DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-868

Pfizer Global Research & Development
Attention: Brian Green, M.S.
Associate Director, Worldwide Regulatory Affairs
50 Pequot Avenue
MS 6025 - B2172
New London, CT 06320

Dear Mr. Green:

Please refer to your new drug application (NDA) dated December 27, 2004, received December 28, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Exubera (insulin human [rDNA origin]) inhalation powder) and Exubera Inhaler.

We acknowledge receipt of your submissions dated January 12, February 23, March 17, April 26, May 6, 12, and 31, June 10, 13, and 22, July 5, 13, 19, 21, 25, 26, and 29, August 2, 4, 9, 12, 19, 23, and 26, September 21, 22, 28, and 30 (email), October 3, 6, 10, and 28, November 11, and December 21 and 23, 2005, and January 12, 26, and 27, 2006.

This new drug application provides for the use of Exubera for the treatment of adult patients with diabetes mellitus for the control of hyperglycemia.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling text for the package insert, Medication Guide that includes Patient Instructions for Use, and carton and immediate container labels submitted by email on January 27, 2006. These include container and carton labels for Exubera Inhaler; Exubera Release Units; Exubera Chamber; Exubera 1-mg and 3-mg Combination Patient Pack, which contains ninety 1-mg insulin blisters, ninety 3-mg insulin blisters, and two Exubera Release Units; Exubera 1-mg Patient Pack, which contains ninety 1-mg blisters and two Exubera Release Units; Exubera 3-mg Patient Pack, which contains ninety 3-mg blisters and two Exubera Release Units; and Exubera CareKit, which contains one Exubera Inhaler, one Exubera Chamber, and one Exubera Release Unit. Marketing the products with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA.* For administrative purposes, designate this submission "**FPL for approved NDA 21-868**." Approval of this submission by FDA is not required before the labeling is used.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are waiving the pediatric study requirement for ages 0 through 5 years and deferring pediatric studies for ages 6 through 17 years for this application.

Your deferred pediatric study required under section 2 of the Pediatric Research Equity Act (PREA) is considered a required postmarketing study commitment. The status of this postmarketing study shall be reported annually according to 21 CFR 314.81. This commitment is listed below.

1. Deferred pediatric study under PREA for the treatment of patients with diabetes mellitus for the control of hyperglycemia in children and adolescents ages 6 through 17.

   Protocol Submission Date: September 30, 2006
   Study Start Date: January 2, 2007
   Final Report Submission Date: December 31, 20011

Submit the final study report to this NDA. For administrative purposes, all submissions related to this pediatric postmarketing study commitment should be clearly designated "**Required Pediatric Study Commitment.**"

We remind you of your postmarketing study commitments in your submission dated January 27, 2006. These commitments are listed below.

2. A 5-year, large, simple trial in 5,000 diabetics with Type 1 or Type 2 diabetes, with 1:1 randomization to either Exubera or usual care. This trial will have two objectives. The first objective is to estimate the relative risk of development of clinically significant (>20%) decline in lung function as measured by pulmonary function tests. The second objective is to further investigate the potential clinical risk associated with increases in insulin antibody formation, with assessment of the relative risk of development of allergic and immune disorders.

   Protocol Submission Date: April 28, 2006
   Study Start Date: July 28, 2006
   Final Report Submission Date: December 31, 2015

3. Completion of Study 1022 in Type 1 diabetes to obtain data regarding changes in lung function over 5 continuous years and 7 cumulative years of Exubera exposure.

   Protocol Submission Date: N/A (Study in progress)

Study Start Date: *N/A (Study in progress)*
Final Report Submission Date: *December 31, 2013*

4. Completion of Study 1029 in Type 2 diabetes to obtain data regarding changes in lung function over 5 continuous years and 7 cumulative years of Exubera exposure.

   Protocol Submission Date: *N/A (Study in progress)*
   Study Start Date: *N/A (Study in progress)*
   Final Report Submission Date: *December 31, 2013*

5. Completion of Study 1028 in diabetics with mild to moderate asthma. This study will assess change in forced expiratory volume in one second (FEV1) and diffusion capacity for carbon monoxide (DLco), control of diabetes and underlying lung disease, and frequency and severity of exacerbations of underlying lung disease.

   Protocol Submission Date: *N/A (Study in progress)*
   Study Start Date: *N/A (Study in progress)*
   Final Report Submission Date: *December 31, 2008*

6. Completion of Study 1030, in diabetics with COPD. This study will assess change in forced expiratory volume in one second (FEV1) and diffusion capacity for carbon monoxide (DLco), control of diabetes and underlying lung disease, and frequency and severity of exacerbations of underlying lung disease.

   Protocol Submission Date: *N/A (Study in progress)*
   Study Start Date: *N/A (Study in progress)*
   Final Report Submission Date: *December 31, 2012*

7. A study to determine the effectiveness of the Package Insert for prescribers, and of the Medication Guide for patients, in preventing the use of Exubera by smokers. This study will begin at first marketing of Exubera and include data for three years of use, with annual interim reports.

