DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

WRITTEN REQUEST

IND 58,994

Pfizer, Inc.
50 Pequot Avenue
New London, CT 06320

Attention: Perc W. Reeve, D.V.M.
Director, Regulatory Affairs
Worldwide Regulatory Affairs and Quality Assurance

Dear Dr. Reeve:

Reference is made to your December 21, 2006, Proposed Pediatric Study Request submitted to IND 58,994 for varenicline.

To obtain needed pediatric information on varenicline, 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), that you submit information from the following studies.

Background Comments on Pediatric Smoking Cessation

The Agency finds that it is not possible to extrapolate efficacy data on smoking cessation in adults to support an indication of smoking cessation in the pediatric population. Studies demonstrate that non-pharmacologic smoking cessation methods that are effective in adults are not effective in adolescents. Furthermore, pharmacologic therapies are aimed at treating addiction to cigarettes and there is little information on the appropriate identification of addiction in adolescent smokers, who are believed to smoke for a variety of reasons besides addiction to nicotine. Accordingly, efficacy data are needed to support a smoking cessation indication in the adolescent population. One objective of the development program for smoking cessation in adolescents is to develop a method of identifying patients who have the same disorder seen in adults (tobacco addiction), and are likely to respond to the same pharmacologic therapies that are effective in adults. It is our expectation that treatments effective in adults would be effective in a properly-identified population of adolescents with tobacco addiction. Therefore, we consider that a single efficacy study with positive results in a properly-identified population of adolescents, along with confirmatory evidence from other sources, such as adult efficacy data, should suffice to support a new pediatric indication for varenicline.

In addition, an adolescent smoking cessation program will need to include pharmacokinetic (PK) and safety information in the relevant age group. For pediatric smoking cessation, we consider the relevant age group to include adolescents (ages 12 – 16).

Specific Study Requirements for Development Program in Smoking Cessation
The specific study requirements are described below.

Indication: Use as an aid to smoking cessation treatment.

Study 1: Pharmacokinetics and Tolerability
Objective/Rationale:

- To determine the multiple-dose pharmacokinetics of varenicline following administration of immediate-release tablets in adolescent patients. The results of this study will aid in the selection of the dosing regimen for future efficacy and safety evaluations in adolescent smokers.
- To determine the adverse event profile of varenicline in adolescent patients during two weeks of treatment with varenicline and to determine whether there is any group (defined by age, weight, gender, or other characteristic) for whom varenicline is so poorly tolerated that its utility as an aid to smoking cessation treatment should not be evaluated in that group.

Study Design: We acknowledge that you have already conducted a single-dose PK study in adolescents and that the results were submitted with the original NDA. Conduct a multiple-dose (steady-state) pharmacokinetic study of varenicline in various doses that may be more appropriate for smaller patients than the currently approved adult dose. The protocol for this study must specify a maximum allowable dose per kilogram body weight. Participants may be randomized to any dose that does not exceed the maximum based on body weight.

A sufficient number of blood samples must be drawn in order to capture the varenicline PK profile. The total volume of blood drawn and the PK methods to be employed in the data analysis must be determined *a priori* and stated in the protocol. If sparse sampling methods, i.e., population pharmacokinetics, are employed, blood samples should be dispersed throughout the profile to ensure proper parameter estimation.

The results obtained from this PK study must be utilized in the design of an efficacy study.

Study Endpoints:

- Descriptive statistics must be derived employing traditional or population pharmacokinetic methods for pharmacokinetic parameters of varenicline such as C_{max}, C_{min}, t_{max}, $t_{1/2}$, AUC and accumulation index, elimination rate constant and clearance. Dose-proportionality between the doses tested must be assessed, and the results obtained in adolescents in this study compared with the historical results obtained from adult trials.
- Assessment of tolerability and adverse event profile.

Inclusion/Exclusion Criteria: Male and female smokers between the ages of 12 and 16 years, inclusive. A minimum of 3 patients per treatment group must be 13 years of age or younger, with adequate representation of females between treatment groups.

Number of Patients to be Studied: A minimum of 12 adolescents per treatment group must be studied to adequately characterize the multiple-dose pharmacokinetics and tolerability of varenicline at the doses chosen. As mentioned above, if sparse sampling methods, i.e., population pharmacokinetics, are employed, the number of patients must be determined *a priori* to ensure proper PK parameter estimation.

Study 2: Dose Ranging Efficacy/Safety
Objective/Rationale: The objectives of this trial are

- to establish that varenicline, as part of a smoking cessation program, is effective in achieving and maintaining smoking abstinence for at least one month in tobacco-addicted adolescents;
- to determine a safe and effective dose; and
- to document the ability of treating physicians to select appropriate patients.

Study Design: The trial will be a randomized, double-blind, placebo-controlled, dose-ranging, parallel-group study. Treatment duration should be 12 weeks, with 1 week of medication prior to the quit day and 11 weeks of treatment during the quit attempt. The protocol must include follow-up visits at monthly intervals for an additional nine months following the end of the treatment phase. The dosing regimen should be based on results of previous PK studies. The data in adults showed efficacy at doses lower than the 1 mg b.i.d. dose recommended in labeling, and a clear dose-dependency of adverse events. It is possible that adolescents may be differently affected by adverse events, more prone to drop out due to adverse events, or otherwise may have a different risk/benefit ratio from adults. Therefore, it is necessary to study both a dose which targets a similar exposure to the adult-recommended dose and at least one dose that is lower.

