

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-868**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**

**EXUBERA® (insulin [rDNA origin] powder for oral inhalation)**  
**1 mg and 3 mg Unit Dose Blisters**  
**New Drug Application / NDA 21-868**

**Notice of Claimed Exclusivity**  
**21 C.F.R. § 314.50(j)**

Pfizer Inc. hereby claims three (3) years of marketing exclusivity from the date of approval of EXUBERA® (insulin [rDNA origin] powder for oral inhalation) 1 mg and 3 mg unit dose blisters for the treatment of adult patients with diabetes mellitus for the control of hyperglycemia, pursuant to Sections 505(c)(3)(D)(ii) and 505(j)(5)(D)(ii) of the Federal Food, Drug and Cosmetic Act and 21 C.F.R. § 314.108(b)(4).

We hereby certify that this application contains the following reports of “new clinical investigations” (other than bioavailability studies) that are “essential to the approval of the application” and were “conducted or sponsored by the applicant” (*i.e.*, Pfizer):

- Study 217-106:** Efficacy and Safety of Inhaled Compared With Subcutaneous Human Insulin Therapy in Subjects With Type 1 Diabetes Mellitus: A Six-Month, Outpatient, Parallel Comparative Trial
- Study 217-107:** Efficacy and Safety of Inhaled Compared With Subcutaneous Human Insulin in an Intensive Insulin Regimen for Subjects With Type 1 Diabetes Mellitus: A Six-month, Outpatient, Parallel Comparative Trial
- Study 217-108:** Efficacy and Safety of Inhaled Compared With Subcutaneous Human Insulin Therapy in Subjects With Type 2 Diabetes Mellitus: A Six-Month, Outpatient, Parallel Comparative Trial
- Study 217-109:** Efficacy and Safety of Exubera™ (Inhaled Insulin) Therapy in Subjects With Type 2 Diabetes Mellitus Not Well Controlled With Combination Oral Agents: A Three-Month, Outpatient, Parallel Comparative Trial
- Study 217-110:** Efficacy and Safety of Exubera™ (Inhaled Insulin) Therapy in Subjects With Type 2 Diabetes Mellitus Not Optimally Controlled With Diet and Exercise: A Three-Month, Outpatient, Parallel Comparative Trial
- Study A2171022:** Efficacy and Safety of Exubera® (Inhaled Insulin) Compared with Subcutaneous Human Insulin Therapy in Adult Subjects with Type 1 Diabetes Mellitus: A Two- Year, Outpatient, Open-Label, Parallel-Group Comparative Trial
- Study A2171029:** Efficacy and Safety of Exubera® (Inhaled Insulin) Compared with Subcutaneous Human Insulin Therapy in Adult Subjects with Type 2 Diabetes Mellitus: A Two- Year, Outpatient, Open-Label, Parallel-Group Comparative Trial

- Study A2171028:** Efficacy and Safety of Inhaled Human Insulin (Exubera®) Compared with Subcutaneous Human Insulin in the Therapy of Adult Subjects with Type 1 or Type 2 Diabetes Mellitus and Chronic Asthma: A One-Year, Multicenter, Randomized, Outpatient, Open-Label, Parallel-Group Comparative Trial
- Study A2171030:** Efficacy and Safety of Inhaled Human Insulin (Exubera®) Compared with Subcutaneous Human Insulin in the Therapy of Adult Subjects with Type 1 or Type 2 Diabetes Mellitus and Chronic Obstructive Pulmonary Disease: A One-Year, Multicenter, Randomized, Outpatient, Open-Label, Parallel-Group Comparative Trial
- Study A2171027** A Short-Term, Multicenter, Randomized, Open-Label, Parallel-Group Study Assessing the Pulmonary Effects of Chronically-Dosed Inhaled Insulin or Subcutaneous Insulin Therapy
- Study A2171026:** Longitudinal Insulin Pharmacokinetics and Pharmacodynamics Associated with an Exubera® (Inhaled Insulin) Treatment Regimen versus a Subcutaneous Insulin Treatment Regimen: A 24-week Prospective, Randomized, Open-Label, Parallel Group Comparative Trial in Subjects with Type 1 Diabetes
- Study 217-111** Long Term Safety of Exubera™ (Inhaled Insulin): Extension of Therapy in Subjects with Type 1 or Type 2 Diabetes Mellitus Completing Phase III Randomized Treatment Trials [*Trends in Pulmonary Function After Discontinuation of Exubera™ (Inhaled Insulin)*]

- The clinical investigations are defined as “new” as they have not been relied on by the FDA to demonstrate substantial evidence of effectiveness of a previously approved drug product for any indication or of safety for a new patient population and do not replicate the results of another investigation that was relied on by FDA to demonstrate the effectiveness or safety in a new patient population of a previously approved drug application.
- The new clinical investigations are deemed “essential to the approval of the application” in that there are no other data available that could support FDA approval of the application. Module 1.3.9.4 of this application contains a list of published studies or publicly available reports of clinical investigations known to Pfizer through a literature search that are relevant to the use of EXUBERA as treatment of adult patients with diabetes mellitus for the control of hyperglycemia. Pfizer has thoroughly searched the literature and to the best of our knowledge, the list is complete and accurate. In Pfizer’s opinion, such published studies or publicly available reports do not provide a sufficient basis for the approval of EXUBERA as treatment of adult patients with diabetes mellitus for the control of hyperglycemia.
- These investigations were “conducted or sponsored by the applicant (*Pfizer*)” in that Pfizer is the sponsor named on the Form FDA-1571 for IND 43,313, under which the new clinical investigations that are essential to approval of this NDA were conducted.

**NDA 21-868**

**EXUBERA<sup>®</sup> (insulin [rDNA origin] powder for oral inhalation)  
1 mg and 3 mg Unit Dose Blisters**

**DEBARMENT CERTIFICATION**

**[FD&C Act 306(k)(1)]**

Pfizer hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

Brian A. Green  
Signature of Company Representative

17 November 2004  
Date



## Global Research & Development

27 January 2006

Mary Parks, MD, Acting Director  
Division of Metabolism and Endocrinology Products (HFD-510)  
Office of Drug Evaluation II, CDER, FDA  
ATTN: CENTRAL DOCUMENT ROOM  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

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WRITTEN CONSENT OF PFIZER INC.

**Re: NDA 21-868 / EXUBERA® (insulin human [rDNA origin]) Inhalation Powder  
Post-Marketing Agreements (CMC) and Post-Marketing Commitments (Ped/Clin)**

Dear Dr. Parks:

Reference is made to our pending New Drug Application (NDA 21-868) for EXUBERA® (insulin human [rDNA origin]) Inhalation Powder, submitted on 27 December 2004. Reference is also made to several discussions throughout the review cycle with chemistry and medical reviewers concerning the post-marketing agreements (CMC) and commitments (Pediatric and Clinical).

**Pfizer hereby agrees to the following Post-Marketing Agreements, as communicated in our response dated 23 December 2005.**

1. Implement the agreed upon run qualification acceptance criteria for [REDACTED]. For the 3 mg blister: [REDACTED]. For the 1 mg blister (as agreed in the 19 December 2005 telecon with the Agency): [REDACTED] between [REDACTED].")
2. Pfizer agrees to perform a [REDACTED] for [REDACTED] additional lots ( [REDACTED] for each strengths) consisting of [REDACTED] mouthpiece). Additionally, [REDACTED] will also be performed for the first three commercial lots at the initial time points and at [REDACTED] for the 25°C/60%RH storage condition. Results will be reported as a general correspondence upon completion of the [REDACTED] additional batches and when data for the stability lots are available.
3. Pfizer agrees to investigate the high batch-to-batch and time-dependent variability observed with the [REDACTED] particle size stability data, in the production-scale batches and report the results associated within 6 months of the approval of the NDA. If necessary, at that time, Pfizer will pursue appropriate follow-up action.
4. Pfizer agrees 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.

5. Immediately post approval initiate a planned return program for risk management studies and on going evaluation of inhaler components
6. Within three months, Pfizer agrees to provide complete responses to comments communicated in the Agency's letter Sept. 30, 2005.
  - a) 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 \_\_\_\_\_ Provide an explanation as to why this difference in pressures does not impact the measurement errors for the Low and High groups (comment 1a).
  - b) Justify the use of \_\_\_\_\_ as an acceptance criterion in lieu of using the \_\_\_\_\_ (comment 1b).
  - c) For the method for determination of the Insulin release unit \_\_\_\_\_ repeatability experiments to provide actual results for \_\_\_\_\_ t \_\_\_\_\_ c
  - d) For the method pertaining to the Insulin release unit \_\_\_\_\_ justify the results observed in the Table 3.2.P(2).5.3-52 Summary of System Precision which indicate that the difference in the \_\_\_\_\_ exceed the proposed acceptance criteria \_\_\_\_\_ (comment 3a). In addition, provide the validation results for Insulin release unit \_\_\_\_\_ as measured on commercial/online equipment as opposed to the laboratory equipment (Comment 3b).
  - e) A proposal to improve the visibility of the locked/unlocked symbols next to the top of the Insulin release unit. In addition, Pfizer agrees to evaluate the orientation and force necessary to replace the insulin release unit. Pfizer will provide the results of this evaluation and their proposal to the Agency for discussion (comment 20).
  - f) For your \_\_\_\_\_ of certain materials describe how age-related changes of these materials will be controlled to ensure adequate function of the components Comment 22e(1).

a) For the data provided to support the two week lifetime of the insulin release unit:

- 1)

2) Justify the                      of Fine Particle Dose (FPD) values in this study                      by taking the following action.

Verify experimentally and provide data to support any claim of \_\_\_\_\_  
(comment 21a).

- b) Verify that the \_\_\_\_\_ used in the device is \_\_\_\_\_ Provide  
\_\_\_\_\_ data as part of the response (comment 21c).
- c) Further evaluate \_\_\_\_\_ to demonstrate  
whether or not an \_\_\_\_\_ is reached. Provide a scientific basis for estimating a  
patients daily exposure to \_\_\_\_\_  
(comment 22a).
- d) This pertains to \_\_\_\_\_ 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, pg.88 of your response). Indicate the basis for \_\_\_\_\_  
Provide an estimate of molecular weights or molecular  
weight ranges for \_\_\_\_\_ and if possible, estimates of the mass present  
including the total mass of \_\_\_\_\_ Provide a safety assessment of the levels of the  
(comment 22c)

8. Within **twelve months**, Pfizer agreed to provide complete responses to comments listed  
below in their response dated Sept. 30, 2005. The comment numbers and relevant  
information are highlighted below

- a) Add the \_\_\_\_\_ test to the pulmonary inhaler specification. The  
specification will be revised 12 months following the action date due to the need for  
transfer and validation of equipment at the release site, i.e. Pfizer Terre Haute (comment  
10).
- b) Perform a complete and well-designed study to assess \_\_\_\_\_ from the inhaler  
(comment 13).
- c) Explain the large variabilities in the proposed acceptance criteria for the \_\_\_\_\_  
\_\_\_\_\_ and demonstrate whether the variabilities are due to the composition of the  
material, or the sample preparation/analytical method. Examples of this include (but are  
not limited to) the following:  
\_\_\_\_\_

- d) 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 \_\_\_\_\_  
\_\_\_\_\_ in the list of validated limits for the \_\_\_\_\_ method  
(comment 22b)

- 1) Specify validated limits for \_\_\_\_\_ using appropriate standards.

- 2) Clarify whether the limits in Table 3-1 pertain to limits of quantitation.
  - 3) Provide validation data for the method.
  - 4) Provide justification for validating the method as a limit test.
  - 5) Indicate the amounts of \_\_\_\_\_
  - 6) Comment on the variability of the mean data used for background correction, to remove the contribution of the \_\_\_\_\_
  - 7) Clarify whether the \_\_\_\_\_ used is capable of detecting and quantitating all \_\_\_\_\_ that were identified
  - f) Investigate improvement of the extraction and analytical procedures for \_\_\_\_\_ (with quantitative limits) from the \_\_\_\_\_ so that the data are more consistent and that \_\_\_\_\_ only one maximum limit has been proposed. The investigation should also examine the composition, manufacture and control of the \_\_\_\_\_ insofar as is possible (comment 22d(3)).
9. Within **twelve months following Agency endorsement of the proposal**, Pfizer agrees to implement the \_\_\_\_\_ for the insulin release unit. (comment 20)
10. Pfizer Agreed to provide the following changes as comparability protocols
- (a) \_\_\_\_\_ **Comparability Protocol**  
Pfizer agrees to submit the proposed change for the \_\_\_\_\_ as a CBE-30 supplement. The requested comparative data will be provided in the CBE-30 supplement.
  - (b) \_\_\_\_\_ **Comparability Protocol**  
Pfizer agrees to submit the proposed change for the \_\_\_\_\_ as a CBE-30 supplement. The requested comparative data will be provided in the CBE-30 supplement.
  - (c) **Process Change to \_\_\_\_\_ Comparability Protocol**  
Pfizer agrees to submit the proposed change to \_\_\_\_\_ as a prior approval supplement (PAS). Pfizer commits that a \_\_\_\_\_ batch size will be used to validate the \_\_\_\_\_. The Agency non-acceptance of removing the in-process control for \_\_\_\_\_ is recognized, therefore Pfizer will gather data and withdraw this approach from the comparability protocol. Release and stability data for the \_\_\_\_\_ tablets will be provided as a part of the PAS, with the comparability protocol updated accordingly. Pfizer, as a part of their continuous improvement process, will evaluate \_\_\_\_\_
11. In the submission dated January 12, 2006, Pfizer committed to monitor the levels of \_\_\_\_\_ throughout the stability studies for three commercial scale batches. If \_\_\_\_\_



levels significantly increase over time, you commit to revising the specification to include this attribute.

A summary of the CMC post marketing agreements is presented as an attachment to this letter.

**Pfizer also hereby agrees to the following Pediatric and Clinical Post-Marketing Commitments, as discussed on 25 January 2006.**

***Pediatric PMC***

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 to 17.

Protocol Submission Date: September 30, 2006

Study Start Date: January 2, 2007

Final Report Submission: December 31, 2011

***Clinical PMCs***

1. A 5-year large simple trial in 5,000 diabetics with Type 1 or Type 2 diabetes, with 1:1 randomization to either EXUBERA<sup>®</sup> or usual care. This trial has two objectives. The first objective is to estimate the relative risk of development of clinically significant (>20%) declines 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: by April 28, 2006

Study Start Date: by July 28, 2006

Final Study Report Submission Date: by December 31, 2015

2. Completion of Studies 1022 and 1029, in Types 1 and 2 diabetes respectively, to obtain data regarding changes in lung function over 5 continuous years and 7 cumulative years of Exubera<sup>®</sup> exposure.

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

Study Start Date: N/A (Study is in progress)

Final Study Report Submission Date: by December 31, 2013

3. Completion of Studies 1028 and 1030, in diabetics with mild to moderate asthma and COPD respectively. These studies are to assess change in FEV<sub>1</sub> and diffusion capacity for carbon monoxide (DLco), control of diabetes and underlying lung disease, and frequency and severity of exacerbations of underlying lung disease.

A. For Study 1028:

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

Study Start Date: N/A (Study is in progress)

Final Study Report Submission Date: by December 31, 2008

Final Study Report Submission Date: by December 31, 2008

B. For Study 1030:

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

Study Start Date: N/A (Study is in progress)

Final Study Report Submission Date: by December 31, 2012

4. A study to determine the effectiveness of the Package Insert for prescribers, and of the Medication Guide for patients, in preventing use of EXUBERA<sup>®</sup> by smokers. This study should begin at first marketing of EXUBERA<sup>®</sup> and include data for three years of use, with annual interim reports.

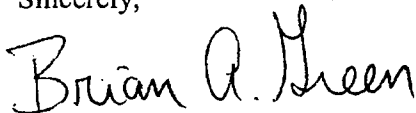
Protocol Submission Date: 28 Apr 2006

Study Start Date: First Marketing (by August 31, 2006)

Interim Study Reports: Annually along with your Annual Reports

Final Study Report: by December 31, 2011

Sincerely,

A handwritten signature in black ink that reads "Brian A. Green". The signature is written in a cursive, flowing style.

