shorter for pregnant inhaled insulin patients in this study (210 minutes) than for nonpregnant Type 2 diabetics receiving inhaled insulin in Study 1004, where the time to maximum decline in glucose was 248 minutes. The maximum decline in glucose concentration was less in these pregnant diabetics exposed to inhaled insulin than it was in nonpregnant Type 2 diabetics in study 1004, but significant differences in baseline glucose levels and patient age limit the interpretability of this observation.

Clinically apparent spontaneous abortions occur in insulin-requiring diabetic women at a rate roughly twice that of the normal population of pregnant women (29.5% vs 10-15%) (Miodovnik 1988). In the Exubera® development program, 4/10 women who became pregnant while taking inhaled insulin had a spontaneous abortion. In Studies 106 and 107, mean end-of-study insulin binding activity (which reflects insulin antibody levels) for Type 1 nonpregnant diabetic women was 32.6% binding (SD 22.46) for the semiquantitative Mayo assay, and 435.0 μU/mL (SD 1194.2) for the quantitative Esoterix® assay. None of the women in the development program who had adverse pregnancy outcomes had known insulin binding activity higher than these means.

The information obtained about human reproductive risk of Exubera® is not substantial enough at this time to conclude that Exubera® can cause fetal harm, and thus Pregnancy Categories D or X are not warranted. The clinical reviewer concurs with assignment of Pregnancy Category C for Exubera®.

Pharmacokinetic studies of inhaled insulin in hepatic and renal impairment were not submitted by the applicant.

Some data were submitted to characterize the use of inhaled insulin in COPD patients. Study 1005 compared inhaled insulin PK between healthy patients and those with COPD. Following administration of 3 mg of inhaled insulin, Cmax was greater (by up to 50%) in COPD patients than in healthy subjects. Tmax occurred 25-50 minutes earlier in COPD patients compared to normal subjects. Overall insulin exposure (AUC_{0-360}) was greater in COPD patients than in healthy subjects (by approximately 15%). Bioavailability of inhaled insulin was 11% in healthy controls compared to 23-25% in COPD patients.

As of 1 Sep 04, four patients with COPD had died; one of these was taking inhaled insulin and died of metastatic colon cancer. No asthma patients had died as of 1 Sep 04.

Hypoglycemia event rates did not differ between underlying lung disease patients (with COPD or asthma), and those without these disorders, for either inhaled insulin or comparator patients. Patients with either asthma or COPD who were taking inhaled insulin appeared to experience asthenia more frequently than comparator patients (with or without underlying lung disease), and more frequently than inhaled insulin patients without underlying lung disease. Otherwise, the small number of each type of event within the underlying lung disease groups precludes meaningful conclusions regarding other types of events.

Declines in FEV1 and DLco occurred more frequently among inhaled insulin patients than among control patients in the controlled Phase 2/3 population, and are further discussed in Dr. Seymour's pulmonary review. The clinical reviewer examined nonpulmonary adverse events in those patients who had significant declines in PFTs, defined as declines from baseline to last observation of ≥15% in FEV1, TLC or FVC, and/or ≥20% decline in DLco. Hypoglycemia rates (by study definition of requirement for assistance, or value <36 mg/dL) were similar between patients who had significant PFT declines and those who did not, for both inhaled insulin and comparator patients. Hypoglycemia rates among patients who had declines in PFTs were similar between inhaled insulin and comparator patients. Reported adverse events of hypoglycemia occurred more commonly in inhaled insulin patients who had significant declines in PFTs than in comparator patients who had significant declines in PFTs [154/218 (70.6%) vs 86/154 (55.8%)], but at an equal rate to that seen in comparator patients who did not have significant declines in PFTs (1069/1512, 70.7%). Total cardiovascular events occurred at a higher rate in inhaled insulin patients who had a significant decline in PFTs (45/218, 20.6%) than in comparator patients who had a significant decline in PFTs (26/154, 16.9%) and comparator patients who did not have a significant decline in PFTs (202/1512, 13.4%). No single cardiovascular event occurred at a significantly higher rate among inhaled insulin patients who had significant declines in PFTs.

Tobacco smoking within six months prior to randomization was an exclusion criterion for Phase 2/3 studies. In clinical pharmacology studies (005, 016, 1003, 1020), inhaled insulin pharmacokinetics and pharmacodynamics were significantly different in smokers. In nondiabetic and Type 2 diabetic smokers, Cmax, Tmax and AUC of inhaled insulin was 2-5 fold higher than that of nonsmokers. Smoking cessation led to a decline in insulin exposure within 3 days of abstinence, with further attenuation over time; by 7 days, insulin exposure was near that seen in nonsmokers. Resumption of smoking after abstinence resulted, within 2-3 days, in increased exposure similar to that seen prior to smoking cessation. The applicant is concerned about these findings, and considers the potential for rapid changes in systemic insulin exposure to be a prohibitive risk associated with cigarette smoking. The applicant recommends that patients should abstain from smoking for at least 6 months before inhaled insulin treatment, and should remain abstinent during inhaled insulin treatment. However, in order to reduce the likelihood that smokers will use inhaled insulin, specific education of patients and providers may be needed, with enhanced emphasis on the risk. Physicians may overlook the smoking statement in a long product label, and patients sometimes do not share their smoking history with their physicians.

Animal carcinogenicity and reproductive toxicity studies were not performed. The lack of carcinogenicity data is a potential concern; insulin is a growth factor, and inhaled insulin appears to be a clinical lung irritant. Although no difference was noted between inhaled insulin and comparator groups for the incidence of lung carcinoma, the duration of study was shorter than the usual duration of time needed from an initial lung insult to the development of a malignancy. However, Dr. Alavi, the animal toxicology reviewer, states that it is unlikely that animal carcinogenicity studies would have resolved questions regarding human carcinogenic potential, due to problems administering the drug chronically via inhalation to rodents, and due to a potential nonrelevant tumorigenic response in rodents, which have insulin receptors in the lung.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

The applicant pooled safety data from Phase 2 and Phase 3 studies for safety analyses, with separate analyses for Type 1 and Type 2 patients. Exclusion criteria were similar across studies. Relative rates of severe hypoglycemia were similar across studies. Pooling of safety data, with separation into Type 1 and Type 2 diabetic groups, appears to have been appropriate.

7.4.1.2 Combining data

Because inhaled insulin exposure was much greater than that for comparators for the "All Phase 2/3" population, the clinical reviewer compared rates of events using patient-month exposure data when possible.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

Among inhaled insulin patients in all Phase 2/3 studies, most adverse events in general did not appear to be dose-dependent. Among Type 1 diabetics, increased sputum production may be dose-related. When one examines the overall incidence of accidents and fractures, these events occurred at a higher numerical rate in patients on higher doses. This is of concern, because of a possible relationship to hypoglycemia. However, the applicant did specifically examine all cases of serious accidents and injuries for possible relationship to hypoglycemia, and no difference between treatment groups was noted.

Table 7.4.2.1.1 Adverse Events by Daily Inhaled Insulin Dose at Time of Onset of Adverse Event, Adult Type 1 Patients, All Phase 2/3 Studies

	Inh Ins Dose (mg)		
	<10 # (%) of Patients with Event	10-15 # (%) of Patients with Event	>15 # (%) of Patients with Event
Respiratory (all events)	389 (58.7)	353 (53.8)	242 (55.3)
Cough	135 (20.4)	107 (16.3)	84 (19.2)
Respiratory disorder	39 (5.9)	35 (5.3)	29 (6.6)
Dyspnea	22 (3.3)	11 (1.7)	12 (2.7)
Asthma	7 (1.1)	7 (1.1)	7 (1.6)
Bronchitis	19 (2.9)	30 (4.6)	6 (1.4)
Pneumonia	5 (0.8)	5 (0.8)	6 (1.4)
Respiratory tract infection	209 (31.5)	215 (32.8)	151 (34.5)
Rhinitis	72 (10.9)	58 (8.8)	57 (13.0)

Table 7.4.2.1.1 Adverse Events by Daily Inhaled Insulin Dose at Time of Onset of Adverse Event, Adult Type 1 Patients, All Phase 2/3 Studies

