DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-868/S-016 and S-017

Pfizer, Inc.
Attention: Susan DeCorte, R.Ph., R.A.C.
Senior Director, Worldwide Regulatory Affairs and Quality Assurance
MS 6025-B4139
50 Pequot Avenue
New London, CT 06320

Dear Ms. DeCorte:

Please refer to your supplemental new drug application dated April 8, 2008, received April 8, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Exubera (insulin human [rDNA origin]) Inhalation Powder, 1 mg and 3 mg.

We also refer to your amendment dated May 6, 2008, to Supplement-016. The "Changes Being Effected" supplemental new drug application, **Supplement-016,** adds information regarding lung cancer to the *WARNINGS* section of the package insert for Exubera. See Attachment A.

The "Prior Approval" supplemental new drug application, **Supplement-017,** adds information to the Patient Medication Guide for Exubera regarding lung cancer. See Attachment A.

We have completed our review of these applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

Since Exubera was approved on January 27, 2006 for the treatment of adult patients with diabetes mellitus for the control of hyperglycemia, we have conducted an analysis of the available clinical trial data, spontaneous postmarketing reports, and the medical literature that show an imbalance in lung cancer cases between Exubera and controls across the clinical trial program. Based on this new analysis, we conclude that the current Exubera labeling does not adequately warn healthcare providers and patients about this possible, rare serious event. We consider this new analysis to be "new safety information" as defined in the Food and Drug Administration Amendments Act of 2007 (FDAAA).

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

Title IX, Subtitle A, Section 901 of FDAAA amends the Federal Food, Drug, and Cosmetic Act (FDCA) to authorize FDA to require the submission of a REMS for an approved drug if FDA becomes aware of new safety information and makes a determination that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)). This provision took effect on March 25, 2008.

Based on the new safety information described above, in accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for Exubera to ensure that the benefits of the drug outweigh the risks. The REMS, once approved, will create enforceable obligations.

Your proposed REMS for Exubera must contain the following:

Medication Guide: As one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. The Medication Guide approved in Supplement -017 will be considered part of the REMS in accordance with 505-1. Under 21 CFR Part 208 and 505-1(e)(2), you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed Exubera.

Communication Plan: We have determined that a communication plan to healthcare providers who are likely to prescribe Exubera will support implementation of the elements of your REMS. The communication plan must include the dissemination of information about labeling, including the Medication Guide, and the elements of the REMS, to encourage implementation by health care providers of relevant portions of the REMS, and to explain certain safety protocols.

The communication plan must include at a minimum the following:

- Information about the new data regarding an imbalance in primary lung cancer cases between Exubera and controls in clinical trials
- Information on the proper technique for use of the inhaler, prohibition against use in patients who smoke cigarettes, the potential for a decrease in lung function, dosing differences between inhaled and subcutaneous insulin, and a lack of dose equivalence between the 1 mg and 3 mg blister packages.
- A description of who will be the audience for the communication plan, stating specifically the types and specialties of healthcare providers to which the communications will be directed.
- Communication materials to be distributed to healthcare providers.
- A schedule for when and how these materials are to be distributed to healthcare providers.
- Append all communication and educational materials to the proposed REMS.

Timetable for Assessment: The proposed REMS must include a timetable for assessment of the REMS that shall be no less frequent than at 18 months, 3 years, and 7 years after the REMS is approved.

Each assessment must assess the extent to which the elements to assure safe use of your REMS are meeting the goals of your REMS and whether the goals or elements should be modified.

In accordance with section 505-1 (a), within 120 days of the date of this letter, you must submit prior-approval supplements containing your proposed REMS.

We suggest that your proposed REMS submission include two parts: a “Proposed REMS” and a “REMS Supporting Document.” Attached is a template for the Proposed REMS that you should complete with concise, specific information about Exubera (see Attachment B). Once FDA finds the content acceptable, we will include this document as an attachment to the approval letter that includes the REMS.

