

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-868

CHEMISTRY REVIEW(S)

ONDQA Division Director's Memo
NDA 21-868 Exubera (Insulin Human [rDNA origin]) Inhalation Powder
Date: January 26, 2006

Introduction

Exubera (Insulin Human [rDNA origin]) Inhalation Powder is a new delivery device for insulin to be used by diabetics. It is a combination drug product consisting of drug formulation containing blisters and an inhalation device component. The device component is mechanically complex and utilizes a puff of atmospheric air to disperse the dry powder formulation into a standing cloud which is then inhaled by the patient.

Administrative

The original submission of this 505(b)(1) NDA was received 27-DEC-2004. Multiple interactive and substantive review cycles have occurred since the original submission. Based on detailed submissions provided by Pfizer as part of their response to deficiencies in August and September of 2005, the review clock was extended by three months.

The following consults have been performed and were found to be acceptable; Biometrics, EES, PharmTox, ODS/DMETS, Microbiology, and EA. Twenty one DMFs were cited in this NDA; 20 were for the container closure and device components.

There are several CMC Phase-IV post-approval agreements with the applicant. The CMC recommendation is for APPROVAL with an eighteen (18) month shelf life at controlled room temperature which includes up to 3 months of out-of-pouch storage at controlled room temperature.

Drug Substance (Insulin Human [rDNA origin])

All CMC information for the drug substance is described in DMF _____ which was found to be adequate to support this NDA. The DMF Holder, _____

Drug Product: Summary of issues.

This combination drug product is designed to deliver an insulin containing powder to the lungs via inhalation. The spray-dried powder formulation is packaged into single-use 1 mg and 3 mg blister packets which are foil and polymer sealed on both sides of the blister and packaged as six blisters to a card. Five cards are packaged on a tray which is sealed within a foil pouch containing a 5 g desiccant packet. The sealed pouch is then boxed.

To use the drug product, the patient places the appropriate dosed blister in the device component. A hand-operated piston system compresses a small volume of atmospheric air into a cylinder. When actuated, the blister is pierced and the compressed air is blown

through and over the blister evacuating the contents into cloud chamber reservoir. The patient then inhales the standing cloud from this reservoir.

In addition to insulin human [rDNA] origin, the formulation contains sodium citrate dihydrate, mannitol, glycine, and sodium hydroxide (for pH adjustment). The ingredients are _____ density spray-dried powder.

_____ impurities are generated during the spray drying process; _____ these impurities are initially present at the _____ level. However, only the _____ increases on stability to as much as _____. This was found to be acceptable. Moisture content in the final packaged blister is essential to maintain drug product quality and physicochemical stability over shelf life (18 months at controlled room temperature).

Drug product manufactured at the clinical (pilot scale) level was found to be NOT bioequivalent with commercial scale batches. The clinical Division does not see this as an approvability issue because this drug product (like other insulin products) is designed to be titrated to the patients needs based on blood-glucose monitoring under essentially real-time conditions. This was not considered an approvability safety issue in the medical and biopharmaceutic reviews.

Although the formulation in the 1 mg and 3 mg blisters is identical, the clinical, biopharmaceutic, and emitted dose performance is not dose proportional. That is; three 1 mg blister doses are not equivalent to one 3 mg blister dose. The labeling reflects this.

Four comparability protocols were contained in the original submission. They are for (1) the addition of a _____ for the spray-dried formulation powder, (2) a change in the manufacturing process _____

_____ (3) a _____, and (4) a change _____]

One consulted CMC reviewer (Dr. Brian Rogers) considers the _____

_____ The overall recommendation from the rest of that consulted CMC team, including myself, is for approval.

The Exubera device contains an _____

It is noteworthy to mention that this drug product is designed to deliver insulin for systemic administration *via* the lungs as opposed to *to* the lungs as a target organ. With more conventional systems designed to deliver (non-titratable) drugs to the lungs as the target organ to treat asthma and COPD, fine control of the particle size and emitted dose distribution is essential. Unlike insulin, the inhaled drugs used to treat asthma and COPD are NOT titratable.

However, in this case, the drug is titratable. Overall, there is lower risk and corresponding lower concern for tightly controlled particle size distribution and emitted dose requirements based on clinical considerations. In clinical trials, it was noted that the occurrence of adverse events for inhaled insulin were no greater than for sc administered insulin.

Pfizer agrees to post-marketing agreements in the following major areas:

Late in the extended review cycle, Pfizer had proposed a _____ procedure. _____

This was rejected and the applicant is reminded in the action letter that any OOS results must be dealt with under current regulations and cGMP practices. _____

Pfizer was encouraged to put additional lots on stability early to support their planned agreements and comparability protocols.

The CMC recommendation is for APPROVAL with an eighteen (18) month shelf life at controlled room temperature which includes up to 3 months of out-of-pouch storage at controlled room temperature.