	Inh Ins Dose (mg)		
	<10 # (%) of Patients with Event	**10-15 # (%) of Patients with Event**	**>15 # (%) of Patients with Event**
Sinusitis	47 (7.1)	30 (4.6)	39 (8.9)
Sputum increased	7 (1.1)	18 (2.7)	12 (2.7)
Chest pain	24 (3.6)	11 (1.7)	9 (2.1)
Dry mouth	9 (1.4)	8 (1.2)	6 (1.4)
Epistaxis	6 (0.9)	4 (0.6)	2 (0.5)
Accidental injury	61 (9.2)	63 (9.6)	46 (10.5)
Motor vehicle accident	1 (0.2)	2 (0.3)	0
Bone fracture accidental	18 (2.7)	17 (2.6)	21 (4.8)
Pathological fracture	0	0	1 (0.2)
Leukopenia	2 (0.3)	1 (0.2)	3 (0.7)
Convulsion	2 (0.3)	4 (0.6)	6 (1.4)
Grand mal convulsion	1 (0.2)	0	1 (0.2)
Coma	1 (0.2)	1 (0.2)	0
Diabetic coma	0	1 (0.2)	0
Hypoglycemia (reported as AE)	617 (93.1)	604 (92.1)	395 (90.2)
Hyperglycemia	7 (1.1)	5 (0.8)	4 (0.9)
Breast carcinoma	2 (0.3)	0	0

Source: Applicant's Table 4.2.4.1.1, Section 2.7.4

Among Type 2 diabetics, the incidence of dyspnea appeared to be dose-related. Several respiratory events occurred with lower frequency in patients who were taking <10 mg/day of inhaled insulin than in those taking ≥ 10 mg/day, but with roughly equal frequency between patients taking 10-20 mg/day and those taking >20 mg/day. These events included total respiratory events, bronchitis, respiratory tract infection, and rhinitis. The overall incidence of cardiovascular events appeared to be dose-related, although no one type of event predominated. Accidental injury and fracture also appear to be dose-related, which is concerning for a possible relationship to hypoglycemia. However, there was no difference between treatment groups or dose groups for the percentage of hypoglycemic events that were associated with injury. Retinal disorders appear to be dose-related. The overall incidence of malignant neoplasms does not appear to be dose-related, nor does the incidence of any single malignancy.

While the possible dose-relatedness of these events is concerning, these findings must be interpreted with caution. As Type 2 diabetes progresses, beta cell failure occurs with progressive loss of endogenous insulin secretion and increasing requirement for drug therapy, and eventually for increasing insulin requirement. A higher insulin requirement may be a reflection of duration of disease, which is in turn associated with aging; either duration of disease or aging could be associated with an increased incidence of many adverse events.

Table 7.4.2.1.2 Adverse Events by Daily Inhaled Insulin Dose at Time of Onset of Adverse Event, Type 2 Patients, All Phase 2/3 Studies

	Inh Ins Dose (mg)		
	<10 # (%) of Patients with Event	**10-20 # (%) of Patients with Event**	**>20 # (%) of Patients with Event**
Respiratory (all events)	400 (38.4)	676 (53.6)	333 (51.7)
Cough	132 (12.7)	213 (16.9)	96 (14.9)
Respiratory disorder	43 (4.1)	72 (5.7)	46 (7.1)
Dyspnea	23 (2.2)	45 (3.6)	36 (5.6)
Asthma	14 (1.3)	33 (2.6)	13 (2.0)
Bronchitis	30 (2.9)	58 (4.6)	32 (5.0)
Lung fibrosis	0	0	1 (0.2)
Pneumonia	8 (1.6)	20 (1.6)	10 (1.6)
Respiratory tract infection	214 (20.5)	375 (29.8)	203 (31.5)
Rhinitis	50 (4.8)	107 (8.5)	50 (7.8)
Sinusitis	43 (4.1)	82 (6.5)	44 (6.8)
Sputum increased	16 (1.5)	29 (2.3)	14 (2.2)
Cardiovascular (all events)	143 (13.7)	221 (17.6)	129 (20.0)
Chest pain	36 (3.5)	55 (4.4)	31 (4.8)
Dry mouth	15 (1.4)	19 (1.5)	3 (0.5)
Accidental fall	3 (0.3)	3 (0.2)	1 (0.2)
Accidental injury	67 (6.4)	110 (8.7)	76 (11.8)
Motor vehicle accident	0	2 (0.2)	0
Bone fracture accidental	11 (1.1)	25 (2.0)	18 (2.8)
Pathological fracture	0	1 (0.1)	1 (0.2)
Leukopenia	0	1 (0.1)	0
Convulsion	1 (0.1)	1 (0.1)	9 (1.4)
Hypoglycemia (reported as AE)	474 (45.4)	694 (55.1)	318 (49.4)
Hyperglycemia (reported as AE)	5 (0.5)	6 (0.5)	2 (0.3)
Weight gain (reported as AE)	10 (1.0)	19 (1.5)	17 (2.6)
Bladder carcinoma	0	1 (0.1)	0
Breast carcinoma	1 (0.1)	0	1 (0.2)
Endometrial carcinoma	0	1 (0.2)	0
Gastrointestinal carcinoma	1 (0.1)	1 (0.1)	0
Lung carcinoma	0	3 (0.2)	0
Lymphoma malignant	0	0	2 (0.3)
Melanoma	0	1 (0.1)	1 (0.2)
Prostate carcinoma	1 (0.2)	4 (0.5)	1 (0.2)
Renal carcinoma	0	1 (0.1)	0
Thyroid carcinoma	1 (0.1)	0	0
Eye hemorrhage	5 (0.5)	11 (0.9)	6 (0.9)
Retinal hemorrhage	2 (0.2)	6 (0.5)	3 (0.5)
Retinal detachment	1 (0.1)	0	0
Retinal disorder	23 (2.2)	49 (3.9)	28 (4.3)

Source: Applicant's Table 4.2.4.1.2, Section 2.7.4

7.4.2.2 Explorations for time dependency for adverse findings

Among Type 1 patients, for respiratory events in general, and for some specific respiratory events (cough, respiratory tract infection, rhinitis, sputum increased, epistaxis), the time interval in which these adverse events were more likely to be reported (per patient) was during the first 6 months of inhaled insulin treatment. Decreased reporting of these events in subsequent treatment time intervals could be due to a true decrease in the occurrence of the event, to dropout due to the

event, or to nonreporting by patients who felt they had already brought the event to the attention of investigators, and therefore did not report it again.

For Type 1 patients, accidental injury, motor vehicle accidents, and accidental fractures were more likely to be reported (per patient) during the time interval beyond 24 months. This could be due to a true increase in the incidence of the events, or to longer per-patient exposure during this time period.

Among Type 1 patients, hyperglycemia and hypoglycemia were more likely to be reported as adverse events (per patient) in the time interval of 0-6 months of inhaled insulin treatment. This may be due to the learning process involved in instituting a novel treatment. As with respiratory adverse events, decreased reporting of these metabolic events in subsequent treatment time intervals could either be due to a true decrease in the occurrence of the event, to dropout due to the event, or to nonreporting by patients who felt they had already brought the event to the attention of investigators, and therefore did not report it again.

For Type 1 patients, retinal disorders were more likely to be reported (per patient) during the time interval beyond 24 months. This could be due to a true increase in the incidence of the events, or to longer per-patient exposure during this time period.

Table 7.4.2.2.1 Prevalence of Adverse Events by Time Interval of Treatment, Adult Type 1 Patients, All Phase 2/3 Studies

	Interval of Treatment (months)				
	>0-6 # (%) of Patients with Event	>6-12 # (%) of Patients with Event	>12-18 # (%) of Patients with Event	>18-24 # (%) of Patients with Event	>24 # (%) of Patients with Event
Respiratory (all events)	604 (65.8)	312 (45.5)	266 (45.4)	172 (43.8)	129 (52.0)
Cough increased	215 (23.4)	56 (8.2)	46 (7.8)	41 (10.4)	34 (13.7)
Respiratory disorder	44 (4.8)	29 (4.2)	25 (4.3)	19 (4.8)	16 (6.5)
Lung disorder	0	0	1 (0.2)	1 (0.3)	1 (0.4)
Dyspnea	20 (2.2)	9 (1.3)	14 (2.4)	4 (1.0)	4 (1.6)
Asthma	6 (0.7)	7 (1.0)	9 (1.5)	5 (1.3)	4 (1.6)
Bronchitis	20 (2.2)	18 (2.6)	12 (2.0)	4 (1.0)	7 (2.8)
Pneumonia	3 (0.3)	4 (0.6)	6 (1.0)	2 (0.5)	1 (0.4)
Respiratory tract infection	324 (35.3)	163 (23.8)	154 (26.3)	82 (20.9)	76 (30.6)
Rhinitis	110 (12.0)	52 (7.6)	30 (5.1)	15 (3.8)	24 (9.7)
Sinusitis	53 (5.8)	23 (3.4)	29 (4.9)	15 (3.8)	15 (6.0)
Sputum increased	25 (2.7)	6 (0.9)	6 (1.0)	0	3 (1.2)
Epistaxis	9 (1.0)	4 (0.6)	1 (0.2)	0	2 (0.8)
Accidental injury	77 (8.4)	44 (6.4)	29 (4.9)	20 (5.1)	36 (14.5)
Motor vehicle accident	1 (0.1)	0	0	0	2 (0.8)
Bone fracture accidental	18 (2.0)	18 (2.6)	14 (2.4)	7 (1.8)	8 (3.2)
Pathological fracture	0	0	1 (0.2)	0	0
Leukopenia	0	1 (0.1)	2 (0.3)	2 (0.5)	2 (0.8)
Convulsion	1 (0.1)	6 (0.9)	2 (0.3)	2 (0.5)	1 (0.4)
Grand mal convulsion	2 (0.2)	0	0	0	0