   Protocol Submission Date: *April 28, 2006*
   Study Start Date: *First Marketing by August 31, 2006*
   Interim Study Reports *Annually in the Annual Report*
   Final Report Submission Date: *December 31, 2011*

Submit clinical protocols to your IND for this product. Submit all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments should be prominently labeled "**Postmarketing Study Commitment Protocol,**" "**Postmarketing Study Commitment Final Report,**" or "**Postmarketing Study Commitment Correspondence**."

We also remind you of your manufacturing and controls post-marketing agreements in your submissions dated September 30 and December 23, 2005, and January 27, 2006. These agreements are listed below.

A. Implement the agreed-upon run qualification acceptance criteria for (b)(4). For the 3-mg blister: "(b)(4)". For the 1-mg blister (as agreed in the December 19, 2005, teleconference with the Agency): (b)(4)

B. To perform a (b)(4) for (b)(4) additional lots ((b)(4) each strength) consisting of (b)(4). Additionally, to perform (b)(4) for the first 3 commercial lots at the initial time points and at (b)(4), for the 25°C/60%RH storage condition. Results will be reported as general correspondence upon completion of the (b)(4) additional batches and when data for the stability lots are available.

C. To investigate the high batch-to-batch and time-dependent variability observed with the (b)(4) particle size stability data in the production-scale batches and to report the results associated within six months of the date of this letter. And, at that time, if necessary, to pursue appropriate follow-up action.

D. To provide the available insulin-specific aerosol data for samples stored in both the cavity-up and cavity-down orientations from the ICH program within one month of the action date.

E. **Immediately post-approval**, to initiate a planned-return program for risk management studies and on-going evaluation of inhaler components.

F. **Within three months of the date of this letter**, to provide complete responses to the comments communicated in our September 30, 2005, letter.

1) To clarify and provide appropriate calculations to show that the altitude differences at the two sites (The Tech Group and Nektar) result in pressure differences of greater than (b)(4). To provide an explanation as to why this difference in pressures does not impact the measurement errors for the low and high groups (comment 1a).

2) To justify the use of the (b)(4) as an acceptance criterion in lieu of using the (b)(4) (comment 1b).

3) For the method for determination of the Exubera Release Unit (b)(4), to conduct repeatability experiments to provide actual results for (b)(4).

4) For the method pertaining to the Exubera Release Unit [(b)(4)], to justify the results observed in Table 3.2.P(2).5.3-52, Summary of System Precision, which indicate that the difference in the [(b)(4)] exceed the proposed acceptance criteria [(b)(4)] (comment 3a). In rovide the validation results for Exubera Release Unit [(b)(4)] as measured on commercial/online equipment as opposed to the laboratory equipment (Comment 3b).

5) To evaluate the orientation and force necessary to replace the Exubera Release Unit. To provide the results of this evaluation and a proposal to improve the visibility of the locked/unlocked symbols next to the top of the Exubera Release Unit.

6) For your "[(b)(4)]" of certain materials, to describe how age-related changes of these materials will be controlled to ensure adequate function of the components (comment 22e(1).

7) To provide detailed sequential schematic diagrams to demonstrate (mechanistically and functionally) the complete stepwise operation of the drug product. These will include the mechanisms and operation of the Exubera Release Unit (comment 21b).

G. Within **nine months after the date of this letter**, to provide complete responses to the comments listed below and as agreed-to in your September 30, 2005, submission.

1) For the data provided to support the two-week lifetime of the insulin release unit, justify the [(b)(4)] of fine particle dose (FPD) values in this study [(b)(4)] [(b)(4)] Include data to support any claim of [(b)(4)] [(b)(4)] (comment 21a).

2) Provide [(b)(4)] [(b)(4)] data for the [(b)(4)] used in the device (comment 21c).

3) Further evaluate potential [(b)(4)] [(b)(4)] by conducting the [(b)(4)] [(b)(4)] to demonstrate whether or not an [(b)(4)] is reached. Provide a scientific basis for estimating a patient's daily exposure to [(b)(4)], rather than by [(b)(4)] (comment 22a).

4) Regarding the "[(b)(4)] for all relevant components (e.g., see page 79, Table 5-9 of your response to our May 16, 2005, letter, and Table 5-15, page 88 of your response), indicate the basis for [(b)(4)] [(b)(4)]" Provide an estimate of molecular weights or molecular weight ranges for [(b)(4)], and, if possible, estimates of the mass present including the total mass of [(b)(4)]. Provide a safety assessment of the levels of the [(b)(4)] (comment 22c).

H. Within **12 months of the date of this letter**, to provide complete responses to the comments listed below.

1) Add the [(b)(4)] test to the pulmonary inhaler specification. The specification may be revised 12 months following the date of this letter by Prior Approval Supplement due to the need for transfer and validation of equipment at the release site, Pfizer Terre Haute (comment 10).

2) Perform a complete and well-designed study to assess [(b)(4)] from the inhaler (comment 13).

