatric healthcare delivery.

Pediatric Subgroups

We expect that the study of post-surgical pulmonary hypertension will be conducted among patients under one year of age, that the study in PPHN will be conducted with term or near-term newborns, and that the study of primary and secondary pulmonary hypertension will include approximately equal numbers of patients (20-30%) in the age groups of 1 to 2 years, 2 to 6 years, 6 years to Tanner stage 2, and Tanner stage 3 to 16 years.

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.

Primary 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. The study could be conducted in a population that has failed nitric oxide or it could be conducted in centers where nitric oxide is not part of the standard of care. 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 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 or need for rescue therapy. 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.

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.

There should be independent data monitoring committees that assess 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 more than one sildenafil treatment arm with doses separated by factors ≤ 3 and spanning at least the range expected to produce 10 to 90% PDE5 inhibition at peak. The study in older children receiving oral sildenafil should also include arms for once- and twice-daily dosing.

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 circumference¹, 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 of the three studies will be considered adequate support for both, 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 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.

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
- exclude a 10% risk reduction for the primary end point at p<0.05.

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 14 December 2005. 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.

¹ Up to age of 3 years.

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. Zelda McDonald
Regulatory Health Project Manager
(301) 594-5333

Sincerely yours,

Rachel Behrman, M.D., MPH
Deputy Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Rachel Behrman
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