Table 7.4.2.2.1 Prevalence of Adverse Events by Time Interval of Treatment, Adult Type 1 Patients, All Phase 2/3 Studies

	Interval of Treatment (months)				
	>0-6 # (%) of Patients with Event	>6-12 # (%) of Patients with Event	>12-18 # (%) of Patients with Event	>18-24 # (%) of Patients with Event	>24 # (%) of Patients with Event
Coma	1 (0.1)	1 (0.1)	0	0	0
Diabetic coma	1 (0.1)	0	0	0	0
Hypoglycemia (reported as AE)	889 (96.8)	618 (90.2)	521 (88.9)	345 (87.8)	220 (88.7)
Hyperglycemia (reported as AE)	12 (1.3)	2 (0.3)	0	1 (0.3)	1 (0.4)
Eye hemorrhage	5 (0.5)	1 (0.1)	4 (0.7)	1 (0.3)	2 (0.8)
Retinal detachment	0	0	0	1 (0.3)	0
Retinal disorder	9 (1.0)	5 (0.7)	6 (1.0)	5 (1.3)	6 (2.4)
Retinal hemorrhage	0	3 (0.4)	2 (0.3)	1 (0.3)	0
Breast carcinoma	1 (0.1)	1 (0.1)	0	0	0

Source: Applicant's Table 4.2.3.1.1, Section 2.7.4

Among Type 2 patients, for respiratory events in general, and for some specific respiratory events (cough, respiratory tract infection, epistaxis), the time interval in which these adverse events were more likely to be reported (per patient) was during the first 6 months of inhaled insulin treatment. Decreased reporting of these events in subsequent treatment time intervals could be due to a true decrease in the occurrence of the event, to dropout due to the event, or to nonreporting by patients who felt they had already brought the event to the attention of investigators, and therefore did not report it again.

For Type 2 patients, accidental injuries and fractures were more likely to be reported (per patient) during the time interval beyond 24 months. This could be due to a true increase in the incidence of the events, or to longer per-patient exposure during this time period.

Among Type 2 patients, hypoglycemia was more likely to be reported as an adverse event (per patient) in the time interval of 0-6 months of inhaled insulin treatment. This may be due to the learning process involved in instituting a novel treatment. As with respiratory adverse events, decreased reporting of these metabolic events in subsequent treatment time intervals could be due to a true decrease in the occurrence of the event, to dropout due to the event, or to nonreporting by patients who felt they had already brought the event to the attention of investigators, and therefore did not report it again.

No clear temporal pattern emerged among Type 2 patients for malignant neoplasms in general or for any particular neoplasm.

For Type 2 patients, retinal disorders were more likely to be reported (per patient) during the time interval beyond 24 months. This could be due to a true increase in the incidence of the events, or to longer per-patient exposure during this time period.

Table 7.4.2.2.2 Prevalence of Adverse Events by Time Interval of Treatment, Type 2 Patients, All Phase 2/3 Studies

	Interval of Treatment (months)				
	>0-6 # (%) of Patients with Event	>6-12 # (%) of Patients with Event	>12-18 # (%) of Patients with Event	>18-24 # (%) of Patients with Event	>24 # (%) of Patients with Event
Respiratory (all events)	807 (51.1)	534 (41.2)	384 (38.5)	289 (38.2)	212 (41.8)
Cough increased	265 (16.8)	117 (9.0)	77 (7.7)	59 (7.8)	43 (8.5)
Respiratory disorder	71 (4.5)	44 (3.4)	32 (3.2)	33 (4.4)	42 (8.3)
Lung disorder	1 (0.1)	1 (0.1)	2 (0.2)	1 (0.1)	2 (0.4)
Dyspnea	36 (2.3)	26 (2.0)	24 (2.4)	22 (2.9)	20 (3.9)
Asthma	24 (1.5)	16 (1.2)	15 (1.5)	13 (1.7)	11 (2.2)
Bronchitis	47 (3.0)	32 (2.5)	21 (2.1)	23 (3.0)	20 (3.9)
Lung fibrosis	0	0	1 (0.1)	0	1 (0.2)
Pneumonia	8 (0.5)	12 (0.9)	7 (0.7)	7 (0.9)	10 (2.0)
Respiratory tract infection	393 (24.9)	251 (19.4)	179 (17.9)	129 (17.0)	111 (21.9)
Rhinitis	104 (6.6)	50 (3.9)	42 (4.2)	33 (4.4)	39 (7.7)
Sinusitis	70 (4.4)	57 (4.4)	40 (4.0)	31 (4.1)	30 (5.9)
Sputum increased	30 (1.9)	21 (1.6)	13 (1.3)	3 (0.4)	8 (1.6)
Epistaxis	14 (0.9)	12 (0.9)	7 (0.7)	2 (0.3)	3 (0.6)
Cardiovascular (all events)	218 (13.8)	148 (11.4)	140 (14.0)	122 (16.1)	114 (22.5)
Angina	9 (0.6)	6 (0.5)	7 (0.7)	4 (0.5)	3 (0.6)
Chest pain	49 (3.1)	35 (2.7)	18 (1.8)	20 (2.6)	19 (3.7)
Myocardial infarction	9 (0.6)	2 (0.2)	7 (0.7)	2 (0.3)	8 (1.6)
Accidental fall	6 (0.4)	0	1 (0.1)	0	0
Accidental injury	114 (7.2)	56 (4.3)	53 (5.3)	43 (5.7)	47 (9.3)
Motor vehicle accident	1 (0.1)	0	0	1 (0.1)	0
Bone fracture accidental	21 (1.3)	18 (1.4)	14 (1.4)	9 (1.2)	13 (2.6)
Pathological fracture	1 (0.1)	1 (0.1)	0	1 (0.1)	1 (0.2)
Leukopenia	0	0	0	0	1 (0.2)
Convulsion	1 (0.1)	1 (0.1)	1 (0.1)	0	1 (0.2)
Hypoglycemia (reported as AE)	925 (58.6)	595 (45.9)	413 (41.4)	290 (38.3)	216 (42.6)
Hyperglycemia (reported as AE)	5 (0.3)	2 (0.2)	1 (0.1)	4 (0.5)	2 (0.4)
Weight gain (reported as AE)	27 (1.7)	19 (1.5)	17 (1.7)	14 (1.8)	9 (1.8)
Obesity	0	1 (0.1)	0	0	0
Bladder carcinoma	0	0	1 (0.1)	0	0
Breast carcinoma	0	2 (0.2)	0	0	0
Carcinoma	1 (0.1)	2 (0.7)	0	0	0
Endometrial carcinoma	0	0	0	1 (0.4)	0
Gastrointestinal carcinoma	0	0	1 (0.1)	2 (0.3)	0
Lung carcinoma	0	1 (0.1)	0	2 (0.3)	0
Lymphoma	0	0	0	1 (0.1)	2 (0.4)
Melanoma	0	1 (0.1)	1 (0.1)	0	0
Prostate carcinoma	1 (0.1)	1 (0.1)	1 (0.2)	2 (0.4)	2 (0.6)
Renal carcinoma	0	1 (0.1)	0	0	0
Thyroid carcinoma	1 (0.1)	0	0	0	0
Eye hemorrhage	7 (0.4)	9 (0.7)	3 (0.3)	3 (0.4)	4 (0.8)
Retinal detachment	0	1 (0.1)	0	0	0
Retinal disorder	28 (1.8)	32 (2.5)	30 (3.0)	35 (4.6)	36 (7.1)
Retinal hemorrhage	3 (0.2)	2 (0.2)	3 (0.3)	1 (0.1)	4 (0.8)

Table 7.4.2.2.2 Prevalence of Adverse Events by Time Interval of Treatment, Type 2 Patients, All Phase 2/3 Studies

	Interval of Treatment (months)				
	>0-6 # (%) of Patients with Event	>6-12 # (%) of Patients with Event	>12-18 # (%) of Patients with Event	>18-24 # (%) of Patients with Event	>24 # (%) of Patients with Event
Retinal vascular disorder	0	0	0	1 (0.1)	0

Source: Applicant's Table 4.2.3.1.2, Section 2.7.4

7.4.2.3 Explorations for drug-demographic interactions

The applicant provided demographic analyses of adverse events by age, race and gender. Events analyzed included those events that occurred at a higher frequency in inhaled insulin group patients than in SQ patients, in the controlled Phase 2/3 population. For Type 1 diabetics, the applicant analyzed cough, respiratory disorder, chest pain, dry mouth, dyspnea, epistaxis, hyperglycemia, and sputum increased. For Type 2 diabetics, events analyzed included cough, dry mouth, dyspnea, and sputum increased.

