CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-868

MEDICAL REVIEW

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

OFFICE DIRECTOR'S DECISIONAL MEMORANDUM

Memorandum author:	Robert J. Meyer, MD, Director, ODE II
Date:	January 27th, 2006
NDA:	21-868
Sponsor:	Pfizer
Proprietary Name:	Exubera insulin (human) inhalation powder
Date of submission:	December 28th, 2004
Regulatory Due Date:	January 28th, 2006

Introduction: The NDA was submitted in December 2004 and was given a standard review cycle. The clock was extended from October due to a major CMC amendment. This is the first of the inhaled insulins under development to be submitted to the FDA as an NDA and represents an entirely novel way to deliver short-acting insulin to type 1 and 2 diabetes patients.

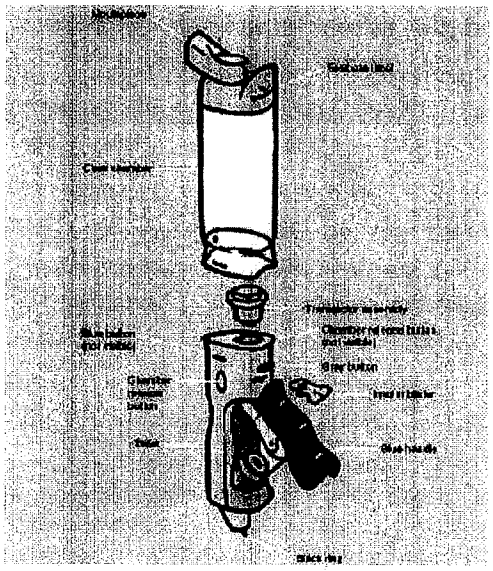
Since insulin is a peptide moiety, it is not possible to deliver insulin therapy by the enteral route, since enteric proteolytic enzymes would break ingested insulin down prior to absorption. Therefore, injectable insulin has been the only way insulin can be delivered since its discovery in the early part of the 20th century. The lung, with its extensive network of alveolar blood vessels (with a total air-circulation surface area approximating the surface area of a tennis court) is an attractive route for the administration of protein products and other drugs. However, the safety of chronically administering a protein to the lung, where it may reach very high local concentration is of particular concern, particularly given insulin is a growth factor. Additionally, this particular formulation has some unique characteristics compared to usual inhalational medicines (since the carrier sugar is also a part of the inhalable fraction), and these themselves pose some safety unknowns. Lastly, being a new route of administration, it is very important to understand the resultant pharmacokinetics in depth, particularly circumstances or conditions that might alter the PK profile of the insulin unpredictably.

Exubera is a drug-device combination (see depiction below). The product consists of human, recombinant regular insulin in a powder formulation with mannitol that is spray-dried to a respirable particle size and contained in unit packets (1 mg or 3 mg). These packets are individually placed into the chamber of "transjector" in a proprietary, new inhaler system. The system is then cocked like an air-rifle and actuated, whereby the insulin/mannitol powder is released into a clear holding chamber whence the patient inspires the formulation. The device was developed by a company now called Nektar, which partnered with Pfizer on this project. The insulin supplier is sanofi-aventis, though

Pfizer now has obtained full rights to the insulin. It is notable that this particular insulin is not the basis for an approved NDA in the U.S., so the drug substance is itself a new recombinant insulin product that has not been previously reviewed by the agency.

The Exubera comes as a unit dose in a foil blister. Exubera is supplied in a 1.0mg or 3.0mg nominal dose blister package. The inhaler is a reusable mechanical inhaler, which is illustrated in Figure 5, below.

Figure 5 Insulin Pulmonary Inhaler



Source: N21868/N_000/2004-12-27/summary/quality_summary.pdf, pg 120

The Exubera program involved extensive work by the sponsor with frequent communication between the FDA (both the Endocrine and the Pulmonary review staff). While the sponsor did not meet every expectation of the agency in this program, they did do a large, careful work up of the safety and efficacy of their product, as reflected by their NDA submission. It should also be noted that this application was discussed at the EMDAC in a meeting where the committee was augmented by several expert pulmonologists on Sept. 8th, 2005. The committee recommended approval in both patients with type 1 and 2 diabetes (7 for, 2 against) and was unanimous in stating that pulmonary safety in patients without lung disease had been sufficiently addressed for this product (but not the safety in patients with pulmonary disease).

Lastly, the various reviewers for this application have done excellent review work, including Dr. Mahoney of DMEP and Dr. Seymour of DPAP, who respectively did the efficacy/non-pulmonary safety review and the pulmonary safety review. Dr. Mary Parks, the Acting Director of DMEP, has likewise done an excellent summary memorandum for this application, which I have co-signed. I will not therefore do an extensive summary of the overall information, particularly the details of the efficacy and non-pulmonary safety review. Rather, I refer the reader to those primary and secondary documents. This memorandum will focus on important regulatory and scientific issues to serve as the basis of understanding for the regulatory decision.

Chemistry/ Device

The CMC aspects of the application were reviewed by Drs. Janice Brown (focusing on the insulin drug substance) and Prasad Peri (inhalation dosage form and device) of ONDQA. While a CDRH consult was obtained, the detailed review of the device performance rested with Dr. Peri. The CMC team has recommended approval of the product. The insulin drug substance, a human sequence recombinant product, was found acceptable in its important attributes. The device and powder formulation are reasonably complex and the review turned up some interesting findings. For instance,

[redacted]

Since this is a titrated drug and since this phenomenon was likely true of the clinical supplies, this issue does not preclude approval. The sponsor provided data to allow for 18 months expiry for both dosage strengths, according to Dr. Peri's summary memo. The CMC team and the sponsor have agreed to a number of post-marketing adjustments to the manufacturing and testing of the device that will be included in the action letter, but they have determined that there are sufficient data to allow for approval at this time.

Pharmacology/Toxicology

The toxicology of insulin is well known in terms of its systemic actions. Therefore, the PT program for this product appropriately focused on the issue of pulmonary safety. Inhalation toxicology was performed primarily in rats and monkeys. Dosing was limited in these animals by the pharmacodynamic effects of insulin itself (i.e., hypoglycemia). These bridging toxicology studies did not show any clear toxicities to the lungs from the formulation/drug. However, there were tolerability issues in monkeys (frequent coughing and sneezing) and there were occasionally noted increases in lung weights and sporadic alveolar inflammation in rats from the 1-month bridging study. Without clear, dose-related toxicity seen, the maximum studied dose in rats (5.8 mg/kg/d) and monkeys (0.64 mg/kg/d) were therefore deemed to be the NOAELs and therefore the safety margins based on the NOAEL dose in rats and monkeys were approximately 6X and 1.4 X the clinical dose of 0.15 mg/kg/d based on mg/m2, respectively. The non-clinical studies provided significant safety margins for the other components of the formulation as well, specifically the mannitol, which has not previously been approved in any inhalation dosage form.

Biopharmaceutics

Pfizer performed an extensive PK program, examining various conditions that might impact on the bioavailability of an inhaled product (various airway diseases, URIs, smoking status, etc.). The inhalation of insulin from Exubera leads to a fairly rapid peak insulin concentration (40 to 90 minutes) that exceeds the rapidity of regular human insulin given SQ. The duration of action with Exubera is comparable to injectable regular insulin. The fractional bioavailability of insulin from this formulation and device is in the 0.1 range (i.e., about 10% of the nominal dose is absorbed).

It was known, even prior to this program, that smoking might increase the bioavailability of insulin. Indeed, smokers given Exubera had 2 – 5 fold higher systemic exposure to insulin than non-smokers. Smoking cessation leads to a gradual diminution of this disparity, but resumption of smoking leads to a rapid increase in insulin bioavailability. Acute exposures to second hand smoke, paradoxically, lead to diminished insulin absorption. Asthma patients have a somewhat lower absorption of inhaled insulin from Exubera compared with normals and this is at least partly reversed with albuterol pretreatment. COPD patients have approximately a 50% increase in absorption. All of these changes are of somewhat unclear etiologies. Due to the higher insulin exposures in smokers and the variability of this response when smoking habits are changed, Pfizer has not extensively studied clinical safety and efficacy in smokers and plans to contraindicate the product in smokers at this time.

One other biopharmaceutic issue worth noting is that the 3 mg and 1 mg blisters do not have good dose equivalence, in that three 1 mg blisters lead to more insulin absorption than does one 3 mg blister, due in part to somewhat different aerodynamic particle distributions of the two dosage strengths. Therefore, if one were stable on 3 mg of Exubera and the 3 mg blisters were temporarily not available, the best course of action would be to take two 1 mg blisters, which would slightly under dose, rather than three 1 mg blisters, which would over dose. The consequence of the former would be temporary diminution of glycemic control, while the latter could result in hypoglycemia – a potentially more dangerous event. This issue of dose-equivalency is highlighted in many places on the PI, the Medication Guide and the carton/container labeling.

Clinical

The clinical reviews were done by Karen Mahoney of DMEP (efficacy and systemic safety) and Sally Seymour (pulmonary safety), and summarized nicely by Dr. Park's Division Director memorandum. Regarding the efficacy findings, suffice it to say that this is an effective insulin and the inhaled route allows for sufficient predictability to lead to safe glycemic control when inhaled insulin is used in place of SQ short-acting insulins. That means that for patients with type 1 diabetes, this product may serve as a replacement for mealtime insulin on the setting of a background of injectable long-acting insulin or insulin analogues. For type 2 diabetes, Exubera was studied as the solitary hypoglycemic agent, as an addition to oral agents (such as sulfonylureas and metphormin) or as an addition to regimens including long-acting insulins.

Below is a table from the original NDA which depicts the extent and duration of the safety exposures:

Table 9 Duration of Exposure to Study Medication Adult Subjects in Controlled Phase 2 and 3 Studies n (%)					
	Number (%) of subjects*				
	Type 1		Type 2		
Exposure (months)	INH N=698	SC N=705	INH N=1277	SC N=488	OA N=644
>0-3	159 (22.8)	165 (23.4)	365 (28.6)	45 (9.2)	209 (32.5)
>3-6	264 (37.8)	249 (35.3)	288 (22.6)	141 (28.9)	137 (21.3)
>6-12	61 (8.7)	64 (9.1)	249 (19.5)	121 (24.8)	99 (15.4)
>12-18	158 (22.6)	169 (24.0)	183 (14.3)	148 (30.3)	48 (7.5)
>18-24	56 (8.0)	58 (8.2)	136 (10.6)	33 (6.8)	107 (16.6)
>24-30	0	0	56 (4.4)	0	44 (6.8)
Median exposure	5.59	5.65	5.88	9.71	5.60
Overall exposure (subjects-months)	5894	6052	12187	4868	6453

*The numbers are not cumulative. Subjects are counted only in their final treatment duration category
Source: N21868/N_000/2004-12-27/clinstat/summary-clin-safety.pdf, pg 136-137

The rate of hypoglycemia seen in clinical trials with inhaled insulin was comparable to that seen in the comparator SQ insulin groups. Hypoglycemia was more prevalent in type 2 patients when compared Exubera was compared to non-insulin treatments, but that is to be expected of any insulin and does not signal a unique concern with Exubera. Again, however, it should be noted that smokers were not allowed in the clinical studies and therefore it is unknown if smokers, particular those with irregular smoking habits, would have more variable responses and more serious hypoglycemic episodes. Given this lack of information and potentially serious outstanding question, the contraindication proposed by the sponsor for smoking makes sense.

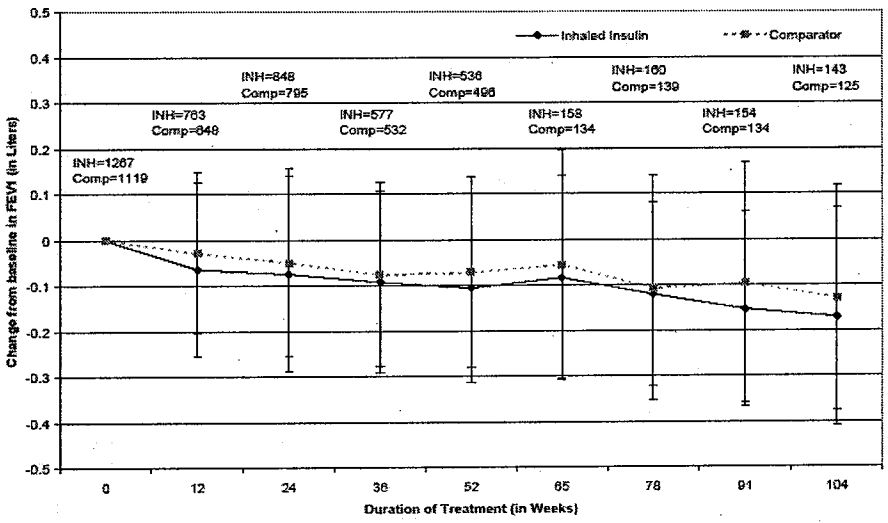
Interestingly, the rate of insulin antibody seroconversion (predominantly IgG) is very high for inhaled insulin in comparison to SQ insulin (the subcutaneous route is often held to be itself the most immunogenic). However, there was no signal of a clinical consequence of the antibodies developing in terms of efficacy (i.e., these were not neutralizing), no correlation to lung function declines and no apparent increased risk of systemic allergic reactions. This issue bears some consideration for post-marketing assessments.

A major concern of the FDA for this novel product is the pulmonary safety, both in normal subjects, as well as those with underlying lung disease. I should note that I was the original consulting pulmonologist on this development program and reviewed many of the early clinical and PK study protocols. So I have had a long-term interest and concern on these matters. Although diabetes itself may have pulmonary ramifications (in terms of pulmonary function and gas exchange), for the most part this issue is not well worked out and therefore the "normal" patients in this database were diabetics without significant unrelated lung diseases, such as asthma or COPD. The sponsor performed a reasonably extensive program examining the safety in this population (though the data for patients with asthma and COPD available to date is much less extensive in numbers studied and duration). The findings of PFTs and high resolution chest CTs are reasonably reassuring; with the latter showing no clear evidence of chronic pulmonary parenchymal changes related to inhaled insulin in this formulation. The PFTs – particularly FEV_1 and DLCO –

show early mean decrements of a fairly minor degree in comparison to the comparator patients, but these do not seem to be progressive beyond the first few weeks out to 2 years. For instance, the annual rate of decline in FEV_1 in type 1 patients on inhaled insulin was 66 ml/year and it was 39 ml/year in the comparator patients, a delta of 27 ml on average at the end of the year, a relatively insignificant amount given it does not appear to be progressive beyond the first few weeks of therapy. There is at least some data to suggest that after stopping the insulin, the FEV_1 and DLCO revert to that of the comparator group. The physiologic basis of these observed changes is not clear, but it does appear from distribution analyses that this is a phenomenon that appears fairly uniform and no extreme outliers attributable to treatment were observed. In other words, the mean decrement appear to occur from many patients falling in FEV_1 and DLCO to a small degree, not due to a few patients falling greatly in their lung function. On balance, then, these data are reassuring on the pulmonary safety given the large amount and duration of the studies. A typical graph of the data for the type 2 patients is displayed below (from the biostastician's review from Dr. Buenconsejo's review). DLCO data and the type 1 patient data for both parameters were similar:

Pulmonary Consultation
NDA# 21-868 N000, Exubera (Insulin inhalation powder)
Sally M. Seymour, M.D.

Figure 3 Mean Change from Baseline FEV_1 over Time in the Phase 2 and 3 Controlled Studies in Adults with Type 2 Diabetes (Mean +/- SD)



Safety in COPD and Asthma: The safety data in subjects with underlying lung disease are limited and primarily were derived from two studies that were underway when the NDA was submitted. The interim data for patients with asthma suggest that there is an increase in the treatment group difference in change from baseline FEV_1 and DLCO at Week 52, favoring the comparator and these limited data (27 subjects) suggest the PFTs may be continuing to decline throughout the treatment relative to the comparator group, but this is very preliminary. The interim data from the study of COPD patients at one year are

suggestive of Exubera causing a greater mean decline in FEV_1 than the comparator group, though the comparator group had a greater mean decline in DLCO than the Exubera. Again, there are very limited data to support any conclusions with only 30 subjects contributing the 1 year observations. Since the long-term safety of Exubera has not been adequately studied in asthma and COPD, these patients will not be recommended to receive Exubera until the complete study reports are available and reviewed. The completion and timely reporting of these data will be a post-marketing commitment by the sponsor.

More routine pulmonary safety was reasonably studied and assured. A table from the original NDA summarizes this experience:

Table 13 All Causality Respiratory Adverse Events in Adult Controlled Phase 2 and 3 Studies – Combined Type 1 and Type 2 Diabetes

Number of subjects (%)	Exubera n=1975	Comparator n=1837
Any Respiratory Adverse Events	**1254 (63.5)**	**926 (50.4)**
Apnea	1 (0.05)	0
Asthma	**32 (1.6)**	**19 (1.0)**
Atelectasis	0	1 (0.05)
Bronchiectasis	0	1 (0.05)
Bronchiolitis	1 (0.05)	0
Bronchitis	**81 (4.1)**	**70 (3.8)**
Carcinoma of lung	1 (0.05)	1 (0.05)
Cough increased	**464 (23.5)**	**119 (6.5)**
Dyspnea	**69 (3.5)**	**22 (1.2)**
Edema pharynx	1 (0.05)	2 (0.1)
Emphysema	1 (0.05)	1 (0.05)
Epistaxis	**24 (1.2)**	**9 (0.5)**
Hemoptysis	1 (0.05)	0
Hyperventilation	1 (0.05)	1 (0.05)
Hypoventilation	1 (0.05)	0
Laryngitis	**15 (0.8)**	**7 (0.4)**
Lung disorder	**4 (0.2)**	**1 (0.05)**
Lung edema	1 (0.05)	2 (0.1)
Nasal polyp	1 (0.05)	1 (0.05)
Pharyngitis	**242 (12.2)**	**184 (10.0)**
Pleural disorder	1 (0.05)	1 (0.05)
Pneumonia	16 (0.8)	17 (0.9)
Respiratory disorder	**110 (5.6)**	**79 (4.3)**
Respiratory distress syndrome	0	2 (0.1)
Respiratory tract infection	**647 (32.8)**	**572 (31.1)**
Rhinitis	**199 (10.1)**	**132 (7.2)**
Sinusitis	**129 (6.5)**	**104 (5.7)**
Sputum increased	**61 (3.1)**	**15 (0.8)**
Voice alteration	**15 (0.8)**	**3 (0.2)**
Yawn	1 (0.05)	1 (0.05)

Source: [N21868/N 000/2004-12-27/pulm.pdf, pg 19]

Cough is the most obvious common pulmonary AE, but rarely led to significant problems or withdrawals (20 total withdrawals due to cough) and is reported to abate with continued

use. Importantly, in patients with cough, declines in FEV_1 were no greater on average than those not reporting cough.

DSI Audits
Two representative clinical sites (Cefalu, Burlington VT and Schwartz, San Antonio TX) were inspected by FDA, both considered to have performed sufficiently well in clinical study management and record keeping to be acceptable for consideration. There was no evidence of systemic data issues.

Financial disclosure
See pages 24 – 27 of Dr. Mahoney's review. There were some investigators (including Dr. Cefalu, who was audited as above) with significant financial conflicts of interest. Re-analyses of the efficacy data by our statistical reviewers removing data for these sites did not change the efficacy conclusions substantially and it is felt therefore that these financial interests do not preclude us making overall discussions based on the data presented.

DMETS/nomenclature
DDMAC recommended against the name Exubera as being fanciful and promotional. Dr. Mahoney has written a memorandum documenting why the division feels the name is acceptable (if not ideal) in light of the sponsor's arguments. While I do find the name somewhat fanciful and promotional, I am overall in agreement with the division and will not follow DDMAC's recommendation. DMETS has been extensively involved in the labeling and their recommendations have, in general, been considered and implemented with regard to carton and container labeling.

Labeling
Satisfactory labeling has been developed in multiple iterations with the sponsor. The labeling includes a Medication Guide, done on the basis of the criterion from the relevant regulation that states (paraphrased) a Medication Guide may be required when FDA has determined that patient instructions are important to health, and patient adherence to directions for use is crucial to the product's effects. Pfizer has agreed to this and Jeanine Best has been very helpful in reaching satisfactory language on this guide.