Rik Lostritto, Director, ONDQA Division I

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/s/

Richard Lostritto
1/26/2006 03:38:17 PM
CHEMIST



**NDA 21-868
Chem. Rev. 1**

Exubera®

(Insulin Human [rDNA origin]) Inhalation Powder

Pfizer Inc.

**Prasad Peri, Ph.D.
Brian Rogers, Ph.D.
Alan Schroeder, Ph.D.
Edwin Jao, Ph.D.
Arthur Shaw, Ph.D.**

Division of Pulmonary and Allergy Drug Products



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Chemistry Review Data Sheet

1. NDA 21-868
2. REVIEW #: 1
3. REVIEW DATE: Jan. 26, 2006
4. REVIEWERS: Prasad Peri, Brian Rogers, Edwin Jao, Alan Schroeder,
Arthur Shaw
5. PREVIOUS DOCUMENTS:

Previous DocumentsDocument Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) ReviewedDocument Date

Original Application	27-Dec-2004
Labeling	1-Jan-2005
Amendment (SAS transport files, QOS, DMF LOA)	12-May-2005
Amendment (Sample Devices)	31-May-2005
Amendment (SAS transport files)	13-July-2005
Amendment (Responses to IR letters 1 and 2)	25-July-2005
Amendment (SAS transport files-Production batches)	2-Aug-2005
Amendment (Responses to email comments dated 7/29/05)	9-Aug-2005
Amendment (Responses to IR letter 3 dated 7/12/05)	12-Aug-2005
Amendment (Additional and corrected SAS transport files)	19-Aug-2005
Amendment (Response to email regarding blister conditions)	23-Aug-2005
Amendment (Stability data (12 m in-pouch and 4 m OOP for PQ batches)	26-Aug-2005
Amendment (Stability data (12 m in-pouch and 4 m OOP for PQ batches)	30-Sept-2005
Amendment (Responses to IR letter 4 dated 9/26/05)	30-Sept-2005
Amendment (Responses to email sent to Pfizer on 10/3/05)	06-Oct-2005
Amendment (Responses to IR6 sent to Pfizer on 12/7/05)	23-Dec-2005
Amendment (Responses to IR6 sent to Pfizer on 12/7/05)	12-Jan-2006



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7. NAME & ADDRESS OF APPLICANT:

Name:	Pfizer Inc
Address:	MS 6025-B6275 50 Pequot Avenue New London, CT 06320
Representative:	Brian A. Green
Telephone:	(860)-732-0959

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Exubera
- b) Non-Proprietary Name (USAN): (insulin human (rDNA origin)) inhalation powder
- c) Code Name/# (ONDC only):
- d) Chem. Type/Submission Priority (ONDC only): S
 - Chem. Type:
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505b (1)

10. PHARMACOL. CATEGORY:

11. DOSAGE FORM: inhalation powder

12. STRENGTH/POTENCY: 1 mg and 3 mg blisters

13. ROUTE OF ADMINISTRATION: Oral Inhalation

14. Rx/OTC DISPENSED: ___ Rx ___ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

X SPOTS product – Form Completed

Not a SPOTS product

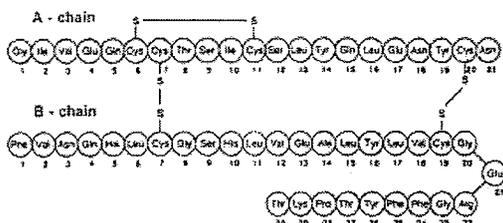


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16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Molecular Formula: C₂₅₇H₃₈₃N₆₅O₇₇S₆

Molecular Weight: 5708

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMFs in this Review pertain to the Drug Product only. Review of Drug Substance (recombinant Insulin) DMF was performed by Ms. Janice Brown.

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE of REVIEW	COMMENTS	
1	III	[Redacted]	Blister Pack Bottom Foil	1	Inadequate Adequate	6/15/05 9/7/05		
2	III			1	Adequate	6/15/05		
3	III				1	Inadequate Adequate	6/14/05 9/06/05	
4	III			Push through blister foil, Foil pouch	1	Inadequate Adequate	6/20/05 11/3/2005	
5	III				1	Inadequate Adequate	6/29/05 12/10/05	
6	III				1	Inadequate Adequate	6/29/05 9/28/05 1/26/06	Preliminary assessment of faxed information
7	III				7	N/A	N/A	
8	III				7	N/A	N/A	
9	III				1	Inadequate Adequate	6/22/05 9/23/05	
10	III				1	Inadequate Adequate	6/13/05 9/26/05 12/15/05	
11	III				1	Adequate	6/15/05 9/08/05	
12	III				7	N/A	N/A	
13	III				7	N/A	N/A	
14	III				1	Inadequate Adequate	6/3/05 9/26/05 1/26/06	Preliminary evaluation of composition



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15	III		7	N/A	N/A	
16	III		7	N/A	N/A	
17	III		7	N/A	N/A	
18	III		1	Adequate	9/23/05	
19	III		1	Inadequate Adequate	9/26/05 1/26/06	New DMF to be sent in. No safety issue based quantitative composition provided in the fax. DMF holder indicates studies in DMF.
20	III		1	Inadequate Adequate	9/28/05 1/26/06	Preliminary evaluation of updated data in DMF.