For Type 1 diabetics, the only event in the applicant's analysis that showed apparent differences in demographic patterns between inhaled insulin and SQ patients was "sputum increased", which showed a relative increased incidence among older patients and males in the inhaled insulin groups. There were too few non-Caucasians for meaningful comparisons between racial groups.

Table 7.4.2.3.1 Incidence of "Sputum Increased" by Age and Gender, Type 1 Diabetics, Controlled Phase 2/3 Studies

		Inh Ins n (%)	SQ n (%)
Age (years)	< 18	2 (1.3)	2 (1.4)
	18-44	19 (3.8)	6 (1.2)
	45-64	8 (4.2)	2 (1.0)
Gender	Male	20 (5.1)	3 (0.8)
	Female	7 (2.3)	5 (1.6)

Source: Applicant's Tables 13 and 14, ISS

For Type 2 diabetics, dry mouth appeared to decrease in incidence by age for both inhaled insulin and OA group patients. For all treatment groups, women were more likely to experience cough than men. Numbers of non-Caucasians were too small to permit meaningful comparisons.

Table 7.4.2.3.2 Incidence of "Sputum Increased" and Cough by Age and Gender, Type 2 Diabetics, Controlled Phase 2 and Phase 3 Studies

		Sputum Increased			Cough		
		Inh Ins	SQ	OA	Inh Ins	SQ	OA
Age (yrs)	18-44	3 (2.3)	1 (1.3)	1 (1.4)	34 (26.2)	3 (4.0)	2 (2.8)
	45-64	24 (2.8)	2 (0.7)	1 (0.2)	172 (20.2)	21 (6.9)	18 (4.2)
	65-74	6 (2.3)	1 (1.0)	1 (0.8)	59 (22.3)	11 (10.8)	4 (3.3)
	≥75	1 (3.3)	0	0	3 (10.0)	1 (12.5)	0
Gender	Male	23 (2.9)	4 (1.3)	1 (0.3)	140 (17.6)	21 (6.8)	12 (3.3)
	Female	11 (2.3)	0	2 (0.7)	128 (26.6)	15 (8.3)	12 (4.2)

Source: Applicant's Tables 24 and 25, ISS

The clinical reviewer examined all adverse events by age and gender, and noted the following events that appeared to have an association with either age or gender for inhaled insulin patients. Rates in comparator patients are also provided.

Table 7.4.2.3.3 Additional Events with Possible Relationship to Age for Type 1 Diabetic Inhaled Insulin Patients, Controlled Phase 2/3 Trials

	Inh Ins			SQ		
Adverse Event	<18 Yrs (total n = 153) n (%)	18-44 Yrs (total n = 506) n (%)	45-64 Yrs (total n = 190) n (%)	<18 Yrs (total n = 148) n (%)	18-44 Yrs (total n = 508) n (%)	45-64 Yrs (total n = 196) n (%)
Accidental injury	23 (15.0)	55 (10.0)	22 (11.6)	27 (18.2)	58 (11.4)	21 (10.7)
Tremor	51 (33.3)	97 (19.2)	25 (13.2)	49 (33.1)	97 (19.1)	30 (15.3)
Overall Respiratory Events	112 (73.2)	377 (74.5)	137 (72.1)	104 (70.3)	319 (62.8)	108 (55.1)
Pharyngitis	34 (22.2)	97 (19.2)	25 (13.2)	31 (20.9)	83 (16.3)	19 (9.7)
Otitis media	10 (6.5)	2 (0.4)	2 (1.1)	5 (3.4)	7 (1.4)	1 (0.5)

Source: Applicant's Table 4.1.3.1.1, Section 2.7.4

Accidental injury, tremor and pharyngitis occurred with decreasing frequency by age among Type 1 diabetics; this pattern did not differ between inhaled insulin and SQ groups. In the SQ group, overall respiratory events occurred with decreasing frequency by age, but in inhaled insulin groups, overall respiratory events occurred with approximately equal frequency between age groups. This suggests that, in Type 1 adults, respiratory adverse events are drug-related in inhaled insulin patients. Otitis media occurred more frequently in inhaled insulin group children than in SQ group children; in other age groups, otitis media occurred with low and roughly equal frequency between inhaled and SQ groups.

Table 7.4.2.3.4 Additional Events with Possible Relationship to Age for Type 2 Diabetic Inhaled Insulin Patients, Controlled Phase 2/3 Trials

	Inh Ins				SQ				OA			
Event	**18-44 Yrs N=130 n (%)**	**45-64 Yrs N=853 n (%)**	**65-74 Yrs N=264 n (%)**	**≥ 75 Yrs N=30 n (%)**	**18-44 Yrs N=75 n (%)**	**45-64 Yrs N=303 n (%)**	**65-74 Yrs N=102 n (%)**	**≥75 Yrs N=8 n (%)**	**18-44 Yrs N=72 n (%)**	**45-64 Yrs N=426 n (%)**	**65-74 Yrs N=122 n (%)**	**≥ 75 Yrs N=24 n (%)**
Accidental injury	13 (10.0)	66 (7.7)	18 (6.8)	1 (3.3)	8 (10.7)	31 (10.2)	14 (13.7)	2 (25.0)	3 (4.2)	30 (7.0)	6 (4.9)	2 (8.3)
Nausea	12 (9.2)	57 (6.7)	10 (3.8)	0	1 (1.3)	17 (5.6)	6 (5.9)	1 (12.5)	5 (6.9)	22 (5.2)	2 (1.6)	4 (16.7)
Hypoglycemia	76 (58.5)	533 (62.5)	165 (62.5)	20 (66.7)	56 (74.7)	223 (73.6)	75 (73.5)	6 (75.0)	20 (27.8)	114 (26.8)	45 (36.9)	6 (25.0)
Anxiety	9 (6.9)	38 (4.5)	2 (0.8)	0	2 (2.7)	29 (9.6)	0	0	2 (2.8)	12 (2.8)	0	0
Tremor	29 (22.3)	142 (16.6)	37 (14.0)	4 (13.3)	12 (16.0)	64 (21.1)	15 (14.7)	2 (25.0)	9 (12.5)	36 (8.5)	11 (9.0)	2 (8.3)
Overall Respiratory Events	77 (22.3)	489 (57.3)	157 (59.5)	16 (53.3)	12 (16.0)	163 (53.8)	56 (54.9)	6 (75.0)	9 (12.5)	150 (35.2)	35 (28.7)	3 (12.5)
Bronchitis	5 (3.8)	38 (4.5)	16 (6.1)	2 (6.7)	3 (4.0)	10 (3.3)	3 (2.9)	1 (12.5)	1 (1.4)	21 (4.9)	4 (3.3)	0
Respiratory disorder	9 (6.9)	45 (5.3)	10 (3.8)	1 (3.3)	11 (14.7)	22 (7.3)	7 (6.9)	1 (12.5)	1 (1.4)	8 (1.9)	2 (1.6)	0
Sinusitis	10 (7.7)	43 (5.0)	12 (4.5)	0	12 (16.0)	24 (7.9)	5 (4.9)	0	5 (6.9)	9 (2.1)	1 (0.8)	0
Overall Urogenital Events	10 (7.7)	90 (10.6)	29 (11.0)	5 (16.7)	8 (10.7)	36 (11.9)	14 (13.7)	0	14 (9.4)	50 (11.7)	9 (7.4)	5 (20.8)

Source: Applicant's Table 4.1.3.1.2, Section 2.7.4

The following observations are drawn from the above table regarding Type 2 patient adverse events and age:

- Small numbers of patients age ≥ 75 years make interpretation of event rates difficult in this age group.
- Rates of accidental injury were approximately equal between Type 2 inhaled insulin and SQ patients for those ages 18-44 years. In the inhaled insulin group, this declined with increasing age, while with SQ insulin, accidental injury increased with age. No age pattern was noted for accidental injury for OA patients.
- For inhaled insulin patients, there was a decline in the incidence of nausea and "respiratory disorder" by age group; this pattern was not seen for SQ or OA patients.
- For inhaled insulin patients, the incidence of hypoglycemia reported as an adverse event increased with age, while for SQ patients, the incidence was equal between age groups. However, the incidence for each age group was always higher for SQ patients than for inhaled insulin patients, and the incidence for oral agent patients was always much lower than that seen with either insulin treatment.
- The incidence of respiratory adverse events appeared to increase with age in all treatment groups. For each age group, the incidence among inhaled insulin patients was always higher than that seen in either comparator group, with the exception of those patients ≥ age 75 years, where small patient numbers make interpretation difficult.
- The incidence of bronchitis appeared to increase with age for inhaled insulin group patients; this pattern was not seen for comparator agents

- The incidence of sinusitis appeared to decline with age for all treatment groups.
- Overall urogenital events appeared to increase with age for all treatment groups.