Recommendation
As a pulmonologist, I have been quite skeptical of the safety of this product from early in its development. However, despite the extensive work done by Pfizer, including long-term follow-up with PFTs and HRCTs in patients without underlying lung disease, little evidence of a significant, progressive lung effect has resulted. Further, the animal data are quite reassuring. Therefore, Exubera should be approved for use in both type 1 and type 2 diabetes as a substitute for short-acting (e.g., mealtime dosed) insulin. However, it is prudent, and the company has agreed, to conduct a large simple trial post-approval to assess even more patients for longer durations in terms of PFTs to add to the assurance of pulmonary safety. Given the lack of safety and efficacy data in smokers and the issue of variability in pharmacokinetics, it will be contraindicated in smokers at present. Exubera use will be recommended against in asthma and COPD until FDA has received and reviewed longer term and more substantive safety data in such patients. Given the

variability of PK related to variable lung function (e.g., asthma patients with wide swings in flow rates), it will also be contraindicated in unstable patients with lung disease. Finally, FDA asked Pfizer not to extensively study Exubera in pediatric patients until the safety in adults was assessed. Pediatrics down to age 6 will need to be assessed under PREA. Patients aged 5 years and younger will not be required due to the limitations of the dosage form in younger children as well as the fact that young diabetics will be predominantly type 1 and therefore they will still need injectable insulin irrespective of this product's availability.

There are several phase 4 commitments that will be undertaken by the sponsor. These are listed and discussed below:

1. A large simple safety study to assess the long-term pulmonary safety in type 1 and 2 patients. Pulmonary had originally suggested a total of 10,000 patients, but the sponsor has proposed 5,000 and the pulmonary reviewers and I feel this is reasonable. This study will also examine immune events (hypersensitivity examinations and/or antibody response)
2. Completion of on-going trials, particularly the trials in COPD and asthma that will, perhaps, allow for indicating the drug in these patients (if the data indeed allow for this).
3. A survey of prescribing practices to assess use in smokers annually for 3 years. If there proves to be use in smokers at a significant level (e.g., 10%), we would then need to press Pfizer to either take measures to decrease such use, or to study the efficacy and safety in this population.
4. Pediatric data under PREA.

Note that the EMEA has asked for data from bronchoalveolar lavage samples in treated patients to assess for inflammatory cytokines and biomarkers. I do not see this as a necessary or particularly informative exercise, since the correlation of many of the assessed markers and cytokine to any specific lung process is not established. Also, the EMEA is asking for a long-term primary care database study to assess the lung malignancy risk in long-term treated patients. The FDA is not particularly worried that insulin will induce or permit lung cancer, since insulin at other injection sites has not proven to be procarcinogenic. Therefore, FDA will not require such a study, though we will be glad to receive the results of the investigation.

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/s/

Robert Meyer
1/27/2006 01:30:44 PM
MEDICAL OFFICER

ACTING DIVISION DIRECTOR MEMO

NDA	21-868
Sponsor	Pfizer Pharmaceuticals
Product name	Exubera® insulin (human) inhalation powder
Indication	Treatment of Type 1 and 2 diabetes mellitus

INTRODUCTION

Insulin therapy for diabetes treatment is certainly not a novel concept and since the isolation of this hormone from dog pancreas in the 1920s, several treatment regimens involving insulin have been established for both Type 1 and 2 diabetes. For type 1 diabetes, insulin therapy is a necessity as complete or near-complete destruction of pancreatic beta cells do not allow for sufficient endogenous production of insulin to maintain glucose homeostasis, let alone survival. The therapeutic use of this hormone has undergone significant changes over the past several decades including its source (cows and pigs to recombinant technology producing hormone identical to native sequence human insulin) and formulation (short-acting, long-acting, and rapid-acting). All these changes have improved the purity, immunogenicity, and pharmacokinetics of the protein to enable insulin treatment that would more closely approximate the pancreatic response to glucose surges post-prandially or in response to other hormonal signals (e.g., cortisol, glucagons, growth hormone, etc.).

For type 1 diabetics, the goal of maintaining glucose homeostasis requires multiple injections with different insulin preparations and with careful monitoring of glucose levels to ensure adequacy of efficacy and to mitigate risk of hypoglycemia. In 1993, the necessity for intensive and, in some case, complex treatment (e.g., continuous pump infusion) of Type 1 diabetics was affirmed by the results of a long-term study called the Diabetes Control and Complications Trial or DCCT that answered once and for all that tight control of glycemia in Type 1 diabetics would reduce the risk of long-term microvascular complications. Longer follow-up of subgroups from the original DCCT cohort has shown that intensive treatment also reduces macrovascular complications, even though tight control did not last beyond the original study period. Hence, insulin therapy in type 1 diabetics is no longer just for management of day-to-day glucose excursions but is to prevent the long-term complications of the disease.

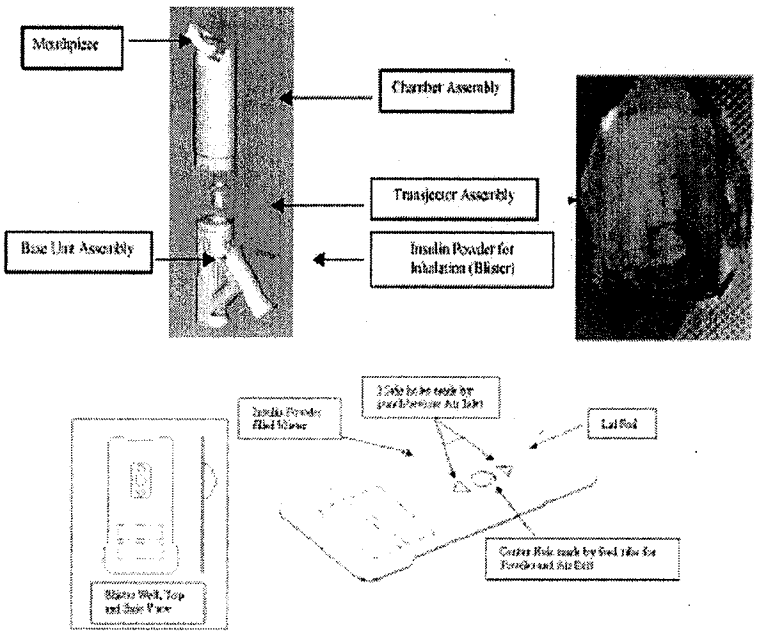
The pathogenesis of type 2 diabetes is multifactorial and translates into varied clinical presentations from mild forms responding to diet and exercise to severe, progressive forms with increasing insulin resistance, decreased insulin sensitivity and pancreatic beta cell failure necessitating therapy with insulin. The intermediate forms may respond to oral agents such as insulin secretagogues, insulin sensitizers, or metformin. While unequivocal evidence of CV benefit with intensive glycemic control in Type 2 diabetes has yet to be established, several epidemiologic studies have demonstrated a marked risk of developing CV disease in the type 2 diabetic population that is estimated to be 2 to 4-fold that of the age-matched non-diabetic population. Extrapolating from evidence of benefit in the type 1 diabetic studies, the goal of therapy in type 2 is, therefore, to also reduce the risks of long-term complications.

To achieve this goal, all type 1 diabetics and many type 2 diabetics must receive insulin therapy which can only be administered via subcutaneous (sc) injection. While accepted in the type 1 population primarily as no other alternative is available to assure survival, initiation of insulin

therapy in type 2 diabetes can be met with resistance and outright refusal of treatment because of the necessity for the injection route of administration for insulin. This new drug application (NDA) for Exubera® is the first for recombinant human insulin to be administered not as an injection but through inhalation.

Exubera® is a combination drug-device. As shown in Figure 1, the recombinant insulin is available as a powder packaged in a foil blister to be inserted into the base of the inhaler device. The patient must pump the handle in the base portion of the device and press and chamber release button to pierce the blister and allow the powder to be dispersed into a resultant jet of air, thereby dispersing the insulin powder into the chamber beneath the mouthpiece. The insulin in the chamber is then inhaled through the mouth, with much of the powder entering into the lower airways and lung.[1]

Figure 1. Inhaler, Blister Assembly, and Sample of Dissected Blister



While the availability of insulin through a non-injectable route of administration can be viewed as an attractive addition to therapeutic armamentarium that will be welcomed by many patients wary of taking sc injections, the review of this NDA must take into consideration whether this new route of administration will deliver, in a consistent and predictable manner, an appropriate amount of insulin that will allow effective and safe management of type 1 and 2 diabetes. The novel route of administration importantly presents a different array of safety concerns not present with injectable insulin, including whether the chronic exposure of the pulmonary epithelium to a known tissue growth factor (or to the novel excipients in this formulation) presents unacceptable toxicities. And clearly, the factors related to the device and patient use of the device and how this would impact the safe and effective delivery of insulin had to be considered in the approvability of Exubera.

[1] Instructions for use are provided to the patient in a Medication Guide including step-by-step diagram. See FDA review of MedGuide submitted into DFS on 1/20/2006

The review of Exubera® is an example of a well-orchestrated, multidisciplinary evaluation of an NDA by FDA staff. This memo cannot sum up all the complexities of the reviews, nor can it provide a thorough account of all the thoughtful questions and concerns raised by reviewers throughout the entire development program of this product. The reader is encouraged to read the primary reviews by CMC, pharmacology/toxicology, biopharmaceutics, clinical/statistical, postmarketing safety, other staff, and to recognize the efforts of the regulatory project management staff in order to appreciate the immense contribution made by this review team.

EFFICACY FINDINGS

Efficacy in Type 1 Diabetes

Four controlled clinical studies were conducted in Type 1 diabetics with studies 217-106 and 217-107 considered pivotal. Study 217-106 evaluated the efficacy of inhaled insulin as conventional prandial treatment in type 1 diabetes, whereas Study 217-107 evaluated efficacy of the inhaled insulin as a prandial insulin treatment as a part of an intensive treatment regimen. Both these studies were randomized, open-label, noninferiority studies to sc regular insulin with the primary efficacy endpoint being change in HbA1c from baseline to week 24 of treatment. A noninferiority margin of 0.5% was specified. Conventional sc insulin therapy consisted of two injections of insulin per day as a mixture of NPH and regular insulin administered before breakfast and supper. Intensive insulin therapy consisted of NPH insulin administered before breakfast and bedtime and regular insulin administered before meals. Patients randomized to inhaled insulin in Study 106 received their doses before meals along with one injection of Ultralente insulin at bedtime. In Study 107, the inhaled insulin group received their doses before meals along with two injections of NPH insulin; one before breakfast and one at bedtime.

In both conventional and intensive Type 1 diabetes treatment, inhaled insulin was demonstrated to be noninferior to subcutaneous regular insulin as measured by percent change in HbA1c from baseline to Wk 24 of treatment. The following two tables from Dr. Mahoney's review summarize the primary efficacy findings from Studies 106 and 107.

Table 6.1.4.2.2 Mean Percent Change from Baseline in HbA1c to Week 24, Intention to Treat (ITT) Population, Study 106 (Control = "Conventional" SQ)

	Inh Ins (n = 169)		SQ (n = 161)	
	Mean	SD[1]	Mean	SD[1]
Baseline HbA1c	8.1	1.0	8.1	1.0
Week 24 (LOCF)[2]	7.9	1.1	7.7	0.9
Unadjusted change from baseline	-0.2	0.9	-0.4	0.7
Adjusted change from baseline[3]	-0.2	0.1	-0.4	0.1

1 SE used instead of SD for adjusted change from baseline
2 Last observation carried forward
3 Least Squares Means
Source: Applicant's Table 5.2.1, Study 106 Report, pg 122

Table 6.1.4.2.1 Mean Percent Change from Baseline in HbA1c to Week 24, Intention to Treat (ITT) Population, Study 107 (Control = "Intensive" SQ)

	Inh Ins (n = 162)		SQ (n = 165)	
	Mean	SD[1]	Mean	SD[1]
Baseline HbA1c	8.0	0.9	8	1.0
Week 24 (LOCF)[2]	7.7	1.0	7.8	1.2
Unadjusted change from baseline	-0.3	0.8	-0.1	0.9
Adjusted change from baseline[3]	-0.3	0.1	-0.1	0.1

1 SE used instead of SD for adjusted change from baseline
2 Last observation carried forward
3 Least Squares Means
Source: Applicant's Table 5.2.1, Study 107 Report, pg 139

In the intensive treatment study (107), the percentage of patients achieving ADA-recommended targeted goal of HbA1c < 7% was similar in both treatment groups. Approximately 23% of inhaled insulin-treated patients vs. 22% of the sc insulin-treated patients achieved this target.

In conclusion, these two clinical studies provide evidence to support an indication for the use of inhaled insulin along with long-acting insulin for the treatment of adult Type 1 diabetics.

Efficacy in Type 2 Diabetics

The clinical development program in Type 2 diabetics included evaluation of inhaled insulin as monotherapy and in combination with long-acting insulins and/or with several different oral agents.

Monotherapy in Type 2 Diabetics

Two studies evaluated the efficacy of inhaled insulin as monotherapy in type 2 diabetics. Study 109 was a 3-month, open-label study which enrolled patients not adequately controlled on combination oral agent (oral secretagogue + another oral agent) and randomized them into one of the following three treatment arms:

- premeal inhaled insulin monotherapy
- premeal inhaled insulin + continued oral agents
- continued combination oral agents

This study showed that Type 2 diabetics who were poorly controlled on combination oral agents (HbA1c ~ 8-11%) had a greater mean change in HbA1c from baseline when switched to premeal inhaled insulin monotherapy than continuing oral therapy. The addition of inhaled insulin to continued oral therapy also resulted in greater mean change in HbA1c from baseline than continuing oral therapy alone or switching to inhaled insulin monotherapy. The following table from Dr. Mahoney's review summarizes these findings.

Table 6.2.4.2.1 Mean Change from Baseline in HbA1c, Study 109, ITT Population							
Group	N	BL	Wk 12	Adjusted Change[a]	Difference (Inh Grp vs OA)	95% CI Limits for Difference between Grps	p-Value
Inh Ins Monotherapy	102	9.3	7.9	-1.4	-1.18[b]	-1.41, -0.95	<0.0001[b]
Inh Ins + OA	100	9.2	7.3	-1.9	-1.67[c]	-1.90, -1.44	<0.0001[c]
OA	96	9.3	9.1	-0.2			
a Least Squares Means based on the primary model with terms for baseline, treatment and center b Comparison of inh ins monotherapy to OA c Comparison of inh ins + OA to OA Source: Applicant's Table 5.2.1, p 42, Study 109 report							

Study 110 was a 3 month, open-label study which compared premeal inhaled insulin monotherapy to rosiglitazone therapy. Patients had not been treated with insulin previously and HbA1c levels were from 6 to 11% at baseline. The primary efficacy measure was percentage of patients achieving HbA1c < 8%. A higher percentage of patients achieved a HbA1c goal of < 8% and 7% in the inhaled insulin group (82.7% and 44%, respectively) versus the rosiglitazone group (58.2% and 17.9%, respectively). Consistent with the primary efficacy results, a greater mean reduction in HbA1c was noted in the inhaled insulin group compared to rosiglitazone (see table below from Dr. Mahoney's review).

Table 6.2.4.3.2.1 Mean Change from Baseline in HbA1c, Study 110, ITT Population						
Group	N	BL HbA1c (SD)	Wk 12 HbA1c (SD)	Adjusted Change[a]	Difference (Inh Grp vs Rosi)	95% CI Limits for Difference between Grps
Inh Ins Monotherapy	75	9.5 (1.1)	7.2 (1.0)	-2.3 (1.2)	-0.89	-1.23, -0.55
Rosi	67	9.4 (0.9)	8.0 (1.3)	-1.4 (1.2)		
Source: Applicant's Table 5.2.1, Study 110 report a Least Squares Means based on the primary model with terms for baseline, treatment and center						

In conclusion, these three studies provided evidence to support an indication for monotherapy use of inhaled insulin administered as premeal doses in Type 2 diabetics.

Combination Therapy with Long-Acting Insulins in Type 2 Diabetics

The effectiveness of premeal inhaled insulin in combination with Ultralente long-acting insulin administered at bedtime was evaluated in Study 108. Type 2 diabetics who were on a stable regimen of sc insulin (HbA1c 6 to 11%) were randomized to premeal inhaled insulin + hs Ultralente or bid mixture of sc regular insulin + NPH insulin. Treatment duration was 6 months with the primary efficacy measure being change in HbA1c from baseline at 24 wks.

Inhaled insulin was noninferior to bid reg/NPH sc insulin treatment regimen as summarized in the following table.

Table 6.3.4.2 Mean Change from Baseline in HbA1c, Study 108, ITT Population							
Group	N	BL (SD)	Wk 24 (SD)	Adjusted Change[a] (SD)	Difference (Inh Grp vs SQ)	95% CI Limits for Difference between Grps	p-Value
TID premeal Inh Ins + hs UL	146	8.1 (1.1)	7.4 (1.5)	-0.7 (1.2)	-0.07	-0.31, 0.17	NS
BID SQ mixed NPH and regular insulin	149	8.2 (1.1)	7.6 (1.1)	-0.6 (1.1)			
a Least Squares Means based on the primary model with terms for baseline, treatment and center Source: Applicant's Table 5.2.1, Study 108 report							

A higher percentage of patients in the inhaled insulin/hs UL treatment group achieved HbA1c < 8% and < 7% compared to the bid reg/NPH sc insulin treatment group.

This study supports a conclusion that Type 2 diabetics who are on a stable regimen of sc insulin can be switched from their regular insulin regimen to inhaled insulin with no significant change in their glycemic control.

Combination Therapy with Oral Agents in Type 2 Diabetics

In addition to Study 109 described under the *Monotherapy in Type 2 Diabetics* section, the applicant provided data from the combined studies, Study 1001 (used sulfonylureas) and 1002 (used metformin), to support combination therapy with oral agents in type 2 diabetics.

In both these studies, patients who were poorly controlled (HbA1c 8 to 12%) on a prior oral agent regimen were randomized to receive inhaled insulin added on to their current regimen or to receive a second oral agent added on to their current regimen. The study design is summarized in the following table:

Studies Evaluating Efficacy Combination Inhaled Insulin w/ Oral Agents

	Baseline treatment	Randomized treatment groups *
Study 1001	Type 2 diabetics poorly controlled on SU, HbA1c 8-11%	TID premeal inhaled insulin + SU (n=222)
		Metformin 1gm BID + SU (n=201)
Study 1002	Type 2 diabetics poorly controlled on metformin, HbA1c 8-11%	TID premeal inhaled insulin + metformin (n=235)
		Glibenclamide, max 5mg bid + metformin (n=229)

*the treatment groups were stratified by HbA1c 8-9.5% and 9.6-12%

The primary endpoint for both studies was change in HbA1c from baseline at week 24.

Table 6.4.4.2.1 Mean Change from Baseline in HbA1c at 6 Months, Study 1001, ITT Population

Group	N	BL (SD)	Wk 24 (SD)	Adjusted Change[a] (SD)	Difference (Inh + Continued SU vs Met + Continued SU)	95% CI Limits for Difference between Grps	p-Value
Inh + Continued SU, Baseline HbA1c 8-9.5%	101	8.8 (0.5)	7.4 (0.8)	-1.4 (0.8)	-0.07	-0.33, 0.19	0.610
Met + Continued SU, Baseline HbA1c 8-9.5%	93	8.8 (0.5)	7.4 (0.8)	-1.4 (0.9)			
Inh + Continued SU, Baseline HbA1c >9.5-12%	113	10.5 (0.7)	7.9 (1.0)	-2.7 (1.1)	-0.38	-0.63, -0.14	0.002
Met + Continued SU, Baseline HbA1c >9.5-12%	103	10.6 (0.9)	8.3 (1.2)	-2.4 (1.2)			

a Least Squares Means based on the primary model with terms for baseline, treatment and center
Source: Applicant's Tables 5.2.1.2 and 5.2.1.3, Study 1001 report

From Table 6.4.4.2.1 (above and in Dr. Mahoney's review), the addition of inhaled insulin to failed SU was noninferior to the addition of metformin to failed SU; however, patients with very poor glycemic control at baseline (stratum > 9.5%-12%) had more improved glycemic control with the addition of inhaled insulin over metformin to their SU regimen. Similar results were noted for the addition of inhaled insulin to failed metformin therapy as summarized in the following table.