Brian A. Green, MS

Associate Director

Worldwide Regulatory Strategy

Worldwide Regulatory Affairs and Quality Assurance

**ATTACHMENT: Summary of NDA 21-868 CMC Post Marketing Agreements**

IR Date	Query #	Verbatim Agreement	"Short Version" Post-Action Commitment	Timing - Following Action Date
7 Dec 2005	2	Implement the agreed upon run qualification acceptance criteria for <u>                    </u> (For the 3 mg blister: <u>                    </u> of TDD <u>                    </u> % of TDD." For the 1 mg blister (as agreed in the 19 December 2005 telecon with the Agency): <u>                    </u> of TDD. <u>                    </u> of TDD."	Run qualification AC. <u>                    </u>	<u>                    </u>
7 Dec 2005	3	Pfizer agrees to perform <u>                    </u> determination for <u>                    </u> additional lots ( <u>                    </u> for each strengths) consisting of <u>                    </u> recovery of insulin <u>                    </u> mouthpiece). Additionally <u>                    </u> will also be performed for the first three commercial lots at the initial time points <u>                    </u> , for the <u>                    </u> 25°C/60%RH storage condition. Results will be reported as a general correspondence upon completion of the <u>                    </u> additional batches and when data for the stability lots are available.	<u>                    </u>	<u>                    </u>
7 Dec 2005	5	Pfizer agrees to investigate the high batch-to-batch and time-dependent variability observed with the <u>                    </u> particle size stability data, in the production-scale batches and report the results associated within 6 months of the approval of the NDA. If necessary, at that time, Pfizer will pursue appropriate follow-up action.	<u>                    </u> evaluation	<u>                    </u>
7 Dec 2005	6	Pfizer agrees 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.	Insulin specific aerosol data for ICH (pilot scale) stability	<u>                    </u>
26 Sep 2005	1.a	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 <u>                    </u>	Pressure differences -- calculations and explanations	3 months

IR Date	Query #	Verbatim Agreement	"Short Version" Post-Action Commitment	Timing - Following Action Date
		Provide an explanation as to why this difference in pressures does not impact the measurement errors for the Low and High groups		
26 Sep 2005	1.b.	Justify the use of the _____ as an acceptance criterion in lieu of using the _____	Justification of use of _____	3 months
26 Sep 2005	2.a.	For the method for determination of the Insulin release unit experiments to provide actual results for _____ repeatability	_____	3 months
26 Sep 2005	3.a.	For the method pertaining to the Insulin release unit _____ results observed in the Table 3.2.P(2).5.3-52 Summary of System Precision which indicate that the difference in the criteria _____ exceed the proposed acceptance	_____ observations	3 months
26 Sep 2005	3.b.	In addition, provide the validation results for Insulin release unit _____	_____	3 months
26 Sep 2005	10	Add the i _____ test to the pulmonary inhaler specification. The specification will be revised 12 months following the action date due to the need for transfer and validation of equipment at the release site, i.e. Pfizer Terre Haute	_____	12 months
26 Sep 2005	11	_____	Continuous evaluation of inhalers and major constituents	Immediate
26 Sep 2005	13	Perform a complete and well-designed study to assess _____ from the inhaler	Study of _____ from device	12 months

27 January 2006  
Page 9 of 12

<sup>1</sup> Formerly identified as — and insulin release unit

IR Date	Query #	Verbatim Agreement	"Short Version" Post-Action Commitment	Timing - Following Action Date
		2) Justify the correction of Fine Particle Dose (FPD) values in this study _____ by taking the following action.  Verify experimentally and provide data to support any claim of non recoverable wall losses in the _____		
26 Sep 2005	21.c.	Verify that the _____ used in the device is free of residual solvents. Provide characterization data as part of the response	_____	9 months
26 Sep 2005	22.a.	Further evaluate potential _____ by conducting the _____ to demonstrate whether or not an _____ is reached. Provide a scientific basis for estimating a patients daily exposure _____	_____	9 months
26 Sep 2005	22.b.	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 _____ in the list of validated limits for the _____ (comment 22b)  1) Specify validated limits for these _____ using appropriate standards.  2) Clarify whether the limits in Table 3-1 pertain to limits of quantitation.  3) Provide validation data for the method.  4) Provide justification for validating the method as a limit test.	Device _____	12 months

IR Date	Query #	Verbatim Agreement	"Short Version" Post-Action Commitment	Timing - Following Action Date
26 Sep 2005	22.c.	<p>5) Indicate the amounts of _____</p> <p>6) Comment on the variability of the mean data used for background correction, to remove the contribution of the _____</p> <p>7) Clarify whether the _____ used is capable of detecting and quantitating all _____ that were identified</p> <p>This pertains to _____ and _____ 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, pg.88 of your response). Indicate the basis for these _____ being labeled "_____"</p> <p>Provide an estimate of molecular weights or molecular weight ranges for these _____ and if possible, _____</p> <p>Provide a safety assessment of the levels of the _____</p>	<p>_____ identification</p> <p>_____</p>	9 months
22.d.(3)		<p>Investigate improvement of the extraction and analytical procedures for _____ (with _____ that the data are more consistent and that _____ may be proposed where only one maximum limit has been proposed. The investigation should also examine the composition, manufacture and control _____, insofar as is possible</p>	_____	12 months
22.e.(1)		Describe how age-related changes of these materials will be controlled to ensure adequate function of the components.	Age-related changes for _____	3 months
26 Sep 2005	22.e.(2).a	Pfizer agrees to submit the proposed change for the _____ as a CBE-30 supplement. The requested comparative data will be provided in the CBE-30	_____	TBD

IR Date	Query #	Verbatim Agreement	"Short Version" Post-Action Commitment	Timing - Following Action Date
		supplement.		
26 Sept 2005	22.e(2).b	Pfizer agrees to submit the proposed change for the <del>as a CBE-30 supplement</del> . The requested comparative data will be provided in the CBE-30 supplement.	<del></del>	TBD
26 Sept 2005	22.e(2).c	Pfizer agrees to submit the proposed change to <del>as a prior approval supplement (PAS)</del> . Pfizer commits that a <del>batch size</del> will be used to validate the <del>acceptance of removing the in-process control for</del> <del>The Agency non-</del> <del>is recognized, therefore Pfizer will gather</del> data and withdraw this approach from the comparability protocol. Release and stability data for the <del>blisters will be provided as a part of the PAS, with the</del> comparability protocol updated accordingly. Pfizer, as a part of their continuous improvement process, will evaluate <del></del>	<del></del>	TBD
09 Jan 2006		Pfizer commits to monitor the levels of <del>commercial scale</del> throughout stability studies for <del>commercial scale</del> batches. In addition, if the levels significantly increase over time, Pfizer will commit to revising the specification to include this attribute.	<del></del>	After setup of first <del>production</del> batches on stability



WorldWide Regulatory Affairs  
Pfizer Inc  
50 Pequot Avenue  
New London, CT 06320



## Global Research & Development

27 January 2006

Mary Parks, MD, Acting Director  
Division of Metabolism and Endocrinology Products (HFD-510)  
Office of Drug Evaluation II, CDER, FDA  
ATTN: CENTRAL DOCUMENT ROOM  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

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**Re: NDA 21-868 / EXUBERA<sup>®</sup> (insulin human [rDNA origin]) Inhalation Powder  
Package Insert and Medication Guide**

Dear Dr. Parks:

Reference is made to our pending New Drug Application (NDA 21-868) for EXUBERA<sup>®</sup>  
(insulin human [rDNA origin]) Inhalation Powder, submitted on 27 December 2004.

Enclosed please find the Package Insert and Medication Guide that were agreed upon with  
Agency on 27 January 2006.

Sincerely,

A handwritten signature in black ink that reads "Brian A. Green". The signature is written in a cursive, flowing style.

Brian A. Green, MS  
Associate Director  
Worldwide Regulatory Strategy  
Worldwide Regulatory Affairs and Quality Assurance

**NDA REGULATORY FILING REVIEW**  
(Including Memo of Filing Meeting)

NDA # 21-868

Supplement #

Efficacy Supplement Type SE-

Trade Name: Exubera

Established Name: Insulin [rDNA origin] Inhalation Product

Strengths: 1 and 3 mgs

Applicant: Pfizer, Inc.

Agent for Applicant: Brian Green

Date of Application: December 27, 2004

Date of Receipt: December 28, 2005

Date clock started after UN:

Date of Filing Meeting: February 10, 2005

Filing Date: February 26, 2005

Action Goal Date (optional): October 3, 2005

User Fee Goal Date: October 28, 2005

Indication(s) requested: Treatment of Hypoglycemia in DM patients

Type of Original NDA:

(b)(1) ☒

(b)(2) ☐

OR

Type of Supplement:

(b)(1) ☐

(b)(2) ☐

**NOTE:**

(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2), complete Appendix B.

(2) If the application is a supplement to an NDA, please indicate whether the NDA is a (b)(1) or a (b)(2) application:

☒ NDA is a (b)(1) application

OR

☐ NDA is a (b)(2) application

Therapeutic Classification: S ☒

P ☐

Resubmission after withdrawal? ☐

Resubmission after refuse to file? ☐

Chemical Classification: (1,2,3 etc.) 3,5

Other (orphan, OTC, etc.)

Form 3397 (User Fee Cover Sheet) submitted:

YES ☒ NO ☐

User Fee Status:

Paid ☒

Exempt (orphan, government) ☐

Waived (e.g., small business, public health) ☐

**NOTE:** If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling.

Version: 12/15/2004

This is a locked document. If you need to add a comment where there is no field to do so, unlock the document using the following procedure. Click the 'View' tab; drag the cursor down to 'Toolbars'; click on 'Forms.' On the forms toolbar, click the lock/unlock icon (looks like a padlock). This will allow you to insert text outside the provided fields. The form must then be relocked to permit tabbing through the fields.

*If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the user fee staff.*

- Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application? YES ☐ NO ☒  
If yes, explain:
- Does another drug have orphan drug exclusivity for the same indication? YES ☐ NO ☒
- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES ☐ NO ☐

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES ☐ NO ☒  
If yes, explain:
- If yes, has OC/DMPQ been notified of the submission? YES ☐ NO ☐
- Does the submission contain an accurate comprehensive index? YES ☒ NO ☐
- Was form 356h included with an authorized signature? YES ☒ NO ☐  
**If foreign applicant, both the applicant and the U.S. agent must sign.**
- Submission complete as required under 21 CFR 314.50? YES ☒ NO ☐  
If no, explain:
- If an electronic NDA, does it follow the Guidance? N/A ☐ YES ☒ NO ☐  
**If an electronic NDA, all forms and certifications must be in paper and require a signature.**  
Which parts of the application were submitted in electronic format? all not requiring original signature

Additional comments:

- If an electronic NDA in Common Technical Document format, does it follow the CTD guidance? N/A ☐ YES ☒ NO ☐
- Is it an electronic CTD (eCTD)? N/A ☐ YES ☐ NO ☒  
**If an electronic CTD, all forms and certifications must either be in paper and signed or be electronically signed.**

Additional comments:

- Patent information submitted on form FDA 3542a? YES ☒ NO ☐
- Exclusivity requested? YES, 3 Years NO ☐  
**NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.**
- Correctly worded Debarment Certification included with authorized signature? YES ☒ NO ☐  
**If foreign applicant, both the applicant and the U.S. Agent must sign the certification.**

**NOTE:** Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . . ."

- Financial Disclosure forms included with authorized signature? YES ☒ NO ☐  
(Forms 3454 and 3455 must be included and must be signed by the APPLICANT, not an agent.)  
**NOTE:** Financial disclosure is required for bioequivalence studies that are the basis for approval.
- Field Copy Certification (that it is a true copy of the CMC technical section)? Y ☒ NO ☐
- PDUFA and Action Goal dates correct in COMIS? YES ☒ NO ☐  
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.
- List referenced IND numbers: I43,313
- End-of-Phase 2 Meeting(s)? Date(s) 6/2/98? NO ☐  
If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s)? Date(s) 6/9/2004 NO ☐  
If yes, distribute minutes before filing meeting.

### Project Management

- Was electronic "Content of Labeling" submitted? YES ☒ NO ☐  
If no, request in 74-day letter.
- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? YES ☒ NO ☐
- Risk Management Plan consulted to ODS/IO? N/A ☐ YES ☒ NO ☐
- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? Y ☒ NO ☐
- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A ☐ YES ☒ NO ☐
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted? N/A ☒ YES ☐ NO ☐

### If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? N/A ☒ YES ☐ NO ☐
- Has DOTCDP been notified of the OTC switch application? YES ☐ NO ☐

**Clinical**

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?  
YES ☐ NO ☒

**Chemistry**

- Did applicant request categorical exclusion for environmental assessment? YES ☒ NO ☐  
If no, did applicant submit a complete environmental assessment? YES ☐ NO ☐  
If EA submitted, consulted to Florian Zielinski (HFD-357)? YES ☐ NO ☐
- Establishment Evaluation Request (EER) submitted to DMPQ? YES ☒ NO ☐
- If a parenteral product, consulted to Microbiology Team (HFD-805)? YES ☒ NO ☐

ATTACHMENT

MEMO OF FILING MEETING

DATE: February 10, 2005

BACKGROUND: Agenda

Exubera (Insulin [rDNA Origin] Inhalation Product) Filing Meeting  
NDA 21-868  
February 10, 2005

1. Discuss filing issues:
  - A. Chemistry - Drug Product to be reviewed jointly between DMEDP and DPADP
    - Did sponsor request a categorical exclusion for Environmental assessment? Y
    - Establishment Evaluation Request (EER) package submitted? Y
    - Parenteral Application Consulted to Sterile Products (HFD-805)? Y
  - B. Pharmacology - No Issues
  - C. Biopharm - 3x1mg dose is 40% more bioequivalent than the 1x3mg dose
  - D. Statistics - adolescent datasets missing
  - E. Clinical
    - DMEDP - No Filing Issues
    - DPADP - No Filing Issues
  - F. Office of Drug Safety
  - G. CDRH
2. Standard Review
3. Financial Disclosure Information in Application
4. DSI Audits
5. Advisory Committee Meeting: September 8, 2005 (See Timeline)  
Rehearsals will be scheduled after specific date has been identified.
6. Goal to finish reviews with team leader sign-off: October 3, 2005

Action Package should start circulating on October 10, 2005

Action Goal Date: October 22, 2005

7. Status Meetings: March 17, and June 1, 2005
8. User Fee Date: October 28, 2005

(Provide a brief background of the drug, e.g., it is already approved and this NDA is for an extended-release formulation; whether another Division is involved; foreign marketing history; etc.)

ATTENDEES:

ASSIGNED REVIEWERS (including those not present at filing meeting) :

Discipline

Reviewer

Medical:

Medical: Karen Mahoney (David Orloff, Team Leader)

- Secondary Medical: Sally Seymour (Eugene Sullivan, Team Leader)
- Statistical: Joy Mele (Efficacy) and JoAnne Buenconsuejo (Safety) (Todd Sahlroot, Team Leader)
- Pharmacology: Herman Rhee (Jeri El Hage, Team Leader)
- Chemistry: Janice Brown (Steve Moore, Team Leader)

- DPADP Chemistry: Rick Lostritto. Team Leader
- Environmental Assessment:
- Biopharmaceutics: Jim Wei (Hae Young Ahn, Team Leader)
- Microbiological: James McVey
- DSI: Andrea Slaven
- Regulatory Project Management: Oluchi Elekwachi (Kati Johnson, Team Leader)
- DDMAC: Catherine Gray
- ODS:
- o Risk Management: Mary Dempsey, Lahn Green, Sandra Birdsong, Joslyn Swann, Claudia Karowski
- o Labeling: Charles Hoppes
- o PPI: Jeanine Best
- CDRH: Ann Graham

Secondary Medical:

Statistical:

Pharmacology:

Statistical Pharmacology:

Chemistry:

Environmental Assessment (if needed):

Biopharmaceutical:

Microbiology, sterility:

Microbiology, clinical (for antimicrobial products only):

DSI:

Regulatory Project Management:

Other Consults:

Per reviewers, are all parts in English or English translation?  
If no, explain:

YES ☒ NO ☐

CLINICAL

FILE ☒

REFUSE TO FILE ☐

• Clinical site inspection needed? YES ☒ NO ☐

• Advisory Committee Meeting needed? YES, date if known September 8, 2005 NO ☐

• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?

N/A ☒ YES ☐ NO ☐

CLINICAL MICROBIOLOGY

N/A ☒

FILE ☒

REFUSE TO FILE ☐

STATISTICS

N/A ☐

FILE ☒

REFUSE TO FILE ☐

BIOPHARMACEUTICS

FILE ☒

REFUSE TO FILE ☐

• Biopharm. inspection needed? YES ☐ NO ☐

PHARMACOLOGY

N/A ☐

FILE ☒

REFUSE TO FILE ☐

• GLP inspection needed? YES ☐ NO ☐

CHEMISTRY

FILE ☒

REFUSE TO FILE ☐

- Establishment(s) ready for inspection?
- Microbiology

YES	<input checked="" type="checkbox"/>	NO	<input type="checkbox"/>
YES	<input checked="" type="checkbox"/>	NO	<input type="checkbox"/>

ELECTRONIC SUBMISSION:  
Any comments: electronic NDA

**REGULATORY CONCLUSIONS/DEFICIENCIES:**  
**(Refer to 21 CFR 314.101(d) for filing requirements.)**

- ☐ The application is unsuitable for filing. Explain why:
- ☒ The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.
- ☒ No filing issues have been identified.
- ☐ Filing issues to be communicated by Day 74. List (optional):

**ACTION ITEMS:**

1. ☐ If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
2. ☐ If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
3. ☒ Convey document filing issues/no filing issues to applicant by Day 74.

Oluchi Elekwachi, PharmD, MPH  
Regulatory Project Manager, HFD-510



## Appendix A to NDA Regulatory Filing Review

An application is likely to be a 505(b)(2) application if:

- (1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
- (2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
- (4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

**Appendix B to NDA Regulatory Filing Review  
Questions for 505(b)(2) Applications**

1. Does the application reference a listed drug (approved drug)? YES ☐ NO ☐

*If "No," skip to question 3.*

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):
3. The purpose of this and the questions below (questions 3 to 5) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval and that should be referenced as a listed drug in the pending application.

- (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?

YES ☐ NO ☐

*(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))*

*If "No," skip to question 4. Otherwise, answer part (b).*

- (b) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES ☐ NO ☐  
(The approved pharmaceutical equivalent(s) should be cited as the listed drug(s).)

*If "Yes," skip to question 6. Otherwise, answer part (c).*

- (c) Have you conferred with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007)?

YES ☐ NO ☐

*If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.*

4. (a) Is there a pharmaceutical alternative(s) already approved? YES ☐ NO ☐

*(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

*If "No," skip to question 5. Otherwise, answer part (b).*

- (b) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES ☐ NO ☐  
(The approved pharmaceutical alternative(s) should be cited as the listed drug(s).)

**NOTE:** *If there is more than one pharmaceutical alternative approved, consult the Director, Division of*

*Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007) to determine if the appropriate pharmaceutical alternatives are referenced.*

*If "Yes," skip to question 6. Otherwise, answer part (c).*

- (c) Have you conferred with the Director, Division of Regulatory Policy II, ORP? YES ☐ NO ☐

*If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.*

5. (a) Is there an approved drug product that does not meet the definition of "pharmaceutical equivalent" or "pharmaceutical alternative," as provided in questions 3(a) and 4(a), above, but that is otherwise very similar to the proposed product?