Table 7.4.2.3.5 Additional Events with Possible Relationship to Gender for Type 2 Diabetic Inhaled Insulin Patients, Controlled Phase 2/3 Trials

	Male	Female	Male	Female
Adverse Event	**Inh Ins N=390 n (%)**	**Inh Ins N=308 n (%)**	**SQ N=385 n (%)**	**SQ N=320 n (%)**
Accidental injury	15 (13.3)	25 (8.1)	46 (11.9)	34 (10.6)
Allergic Reaction	20 (5.1)	11 (3.6)	10 (2.6)	13 (4.1)
Headache	49 (12.6)	56 (18.2)	41 (10.6)	69 (21.6)
Overall Digestive Events	112 (28.7)	122 (39.6)	83 (21.6)	119 (37.2)
Diarrhea	33 (8.5)	17 (5.5)	9 (2.3)	26 (8.1)
Gastroenteritis	15 (3.8)	19 (6.2)	19 (4.9)	17 (5.3)
Nausea	19 (4.9)	39 (12.9)	10 (2.6)	36 (11.3)
Vomiting	14 (3.6)	19 (6.2)	5 (1.3)	21 (6.6)
Overall Hemic and Lymphatic Events	8 (2.1)	10 (3.2)	12 (3.1)	16 (5.0)
Arthralgia	19 (4.9)	24 (7.8)	17 (4.4)	15 (4.7)
Overall Nervous System Events	112 (28.7)	145 (47.1)	127 (33.0)	141 (44.1)
Anxiety	17 (4.4)	32 (10.4)	14 (3.6)	25 (7.8)
Dizziness	22 (5.6)	36 (11.7)	27 (7.0)	24 (7.5)
Insomnia	9 (2.3)	14 (4.5)	2 (0.5)	12 (3.8)
Tremor	43 (11.0)	79 (25.6)	52 (13.5)	75 (23.4)
Overall Respiratory Events	276 (70.8)	239 (77.6)	219 (56.9)	209 (65.3)
Dyspnea	11 (2.8)	16 (5.2)	1 (0.3)	3 (0.9)
Pharyngitis	60 (15.4)	63 (20.5)	44 (11.4)	59 (18.4)
Respiratory disorder	19 (4.9)	26 (8.4)	14 (3.6)	13 (4.1)
Sinusitis	26 (6.7)	38 (12.3)	16 (4.2)	32 (10.0)
Sweating	22 (5.6)	38 (12.3)	39 (10.1)	35 (10.9)
Overall Urogenital Events	18 (4.6)	61 (19.8)	13 (3.4)	71 (22.2)
Urinary tract infection	3 (0.8)	20 (6.5)	2 (0.5)	29 (9.1)

Source: Applicant's Table 4.1.4.1.1, Section 2.7.4

The following adverse events occurred with higher frequency in males than in females in the inhaled insulin group, but not in the SQ group: allergic reaction, diarrhea.

The following adverse event occurred with higher frequency in males than in females in both treatment groups: accidental injury.

The following adverse events occurred with higher frequency in females than in males in both treatment groups: headache, overall digestive events, gastroenteritis, nausea, vomiting, overall hemic and lymphatic events, arthralgia, overall nervous system disorders, dizziness, insomnia, tremor, overall respiratory events, dyspnea, pharyngitis, respiratory disorder, sinusitis, sweating, overall urogenital events, urinary tract infection.

Table 7.4.2.3.6 Additional Events with Possible Relationship to Gender for Type 2 Diabetic Inhaled Insulin Patients, Controlled Phase 2/3 Trials

	Inh Ins		SQ		OA	
Adverse Event	**Male N=795 n (%)**	**Female N=482 n (%)**	**Male N=307 n (%)**	**Female N=181 n (%)**	**Male N=361 n (%)**	**Female N=283 n (%)**
Accidental injury	73 (9.2)	25 (5.2)	32 (10.4)	23 (12.7)	21 (5.8)	20 (7.1)
Back pain	47 (5.9)	50 (10.4)	25 (8.1)	28 (15.5)	16 (4.4)	24 (8.5)
Pain	43 (5.4)	46 (9.5)	22 (7.2)	18 (9.9)	14 (3.9)	21 (7.4)
Headache	79 (9.9)	85 (17.6)	13 (4.2)	20 (11.0)	32 (8.9)	35 (12.4)
Overall Digestive Events	231 (29.1)	162 (33.6)	68 (22.1)	67 (37.0)	98 (27.1)	96 (33.9)
Diarrhea	50 (6.3)	38 (7.9)	16 (6.3)	12 (6.6)	28 (7.8)	40 (14.1)
Nausea	33 (4.2)	46 (9.5)	15 (4.9)	10 (5.5)	12 (3.3)	21 (7.4)
Vomiting	12 (1.5)	20 (4.1)	8 (2.6)	7 (3.9)	10 (2.8)	13 (4.6)
Hypoglycemia	517 (65.0)	277 (57.5)	222 (72.3)	138 (76.2)	105 (29.1)	80 (28.3)
Arthralgia	46 (5.8)	38 (7.9)	24 (7.8)	17 (9.4)	15 (4.2)	24 (8.5)
Anxiety	25 (3.1)	28 (5.8)	11 (3.6)	22 (12.2)	5 (1.4)	10 (3.5)
Paresthesia	29 (3.6)	26 (5.4)	6 (2.0)	2 (1.1)	14 (3.9)	5 (1.8)
Bronchitis	31 (3.9)	30 (6.2)	10 (3.3)	7 (3.9)	11 (3.0)	15 (5.3)
Respiratory disorder	46 (5.8)	19 (3.9)	26 (8.5)	15 (8.3)	7 (1.9)	4 (1.4)
Respiratory tract infection	232 (29.2)	125 (25.9)	102 (33.2)	64 (35.4)	69 (19.1)	58 (20.5)
Sinusitis	30 (3.8)	35 (7.3)	21 (6.8)	20 (11.0)	3 (0.8)	12 (4.2)
Rash	27 (3.4)	24 (5.0)	10 (3.3)	11 (6.1)	3 (0.8)	10 (3.5)
Urinary tract infection	10 (1.3)	40 (8.3)	6 (2.0)	19 (10.5)	5 (1.4)	19 (6.7)

Source: Applicant's Table 4.1.4.1.2, Section 2.7.4

The following adverse events occurred with higher frequency in males than in females in the inhaled insulin group, but not in the comparator groups: accidental injury, hypoglycemia, respiratory tract infection.

The following adverse event occurred with higher frequency in females than in males in the inhaled insulin group, but not in the comparator groups: paresthesia.

The following adverse events occurred with higher frequency in females than in males in all treatment groups: back pain, pain, headache, overall digestive events, diarrhea, nausea, vomiting, arthralgia, anxiety, bronchitis, respiratory disorder, sinusitis, rash, urinary tract infection.

A summary of the observations for demographic differences for adverse events includes:

- Numbers of non-Caucasian patients were too small to permit meaningful comparisons between treatment groups. The lack of data regarding safety in African American patients has clinical implications. Diabetes is increasing in frequency in African Americans, and, as discussed earlier, baseline lung function is lower in African Americans than in Caucasian Americans or Mexican-Americans. More data are needed regarding the pulmonary safety of inhaled insulin in African Americans.
- For Type 1 patients, the event "sputum increased" had a higher incidence in older patients and in males in inhaled insulin patients, but not in SQ patients.
- For Type 1 patients in the SQ group, overall respiratory events occurred with decreasing frequency by age group, but in inhaled insulin patients, overall respiratory events occurred

with approximately equal frequency between age groups. For patients age 18 and older, overall respiratory events occurred more frequently among inhaled insulin group patients than among SQ patients.