Table 6.4.4.2.2 Mean Change from Baseline in HbA1c (%) at 6 Months, Study 1002, ITT Population

Group	N	BL (SD)	Wk 24 (SD)	Adjusted Change[a] (SD)	Difference (Inh + Continued Met vs Glibenclamide + Continued Met)	95% CI Limits for Difference between Grps	p-Value
Inh + Continued Met, Baseline HbA1c 8-9.5	125	8.6 (0.5)	7.2 (0.8)	-1.4 (0.8)			
Glibenclamide + Continued Met, Baseline HbA1c 8-9.5	119	8.7 (0.5)	7.1 (0.9)	-1.6 (0.9)	0.04	-0.19, 0.27	0.733
Inh + Continued Met, Baseline HbA1c >9.5-12	109	10.4 (0.7)	7.5 (1.1)	-2.9 (1.2)	-0.37	-0.62, -0.12	0.004
Glibenclamide + Continued Met, Baseline HbA1c >9.5-12	103	10.6 (0.7)	8.0 (1.2)	-2.6 (1.2)			

a Least Squares Means based on the primary model with terms for baseline, treatment and center
Source: Applicant's Tables 5.2.1.2 and 5.2.1.3, Study 1002 report

SAFETY FINDINGS

Hypoglycemia

Hypoglycemia is an expected side-effect and safety concern associated with insulin therapy. This concern by patients and physicians may represent the limiting factor for intensive diabetes control in insulin-requiring diabetics. In her safety review of NDA 21-868, Dr. Mahoney evaluated the risk of severe hypoglycemia associated with inhaled insulin therapy based on several different definitions used to capture such adverse events. The reader is referred to Section 7.1.3.3 of Dr. Mahoney's review for a detailed discussion of her findings. Overall, the risk of severe hypoglycemia does not appear to be greater with inhaled insulin therapy compared to sc insulin therapy. Dr. Mahoney did note that in Study 107 which targeted tight glycemic control in Type 1 diabetics, there was a greater tendency for early morning hypoglycemia with inhaled insulin

treatment. In this same study, the sc regular insulin group had a higher frequency of mid-day hypoglycemia than inhaled insulin therapy.

In type 2 diabetics who were previously on insulin therapy, the risk of severe hypoglycemia did not appear different in those who were placed on inhaled insulin treatment versus those who continued with sc insulin. The risk of severe hypoglycemia was higher in the inhaled insulin group compared to the oral agent treatment groups. Dr. Mahoney pointed out that the degree of glycemic control was greater with the inhaled insulin group and the finding of more hypoglycemic episodes is therefore not an unexpected finding. For studies in which an insulin-sensitizing drug was the only comparator (e.g., Study 110 which used rosiglitzone), a higher rate of severe hypoglycemia with inhaled insulin is not surprising as hypoglycemia is not an expected side-effect of insulin-sensitizing drugs.

The findings from Studies 1001 and 1002 merit some discussion as the frequency of severe hypoglycemic episodes is higher in the inhaled insulin group compared to the comparator groups: metformin + SU or glibenclamide + metformin. As discussed under the efficacy section of Dr. Mahoney's review and summarized above in this memo, these two studies showed that inhaled insulin added on to failed SU or metformin therapy in Type 2 diabetics was *noninferior* to the addition of a second oral agent to failed SU or metformin therapy with the exception of those patients who had very poor glycemic control at baseline (HbA1c > 9.5%). The safety findings in these two studies, with respect to risk of severe hypoglycemia, should be noted in labeling as the decision to add inhaled insulin to failed SU or metformin in Type 2 diabetics versus treatment with two oral agents should consider the higher risk of hypoglycemia observed with the former treatment approach. In the following table from Dr. Mahoney's review, it appears that the addition of inhaled insulin to failed SU therapy, in particular, carries a higher risk of severe hypoglycemia than the addition of inhaled insulin to failed metformin therapy. While it is noted that the 95% CI of the RR crosses 1.0, the incidence is 2 to 4 times higher in the inhaled insulin group compared to the OA group.

Table 7.1.3.3.1.2.1 Severe Hypoglycemic Events (Defined as Blood Glucose ≤ 36 mg/dL, or Patient Requiring Assistance), Adult Type 2 Patients, Full ITT Population[1]

Study	Treatment Group	Total # Patients in Treatment Group	N (% with Severe Hypoglycemic Event)	Total Events	Total Subject-months	Events per Subject-month	Risk Ratio (95% CI)
All Patients who Were not Using Insulin at Study Entry	Inh ins	757	77 (10.2)	135	3320.1	0.041	3.48 (2.37-5.12)
	Comparator	617	19 (3.1)	32	2803.8	0.011	
Study 104[2]	Inh ins	32	2 (6.3)	2	88.5	0.023	NE[4]
	OA[5]	36	0	0	99.4	0	
Study 109[3]	Inh ins	102	17 (16.7)	23	283.3	0.081	NE
	Inh ins + OA	100	21 (21.0)	48	284.3	0.169	
	OA	96	0	0	266.3	0	
Study 110[3]	Inh ins	75	9 (12.0)	15	214.6	0.07	NE
	Rosi[6]	67	0	0	186.9	0	
Study 1001-L[7]	Inh ins + SU	101	4 (4.0)	6	555.5	0.011	1.83 (0.46-7.32)
	Met[8] + SU	93	1 (1.1)	3	505.6	0.006	
Study 1001-H[7]	Inh ins + SU	113	11 (9.7)	14	630.7	0.022	2.09 (0.80-5.44)
	Met + SU	103	6 (5.8)	6	554.5	0.011	
Study 1002-L[7]	Inh ins + Met	125	7 (5.6)	14	683.7	0.023	1.01 (0.50-2.05)
	Gli[9] + Met	119	9 (7.6)	15	634	0.024	
Study 1002-H[7]	Inh ins + Met	109	6 (5.5)	11	579.7	0.019	1.33 (0.53-3.30)
	Gli + Met	103	3 (2.9)	8	557.3	0.014	

1 Includes Studies 103, 104, 108, 109, 110, 1001, 1002, 1029
2 Patients were insulin-using at Study Entry
3 Patients were not using insulin at Study Entry
4 Not estimable
5 Oral agent
6 Rosiglitazone
7 In Studies 1001 and 1002, patients were stratified on the basis of baseline HbA1c; L = 8-9.5; H ≥ 9.5-12. Data are for first 6 months of study for both studies.
8 Metformin
9 Glibenclamide
Source: Applicant's Table 27, Section 2.7.3.3.3.1.6, pg 53

In conclusion, the risk of hypoglycemia associated with inhaled insulin appears comparable to that of regular sc insulin. The addition of insulin to any anti-diabetic regimen carries some risk of hypoglycemia and appropriate blood glucose monitoring is necessary for the safe and effective use of this drug. In a Type 2 diabetic poorly controlled with a single oral agent regimen, the addition of inhaled insulin may carry a slightly higher risk of hypoglycemia than the addition of a second oral agent.

Insulin Antibodies

A higher rate of seroconversion to positive insulin antibodies, predominantly IgG, was detected in the inhaled insulin group versus control groups. Reviewers from the clinical and biometrics team evaluated these findings and concluded the following:

- no evidence that the higher frequency of developing insulin antibodies contributed to a higher risk of allergic adverse events
- no correlation between hypoglycemic episodes and antibody binding affinity
- no evidence that these antibodies were neutralizing antibodies that would result in diminished efficacy as determined by increasing insulin requirements or worsening HbA1c, postprandial glucose levels, or fasting glucose levels
- no correlation between mean change from baseline in FEV1, DLCO, FVC, TLC, and FRC and insulin antibody titer
- discontinuation of inhaled insulin results in decreases in insulin binding activity

Pulmonary Safety

Pulmonary function tests (PFTs) were assessed at baseline and at different time points throughout the clinical studies. For the most part, pulmonary safety measures in these studies included spirometry, lung volumes, DLCO, CXR and, in a subset of patients, high resolution chest CTs (HRCT) were performed. In selected studies, cough questionnaires were administered to study subjects who experienced cough not determined to be due to some other cause/condition.

Dr. Sally Seymour has thoroughly reviewed the pulmonary safety data currently available to the agency and has done an excellent job of summarizing these findings and her conclusions in her consult submitted into DFS on January 6, 2006. Please review her document for a more extensive discussion of pulmonary safety for NDA 21-868. This memo will only highlight findings from pulmonary function studies summarized under section 7.1.6 of her consult.

There was a progressive decline in FEV1 and DLCO in both the inhaled insulin treatment group and comparators; however, patients treated with inhaled insulin had a greater mean decrease than patients treated with the comparator agents. Dr. Seymour provided some perspective on FEV1 changes over time in patients with underlying lung disease from cohort studies in patients with varying degrees of lung pathology or smoking histories. Based on this information, it appears that all patients studied in this NDA had a greater rate of decline in FEV1 than would be expected for non-smokers without underlying lung disease. Controlled data out to 96 weeks showed a fairly constant mean treatment group difference between inhaled insulin and comparators after the first year of treatment. However, data from uncontrolled studies with exposures out to 84 months suggest further decline but the absence of a control group limits any conclusion on whether this is due to drug or that it represents expected declines for this patient population. The applicant also presented data on the reversibility of these findings. Dr. Seymour has summarized these findings and the limitation of these data. I concur with her that at present, we cannot conclude that these changes in FEV1 with long-term exposure to inhaled insulin in the Type 1 diabetic population are definitively reversible.

These progressive decline in FEV1 and DLCO apply to both the Type 1 and Type 2 diabetic population; however, the annual rate of decline for FEV1 associated with inhaled insulin therapy in Type 2 diabetics is higher than in Type 1 diabetics (-85mL/year vs -66mL/year). This difference may reflect an older age group in the Type 2 diabetics which had a mean age of 57 yrs compared to a mean age of 38 yrs in Type 1 diabetics. Consistent with this is the observation that the annual rate of decline in FEV1 in the comparator group was also greater in the type 2 diabetic population (-65 mL/year) than in the type 1 population (-39 mL/year).

The clinical safety database for inhaled insulin is extensive. The completed controlled Phase 2 and 3 studies in Type 1 and 2 diabetics were reviewed which provided data from 12 to 24 weeks' duration of exposure to drug. In addition, two ongoing studies were reviewed which provided additional controlled safety data out to 24 months. Table 9 from Dr. Seymour's review summarizes the exposure in controlled Phase 2/3 studies at the time of NDA submission. She has also pointed out that uncontrolled extension studies provide patient exposure data in over 200 type 1 diabetics and 500 type 2 diabetics for more than 2 years. While these are uncontrolled data they do provide longer duration of exposure to inhaled insulin. Her review of pulmonary adverse events, CXRs, and HRCTs has not noted development of serious clinical deterioration associated with the changes in PFTs. However, it should be noted that the majority of the pulmonary safety data was derived from Type 1 and 2 diabetics *without* underlying lung disease although part way through the clinical development program, Pfizer did allow for patients with mild-to-moderate asthma or COPD to be enrolled provided their FEV1 or DLCO was not < 70% predicted (see section 8.1.1.1 of Dr. Seymour's review for other pulmonary exclusion criteria). Two studies

assessing the safety of inhaled insulin in patients with asthma (Study 1028) and COPD (1030) are ongoing and will be completed as part of a Phase 4 commitment.

In conclusion, inhaled insulin is associated with a greater decline in FEV1 and DLCO than comparator agents in both the Type 1 and 2 diabetic populations; however, extensive clinical evaluation including of patients with exposures beyond 2 years in open-label extension studies has not revealed serious clinical consequences as a result of these changes and the decline relative to the comparators in non-smokers without diagnosed significant lung disease appears to occur early and thereafter the differences are maintained. Recommendations for baseline and periodic PFTs with use of inhaled insulin should be included in labeling. It should also be recommended that patients discontinue use of inhaled insulin and switch to appropriate anti-diabetic therapies if persistent reductions in PFTs are noted. Given the limited safety data in patients with underlying lung disease, inhaled insulin should not be recommended for use in this population pending the results of Study 1028 and 1030.

BIOPHARMACEUTICS ISSUES

Please see Dr. Sayed Al-Habet's review for detailed discussion of clinical pharmacology issues.

Pharmacokinetics/Pharmacodynamics

Exubera human insulin for inhalation has overlapping pharmacokinetics with rapid-acting and short-acting insulin analogues. It has a rapid absorption with Tmax comparable to the rapid-acting sc insulins (~40 to 90 min). Its bioavailability relative to regular sc insulin is approximately 10% (range 5-10%). The pharmacodynamics of inhaled insulin reflect the pharmacokinetics with an early onset of action similar to rapid-acting insulin Lispro but a duration of action that is similar to regular sc insulin. Consequently, the dosing instructions for Exubera must take into consideration the pharmacokinetics. In particular, patients are instructed to take Exubera no more than 10 minutes before a meal.

The pharmacokinetics of inhaled insulin have clinical relevance under several circumstances that will be highlighted in this memo as labeling will also discuss these findings.

Dose Equivalence

A critical finding in the OCPB review of Exubera is the dosage strength bioinequivalence. Specifically, the Cmax and AUC observed with three 1-mg blisters are consistently 30 to 40% higher than one 3-mg blister. As a result, a patient can not substitute three 1-mg blisters for one 3-mg blister as the consequence would be a higher exposure to insulin with the former dosing regimen and an increased risk of hypoglycemia. This finding will be discussed in labeling and the Medication Guide to be provided to the patient with each prescription fill.

Cigarette Smoking (active and passive)

The pharmacokinetics of Exubera are affected by cigarette smoking. As summarized on page 7 of Dr. Al-Haber's review, exposure to inhaled insulin is increased 2- to 5-fold in smokers than non-smokers. Cessation of smoking appears to reduce the level of drug exposure but exposure again increases relatively rapidly if smoking is resumed. Given the change in pharmacokinetics of inhaled insulin with varying degrees of smoking habits, the label will contraindicate the use of Exubera in patients who smoke or have discontinued smoking less than 6 months prior to considering therapy with Exubera. The label will also recommend that Exubera be discontinued if a patient starts smoking.

In contrast to the findings of increased drug exposure with active cigarette smoking, a study in patients secondarily exposed to cigarette smoking (passive smokers) acutely shows a decrease in

exposure of approximately 20 to 30%. To evaluate the clinical relevance of these findings, the applicant will be asked to conduct a clinical study of Exubera in individuals chronically exposed to passive smoking.

Chronic Lung Disease
In a pK study of inhaled insulin in patients with COPD and healthy volunteers, the exposure (AUC and Cmax) of inhaled insulin was approximately 50% higher in the COPD patients than healthy individuals. In contrast, a pK study in patients with mild asthma demonstrated decreased bioavailability of inhaled insulin. The administration of albuterol in patients with mild and moderate asthma prior to inhaled insulin increases the AUC and Cmax of inhaled insulin by 25 and 50%, respectively, compared to when inhaled insulin is administered without albuterol, suggesting a role for airway caliber in the diminished bioavailability in asthma.

The pK findings from these two studies will be conveyed in labeling. As discussed under the pulmonary safety section of this memo, the absence of adequate safety data in patients with underlying lung disease added to the highly variable pharmacokinetics in patients with COPD and asthma merit a recommendation in labeling *against* use of inhaled insulin in these patients until additional safety and efficacy data are available.

CMC
Please see reviews from Drs. Prasad Peri and Janice Brown for details of chemistry, manufacturing, and control. The recommended shelf life for the 1 and 3 mg blisters of insulin powder is 18 months; however, it is noted that several factors may influence this shelf life including shipping of drug product, the higher variability in emitted dose with the 1 mg blister, and the change over time in the ability of the device to generate sufficient air pressure for the aerosolization of the insulin powder. Consequently, several postmarketing agreements and commitments have been negotiated with the applicant and are outlined in the FDA's CMC reviews.

PEDIATRICS
Study 1009 involved Type 1 diabetics < 18 yrs of age and two studies (106 and 107) included patients under the age of 18 yrs. These 3 studies have been reviewed by Dr. Mahoney. While the applicant is not seeking an indication for pediatric use, I concur with Dr. Mahoney that there is insufficient data, at present, to include any information in labeling that might encourage the off-label use of Exubera in the pediatric population.

PHASE 4 COMMITMENTS
The following studies are Phase 4 commitments required of the applicant.

1. A large simple trial in 5,000 diabetics with Type 1 or Type 2 diabetes, with 1:1 randomization to either Exubera® or usual care. This trial is to estimate the relative risk of clinically significant (>20%) declines in lung function as measured by pulmonary function tests.
2. Completion of Studies 1022 and 1029, in Types 1 and 2 diabetes respectively, to obtain data regarding changes in forced expiratory volume in one second (FEV1) and DLCO over 5 continuous years of Exubera® exposure. Data on immune-mediated adverse events should also be collected in these studies.
3. Completion of Studies 1052 and 1053, in Types 1 and 2 diabetes respectively, to obtain bronchoalveolar lavage data for mechanistic information regarding changes in airway lining fluid.

4. Completion of Studies 1028 and 1030, in diabetics with mild to moderate asthma and COPD respectively. These studies are to assess change in FEV1 and diffusion capacity for carbon monoxide (DLco), control of diabetes and underlying lung disease, and frequency and severity of exacerbations of underlying lung disease.
5. Further pediatric studies, responsive to PREA
6. Proposal of a plan to assess the effectiveness of labeling against use in smokers.

OTHER REGULATORY/ADMINISTRATIVE ISSUES

Financial Disclosure
This information has been reviewed by Dr. Mahoney and found to be acceptable.

Site Inspections/DSI Audits
Two study sites were selected for DSI inspection (see section 4.4 of Dr. Mahoney's review). Only minor deficiencies were noted and it was concluded that the data from these sites were acceptable in support of this application.

Tradename Review
Please see the memo by Dr. Mahoney entered into DFS on May 13, 2005. The Division of Medication Errors and Technical Support objected to the proposed tradename, Exubera®. Dr. Mahoney clearly argues in her memo against the objection and I concur with her that the proposed name is acceptable.

LABELING

Labeling negotiations are underway with the applicant. Please see final approved labeling with issuance of action letter.

Exubera will be approved with a Medication Guide (Medguide) that will also incorporate the patient package instruction (PPI). Please see reviews by Jeanine Best and Toni Piazzi-Hepp entered into DFS on January 20, 2006 for detailed discussion of the proposed MedGuide.

CONCLUSIONS AND RECOMMENDATIONS

The NDA for Exubera® has been thoroughly reviewed by FDA and publicly vetted by members of the Endocrine and Metabolic Drugs Advisory Committee in September 2005. Overall, sufficient evidence has been provided by the applicant to support approval of Exubera® for the treatment of adult patients with type 1 and 2 diabetes. Given the variable pharmacokinetics of inhaled insulin in smokers, the label will include a contraindication in current smokers or those who have only recently stopped smoking. As insufficient data are available for patients with underlying lung disease, Exubera should not be recommended for use in these patients until data from ongoing studies in patients with COPD and asthma are available.

Since this is a novel route of administration and the first of likely many such products, Exubera will have its postmarketing safety data carefully monitored by FDA staff for safety concerns that arise with use by the general population not under the setting of a clinical investigation, similar to a first in class new molecular entity. As additional data become available from post-approval use and ongoing clinical studies, it should be fully expected that labeling for Exubera will be updated to incorporate new information in support of safe and effective use of the product.

Pending labeling negotiations and confirmation by the applicant to the conduct of certain Phase 4 studies, this NDA should be approved.

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

/s/

Mary Parks
1/26/2006 10:56:12 AM
MEDICAL OFFICER

Robert Meyer
1/26/2006 11:14:19 AM
MEDICAL OFFICER
I am in substantial agreement with this memorandum. There will be a separate ODE II memorandum, however.