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics Evaluation of batch effect changed to shelf life based on further analysis of for production stability batches of Stages	shelf life proposed since only data were evaluated.	1/10/2006	Qian, Li
EES	Acceptable	1/24/06	OC
Pharm/Tox	Evaluation of are acceptable based on pharmacologist review. in	9/21/2005	Dr. Fred Alavi
Biopharm	N/A		



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LNC	DMETS has no issues with the name. DMETS Labeling comments have been provided		
Methods Validation	To be pursued once acc. crit. and methods are established		
ODS/DMETS	Acceptable	22-Jul-2005	Charlie Hoppes, R.Ph., M.P.H.
EA	Acceptable	15-Dec-2005	Janice Brown, Biologist
Microbiology	Acceptable	30-Nov-2005	James McVey, Microbiologist

APPEARS THIS WAY ON ORIGINAL



The Chemistry Review for NDA 21-868

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Exubera is a dry powder inhaler system for insulin. Insulin powder formulation is packaged in 1 mg strength and 3 mg strength for use in a delivery device.

Major Recommendations are in bold below.

The NDA is recommended to be approved from a CMC standpoint based on evaluation of its CMC performance characteristics. The following critical parameters for the drug product merit special attention as they influence the shelf life of the drug product.

1. **Emitted Dose for the 1 mg blisters is more variable than for the 3 mg blisters.**
- 2.

_____ for the 1 mg shows a _____ two of the three production qualification batches and **may potentially impact efficacy** at the end of the applicant proposed 18 month shelf life for the 1 mg blisters **as indicated in the review by Dr. Rogers**. This has been communicated to the clinical reviewers and the applicant in a letter dated Dec. 7, 2005. Since this _____ not seen in the data provided for the clinical batches, Pfizer agreed to monitor this parameter closely for future batches. However, since this drug does not act locally, based on risk assessments the _____ may not really impact overall efficacy. The applicant has committed to analyze these trends and report data to the Agency from future commercial batches.

4. A biometrics consult was requested to analyze the above mentioned trends for the amount of insulin deposited on _____ and project the shelf life for the blisters. Based on the statistician's analysis of the _____ months data the consulted statistician does not support using the analysis results to extrapolate the shelf life beyond the time period of data which were at the time of the consult _____ months). However based on the analysis performed by this reviewer of the updated data (18 months) presented by the applicant, an 18 month shelf life for the 1 mg and 3 mg blisters may be supported and will be recommended to the applicant.
5. The device base pressure from the _____ at the end of the use life. The device base pressure of _____ is acceptable for performance although it is at the lower limit of the acceptance criterion.

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6. Several post approval agreements are in place and are listed below.**Scope of this Review**

The following sections of the drug product have been assigned and reviewed by HFD 570 (for review and it is the understanding of the CMC review team in that the remaining CMC issues will be evaluated and addressed by the CMC team in HFD-510.

- Performance of the drug product (including characterization studies) in terms of _____
- Stability of the device and shelf life determination
- Specifications and performance of the individual device components, the whole device.
- _____
- DMFs associated with device/blister packaging.

A summary of the review follows the general description of the drug product**Drug Substance**

- The drug substance is recombinant (isolated from *E. coli*) human insulin and is manufactured by Diabel Inc. (a joint venture between Pfizer and Aventis) and described in a DMF by Aventis. The DMF was reviewed by Ms. Janice Brown and found acceptable. The spray dried insulin formulation filled in blisters contains 60% insulin, _____ mannitol _____ sodium citrate, dihydrate (_____) _____ glycine _____ sodium hydroxide _____ . The spray dried formulation is stable and can be stored at room temperature as opposed to sub-cutaneous insulin.

Drug Product Blister

- The formulation is filled in unit dose blisters made from _____ composed of PVC/foil _____ PVC. The 1 mg strength blisters are filled with 1.7 mg formulation and the 3 mg blisters are filled with 5.1 mg of the formulation. The two strengths are differentiated by unique tactile markings and print colors and are designed to be used in the same device.

Drug Product Device

- The Exubera device consists of three components: the base unit, the chamber, and the insulin release unit (formerly called transjector). The device accepts both the 1 and 3 mg strengths at the same location. When the blister is inserted and the pump handle actuated, mechanical energy converted to air pressure is stored within the device and ready to be used for the aerosolization. Depressing the blue button on the device punches holes on the top surface of the blister and also causes the compressed air pressure to release causing aerosolization of the contents of the blister to the chamber. The patient unlocks the mouthpiece and inhales the standing cloud of chamber within 3 seconds.

