DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021928

REVISED WRITTEN REQUEST
AMENDMENT #2

Pfizer, Inc.
235 East 42nd Street
New York, NY 10017

Attention: Lilya I. Donohew, Ph.D.
Senior Director, Worldwide Regulatory Affairs

Dear Dr. Donohew:

Please refer to your correspondence dated December 18, 2012, requesting changes to FDA's June 12, 2007, Written Request for pediatric studies for varenicline.

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 June 12, 2007, and as amended on June 2, 2010, remain the same. (Text added is underlined. Text deleted is ~~strikethrough~~.)

Study 2: Dose-Ranging Efficacy/Safety

Timeframe for submitting reports of the studies: ~~Reports of the above studies must be submitted to the Agency on or before October 15, 2014.~~

Reports of the above studies must be submitted to the Agency on or before April 15, 2016.

For ease of reference, a complete copy of the Written Request, as amended, is attached to this letter.

Reports of the studies that meet the terms of the Written Request dated June 12, 2007, as amended by this letter and by the previous amendment dated June 6, 2010, must be submitted to the Agency on or before April 15, 2016, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

Submit reports of the studies as a supplement to an approved NDA with the proposed labeling changes you believe are 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. In addition, send a copy of the cover letter of your submission, via fax (240-276-9327) or messenger, to the Director, Office of Generic Drugs, HFD-600, Metro Park North IV, 7519 Standish Place, Rockville, MD 20855-2773.

If you wish to discuss any amendments to this Written Request, submit proposed changes and the reasons for the proposed changes to your application. Clearly mark submissions of proposed changes to this request **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. We will notify you in writing if we agree to any changes to this Written Request.

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 studies demonstrate that varenicline is safe and effective, or whether such study results are inconclusive in the studied pediatric population or subpopulation, the labeling must include information about the results of the studies.

- 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 reports. 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 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.

If you have any questions, contact Ayanna Augustus, Ph.D., Regulatory Project Manager, at ayanna.augustus@fda.hhs.gov or (301)-796-3980.

Sincerely,

{See appended electronic signature page}

Curtis J. Rosebraugh, M.D., M.P.H.
Director
Office of Drug Evaluation II
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE(S):
Complete Copy of Written Request as Amended

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.

Indication: Use as an aid to smoking cessation treatment.

Study 1: Pharmacokinetics and Tolerability

- ***Type of study*:**
  We acknowledge that you have already conducted a single-dose PK study in adolescents and that the results were submitted with the original NDA. This study will be 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 1 mg BID. 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.

- ***Objectives of study****:*
  1. 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.
  2. 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 (as 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.

- ***Age group in which study will be performed*****:**
  Male and female smokers between the ages of 12 and 16 years, inclusive. The number of smokers should be evenly distributed between genders and generally well distributed across the age and weight range.

- ***Study endpoints:***
  1. 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.

  2. Assessment of tolerability and adverse event profile.

- ***Statistical information, including power of study and statistical assessments:***
  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 for population pharmacokinetics analysis are employed, the number of patients must be determined *a priori* to ensure proper PK parameter estimation.

Study 2: Dose-Ranging Efficacy/Safety

- ***Type of study*****:**
  The trial will be a randomized, double-blind, placebo-controlled, parallel-group, dose-ranging efficacy and safety study. The treatment duration will be 12 weeks, which includes a titration period of at least one week of medication prior to the quit day. The protocol must include follow-up contacts at pre-specified intervals for an additional nine months after the treatment phase. The follow-up can consist of clinic visits or other forms of contact with the patients (phone, electronic communication) to obtain the long-term efficacy and safety data. The total duration of the study will be one year.

To be eligible to participate, patients must be cigarette smokers desiring to quit, who meet the selection criteria for tobacco addiction. Smokers who are not addicted should not be enrolled, and the determination of eligibility should be based on screening methods that can be employed in the clinical setting. The protocol should include documentation of the proportion of potential subjects who are deemed ineligible for participation due to not meeting the criteria for addiction using the methods in the protocol.

The dosing regimen must be based on results of previous PK studies. The data in adults showed efficacy at doses lower than the 1 mg BID 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 that targets a similar exposure to the adult-recommended dose and at least one dose that is lower. You will need to develop or identify an age-appropriate counseling and support program to be used 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.

- ***Indication to be studied (i.e., objective of the study):*** The indication to be studied is smoking cessation and the objectives of this trial are:

  1. 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.

  2. To determine a safe and effective dose in the adolescent population.

  3. To document the ability of treating physicians to select appropriate patients.

- ***Age group in which study will be performed*:** This study will include patients 12 to 16 years of age inclusive.

- ***Study endpoints****:*

  - ***Efficacy****:* The primary outcome measure will be abstinence from smoking for a period of four consecutive weeks, based on weekly self-reporting of smoking behavior and assessment of objective biochemical markers during the last four 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, particularly neuropsychiatric events at appropriate intervals during treatment and follow-up. Patients should be followed to the resolution of any treatment-emergent adverse 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. The following safety parameters will be assessed:

  1. Physical examination including height (utilizing stadiometry), weight, and vital signs at each visit. Blood pressure must be obtained utilizing appropriate norms. The z-scores for height and weight must be provided.

  2. Incidence of adverse events, with particular attention to neuropsychiatric adverse events such as behavior changes, hostility, depression, and suicidality.

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

- ***Drug information***

  - *dosage form:* 0.5 mg tablets
  - *route of administration:* oral
  - *regimen:* once or twice daily

- ***Drug-specific safety concerns*:** The safety concerns that will require monitoring are as follows:
  - Neuropsychiatric symptoms: The label of varenicline has warnings regarding serious neuropsychiatric events. These neuropsychiatric events include changes in behavior, hostility, agitation, abnormal dreams, depressed mood, and suicide-related events, including ideation, behavior, and attempted suicide.
  - Angioedema and hypersensitivity reactions: Postmarketing reports of hypersensitivity reactions include angioedema, and in some cases these reactions were life-threatening.
  - Serious skin reactions: There have been rare postmarketing reports of serious skin reactions, including Stevens-Johnson syndrome and erythema multiforme.
  - Weight increase: Weight increase was reported frequently in the adult trials.

- ***Statistical information, including power of study and statistical assessments:*** 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. The following analysis of the data must 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

- ***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.

  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.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* available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf.

- ***Timeframe for submitting reports of the studies:*** Reports of the above studies must be submitted to the Agency on or before **April 15, 2016**. 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. .

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 ((240-276-9327)) or messenger, to the 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, submit the 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.

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response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following:

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

FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM049872

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.

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Sincerely,

{See appended electronic signature page}

Curtis J. Rosebraugh, M.D., M.P.H.
Director
Office of Drug Evaluation II
Office of New Drugs
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 J ROSEBRAUGH
03/07/2013