You will need to develop a means for determining reliable criteria for appropriate patient selection of tobacco-addicted adolescents so that young smokers who are not addicted will not be recruited, and so that labeling can convey these criteria to treating physicians across the different specialties who may wish to use the drug in this population. A survey to determine the knowledge, attitudes, and practices of treating physicians with respect to smoking cessation may be helpful to you in designing these criteria. You will also need to develop or identify an age-appropriate counseling and support program to be included in these studies. Because varenicline is intended to be used in conjunction with appropriate supportive counseling and educational materials, an overall smoking cessation program designed to effectively motivate adolescent smokers to remain abstinent from cigarettes must be an integral component of the clinical trial design.

Clinical Endpoints
Efficacy: The primary outcome measure will be abstinence from smoking for a period of 4 consecutive weeks, based on weekly self-reporting of smoking behavior and assessment of objective biochemical markers during the last 4 weeks of treatment (Weeks 9, 10, 11, and 12), using meaningful, validated markers of cigarette smoking that can be demonstrated as sensitive and reliable indicators of tobacco use in the pediatric population.

Safety: The protocol must include collection of information about adverse events at appropriate intervals during treatment and follow-up, and patients should be followed to the resolution of any

treatment-emergent events. Adverse events that occur during treatment or follow-up must be recorded and submitted as part of the study report. The circumstances surrounding any deaths, discontinuations, and serious adverse events must be adequately documented and transmitted within the study report.

PK data must also be collected to broaden an understanding of the pharmacokinetic variables and the relationship between pharmacokinetic variables, safety, and efficacy endpoints.

Inclusion/Exclusion Criteria: To be eligible to participate, patients must be cigarette smokers desiring to quit, who meet the selection criteria for tobacco addiction. Patients must be recruited from age groups 12 – 16, inclusive, unless the results of Study 1 reveal that varenicline is so poorly tolerated in a group of patients that its use should not be explored. In that case, patients must be recruited from the groups that appear to tolerate the medication.

Number of Patients to be Studied: At a minimum, a sufficient number of patients must be enrolled to detect a 20 percent attributable "quit rate" between any two groups with power of 0.8 and significance level of 0.05 (two-sided). Quit rate is defined as the proportion of patients meeting the criteria for continuous abstinence during Weeks 9, 10, 11, and 12 of treatment. Note that this requirement describes the minimum size of the trial and should not be construed to establish a minimum attributable quit rate necessary to demonstrate efficacy.

Analysis of the Data to be Performed:

- A detailed statistical analysis plan is required prior to beginning enrollment and must accompany the study protocol submission.
- Demographic and safety data must be tabulated and a descriptive analysis of safety data must be provided.
- Exposure/response analyses of efficacy and safety must be conducted and reported.

Drug Information:
Formulation: oral tablet

Labeling that may result from the studies:
Appropriate sections of the label may be changed to incorporate the findings of the studies.

Format of reports to be submitted: Full study reports not previously submitted to the Agency addressing the issues outlined in this request with full analysis, assessment, and interpretation. In addition, the reports are to include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the studies should be categorized using one of the following designations for race: American Indian or Alaska 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.

Timeframe for submitting reports of the studies: Reports of the above studies must be submitted to the Agency on or before February 10, 2011. Please keep in mind 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.

Response to Written Request: As per the Best Pharmaceuticals for Children Act, section 4(A), within 180 days of receipt of this Written Request you must notify the Agency as to your intention to act on the Written Request. If you agree to the request then you must indicate when the pediatric studies will be initiated.

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. Notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Clearly mark your 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 New Drug Application (NDA) or 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, please 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. Please also send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger, to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

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

1. the type of response to the Written Request (complete or partial);
2. the status of the supplement (withdrawn after the supplement has been filed or pending);
3. the action taken (i.e. approval, approvable, not approvable); or
4. the exclusivity determination (i.e. granted or denied).

FDA will post the medical and clinical pharmacology review summaries on the FDA website at http://www.fda.gov/cder/pediatric/Summaryreview.htm and publish in the *Federal Register* a notification of availability.

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.

As required by the Food and Drug Modernization Act and the Best Pharmaceuticals for Children Act, you are also responsible for registering certain clinical trials involving your drug product in the Clinical Trials Data Bank (http://clinicaltrials.gov & http://prsinfo.clinicaltrials.gov/). If your drug is intended for the treatment of a serious or life-threatening disease or condition and you are conducting clinical 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 and the FDA Draft Guidance for Industry, "Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions," is available at the Protocol Registration System (PRS) Information Site http://prsinfo.clinicaltrials.gov/.

If you have any questions, call Dominic Chiapperino, Regulatory Project Manager, at 301-796-1183.

Sincerely,

{See appended electronic signature page}

Curtis Rosebraugh, MD, MPH
Deputy Director
Office of Drug Evaluation II
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/

Curtis Rosebraugh
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