3 Page(s) Withheld

8 § 552(b)(4) Trade Secret / Confidential

 § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

Withheld Track Number: Chemistry-

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Drug Product Characterization studies

Several DP characterization studies have been evaluated by the applicant during development and appropriate comments incorporated into the labeling.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Pfizer agreed to the following post-marketing Agreements in their response dated Dec. 23, 2005.

1. Implement the agreed upon run qualification acceptance criteria for _____ (For the 3 mg blister: '_____' " For the 1 mg blister (as agreed in the 19 December 2005 telecon with the Agency): _____)
2. Pfizer agrees to perform _____ for _____ additional lots (_____ for each strengths) consisting of _____. Additionally, _____ will also be performed for the first three commercial lots at the initial time points and at _____, for the 25°C/60%RH storage condition. Results will be reported as a general correspondence upon completion of the _____ 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 _____ 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.

Pfizer agrees to the following post approval agreements as per their response dated Sept. 30, 2005.



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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 the _____ as an acceptance criterion in lieu of using the _____ reference standard (comment 1b).
 - c) For the method for determination of the Insulin release unit Flow (_____) repeatability experiments to provide actual results for _____ : unit at _____
 - 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 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 _____

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- g) For your _____ certain materials describe how age-related changes of these materials will be controlled to ensure adequate function of the components
Comment 22e(1).
7. Within **nine months post action**, Pfizer agrees to provide complete responses to comments listed below and as agreed to in their response dated Sept. 30, 2005. The comment numbers and relevant information are highlighted below
- a) Information associated with _____ investigations
_____ (comment 21a, and _____)
- b) Verify that the _____ used in the device is _____. Provide characterization data as part of the response (comment 21c).
- c) Further evaluate _____ by conducting the _____ to demonstrate whether or not an _____ is reached. Provide a scientific basis for estimating a patient's 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 _____
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) _____
- e) 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 (#6092) (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.
 - 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 of _____ that were identified
- f) Investigate improvement of the extraction and analytical procedures for _____ and _____ (with quantitative limits) from the _____ the _____ so 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 of the _____ insofar as is possible (comment 22d(3)).

10. Pfizer Agreed to provide the following changes as comparability protocols

(a) _____ **Comparability Protocol**

Pfizer agrees to submit the proposed change _____ 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 _____ as a CBE-30 supplement. The requested comparative data will be provided in the CBE-30

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supplement.

(c) **Process Change to _____ Blister 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 _____ blisters will be provided as a part of the PAS, with the comparability _____ updated accordingly. Pfizer, as a part of their continuous improvement process, will evaluate _____

Additional comments for the AP letter

We remind you that any OOS results to the Drug Product should be dealt with in accordance to cGMP practices and regulations and you may not use an internal statistical protocol in lieu of them.

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

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The drug substance is recombinant human insulin that is spray dried and obtained as a white _____ powder. The insulin is _____ along with other excipients mannitol, glycine, sodium citrate, and sodium hydroxide and spray dried again to give a white _____ powder that packaged in blisters. The spray dried powder contains is about _____ micrograms of insulin per mg of formulation.

The formulations are filled into PVC/Aluminum blisters that are used with the pulmonary inhaler. The applicant proposes to market two strengths of insulin based on the amount of insulin per blister: 1 mg and 3 mg. This corresponds to 1.7 mg and 5.1 mg formulation per blister respectively. The proposed blisters are to be marketed in a PET (plastic) trays that are over-wrapped in an aluminum foil pouch. Each tray holds either _____ blisters of the 1 mg strength and _____ of the 3 mg strength. The blister tray is over wrapped in a aluminum foil pouch. The applicant proposes a _____ out of pouch shelf life which is found acceptable.

The drug product consists of two main components: the pulmonary inhaler and the blister. The pulmonary inhaler is a tubular device about six inches long that incorporates a base unit,

**Chemistry Assessment Section**

a chamber, (that acts as a spacer) and an insulin release unit. The base unit is very complex and consists of approximately _____ components. The base unit utilizes compressed air energy that is generated by mechanical pumping of a piston and stored as compressed air pressure in a valve diaphragm. When the device is actuated by pushing the blister against the sharp needles of the insulin release unit the compressed energy is released in the form of air pressure which aerosolizes the contents of the blister into the device chamber. The patient then inhales the contents of the chamber.

B. Description of How the Drug Product is Intended to be Used

Exubera device and the blisters are labeled clearly and are to be used as per the instructions provided in the patient's instructions for use. The device should be held upright while using it.