DIVISION OF PULMONARY AND ALLERGY PRODUCTS
MEDICAL OFFICER CONSULTATION

Date:	January 6, 2006
To:	Karen Mahoney, M.D., Medical Officer, DMEP
From:	Sally Seymour, M.D., Medical Officer, DPAP
Through:	Eugene Sullivan, M.D., Deputy Director, DPAP
Subject:	Pulmonary safety evaluation of Exubera (inhaled human insulin)

General Information

NDA/IND#:	NDA# 21-868, N000
Applicant:	Pfizer
Drug Product:	Inhaled human insulin (Exubera)
Protocol:	Not Applicable
Request From:	Karen Mahoney, M.D., Medical Officer, DMEP
Date of Request:	January 24, 2005
Materials Reviewed:	NDA# 21-868, N000 submissions dated: December 27, 2004; January 12, 2005; April 26, 2005; May 6, 2005; June 10, 2005; June 22, 2005; July 5, 2005; July 19, 2005; July 29, 2005; August 2, 2005; August 12, 2005; September 21, 2005; September 28, 2005; October 5, 2005; October 10, 2005; October 28, 2005

This is a consultation from the Division of Pulmonary and Allergy Products intended to respond to the request for consultation issued by the Division of Metabolic and Endocrine Products, regarding the pulmonary safety of inhaled human insulin (Exubera). This consult addresses the pulmonary safety of Exubera, specifically the respiratory adverse events, pulmonary function tests, chest x-ray, and high resolution computed tomography (HRCT) findings in subjects with type 1 and type 2 diabetes. In addition, this consult addresses the pulmonary safety of Exubera in subjects with underlying lung disease, such as asthma and COPD.

This document follows the NDA review template format. The Executive Summary contains a detailed overview of the pulmonary safety findings associated with Exubera, while the body of the review contains a detailed review of the integrated pulmonary safety of Exubera. Finally, the Appendices contain supplemental information and reviews of the individual studies contributing to the pulmonary safety database. The specific questions posed by the DMEP are addressed below.

The DMEP requested response to the following questions shown in **bold** face, followed by the DPAP response in *italics*:

1. Does NDA 21868 contain adequate information for the assessment of the pulmonary safety of Exubera?

NDA# 21-868 contains adequate information to assess the pulmonary safety of Exubera in subjects with type 1 and type 2 diabetes who do not have significant underlying lung disease. However, while the currently available database is deemed adequate to assess pulmonary safety for marketing, if the application is to be approved, we recommend that the Applicant continue to further assess the long-term pulmonary safety of Exubera in the post-marketing period. In addition, the following limitations of the pulmonary safety database should be noted. First, NDA# 21-868 does not contain adequate information to assess the pulmonary safety of Exubera in subjects with asthma and COPD. Second, there are a limited amount of data in non-Caucasian subjects. Finally, the pulmonary safety of exposure to Exubera beyond two years has not been studied in a controlled fashion.

2. If adequate pulmonary safety information has been provided, what are the pulmonary risks associated with Exubera?

For a detailed overview of the pulmonary safety findings, please refer to the Executive Summary. The following is a synopsis of the pulmonary safety of Exubera. Exubera is associated with an increase in respiratory SAEs, AEs, and discontinuations due to respiratory AEs compared to the comparator group. SAEs reported in more than one subject and more common in the Exubera group were asthma and bronchitis. More subjects discontinued the study in the Exubera group (n=39) due to respiratory AEs than in the comparator group (n=2). In the Exubera group, cough was the most common respiratory AE leading to discontinuation followed by asthma and dyspnea. Exubera is associated with an increase in respiratory AEs. Cough was the respiratory adverse event with the largest difference in incidence between treatment groups, favoring the comparator. Other respiratory AEs more common in the Exubera group than in the comparator groups included rhinitis, sputum increased, dyspnea, and respiratory tract infection.

Exubera is associated with a greater decline in pulmonary function, specifically FEV_1 and DLCO, than the comparator groups in both type 1 and type 2 diabetes. One study showed that a decline in FEV_1 and DLCO occurred within the first two weeks of treatment with Exubera. After two years exposure to Exubera, in subjects with type 1 or type 2 diabetes, the Exubera group had approximately a 40mL greater decline in FEV_1 than the comparator group. The treatment group difference did not seem to progress over the two year treatment period. A treatment group difference of change from baseline FEV_1 of 40mL in two years seems unlikely to be clinically significant as long as the treatment group difference does not continue to progress.

During two years of exposure to Exubera, in subjects with type 1 diabetes, the Exubera group had a 0.5 to 0.9mL/min/mmHg greater decline in DLCO than the comparator group. In subjects with type 2 diabetes, during the 2 year treatment period, the Exubera group had a 0.4 to 0.6mL/min/mmHg greater decline in DLCO than the comparator group. Again, the treatment group difference did not seem to progress over the two year treatment period. A treatment group difference of decline from baseline DLCO of this

magnitude in two years seems unlikely to be clinically significant as long as the treatment group difference does not continue to progress.

The reversal of the effect of Exubera on pulmonary function is not clear. Some data are suggestive of reversal of effect, but design issues limit drawing definitive conclusions. However, since the treatment group difference between Exubera and the control group is not progressive over two years exposure, reversal of effect may not be as important than if the treatment group difference was progressive.

The two year HRCT data and CXR data did not suggest a definitive safety signal with Exubera use.

The safety data in subjects with underlying lung disease are limited and primarily come from two ongoing studies. The interim (one year) data from Study 1028 (asthma) suggests that there is an increase in the treatment group difference in change from baseline FEV_1 and DLCO at Week 52, favoring the comparator. However, it should be noted that the 52 week data are based upon 27 subjects. The interim data from Study 1030 (COPD) suggest that the Exubera had a greater decline in FEV_1 than the comparator group and the comparator group had a greater decline in DLCO than the Exubera group at Week 52. However, it should be noted that the 52 week data are based upon 30 subjects. Because of the limited number of subjects with 52 week data in these ongoing studies, the safety of Exubera in subjects with underlying lung disease cannot adequately be assessed.

3. What information for pulmonary safety do you suggest for the Exubera product label?

A detailed labeling review was performed for this consult and a line-by-line edited label has been conveyed to the DMEP. The following are general recommendations for the Exubera product label.

- *Include the following language in the Precautions section: Respiratory.*

2 Page(s) Withheld

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

__X__ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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Potential Phase Four Commitments

If you determine that this application is to be approved, the following are potential phase four commitments:

- *The Applicant should reevaluate the two year HRCT data from ongoing Study 1029 by blinding the reading radiologist to treatment group and time.*
- *The Applicant should conduct a large controlled study designed to further assess the long term pulmonary safety of Exubera. In the absence of a specific safety signal, the most appropriate duration and size of the study are unclear. We suggest a minimum of 5000 patients in each treatment arm for duration of at least 5 years. Enrollment in this study should include a significant number of non-Caucasian patients. Ideally, the study should include assessment of FEV_1 and DLCO.*

- *The Applicant should complete Studies 1028 and 1030 to provide more data regarding the safety and efficacy of Exubera in patients with underlying lung disease.*
- *The Applicant should complete Studies 1022 and 1029 to provide additional pulmonary safety data for up to 5 years of Exubera exposure.*

Table of Contents

1 Executive Summary

1.1 *Recommendation on R*egulatory Action

This review is limited to the analysis of the pulmonary safety of Exubera. Non-pulmonary safety and efficacy are not addressed in this review; therefore, the recommendation on the regulatory action on this application is deferred to the DMEP. The pulmonary safety findings associated with Exubera are described in detail in this review as well as the limitations of the pulmonary safety database. The DMEP should weigh the pulmonary safety findings in the risk/benefit analysis regarding the approval of Exubera.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

The Applicant submitted a Risk Management Plan which proposed routine phamacovigilance activities, completion of ongoing clinical studies, and several clinical studies relevant to pulmonary safety that may provide some additional information regarding the pulmonary safety of Exubera. The Applicant's proposed studies include the following:

- A large simple 5 year post-marketing trial in 5000 patients with diabetes mellitus to estimate the relative risk of clinically significant declines in pulmonary function in patients treated with Exubera
-
-

1.2.2 Required Phase 4 Commitments

If this application is to be approved, the following are potential phase four commitments regarding pulmonary safety:

- The Applicant should reevaluate the two year HRCT data from ongoing Study 1029 by blinding the reading radiologist to treatment group and time.
- The Applicant should conduct a large controlled study designed to further assess the long term pulmonary safety of Exubera. In the absence of a specific safety signal, the most appropriate duration and size of the study are unclear. We suggest a minimum of 5000 patients in each treatment arm for duration of at least 5 years. Enrollment in this study should include a significant number of non-Caucasian patients. Ideally, the study will include assessment of FEV_1 and DLCO.

- The Applicant should complete Studies 1028 and 1030 to provide more data regarding the safety and efficacy of Exubera in patients with underlying lung disease.
- The Applicant should complete Studies 1022 and 1029 to provide additional pulmonary safety data for up to 5 years of Exubera exposure.

1.3 Summary of Clinical Findings

In this NDA, the Applicant has developed Exubera Insulin Inhalation Powder for the treatment of adult patients with diabetes mellitus for the control of hyperglycemia. This is the first NDA for an inhaled insulin drug product. The clinical efficacy and overall safety of Exubera were reviewed by Dr. Karen Mahoney of the Division of Metabolic and Endocrine Products (DMEP). Because of the novel method of delivery of insulin in this application, the Division of Pulmonary and Allergy Products has provided input regarding assessment of the pulmonary safety of Exubera during clinical development. The focus of this review is the pulmonary safety of Exubera, which will supplement Dr. Mahoney's clinical review of the efficacy and non-pulmonary safety of Exubera.

1.3.1 Brief Overview of Clinical Program for Pulmonary Safety

The Applicant's clinical program to evaluate the safety and efficacy of Exubera includes 20 phase 2 and phase 3 clinical studies as well as 31 clinical pharmacology studies. The Applicant has completed 14 clinical studies evaluating the efficacy and safety of Exubera in subjects with type 1 and type 2 diabetes. In addition, the Applicant has 6 ongoing clinical studies at the time of this review (1022, 1028, 1029, 1030, 1036, and 1017). The majority of the studies are controlled studies; however, two of the studies are extension studies (1036 and 111), which are not controlled.

Most of the studies were limited to adult subjects ($\geq$ 18 years) with diabetes; however, one study (1009) was conducted in subjects <18 years of age and two other studies (106, 107) included some subjects <18 years of age. The Applicant is not seeking an indication in subjects <18 years of age at this time; therefore, the focus of this review was the pulmonary safety data in adult subjects.

The primary sources for the pulmonary safety database were the pooled controlled phase 2 and 3 studies in adult subjects with type 1 and type 2 diabetes. Pulmonary safety data from the ongoing studies were included in the pooled dataset primarily because the ongoing studies provide data for subjects exposed to Exubera for 1 to 2 years.

To assess the pulmonary safety of Exubera, the Applicant performed pulmonary function tests (PFTs) at baseline and at different time points during each clinical study. PFTs included spirometry, lung volumes, and DLCO. Although the focus of the effect on pulmonary function is FEV_1 and DLCO, other key PFTs were reviewed. In addition, the Applicant performed a baseline chest x-ray (CXR) and end of study CXR in most of the clinical studies. High resolution computed tomography (HRCT) of the thorax was performed in a subset of subjects. In some of the later studies, the Applicant utilized a cough questionnaire and the Mahler Dyspnea Indices to further assess cough adverse

events and dyspnea. This review addresses the PFT, CXR, and HRCT findings in addition to the respiratory adverse events.

The number of subjects exposed to Exubera in the controlled clinical studies, greater than 600 subjects with type 1 diabetes and greater than 1200 subjects with type 2 diabetes, is reasonable to assess the pulmonary safety of Exubera in subjects without underlying lung disease. In addition, the duration of Exubera exposure, up to 2 years in >200 subjects with type 1 diabetes and up to 2 years in approximately 150 subjects with type 2 diabetes, is reasonable to assess the pulmonary safety of Exubera in subjects without underlying lung disease. It should be noted that there are limited data in non-Caucasian subjects.

The Applicant's clinical program also includes two ongoing studies specifically designed to assess pulmonary safety in subjects with asthma (1028) and COPD (1030). The limited pulmonary safety data in subjects with underlying lung disease are not adequate to assess the pulmonary safety of Exubera in subjects with underlying lung disease.

Overall, while the currently available database is deemed adequate to assess pulmonary safety for marketing, if the application is to be approved, the Applicant should continue to further assess the long-term pulmonary safety of Exubera in the post-marketing period.

1.3.2 Respiratory Adverse Events

In the controlled phase 2 and 3 studies, there were more respiratory serious adverse events (SAEs), respiratory adverse events (AEs), and discontinuations due to respiratory AEs in the Exubera group than in the comparator groups. All of the respiratory SAEs were in subjects with type 2 diabetes. There were no respiratory SAEs in the completed studies in subjects with type 1 diabetes. Asthma and bronchitis were the respiratory SAEs reported in more than one subject in the Exubera group and more common in the Exubera group than the comparator group. There were no respiratory deaths in the controlled phase 2 and 3 studies.

More subjects discontinued due to respiratory AEs in the Exubera group than in the comparator groups. Cough was the most common AE leading to discontinuation in subjects with either type 1 and type 2 diabetes. Twenty subjects discontinued due to cough AEs in the Exubera group compared to none in the comparator groups. Asthma and dyspnea were the next most common AEs leading to discontinuation. In addition to permanent discontinuations due to respiratory AEs, there were more respiratory AEs leading to temporary discontinuation of therapy in the Exubera group, than in the comparator groups.

Respiratory adverse events were more common in the Exubera group than in the comparator groups. Cough was the respiratory AE with the largest difference in incidence between treatment groups, favoring the comparator. Other respiratory AEs more common in the Exubera group than in the comparator groups included rhinitis, sputum increased, dyspnea, and respiratory tract infection.

Cough adverse events were further assessed through the administration of a cough questionnaire in three individual studies. It should be noted that the cough questionnaire was not administered to every subject with a cough adverse event, but only to those subjects with cough AEs not attributed by the investigator to another condition. The cough questionnaire data suggested that for most subjects cough was rare or occasional during the day and rare or absent at night. For most subjects the severity of cough events was primarily mild. In general, the cough was not productive. Finally, a majority of subjects reported the timing of the cough event within seconds to minutes after Exubera dosing; however, some subjects did report no relationship between cough and Exubera dosing.

Some uncommon respiratory adverse events are worth noting. There were four cases of malignant lung neoplasms reported in the clinical studies. Three cases were in the Exubera group and one in the comparator group. One case in the Exubera group is likely not related to study medication since the subject had a lung nodule at screening. Three cases of "pulmonary fibrosis" were noted in the uncontrolled extension studies; however, in two of the cases an HRCT was not performed, which calls into question the diagnosis of pulmonary fibrosis.

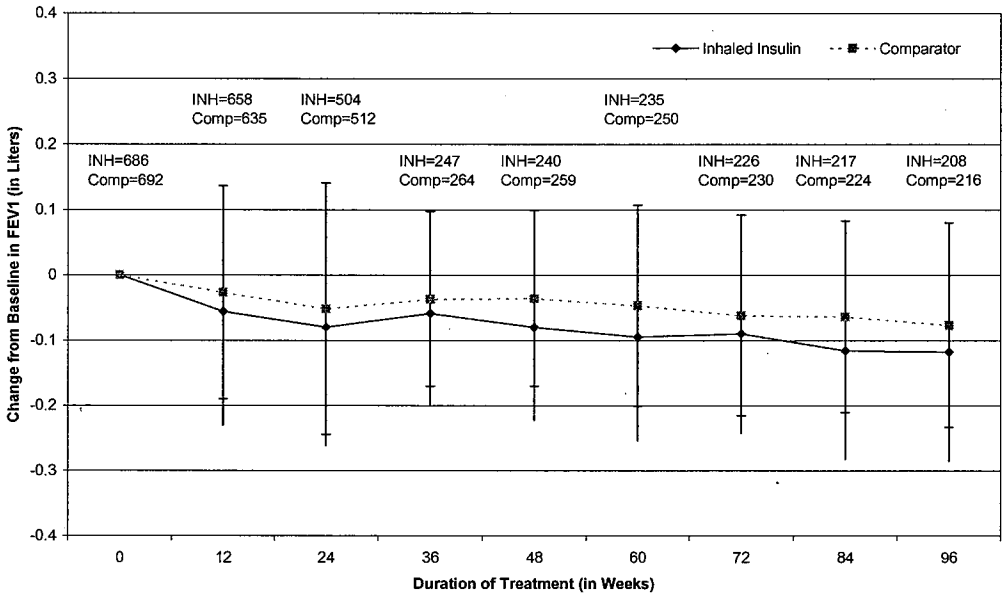
It should be noted that interpretation of the respiratory adverse events data is affected by the open label nature of the clinical studies. For example, subjects may be less likely to discontinue study drug for certain AEs, such as cough if the study drug is SC insulin.

1.3.3 Effect on Pulmonary Function in Type 1 Diabetes

1.3.3.1 FEV_1

In the individual phase 2 and 3 studies and the pooled phase 2 and controlled studies, subjects with type 1 diabetes treated with Exubera consistently showed a greater mean decline from baseline FEV_1 over time compared to the comparator group. One study suggested Exubera has an effect on FEV_1 within the first few weeks of exposure. The effect of Exubera on FEV_1 progressed during the first year of exposure then stabilized between the first and second year as shown below in Figure 1.

Figure 1 Mean Change from Baseline FEV_1 (L) by Time in Phase 2 and 3 Controlled Studies in Adults with Type 1 Diabetes (Mean +/- SD)



Source: Dr. Joan Buenconsejo's Biometrics Review

In the phase 2 and 3 controlled studies, after 2 years of treatment, subjects in the Exubera group had a mean decline from baseline FEV_1 of 118mL while subjects in the comparator group had a mean decline from baseline FEV_1 of 77mL. Both treatment groups demonstrated a larger mean FEV_1 decline than what would be expected in non-smoking subjects without significant lung disease. The 2-year mean treatment group difference between Exubera and the comparator group was approximately 40mL, favoring the comparator group.

Controlled data are not available to assess the effect of Exubera after 2 years of exposure. However, in non-controlled extension studies some subjects have been exposed to Exubera for up to 84 months. The non-controlled extension study data suggest that the mean decline from baseline FEV_1 continues with continued exposure to Exubera. However, without a comparator group, it is unknown if the treatment group difference changes with time.

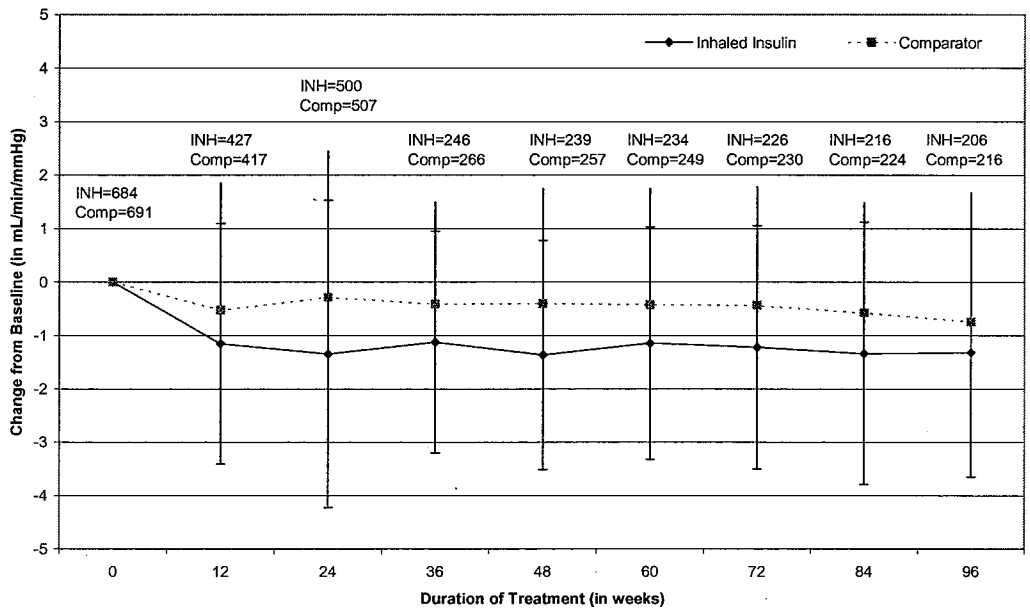
Reversal of the effect of Exubera on FEV_1 was evaluated in a controlled fashion in Study 1027. However, Study 1027 does not adequately address reversal of the effect of Exubera on FEV_1 in type 1 diabetes primarily because there was essentially no difference between groups in the mean change from baseline FEV_1 at Week 12 prior to discontinuation of Exubera. Reversal of the effect of long term Exubera use was assessed in the non-controlled extension Study 111. However, the study design and results have issues which limit the interpretability of the data. Thus, the submitted data are not adequate to support that the change from baseline FEV_1 treatment group difference noted with Exubera in type 1 diabetes is reversible.