YES ☐ NO ☐

*If "No," skip to question 6.*

*If "Yes," please describe how the approved drug product is similar to the proposed one and answer part (b) of this question. Please also contact the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007), to further discuss.*

- (b) Is the approved drug product cited as the listed drug? YES ☐ NO ☐
6. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").
7. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)).) YES ☐ NO ☐
8. Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 21 CFR 314.101(d)(9)). YES ☐ NO ☐
9. Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application should be refused for filing under 21 CFR 314.101(d)(9)). YES ☐ NO ☐
10. Are there certifications for each of the patents listed for the listed drug(s)? YES ☐ NO ☐
11. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)  
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)  
Patent number(s):

- ☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)  
Patent number(s):
- ☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)  
Patent number(s):

**NOTE:** IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must **subsequently** submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)].

- ☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.
- ☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)  
Patent number(s):
- ☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).  
Patent number(s):
- ☐ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.  
Patent number(s):

12. Did the applicant:

- Identify which parts of the application rely on information (e.g. literature, prior approval of another sponsor's application) that the applicant does not own or to which the applicant does not have a right of reference?  
YES ☐ NO ☐
- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?  
YES ☐ NO ☐
- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?  
N/A ☐ YES ☐ NO ☐
- Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).)?  
N/A ☐ YES ☐ NO ☐

13. If the (b)(2) applicant is requesting 3-year exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

- Certification that at least one of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

YES ☐ NO ☐

- A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

YES ☐ NO ☐

- EITHER

The number of the applicant's IND under which the studies essential to approval were conducted.

IND# \_\_\_\_\_ NO ☐

OR

A certification that the NDA sponsor provided substantial support for the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

YES ☐ NO ☐

14. Has the Associate Director for Regulatory Affairs, OND, been notified of the existence of the (b)(2) application?

YES ☐ NO ☐

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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.**  
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/s/

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Oluchi Elekwachi  
3/27/05 10:38:30 PM  
CSO

69 Page(s) Withheld

\_\_\_\_\_ § 552(b)(4) Trade Secret / Confidential

X § 552(b)(4) Draft Labeling

\_\_\_\_\_ § 552(b)(5) Deliberative Process

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/s/

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Karen Mahoney  
5/13/05 03:51:06 PM  
MEDICAL OFFICER

David Orloff  
5/13/05 04:45:30 PM  
MEDICAL OFFICER





## Global Research & Development

27 January 2006

Mary Parks, MD, Acting Director  
Division of Metabolism and Endocrinology Products (HFD-510)  
Office of Drug Evaluation II, CDER, FDA  
ATTN: CENTRAL DOCUMENT ROOM  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

THIS DOCUMENT CONTAINS CONFIDENTIAL  
AND/OR TRADE SECRET INFORMATION THAT IS  
DISCLOSED ONLY IN CONNECTION WITH THE  
LICENSING AND/OR REGISTRATION OF  
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COMPANIES. THIS DOCUMENT SHOULD NOT BE  
DISCLOSED OR USED, IN WHOLE OR IN PART, FOR  
ANY OTHER PURPOSE WITHOUT THE PRIOR  
WRITTEN CONSENT OF PFIZER INC.

**Re: NDA 21-868 / EXUBERA® (insulin human [rDNA origin]) Inhalation Powder  
Revised Container and Carton Labeling**

Dear Dr. Parks:

Reference is made to our pending New Drug Application (NDA 21-868) for EXUBERA®  
(insulin human [rDNA origin]) Inhalation Powder, submitted on 27 December 2004.

Enclosed please find the revised, hand-written container and carton labeling mock-ups that were  
submitted and agreed upon with Agency on 27 January 2006.

Sincerely,

A handwritten signature in black ink that reads "Brian A. Green".

Brian A. Green, MS  
Associate Director  
Worldwide Regulatory Strategy  
Worldwide Regulatory Affairs and Quality Assurance

BAG/ms  
0038

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\_\_\_\_\_ § 552(b)(4) Trade Secret / Confidential

\_\_\_\_\_ § 552(b)(5) Deliberative Process

X § 552(b)(4) Draft Labeling

Meeting Date: August 18, 2000      Time: 3:00 – 4:30 PM      Location: Conf. Rm. C

IND 43,313 Exubera (insulin dry powder/pulmonary inhaler)

Type of Meeting: Guidance

External participant: **Pfizer Central Research**

Meeting Chair: Dr. Saul Malozowski

External participant lead: Ms. Nancy Martin

Meeting Recorder: Mr. Randy Hedin

FDA Attendees and titles:

Dr. John Jenkins, Director, ODE II  
Dr. Saul Malozowski, Clinical Team Leader, DMEDP  
Dr. Elizabeth Koller, Clinical Reviewer, DMEDP  
Dr. Eugene Sullivan, Clinical Reviewer, DPADP  
Dr. Badrul Chowdhury, Acting Clinical Team Leader, DPADP  
Dr. Todd Sahlroot, Biometrics Team Leader, DOB II  
Ms. Steven Moore, Chemistry Team Leader DMEDP  
Mr. Randy Hedin, CSO DMEDP

External participant Attendees and titles:

Dr. Ralf Rosskamp, Aventis, Clinical Research  
Dr. Robert Gelfand, Pfizer, Global Candidate Team Leader  
Dr. John Teeter, Pfizer, Clinical Research (Pulmonary)  
Dr. Sue Sha, Pfizer, Clinical Pharmacology  
Dr. Cecile Balagtas, Pfizer, Biometrics  
Ms. Nancy Martin, Pfizer, Regulatory  
Dr. Cheryl Graham, Pfizer, Regulatory  
Dr. Jeffrey Blumenstein, Pfizer,  
Dr. \_\_\_\_\_  
Dr. Alan Krasner, Pfizer, Clinical Research  
Dr. James Spavins Pfizer, Chemistry, Manufacturing & Controls  
Ms. Susan DeCorte, Pfizer, Regulatory

## Meeting Objectives:

The meeting was requested by Pfizer Central Research to discuss clinical, technical, and regulatory aspects of the inhaled insulin development program.

## Discussion Points and Decisions (agreements) reached:

- Pfizer Central Research submitted the following questions in a July 24, 2000 correspondence. The Division's response (in bold) and the discussion from the meeting follow each question.

### Question 1:

Does the Agency agree that the proposed pulmonary safety program will provide sufficient data for an approvable NDA?

**No.**

**In the absence of a concurrent standard-care control group it will be very difficult to interpret any safety signals which arise from the long-term safety experience. Analyses of pre-existing databases will not provide a relevant comparator and cannot be a substitute for concurrent controls.**

**The development program should address the acute and chronic effects of inhaled insulin in patients with underlying lung disease (asthma and COPD).**

Discussion: The firm presented a slide on studies that have been done with patients with underlying lung disease; however, all these studies were single-dose pharmacokinetic studies. The Division stated that they are inadequate to demonstrate safety and asked what the label will read concerning administration with lung disease. The firm responded that a cautionary statement will be proposed. The Division stated that cautionary labeling will not be an acceptable alternative to data on the acute and chronic effects of inhaled insulin in patients with underlying lung disease.

The Division stated concerning the phase 3 trials that the firm should have at least one-year well-controlled data for the NDA submission. If the firm submits only uncontrolled long-term data in the NDA submission and any safety signals are seen the application would probably be not-

approvable. The firm stated that it expects the long-term uncontrolled data to stand on its own and the Division replied that the firm would be taking a great risk by submitting such an application. It is improbable that no signal will be seen. The Division further stated that it is very concerned with long-term adverse events; some patients may be treated for life, and many for 15 to 20 years or more, and we don't want patients developing lung disease for convenience to avoid insulin injection. Therefore, long-term controlled safety data will be required. The firm asked how long a controlled study will be needed and with how many patients? The Division responded that the firm should propose a study, and the Division would review the proposal and comment.

Question 2:

Does the Agency agree that the following issues deserve discussion and agreement prior to submission of the NDA? If so, then what arrangements can be made now to assure that these issues are discussed and resolved in a timely fashion?

- Insulin manufacturing facility proposed for commercialization
- Scale-up protocols for spray drying and filling operations.
- Specifications for insulin powder for inhalation.
- Pulmonary inhaler controls and linkage of clinical manufacture to that proposed for commercialization.

**It's the Division's policy to meet and resolve important issues in a timely manner. Please submit a written request for a CMC meeting when appropriate. This request should include:**

- 1. A brief statement of the purpose of the meeting**
- 2. A listing of the specific objectives/outcomes you expect from the meeting**
- 3. A proposed agenda, including estimated times needed for each agenda item**
- 4. A listing of planned external attendees**
- 5. A listing of requested participants from CDER and CDRH**
- 6. The approximate time at which supporting documentation for the meeting will be sent to CDER prior to the meeting.**

Discussion: The Division stated that having three or four CMC meetings

seemed excessive. Perhaps some of these proposed meetings can be combined.

Question 3:

Clarification is sought on the review process envisioned by the FDA for the EXUBERA NDA. Specifically:

- Does it still appear favorable that the EXUBERA NDA will be assigned a Priority Review?
- To facilitate both the pre-filing dialogue and NDA review process, would the Agency advise any alternative submission strategies such as Fast-Track designation?
- Will the review of the EXUBERA NDA be coordinated by one FDA designated Team Leader across the review disciplines (i.e. Clinical, CMC, etc.) or will there be a Team Leader assigned per review discipline from the Division of Metabolism and Endocrine Drug Products?
- Will the Team Leader have overall responsibility for the consultants from the Pulmonary Division and CDRH, i.e. establishment of overall timelines and schedules?
- How can Pfizer facilitate this effort in terms of forthcoming submissions, i.e. number of submission copies, identification of FDA distribution lists, meeting requests, establishing electronic access, e-mail communications, and response/query dialogues?

The above bullets are generally internal review issues.

The priority designation will be made when the NDA is submitted.

Section 506(a)(1) of the Act states that a drug designated as a fast track product is intended for the treatment of a serious or life-threatening condition and demonstrates the potential to address unmet medical needs for the condition. Regardless, whether this drug meets the criteria for fast track, the designation of fast track offers very little advantage.

- We meet with sponsors regularly.
- Rolling NDA reviews offer little advantage because with our workload we generally do not have the resources to review NDAs until the entire submission is received and it's on a regulatory timeline.

Discussion: The Division stated that the firm should work through the Project Manager in DMEDP, and he will coordinate the review, when appropriate, with other Divisions.

- The firm gave a demonstration on how to use the device that delivers the inhaled insulin. The firm stated that the life of the device is \_\_\_\_\_ months of continuous use data at this time. The Division stated that there were problems that presented themselves that were not apparent without patient handling of the device e.g. \_\_\_\_\_. This has resulted in changes in the device. The firm stated that all failures have been engineered out of the device. The Division stated that the NDA must include data on device performance for the entire life of the device. The Division stated that this information should be submitted with the NDA, and asked if the same device was used throughout the trials. The firm responded that the same device was used in the phase 3 trials, with the above engineering changes, and this device, with minor changes to facilitate manufacturing, will be the marketed product. The Division stated that any changes in the device during or subsequent to clinical testing must not alter the performance characteristics of the device. The sponsor was asked to submit data on how often the patient did not receive a dose because of device failure, and what percent of the time the patient did not know there was a problem. The Division asked if the inhaler will be used for any other drugs, and the firm replied negatively.

Unresolved or issues requiring further discussion:

- None

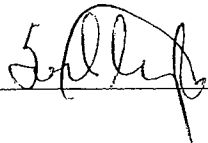
Action Items:

- None

Signature, minutes preparer:



Concurrence Chair:

 9/2/00

cc: NDA Arch

HFD-510

Attendees

HFD-510/EGalliers

HFD-511/RHedin/8.14.00/I43313\_MN1

Concurrences: SMoore/SMalozowski/8.25ESullivan/BChowdhury/8.28/

EKoller/8.30.00/No Response/JJenkins/TSahlroot

43,313

## MEMORANDUM OF MEETING MINUTES

**Meeting Date:** October 18, 1999

**Time:** 1:30 – 3:30 pm

**Location:** Parklawn Building 3<sup>rd</sup> fl c/r "C"

**Application:** IND 43,313 Insulin Dry Powder/Pulmonary Inhaler

**Sponsor:** Pfizer, Inc.

**Type of Meeting:** End-of-Phase 2 (CMC)

**Meeting Chair:** Stephen Moore, Ph.D.

**Meeting Recorder:** Julie Rhee

**Attendees:**

**FDA:**

John Gibbs, Ph.D., Director, Division of New Drug Chemistry II

Stephen Moore, Ph.D., Chemistry Team Leader, DMEDP

Alan Schroeder, Ph.D., Chemist, DPDP

Julie Rhee, Project Manager, DMEDP

**Pfizer, Inc.:**

Nancy Martin, Senior Associate Director, Regulatory Strategy and Registration

David Dresback, Senior Director, Technical Assistant

Jackie Schumacher, Senior Supervisor, Regulatory CMC Operations

Jeffrey Blumenstein, Director, Regulatory CMC Operations

Robert Casson, Director, Corporate Quality Assurance

James Spavins, Group Director, Analytical Research and Development

---

### Discussion Points:


#### Insulin Inhalation Powder:

The following comments are preliminary comments based on information which has been provided to the Agency.

1. Phase 3 studies started June of this year. NDA submission is expected June 2001.
2. The stability protocol should include additional storage conditions of 25°C/75% RH for one-third of the proposed expiration dating period, because protective packaging is proposed. We have found that in some cases, 25°C/75% R.H. is more stressful than 30°C/60% R.H. Alternatively, if 30°C/60% R.H. conditions can be shown to be equally stressful or more stressful than the 25°C/75% R.H.



conditions, by their effect on exposed powder formulation, the 30°C/60% R.H. condition may be acceptable in place of the 25°C/75%R.H. conditions.

3. In response to a question by the sponsor, the Agency noted that the 30°C/60% R.H. conditions may also be acceptable if there are no particle size distribution failures or failures of content uniformity at 40°C/75%R.H. over 6 months, provided that the specifications are acceptable to us.
4. 
5. Include foreign particulates in the shelf-life studies protocol. Drug product characterization studies should include temperature cycling.
6. Blister packs without overwrap are said to be stable for 3-months.
7. The Agency agreed to work with the sponsor on biological potency testing. The sponsor is to submit a validation protocol to demonstrate that there is no effect on potency as a result of drug product manufacturing.
8. Insulin from Hoechst and Lilly are used in clinical trials. However, the sponsor stated that Hoechst and Lilly insulins have comparable purity.
9. The Agency expressed additional concern about impurities and degradation products which may be present in excipients because the drug product is delivered by the inhalation route. In order to insure the strength, quality and purity of the excipients, additional controls besides those in USP and NF monographs may be needed.
10. Depending on the changes made to the device, utilizing *in vitro* studies alone may not be sufficient to support the scale-up proposal for the device, and it is possible that our clinical and biopharm disciplines may require additional studies other than *in vitro* studies for the device scale-up.
11. Recover the devices that were used in clinical studies and re-evaluate their performance (i.e., *in vitro* testing). Also, re-evaluate the device at the end of its expected life-cycle.
12. Since the drug product is going to be supplied as a kit, the drug product lot number would be traceable using a kit lot number.
13. The Agency stated that we could not respond immediately to their proposal for multiple interchangeable components, with different lot numbers. This is a new approach and would have to be carefully considered by the Agency. We have

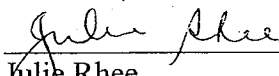
concerns should the components of the device turn out to be not fully interchangeable, especially if manufactured at different sites. It was reiterated that the Agency considers the drug product as the drug-device combination.

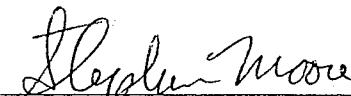
14. The sponsor is advised to submit specific device questions to the DMEDP.
15. Routine extraction controls (acceptance controls for device) should include some type of extraction profile for identity to insure that composition has not changed, since composition may affect component performance, molding process, etc. This is similar to the requirements for the MDI mouthpiece. Extractable testing should include controls on device components that come into contact with drug and the patient's mouth, and those which may affect the performance of the device. Once the reliability of the supplier's test results is established, a reduced testing schedule may be considered.
16. The sponsor should verify that release testing on drug/device combination will be done, since this constitutes the drug product. The device itself should be released based on performance testing (using drug formulation), not solely on functional tests (e.g., pressure test, air flow test).
17. Clinical trials should include the device through its proposed lifetime; performance of the device should be tested through its lifetime.
18. The sponsor should consider whether the spacer can be removed and content uniformity be determined on emitted dose. This should allow tighter specifications.
19. The agency asked why the transjector needs to be replaced every two weeks, and what is the consequence of not doing so. The sponsor indicated that without cleaning, there would be a gradual deterioration of performance, and the patient would not be aware of it.
20. The proposed content uniformity specifications are wider than those usually accepted by the Agency.
21. FDA asked what is meant (pg. 32) by the statement that the device chamber components will be supplied separately from the fully assembled unit. The sponsor said that this situation may occur if the components were damaged by the patient. The chamber will not be replaced routinely, however.
22. The stability of the aerosol cloud in the chamber ("hang time") was discussed. The sponsor noted that there is a slight increase in particle sizes over 30 seconds, and that this represents two competing tendencies: aggregation vs. precipitation. Data show that the emitted dose decreases after 30 seconds (e.g., 80% to 60%).