The 1 mg or 3 mg insulin blister is inserted into the device and the device handle pumped to generate the air pressure to empty the blister. The device is actuated by pressing the blue button on the base unit which provides a standing cloud of insulin in the chamber. The patient then quickly opens the mouthpiece (by turning it), places his mouth around it and inhales the contents of the chamber. The patient is advised to hold their breath for 5 seconds and then breath normally. If a second dose is required, the patient is advised to follow the same instructions a second time.

Patients are advised to replace the insulin release unit after every two weeks of use and after one year of use of the whole device.

C. Basis for Approvability or Not-Approval Recommendation

All safety and quality control issues have been resolved from a CMC stand point. Several agreements have been made with the applicant that will need studies performed and results provided to the Agency (see list of phase IV agreements).

III. Administrative**A. Reviewer's Signature****B. Endorsement Block**

ChemistName/Date: Same date as draft review
ChemistryTeamLeaderName/Date
ProjectManagerName/Date

C. CC Block

397 Page(s) Withheld

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

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

*Withheld Track Number: Chemistry*_____

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NDA 21-868

ExuberaTM (Insulin Human [rDNA origin]) Inhalation Powder

Pfizer, Inc.

**Janice Brown, HFD-510
Division of Metabolic and Endocrine Products**



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I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data.....	
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P DRUG PRODUCT [Name, Dosage form]	
A APPENDICES.....	
R REGIONAL INFORMATION	
II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1	
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B. Environmental Assessment Or Claim Of Categorical Exclusion	
III. List Of Deficiencies To Be Communicated	



Chemistry Review Data Sheet

1. NDA: 21-868
2. REVIEW #: 1
3. REVIEW DATE: 12-Jan-2006
4. REVIEWER: Janice Brown, Mail Stop 2562
5. PREVIOUS DOCUMENTS:

Previous DocumentsDocument Date

IND 43,313

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original NDA	27-Dec-2004
Amendment N000BL	23-Feb-2005
Amendment N000BC	02-Aug-2005
Amendment N000BC	06-Oct-2005
Amendment N000BI	11-Nov-2005
Amendment N000BL	21-Dec-2005
Amendment N000BC	12-Jan-2006

7. NAME & ADDRESS OF APPLICANT:

Name:	Pfizer, Inc.
Address:	MS 6025 - B6275 50 Pequot Avenue New London, CT 06320
Representative:	Brian A. Green
Telephone:	(860) 732-0959

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

Chem. Type/Submission Priority (ONDC only):

- A. Proprietary Name: Exubera
- B. Non-Proprietary Name (USAN): Insulin (rDNA) powder for oral inhalation
- a) Code Name/# (ONDC only):
- b) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 3 (New Dosage Form)
 - Submission Priority: Standard

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Treatment of Diabetes Mellitus

11. DOSAGE FORM: Lyophilized Powder for Inhalation

12. STRENGTH/POTENCY: 3mg/blister and 1mg/blister

13. ROUTE OF ADMINISTRATION: Powder for Inhalation

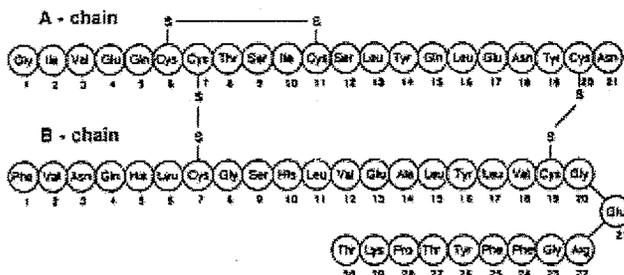
14. Rx/OTC DISPENSED: X Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

 X SPOTS product – Form Completed

 Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:





CHEMISTRY REVIEW



Chemistry Review Data Sheet

Molecular Formula: C₂₅₇H₃₈₃N₆₅O₇₇S₆

Molecular Weight: 5708

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs: Refer to the CMC pulmonary review for the container-closure DMF information.

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
—	Type II	—	Insulin drug substance	1	Adequate		None

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed).

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	--	--	--
EES	Pending	--	--
Pharm/Tox		--	--



CHEMISTRY REVIEW



Chemistry Review Data Sheet

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biopharm	--	--	--
LNC	--	--	--
Methods Validation	Pending	--	--
ODS/DMETS	Acceptable	22-Jul-2005	Charlie Hoppes, R.Ph., M.P.H.
EA	Acceptable	15-Dec-2005	Janice Brown, Biologist
Microbiology	Approval	30-Nov-2005	James McVey, Microbiologist
CMC Pulmonary	Pending		Prasad Peri, Chemist
CDRH	Pending		Ann Graham, RN

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt.