- For Type 1 diabetic children, otitis media occurred more frequently in inhaled insulin group children than in SQ group children. Otitis media occurred with low and approximately equal frequency in adult Type 1 patients in both treatment groups.
- For Type 1 patients, the events "allergic reaction" and "diarrhea" occurred with higher frequency among males than among females in the inhaled insulin group. This gender difference was not apparent in comparator groups.
- For Type 2 patients, the event "dry mouth" appeared to decrease in incidence with age in inhaled and oral agent groups, but not in the SQ group.
- For Type 2 patients, for all treatment groups, women were more likely to experience cough than men; for both genders, cough occurred much more frequently in inhaled insulin group patients than in comparator patients.
- For Type 2 patients, the incidence of bronchitis increased by age group for inhaled insulin patients, but not for comparator patients.
- For Type 2 patients, accidental injury, hypoglycemia, and respiratory tract infection occurred more frequently in men than in women in the inhaled insulin group. This gender difference was not observed in the comparator groups.
- For Type 2 patients, paresthesia occurred more frequently in women than in men in the inhaled insulin group. This gender difference was not observed in the comparator groups.

Among these observations, those most likely to have clinical significance include:

- Otitis media in children appears related to inhaled insulin treatment.
- The incidence of bronchitis appears to increase by age group for inhaled insulin patients, but not for comparator patients.
- For Type 2 patients, accidental injury and hypoglycemia appear to occur more frequently in men than in women taking inhaled insulin. This gender difference was not observed in the comparator groups.
- More data are needed regarding pulmonary safety of inhaled insulin in African Americans.

7.4.2.4 Explorations for drug-disease interactions and other extrinsic factor interactions

Pharmacokinetic studies of inhaled insulin in hepatic and renal impairment were not submitted by the applicant.

Study 1005 compared inhaled insulin PK between healthy patients and those with COPD. Following administration of 3 mg of inhaled insulin, Cmax was greater (by up to 50%) in COPD patients than in healthy subjects. Tmax occurred 25-50 minutes earlier in COPD patients compared to normal subjects. Overall insulin exposure (AUC_{0-360}) was greater in COPD patients than in healthy subjects (by approximately 15%). Bioavailability of inhaled insulin was 11% in healthy controls compared to 23-25% in COPD patients. Please see Dr. Seymour's review for further discussion of the interaction between inhaled insulin and COPD.

As of 1 Sep 04, four patients with COPD had died; one of these was taking inhaled insulin and died of metastatic colon cancer. No asthma patients had died as of 1 Sep 04.

Hypoglycemia event rates did not differ between COPD and asthma patients, and those without these disorders, for either inhaled insulin or comparator patients. The following adverse events had an incidence of at least 2% greater in asthma or COPD patients than in patients without these disorders:

Table 7.4.2.4.1 Incidence of Adverse Events Occurring with Greater Frequency for Patients with Underlying Lung Disease (Retrospectively and Prospectively Identified), than in Patients without Underlying Lung Disease, Adults, Controlled Phase 2/3 Studies

	Inh Ins			Comparator		
Event	**With BL Asthma N=70 n (%)**	**With BL COPD N=80 n (%)**	**W/O BL Lung Dz N=1901 n (%)**	**With BL Asthma N=79 n (%)**	**With BL COPD N=78 n (%)**	**W/O BL Lung Dz N=1756 n (%)**
Asthenia	9 (12.9)	8 (10.0)	167 (8.8)	5 (6.3)	6 (7.7)	123 (7.0)
Chest pain	2 (2.9)	1 (1.3)	22 (1.2)	1 (1.3)	1 (1.3)	6 (0.3)
Hot flushes	2 (2.9)	0	5 (0.3)	0	1 (1.3)	6 (0.3)
Vasodilation	2 (2.9)	0	10 (0.5)	0	0	10 (0.6)
Nausea	4 (4.3)	0	44 (2.3)	1 (1.3)	2 (2.6)	28 (1.6)
Hypercholesterolemia	3 (4.3)	1 (1.3)	4 (0.2)	0	1 (1.3)	4 (0.2)
Peripheral edema	2 (2.9)	3 (3.8)	25 (1.3)	2 (2.5)	1 (1.3)	21 (1.2)
Arthralgia	3 (4.3)	1 (1.3)	17 (0.9)	0	3 (3.8)	26 (1.5)
Arthritis	0	3 (3.8)	17 (0.4)	0	3 (3.8)	13 (0.7)
Circumoral paresthesia	0	2 (2.5)	2 (0.1)	0	0	2 (0.1)
Paresthesia	2 (2.9)	0	28 (1.5)	1 (1.3)	0	15 (0.9)
Bronchitis	1 (1.4)	2 (2.5)	9 (0.5)	0	1 (1.3)	0
Cough increased	4 (5.7)	8 (10.0)	290 (15.3)	1 (1.3)	1 (1.3)	18 (1.0)
Dyspnea	2 (2.9)	1 (1.3)	27 (1.4)	0	2 (2.6)	6 (0.3)
Respiratory disorder	0	2 (2.5)	23 (1.2)	1 (1.3)	2 (2.6)	3 (0.2)
Respiratory tract infection	3 (4.3)	3 (3.8)	36 (1.9)	4 (5.1)	1 (1.3)	29 (1.7)
Epididymitis (males only)	1 (4.2)	0	0	0	0	0

Source: Applicant's Tables 13.4.8.1-13.4.8.3, Section 5.3.5.3.1

Patients with either asthma or COPD who were taking inhaled insulin appeared to experience asthenia more frequently than comparator patients (with or without underlying lung disease), and more frequently than inhaled insulin patients without underlying lung disease. Otherwise, the small number of each type of event within the underlying lung disease groups precludes meaningful conclusions regarding other types of events.

Declines in FEV1 and DLco occurred more frequently among inhaled insulin patients than among control patients in the controlled Phase 2/3 population, and are further discussed in Dr. Seymour's pulmonary review. The clinical reviewer examined nonpulmonary adverse events in those patients who had significant declines in PFTs, defined as declines from baseline to last observation of $\geq$ 15% in FEV1, TLC or FVC, and/or $\geq$ 20% decline in DLco. Hypoglycemia rates (by study definition of requirement for assistance, or value <36 mg/dL) were similar between patients who had significant PFT declines and those who did not, for both inhaled insulin and comparator patients. Hypoglycemia rates among patients who had declines in PFTs were similar between inhaled insulin and comparator patients (source: applicant's Table 17.12,

Section 5.3.5.3.1). Reported adverse events of hypoglycemia occurred more commonly in inhaled insulin patients who had significant declines in PFTs than in comparator patients who had significant declines in PFTs [154/218 (70.6%) vs 86/154 (55.8%)], but at an equal rate to that seen in comparator patients who did not have significant declines in PFTs (1069/1512, 70.7%). Total cardiovascular events occurred at a higher rate in inhaled insulin patients who had a significant decline in PFTs (45/218, 20.6%) than in comparator patients who had a significant decline in PFTs (26/154, 16.9%) and comparator patients who did not have a significant decline in PFTs (202/1512, 13.4%). No single cardiovascular event occurred at a significantly higher rate among inhaled insulin patients who had significant declines in PFTs.

Tobacco smoking within six months prior to randomization was an exclusion criterion for Phase 2/3 studies. In clinical pharmacology studies (005, 016, 1003, 1020), inhaled insulin pharmacokinetics and pharmacodynamics were significantly different in smokers. In nondiabetic and Type 2 diabetic smokers, Cmax, Tmax and AUC of inhaled insulin was 2-5 fold higher than that of nonsmokers. Smoking cessation led to a decline in insulin exposure within 3 days of abstinence, with further attenuation over time; by 7 days, insulin exposure was near that seen in nonsmokers. Resumption of smoking after abstinence resulted, within 2-3 days, in increased exposure similar to that seen prior to smoking cessation. The applicant is concerned about these findings, and considers the potential for rapid changes in systemic insulin exposure to be a prohibitive risk associated with cigarette smoking. The applicant recommends that patients should abstain from smoking for at least 6 months before inhaled insulin treatment, and should remain abstinent during inhaled insulin treatment. However, in order to reduce the likelihood that smokers will use inhaled insulin, education of patients and providers may be needed, with enhanced emphasis on the risk. Physicians may overlook the smoking statement in a long product label, and patients sometimes do not share their smoking history with their physicians.