24. FDA noted a concern, if components from different manufacturing sites for the device are interchanged.

**Decisions (agreements) reached:**

1. Stability protocol for Insulin Powder spray-dried at commercial scale and filled into 1 and 3 mg blister packs, with 6 months data available at submission, is acceptable.
2. Stability protocol to support product labeling for in-patient use, i.e., blister packs without overwrap, is acceptable.
3. The sponsor agreed to submit extensive validation protocol for biological potency testing.
4. FDA indicated that some questions/issues may need to be deferred, pending review of additional data and understanding of the device. We need to have a sample of the device, and a disassembled device to show operation. The sponsor agreed to provide samples of the device and more detailed information about its operation and function. The Agency and the sponsor agreed to continue dialogue on the device.
5. In vitro studies may not be enough for the scale-up requirements for the inhaler. Clinical and biopharm disciplines may require additional studies for the scale-up for the inhaler.
6. Stability and patient use and "storage excursion studies" for the inhaler appear to be acceptable.

 11-17-99  
Julie Rhee  
Minutes Preparer

 11-17-99  
Stephen Moore, Ph.D.  
Chair Concurrence

Attachments: Copy of overhead presentation

Page 5  
IND 43,313  
10/18/99 meeting minutes

cc: Original IND  
HFD-510/Div. Files  
HFD-510/Moore  
HFD-570/Schroeder  
HFD-820/Gibbs  
Drafted by: JRhee 10-21-99  
Initialed by: Gibbes 11-5-99/Schroeder 11-17-99/Moore 11-17-99  
final: JRhee 11-17-99

MEETING MINUTES



**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-868

**INFORMATION REQUEST LETTER**

Pfizer Global Research & Development  
Attention: Brian Green, M.S.  
Associate Director, Worldwide Regulatory Affairs  
50 Pequot Avenue  
MS 6025 - B6275  
New London, CT 06320

12/7/05

Dear Mr. Green:

Please refer to your December 27, 2004 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Exubera (Insulin [rDNA origin] Inhalation Powder) 1 and 3 mgs.

We also refer to your submission dated January 12, February 23, March 17, April 26, May 6, 12, 31, June 10, 13, 22, and July 5, 13, 19, 21, 25, 26, 29, August 2, 4, 9, 12, 19, 23, 26, September 21, 22, 28, October 3, 6, 10, 28, and November 11, 2005.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

A large, handwritten signature in black ink is written across the bottom half of the page. The signature is cursive and appears to be a name, possibly "Brian Green", though it is difficult to read with certainty. It starts with a large, sweeping 'B' and ends with a long, trailing stroke.

1 Page(s) Withheld

9 § 552(b)(4) Trade Secret / Confidential

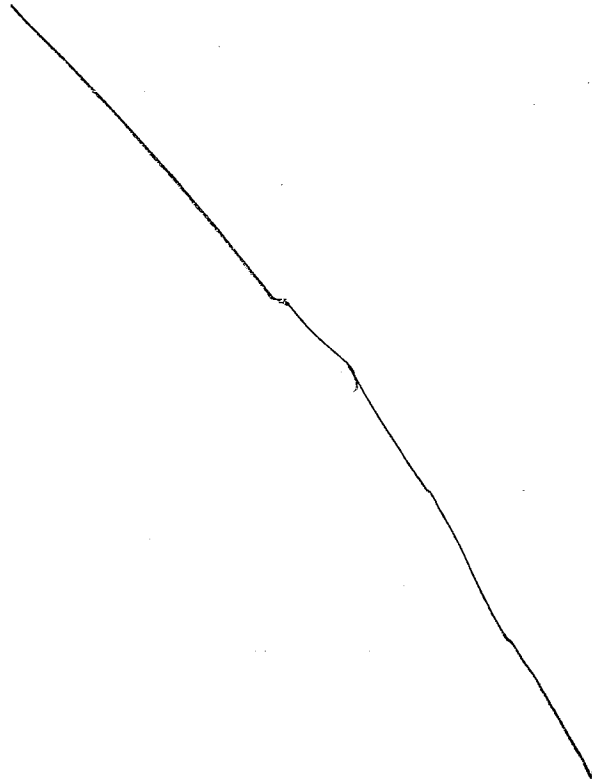
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If you have any questions, call Oluchi Elekwachi, Pharm.D., M.P.H., Regulatory Health Project Manager, at 301-796-1207.

Sincerely,

Blair Fraser, Ph.D.  
Branch II Chief  
Division of Pre-Marketing Assessment I  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

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/s/

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Blair Fraser

12/7/2005 05:04:45 AM





**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-868

**INFORMATION REQUEST LETTER**

Pfizer Global Research & Development  
Attention: Brian Green, M.S.  
Associate Director, Worldwide Regulatory Affairs  
50 Pequot Avenue  
MS 6025 - B6275  
New London, CT 06320

11/30/05

Dear Mr. Green:

Please refer to your December 27, 2004 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Exubera (Insulin [rDNA origin] for Inhalation) 1 and 3 mgs.

We also refer to your submission dated January 12, February 23, March 17, April 26, May 6, 12, 31, June 10, 13, 22, and July 5, 13, 19, 21, 25, 26, 29, August 2, 4, 9, 12, 19, 23, 26, September 21, 22, 28, October 3, 6, 10, 28, and November 11, 2005.

We are reviewing the Risk Management section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. As stated in our correspondence dated November 7, 2005, we recommend a Medication Guide (MG) for Exubera because the Patient Information Subcommittee (PISC) of CDER's Medical Policy Coordination Committee determined on October 6, 2005, that Exubera meets the criteria for a MG in that required written patient information is necessary for a patient's safe and effective use of this product.
  - a. The Sponsor should develop the MG and submit it to FDA for review
  - b. The Medication Guide should follow the content and format requirements set forth in 21 CFR 208.20 and the MG content should be based on the professional product labeling.
2. The Sponsor should submit data regarding comprehension testing or actual use studies of device and dosing training materials for patients that were conducted outside of the clinical trial setting, to ensure educational materials are understandable and effective. If no such data exist, the Sponsor should conduct this research as a Post-marketing Commitment (PMC).
3. We request details of the sponsor's evaluation plan and recommend it address the following at a minimum:

- a. Determination of appropriate patient selection (e.g., limiting use in patients who smoke, patients with certain underlying lung diseases, or pediatric patients).
  - b. Determination of whether clinicians are performing recommended Pulmonary Function Tests (PFTs).
  - c. Determination of patients' adverse events of hypoglycemia due to smoking or inappropriate dose substitution.
  - d. Determination of the extent of use in the pediatric patient population.
4. Post-marketing commitments should include further studies to address the long term safety issues such as risk of lung cancer and deterioration of pulmonary function.
  5. Please describe your best estimate of the projected size of the Diabetes Mellitus (DM) population that has either asthma or COPD.
  6. Please provide the number and percentage of former smokers who resumed smoking during the Randomized Clinical Trials (RCTs) and the rationale for selecting a cutoff of 6 months cessation of tobacco smoking for exclusion from study.

If you have any questions, call Oluchi Elekwachi, Pharm.D., M.P.H., Regulatory Health Project Manager, at 301-796-1207.

Sincerely,

*{See appended electronic signature page}*

David Orloff, MD  
Director  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/

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David Orloff

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**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-868

**INFORMATION REQUEST LETTER**

Pfizer Global Research & Development  
Attention: Brian Green, M.S.  
Associate Director, Worldwide Regulatory Affairs  
50 Pequot Avenue  
MS 6025 - B6275  
New London, CT 06320

11/7/05

Dear Mr. Green:

Please refer to your December 27, 2004, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Exubera (Insulin [rDNA origin] Inhalation Powder) 1 and 3 mgs.

We also refer to your submissions dated January 12, February 23, March 17, April 26, May 6, 12, 31, June 10, 13, 22, and July 5, 13, 19, 21, 25, 26, 29, August 2, 4, 9, 12, 19, 23, 26, September 21, 22, 28, October 3, 6, 10, and 28, 2005.

We are reviewing the Labeling section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

We have determined per 21 CFR 208.1(c)(1) and (2) that a Medication Guide is necessary for a patient's safe and effective use of Exubera (Insulin [rDNA origin] Inhalation Powder) 1 and 3 mgs. Please submit a Medication Guide following the general requirements set forth in 21 CFR 208.20. The Medication Guide will replace your Patient Package Insert (PPI). We suggest, although not required, that you append the Patient Instructions for Use to the Medication Guide so that patients receive their information in one document.

If you have any questions, call Oluchi Elekwachi, Pharm.D., M.P.H., Regulatory Health Project Manager, at 301-796-1207.

Sincerely,

*{See appended electronic signature page}*

David G. Orloff, MD  
Director  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/

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David Orloff  
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2 § 552(b)(4) Trade Secret / Confidential

       § 552(b)(4) Draft Labeling

       § 552(b)(5) Deliberative Process

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**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-868

10/18/05

Pfizer Global Research & Development  
Attention: Brian Green, M.S.  
Associate Director, Worldwide Regulatory Affairs  
50 Pequot Avenue  
MS 6025 - B6275  
New London, CT 06320

Dear Mr. Green:

Please refer to your December 20, 2004 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Exubera ((Insulin [rDNA origin] Inhalation Powder) 1 and 3 mgs.

On October 4, 2005, we received your October 3, 2005 major amendment to this application. The receipt date is within 3 months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is January 28, 2006.

If you have any questions, call me at 301-796-1207.

Sincerely,

*{See appended electronic signature page/}*

Oluchi Elekwachi, Pharm.D., M.P.H.  
Regulatory Health Project Manager  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/

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Oluchi Elekwachi  
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**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-868

**INFORMATION REQUEST LETTER**

Pfizer Global Research & Development  
Attention: Brian Green, M.S.  
Associate Director, Worldwide Regulatory Affairs  
50 Pequot Avenue  
MS 6025 - B6275  
New London, CT 06320

9/13/05

Dear Mr. Green:

Please refer to your December 27, 2004 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Exubera 1 and 3 mgs.

We also refer to your submissions dated January 12, February 23, March 17, April 26, May 6, 12, 31, June 10, 13, 22, July 5, 13, 19, 21, 25, 26, 29, August 2, 4, 9, 12, 19, 23, and 26, 2005.

We are reviewing the Clinical section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. In the Exubera® Advisory Committee meeting on September 8, 2005, and in the briefing package you presented data for the annual rate of change for FEV1 and DLCO in Studies 1022, 1029, and 1001-1002. Please provide the SAS program that generates your results.
2. In the Advisory Committee meeting on September 8, 2005, you presented data for subjects with notable declines in pulmonary function. During that presentation you identified several subjects who discontinued due to declines in pulmonary function.
  - a. Provide a list of subjects who discontinued from any of the clinical studies due to a change in pulmonary function. Include the protocol number and location of the narrative for each of the subjects. In addition, provide any follow up information for these subjects.
3. In your submission dated July 29, 2005, you provided the investigator terms coded to the preferred term "Respiratory Disorder." In the pooled controlled phase 2/3 data, there is an imbalance in respiratory disorder adverse events in the treatment groups. Many of the investigator terms coded to respiratory disorder relate to a decrease in pulmonary function tests.
  - a. In the controlled phase 2 and 3 studies, list the investigator terms coded to respiratory disorder by treatment group. Indicate if an investigator term was used more than once. Provide a separate list for type 1 and type 2 diabetes.
  - b. Were there any guidelines for the investigators to report a change in the pulmonary function tests as an adverse event?
4. Provide a list of subjects with a "notable" decline in pulmonary function ( $\geq 15\%$  decline in FEV1 or  $\geq 20\%$  decline in DLCO) in the controlled phase 2/3 studies at Months 3, 6, 9, 12, 15, 18, 21, and 24. Include the two year PFT data from ongoing Studies 1022 and 1029 to generate the list of subjects.
  - a. Provide the study number for each subject and the location of the narrative (if available) for each subject.

If you have any questions, call Oluchi Elekwachi, Pharm.D., M.P.H., Regulatory Health Project Manager, at 301-827-6381.

Sincerely,

*{See appended electronic signature page}*

David G. Orloff, MD

Director

Division of Metabolic and Endocrine Drug Products

Office of Drug Evaluation II

Center for Drug Evaluation and Research

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/s/

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David Orloff

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**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 81-868

**INFORMATION REQUEST LETTER**

Pfizer Global Research & Development  
Attention: Brian Green, M.S.  
Associate Director, Worldwide Regulatory Affairs  
50 Pequot Avenue  
MS 6025 - B6275  
New London, CT 06320

8/29/05

Dear Mr. Green:

Please refer to your December 27, 2004 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Exubera (Insulin [rDNA Origin] powder for oral inhalation) 1 and 3 mgs.

We also refer to your submissions dated January 12, February 23, March 17, April 26, May 6, 12, 31, June 10, 13, 22, and July 5, 13, 19, 21, 25, 26, 29, August 2, 4, 9, 12, and 19, 2005.

We are reviewing the Microbiology section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

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Please call David Hussong, Ph.D. Associate Director for New Drug Microbiology or James L. McVey at (301) 827-7504 for clarification if necessary. All written responses to this correspondence should be sent to the FDA Central Document Room.

Sincerely,

*{See appended electronic signature page}*

David G. Orloff, MD  
Director  
Division of Metabolic and Endocrine Drug Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/

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David Orloff  
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NDA 21-868

## INFORMATION REQUEST LETTER

Pfizer Global Research & Development  
Attention: Brian Green, M.S.  
Associate Director, Worldwide Regulatory Affairs  
50 Pequot Avenue  
MS 6025 - B6275  
New London, CT 06320

8/3/05

Dear Mr. Green:

Please refer to your December 27, 2004 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Exubera 1 and 3 mg.

We also refer to your submissions dated January 12, February 23, March 17, April 26, May 6, 12, 31, June 10, 13, 22, and July 5, 13, 19, 21, 25, and 26, 2005.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Submit data supporting that Unknown 1, Unknown 2, Unknown 3 and other drug product related impurities and insulin degradants classified under Insulin Related Substances have bioactivities similar to that insulin. Alternatively, if bioactivity data is not available, these may be categorized as impurities.
2. Provide a summary of your attempts to detect \_\_\_\_\_.
3. Provide a summary of your attempts to detect \_\_\_\_\_.
4. Revise the test identifier Insulin content (Mean) to Insulin Assay (Mean).
5. Unknown 1 has been identified as an \_\_\_\_\_; therefore revise the specifications and replace unknown 1 with \_\_\_\_\_ product.
6. Page 720 of the submission states that Unknowns 2 and 3 are drug substance degradation products. Clarify whether the identity of these degradation products are known.
7. Bioequivalence studies have shown that the commercial scale lot for the 1 mg strength \_\_\_\_\_ is not bioequivalent to the clinical scale lot \_\_\_\_\_; therefore, the clinical lots used to support the shelf-life can not be used as primary data. However, these studies can be used as supportive data. In order to grant a shelf-life, submit long-term and accelerated stability results updates for commercial batches \_\_\_\_\_.

8. Provide a summary table comparing the physicochemical characteristics and biological activity of insulin lots manufactured at pilot scale compared to the lots manufactured at commercial scale.

If you have any questions, call Oluchi Elekwachi, Pharm.D., M.P.H., Regulatory Health Project Manager, at 301-827-6381.

Sincerely,

Stephen K. Moore, Ph.D.  
Chemistry Team Leader I, for the  
Division of Metabolic and Endocrine Drug Products,  
HFD-510  
DNDC II, Office of New Drug Chemistry  
Center for Drug Evaluation and Research



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/s/

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Stephen Moore  
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**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-868

**INFORMATION REQUEST LETTER**

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

7/12/05

Dear Mr. Green:

Please refer to your December 27, 2004 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Exubera 1 and 3 mgs.

We also refer to your submissions dated January 12, February 23, March 17, April 26, May 6, 12, June 10, 13, 22, and July 5, 2005.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

3 Page(s) Withheld

1 § 552(b)(4) Trade Secret / Confidential

       § 552(b)(4) Draft Labeling

       § 552(b)(5) Deliberative Process

Provide robustness data for the methods in terms of chromatographic parameters

If you have any questions, call Oluchi Elekwachi, Pharm.D., M.P.H., Regulatory Health Project Manager, at 301-827-6381.

Sincerely,

Stephen K. Moore, Ph.D.  
Chemistry Team Leader I for the  
Division of Metabolic and Endocrine Drug  
Products, HFD-510  
DNDC II, Office of New Drug Chemistry  
Center for Drug Evaluation and Research

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/s/

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Chien-Hua Niu  
7/12/05 03:53:12 PM  
Signing for Stephen Moore, Ph.D.



**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-868

**INFORMATION REQUEST LETTER**

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

7/7/05

Dear Mr. Green:

Please refer to your December 28, 2004 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Exubera 1 and 3 mgs.

We also refer to your submissions dated January 12, February 23, March 17, April 26, May 6, 12, June 10, 13, 22, and July 5, 2005.

We are reviewing the Clinical section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. In the pooled HRCT data from Studies 106, 107, and 108 in the Summary of Clinical Safety (Table 11.1.3.1), there are 116 subjects with HRCT data. However, in the individual study reports, in Study 106 there were 39 subjects with HRCT data, in Study 107 there were 28 subjects with HRCT data, and in Study 108 there were 65 subjects who had HRCT scans at the baseline and end of study. The sum of the number of subjects with HRCT data in the 3 individual studies is higher than the number of subjects with HRCT data in Table 11.1.3.1 in the Summary of Clinical Safety. Clarify how you pooled the HRCT data.
2. Were there any "for cause" HRCTs in Studies 1022, 1026, 1027, 1002, and 1001? If so, provide the data listings.
3. Were the primary analysis population and full analysis population pre-specified in the protocol for Studies 1027?
4. Regarding significant changes in the CXR between baseline and last observation, explain how you pooled the data. The significant changes from baseline you report in Table 11.1.1.1 and Table 11.1.1.2 in the Summary of Clinical Safety are less than the number of changes from baseline from the sum of the individual studies. Also, submit the change from baseline CXR (12 month) line listings for Studies 1022 and 1029. If the CXR data for Studies 1022 and 1029 are included in the current submission, indicate the location.
5. Provide the study number and patient identification number for the 5 subjects with pleural effusion noted in the extension studies and the location of the narratives. Submit the narratives if not included in the NDA submission.
6. Provide a summary of the oxygen saturation data in the studies in which oxygen saturation was collected with the pulmonary function tests. Provide a list of subjects with decline in oxygen saturation >5% or oxygen saturation <93%.