Yes No If no, explain reason(s) below:

APPEARS THIS WAY ON ORIGINAL



The Chemistry Review for NDA 21-868

The Executive Summary – This revised Executive Summary includes the following changes: (1) Correction of the Heading (see above) from “The Chemistry Review for NDA 21-536” to “The Chemistry Review for NDA 21-868” and (2) Clarification under I(B) of the Phase 4 agreements.

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application can be Approved pending (1) an acceptable consult review by CDRH, (2) a satisfactory cGMP inspection of facilities used to manufacture the drug substance and the drug product.

Based on the — month in-pouch stability data for the commercial scale batches, a 18 month shelf-life for insulin human inhalation powder packaged in a 30-blister count desiccated foil pouch when stored below 30°C is granted instead of — months as requested.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

From a CMC standpoint, this application can be Approved. There are a number of CMC agreements listed in the CMC Pulmonary review and one from the CMC review. For clarity the following CMC agreement was agreed to:

Pfizer commits to monitor the levels of _____ insulin throughout the stability studies for three commercial scale batches. If levels significantly increase over time, Pfizer commits to revising the specification to include this attribute.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

DRUG SUBSTANCE: All CMC information for the insulin human drug substance is described in a Drug Master File — Insulin human is a — amino acid polypeptide consisting of two polypeptide chains. The A and B chain, consisting of 21 and 30 amino acid residues, respectively, are linked by 2 disulfide bridges. The A chain contains one intra-chain disulfide bridge. The executive summary for the drug substance is provided in section 3.2 of DMF —

DEVICE: Refer to the CMC pulmonary review and CDRH consult review (pending).

DRUG PRODUCT: Exubera is a white to off white powder filled in single dose perforated blisters. The unit dose blisters contains either 1 mg or 3 mg of insulin that delivers a fine particle



CHEMISTRY REVIEW TEMPLATE



dose of 0.4 and 1 mg of insulin, respectively. The unit dose blisters have been developed specifically for use with the Exubera pulmonary inhaler. For each inhalation, a blister is inserted into the slot on the inhaler. During use, the patient pumps the inhaler lever to compress and store the air needed for powder aerosolization. On actuation, the blister is pierced when it rises into the transjector and the compressed air is released into the blister producing a cloud of insulin powder. The cloud of insulin powder is held in a chamber and the patient inhales the cloud through the mouthpiece. During inhalation, ambient air is pulled into the chamber of the device as the patient's inhalation removes the aerosol out of the chamber and into the lungs. Each dose is inhaled using one slow deep inhalation. Doses requiring multiple blisters are administered by repeating this procedure.

Components/Composition:

The composition of the 1mg and 3mg blisters are summarized in table 1-1. All excipients meet the USP requirements and are also additionally tested for bioburden.

Table 1-1: Composition of the Dosage Form (1 mg and 3 mg)

Name of Ingredient	Unit Formula (mg/blister)		Function
	1 mg blister Formulation Code No.: 97060/97061	3 mg blister Formulation Code No.: 97060/97063	
Insulin, Human Recombinant	—	—	Active
Sodium Citrate, Dihydrate	—	—	—
Mannitol	—	—	
Glycine	—	—	
Sodium Hydroxide	—	—	
—	—	—	
— Foil/PVC Unit Dose Blister	—	—	—
Total Weight (mg)	1.70	5.10	

N/A = Not applicable.

a: Based on sodium ion

b: — during spray drying

PHARMACEUTICAL DEVELOPMENT

4 Page(s) Withheld

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

 § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

Withheld Track Number: Chemistry-



B. Description of How the Drug Product is Intended to be Used

EXUBERA is indicated for the treatment of adult patients with diabetes mellitus for the control of hyperglycemia. EXUBERA is supplied in 1 mg and 3 mg unit dose blisters on perforated blister cards of 6 unit dose blisters. Five blister cards are packaged in a clear plastic (PET) thermoformed tray with a desiccant and covered with a clear plastic (PET) lid. The tray of 5 blister cards (30 unit dose blisters) is sealed in a foil laminate pouch with a desiccant.

Unopened blisters are stable for 18 months when stored below 30°C (86°F). Once the foil overwrap is opened, unit dose blisters should be protected from moisture, stored at 25°C (77°F). Unit dose blisters should be used within 3 months of opening the foil overwrap. This product should not be refrigerated or frozen. Do not freeze. Do not refrigerate.

C. Basis for Approvability or Not-Approval Recommendation

This application can be Approved from a CMC viewpoint, pending an acceptable Microbiology and the CMC pulmonary review. A final recommendation by the Office of Compliance is also pending.

III. Administrative

A. Reviewer's Signature

See electronic signature page

B. Endorsement Block

Chemist: J. Brown (see appended electronic signature page)

Pharmaceutical Assessment Lead: S. Moore (see appended electronic signature page)

C. CC Block

ONDQA/E. Duffy

ONDQA/B. Fraser

DMEP/Division File/NDA 21-868

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

/s/

Janice Brown
1/26/2006 12:45:28 PM
CHEMIST

Richard Lostritto
1/26/2006 12:57:05 PM
CHEMIST



NDA 21-868

ExuberaTM (Insulin Human [rDNA origin]) Inhalation Powder

Pfizer, Inc.