The applicant conducted a rhinoviral challenge study, in which volunteers were inoculated with either rhinovirus or saline. Among those rhinovirally challenged patients who developed a cold, insulin Cmax was numerically greater than it was among saline group patients who did not develop a cold, although this difference was not statistically significant. On Day 4, Tmax was statistically significantly longer in patients who developed a cold.

Table 7.4.2.4.2 Insulin Pharmacokinetic Parameters after Rhinoviral Challenge, Study 010

Summary of Statistical Analysis of Pharmacokinetic Parameters

Parameter	Day	Adjusted Geometric Means*			Cold vs Virus No Cold		Cold vs Saline	
		Cold	Virus No Cold	Saline	Adjusted Ratio * (90% CI)	p-value	Adjusted Ratio * (90% CI)	p-value
AUC (µU.min/mL)	3	703	1209	455	0.58 (0.33, 1.04)	0.1218	1.55 (0.76, 3.14)	0.3010
	4	692	584	782	1.19 (0.57, 2.48)	0.6940	0.89 (0.36, 2.19)	0.8186
Cmax (µU/mL)	3	11.88	13.58	6.48	0.88 (0.48, 1.61)	0.7083	1.83 (0.85, 3.97)	0.1895
	4	11.27	7.71	8.18	1.46 (0.80, 2.66)	0.2856	1.38 (0.64, 2.94)	0.4741
	Day	Arithmetic Means			Cold vs Virus No Cold		Cold vs Saline	
		Cold	Virus No Cold	Saline	Estimated Difference (90% CI)	p-value	Estimated Difference (90% CI)	p-value
Tmax (min)	3	35.8	40.7	33.8	-4.9 (-19.8, 9.9)	0.5718	2.0 (-16.0, 20.1)	0.8494
	4	47.3	50.0	22.5	-2.7 (-15.9, 10.5)	0.7287	24.8 (8.7, 40.9)	0.0148

* For AUC and Cmax the Day 1 log (AUC) or log (Cmax) was used as a covariate in the model. CI = confidence interval
Day 1: Before inoculation; Days 3 and 4: Post-inoculation

Source: Applicant's Study 010 report, pg 9

Glucose Cmax was higher on days 3 and 4 after rhinoviral inoculation than after saline inoculation. AUC was also higher, but baseline differences limit the interpretability of this finding.

Table 7.4.2.4.3 Glucose Pharmacodynamic Parameters with Rhinoviral Challenge, Study 010

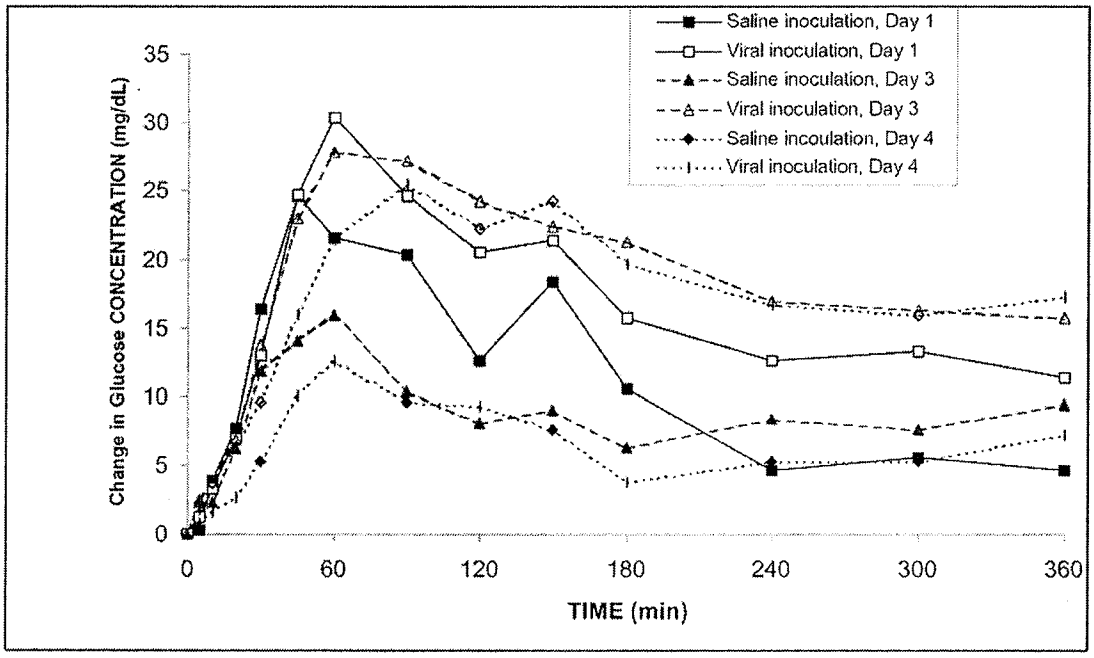
Arithmetic Mean (CV%) of Glucose Pharmacodynamic Parameters

	Virus (N=20)			Saline (N=4)		
	Day 1	Day 3	Day 4	Day 1	Day 3	Day 4
AUC0-360 (mg·min/mL)	5830 (47)	6900 (49)	6460 (47)	3930 (53)	3150 (53)	2370 (34)
Cmax (mg/dL)	33.2 (35)	31.4 (43)	29.2 (45)	28.4 (74)	18.6 (59)	16.1 (65)
Tmax (min)	75.0 (77)	81.0 (43)	136 (66)	75.0 (67)	165 (86)	120 (71)

Day 1: Before inoculation; Days 3 and 4: Post-inoculation
Source: Table 5.4.1-5.4.3

Figure 7.4.2.4.1 Mean Glucose Concentrations over Time, After Rhinoviral Challenge, Study 010

Inhaled Human Insulin Protocol 010
Mean Change in Glucose Concentrations Following Administration of 3 mg Inhaled Insulin to Subjects on Days 1, 3 and 4 with Nasal Inoculation 6 Hours After Dosing on Day 1



Source Data: Section 13, Tables 2.4, 2.5 and 2.6

Source: Applicant's Figure 1.4, Study 010 report

The applicant's proposed label states that Exubera® may be used during intercurrent respiratory illness. The absence of a significant difference in insulin Cmax after rhinoviral infection is a

useful finding, but rhinoviral challenge does not cover the spectrum of intercurrent respiratory illness.

7.4.2.5 Explorations for drug-drug interactions

Study 1005 included pharmacokinetic data regarding co-administration of inhaled insulin and inhaled albuterol. While overall, inhaled insulin PK did not differ from 30 minutes pre- to 30 minutes post- albuterol, the small subset of emphysema patients (5/12 total COPD patients) had mean insulin exposure that was 46% higher post-albuterol than pre-albuterol.

No other specific drug interaction studies were reported.

7.4.3 Causality Determination

The following adverse events appear to have a causal relationship to inhaled insulin use:

- serious hypoglycemia in intensively treated Type 1 diabetics (by the applicant's analysis; FDA biostatistics reanalysis indicates there may be no difference between treatment groups)
- cough in Type 1 adult, Type 2 adult, and Type 1 child patients
- declines in pulmonary function tests (FEV1 and DLco) in Type 1 and Type 2 adults
- pharyngitis in Type 1 and Type 2 adults
- rhinitis and sinusitis in Type 1 adults
- otitis media and other ear events in Type 1 children

Other respiratory adverse events which may have a causal relationship to inhaled insulin are discussed in the pulmonary safety review.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

In the DOSAGE AND ADMINISTRATION section of the proposed product label, the applicant proposes a similar regimen to that used in clinical trials. Administration 10 minutes prior to meals is proposed. Calculation of initial dosage based on body weight is proposed, with a formula: body weight (kg) x 0.05 mg, rounded down to nearest whole mg, = premeal dose, assuming 3 meals/day. The applicant does not propose instructions for transitioning from subcutaneous premeal insulin to inhaled insulin, based on the patient's current premeal subcutaneous insulin dose. However, in a revised proposed label submitted by email to Dr. Elekwachi on 26 Sep 05, the applicant included a table with a column for equivalent IU of subcutaneous shortacting insulin to mg of inhaled insulin. No formula is presented for dosing by carbohydrate exchanges, and there are no recommendations for calculation of bedtime snack doses. The label does not include recommendations for titration increments. Mention is made of the fact that three 1 mg unit dose blisters cause greater insulin exposure than one 3 mg dose

blister. The dosage and administration section does not mention a need for close monitoring by the patient and physician during initiation of inhaled insulin.