The REMS Supporting Document should provide a thorough explanation of the rationale for and supporting information about the content of the proposed REMS and should include the following sections as well as a table of contents:

a. Background
b. Goals
c. Supporting Information on Proposed REMS Elements
    a. Medication Guide and/or Package Insert
    b. Communication Plan
    c. Elements to Assure Safe Use
    d. Implementation System
    e. Timetable for Assessment of the REMS
    f. Information Needed for Assessments
d. Other Relevant Information

Information needed for the assessment must include but may not be limited to, the following:

1) A survey of patients' or health care providers' understanding of the serious risks of Exubera
2) A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24
3) A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance
4) An assessment of how Exubera is being used in the postmarketing setting, including:
    a) Determination of appropriate patient selection (e.g., patients without asthma or COPD)
    b) Determination of whether clinicians are doing baseline and follow-up monitoring of PFTs.
    c) Determination of patients' adverse events of hypoglycemia due to smoking or inappropriate dose substitution
    d) Determination of use in the pediatric patient population.

Prominently identify the amendment containing the proposed REMS with the following wording in bold, capital letters at the top of the first page of the submission:

NEW PROPOSED REMS FOR NDA 21-868:

For subsequent submissions related to the already-submitted proposed REMS, prominently identify the submission with the following wording in bold, capital letters at the top of the first page of the submission:

NDA 21-868: PROPOSED REMS–AMENDMENT

POSTMARKETING REQUIREMENTS UNDER 505(o)

You previously committed to conduct the following postmarketing trials and studies identified as Numbers 2 to 7 in our letter dated January 26, 2006. At this time, we are releasing these commitments, because they are being replaced by postmarketing requirements.

Title IX, Subtitle A, Section 901 of FDAAA amends the FDCA to authorize FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A), 21 U.S.C. 355(o)(3)(A)). This provision took effect on March 25, 2008. Based on the new information described above about the risk of lung cancer, we have determined that clinical trials must be conducted to assess this signal of a serious risk.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess this signal of a serious risk.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is thus not sufficient to assess this signal of a serious risk.

Finally, we have determined that only clinical trial data (rather than nonclinical or observational study data) will be sufficient to assess this signal of a serious risk.

Therefore, based on appropriate scientific data, we have determined that you are required, pursuant to section 505(o)(3) of the FDCA, to conduct the following clinical trials:

1. An international, multicenter, large simple trial to evaluate the long-term pulmonary and cardiovascular safety of Exubera® in patients with diabetes mellitus (Study A2171069).

   You must submit a timetable for submitting data from this trial. You may use the following timetable, from our letter dated July 15, 2008:

Protocol Submission:	N/A (Study in progress)
Trial Start Date:	N/A (Study in progress)
Final Report Submission:	December 31, 2011

2. A long-term, outpatient, open-label, parallel-group comparative trial of the efficacy and safety of Exubera® compared with subcutaneous human insulin therapy in adult subjects with type 1 diabetes mellitus (Study A2171022).

   You must submit a timetable for submitting data from this trial. You may use the following timetable, from our letter dated July 15:

Protocol Submission:	N/A (Study in progress)
Trial Start Date:	N/A (Study in progress)
Final Report Submission:	December 31, 2011

3. A long-term, outpatient, open-label, parallel-group comparative trial of the efficacy and safety of Exubera® compared with subcutaneous human insulin therapy in adult subjects with type 2 diabetes mellitus (Study A2171029).

You must submit a timetable for submitting data from this trial. You may use the following timetable, from our letter dated July 15:

Protocol Submission:	N/A (Study in progress)
Trial Start Date:	N/A (Study in progress)
Final Report Submission:	December 31, 2011

4. A one-year, multicenter, randomized, out-patient, open-label, parallel-group comparative trial of the efficacy and safety of Exubera® compared with subcutaneous human insulin therapy of adult subjects with type 1 or type 2 diabetes mellitus and chronic asthma (Study A2171028).

   You must submit a timetable for submitting data from this trial. You may use the following timetable, from our letter dated July 15:

Protocol Submission:	N/A (Study in progress)
Trial Start Date:	N/A (Study in progress)
Final Report Submission:	December 31, 2011

5. A one-year, multicenter, randomized, out-patient, open-label, parallel-group comparative trial of the efficacy and safety of Exubera® compared with subcutaneous human insulin therapy of adult subjects with type 1 or type 2 diabetes mellitus and chronic obstructive pulmonary disease (Study A2171030).

You must submit a timetable for submitting data from this trial. You may use the following timetable, from our letter dated July 15:

Protocol Submission:	N/A (Study in progress)
Trial Start Date:	N/A (Study in progress)
Final Report Submission:	December 31, 2011

6. 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.