**Janice Brown, HFD-510
Division of Metabolic and Endocrine Products**



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R REGIONAL INFORMATION	
II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1	
A. Labeling & Package Insert	
B. Environmental Assessment Or Claim Of Categorical Exclusion	
III. List Of Deficiencies To Be Communicated	



Chemistry Review Data Sheet

1. NDA: 21-868
2. REVIEW #: 1
3. REVIEW DATE: 12-Jan-2006
4. REVIEWER: Janice Brown, Mail Stop 2562
5. PREVIOUS DOCUMENTS:

Previous Documents

IND 43,313

Document Date

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original NDA	27-Dec-2004
Amendment N000BL	23-Feb-2005
Amendment N000BC	02-Aug-2005
Amendment N000BC	06-Oct-2005
Amendment N000BI	11-Nov-2005
Amendment N000BL	21-Dec-2005
Amendment N000BC	12-Jan-2006

7. NAME & ADDRESS OF APPLICANT:

Name:	Pfizer, Inc.
Address:	MS 6025 - B6275 50 Pequot Avenue New London, CT 06320
Representative:	Brian A. Green
Telephone:	(860) 732-0959



CHEMISTRY REVIEW



Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

Chem. Type/Submission Priority (ONDC only):

A. Proprietary Name:

Exubera

B. Non-Proprietary Name (USAN):

Insulin (rDNA) powder for oral inhalation

a) Code Name/# (ONDC only):

b) Chem. Type/Submission Priority (ONDC only):

• Chem. Type: 3 (New Dosage Form)

• Submission Priority: Standard

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Treatment of Diabetes Mellitus

11. DOSAGE FORM: Lyophilized Powder for Inhalation

12. STRENGTH/POTENCY: 3mg/blister and 1mg/blister

13. ROUTE OF ADMINISTRATION: Powder for Inhalation

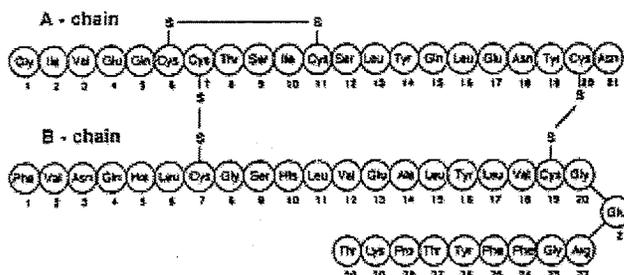
14. Rx/OTC DISPENSED: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:





CHEMISTRY REVIEW



Chemistry Review Data Sheet

Molecular Formula: C₂₅₇H₃₈₃N₆₅O₇₇S₆

Molecular Weight: 5708

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs: Refer to the CMC pulmonary review for the container-closure DMF information.

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
	Type II	_____	Insulin drug substance	1	Adequate		None

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed).

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	--	--	--
EES	Pending	--	--
Pharm/Tox		--	--



CHEMISTRY REVIEW



Chemistry Review Data Sheet

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biopharm	--	--	--
LNC	--	--	--
Methods Validation	Pending	--	--
ODS/DMETS	Acceptable	22-Jul-2005	Charlie Hoppes, R.Ph., M.P.H.
EA	Acceptable	15-Dec-2005	Janice Brown, Biologist
Microbiology	Approval	30-Nov-2005	James McVey, Microbiologist
CMC Pulmonary	Pending		Prasad Peri, Chemist
CDRH	Pending		Ann Graham, RN

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt.

Yes No If no, explain reason(s) below:

APPEARS THIS WAY ON ORIGINAL

**The Chemistry Review for NDA 21-536****The Executive Summary*****I. Recommendations*****A. Recommendation and Conclusion on Approvability**

The application can be Approved pending (1) an acceptable consult review by CDRH, (2) a satisfactory cGMP inspection of facilities used to manufacture the drug substance and the drug product.

Based on the 18-month in-pouch stability data for the commercial scale batches, a 18 month shelf-life for insulin human inhalation powder packaged in a 30-blister count desiccated foil pouch when stored below 30°C is granted instead of 12 months as requested.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable – None***II. Summary of Chemistry Assessments*****A. Description of the Drug Product(s) and Drug Substance(s)**

DRUG SUBSTANCE: All CMC information for the insulin human drug substance is described in a Drug Master File. Insulin human is a 51-amino acid polypeptide consisting of two polypeptide chains. The A and B chain, consisting of 21 and 30 amino acid residues, respectively, are linked by 2 disulfide bridges. The A chain contains one intra-chain disulfide bridge. The executive summary for the drug substance is provided in section 3.2 of DMF.