7. In the Summary of Clinical Safety, Table 6.1.1.3, (page 1872), for the inhaled insulin group, clarify if the total number of SAE events for the Respiratory, Thoracic and Mediastinal Disorders should be 9 or 10.
8. Regarding Discontinuations due to Adverse Events (AE)  
In the Summary of Clinical Safety, Table 7.1.6.1 (Discontinuation due to AEs), there appears to be 12 Type 1 subjects treated with inhaled insulin who discontinued due to adverse events with respiratory body system AEs as listed below. Your Table 11 (pg 30) in the Summary of Pulmonary Safety indicates 11 subjects discontinued due to respiratory AEs. Please explain the difference.

106	50556135
107	51027141
1022	1005241
1022	1007359
1022	1017949
1022	10251425
1022	10472728
1022	50743085
1022	51563797
1027	1004154
1027	1006251
1027	1012503

9. The COSTART preferred term for subject 1007359 in Study 1022 was respiratory distress syndrome, but respiratory distress syndrome is not listed in Table 11 in the Summary of Pulmonary Safety (pg 30). Please clarify.
10. In the Summary of Clinical Safety, Table 7.1.6.2 (Discontinuation due to AEs), there are 30 subjects (inhaled insulin) and 2 subjects (oral agents) who discontinued with respiratory body system AEs. Your Table 11 (pg 30) in the Summary of Pulmonary Safety indicates 28 inhaled insulin subjects and 2 oral agents subjects discontinued due to respiratory AEs. Please explain the difference.
11. In the Summary of Clinical Safety, Table 7.1.6.2 (Discontinuation due to AEs), there are 8 subjects with 9 dyspnea adverse events, but Table 11 (pg 30) in the Summary of Pulmonary Safety only lists 5 dyspnea adverse events. Please explain the difference. Also, there are 3 respiratory disorder AEs listed in Table 7.1.6.2 (Discontinuation due to AEs), but Table 11 in the Summary of Pulmonary Safety lists 2. Please explain the difference.

If you have any questions, call Oluchi Elekwachi, Pharm.D., M.P.H., Regulatory Health Project Manager, at 301-827-6381.

Sincerely,

*{See appended electronic signature page}*

David Orloff, MD  
Director  
Division of Metabolic and Endocrine Drug Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/

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Mary Parks  
7/7/05 01:57:08 PM  
for Dr. Orloff





**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-868

**INFORMATION REQUEST LETTER**

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

6/21/05

Dear Mr. Green:

Please refer to your December 27, 2004 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Exubera (Insulin [rDNA origin] Inhalation Powder) 1 and 3 mgs.

We also refer to your submissions dated January 12, February 23, March 17, April 26, May 6, and May 12, 2005.

We are reviewing the Clinical and Statistical sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

**Biometrics**

1. Explain the difference between CPEVENT and VISITWIN (e.g. in Study 1022, 1026, 1027). When do you use CPEVENT and when do you use VISITWIN, particularly in terms of PFT?
2. Provide the dataset for Study 1027 (all weekly PFT data), STUDY 103 (baseline, week 6 and week 12), STUDY 104 (baseline, week 6 and week 12). Provide the datasets you used to generate the results for the study reports.
3. Provide datasets for the new safety updates (dated April 26, 2005). Furthermore, please update your inhaled insulin pulmonary safety report, as well as its datasets incorporating these new findings.

**Clinical**

1. Provide datasets for the updated individual studies (1017, 1022, 1028, 1030) submitted in the April 26, 2005, safety update. The cut-off date for the datasets should be the same cut-off date as used for the safety update. Submit the datasets by June 24, 2005.
2. Your April 26, 2005, safety update did not address pulmonary safety. Provide an update for the pulmonary safety based on all data available up until the cut-off date for the April 26, 2005 submission.
3. You have proposed to submit the following additional information:
  - Full interim study report for Study 1022
  - HRCT data for Study 1029
  - Preliminary interim study report for Study 1029.
  - Provide updated datasets with the submission of the updated study reports.
4. Some subjects were noted to have new findings on End of Study CXR or HRCTs, such as lung nodules, which may have warranted further evaluation. Provide any additional information regarding follow up for these subjects or an explanation as to why there was no follow-up.

5. What criteria were used to determine subjects were not eligible for the extension periods of Studies 1001 and 1002 as listed in Section 13, Table 25.1 and Table 25.2 of 1001-1002.pdf.
6. In Study 217-108, clarify why Table 6.1.3. lists four subjects in the SC insulin group with increased cough, but the number of subjects with cough AEs in the SC insulin group in Table 6.8.1, 6.8.2, and 6.8.3 is three.
7. In some studies, the number of subjects with changes in CXR findings in the CXR dataset differs from the number of subjects with CXR changes in the study report. For example, in Study 217-108, the study report discusses 13 subjects with a significant change from baseline; however, XRAY\_1V lists 15 subjects with changes from baseline. Explain why there is a difference.
8. In Study 217-1029, Table 6.8.2 indicates none of the cough events were severe. However the all cause AE by Body System Table 6.1.2 indicates one cough AE was severe. Clarify.
9. Respiratory disorder is one of the COSTART preferred terms you utilized to report AEs. Clarify what respiratory disorder means.

If you have any questions, call Oluchi Elekwachi, Pharm.D., M.P.H., Regulatory Health Project Manager, at 301-827-6381.

Sincerely,

*{See appended electronic signature page}*

David G. Orloff, M.D.  
Director  
Division of Metabolic and Endocrine Drug Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/

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Mary Parks  
6/21/05 04:47:42 PM  
for Dr. Orloff



**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-868

**INFORMATION REQUEST LETTER**

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

6/7/05

Dear Mr. Green:

Please refer to your December 27, 2004 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Exubera (Insulin [rDNA Origin] powder for oral inhalation) 1 and 3 mgs.

We also refer to your submissions dated January 12, February 23, March 17, April 26, May 6, and May 12, 2005.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. The following comments pertain to the stability data in SAS transport data sets
  - a. Provide individual and mean determinations for all parameters and in separate files.
  - b. Provide files with individual results in addition to mean results.
  - c. Provide Individual Stage data in both gravimetric and insulin-specific determinations in Particle Size Distribution data files. Tables containing individual determinations and means should be provided in separate files.

**N21-868**

10. You have indicated that you made

Identify these materials. Describe the nature and frequency of testing of this material, as well as any additional tests needed to ensure long term stability. [Reference, section 3.2.P(4), page 196 of the attachment.]

If you have any questions, call Oluchi Elekwachi, Pharm.D., M.P.H., Regulatory Health Project Manager, at 301-827-6381.

Sincerely,

Stephen K. Moore, Ph.D.  
Chemistry Team Leader I for the  
Division of Metabolic and Endocrine  
Drug Products, (HFD-510)  
DNDC II, Office of New Drug Chemistry  
Center for Drug Evaluation and Research

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/s/

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Stephen Moore

6/7/05 04:31:00 PM



**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-868

**INFORMATION REQUEST LETTER**

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

5/16/05

Dear Mr. Green:

Please refer to your December 27, 2004 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Exubera Inhaled Insulin.

We also refer to your submission dated January 12, February 23, March 17, April 26, and May 6, 2005.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. It should be demonstrated that the performance of the total drug product is equivalent across all the changes made to the device during pivotal and critical clinical studies, and to the commercial device. Provide a concise summary of comparative data to show this, including \_\_\_\_\_. These data should not only include parameters such as \_\_\_\_\_

The comparative data should also identify the device manufacturing site and changes in device manufacturing methods, and comparative stability data should be provided (for the clinical drug product this should cover the longest time period from time of manufacture through the end of the study).

2. Provide details of the testing protocol used in the "accelerated patient use scenario" (pg. 250 of section 3.2.P(2).2.).

- 3.

4. Provide assurance that each device manufacturer uses the identical processes, raw materials and controls described in this NDA. Provide any site specific manufacturing and controls documentation to the NDA for each manufacturer
5. Provide an agreement with the contract manufacturers that there should be no changes to the process, materials and controls without Pfizer's prior agreement and appropriate notification of the Agency of proposed changes.
6. Provide engineering drawings of each device component with critical dimensions and their tolerances.
7. Provide the complete chemical composition of each device component including additives
8. Provide (or reference) data pertaining to the the device and appropriate components of the device, and their controls.
9. Clarify that material and component part numbers are consistent across the various device manufacturers.
10. Provide detailed sequential schematic diagrams to demonstrate the complete stepwise operation of the drug product over the time period of its use to deliver a dose.
11. Routine controls should be employed for from all critical components, and this includes inks, adhesives and metal components of the drug path, air path, as well as the controls for other mouth contact components.
12. Develop and establish extraction controls for critical components which affect the mechanics or overall performance of the device. The purpose of this is to ensure that the composition of the component has not been intentionally or inadvertently changed or mixed up.
13. The pulmonary device (inhaler) produced by Nektar has the following part number: (per page 2 of 337, Section 3.2.P(2). Provide the part number for this device produced at other sites (The Tech Group

If you have any questions, call Oluchi Elekwachi, Pharm.D., M.P.H., Regulatory Health Project Manager, at 301-827-6381.

Sincerely,

Stephen K. Moore, Ph.D.  
Chemistry Team Leader I, DNDC II for the  
Division of Metabolic and Endocrine Drug Products, HFD-510  
DNDC DNDC II, Office of New Drug Chemistry  
Center for Drug Evaluation and Research



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/s/

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Stephen Moore  
5/16/05 02:40:04 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-868

Pfizer Global Research & Development  
Attention: Brian Green, MS  
Worldwide Regulatory Affairs  
50 Pequot Avenue  
New London, CT 06320

3/11/05

Dear Mr. Green:

Please refer to your December 27, 2005, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Exubera (Insulin [rDNA Origin] powder for oral inhalation).

We also refer to your submissions dated January 12 and February 23, 2005.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on February 26, 2005, in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issues:

Microbiology

- Skip lot testing, as indicated for the \_\_\_\_\_ will not be acceptable without sufficient history of process control. This is not usually available for a new manufacturing process.

Pulmonary

- Two year HRCT data were not included and this may impact the ability to fully evaluate the safety of this product in this review cycle. You indicated this data would arrive by the end of July 2005.

Biometrics

- There is an exclusion of adolescent data from the studies; though a pediatric indication is not being sought, all data from a study should be included in the database.
- Studies 1022 and 1029 have study reports but no datasets.

Division of Drug Marketing, Advertising, and Communications

- DDMAC objects to the trade name "Exubera" because it is overly fanciful and overstates the efficacy of the drug. This name is very similar to "exuberant", or "exuberance", implying a state of unrestrained enthusiasm or joy. This could easily be extrapolated in promotional materials to imply a level of effectiveness that renders any or all patient(s) in

such a state, when such a level of effectiveness has not been demonstrated but substantial evidence or clinical experience.

- Please note that 21 CFR 201.10(c)(3) states that a proprietary name that implies that the drug or ingredient has some unique effectiveness or composition would be misleading, if the drug or ingredient is a common substance, the limitations of which are readily recognized when the drug or ingredient is listed by its established name.
- In addition, the statute also provides that labeling or advertising can misbrand a product if misleading representations are made, whether through a trade name or otherwise; this includes suggestions that a drug is better, more effective, useful in a broader range of conditions or patients, safer, has fewer, or lower incidence of, or less serious side effects or contraindications than has been demonstrated by substantial evidence or substantial clinical experience. [21 U.S.C 321(n); see also 21 U.S.C. 352(a) & (n); 21 CFR 202.1(e)(5)(i);(e)(6)(i)].

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

We also request that you submit the following information:

- Correspondence to address the concerns listed above
- Proposal of other possible trade names

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, call Oluchi Elekwachi, PharmD, MPH, Regulatory Project Manager, at (301) 827-6831.

Sincerely,

*{See appended electronic signature page}*

Kati Johnson  
Chief, Project Management Staff  
Division of Metabolic and Endocrine Drug Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/

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Oluchi Elekwachi  
3/11/05 09:09:23 AM  
signing for Kati Johnson



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-868

1/31/05  
JWC  
1/31/05

Pfizer Global Research & Development  
Attention: Brian Green, MS  
Worldwide Regulatory Affairs  
50 Pequot Avenue  
New London, CT 06320

Dear Mr. Green:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Exubera (Insulin [rDNA Origin] powder for oral inhalation)

Review Priority Classification: Standard (S)

Date of Application: December 27, 2004

Date of Receipt: December 28, 2004

Our Reference Number: NDA 21-868

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 26, 2005 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be October 28, 2005.

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 reference the deferral granted on December 22, 2000, for the pediatric study requirement for this application.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Send all electronic or mixed electronic and paper submission to the Central Document Room at the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research

• NDA 21-868  
Page 2

Central Document Room (CDR)  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

If your submission only contains paper, send it to the following address:

U.S. Postal Service/Courier/Overnight Mail:  
Center for Drug Evaluation and Research  
Division of Metabolic and Endocrine Drug Products  
Attention: Fishers Document Room, 8B-45  
5600 Fishers Lane  
Rockville, Maryland 20857

If you have any questions, call me at (301) 827-6381.

Sincerely,

*{See appended electronic signature page}*

Oluchi Elekwachi, PharmD, MPH  
Regulatory Project Manager  
Division of Metabolic and Endocrine Drug  
Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/

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Oluchi Elekwachi  
1/31/05 12:20:12 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

IND 43,313

7/9/04

Pfizer Global Research & Development  
Attention: Brian Green, MS  
Worldwide Regulatory Affairs  
50 Pequot Avenue  
New London, CT 06320

Dear Mr. Green:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Exubera (Insulin Dry Powder/ Pulmonary Inhaler).

We also refer to the meeting between representatives of your firm and the FDA on June 9, 2004. The purpose of the meeting was to discuss Pre-NDA issues in order for Pfizer to gain FDA's agreement on your developmental plan.

The official minutes of that meeting will follow this correspondence. This initial correspondence is to provide comments from the Office of Drug Safety, as promised in the meeting.

If you have any questions, call me at (301) 827-6381.

Sincerely,

*{See appended electronic signature page}*

Oluchi Elekwachi, PharmD, MPH  
Regulatory Project Manager  
Division of Metabolic and Endocrine Drug  
Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosure: Pre-NDA Office of Drug Safety Guidance



18 Page(s) Withheld

X § 552(b)(4) Trade Secret / Confidential

       § 552(b)(4) Draft Labeling

       § 552(b)(5) Deliberative Process

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/s/

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Oluchi Elekwachi  
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

IND 43,313

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

Dear Mr. Green:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Exubera (Insulin Dry Powder/Pulmonary Inhaler).

We also refer to the meeting between representatives of your firm and the FDA on April 28, 2004. The purpose of the meeting was to gain agreement of your Chemistry and Manufacturing Control (CMC) issues.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 827-6381.

Sincerely,

*{See appended electronic signature page}*

Oluchi Elekwachi, Pharm.D. M.P.H.  
Regulatory Project Manager  
Division of Metabolic and Endocrine Drug  
Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosure: Meeting Minutes

## MEMORANDUM OF TELECON

DATE: April 20, 2004

APPLICATION NUMBER: IND 43,313, Exubera (Insulin Dry Powder/ Pulmonary Inhaler)

BETWEEN:

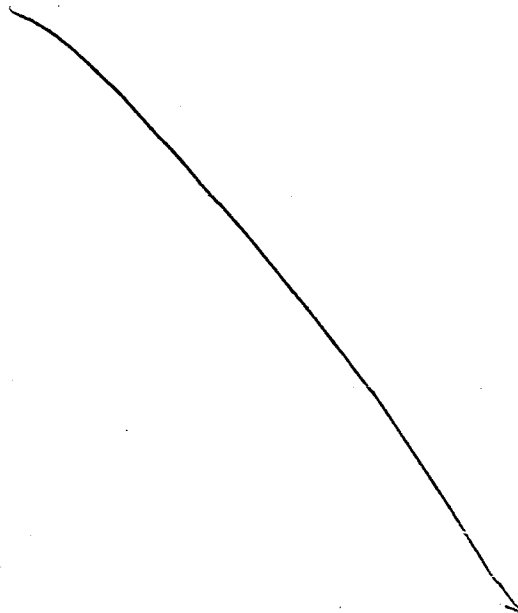
Name: Brian Green, Associate Director, Worldwide Regulatory Affairs  
Phone: 860-732-0959  
Representing: Pfizer Global Research and Development

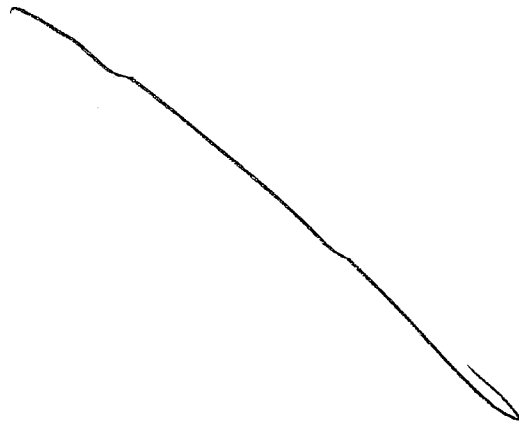
AND

Name: Oluchi Elekwachi, Pharm.D., M.P.H., Regulatory Health Project Manager  
Division of Metabolic and Endocrine Drug Products, HFD-510

SUBJECT: CMC Comments and Information Requests for I43,313 Exubera Meeting (4/28/04)

The following pre-meeting comments are provided on your meeting package dated March 30, 2004:



A handwritten signature in black ink, consisting of a series of connected loops and a final downward stroke.