1.3.3.2 DLCO

Subjects with type 1 diabetes treated with Exubera consistently showed a greater mean decline from baseline DLCO over time compared to the comparator group in most of the individual studies as well as in the pooled adult controlled phase 2 and 3 studies in type 1 diabetes. A single study (1027) suggested that Exubera affects the DLCO within the first two weeks of exposure. In the pooled phase 2 and 3 controlled studies in type 1 diabetes, the Exubera group had a greater decline in DLCO than the comparator group, thus, there is a treatment group difference favoring the comparator.

In the pooled phase 2 and 3 controlled studies, the mean treatment group difference in change from baseline DLCO fluctuated throughout the treatment period. At Week 96, the mean treatment group difference was approximately -0.5 to -0.6mL/min/mmHg, favoring the comparator. The maximum mean treatment group difference favoring the comparator was -1 mL/min/mmHg, which was noted at Week 24. It should be noted, though that the Week 96 data and Week 12 DLCO data showed a similar mean treatment group difference. The effect of Exubera on DLCO did not appear to progress over 2 years of treatment as shown below in Figure 2.

Figure 2 Mean Change from Baseline DLCO (mL/min/mmHg) by Time in Phase 2 and 3 Controlled Studies in Adults with Type 1 Diabetes (Mean +/- SD)



Source: Dr. Joan Buenconsejo's Biometrics Review

Exposure to Exubera longer than 24 months in type 1 diabetes has not been studied in controlled studies. One non-controlled extension study (Study 1036) has exposed subjects to Exubera up to 84 months. The data suggest that after a decline from baseline DLCO in the first 12 months, the mean change from baseline DLCO does not continue to progress through 84 months of exposure.

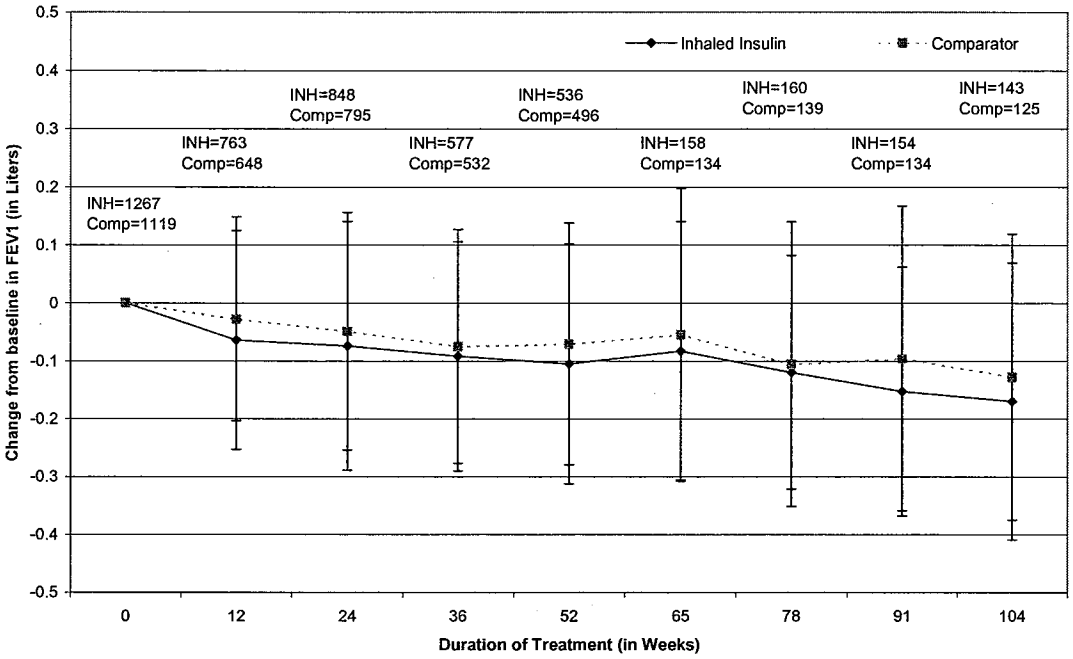
Reversal of the effect of Exubera on DLCO was evaluated in a controlled fashion in Study 1027. The data from Study 1027 does suggest that after discontinuation of Exubera following 12 weeks of Exubera treatment, the mean treatment group difference decreases and favors the Exubera group (after 12 weeks of discontinuation) However, Study 1027 does not adequately address the reversal of the effect of Exubera. Although the discontinuation data suggests the effects of Exubera on DLCO are reversible after 12 weeks of Exubera exposure, the effects of Exubera on DLCO may not be reversible after longer Exubera exposure. Reversal of the effect of long term Exubera use was also assessed in the extension Study 111. However, the study design and results have issues which limit the interpretability of the data. Thus, there are not adequate controlled data to determine if the long term effects on DLCO from exposure to Exubera are reversible in subjects with type 1 diabetes.

1.3.4 Effect on Pulmonary Function in Type 2 Diabetes

1.3.4.1 FEV_1

Subjects with type 2 diabetes treated with Exubera showed a greater mean decline from baseline FEV_1 over time compared to the comparator group in most of the individual studies as well as in the pooled adult controlled phase 2 and 3 studies. The pooled controlled studies indicate that the mean treatment group difference favors the comparator within 3 months of exposure. The mean treatment group difference fluctuates during the 104 week treatment period; however, the mean treatment group difference at Week 12 and Week 104 are similar, which suggests that the effect of Exubera on FEV_1 in type 2 diabetes is not progressive over 2 years.

Figure 3 Mean Change from Baseline FEV_1 over Time in the Phase 2 and 3 Controlled Studies in Adults with Type 2 Diabetes (Mean +/- SD)



Source: Dr. Joan Buenconsejo's Biometrics Review

In the phase 2 and 3 controlled studies, after two years of treatment, the Exubera group demonstrated a mean decline from baseline FEV_1 of 170mL, while subjects in the comparator group demonstrated a mean decline from baseline FEV_1 of 128mL. Both treatment groups demonstrated a larger mean decline from baseline FEV_1 than would be expected in non-smoking subjects without significant lung disease. At Week 104, the mean treatment group difference is approximately 40mL, which is similar to the mean treatment group difference for change from baseline FEV_1 in subjects with type 1 diabetes.

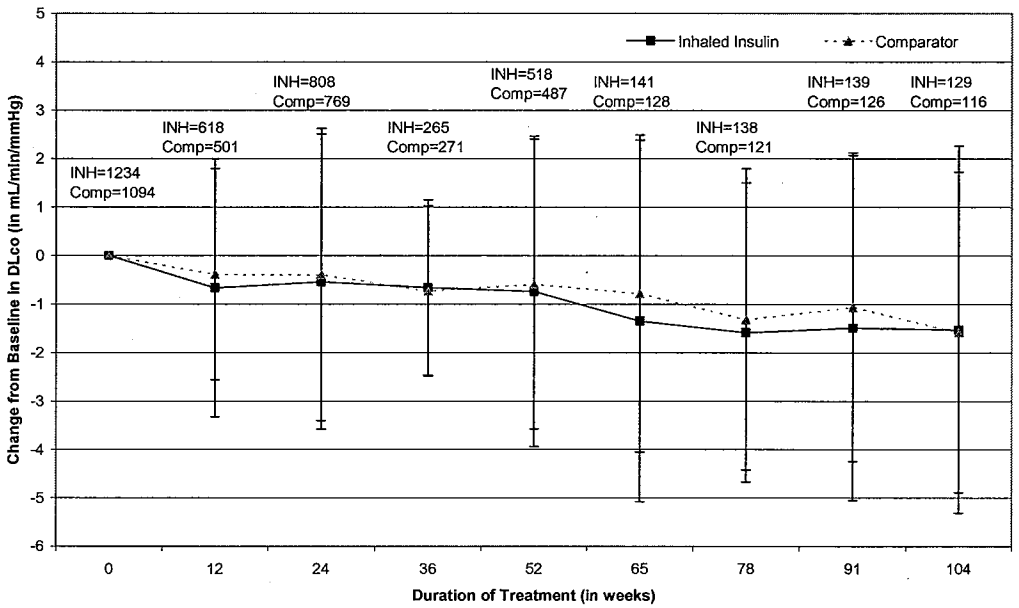
Exposure to Exubera longer than 24 months in type 2 diabetes has not been studied in controlled studies. However, non-controlled extension studies have exposed subjects to Exubera up to 84 months. The non-controlled PFT data from Study 1036 suggests that the mean decline from baseline FEV_1 continues with continued exposure. However, without a comparator group, it is unclear if the mean treatment group difference changes further with time.

Reversal of the effect of Exubera on FEV_1 after 2 years exposure was evaluated in combined Study 1001-1002. The results of combined Study 1001-1002 show that the mean treatment group difference after Exubera treatment for 104 weeks was 40mL, favoring the comparator. However, after discontinuation of Exubera for 6-12 weeks, there was minimal mean treatment group difference, which suggests the effects of Exubera treatment (up to 104 weeks) on FEV_1 may be reversible.

1.3.4.2 DLCO

Subjects with type 2 diabetes treated with Exubera in general showed a greater mean decline from baseline DLCO at most time points compared to the comparator group in most of the individual studies as well as in the pooled adult controlled phase 2 and 3 studies in type 2 diabetes. In the pooled phase 2 and 3 controlled studies in type 2 diabetes, the mean treatment group difference at most time points favored the comparator; however the mean treatment group difference fluctuated throughout the 104 week treatment period. The maximum mean unadjusted treatment group difference was approximately -0.6mL/min/mmHg at Week 65, favoring the comparator. This mean treatment group difference is similar to the mean treatment group difference noted in subjects with type 1 diabetes. However, at Week 104, the mean treatment group difference favored the Exubera group. Thus, the effect of Exubera on DLCO did not appear to progress over 2 years of treatment as shown below in Figure 4.

Figure 4 Mean Change from Baseline DLCO over Time in Phase 2 and 3 Controlled Studies in Adults with Type 2 Diabetes (Mean +/- SD)



Source: Dr. Joan Buenconsejo's Biometrics Review

Exposure to Exubera longer than 24 months in type 2 diabetes has not been studied in controlled studies. One non-controlled extension study (Study 1036) has exposed subjects to Exubera up to 84 months and suggests that after a decline from baseline DLCO in the first 12 months, the mean change from baseline DLCO does not continue to progress.

Reversal of the effect of Exubera on DLCO was evaluated in a controlled fashion in combined Study 1001-1002. The results of combined Study 1001-1002 suggest that at Week 104 there is essentially no mean treatment group difference. Following discontinuation of study medication, both treatment groups showed an improvement in

DLCO. After 12 weeks of discontinuation, there was a slight treatment group difference favoring the comparator.

1.3.5 Chest X-ray and High Resolution Computed Tomography

Baseline and end of study chest x-rays (CXRs) were performed in almost all of the clinical studies. The CXR data in the phase 2 and 3 adult controlled clinical studies demonstrate that there were more significant changes from baseline CXR in the Exubera treatment group than in the comparator group. This was true in both type 1 and type 2 diabetes. The most common new findings on CXR were nodular density, opacity, nodule, atelectasis, cardiomegaly, and enhanced vasculature or pulmonary edema. Although new significant changes were more common in the Exubera group than in the comparator group, follow up imaging (CT scan, additional CXR) indicated resolution in most cases.

Baseline and two year high resolution computed tomography (HRCT) scans of the thorax in 50 subjects treated with Exubera and 50 subjects treated with comparator were requested by the Agency to assess for parenchymal lung changes associated with Exubera use. The Applicant submitted controlled HRCT data at baseline and 24 weeks in 116 subjects, controlled HRCT data at baseline and 24 months in 104 subjects, and "for cause" HRCT data in 48 subjects. The controlled HRCT data does not suggest an increase in abnormal findings associated with Exubera use compared to SC insulin at 24 weeks or 24 months. Because the majority of the "for cause" HRCTs were performed in the extension studies in which all subjects received Exubera, it is difficult to draw any conclusions from the "for cause" HRCT data.

1.3.6 Exploratory Analyses

The Applicant's clinical studies showed that Exubera is associated with a greater increase in insulin antibody levels and higher seroconversion (non-measurable insulin antibodies at baseline to measurable insulin antibodies at end of study) rates than SC insulin or oral agents. The Biometrics reviewer performed exploratory analyses to assess for a correlation between change in pulmonary function and insulin antibody titer. The analyses in subjects with type 1 diabetes and type 2 diabetes do not suggest a correlation between mean change from baseline FEV_1, DLCO, FVC, TLC, FRC and insulin antibody titer.

The association between insulin exposure and change in pulmonary function was explored in several individual studies. The Biometrics reviewer analyzed the association between the average total daily insulin dose and change from baseline FEV_1, DLCO, FVC, TLC, and FRC as well as the association between the cumulative insulin dose and the change from baseline FEV_1, DLCO, FVC, TLC, and FRC at different time points in the individual studies. The analyses do not suggest a correlation between change from baseline FEV_1, DLCO, FVC, TLC, and FRC and the average total daily Exubera dose or the cumulative Exubera dose.

Based upon these exploratory analyses, it does not appear that either insulin antibodies or total exposure would be expected to predict who may be at risk for declines in pulmonary function.

1.3.7 Special Populations - Underlying Lung Disease

The Agency requested the Applicant prospectively assess the effects of Exubera in subjects with underlying lung disease, such as asthma and COPD. The Applicant's clinical program includes two ongoing studies: one in subjects with asthma and one in subjects with COPD. These studies were specifically designed to assess the efficacy and safety of Exubera in these populations. However, because of the limited number of subjects with 52 week data in these ongoing studies, the safety of Exubera in subjects with underlying lung disease cannot adequately be assessed. The focus of this section is on the pulmonary safety in subjects with asthma and COPD.

2 Introduction and Background

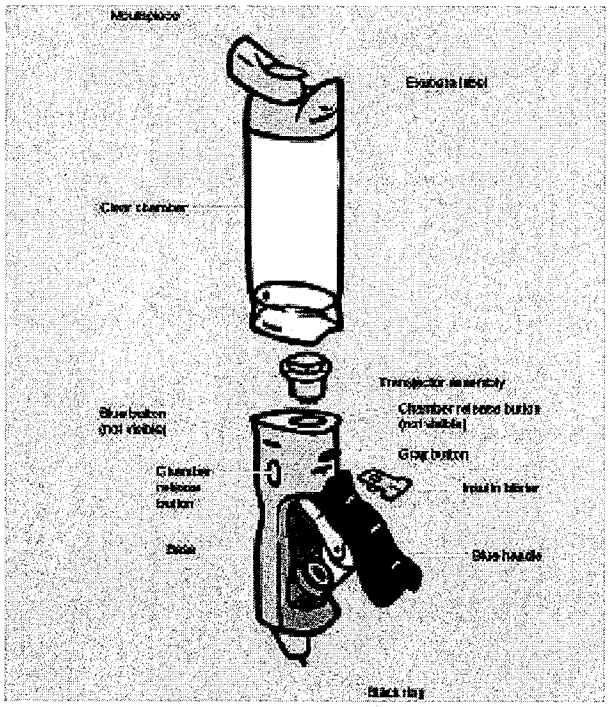
2.1 Product Information

The Applicant has developed a dry powder recombinant human insulin to be administered by oral inhalation via a specially designed pulmonary inhaler for the indication of the treatment of adult patients with diabetes mellitus for the control of hyperglycemia. Exubera was developed as an alternative mode of delivery to injected insulin. The proposed trade name is Exubera. It is proposed to be administered immediately prior to meals.

The drug substance [redacted] /HMR-4006, which is a recombinant human insulin produced by Aventis. The rDNA insulin is produced by *Escherichia coli*. The drug product is a white to off-white powder, which contains sodium citrate, mannitol, glycine, and sodium hydroxide.
Reviewer's Comment: The Agency's Inactive Ingredient Search for Approved Drug Products was accessed to assess if sodium citrate, mannitol, and glycine are common excipients in inhaled drug products. Mannitol and glycine were not listed as inactive ingredients in currently approved drug products. Sodium citrate is listed as an inactive ingredient at a maximum potency of 0.6% in an inhalation solution in the Agency's Inactive Ingredient Search for Approved Drug Products listing [www.accessdata.fda.gov/scripts/cder/iig/index.cfm].

The Exubera comes as a unit dose in a foil blister. Exubera is supplied in a 1.0mg or 3.0mg nominal dose blister package. The inhaler is a reusable mechanical inhaler, which is illustrated in Figure 5, below.

Figure 5 Insulin Pulmonary Inhaler



Source: N21868/N_000/2004-12-27/summary/quality_summary.pdf, pg 120

The base contains the air pump system and valves that generate, store, and release compressed air. This compressed air is the source of energy to extract the powder and generate the aerosolized insulin cloud. No propellants are used. The patient manually pumps the base handle to store the compressed air and then compresses the trigger button, which raises the blister into the transjector for puncture. The valve releases the compressed air into the transjector, which leads to aerosolization of the powder from the blister pack [N21868/N_000/2004-12-27/summary/quality_summary.pdf, pg 119].

Reviewer's Comment: For more information regarding the drug substance and drug product as well as a detailed review of the CMC information, refer to the CMC review.

2.2 Pre-submission Regulatory Activity

The following is a list of key regulatory meetings between the Applicant and the Agency.

August 18, 2000, Industry Meeting

- The Agency recommended at least one year controlled data for the NDA submission to assess pulmonary safety.
- The Agency stated the development program should address the acute and chronic effects of Exubera in subjects with underlying lung disease.

- The Agency stated that the NDA must include data on device performance for the entire life of the device.

April 16, 2001, Teleconference

- The Agency raised the following concerns:
  - Lack of adequate and long-term controlled pulmonary safety data
  - Relatively small number of subjects on Exubera
  - Relatively short duration of exposure data
  - Limited data in Type 1 diabetics
  - Potential bias introduced by non-random participation in the two proposed extension studies
  - Lack of adequate safety and efficacy data in subjects with concurrent lung disease.
- The Agency requested the long-term pulmonary safety database include safety and efficacy assessments on the following groups of subjects studied for $\geq$ 1 year in a controlled fashion:
  - Subjects with COPD ($n \geq 100$ subjects)
  - Subjects with asthma ($n \geq 100$ subjects)
  - Subjects with Type 1 diabetes and no underlying lung disease ($n \geq 100$)
- The Agency informed the Applicant that subjects enrolled in studies in which lung disease was an exclusion criterion, and classified post hoc as having asthma or COPD will not be sufficient.
- The Agency stated the presentation of the PFT should include shift tables
- The Agency reminded the Applicant that labeling precautions would not be accepted in lieu of further safety data

April 5, 2002, Teleconference

- The Agency reiterated the request for safety and efficacy assessment of the following additional groups of subjects, studied for $\geq$ 1 year in a controlled fashion:
  - Subjects with COPD ($n \geq 100$ subjects)
  - Subjects with asthma ($n \geq 100$ subjects)
  - Subjects with Type 1 diabetes and no underlying lung disease ($n \geq 100$)

November 15, 2002, Teleconference

- The Agency recommends approximately 50 subjects on drug and 50 subjects on standard therapy undergo HRCT at 0 and 24 months.
- The 2-year HRCT data may not be a filing issue, but the HRCT data requested will be necessary in order for the application to be complete.
- The Agency recommended the need for pulmonary consultation in subjects with the largest decline in FEV_1 and DLCO and highest titers of circulating anti-insulin IgG. In addition, a consideration of bronchoscopic lung biopsy with appropriate staining of the tissue (about 5-10) for subjects with high IgG titer.