3) Explain the large variabilities in the proposed acceptance criteria for the [(b)(4)] [(b)(4)], and demonstrate whether the variabilities are due to the composition of the material, or the sample preparation/analytical method. Examples include, but are not limited to, the following:

[(b)(4)]

- [(b)(4)]
-

4) Respond to the following comments pertaining to your responses to our June 7, 2005, letter. Table 3-1 of your response (page 18) does not include [(b)(4)] [(b)(4)] in the list of validated limits for the [(b)(4)] method [(b)(4)] (comment 22b).

   a. Specify validated limits for [(b)(4)] using appropriate standards.

   b. Clarify whether the limits in Table 3-1 pertain to limits of quantitation.

   c. Provide validation data for the method.

   d. Provide justification for validating the method as a limit test.

   e. Indicate the amounts of [(b)(4)] [(b)(4)]

   f. Comment on the variability of the mean data used for background correction, to remove the contribution of the [(b)(4)].

   g. Clarify whether the [(b)(4)] used is capable of detecting and quantitating all [(b)(4)] that were identified

5) Investigate improvement of [(b)(4)] and analytical procedures for [(b)(4)] [(b)(4)] (with quantitative limits) from the [(b)(4)] [(b)(4)] [(b)(4)] so that the data are more consistent and that [(b)(4)] only one maximum limit has been proposed. The

investigation should also examine the composition, manufacture, and control [redacted], insofar as is possible (comment 22d(3)).

I. Within **12 months following Agency endorsement of the proposal**, to implement the [redacted] for the Exubera Release Unit (comment 20).

J. To provide the following changes as comparability protocols.

1) [redacted] Comparability Protocol

To submit the proposed change for the [redacted] and the requested comparative data as a CBE-30 supplement.

2) [redacted] Comparability Protocol

To submit the proposed change for the [redacted] and the requested comparative data as a CBE-30 supplement.

3) Process Change to [redacted] Comparability Protocol

To submit the proposed change to [redacted] as a prior approval supplement (PAS). A commercial batch size will be used to validate the [redacted] The Agency non-acceptance of removing the in-process control for [redacted] is recognized; therefore, Pfizer will gather data and withdraw this approach from the comparability protocol. Release and stability data for the [redacted] blisters will be provided as a part of the PAS, with the comparability ---------- dated accordingly. As a part of the continuous improvement process, [redacted]

K. To monitor the levels of [redacted] throughout the stability studies for three commercial scale batches. If levels significantly increase over time, to revise the specification to include this attribute.

We note that the following comments in your January 27, 2006, electronic correspondence regarding 1-mg Exubera also apply to the 3-mg product:

- "Concerning the marking of the lot number at the bottom of the Inhaler base, Pfizer commits to assess options to increase the prominence of the laser-marked lot number and date code on the inhaler base and, if feasible, implement the improvement six months following the action date."

- "Concerning the blister foil, the printing on the blister packet will be updated by reducing the size of the strength to allow for the established name to be printed following the proprietary name. Due to size limitations, the established names will be printed on two lines as follows."

EXP:
LOT:

1 mg
EXUBERA®
(insulin human [rDNA origin])
Inhalation Powder

We remind you that any out-of-specification (OOS) results to the drug product should be dealt with in accordance to cGMP practices and regulations, and you may not use an internal statistical protocol in lieu of them. **Specifically, (b)(4) is not agreed to by the Agency at this time.**

As recommended in our January 6, 2006, teleconference, we strongly suggest that you increase the number of batches placed on post-approval stability protocol (relative to the percentage manufactured) and in order to monitor and gain additional stability experience with this product.

Data that you have submitted support an expiry of eighteen (18) months at controlled room temperature which may include up to three (3) months of out-of-pouch storage at controlled room temperature. The 3 months out-of pouch storage are allowed within the total 18-month time frame and NOT in addition to it. You may add additional total stability time via annual report based on real-time data, but you may not increase the 3-month out-of-pouch allowance unless you submit and receive approval of a Prior Approval Supplement.

We have determined that Exubera poses serious and significant public health concerns as outlined under 21 CFR 208(c)(1) and (3). These concerns require distribution of a Medication Guide under 21 CFR 208.24 in order to prevent serious adverse effects, inform patients of information concerning risks that could affect their decision to use or to continue to use the drug, and/or assure effective use of the drug. You are responsible for ensuring that the Medication Guide is available for every patient who is dispensed Exubera. In addition, the carton and immediate container labels for Exubera must include a prominent and conspicuous instruction to provide the Medication Guide to each patient dispensed the drug. The labels must state how the Medication Guide is provided (e.g., affixed on the container, provided with the product, etc.).

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Metabolism and Endocrinology Products and two copies of both the promotional materials and the package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

Please submit one market package of the drug product when it is available.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Oluchi Elekwachi, PharmD, MPH, Regulatory Project Manager, at (301) 796-1207.

Sincerely,

{See appended electronic signature page}

Robert J. Meyer, M.D.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure: Package Insert and Medication Guide including Patient Instructions for Use

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Robert Meyer

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