This information will also be faxed to your attention at: 860-732-0992

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Oluchi Elekwachi, Pharm.D., M.P.H.  
Regulatory Health Project Manager

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/s/

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Oluchi Elekwachi  
4/20/04 09:02:05 AM  
CSO

## **MEMORANDUM OF MEETING MINUTES**

**MEETING DATE:** April 5, 2002

**TIME:** 11:30am-12noon

**LOCATION:** Parklawn Conference Room 14B45 (teleconference)

**APPLICATION:** IND 43,313; Exubera (Insulin Dry Powder/Pulmonary Inhaler)

**INDICATION:** Diabetes Mellitus

**SPONSOR:** Pfizer Global Research & Development

**TYPE OF MEETING:** Telecon to clarify additional monotherapy

**MEETING CHAIR:** David Orloff, M.D.

**MEETING RECORDER:** Su Yang, Project Manager

### **FDA ATTENDEES AND TITLES:**

Division of Metabolic and Endocrine Drug Products:

David Orloff, M.D., Division Director (Team Leader, Diabetes Group)  
Beth Koller, M.D., Medical Officer  
Robert Misbin, M.D., Medical Officer  
Kati Johnson, R.Ph., Chief, Project Management Staff  
Su Yang, MSN, RN, Regulatory Project Manager

### **PFIZER ATTENDEES AND TITLES:**

Dr. Alan Krasner, Clinician  
Dr. John Teeter, Pulmonologist  
Dr. William Landschulz, Global Clinical Leader  
Ms. Susan DeCorte, Global Regulatory Leader  
Ms. Nancy Martin, US Regulatory  
Dr. Shu-lin Cheng, Global Biometrics Leader  
Dr. Jeffrey Blumenstein, Chemist  
Dr. Sue Sha, Clinical Pharmacologist

### **AVENTIS ATTENDEES AND TITLES:**

Dr. Phil Smits, Global Clinical Leader  
Dr. Ralf Roskamp, V.P. Clinical Research

## **BACKGROUND:**

IND 43,313 Exubera (Insulin Dry Powder/Pulmonary Inhaler, CP-464,005) was initially submitted on September 2, 1993 for the development of inhaled insulin in patients with type 1 and 2 diabetes mellitus. The sponsor indicated that phase 3 studies were completed based on the phase 3 study plan agreed upon at the End-of-Phase 2 meeting on June 3, 1998. The sponsor requested this teleconference on February 4, 2002. The intent was to clarify the Agency's request for additional studies of Exubera monotherapy compared to injectable insulin discussed during the Telecon on November 30, 2001 (during which the immunogenicity issue was discussed) and in the Information Request (IR) letter dated January 7, 2001. The pre-meeting background information packet was submitted on March 5, 2002.

## **MEETING OBJECTIVES:**

To discuss and clarify the need for additional inhaled insulin (plus basal insulin) monotherapy studies.

## **DISCUSSION POINTS:**

The Sponsor's Questions and FDA Responses (**Bolded**):

1. We believe that Study 107 addresses the Agency's request for a monotherapy study comparing insulin-dependent patients dosed comparably with injectable insulin. If the Agency does not share this opinion, please explain to us what new elements you are looking for, which have not been addressed in Study 107.
  - a) **The Study #107 intensive therapy in type 1 diabetes (inhaled insulin TID vs. regular insulin SC TID) appears adequately designed, however, the number of patients exposed to the inhaled insulin is not sufficient. More data are required to assess the safety and efficacy and to provide information on the precision and reproducibility of the drug and the reliability of the device. The Study #106 in type 1 diabetes (inhaled insulin TID vs. regular insulin SC BID) is not an adequately designed study because of the well established differences in glycemic control for intensive vs. conventional therapy (see DCCT results); however, the results can be useful as a supportive data.**
  - b) The firm reported that they are submitting a new protocol in type 1 patients; however, the study was designed for safety as a primary endpoint and HbA1c as a secondary endpoint. The firm also inquired as to whether uncontrolled data were useful.
  - c) **The Agency reiterated that more type 1 patients should be exposed to the inhaled insulin and safety and efficacy data should derived from the study. Uncontrolled data can only be useful as a supportive information.**
2. At our June 3, 1998 End of Phase 2 Meeting, Pfizer was under the impression that the Agency had concurred that the Phase 3 clinical program as discussed that day would support EXUBERA as a treatment for Diabetes Mellitus (Type 1 and Type 2). Since that meeting, the Agency has identified, during our meetings of August 18, 2000 and



April 16, 2001, some specific pulmonary safety issues they would like to see further explored. Pfizer has incorporated the FDA's pulmonary recommendations into new EXUBERA studies that are identified at the end of Attachment 1. Enhanced by these requested pulmonary data, we are of the opinion that the completed core Phase 3 program (Studies 106, 107, 108, 109, 110, 1001 and 1002) will demonstrate the safety and efficacy of EXUBERA as a treatment for Diabetes Mellitus. Does the Agency share this opinion? If no, please explain.

- a) Since Exubera is a cutting edge drug-device product, we acknowledge the difficulty to foresee such issues as pulmonary safety or antigenicity. Additional studies are required as they have evolved from new information and new insights.
- b) The firm was requested to provide a table that clearly shows the number of type 1, type 2, and patient with underlying lung disease exposed to the study drug along with the duration of exposure. Also provide the time line, when the data be available, for the NDA application.
- c) The Agency reiterated the requirement of pulmonary safety data requested at the Pulmonary Safety Meeting on April 16, 2001. This includes safety and efficacy assessment of the following additional groups of patients, studied for  $\geq 1$  year, in a controlled fashion:
  - Patients with COPD ( $n \geq 100$  patients)
  - Patients with asthma ( $n \geq 100$  patients)
  - Patients with Type I diabetes and no underlying lung disease ( $n \geq 100$ )
- d) Long-term safety data must be included with the initial NDA application.  
When the firm indicated that the difficulty recruiting patients with underlying lung disease, the Agency suggested that the firm to consider recruiting patients from allergists as well as endocrinologists. Alternatively, the firm may propose an alternate plan that addresses the issues on long-term pulmonary safety for patients with underlying lung disease.

**DECISIONS (AGREEMENTS) REACHED:**

Confirmatory data are required for Exubera NDA application.

**UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:**

None

**ACTION ITEMS:**

- 1) The firm will submit a table containing phase 3 study information.
- 2) The firm may submit an alternate plan to address long-term pulmonary safety study requirements on patients with underlying lung disease.

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David Orloff  
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**MEMORANDUM OF MEETING MINUTES**

**Meeting Date:** April 16, 2001  
**Time:** 2:00 – 3:30 p.m.  
**Location:** Parklawn Bldg. 3<sup>rd</sup> fl c/r "Potomac"  
**Application:** EXUBERA™ (insulin dry powder/pulmonary inhaler)  
**Sponsor:** Pfizer  
**Type of Meeting:** Pulmonary safety follow-up  
**Meeting Chair:** David Orloff, M.D.  
**Meeting Recorder:** Julie Rhee

**Attendees:****FDA:**

David Orloff, M.D., Director, Division of Metabolic and Endocrine Drug Products  
Saul Malozowski, M.D., Medical Team Leader, DMEDP  
Elizabeth Koller, M.D., Medical Officer, DMEDP  
Robert Misbin, M.D., Medical Officer, DMEDP  
Todd Sahlroot, Ph.D., Statistical Team Leader, DMEDP  
Herman Rhee, Ph.D., Pharmacologist, DMEDP  
Robert Meyer, M.D., Director, Division of Pulmonary and Allergy Drug products  
Badrul Chowdhury, M.D., Medical Team Leader, DPADP  
Eugene Sullivan, M.D., Medical Officer, DPADP  
Su Yang, Regulatory Project Manager, DMEDP  
Julie Rhee, Regulatory Project Manager, DMEDP

**Pfizer:**

Nancy Martin, M.S., U.S., Regulatory

William Dougherty, Ph.D., Toxicologist  
Cecile Balagtas, Ph.D., Global Biometrics Team Leader  
Julie Krop, M.D., Endocrinologist  
Alan Krasner, M.D., Clinician  
Allen Kraska, Ph.D., Global Head of Metabolism & Endocrine Drug Products

John Teeter, M.D., Pulmonologist  
Jayne Douglas, M.D., Global Clinical Leader  
Michael Berelowitz, M.D., Director, Pfizer New York Medical  
Andre Daniels, M.D., Clinical Safety & Risk Management  
Susan DeCorte, M.S., Global Regulatory Leader

**Aventis:**

Ralf Roskamp, M.D., Global Clinical Leader  
Paul Walrant, Ph.D., Global Regulatory Leader

**Background:**

During the August 18, 2000, meeting with the sponsor, the Agency expressed concerns regarding the pulmonary safety assessment limitations of the EXUBERA™ safety database without a

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4/16/01 meeting minutes

long-term concurrent control group. The sponsor has developed a plan to address our concerns and wishes to get the Agency's agreement.

**Sponsor's questions/FDA's responses:**

*Question 1. Pfizer seeks reconfirmation from the Agency that the EXUBERA<sup>TM</sup> toxicology program as described in this pre-meeting package fulfills the preclinical registration requirements and sufficiently supports the intended long-term use of this product.*

The program appears to be adequate.

Questions 2-4 will be covered, in the following order: 3, 5, 2, 4.

*Question 3. We seek concurrence from the Agency that the proposed timing of 2Q02 for the submission of the 1-year controlled pulmonary safety data on 200 subjects (100 subjects on EXUBERA<sup>TM</sup>) from Protocols 1001 and 1002 will be acceptable during the EXUBERA<sup>TM</sup> NDA review cycle, without impacting the 10/12 month action date.*

The application, including long-term safety data, should be complete at the time of initial submission.

*Question 5. We seek concurrence from the Agency that the proposed safety analysis plan for the pulmonary function data is acceptable and completes the pulmonary function analysis expected for the EXUBERA<sup>TM</sup> NDA submission.*

The safety analysis plan is adequate with the following comments. Longitudinal data analysis of PFT data in the controlled pulmonary safety studies is acceptable. The presentation of the PFT data should also include shift tables indicating the numbers of subjects in each group demonstrating a specified change in each parameter to allow identification of change, even if the change did not result in values that are outside the range of normal.

The pulmonary function analysis and database expected for the EXUBERA<sup>TM</sup> NDA submission is possibly adequate for filing; however, it may not be adequate to support approval of the product from a safety standpoint. The concerns are:

- a) Lack of adequate long-term controlled pulmonary safety data
- b) Lack of adequate safety and efficacy data in patients with concurrent lung diseases, such as asthma, and COPD.

*Question 2. We seek concurrence from the Agency that the submission of 1-year controlled pulmonary safety data on a minimum of 200 subjects (100 subjects on EXUBERA<sup>TM</sup>) from Protocols 1001 and 1002 fulfills the Agency's need for long-term controlled pulmonary data.*

The two proposed extension studies will provide some additional information regarding the long-term pulmonary safety of EXUBERA<sup>TM</sup>. However, the overall long-term safety database may not be adequate to establish the long-term pulmonary safety of this product.

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Limitations of the long-term safety database:

- Relatively small number of patients on EXUBERA™
- Relatively short duration of exposure data
- Limited data in patients with underlying lung disease
- Limited data, if any, in type I diabetics
- Potential bias introduced by non-random participation in the two proposed extension studies

*Question 4. We seek concurrence from the Agency that the planned subset analysis of approximately 250 subjects (half of whom will be on EXUBERA™) with underlying respiratory disease fulfills the Agency's need for safety and efficacy data of EXUBERA™ in diabetics with underlying lung conditions.*

The proposed subset analysis may not be adequate to establish the long-term pulmonary safety and efficacy of EXUBERA™ in patients with underlying lung diseases.

Limitations of the database:

- Numbers of patients with specific lung diseases (e.g. asthma, COPD) is not provided, and is possibly, relatively small
- Many patients now classified as having lung disease participated in trials in which lung disease was an exclusion criterion. These patients may not be representative of patients with clinically identified lung disease
- Duration of exposure to EXUBERA™ for these patients is not provided
- Data from single-dose PK studies are not adequate

Given the long-term controlled pulmonary safety database, and safety and efficacy database on patients with underlying lung disease, proposed additional long-term database would include specific safety and efficacy assessment of the following additional groups of patients, studied for 1 year, in a controlled fashion:

- a) Patients with COPD (n 100 patients)
- b) Patients with asthma (n 100 patients)
- c) Patients with Type I diabetes and no underlying lung disease (n 100)

**Discussion Points:**

1. Lack of long-term pulmonary safety data would likely be a review issue, rather than a filing issue. However, an NDA package should be complete at the time of submission. This NDA will be reviewed jointly by the Division of Metabolic and Endocrine Drug products (DMEDP) and the Division of Pulmonary and Allergy Drug products (DPADP). ← \*
2. In addition to the longitudinal data analysis of PFT data in the controlled pulmonary safety studies, the Agency requested that statistical analyses of LOCF data also be provided. The Agency requested that a more detailed statistical analysis plan be included when Pfizer submits a pre-NDA package. The sponsor agreed to do so.

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3. The Agency stated that since the end result is data driven, it is important for the pulmonary safety database to be of sufficient size, and include an adequate number of patients with concurrent lung diseases to establish the pulmonary safety of EXUBERA™ in all patient populations where the drug may be used. The Agency did not make a commitment concerning the required sample size or the study duration for pulmonary studies that are necessary for an approval of EXUBERA™ since they do not have enough data to make an informed decision. However, an estimate was given in specific response to Question 4 (see above).
4. EXUBERA™ NDA is likely to be discussed at an Advisory Committee meeting during the NDA's review cycle.
5. Long-term cumulative effects of inhaled insulins, including EXUBERA™, on the lung are a major concern. The available information addressing safety is based on a limited sample size and study duration. The Agency recommended that the sponsor conduct longer than one-year trials if there are any safety signals. Also, inclusion of both patients with type 1 diabetes without any underlying disease, and patients with type 2 diabetes who may have impaired lung function (based on obesity, past smoking, etc) will be necessary.
6. The sponsor needs to address long-term pulmonary effects on all age groups of type 1 diabetic children.
7. The sponsor raised the possibility of using labeling precautions in lieu of further safety data in patients with concurrent lung disease. The Agency pointed to the meeting minutes of August 18, 2000, indicating that this was not acceptable.
8. The sponsor stated that between 400 to 600 patients out of 900 patients are expected to continue in the extension studies, 1001 and 1002.
9. Stratification by smoking is recommended for patients with COPD, and by steroid treatment in patients with asthma.
10. Patients included in the pulmonary safety database should have clearly defined underlying disease, either COPD or asthma. Data on patients who were enrolled in studies, in which lung disease was an exclusion criterion, and classified post hoc as having asthma or COPD will not be sufficient.
11. For an approval of this drug product, the sponsor needs to demonstrate safety and efficacy. Convenience of inhaled delivery is not a basis for approval.
12. The sponsor plans to request a separate meeting with clinical, CMC, and biopharm reviewers to address EXUBERA's convenience dosage reliability.

**Decisions (agreements) reached:**

1. The pulmonary safety database expected for the forthcoming EXUBERA™ NDA submission is likely fileable. However, pulmonary safety database in the NDA package is not adequate to determine pulmonary safety of EXUBERA™.

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2. The NDA package should be complete at the time of submission. The Agency does not commit to the review (during the first review cycle) of any amendments that are submitted after the initial NDA submission.
3. The sponsor needs to address long-term pulmonary effects, especially with children with type 1 diabetes who are going to have lifetime exposure to the drug product.

**Unresolved issues or issues requiring further discussion:**

None.

Julie Rhee  
Minutes Preparer:

David Orloff, M.D.  
Chair Concurrence:

MEETING MINUTES

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David Orloff  
5/21/01 11:17:13 AM





DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

IND 43,313

Pfizer Global Research & Development  
Attention: Brian Green, MS  
Worldwide Regulatory Affairs  
50 Pequot Avenue  
New London, CT 06320

Dear Mr. Green:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Exubera® (Insulin Dry Powder/Pulmonary Inhaler).

We also refer to the Pre-NDA meeting between representatives of your firm and the FDA on June 9, 2004.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me, at (301) 827-6381.