June 9, 2004, Pre-NDA Meeting

- The Agency informed the Applicant that their proposal for the pulmonary safety database did not follow our recommendations and the adequacy of the safety database will be a review issue, not a filing issue.
- The Agency informed the Applicant that the NDA should include pulmonary safety data in subjects who developed antibodies.
- The Agency requested that the PFT data should include shift tables.
- The Agency reminded the Applicant that the NDA must include device performance data.

3 Significant Findings from Other Review Disciplines

3.1 Animal Pharmacology/Toxicology

The Applicant conducted inhalation toxicology studies in rats and monkeys of 6 months duration. The nonclinical studies were performed with an early formulation containing 20% insulin (Lilly). Later in the development, a 60% insulin (Aventis) formulation was developed. This 60% insulin formulation was used in the phase 3 clinical trials. A 1-month toxicology study in rats was performed to bridge the formulations. The following information is a synopsis of the pulmonary findings in the animal toxicology studies noted in pharmacology/toxicology review by Dr. Fred Alavi.

The 6-month rat studies demonstrated sporadic increases in lung weights, while the 6-month monkey study demonstrated a slight increase in lung weight in the low dose female group. Histologic examination of the lungs in the 6 month-monkey and rat study animals showed focal and multifocal inflammation and aggregation of alveolar histiocytes in all groups. There was no evidence of insulin related increase in lung cell proliferation in the in vitro studies in lung tissues from the 6 month rat and monkey studies. In terms of an effect of Exubera on pulmonary function, the rat studies were unremarkable. In the 6-month monkey study, there was a decrease in lung compliance in the high dose males and an increase in minute volume in both sexes in the high dose groups. During the clinical observation, monkeys treated with excipients and insulin had frequent incidences of coughing and sneezing throughout the 6-month study.
Reviewer's Comment: For a detailed review of the pharmacology/toxicology studies, refer to Dr. Fred Alavi's review.

4 Data Sources, Review Strategy, and Data Integrity

4.1 Sources of Clinical Data

The primary sources of clinical data for this NDA are the clinical studies conducted by the Applicant and submitted with the NDA in December 2004. The Applicant also has several ongoing clinical studies, which are pertinent to the pulmonary safety analyses. Information regarding the ongoing studies was submitted by the Applicant throughout the review period including the safety update on April 26, 2005, the two-year HRCT data from Study 1029 on June 22, 2005, and the two-year PFT data for ongoing Study 1022 on July 5, 2005. Information from these submissions is included in this review.

Reviewer's Comment: The Applicant also submitted the following during the review period, which were not included in this review due to submission late in the review cycle.

- *2-year interim study report for Study 1022 submitted on July 19, 2005*
- *2-year interim study report for Study 1029 submitted on July 21, 2005*
- *Response to information request submitted on July 26, 2005.*

Clinical studies are identified with the prefix 217 followed by the study number, e.g. 217-102. Throughout this review, the prefix may be omitted and the study referred to as Study 102. Several abbreviations are commonly used throughout the review: SC – subcutaneous insulin, INH – Exubera, and OA – oral agents.

The Applicant's clinical program includes 20 phase 2 and phase 3 clinical studies as well as 31 clinical pharmacology studies to support this NDA. The Applicant has completed 14 clinical studies evaluating the efficacy and safety of Exubera. In addition, the Applicant has 6 ongoing clinical studies at the time of this review (1022, 1028, 1029, 1030, 1036, and 1017). The majority of the studies are controlled studies; however, two of the studies are extension studies (1036 and 111) and not controlled. Most of the studies were limited to adult subjects (≥ 18 years) with diabetes; however, one study (1009) was conducted in subjects <18 years of age. In addition, two other studies (106, 107) included subjects <18 years of age. The focus of this review will be the pulmonary safety data in subjects ≥ 18 years of age.

Because of the multitude of studies, there are various logical ways to group the Applicant's studies together, e.g. diabetes type, SC comparator or OA comparator, ongoing or completed, study design, or length of study. Throughout this review, the clinical studies will usually be grouped according to diabetes type. The following tables display the Applicant's clinical studies with a focus on the relevance of each study to the pulmonary safety review. Table 1 displays the controlled clinical studies conducted in subjects with type 1 diabetes. Table 2 displays the controlled clinical studies conducted in subjects with type 2 diabetes. Table 3 displays the controlled clinical studies conducted in subjects with underlying lung disease (asthma and COPD), both of which are still ongoing. Finally, Table 4 displays the non-controlled extension studies (111, 1036), the pediatric study (1009), and an ongoing study (1017), in which the data is reported in a "blinded" fashion.

Table 1 Controlled Adult Clinical Studies in Subjects with Type 1 Diabetes NDA# 21-818

Study #	Study Purpose	Subjects	Design	Treatment Groups	Relevance to Pulmonary Safety Review
102	Efficacy, Safety	Type 1 DM Age 18-56 N = 72	P2, R, MC, OL, // 12 weeks US	-Exubera pre-meal TID and SC HS Ultralente -SC insulin	-PFTs -BL, wk 6 (spiro), wk 12 -AEs
106*	Efficacy, Safety	Type 1 DM Age 11-64 N = 334	P3,R, MC, OL, // 24 weeks US & Canada	-Exubera pre-meal TID and SC HS Ultralente -SC BID regular insulin and BID NPH insulin	-PFTs -BL, wk 12 (spiro), wk 24 -HRCT (subgroup) – BL & 24 wks -AEs -CXR – BL & wk 24
107*	Efficacy, Safety	Type 1 DM Age 11-65 N = 327	P3,R, MC, OL, // 24 weeks US & Canada	-Exubera pre-meal TID and SC AM and PM NPH -SC pre-meal regular insulin and BID NPH insulin	-PFTs -BL, wk 12 (spiro), wk 24 -HRCT (subgroup) – BL & 24 wks -AEs -CXR – BL & wk 24
1026	Efficacy, Safety	Type 1 DM Age 20-50 yrs N = 45	R, SC, OL, // 24 weeks	- Exubera pre-meal and BID NPH - SC BID NPH and regular insulin	-PFTs – BL, wk 11 (spiro), wk 23 -AEs
1027	Efficacy, Safety	Type 1 DM Age 25-65 years N = 226	R, MC, OL, // 12 weeks treatment 12 weeks follow up US, Brazil Canada	-Exubera -SC insulin	-PFTs – BL, 1, 2, 3, 4, 6, 8, and 12wks -PFTs 2, 4, 8, 12 wks after discontinuation -PFTs pre and post insulin dose – Wks 0, 4, 8, and 12 -AEs -Cough Questionnaire -CXR -BL, week 12 -BDI/TDI
1022 **Ongoing**	Efficacy, Safety	Type 1 DM Age 18-65 yrs N = 580	R, MC, OL, // 24 months Multinational	-Exubera -SC insulin	-PFTs – BL, 12 wks, 6, 9, 12, 15, 18, 21, and 24 months -PFTs 1, 3, and 6 months after discontinuation -CXR -AEs -Cough questionnaire -BDI/TDI

DM – diabetes mellitus; P2 – phase 2; P3 – phase 3; R – randomized; MC – multicenter; OL – open label; // - parallel group; SC – subcutaneous insulin; OA – oral agents; PFTs – pulmonary function tests; AEs – adverse events; CXR – chest x-ray; HRCT – high resolution computed tomography of chest; BL – baseline; EOS – end of study

*These studies included some subjects less than 18 years of age

Table 2 Controlled Adult Clinical Studies in Subjects with Type 2 Diabetes NDA# 21-818

Study #	Study Purpose	Subjects	Design	Treatment Groups	Relevance to Pulmonary Safety Review
103	Efficacy, Safety	Type 2 DM Age 35-66 N = 56	P2, R, MC, OL, // 12 weeks US	-Exubera pre-meal TID and SC HS Ultralente -SC insulin	-PFTs - BL, wk 6 (spiro), wk 12 -AEs
104	Efficacy, Safety	Type 2 DM Age 33-69 N = 69	P2,R, MC, OL, // 12 weeks US	-Exubera pre-meal TID & OA -OA	-PFTs - BL, wk 6 (spiro), wk 12 -AEs
108	Efficacy, Safety	Type 2 DM Age 23-80 N = 298	P3,R, MC, OL, // 24 weeks US & Canada	-Exubera pre-meal TID and SC HS Ultralente -SC insulin	-PFTs -BL, wk 12 (spiro), wk 24 -HRCT (subgroup) – BL & 24 wks -AEs -CXR – BL & wk 24
109	Efficacy, Safety	Type 2 DM Age 35-77 N = 306	P3,R, MC, OL, // 12 weeks US & Canada	-Exubera pre-meal TID -Exubera and OA -OA	-PFTs – BL & wk 12 -AEs -CXR – BL & wk 12
110	Efficacy, Safety	Type 2 DM Age 28-80 N = 143	P3,R, MC, OL, // 12 weeks US	-Exubera pre-meal TID -Rosiglitazone	-PFTs– BL & wk 12 -AEs -CXR – BL & wk 12
1001	Efficacy, Safety	Type 2 DM Age 35-80 yrs N = 423	R, MC, OL, // originally 24 wks, then extended to 104 weeks Multinational	-Exubera -Metformin	-PFTs –BL, Wk 24 (spiro), 36 (spiro), 52, 65, 78, 91, and wk 104 -PFTs – after 12 wk discontinuation -AEs -CXR – BL & EOS
1002	Efficacy, Safety	Type 2 DM Age 35-80 yrs N = 470	R, MC, OL, // originally 24 wks, then extended to 104 weeks Multinational	-Exubera -Glibenclamide	-PFTs –BL, Wk 24 (spiro), 36 (spiro), 52, 65, 78, 91, and wk 104 -PFTs – after 12 wk discontinuation -AEs -CXR – BL & wk 12
1029 **Ongoing**	Efficacy, Safety	Type 2 DM Age 35-75 yrs N = 627	R, MC, OL, // 24 months Multinational	-Exubera -SC insulin	-PFTs – BL, wk 12, month 6, 9, 12, 15, 18, 21, and 24 -PFTs – after 1, 3, and 6 m discontinuation -CXR – BL, month 12 and month 24 -AEs -HRCT - BL, 12 months, 24 months

DM – diabetes mellitus; P2 – phase 2; P3 – phase 3; R – randomized; MC – multicenter; OL – open label; // - parallel group; SC – subcutaneous insulin; OA – oral agents; PFTs – pulmonary function tests; AEs – adverse events; CXR – chest x-ray; HRCT – high resolution computed tomography of chest; BL – baseline; EOS – end of study

Table 3 Ongoing Controlled Clinical Studies in Subjects with Underlying Lung Disease NDA# 21-818

Study #	Study Purpose	Subjects	Design	Treatment Groups	Relevance to Pulmonary Safety Review
1028 **Ongoing**	Efficacy, Safety in subjects with **asthma**	Type 1 or 2 DM and Asthma Age 18-74 N =139 (interim) N=250 (planned)	R, MC, OL, // 12 month treatment 6 week follow up Multinational	Exubera SC insulin	-PFTs – BL, 1, 2 , 3, 4, 6, 18, 26, 39, 52 wks (pre and post bronchodilator) -PFTs – 2 and 6 weeks after discontinuation -PFTs – pre and post insulin wks 0, 9, 51 -MCT -AEs -Asthma exacerbations -CXR – BL and wk 52 -BDI/TDI
1030 **Ongoing**	Efficacy, Safety in subjects with **COPD**	Type 1 or 2 DM and COPD Age 40-77 N = 67 (interim) N=250 (planned)	R, MC, OL, // 12 month treatment 6 week follow up Multinational	Exubera SC insulin	-PFTs – BL, 1, 2 , 3, 4, 6, 18, 26, 39, 52 wks -PFTs – 2 and 6 weeks after discontinuation -MCT -COPD exacerbations -CXR – BL and wk 52 -BDI/TDI

DM – diabetes mellitus; P2 – phase 2; P3 – phase 3; R – randomized; MC – multicenter; OL – open label; // - parallel group; SC – subcutaneous insulin; OA – oral agents; PFTs – pulmonary function tests; AEs – adverse events; CXR – chest x-ray; HRCT – high resolution computed tomography of chest; BL – baseline; EOS – end of study

Table 4 Additional Clinical Studies with Exubera

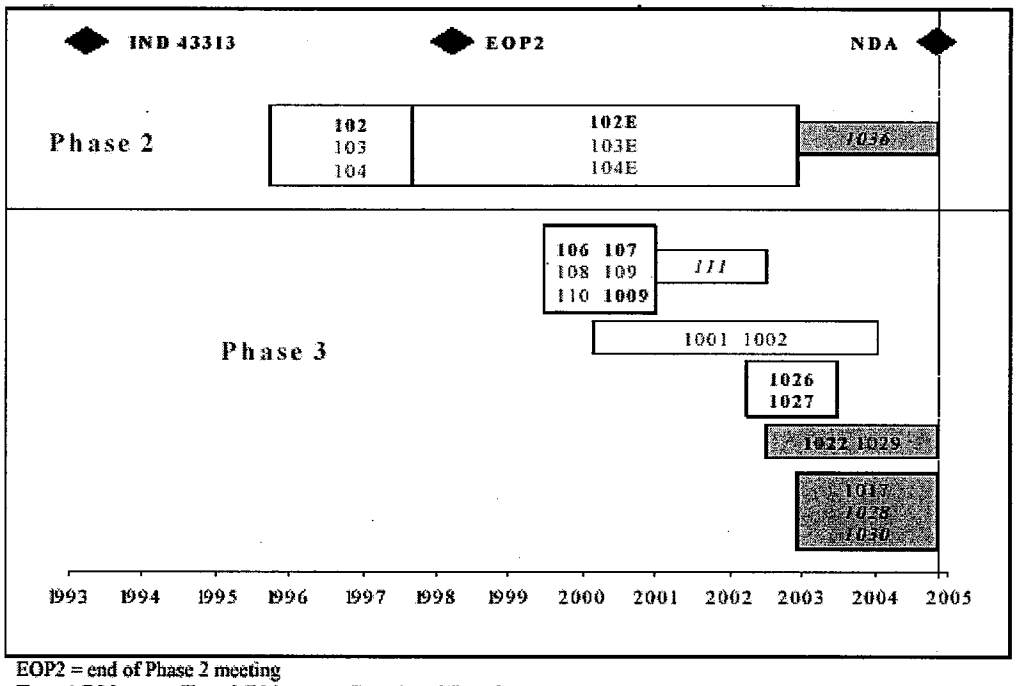
Study #	Study Purpose	Subjects	Design	Treatment Groups	Relevance to Pulmonary Safety Review
111	Safety Extension Study of 106, 107, 108, 109, 110, & 1009 And PFT trends after discontinuation	Type 1 and Type 2 DM Age 5-80 years N = 1290 n=664 Type 1 n=626 Type 2	P3, OL, MC, **extension** of 106, 107, 108, 109, 110, & 1009	-Segment 1: Exubera (all) - Segment 2: Randomized to a) continued Exubera for 6 months then discontinuation of Exubera OR b) discontinuation of Exubera	-PFTs – Q 6 months with spirometry every 3 months; however, extension population no "control" group -AEs
1036	Safety 4 year Extension of 102, 103, 104 **Ongoing**	Type 1 and Type 2 DM N=172 (n=62 ongoing)	P2, OL, MC, **extension** of 102, 103, 104	-Exubera pre-meal TID (all subjects)	-PFTs –Q 6 months with spirometry every 3 months; however, no "control" group -AEs
1009	Efficacy, Safety **Pediatric**	Type 1 DM Age 6-11 N = 120	P3,R, MC, OL, // 12 weeks US	-Exubera pre-meal TID and SC HS Ultralente/NPH or BID Ultralente/NPH -SC insulin	-PFTs – BL and wk 12 -AEs -CXR – BL and wk 12
1017	Efficacy, safety **Ongoing**	Type 2 DM N=223	P3b, R, MC, OL, // 52 weeks	- Exubera - Avandia	-PFTS – BL, wk 12, 24. 36, 52 -CXR – BL and wk 52 -AEs - Data still "blinded"

DM – diabetes mellitus; P2 – phase 2; P3 – phase 3; R – randomized; MC – multicenter; OL – open label; // - parallel group; SC – subcutaneous insulin; OA – oral agents; PFTs – pulmonary function tests; AEs – adverse events; CXR – chest x-ray; HRCT – high resolution computed tomography of chest; BL – baseline; EOS – end of study

The studies listed in Table 4 contribute less to the pulmonary safety review because of the uncontrolled design of Studies 111 and 1036. In addition, Table 4 includes a pediatric study, Study 1009. Although this NDA proposes Exubera for subjects with diabetes >18 years of age, Study 1009 was reviewed for pulmonary safety in subjects <18 years of age. The limited information regarding the pulmonary safety of subjects <18 years of age will be discussed separately. Finally Study 1017 is ongoing and the data in the study report is not "unblinded" and does not contribute to the pulmonary safety database in this application.

Figure 6 displays the timeline for the Exubera clinical development program. The shaded boxes denote the ongoing clinical studies.

Figure 6 Timeline for Exubera Clinical Development Program



EOP2 = end of Phase 2 meeting
Type 1 DM Type 2 DM *Type 1 and Type 2*
Shading denotes study ongoing at time of NDA submission

Source: [N21868/N_000/2004-12-27/clinstat/summary-clin-efficacy.pdf, pg 9].

As discussed in Section 8.1.1, Underlying Lung Disease, the phase 2 studies specified subjects with no significant pulmonary or PFT abnormalities. However, as clinical development proceeded, subjects with mild to moderate underlying lung disease were allowed with FEV_1 and DLCO as low as 70% predicted. The safety of Exubera in subjects with underlying lung disease will be discussed in detail in Section 8.1.1.

4.2 Review Strategy

The pulmonary safety data were analyzed utilizing the pooled controlled phase 2 and 3 studies in type 1 diabetes and type 2 diabetes. This dataset includes data from two ongoing studies, 1022 and 1029. The initial NDA submission included one year data from Study 1022 and 1029; however, the Applicant submitted additional data during the review period as discussed above in Section 4.1. The controlled phase 2 and 3 studies are shown below in Table 5.

Reviewer's Comment: Ideally the dataset utilized for the primary analyses includes data from completed clinical studies; however, because the ongoing studies provide information about the long term safety of Exubera, the data from the ongoing studies was incorporated into this review.

Table 5 Controlled Adult Phase 2 and 3 Studies			
	Contributing Studies	# Subjects INH	# Subjects Comparator
Adult type 1 studies	102, 106, 107, 1022*, 1026, 1027	698	705
Adult type 2 studies	103, 104, 108, 109, 110, 1001, 1002, 1029*	1277	1132
Total subjects		1975	1837
*ongoing studies Source: N21868/N_000/2004-12-27/clinstat/summary-clin-safety.pdf, pg 131			

Reviewer's Comment: This table represents the number of subjects included in the controlled adult phase 2 and 3 protocol set submitted in the December 27, 2004, submission. However, additional data was submitted by the Applicant during the review period for Studies 1022 and 1029. The additional data is incorporated into this review; therefore, the number of subjects may have changed slightly.

The Applicant also specified the all phase 2 and 3 protocol set for the assessment of serious adverse events. This protocol set includes data from both uncontrolled and controlled studies and thus, is not utilized in this review.

Table 6 Adult All Phase 2 and 3 Studies			
	Contributing Studies	# Subjects INH	# Subjects Comparator
Adult type 1 subjects	102, 102E,106, 107, 111†, 1022*, 1026, 1027, 1036*†	918	721
Adult type 2 subjects	103, 103E, 104, 104E, 108, 109, 110, 111†,1001, 1002, 1029*, 1036*†	1578	1144
All subjects		2496	1865
†Includes both type 1 and type 2 subjects *ongoing Source: N21868/N_000/2004-12-27/clinstat/summary-clin-safety.pdf, pg 131			

5 Clinical Pharmacology

The Applicant has conducted 32 clinical pharmacology studies. Several of the clinical pharmacology studies assess the effects of smoking, asthma, COPD, and rhinovirus infection on the bioavailability of Exubera. These studies are of interest and will be briefly discussed in this section.