You must submit a timetable for submitting data from this trial. You may use the following timetable, from our letter dated July 15:

Protocol Submission:	N/A (Study in progress)
Trial Start Date:	N/A (Study in progress)
Interim Study Reports:	Annually in the Annual Report
Final Report Submission:	December 31, 2011

Submit the protocols to your INDs 43,313 with a cross-reference letter to NDA 21-868. Submit all final report(s) to your NDA 21-868. Use the following designators to prominently label all submissions, including supplements, relating to these postmarketing clinical trials as appropriate:

- **Required Postmarketing Protocol under 505(o)**
- **Required Postmarketing Final Report under 505(o)**
- **Required Postmarketing Correspondence under 505(o)**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2(vii) .We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical to the enclosed labeling (text for the package insert submitted November 20, 2007.) Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, **"SPL for approved NDA 21-868/S-016 and S-017"**

Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert(s) 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

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see www.fda.gov/cder/ddmac.

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important safety related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch
Food and Drug Administration
HFD-001, Suite 5100
5515 Security Lane
Rockville, MD 20852

If you have any questions, call Haley Seymour, Regulatory Project Manager, at (301) 796-2443.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation

Enclosures: Attachment A, Attachment B, Prescribing Information, Medication Guide

Attachment A

S-016: The following language will be added to the *WARNINGS* section of the Package Insert.

In the Exubera Prescribing Information:

Warnings

Added statement *"In clinical trials of Exubera, there have been 6 newly diagnosed cases of primary lung malignancies among Exubera-treated patients, and 1 newly diagnosed case among comparator-treated patients. There has also been 1 postmarketing report of a primary lung malignancy in an Exubera-treated patient. In controlled clinical trials of Exubera, the incidence of new primary lung cancer per 100 patient-years of study drug exposure was 0.13 (5 cases over 3800 patient-years) for Exubera-treated patients and 0.03 (1 case over 3900 patient-years) for comparator-treated patients. There were too few cases to determine whether the emergence of these events is related to Exubera. All patients who were diagnosed with lung cancer had a prior history of cigarette smoking."*

S- 017: The following language will be added to the end of the section entitled **"What are some of the possible side effects of Exubera?"**:

In the Exubera Medication Guide:

Under "What are some of the possible side effects of Exubera?":

- Added statements:

"*In studies of Exubera in people with diabetes, lung cancer occurred in a few more people who were taking Exubera than in people who were taking other diabetes medicines. All the people in these studies who developed lung cancer used to smoke cigarettes. There were too few cases to know if the lung cancer was related to Exubera."*

Attachment B

NDA 21-868 Exubera
(insulin human [rDNA origin]) Inhalation Powder

PROPOSED RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL(S):

List the goals and objectives of the REMS.

II. REMS ELEMENTS

A. Medication Guide or PPI

A Medication Guide will be dispensed with each [drug name] prescription. [Describe in detail how you will comply with 21 CFR 208.24.]

B. Communication Plan

[Applicant] will implement a communication plan to healthcare providers to support implementation of this REMS.

List elements of communication plan. Append the printed material and web shots to the REMS Document

C. Elements To Assure Safe Use

List elements to assure safe use included in this REMS. Elements to assure safe use may, to mitigate a specific serious risk listed in the labeling, require that:
A. Healthcare providers who prescribe [drug name] have particular training or experience, or are specially certified. Append any enrollment forms and relevant attestations/certifications to the REMS;

B. Pharmacies, practitioners, or healthcare settings that dispense [drug name] are specially certified. Append any enrollment forms and relevant attestations/certifications to the REMS ;

C. [Drug name] may be dispensed to patients only in certain healthcare settings (e.g., hospitals);

D. [Drug name] may be dispensed to patients with documentation of safe-use conditions;

E. Each patient using [drug name] is subject to certain monitoring. Append specified procedures to the REMS; or

F. Each patient using [drug name] be enrolled in a registry. Append any enrollment forms and other related materials to the REMS Document.

D. Implementation System

Describe the implementation system to monitor and evaluate implementation for, and work to improve implementation of, Elements to Assure Safe Use (B),(C), and (D), listed above .

E. Timetable for Submission of Assessments

Specify the timetable for submission of assessments of the REMS. The timetable for submission of assessments at a minimum must include an assessment by 18 months, 3 years, and in the 7th year after the REMS is initially approved, with dates for additional assessments if more frequent assessments are necessary to ensure that the benefits of the drug continue to outweigh the risks.

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/s/

Mary Parks

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