Sincerely,

*{See appended electronic signature page}*

Oluchi Elekwachi, PharmD, MPH  
Regulatory Project Manager  
Division of Metabolic and Endocrine Drug Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosure: Meeting Minutes

7/21/04

## MEMORANDUM OF MEETING MINUTES

**MEETING DATE:** October 11, 2005  
**TIME:** 12 PM – 2:00 PM  
**LOCATION:** White Oak Conference Room 1417  
**APPLICATION:** N21-868  
**DRUG NAME:** Exubera  
**TYPE OF MEETING:** PreApproval Safety Conference

**MEETING CHAIR:** David G. Orloff, MD

**MEETING RECORDER:** Oluchi Elekwachi, PharmD, MPH

**FDA ATTENDEES:** (Title and Office/Division)

Oluchi Elekwachi, PharmD, MPH	DMEP
David G. Orloff, MD	
Karen M. Mahoney, MD	
Robert Meyer, MD	ODE II
Curtis Roseborough, MD	
Lee Ripper	
Sally Seymour, MD	DPAP
Eugene Sullivan, MD	
Joy Mele, MS	OPSS/OB
Joan Buenconsuejo, PhD	
Sayed (Sam) Al Habet, PhD	OCP
Janice Brown, MS	ONDQA
Eric Duffy, PhD	
Jonca Bull, MD	OPSS
Anne Trontell, MD	ODS
Rosemary Johann-Lange, MD	
Lanh Green, PharmD, MPH	
Lina Mahmud, PharmD	
Joslyn Swann, PharmD	
Catherine Miller	
Jeanine Best, RN	
Lois La Grenade	
Sammie Beam	

**DISCUSSION POINTS:**

Pulmonary Findings/Issues

- Update Safety Information
  - Serious Adverse Events from Ongoing study
- No evidence of proliferation of lung parychema
- No specific lung receptor of binding
- More rapid decline of pulmonary function in asthma patients
- No pulmonary compensation in animals (with mannitol)

- Initially excluded asthma patients then relaxed criteria to allow patients with controlled asthma or COPD
  - Asthma self-reported
  - COPD – history of smoking
- Smoking increases the bioavailability of Exubera
  - FDA and Pfizer propose to contraindicated it in smokers
- Any Additional Risks for Patients?
  - Small and apparently reversible in lung function
  - No significant unknowns
- Pediatric Use
  - Labeling needed to address its contra-recommendation in pediatrics in the special population subsection entitled pediatrics
  - Remove all language permissive to pediatric use.
- Antibody Levels in Pregnant Women
  - Pregnancy Issues not related to antibody levels
    - Same for glycemic control however there maybe an increased risk of hypoglycemia
    - 2 reasons why this is not recommended in pregnancy
      - hypoglycemia
      - high antibody level
- Immunologic Adverse Events
  - Antibody difference would not lend itself to limited market release
  - Low IGg Affinity/High Titer Antibodies such as these don't lend itself to adverse events
  - Despite the high levels, there was no appointment clinical correlate
- Type 1 Diabetes
  - As for as maintaining intensive control in Type 1 Diabetes, this has been difficult to achieve in all clinical trials since DCCT. Therefore glycemic control is titratable and if type 1 patients are not able to achieve this, they have a other insulin alternatives.
- Severe Hypoglycemic Tendencies
  - Patients with this tendency can be managed with frequent monitoring
- Monitoring – Who will do this?
  - Education of MDs and Allied Health Professionals
  - 24 Hour Hotline
- Training
  - In trials there was multiple teachings at the site
  - We should give consideration as to have the sponsor demonstrate proper use via intensive education
    - Dose proportionality
    - Technique of use of the Inhaler
  - Education should focus on:
    - Proper use of the inhaler
    - Frequent monitoring
    - Who shouldn't use it
- An Actual Use Study would be reasonable
- Chemistry Issues –
  - **MAJOR AMENDMENT:** The applicant has presented responses (81 pages) to the Agency's IR letter dated Sept. 26, 2005. The correspondence dated Sept. 30, 2005,

presents rationale for several drug product and device specifications with acceptance limits that are slightly modified or revised from what the Agency recommended. A careful evaluation of the responses has shown that the following specifications need further review and may involve requesting additional data from the applicant.

- Acceptance criteria for \_\_\_\_\_ of the 3 mg blister needs to be evaluated in light of the revised limits proposed by Pfizer). Pfizer has indicated that they are willing to provide additional SAS transport data sets to justify their proposal for revision to \_\_\_\_\_
  - Acceptance criteria for \_\_\_\_\_ is not as per the Agency's recommendation. No justification provided. Hence additional justification will be requested or tightening of the limits will need to be done.
  - Acceptance criteria for \_\_\_\_\_ are not as per the Agency's recommendation. Pfizer has proposed slightly wider limits and these limits need to be evaluated based on the available data for production scale lots. As per the applicant, additional data is available for the Agency to review. From the pulmonary standpoint, we have always evaluated all available information prior to setting acceptance limits. Review of additional data is likely to take a few days depending on the move schedule and available resources.
  - Stability data for the device (individual data points) have not been provided as requested. It appears that this data will take some time to gather and will need to be evaluated. In lieu of the individual data sets, the applicant has provided means and grand means which do not include the whole range of distribution and may have included outliers. Additional data is promised by the applicant which needs to be evaluated.
  - \_\_\_\_\_ of the DMFs in the current state are not adequate to assure the safety and quality of the components used in the manufacture of the device. Extensive documentation and assurance of quality control and in some instances safety assurance of the formulation components are missing from the authorized DMFs. Note that letters are being prepared by Oluchi to be sent to the DMF holders. Re-review of the deficient DMFs will take some time once the deficient letters are responded to, and with the impending move, it may be difficult to predict when this may be accomplished to the Agency's satisfaction. Within the pulmonary division, (to my knowledge) we have not recommended approval for a drug product under these circumstances of DMFs being inadequate due to safety issues.
- Race
    - Use not addressed in Hispanic and Black patients
  - Monitoring Baseline Lung Function in MD Office
    - Baseline and Periodic Monitoring
    - Pattern monitoring of safety of Exubera via a large post-marketing study
  - Pulmonary Function
    - Registry for patient with baseline abnormal pulmonary function
      - In order to help monitor for undiagnosed pulmonary disease
    - Stricter design may be to include in the label that patients with underlying pulmonary disease be excluded from use if a baseline function is taken

- Recommendation – Please insert language in the contraindication section that would allow them to know that patients with pulmonary disease as diagnosed by the baseline pulmonary function test
- Ask flier to provide utilization data in certain populations of interest
- Lung Cancer
  - EMEA has a concern that Exubera may lead to an increase in lung cancer
    - Promote rather than initiate it
  - There were no histological funding in Animals
    - Primates and other animals were used
- Risk Management Plan – Gaps that need to be filled
  - Pulmonary Safety in Blacks
  - PK/PD of folks who are exposed to environmental smoke
  - Provider Educations
  - Literature to ensure smokers do not use this
  - Medguide
- CHF
  - Insulin is associated with salt and water retention but its not unique to inhaled insulin
  - Pharmacokinetics was not evaluated by NYHA class or pulmonary wedge pressure but eh will be evaluated via screening spirometry.
- Smokers of Other Timing
  - Not Known
- Prevalence of Diabetes among these with Pulmonary Disease or Vice Versa

#### **DECISIONS (AGREEMENTS) REACHED:**

- Extend the Review Clock until January 28, 2006 based on Major CMC amendment listed above.

#### **UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:**

- Labeling
- CMC - DMFs

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Oluchi Elekwachi  
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## MEMORANDUM OF MEETING MINUTES

**MEETING DATE:** June 9, 2004  
**TIME:** 2:00PM-3:00PM  
**LOCATION:** Parklawn Conference Room C  
**APPLICATION:** I 43,313  
**DRUG NAME:** Exubera (Insulin for Inhalation)  
**TYPE OF MEETING:** Pre-NDA (Type B)

**MEETING CHAIR:** David Orloff, MD

**MEETING RECORDER:** Oluchi Elekwachi, Pharm.D., M.P.H.

**FDA ATTENDEES:** (Title and Office/Division)

Oluchi Elekwachi	Project Manager	DMEDP
Gary M Gensinger	Supervisor, Regulatory Information	OIM
Kati Johnson	CPMS	DMEDP
Richard T Lostritto	Chemistry Reviewer	DPADP
Karen M Mahoney	Medical Officer	DMEDP
Joy D Mele	Statistician	DMEDP
Robert J Meyer	Director	ODE II
David G Orloff	Director	DMEDP
Lee Ping Pian	Statistician	DMEDP
Jon T Sahlroot	Statistics Team Leader	DMEDP
Eugene J Sullivan	Deputy Director	DPADP
Joslyn R Swann	Regulatory Director	ODS
Anne Trontell	Director	ODS
Xiaoxiong Wei	Biopharmaceutics Reviewer	OCPB

### EXTERNAL CONSTITUENT ATTENDEES:

Neville Jackson	Full Development Team Leader, Pfizer
John Teeter	Director, Clinical Research, Pfizer
Alan Krasner	Director, Clinical Research, Pfizer
Jan Regnstrom	Director, Clinical Safety and Risk Management, Pfizer
Bob Burnside	Director, Clinical Biostatistics, Pfizer
Robert Fountaine	Clinical Sciences, Pfizer
Susan DeCorte	Global Regulatory Leader, Pfizer

Brian Green	Associate Director, Regulatory Affairs, Pfizer
Chris Griffett	Therapeutic Area Leader, Pfizer
Rochelle Chaiken	Worldwide Medical, Pfizer
Carl Mendel	Global Project Team Leader, Aventis
John Pakulski, R.Ph.	Global Regulatory Coordinator, Aventis
Eric Grossman, MD	US Medical, Pfizer

## **BACKGROUND:**

Pre-NDA meeting to gain agreement on Pfizer's developmental plan. Pfizer plans to submit a New Drug Application (NDA) for Exubera, their inhaled insulin, in December, 2004. Meeting packages were received April 12, 2004.

## **DISCUSSION POINTS:**

*We propose that inhaled insulin (INH) be indicated for the treatment of patients 18 years of age and older with type 1 or type 2 diabetes mellitus. Based on this suggested indication, we propose discussion of the following topics:*

1. *In studies in which INH-based regimens were compared to subcutaneous (sc)-based regimens in subjects with type 1 and type 2 diabetes, non-inferiority to SC regimens was demonstrated. These studies meet the requirement previously communicated to Pfizer (30 December 2002 letter from FDA) in that the range of HbA1c values achieved in both the experimental and control groups is consistent with optimized glycemic control achievable for large groups in clinical practice.*

*In studies in subjects with type 2 diabetes mellitus, INH (monotherapy and in combination with oral agents) achieves and maintains generally better glycemic compared to oral agents.*

A summary of the efficacy from these clinical trials is provided in Enclosure 5. In addition, our proposal for presentation of the efficacy data in the SCE (Summary of Clinical Efficacy) is included in Enclosure 8.

**Does the Agency concur that appropriate and adequate efficacy studies have been conducted to support the review of an NDA?**

## **FDA RESPONSE:**

**Yes. The analysis on the ITT population is the primary analysis for both the superiority and the non-inferiority. You didn't mention the non-inferiority margin. We will apply the margin we are using as a standard here.**

2. *To augment the evaluation of efficacy and safety from traditional studies in diabetes, we have further evaluated the safety (both general and pulmonary) of INH longer term in both controlled and uncontrolled settings.*



As of July 2003, 2610 subjects were treated with inhaled insulin for up to 75 months (in extension studies) in Phase 2 and 3 studies. The table below provides an overview of the patient numbers and exposures.

	Total	> 3 mon	> 6 mon	> 1 yr	> 2 yr	Subject-months
Type 1	1164	912	715	604	373	19335
≥ 18 years old	873	632	451	371	246	13092
< 18 years old	291	280	264	233	127	6243
Type 2	1446	1273	1029	834	470	26487
	2610	2185	1744	1438	843	45822

A summary of the safety from completed studies is provided in Enclosure 6. In addition, our proposal for presentation of the safety data in the SCS (Summary of Clinical Safety) for both completed and ongoing trials is included in Enclosure 8.

**Does the Agency concur that appropriate and adequate safety evaluations have been conducted to support the review of an NDA?**

**FDA RESPONSE:**

It remains to be seen at review whether your proposed scope of pulmonary safety studies will be adequate. For years, the Division of Metabolic and Endocrine Drug Products and the Division of Pulmonary and Allergy Drug Products have given you a clear and consistent message in our advice on this matter: pulmonary safety will be of paramount concern in the safety review. The Division of Pulmonary and Allergy Drug Products reiterates portions of its previous advice to you:

To evaluate the long-term safety profile of INH, the Agency requested adequate long-term controlled pulmonary safety data, including:

- “safety and efficacy assessment of the following additional groups of patients, studied for  $\geq 1$  year, in a controlled fashion,
  - Patients with COPD ( $n \geq 100$  patients)
  - Patients with asthma ( $n \geq 100$  patients)
  - Patients with Type I diabetes and no underlying lung disease ( $n \geq 100$ )”

*(Meeting Minutes – April 16, 2001 & April 5, 2002)*

- inclusion of “patients with type 2 diabetes who may have impaired lung function (based on obesity, past smoking, etc) will be necessary.” *(Meeting Minutes – April 16, 2001)*

Your proposal does not provide the information the Agency requested to assess the long term pulmonary safety.

The Division of Pulmonary and Allergy Drug Products has given clear recommendations on what the safety database should include and it is clear that your

**proposal does not follow their recommendations. Our perspective on this issue has not changed. However, you are welcome to submit this information. We gave you the numbers that were required for COPD and asthma studies, but you have indicated that you were not able to recruit the recommended number of subjects, even after we gave you advice regarding possible widening of the inclusion criteria. We acknowledge your stated difficulties with recruitment, and will review what you submit. However, it remains to be seen at review if we will be able to meaningfully characterize the pulmonary safety of Exubera.**

**Pfizer:** We have taken into account your comments and we separated asthma and COPD.

3. *The Division has suggested 2 year, controlled, High Resolution Computerized Tomography (HRCT) data in 100 subjects (with approx. 50 subjects on INH). (July 29, 2002)*

Baseline and End-of-Study chest x-rays have been performed in all completed controlled Phase 2 and Phase 3 studies, with the exception of Study 1026, in which baseline pulmonary consultations were performed. To date, baseline and End of Study x-rays have been performed on the following subjects on INH: 549 at 3 months, 965 at 6 months, 336 at 12 months, 173 at 24 month, ~1300 in Phase 3 extension studies (with a duration of up to 36 months) and 159 in Phase 2 extension studies (with a duration of up to 84 months). An integrated summary of chest x-ray results from these studies will be presented in the NDA.

Based on agreement during our End of Phase 2 meeting of June 3, 1998 (minutes includes in Serial No. 062) that high resolution computed tomography scans (HRCTs) might be useful, HRCTs of the thorax were performed in a subset of subjects participating in early Phase 3 studies. Baseline and End-of-Study HRCTs were performed in 116 (53 on INH) subjects who participated in these 6-month studies.

To address the Agency's July 29, 2002 suggestion, ongoing Protocol 1029 has been amended to enable one- and two-year controlled HRCT data in a subset of subjects. Interim results from this sub-study in approximately 120 (~80 on INH) subjects who have completed one year of treatment will be provided in the NDA.

Finally, approximately 70 subjects (all on INH) have undergone "for cause" HRCTs as part of their clinical evaluation in the Phase 2/3 extension programs. These results will be summarized in the NDA.

We believe that the above data will provide a comprehensive understanding of any HRCT changes in a variety of subjects treated with INH.

**Please comment on the adequacy for review of the HRCT data proposed for inclusion with the initial NDA submission.**

## **FDA RESPONSE**

The Agency requested that "approximately 50 patients on drug and 50 patients on standard therapy undergo HRCT at 0 and 24 months." (*Meeting Minutes, November 15, 2002*)

**You propose to submit:**

- **baseline and end-of-study HRCT data from 6-month studies, for 116 subjects, 53 of whom were on inhaled insulin**
- **controlled HRCT interim data at one and two years for Protocol 1029, for 120 subjects, ~80 of whom will be on inhaled insulin**
- **“For cause” HRCT data, for ~ 70 subjects on inhaled insulin**

**Your proposal does not include the HRCT data the Agency requested to assess the long-term pulmonary safety of INH. This would be a review issue.**

**Pfizer:** We have 2 additional sources of HRCT data. There will be approximately 70 patients dosed in a controlled fashion. There will be a for-cause group dosed for approximately 2 years and this consists of 88 patients. The longest study was for 38 months.

**FDA:** This is not what we asked for but it will be reviewed. This will not be a filing issue.

4. *Based on the evidence to date, insulin antibodies do not appear to have any clinical effect (i.e., glycemic parameters remain unaffected; no antibody-related adverse events observed).*

As previously acknowledged, there are higher levels of insulin antibodies associated with INH therapy than with subcutaneous human insulin. Further details of these findings and the specific assays utilized are included in Enclosure 6. Our proposal for the presentation of antibody data is in Enclosure 8.

To date, no specific adverse events have been attributed to insulin antibody development in individual subjects. To screen for group trends, extensive exploratory analyses have been performed. These completed analyses consist of three basic approaches: scatter plot regression, general and specialized adverse event tables, and binary distribution plots. No specific group trends have been noted.

Further, recognizing the importance of the immunoglobulin (Ig) class or IgG subclass and antibody function and the extensive clinical experience with insulin antibodies generated with SC insulin, we further characterized and compared insulin antibodies produced with INH administration with those produced with SC administration. Details on the types of analyses performed are also included in Enclosure 8 as in our proposed presentation of safety data related to insulin antibodies.

We believe we have sufficiently evaluated the effect of the observed increase in antibodies in INH subjects with respect to their potential effect on efficacy and/or safety.

**Does the Agency agree that the data to be submitted in the NDA will be sufficient for an assessment of the Pfizer’s conclusion that insulin antibodies do not affect glycemic parameters or result in adverse events?**

#### **FDA RESPONSE:**

**Your NDA should include various analyses that examine pulmonary safety in the population of subjects who developed antibodies (e.g. PFTs, HRCTs, adverse events, etc.) We request that you analyze subjects with and without antibody changes for adverse events such as asthma, cough et al.**

**Pfizer:** Antibodies are analyzed in patients with HRCTs and this information will be provided in the submission.

5. *The Division has requested data on subjects with Underlying Lung Diseases (COPD and Asthma) treated with INH (April 16, 2001).*

The absorption of INH in non-diabetic subjects with mild controlled asthma or COPD was evaluated. Absorption of INH (AUC and Cmax) trended lower in asthmatic subjects while absorption of INH trended higher in subjects with COPD.

Diabetic subjects with mild underlying asthma or mild COPD have been allowed to participate in all Phase 3 INH studies. A retrospective analysis of these subjects was performed and will be included in the NDA. It is anticipated that approximately 150 subjects (~ 50 with asthma and 100 with COPD), half of whom will have been treated with INH, will be included in this analysis. Approximately half of these subjects (~ 40 subjects on INH) will have been treated for at least 12 months. Further details regarding the proposed safety and efficacy parameters to be evaluated in this retrospective analysis are included in Enclosure 8.