Reviewer's comment: Although the results of these studies are briefly discussed in this section, it should be noted that this reviewer is not interpreting the significance of these findings because the clinical pharmacology studies are not meant to provide information regarding pulmonary safety but are meant to provide information regarding the effects of intrinsic (COPD and asthma) and extrinsic (smoking and rhinovirus infection) factors on the pharmacokinetics and pharmacodynamics of Exubera. The pharmacokinetic and pharmacodynamic effects are most relevant to the overall efficacy/safety assessment of Exubera.

Study 217-010 was a clinical pharmacology study to assess the effect of a rhinovirus challenge on the bioavailability and tolerability of Exubera in 24 healthy subjects. Subjects were given a single dose of Exubera followed by an intra-nasal dose of rhinovirus (20 subjects) or saline (4 subjects). Subjects then received two additional doses of Exubera, 2 and 3 days later. There were no consistent differences in absorption of Exubera between subjects who developed colds and controls. However, the number of subjects was small, especially in the control groups; thus, it is difficult to draw any definitive conclusions from this study [N21868/N_000/2004-12-27/hpbio/hupharm/010.pdf, pg. 6-10].

Study 217-009 was a clinical pharmacology study to assess the tolerability and bioavailability of Exubera in 24 subjects with mild, controlled asthma compared with 12 healthy subjects. Study 217-009 was a crossover study in which subjects received two doses of Exubera and one dose of SC insulin on 3 separate days with at least one week washout between doses. Exubera AUC_{0-360} and Cmax were consistently lower in subjects with asthma than in normal subjects; however, the differences in PK parameters were not statistically significant [N21868/N_000/2004-12-27/hpbio/hupharm/009.pdf, pg. 6-8].
Reviewer's Comment: In this study with Exubera, the insulin exposure in subjects with mild, stable, controlled asthma was lower than the insulin exposure in healthy subjects. This study did not asses potential intra-subject PK variability related to variations in airflow resistance, which is a hallmark of asthma. Such a phenomenon would be potentially clinically significant.

Study 217-1005 was a clinical pharmacology study to assess the tolerability and bioavailability of Exubera in 39 subjects with COPD (13 chronic bronchitis and 14 emphysema) compared with 12 healthy subjects. Subjects with COPD received one dose of Exubera pre-albuterol, one dose of Exubera post-albuterol, and one dose of SC insulin. Healthy subjects received one dose of Exubera and one dose of SC insulin. The change from baseline insulin AUC and Cmax were greater in subjects with COPD compared to healthy subjects. Although the exposure was slightly higher in subjects with emphysema compared to subjects with chronic bronchitis, the difference was not statistically significant. The change from baseline AUC and Cmax were slightly higher when Exubera was administered post- albuterol compared to pre-albuterol. Of note, two SAEs, myocardial infarctions, were reported in this study [N21868/N_000/2004-12-27/hpbio/hupharm/1005.pdf, pg. 8-13].
Reviewer's Comment: In this study with Exubera, the exposure to Exubera was higher in subjects with COPD compared to healthy subjects.

The Applicant conducted four clinical pharmacology studies to assess the effect of smoking (217-005), cessation of smoking (217-016), and cessation/resumption of smoking (217-1020) in non-diabetic subjects. In addition, the Applicant assessed the effect of smoking in subjects with Type 2 diabetes (217-1003).

In Study 217-005, Exubera was compared to SC insulin in 24 chronic smokers (>15 cigarettes per day for at least 6 months). Exubera produced a more rapid rise from

baseline in insulin concentrations (25 minutes INH vs. 90 minutes SC) in smokers [N21868/N_000/2004-12-27/hpbio/hupharm/005.pdf, pg. 6-8].

In Study 217-016, the effect of cessation of smoking (for 3 and 13 weeks) was assessed in 38 chronic smokers and compared to non-smokers. Prior to cessation, smokers had significantly higher AUC and Cmax and a shorter Tmax than nonsmokers. After 3 weeks of smoking cessation, former smokers had a decrease in Exubera absorption (~50%) and slightly longer Tmax; however, former smokers continued to have a higher bioavailability than nonsmokers. After 13 weeks of smoking cessation, no further significant decrease in AUC or Cmax was noted. Thus, after 13 weeks of smoking cessation, former smokers continued to have greater bioavailability than non-smokers. The results are shown below in Table 7 [N21868/N_000/2004-12-27/hpbio/hupharm/016.pdf, pg. 7-9].

Table 7 PK Parameters for Study 217-016 – Effect of Smoking Cessation on Bioavailability of Exubera

Exubera	Smokers N=38	Non-smokers N=30
$AUC_{0\text{-}360}$ μU·min/ml – baseline	4850	1410
$AUC_{0\text{-}360}$ μU·min/ml – Week 3 smoking cessation	2850	
$AUC_{0\text{-}360}$ μU·min/ml – Week 13 smoking cessation	3260	
Cmax μUml – baseline	72.3	15.8
Cmax μUml – Week 3 smoking cessation	35.7	
Cmax μUml – Week 13 smoking cessation	43.1	
Tmax (min) – baseline	31	53
Tmax (min) – Week 3 smoking cessation	41	
Tmax (min) – Week 13 smoking cessation	40	

Source: N21868/N_000/2004-12-27/hpbio/hupharm/016.pdf, pg 8

In Study 217-1020, the Applicant assessed the effect of short term cessation and resumption of smoking on the bioavailability of Exubera. In this study 20 smokers were compared to10 non-smokers. All subjects were administered Exubera once at baseline. Smokers then stopped smoking for 7 days and had Exubera administered on Day 1, 3, and 7 of the cessation period. Smoking was then resumed. Exubera was administered once after resumption of smoking. The PK results indicated than smokers had a greater exposure to Exubera and shorter Tmax than non-smokers at baseline. Insulin exposure was slightly greater after cessation of smoking for 12 hours. However following cessation of smoking for 3 to 7 days, the insulin exposure decreased. However, the exposure increased after resumption of smoking for 2-3 days. The results of the PK parameters for Exubera are shown below in Table 8 [N21868/N_000/2004-12-27/hpbio/hupharm/1020.pdf, pg. 11-20].

Table 8 PK Parameters for Study 217-1020 – Effect of Smoking Cessation and Resumption on Bioavailability of Exubera

Exubera	Smokers N=20	Non-smokers N=10
AUC_{0-6} μU·min/ml – baseline	2583	1645
AUC_{0-6} μU·min/ml – Day 1 smoking cessation	3165	
AUC_{0-6} μU·min/ml – Day 3 smoking cessation	2321	
AUC_{0-6} μU·min/ml – Day 7 smoking cessation	1887	
AUC_{0-6} μU·min/ml – After smoking resumption	3156	
Cmax μUml – baseline	26.8	9.7
Cmax μUml – Day 1 smoking cessation	33.3	
Cmax μUml – Day 3 smoking cessation	18.5	
Cmax μUml – Day 7 smoking cessation	15.9	
Cmax μUml – After smoking resumption	29.2	
Tmax (min) – baseline	20	53
Tmax (min) – Day 1 smoking cessation	20	
Tmax (min) – Day 3 smoking cessation	30	
Tmax (min) – Day 7 smoking cessation	38	
Tmax (min) – After smoking resumption	30	

Source: N21868/N_000/2004-12-27/hpbio/hupharm/1020.pdf, pg 17

Study 217-1003 was a clinical pharmacology study in type 2 diabetic smokers. As with the studies in non-diabetic smokers discussed above, the results indicated that the rate and extent of absorption of Exubera was increased in type 2 diabetic smokers compared with type 2 diabetic non-smokers [N21868/N_000/2004-12-27/hpbio/hupharm/1003.pdf, pg. 7-12].

Reviewer's Comment: The clinical pharmacology studies to assess the effects of smoking on Exubera exposure suggest the following:

- *Exubera exposure (Cmax and AUC) in smokers is increased compared to nonsmokers.*
- *The absorption of Exubera is more rapid in smokers compared to non-smokers.*
- *Smoking cessation for 3 days results in a decrease in Exubera exposure, but the exposure is still higher than non-smokers.*
- *The resumption of smoking returns the exposure to baseline.*

Reviewer's Comment: The changes in exposure with smoking appear to be clinically important changes. This reviewer defers the determination of how this data effects approval and labeling issues to the DMEP. Of note, the Applicant's proposed label includes language regarding the contraindication of Exubera in current and recent (within 6 months) smokers.

Reviewer's Comment: The clinical pharmacology studies were reviewed in detail by the Dr. Sayed Al-Habet. Refer to Dr. Al-Habet's review for details regarding the clinical pharmacology studies.

6 Integrated Review of Efficacy

This review focuses on the pulmonary safety of Exubera. The efficacy of Exubera is deferred to the clinical reviewer from the Division of Endocrine and Metabolic Products, Dr. Karen Mahoney.

7 Integrated Review of Pulmonary Safety

7.1 Methods and Findings

Patient exposure

The number of subjects exposed to Exubera and the duration of exposure to Exubera are reasonable to assess the pulmonary safety in subjects without underlying lung disease. The Applicant determined the duration of exposure to study medication based upon subject month of exposure. The duration of exposure for the controlled phase 2 and 3 studies was calculated as the cumulative duration of treatment, excluding days during which study drug was not used. As shown below in Table 9, 214 subjects with type 1 diabetes and 375 subjects with type 2 diabetes were exposed to Exubera for greater than 12 months.

Table 9 Duration of Exposure to Study Medication Adult Subjects in Controlled Phase 2 and 3 Studies n (%)

	Number (%) of subjects*				
	Type 1		Type 2		
Exposure (months)	INH N=698	SC N=705	INH N=1277	SC N=488	OA N=644
>0-3	159 (22.8)	165 (23.4)	365 (28.6)	45 (9.2)	209 (32.5)
>3-6	264 (37.8)	249 (35.3)	288 (22.6)	141 (28.9)	137 (21.3)
>6-12	61 (8.7)	64 (9.1)	249 (19.5)	121 (24.8)	99 (15.4)
>12-18	158 (22.6)	169 (24.0)	183 (14.3)	148 (30.3)	48 (7.5)
>18-24	56 (8.0)	58 (8.2)	136 (10.6)	33 (6.8)	107 (16.6)
>24-30	0	0	56 (4.4)	0	44 (6.8)
Median exposure	5.59	5.65	5.88	9.71	5.60
Overall exposure (subjects-months)	5894	6052	12187	4868	6453

*The numbers are not cumulative. Subjects are counted only in their final treatment duration category
Source: N21868/N_000/2004-12-27/clinstat/summary-clin-safety.pdf, pg 136-137

Reviewer's Comment: The above table is based upon the original NDA submission. Due to additional information submitted during the review period, the number of subjects with exposure >12 months is greater than what is shown above.

Reviewer's Comment: If the uncontrolled extension studies are included in the patient exposure analysis, there are over 200 type 1 subjects and 500 type 2 subjects exposed to Exubera for more than 2 years. However, the data from the extension studies is difficult to interpret due to the uncontrolled nature of the studies.

Reviewer's Comment: An exposure analysis based upon the dose of insulin received is also clinically meaningful since the dose of insulin varied from subject to subject. The Biometrics reviewer analyzed the change in pulmonary function tests by total daily insulin dose and total cumulative insulin dose as an exploratory analysis. Refer to Section 7.1.6.7 for details of the exploratory analysis.

Safety Evaluations Performed

The Applicant's monitoring for pulmonary safety in the controlled phase 2 and 3 studies was reasonable. Safety monitoring in the controlled phase 2 and 3 studies pertinent to the pulmonary safety database included adverse events, CXRs, and pulmonary function tests. In a subset of subjects in studies 106, 107, 108, and 1029, HRCTs were also performed.

Observed or volunteered adverse events reported during the study treatment period or within 1 day of the end of treatment were recorded by the investigator on the CRF regardless of treatment group or suspected causal relationship to study drug. In most studies, CXRs were performed at screening and at the end of the study. CXR were performed and read locally at radiology departments available to the clinical sites. There were no specific measures to blind the radiologist to the treatment group. In the subset of subjects who underwent HRCT evaluation, HRCT was performed at baseline and end of study. In study 1029, HRCTs were performed at baseline, 12 months, and 24 months. Study 1029 is currently ongoing. In the subset of subjects who underwent HRCTs, the

HRCT scans were performed at local sites using a standardized algorithm and subsequently interpreted at a central reading site by a third party radiologist blinded to the treatment group.
Reviewer's Comment: During the September 8, 2005, Endocrine and Metabolic Advisory Committee Meeting, the Applicant stated that the radiologist who interpreted the HRCT scans was blinded to treatment group, but not blinded to time.

Pulmonary function tests were performed at baseline and at different time points during each individual study and at the end of each individual study. Usually, full pulmonary function tests were performed (spirometry, lung volumes, and DLCO). However, at some visits, only spirometry was obtained. PFTs were performed in the fasting state prior to dosing of study medication. In some studies, PFTs were performed pre and post insulin dose. In addition, in Studies 1028 and 1030, PFTs were performed pre and post-bronchodilator. All pulmonary function tests were performed according to ATS standards. In addition, more recent studies (1022, 1026, 1027, and 1029) utilized standard PFT equipment and centralized data analyses.

Subjects who were noted to have the following underwent further clinical evaluation: a >15% decline in FEV_1, DLCO, TLC, and or FVC; significant change in CXR or HRCT; new onset and persistent signs or symptoms of respiratory disease.

The Applicant further characterized cough AEs through the use of a cough questionnaire in Studies 1022, 1027, and 1029. In those studies, the cough questionnaire was administered to subjects who experienced cough, which was not explained by a concomitant condition. The cough questionnaire consisted of 6 questions assessing the following:

- Cough frequency at night
- Cough frequency throughout the day
- Cough severity throughout the day
- Cough timing related to short-acting insulin dosing
- Cough severity related to insulin dosing
- Sputum production.

The answers range from 0 to 4 for each question. Zero meaning none/never and 4 meaning almost constant/severe.
Reviewer's Comment: Several issues are worth noting about the Cough Questionnaire. First of all, the Cough Questionnaire was not administered to all subjects with cough AEs, but was administered to subjects with cough AEs not attributable to another condition. Allowing the investigator to determine if the cough was attributable to another condition is not ideal in this open label study. Ideally, the Applicant would have administered the cough questionnaire to every subject with report of a cough AE. Second, the cough questionnaire is confusing for some of the questions in which a grade 0 means no cough or unaware of cough. So a subject can report a cough AE, but respond no cough or unaware of cough for certain questions. Finally, the question of cough severity related to insulin dosing depends upon if the subject noted a relationship of cough to insulin dosing.

The Applicant also further characterized dyspnea through the use of the Mahler Dyspnea Indices in Studies 1022, 1027, and 1029. Dr. Mahler and colleagues developed the Baseline Dyspnea Index (BDI) and Transition Dyspnea Index (TDI) in 1984.[1] The Mahler Dyspnea Indices include the following components:

- Functional Impairment
  - Are there activities which make the patient breathless?
- Magnitude of Task
  - What types of activities make the patient breathless?
- Magnitude of Effort
  - What amount of effort makes the patient breathless?

Each component has one item and the focal TDI or BDI score is the sum of the three items. The Baseline Dyspnea Index is measured first to establish a baseline, whereas the TDI measures changes over time in the three components compared to the baseline state. At return visits, for the TDI the interviewer again asks a series of open-ended questions regarding changes in the three components from baseline: functional impairment, magnitude of effort, and magnitude of task. The interviewer selects a score, which is based on a -3 to +3 scale for the change in each component, as shown below:

- -3 Major Deterioration
- -2 Moderate Deterioration
- -1 Minor Deterioration
- 0 No change
- +1 Minor Improvement
- +2 Moderate Improvement
- +3 Major Improvement

The three scores are summed to determine the TDI Focal Score on a scale of -9 to +9.

All subjects were administered the Baseline Dyspnea Index at screening. The TDI was administered during studies 1022, 1027, and 1029.

7.1.1 Deaths

There were no respiratory deaths in the controlled phase 2/phase 3 studies. No respiratory deaths have been reported at the time of this review in the ongoing phase 3 studies (1022, 1028, 1029, and 1030).

7.1.2 Serious Adverse Events (SAEs) - Respiratory

7.1.2.1 Methods

A serious adverse event is defined as any event that results in any of the following:

- a life-threatening adverse event
- hospitalization or prolongation of existing hospitalization
- persistent or significant disability or incapacity

[1] Mahler DA, Weinberg DH, et. al. The measurement of dyspnea : contents, interobserver agreement, and physiologic correlates of two new clinical indexes. *Chest* 1984; June, 85(6): 751-8.

- congenital anomaly/birth defect.

Investigators could also consider other adverse events to be SAEs based upon clinical judgment if medical or surgical intervention was necessary to prevent an outcome listed above.

For the individual studies, the Applicant utilized COSTART preferred terms to classify the adverse events. However, for the integrated summary of safety, the Applicant utilized MedDRA to organize the SAEs by organ class/preferred term, thus the SAEs will be presented using the MedDRA preferred terms. Of note, the COSTART preferred terms for the Respiratory system include terms such as bronchitis, pneumonia, and lung carcinoma; however, using the MedDRA system, these AEs are classified under Infections and Infestations and Neoplasms. Although classified in a different section using MedDRA, these AEs are relevant to the pulmonary safety analyses for Exubera and therefore, will be included in the discussion of SAEs. Several cases of lung neoplasm were noted in the Applicant's controlled clinical studies. These cases will be discussed in greater detail in Section 7.1.5.1.

In the controlled phase 2 and 3 studies, there were more respiratory SAEs in the Exubera group than in the comparator groups. Interestingly, there were no respiratory SAEs in the completed studies in subjects with type 1 diabetes. In type 2 diabetes, asthma and bronchitis SAEs were reported in more than one subject in the Exubera group and were more common in the Exubera group than the comparator group. Table 10 displays a summary of pulmonary SAEs in the adult controlled phase 2 and 3 studies in type 2 diabetes.

Table 10 Summary of Preferred Terms for All-Causality Respiratory SAEs in Adult Controlled Phase 2 and 3 Studies (Type 2 Diabetes)

Number of events	Exubera n=1277	SC Insulin n=488	Oral Agents n=644
Respiratory SAEs	18	8	4
Asthma	3	0	0
Bronchial carcinoma, metastatic	1	0	0
Bronchitis	2	0	0
Bronchitis acute	1	0	0
Bronchopneumonia	1	0	0
Bronchospasm	1	0	0
Cough	1	0	0
Dyspnea	1	2	2
Epistaxis	1	0	0
Hypoxia	0	1	0
Lung adenocarcinoma	1	0	0
Lung neoplasm malignant	0	0	1
Pneumocystis carinii pneumonia	0	0	1
Pneumonia	2	3	0
Pneumothorax	1	1	0
Respiratory distress	0	1	0
Respiratory failure	1	0	0
Vocal cord polyp	1	0	0

Source: [N21868/N_000/2004-12-27/summary-clin-safety.pdf, pg 56-63, 1868, 1870-1872]

Reviewer's Comment: When this reviewer pooled the pulmonary SAEs from the individual studies, there were some discrepancies with the Applicant's All-Causality Respiratory SAEs among Subjects with Type 2 Diabetes in the Controlled Phase 2 and 3 Studies in the Exubera Pulmonary Safety (pg 25). The majority of the discrepancies were due to the change to the MedRA preferred terms. Some of the respiratory SAEs using COSTART were noted under Infections and Infestations and Neoplasms using MedRA. In addition, the Applicant's pooled SAE table includes information from interim data from the ongoing studies, which may have not been reported in the individual study reports. For example, the pooled data includes a subject with hypoxia and a subject with a pneumothorax from Study 1029. No subjects with hypoxia or pneumothorax were listed or discussed in the study report for Study 1029 submitted in the original NDA. These SAEs were noted after the interim safety report for Study 1029.

For the respiratory SAEs, which were only noted in type 2 diabetics, the SAEs in the Respiratory, Thoracic, and Mediastinal Disorder and certain Infections and Infestations SAEs and Neoplasm SAEs were reviewed as shown in the following table.