DEVICE: Refer to the CMC pulmonary review and CDRH consult review (pending).

DRUG PRODUCT: Exubera is a white to off white powder filled in single dose perforated blisters. The unit dose blisters contains either 1 mg or 3 mg of insulin that delivers a fine particle dose of 0.4 and 1 mg of insulin, respectively. The unit dose blisters have been developed specifically for use with the Exubera pulmonary inhaler. For each inhalation, a blister is inserted into the slot on the inhaler. During use, the patient pumps the inhaler lever to compress and store the air needed for powder aerosolization. On actuation, the blister is pierced when it rises into the transjector and the compressed air is released into the blister producing a cloud of insulin powder. The cloud of insulin powder is held in a chamber and the patient inhales the cloud through the mouthpiece. During inhalation, ambient air is pulled into the chamber of the device as the patient's inhalation removes the aerosol out of the chamber and into the lungs. Each dose is inhaled using one slow deep inhalation. Doses requiring multiple blisters are administered by repeating this procedure.



CHEMISTRY REVIEW



Executive Summary Section

The composition of the 1mg and 3mg blisters are summarized in table 1-1. All excipients meet the USP requirements and are also additionally tested for bioburden.

Table 1-1: Composition of the Dosage Form (1 mg and 3 mg)

Name of Ingredient	Unit Formula (mg/blister)		Function
	1 mg blister Formulation Code No.: 97060/97061	3 mg blister Formulation Code No.: 97060/97063	
Insulin, Human Recombinant	—	—	Active
Sodium Citrate, Dihydrate			
Mannitol			
Glycine			
Sodium Hydroxide			
() Foil/PVC Unit Dose Blister			
Total Weight (mg)	1.70	5.10	

N/A = Not applicable.

a: Based on sodium ion

b: — during spray drying

PHARMACEUTICAL DEVELOPMENT

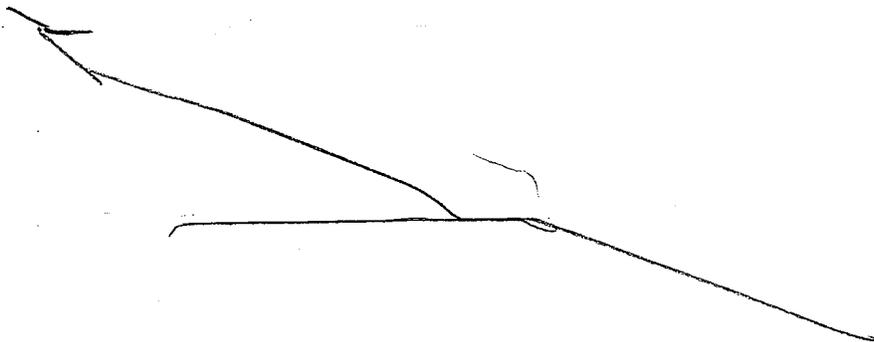
3 Page(s) Withheld

6 § 552(b)(4) Trade Secret / Confidential

 § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

Withheld Track Number: Chemistry-



Scale-up of the Spray Drying Process:



B. Description of How the Drug Product is Intended to be Used

EXUBERA is indicated for the treatment of adult patients with diabetes mellitus for the control of hyperglycemia. EXUBERA is supplied in 1 mg and 3 mg unit dose blisters on perforated blister cards of 6 unit dose blisters. Five blister cards are packaged in a clear plastic (PET) thermoformed tray with a desiccant and covered with a clear plastic (PET) lid. The tray of 5 blister cards (30 unit dose blisters) is sealed in a foil laminate pouch with a desiccant.



Unopened blisters are stable for 18 months when stored below 30°C (86°F). Once the foil overwrap is opened, unit dose blisters should be protected from moisture, stored at 25°C (77°F). Unit dose blisters should be used within 3 months of opening the foil overwrap. This product should not be refrigerated or frozen. Do not freeze. Do not refrigerate.

C. Basis for Approvability or Not-Approval Recommendation

This application can be Approved from a CMC viewpoint, pending an acceptable Microbiology and the CMC pulmonary review. A final recommendation by the Office of Compliance is also pending.

III. Administrative**A. Reviewer's Signature**

See electronic signature page

B. Endorsement Block

Chemist: J. Brown (see appended electronic signature page)

Pharmaceutical Assessment Lead: S. Moore (see appended electronic signature page)

C. CC Block

ONDQA/E. Duffy

ONDQA/B. Fraser

DMEP/Division File/NDA 21-868

140 Page(s) Withheld

~~_____~~ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

Withheld Track Number: Chemistry-_____

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/s/

Janice Brown
1/20/2006 03:04:35 PM
CHEMIST

Stephen Moore
1/20/2006 04:18:09 PM
CHEMIST