In addition, Protocols 1028 and 1030 were specifically designed to prospectively assess the efficacy and safety of INH in type 1 and type 2 diabetic subjects with asthma or COPD, respectively. As previously described, we have modified these protocols to enhance recruitment such that we now anticipate including 6 month data on ~60 subjects with asthma and ~40 subjects with COPD, half of whom will be on INH, in the NDA. In the first safety update, we project that we will provide 6 month data on a total of ~80 subjects with asthma and ~60 subjects with COPD and 3 month data on ~105 subjects with asthma and ~85 subjects with COPD. Longer-term data from these trials will be provided on an ongoing basis.

A summary of the pulmonary safety information is included in Enclosure 6. Our proposal for presentation of safety data with respect to pulmonary safety is included in Enclosure 8.

We believe that the data from the clinical pharmacology studies, the Phase 3 retrospective analysis and the 6-month data from prospectively designed studies will enable us to characterize INH in subjects with mild to moderate asthma or COPD.

**Please comment on the acceptability for review and adequacy of the patient numbers and treatment duration of subjects with COPD and/or asthma that will be included with the proposed NDA submission.**

**FDA RESPONSE:**

We strongly repeat our response to Question 2 above.

**Pfizer:** (Slide Attachment 2: ULD COHORT Project Approximate numbers.)

According to our projections the final cohort will be completed in December 2006.

**FDA RESPONSE:**

**This is not a filing issue; however at the time of submission of your NDA you will not have completed your underlying disease studies, and your state that you plan to submit data on**

**significantly fewer subjects than we recommended. Furthermore, you will have studied those subjects for a significantly shorter duration than recommended.**

**We asked for a certain amount of data and you are proposing not to submit it at the time of submission. We have recently expressed concern to you about your proposals to reduce the numbers of study subjects and duration of study in your underlying lung disease protocols (in our 8 Dec 03 letter to you). In that letter, we stated that the original planned study subject numbers and duration of study were minimum recommended numbers, and that we could not endorse your proposals to reduce study subject numbers and duration of the studies. This is a particular subpopulation about which we are concerned. Again, we will review what you submit, but we do not endorse your proposed cuts.**

6. *We intend to include a Risk Management Plan (RMP) in the initial NDA submission that focuses upon risk identification and evaluation, and in broader terms describes how these issues will be addressed. The intent is to initiate a discussion with the Agency concerning the need for specific tools to address these issues, the strategy and timeline for their implementation, and the means by which we can assess their efficacy.*

The INH RMP is an evolving document. The primary focus of the current document is *pharmacovigilance specification*, which involves the identification, characterization, and evaluation of risk based upon data from the clinical development program, as well as hypothetical risk based on biological plausibility. Ongoing and planned clinical trials designed to refine our understanding of key safety issues will be presented.

The INH RMP further describes the sponsor's commitment to continue monitoring specific safety signals, while evaluating any potentially new safety signals that may arise following product commercialization. As such, the plan will also include the background, strategy, and actions for post approval scientific data gathering activities relating to the detection, assessment, understanding, and prevention of adverse events or any other product-related problems and may also include the conduct of pharmacoepidemiologic studies. Details for the proposed plan are included in Enclosure 7.

Again, our purpose in submitting the plan at this time is to promote a dialog with the Agency regarding identified risks and potential actions so they can be addressed effectively thus, enhancing product safety and patient health.

**Please provide comment on the sufficiency of issues we have chosen to address as the significant safety matters in the proposed RMP.**

**Please provide additional guidance on any other areas the Agency expects to be addressed in the initial RMP.**

#### **FDA RESPONSE:**

##### **Office of Drug Safety Comments:**

- **The Office of Drug Safety notes the RMP proposed by the applicant does not appear to differ substantially from typical new product routine post-marketing safety surveillance, other than by the proposal to conduct Phase IV studies.**

- Internal FDA meetings have discussed potential risks of this product in smokers and among individuals with underlying pulmonary disease such as COPD and asthma. We note the proposed RMP offers no risk assessment nor risk minimization procedures addressing these populations, other than the proposal to conduct Phase IV studies.
- If DMEDP review and expert input from DPADP determine that the risks of Exubera use might exceed the benefits in smokers and individuals with underlying pulmonary disease, then additional risk minimization procedures to avoid exposure would merit consideration
- If, during the course of the NDA review, you and/or FDA believe that there are product risks that merit more than conventional professional product labeling [i.e. package insert (PI) or patient package insert (PPI)] and postmarketing surveillance to manage risks, then you are encouraged to engage in further discussions with FDA about the nature of the risks and the potential need for a risk management program.
- If the NDA/BLA application includes risk minimization action plans (RiskMAP) or pharmacovigilance plans and will be submitted in the Common Technical Document format, please submit as follows:  
**Risk Minimization Action Plans**  
2.5.5 Overview of Safety with appropriate cross references to section  
2.7.4 Summary of Clinical Safety  
and any other relevant sections of the Common Technical Document for the NDA/BLA application.  
**Pharmacovigilance plans**  
2.5.5 Overview of Safety, with any protocols for specific studies provided in 5.3.5.4 Other Clinical Study Reports or other sections as appropriate (e.g., module 4 if the study is a nonclinical study).

If the application is not being submitted as a Common Technical Document, include proposed plans for risk management in NDA Clinical Data Section [21 CFR 314.50 (d)(5)] and clearly label and index them.

- For the most recent publicly available information on the Center for Drug Evaluation and Research's (CDER's) views on risk management plan activities, please refer to the draft guidances on the Development and Use of Risk Minimization Action Plans and Good Pharmacovigilance Practices and Pharmacoeconomic Assessment which can be located electronically at [www.fda.gov/cder/guidance/5766dft.doc](http://www.fda.gov/cder/guidance/5766dft.doc) and [www.fda.gov/cder/guidance/5767dft.doc](http://www.fda.gov/cder/guidance/5767dft.doc)
- If there is any information on product medication errors from the premarketing clinical experience, ODS requests that this information be submitted with the NDA/BLA application.
- You are encouraged to submit the proprietary name and all associated labels and labeling for review as soon as available.
- We are willing to work with you on the development of your RMP.

**Pfizer:** There will be a customer service plan with a call-in number and an educational program for patients and medical professionals. This information will be analyzed and we would like to partner with FDA to develop an effective program.

7. *Consistent with the FDA 1999 electronic submission guidelines, we intend to provide SAS data sets corresponding to individual patient safety and efficacy data.*

A detailed proposal for supplying data sets is contained in the Description of the Proposed NDA/CTD in Enclosure 8.

Does the Division concur with our proposal?

**FDA RESPONSE:**

- Please provide raw and derived datasets
- For CTD we are in the learning stages so please provide guidance in the use of your CTD.
- You may send in datasets with documentation for our review of format prior to submitting the NDA. It will take about one week for this review.
- Although you proposed pooled data for subgroup analysis, additionally we need a separate analysis for each study on subgroups of age, gender, race.
- On study 10-26
  - This study will not have datasets except on a pooled basis

**Specific Comments from DPADP:**

- The presentation of the PFT data should also include shift tables indicating the numbers of subjects in each group demonstrating a specified change in each parameter. (*Meeting Minutes, April 16, 2001*)
- The NDA must include data on device performance for the entire life of the device. (*Meeting Minutes, August 18, 2000*)
- We refer you to Agency input at past meetings regarding the extent of the pulmonary safety database.
- The NDA package should be complete at the time of submission. The Agency does not commit to the review (during the first review cycle) of any amendments submitted after the initial NDA submission. (*Meeting Minutes – April 16, 2001*)
- We encourage you to look at this application from our perspective of efficacy and safety. Think about how much data you would like to put in this application; the more, the better. The closer you come to the FDA expectations, the better the outlook and presentation.

**Pfizer** – We would be interested in pursuing pediatric development

**FDA RESPONSE:**

We would like a full evaluation of use in adults before use in children. By a full evaluation we mean that your NDA for use in adults would have gone through the complete review cycle.

8. *We propose to submit this NDA in the Common Technical Document (CTD) format and the electronic archive in the electronic NDA format.*

A detailed description of the proposed NDA format and proposed Table of Contents is included in Enclosure 8. Specifically, we propose the following:

Documents prepared for the INH NDA will be written in CTD format in accordance with FDA Guidance

**FDA RESPONSE:**

**The Office of Information Management Concurs**

**DECISIONS (AGREEMENTS) REACHED:**

DMEDP and DPADP have emphasized, in multiple meetings and written communications over years, the importance of characterization of pulmonary safety for inhaled insulin. We have given specific recommendations for methods of addressing pulmonary safety. Pfizer proposes submitting substantially less pulmonary safety information in their NDA than we recommended, and the FDA does not endorse this plan. This will likely not prevent filing of the NDA, and DMEDP and DPADP will review what is submitted. Pfizer must clearly understand the risk of inadequate pulmonary safety information.

**UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:**

None

**ACTION ITEMS:**

If the sponsor submits an example derived dataset, DMEDP statistical reviewers expect to be able to give feedback in about one week.

The Office of Drug Safety can provide feedback to Pfizer as they develop their Risk Management Plan.

**ATTACHMENTS/HANDOUTS:**

- Attachment 1: HRCT DATA
- Attachment 2: ULD COHORT Project Approximate numbers



2 Page(s) Withheld

X § 552(b)(4) Trade Secret / Confidential

       § 552(b)(4) Draft Labeling

       § 552(b)(5) Deliberative Process

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

/s/

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Oluchi Elekwachi

7/21/04 09:18:29 AM

# NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA 21-868	Efficacy Supplement Type SE-	Supplement Number	
Drug: Exubera (insulin human) Inhalation Powder		Applicant: Pfizer, Inc.	
RPM: Oluchi Elekwachi, PharmD, MPH		HFD-510	Phone # 301-879-8558
<p>Application Type: ( <input checked="" type="checkbox"/> ) 505(b)(1) ( ) 505(b)(2)            (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p> <p><b>If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.</b></p> <p>( ) Confirmed and/or corrected</p>		<p>Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):</p>	
<b>❖ Application Classifications:</b>			
<ul style="list-style-type: none"> <li>Review priority</li> </ul>		( <input checked="" type="checkbox"/> ) Standard ( ) Priority	
<ul style="list-style-type: none"> <li>Chem class (NDAs only)</li> </ul>		3	
<ul style="list-style-type: none"> <li>Other (e.g., orphan, OTC)</li> </ul>			
<b>❖ User Fee Goal Dates</b>		10.28.05 (Clock Extended to 1.28.06)	
<b>❖ Special programs (indicate all that apply)</b>		( <input checked="" type="checkbox"/> ) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review ( ) CMA Pilot 1 ( ) CMA Pilot 2	
<b>❖ User Fee Information</b>			
<ul style="list-style-type: none"> <li>User Fee</li> </ul>		( <input checked="" type="checkbox"/> ) Paid UF ID number	
<ul style="list-style-type: none"> <li>User Fee waiver</li> </ul>		( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other (specify)	
<ul style="list-style-type: none"> <li>User Fee exception</li> </ul>		( ) Orphan designation ( ) No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) ( ) Other (specify)	
<b>Application Integrity Policy (AIP)</b>			
<ul style="list-style-type: none"> <li>Applicant is on the AIP</li> </ul>		( ) Yes ( <input checked="" type="checkbox"/> ) No	

Version: 6/16/2004

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

*If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ( ) Yes      ( ) No

*If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).*

*If "No," continue with question (5).*

- (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? ( ) Yes      ( ) No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).

*If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).*

*If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.*

❖ Exclusivity (approvals only)	
<ul style="list-style-type: none"> <li>Exclusivity summary</li> <li>Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</li> </ul>	
<ul style="list-style-type: none"> <li>Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</li> </ul>	<span style="float: right;">( ) Yes, Application # _____ (X ) No</span>
Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	3.27.05

General Information	
<b>Actions</b>	
• Proposed action	<input type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA
• Previous actions (specify type and date for each action taken)	
• Status of advertising (approvals only)	<input checked="" type="checkbox"/> Materials requested in AP letter <input type="checkbox"/> Reviewed for Subpart H
<b>❖ Public communications</b>	
• Press Office notified of action (approval only)	<input type="checkbox"/> Yes <input type="checkbox"/> Not applicable
• Indicate what types (if any) of information dissemination are anticipated	<input type="checkbox"/> None <input checked="" type="checkbox"/> Press Release <input type="checkbox"/> Talk Paper <input type="checkbox"/> Dear Health Care Professional Letter
<b>❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))</b>	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	Sent to Sponsor 1.17.06 FDA-revised PI and Carton and Blister Comments from CMC
• Most recent applicant-proposed labeling	9.23.05 – Revised PI 12.21.05 – Revised Carton and Blister Labeling and Proposed MedGuide
• Original applicant-proposed labeling	12.27.04
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings ( <i>indicate dates of reviews and meetings</i> )	DMETS Tradename and Carton and Container Label Review 7.22.05 Labeling Meetings 1.12.06 (internal) 1.19.06 (with sponsor)
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
<b>❖ Labels (immediate container &amp; carton labels)</b>	
• Division proposed (only if generated after latest applicant submission)	Sent to the sponsor: 1.18.2006
• Applicant proposed	12.21.05
• Reviews	
<b>❖ Post-marketing commitments</b>	
• Agency request for post-marketing commitments	
• Documentation of discussions and/or agreements relating to post-marketing commitments	
<b>❖ Outgoing correspondence (i.e., letters, E-mails, faxes)</b>	
<b>❖ Memoranda and Telecons</b>	
<b>❖ Minutes of Meetings</b>	
• EOP2 meeting (indicate date)	
• Pre-NDA meeting (indicate date)	7.21.04
• Pre-Approval Safety Conference (indicate date; approvals only)	10.11.05
• Other	

❖ Advisory Committee Meeting	
• Date of Meeting	9.8.05
• 48-hour alert	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	
<b>Summary Application Review</b>	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) ( <i>indicate date for each review</i> )	
<b>Clinical Information</b>	
❖ Clinical review(s) ( <i>indicate date for each review</i> )	1.5.2005 – K. Mahoney (Overall Safety and Efficacy) 1.9.2005 – S. Seymour (Pulmonary Safety)
❖ Microbiology (efficacy) review(s) ( <i>indicate date for each review</i> )	11.30.2005
❖ Safety Update review(s) ( <i>indicate date or location if incorporated in another review</i> )	N/A
❖ Risk Management Plan review(s) ( <i>indicate date/location if incorporated in another rev</i> )	12.14.2005 (ODS)
❖ Pediatric Page (separate page for each indication addressing status of all age groups)	
❖ Demographic Worksheet ( <i>NME approvals only</i> )	N/A
❖ Statistical review(s) ( <i>indicate date for each review</i> )	10.19.05 J. Mele 10.12.05 J. Buenconsuejo
❖ Biopharmaceutical review(s) ( <i>indicate date for each review</i> )	1.5.2006 S. Al Habet
❖ Controlled Substance Staff review(s) and recommendation for scheduling ( <i>indicate date for each review</i> )	N/A
Clinical Inspection Review Summary (DSI)	
• Clinical studies	8.12.05
• Bioequivalence studies	N/A
<b>CMC Information</b>	
❖ CMC review(s) ( <i>indicate date for each review</i> )	Pending
❖ Environmental Assessment	
• Categorical Exclusion ( <i>indicate review date</i> )	
• Review & FONSI ( <i>indicate date of review</i> )	
• Review & Environmental Impact Statement ( <i>indicate date of each review</i> )	
❖ Microbiology (validation of sterilization & product sterility) review(s) ( <i>indicate date for each review</i> )	
❖ Facilities inspection (provide EER report)	Date completed: ( ) Acceptable ( ) Withhold recommendation
❖ Methods validation	( ) Completed ( ) Requested ( ) Not yet requested
<b>Nonclinical Pharm/Tox Information</b>	
❖ Pharm/tox review(s), including referenced IND reviews ( <i>indicate date for each review</i> )	7.27.05
❖ Nonclinical inspection review summary	
❖ Statistical review(s) of carcinogenicity studies ( <i>indicate date for each review</i> )	
CAC/ECAC report	

**Appendix A to NDA/Efficacy Supplement Action Package Checklist**

An application is likely to be a 505(b)(2) application if:

- (1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
- (2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
- (4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).



**ADRA Rev #21-868 of Action Package for NDA Exubera (human insulin) Inhalation Powder)**

Reviewer: Lee Ripper, HFD-102

Date received: 1/13/06

Date of review: CM 1/27/06

Date original NDA received: 12/28/04

UF goal date: 2/28/06

Proposed Indication: Tx of adult patients with type 1 or type 2 diabetes mellitus for the control of hyperglycemia.

Action type: AP

RPM: Oluchi Elewachi

Drug Classification: 3S

505(b)(1) application

Patent Info on form FDA 3542a: Yes

Debarment Certification: AC

Financial Disclosure: AC, MOR pp 24-27

Safety Update: 4/6/05, discussed in primary MOR p. 171

Risk Management Plan: ODS review 12/14/05; MedGuide and other measures, including postmarketing studies

Clinical Inspection Summary: 2 sites inspected, data acceptable in support of NDA

ODS/DMETS Review of Proprietary Name: AC 7/22/05; DMETS has been involved in labeling review and said they do not need to do a separate re-review of the proprietary name

DSRCS Review of MedGuide: 1/20/06

DDMAC Review: Proprietary Name not AC per DMETS review; see Memo to File by KMahoney 5/13/05

EA: CMC Rev #1 by Janice Brown, categorical exclusion, page 141

EER: AC 1/24/06

PSC/WU Mtg: 10/11/05, minutes in pkg

CMC section to Rik Lostritto, Rik said he did not need to see the CMC action pkg as he is involved in the finalization of the reviews.

P/T section to Ken Hastings, 1/23/06

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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.**  
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/s/

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Leah Ripper  
1/30/2006 03:33:10 PM  
CSO