Source System Organ Class SAEs			
System Organ Class	***Exubera***	***SC Insulin***	***Oral Agents***
Respiratory, Thoracic, and Mediastinal Disorders	*10*	*5*	*2*
Infections and Infestations (bronchitis, bronchopneumonia, pneumonia, pneumocystis carinii pneumonia)	*6*	*3*	*1*
Neoplasms – Lung adenocarcinoma, lung neoplasm malignant, metastatic bronchial carcinoma	*2*	*0*	*1*
Total	*18*	*8*	*4*

Source: [N21868/N_000/2004-12-27/summary-clin-safety.pdf, pg 1868, 1870-1872]

Reviewer's Comment: There were two additional cases of lung neoplasm, one benign (hamartoma) and one malignant (squamous cell carcinoma) noted in the Applicant's clinical studies. However, these cases occurred in Study 111, which was an uncontrolled extension study, and thus, are not included in the above table.

In the safety update submitted April 26, 2005, there were two SAEs – pneumonitis (SC insulin) and mycobacterium avium complex (Exubera) reported in ongoing Study 1022. These SAEs are the only respiratory SAEs reported in subjects with type 1 diabetes.

Using the All Phase 2 and 3 dataset, which included the uncontrolled studies, the following additional SAEs were reported: lung disorder, pulmonary edema, respiratory distress, atelectasis, dyspnea, pleural effusion, pulmonary embolism, and pulmonary edema. Of note was the number of pneumonia SAEs. Using the All Phase 2 and 3 studies, 9 pneumonia SAEs were reported in the Exubera group compared to 4 pneumonia SAEs in the SC insulin group. However, because these SAEs were from uncontrolled extension studies with Exubera, it is difficult to draw any conclusions from the reports [N21868/N_000/2004-12-27/summary-clin-safety.pdf, 1882, 1891, 1897].

7.1.3 Dropouts and Other Significant Adverse Events

More subjects discontinued due to any AE in the Exubera group than in the comparator group. More subjects discontinued due to respiratory AEs in the Exubera group than in the comparator groups as shown in Table 11.

Table 11 Number of Subjects Discontinuing Due to AEs in Adult Controlled Phase 2 and 3 Studies

	Type 1		Type 2		
	Exubera n=698	SC Insulin n=705	Exubera n=1277	SC Insulin n=488	Oral Agents n=644
Subjects discontinued due to any AE	22	6	46	6	21
Subjects discontinued due to respiratory AE	11	0	28	0	2

Source: N21868/N_000/2004-12-27/summary-clin-safety.pdf, pg 2365, 2366, 2380, 2383

Cough was the most common respiratory AE leading to discontinuation in subjects with type 1 or type 2 diabetes. Seven subjects with type 1 diabetes discontinued due to cough and 13 subjects with type 2 diabetes discontinued due to cough in the Exubera group. No subjects in the comparator groups discontinued due to cough adverse events. In subjects

with type 2 diabetes, asthma (7) and dyspnea (5) were the next most common AEs leading to discontinuation. Table 12 displays a summary of discontinuations due to respiratory adverse events.

Table 12 Summary of Respiratory Adverse Events Resulting in Discontinuation in Adult Controlled Phase 2 and 3 Studies

	Type 1		Type 2		
	Exubera n=698	SC Insulin n=705	Exubera n=1277	SC Insulin n=488	Oral Agents n=644
Number of subjects discontinuing due to adverse events	22	6	46	6	21
Number of subjects discontinuing due to respiratory adverse events	11	0	28	0	2
Asthma	1	0	7	0	0
Bronchitis	0	0	3	0	0
Carcinoma of lung	0	0	1	0	1
Cough increased	7	0	13	0	0
Dyspnea	3	0	5	0	1
Laryngitis	1	0	0	0	0
Pharyngitis	2	0	1	0	0
Respiratory disorder	2	0	2	0	0
Respiratory tract infection	1	0	3	0	0
Sinusitis	1	0	0	0	0
Sputum increased	1	0	1	0	0

Source: [N21868/N_000/2004-12-27/summary-clin-safety.pdf, pg 2365-2366, 2380, 2382-2383]

Reviewer's Comment: For a more detailed listing of the respiratory adverse events leading to discontinuation, refer to Table 67 and Table 68 in Section 10.1.

In addition to permanent discontinuations due to respiratory AEs, there were more temporary discontinuations of therapy due to respiratory AEs in the Exubera group, than in the SC insulin group.

7.1.4 Common Respiratory Adverse Events

The Applicant utilized preferred COSTART terms to code AEs. The data was presented by body system, preferred COSTART term, and severity. The combined data for type 1 and type 2 diabetics indicates that asthma, bronchitis, increased cough, dyspnea, epistaxis, laryngitis, lung disorder, pharyngitis, respiratory disorder, respiratory tract infection, rhinitis, sinusitis, sputum increased, and voice alteration were reported in more than one subject and were more common in the Exubera group than in the comparator group as shown below in Table 13.

Table 13 All Causality Respiratory Adverse Events in Adult Controlled Phase 2 and 3 Studies – Combined Type 1 and Type 2 Diabetes

Number of subjects (%)	Exubera n=1975	Comparator n=1837
Any Respiratory Adverse Events	**1254 (63.5)**	**926 (50.4)**
Apnea	1 (0.05)	0
Asthma	**32 (1.6)**	**19 (1.0)**
Atelectasis	0	1 (0.05)
Bronchiectasis	0	1 (0.05)
Bronchiolitis	1 (0.05)	0
Bronchitis	**81 (4.1)**	**70 (3.8)**
Carcinoma of lung	1 (0.05)	1 (0.05)
Cough increased	**464 (23.5)**	**119 (6.5)**
Dyspnea	**69 (3.5)**	**22 (1.2)**
Edema pharynx	1 (0.05)	2 (0.1)
Emphysema	1 (0.05)	1 (0.05)
Epistaxis	**24 (1.2)**	**9 (0.5)**
Hemoptysis	1 (0.05)	0
Hyperventilation	1 (0.05)	1 (0.05)
Hypoventilation	1 (0.05)	0
Laryngitis	**15 (0.8)**	**7 (0.4)**
Lung disorder	**4 (0.2)**	**1 (0.05)**
Lung edema	1 (0.05)	2 (0.1)
Nasal polyp	1 (0.05)	1 (0.05)
Pharyngitis	**242 (12.2)**	**184 (10.0)**
Pleural disorder	1 (0.05)	1 (0.05)
Pneumonia	16 (0.8)	17 (0.9)
Respiratory disorder	**110 (5.6)**	**79 (4.3)**
Respiratory distress syndrome	0	2 (0.1)
Respiratory tract infection	**647 (32.8)**	**572 (31.1)**
Rhinitis	**199 (10.1)**	**132 (7.2)**
Sinusitis	**129 (6.5)**	**104 (5.7)**
Sputum increased	**61 (3.1)**	**15 (0.8)**
Voice alteration	**15 (0.8)**	**3 (0.2)**
Yawn	1 (0.05)	1 (0.05)

Source: [N21868/N_000/2004-12-27/pulm.pdf, pg 19]

Reviewer's Comment: Because all the clinical studies are open-label studies, assignment of causality to adverse events is subject to bias; therefore, only the all-causality adverse events are presented.

When the adverse event data is separated into adverse events in subjects with type 1 and type 2 diabetes, the data indicate that respiratory tract infection, increased cough, pharyngitis, and sinusitis were the most common respiratory AEs reported in both treatment groups. Cough was the respiratory AE reported at much greater incidence in the Exubera group than in the comparator group.

Table 14 All Causality Respiratory Adverse Events in Adult Controlled Phase 2 and 3 Studies

	Type 1		Type 2		
	Exubera n=698	**SC Insulin n=705**	**Exubera n=1277**	**SC Insulin n=488**	**Oral Agents n=644**
All Respiratory Adverse Events	**515 (73.8)**	**428 (60.5)**	**739 (57.9)**	**279 (57.2)**	**219 (34.0)**
Apnea	0	0	1 (0.1)	0	0
Asthma	7 (1.0)	8 (1.1)	25 (2.0)	8 (1.6)	3 (0.5)
Atelectasis	0	0	0	1 (0.2)	0
Bronchiectasis	0	0	0	1 (0.2)	0
Bronchiolitis	1 (0.1)	0	0	0	0
Bronchitis	20 (2.9)	27 (3.8)	61 (4.8)	17 (3.5)	26 (4.0)
Carcinoma of lung	0	0	1 (0.1)	0	1 (0.2)
Cough increased	**196 (28.1)**	**59 (8.4)**	**268 (21.0)**	**36 (7.4)**	**24 (3.7)**
Dyspnea	**27 (3.9)**	**4 (0.6)**	**42 (3.3)**	**9 (1.8)**	**9 (1.4)**
Edema pharynx	0	2 (0.3)	1 (0.1)	0	0
Emphysema	0	0	1 (0.1)	1 (0.2)	0
Epistaxis	**9 (1.3)**	**2 (0.3)**	**15 (1.2)**	**2 (0.4)**	**5 (0.8)**
Hemoptysis	0	0	1 (0.1)	0	0
Hyperventilation	1 (0.1)	1 (0.1)	0	0	0
Hypoventilation	1 (0.1)	0	0	0	0
Laryngitis	**8 (1.1)**	**3 (0.4)**	7 (0.5)	2 (0.4)	2 (0.3)
Lung disorder	0	0	4 (0.3)	1 (0.2)	0
Lung edema	0	1 (0.1)	1 (0.1)	0	1 (0.2)
Nasal polyp	1 (0.1)	1 (0.1)	0	0	0
Pharyngitis	**123 (17.6)**	**103 (14.6)**	**119 (9.3)**	**43 (8.8)**	**38 (5.9)**
Pleural disorder	1 (0.1)	0	0	1 (0.2)	0
Pneumonia	5 (0.7)	7 (1.0)	11 (0.9)	6 (1.2)	4 (0.6)
Respiratory disorder	**45 (6.4)**	**27 (3.8)**	65 (5.1)	41 (8.4)	11 (1.7)
Respiratory distress syndrome	0	1 (0.1)	0	1 (0.2)	0
Respiratory tract infection	**290 (41.5)**	**279 (39.6)**	357 (28.0)	166 (34.0)	127 (19.7)
Rhinitis	**96 (13.8)**	**67 (9.5)**	103 (8.1)	46 (9.4)	19 (3.0)
Sinusitis	**64 (9.2)**	**48 (6.8)**	65 (5.1)	41 (8.4)	15 (2.3)
Sputum increased	**27 (3.9)**	**8 (1.1)**	**34 (2.7)**	**4 (0.8)**	**3 (0.5)**
Voice alteration	1 (0.1)	1 (0.1)	**15 (1.2)**	**0**	**2 (0.3)**
Yawn	1 (0.1)	1 (0.1)	0	0	0

Source: [N21868/N_000/2004-12-27/pulm.pdf, pg 19]

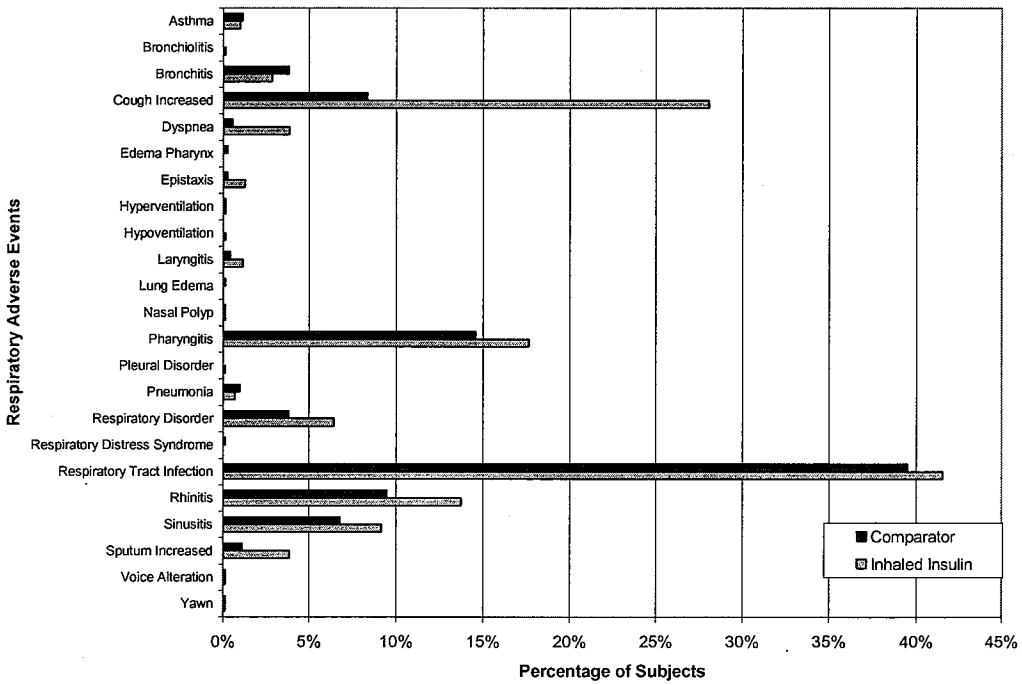
Increased cough, dyspnea, epistaxis, laryngitis, pharyngitis, respiratory disorder, respiratory tract infection, rhinitis, sinusitis, and sputum increased were more common in the Exubera group than in the SC insulin group in subjects with type 1 diabetes. In subjects with type 2 diabetes increased cough, dyspnea, epistaxis, pharyngitis, sputum increased, and voice alteration were more common in the Exubera group than the comparator.

In type 1 diabetes, an imbalance in respiratory disorder AEs was noted between the Exubera group and the SC insulin group. In a Request for Information dated September 13, 2005, the Applicant was asked to provide a list of investigator terms linked to respiratory disorder. In a Response dated September 21, 2005, the Applicant provided the list of investigator terms linked to respiratory disorder. Common terms linked to respiratory disorder included the following: chest congestion, sinus congestion, sinus

drainage, and upper respiratory congestion. Of these, chest congestion appeared to be contributing to the imbalance. Some investigator reports related to a decline in pulmonary function were noted only in the inhaled insulin treatment group. If the terms related to a decline in pulmonary function were combined for type 1 diabetes(7 Exubera, 0 SC insulin), these terms could also have potentially contributed to the imbalance in respiratory disorder between treatment group [N21868/N_000/2005-09-21/13sep05_clin_responses.pdf, pg 55-58].

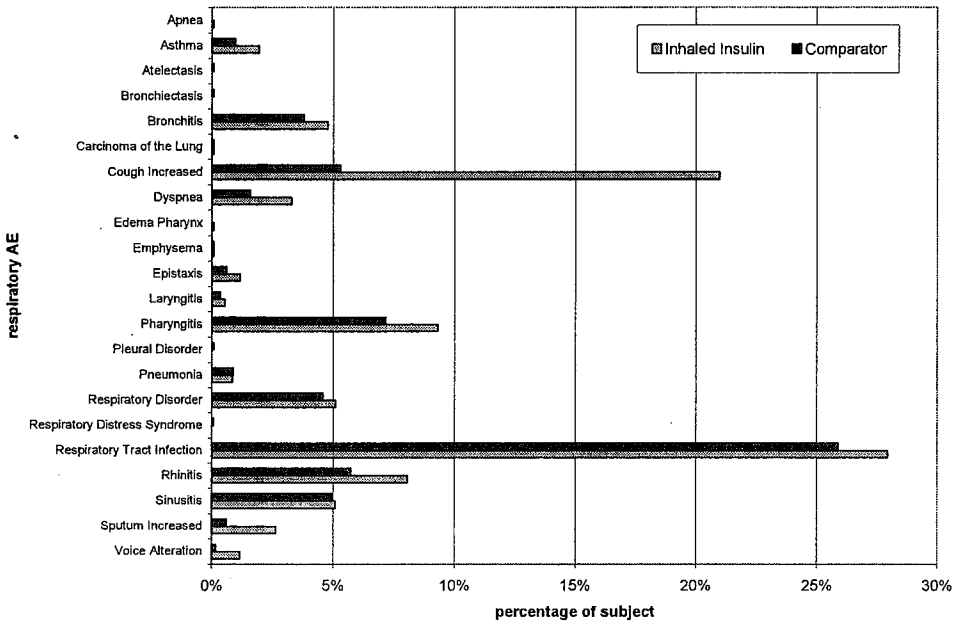
The following figures display the respiratory adverse events by treatment group in the controlled phase 2 and 3 studies in type 1 diabetes and type 2 diabetes, respectively.

Figure 7 Respiratory Adverse Events by Treatment Group in the Controlled Phase 2 and 3 Studies in Type 1 Diabetes, Adults



Source: Dr. Joan Buenconsejo's Biometrics Review

Figure 8 Respiratory Adverse Events by Treatment Group in the Controlled Phase 2 and 3 Studies in Type 2 Diabetes, Adults



Source: Dr. Joan Buenconsejo's Biometrics Review

Reviewer's Comment: In an information request dated September 13, 2005, the Applicant was asked to provide the investigator terms coded to respiratory disorder by treatment group for type 1 and type 2 diabetes. In a response dated September 21, 2005, the Applicant provided the requested data. The most common investigator terms coded to respiratory disorder were chest congestion and sinus congestion [N21868/N_000/2005-09-21/13sep05_clin_responses.pdf, pg. 55-58].

7.1.4.1 Identifying common and drug-related adverse events

Cough

Cough is the respiratory adverse event, which was much more common in the Exubera treatment group compared to the comparator groups. Because cough was a common respiratory adverse event in the Exubera group, the Applicant attempted to further assess the cough adverse events. In the earlier phase 2 and 3 studies, the Applicant collected information regarding cough severity, incidence, prevalence, and duration.

In the controlled phase 2 and 3 adult studies with the type 1 and type 2 data combined, approximately 85% of the cough AEs were graded as mild, 13-16% were graded as moderate and 1-2% were graded as severe. Although there were more cough AEs in the Exubera group, there was no significant difference in the severity of cough between the Exubera group and comparator groups. The data on incidence and prevalence of cough suggested that cough incidence (onset of cough in each time interval) and prevalence (presence of cough in each interval) were more common in the first 3 months of Exubera exposure. The mean duration of cough (number of weeks from reported onset of each event to the reported end of each event) was longer in the Exubera group than in the

comparator group by approximately 2 weeks as shown below in Table 15. The increase in cough duration appears to be primarily driven by the presence of more cough events of duration greater than 8 weeks in the Exubera group [N21868/N_000/2004-12-27/pulm.pdf, pg 20. 100-107].

Table 15 Duration of Cough During the First 6 Months of Exposure in the Adult Controlled Phase 2 and 3 Studies

Treatment Group	# subjects reporting cough event	Total number of events	Duration -weeks mean, (SD)	Duration -weeks median
Type 1 Exubera	179	232	5.36 (8.09)	2.29
Type 1 Comparator	49	54	3.37 (4.13)	1.93
Type 2 Exubera	215	259	7.70 (11.85)	3.00
Type 2 Comparator	42	45	5.08 (9.15)	2.29

Source: [N21868/N_000/2004-12-27/pulm.pdf, pg 104-105]

In studies 1022, 1027, and 1029, the Applicant utilized a cough questionnaire, which consisted of 6 questions assessing the following:

- Cough frequency at night
- Cough frequency throughout the day
- Cough severity throughout the day
- Cough timing related to short-acting insulin dosing
- Cough severity related to insulin dosing
- Sputum production.

The answers range from 0 to 4 for each question. Zero meaning none/never and 4 meaning almost constant/severe. The cough questionnaire was administered to subjects who experienced cough, which was not explained by a concomitant condition.
Reviewer's Comment: In this reviewer's opinion, the cough questionnaire provides more information regarding cough adverse events, than the data from the earlier phase 2 and 3 studies.

The cough questionnaire data from the three individual studies that specified the use of the cough questionnaire were reviewed. The cough questionnaire data suggested that for most subjects cough was rare or occasional during the day and rare or absent at night. As with the other cough data, for most subjects the severity of cough events was primarily mild. In general, the cough was not productive. Finally, a majority of subjects reported the timing of the cough event within seconds to minutes after Exubera dosing; however, some subjects did report no relationship between cough and dosing.

Although the majority of cough adverse events were mild in severity, cough adverse events led to discontinuation in 20 subjects in the Exubera group and no subjects in the comparator group. Twelve of the 20 subjects, who discontinued Exubera due to cough, discontinued in the first 2 months of the study [N21868/N_000/2004-12-27/pulm.pdf, pg 20. 100-101].