Initial dosage based on body weight is a reasonable approach. However, numerous patient factors may affect initial inhaled insulin requirement, including the patient's particular degree of insulin resistance, current glycemic control, hypoglycemia history, et al. These factors could result in significant under- or over- dosing if initial dose is based on weight alone. The proposed label makes mention of the need for consideration of factors other than weight in determining starting dose, but does not provide specific guidance. The potential consequences of initial under- or over- dosing could likely be managed by intensive monitoring by the patient and physician in the first few weeks of initiation of inhaled insulin; the clinical reviewer recommends the addition of this recommendation to the product label.

The applicant's proposed label states, in the DOSAGE AND ADMINISTRATION section, that Exubera® may be used during intercurrent respiratory illness, e.g. bronchitis, upper respiratory infection, and rhinitis. However, some differences in inhaled insulin pharmacokinetics and glucose pharmacodynamics were seen with rhinoviral challenge. Analysis of the effect of acute bronchitis on insulin pharmacokinetics and post-inhaled-insulin glucose pharmacodynamics was not provided. The clinical reviewer recommends that the label state that the effect of intercurrent respiratory illness, such as acute bronchitis, upper respiratory infection, and rhinitis, has not been fully evaluated, and that careful monitoring of blood glucose during intercurrent respiratory illness is recommended. The clinical reviewer also recommends that patients be advised to have subcutaneous insulin and needles available for use during intercurrent respiratory illness, in case glucose control proves difficult with inhaled insulin during that time.

An important consideration in dosage titration is lack of dose bioequivalence, i.e. the fact that insulin Cmax and AUC are higher if one uses three 1-mg blisters than if one uses a single 3-mg blister. In Study 1006, the applicant compared (in healthy subjects) the PK of 3x1 mg and 1x3 mg, as presented in the following table.

Table 8.1.1 Comparison of Insulin Pharmacokinetics with Administration of 3x1 mg and 1x3 mg Inhaled Insulin Blisters in Healthy Volunteers, Study 1006

Statistical Analysis of Insulin Pharmacokinetic Parameter Means

Parameter	3x1 mg*	1x3 mg*	Ratio/Difference	90% CI
$AUC_{0\text{-}360}$ (μU·min/mL)	2599	1859	140%	(117%, 167%)
Cmax (μU/mL)	31.02	24.51	127%	(108%, 148%)
F (%)**	5.80	4.15	140%	(117%, 167%)
Tmax (min)	44.4	42.0	2.4	(-4.4, 9.2)

*Adjusted geometric means for AUC, Cmax, and F; adjusted arithmetic mean for Tmax
**AUCinhaled/AUCsc; calculated from dose-standardized AUCs

Applicant used statistical F-distribution to compute 95% CI for ratio
Source: Study 1006 report, pg 7

Please see the Human Biopharmacology review for a more complete discussion of Study 1006; that review is ongoing as of 28 Sep 05, but will represent the most accurate FDA interpretation

of clinical pharmacology data. Because this study was conducted in nondiabetic subjects, the potential glucodynamic effects of this difference in PK cannot be precisely predicted. However, in these nondiabetic volunteers, mean changes in glucose concentration and AUC were greater with 3x1 mg than with 1x3 mg. The applicant includes information regarding this finding in the DOSAGE AND ADMINISTRATION section, and states that 1x3 mg cannot be substituted for 3x1 mg; however, the potential implications for titration are not presented. A potential problem exists when titrating dose up to a multiple of three mg from a dose that is one mg below that multiple, e.g. titration from 2-3 mg, from 5-6 mg, or from 8-9 mg. One can predict with reasonable certainty that the incremental increase in serum insulin concentration, and the incremental decrease in blood glucose, will be less when one titrates from 2-3 mg (or 5-6 mg) than it was when the patient was titrated from 1-2 mg (or 4-5 mg). If the serum insulin concentration can be predicted to always be greater at 1x3 mg than at 2x1 mg, and the blood glucose concentration can be predicted to always be lower after 1x3 mg than after 2x1 mg, then titration can occur safely and without the need for complicated titration instructions. However, the magnitude of the difference in serum insulin AUC_{0-360} between 3x1 mg and 1x3 mg is large, with a ratio of 140% (90% CI 117%, 167%). This implies that some patients could have lower insulin levels after titration to 1x3 mg than they had before titration at 2x1 mg. For example, assuming that each 1 mg blister inhalation resulted in an equal increase in insulin concentration, one would see the following AUC_{0-360}s:

1x1 mg = appr 866 μU-min/mL
2x1 mg = appr 1733 μU-min/mL
3x1 mg = 2599 μU-min/mL

Under this scenario of the mean values with a ratio of 140%, a patient who was taking 2x1 mg blisters would have an increase in insulin AUC_{0-360} when going from 2x1 mg to 1x3 mg (appr 1733 μU-min/mL to 1859 μU-min/mL). However, if the ratio was at the upper limit of the 90% CI, i.e. 167%, the following would result:

2599/1859 = 140/100
2599/n = 167/100; n = 1556 μU-min/mL for the insulin AUC_{0-360} achieved with 1x3 mg (when the ratio is at the upper limit of the 90% CI)

Therefore, a patient going from 2x1 mg to 1x3 mg apparently could have a paradoxic decline in serum insulin AUC_{0-360}, from appr 1733 μU-min/mL to appr 1556 μU-min/mL.

When looking at this same question using a fixed value for the insulin AUC_{0-360} for 1x3 mg, and assuming the value for 3x1 mg was 167% of that (the upper limit of the 90% CI), one gets the following:

1859/2599 = 100/140
1859/n = 100/167, n = 3104 μU-min/mL for the insulin AUC_{0-360} achieved with 3x1 mg (when the ratio is at the upper limit of the 90% CI)

Again assuming that each 1 mg blister inhalation resulted in an equal increase in insulin AUC, one would see the following AUC_{0-360}s:

1x1 mg = appr 1035 mg
2x1 mg = appr 2070 mg
3x1 mg = appr 3104 mg

In this case, once again, a patient going from 2x1 mg to 1x3 mg apparently could have a paradoxic decline in serum insulin, from approximately 2070 μU-min/mL to approximately 1859 μU-min/mL.

These calculations extrapolate from percentages, and can only be used to give a rough idea of the possibility of titration problems related to the difference between 3x1 mg and 1x3 mg.

Study A2171012, a dose proportionality study, provides further concerns regarding potential problems with titration. In this study, dose proportionality was not demonstrated over a range of doses. Dose proportionality of several dosages was compared, including doses of 1 mg (1x1 mg), 2 mg (2x1 mg), 3 mg (1x3 mg), 4 mg (1x3 mg + 1x1 mg) and 6 mg (2x3 mg). None of the 90% confidence intervals for any AUC comparison fell within the applicant's prespecified bioequivalence boundaries (80-125%).

When examining the actual individual subject data from the trial, one notes that multiple samples obtained for insulin Cmax and AUC for 3 mg dosing had lower values than the mean seen for 2 mg dosing. For Cmax, 10/29 samples obtained for Cmax at the 3 mg dose fell below the mean Cmax for the 2 mg dose. In this study, each patient generally only received 3 of the 5 dose combinations. A total of 6 patients received both the 2 mg dose and the 3 mg dose (doses given at different times during study). Among these 6 patients (each of whom had 2 Cmax values recorded for each dose), 4/6 had a Cmax value for the 3 mg dose that was lower than a Cmax value for the 2 mg dose. A total of 6/26 samples for the 6 mg dose had lower Cmax values than the mean for the 4 mg dose, and 2/6 patients who received both the 4 mg dose and the 6 mg dose had a Cmax value for the 6 mg dose that was lower than a Cmax value for the 4 mg dose.

Similar findings are noted for AUC at each time interval, as illustrated in the following table:

Table 8.1.2 Overlap of Insulin AUC Values Between 2 mg and 3 mg Inhaled Insulin Doses, Study A2171012

	AUC 0-60	AUC 0-120	AUC 0-360	AUC 0-600
Number and percentage of AUC samples for 3 mg dose with lower AUC then the mean AUC for the 2 mg dose	8/29 (28%)	9/29 (31%)	11/29 (38%)	9/29 (31%)
Number and percentage of AUC samples for 6 mg dose with lower AUC then the mean AUC for the 4 mg dose	6/26 (23%)	4/26 (15%)	6/26 (23%)	7/26 (27%)
Number and percentage of patients who had both a 3 mg and 2 mg dose, who had a lower AUC value at the 3 mg dose than a 2 mg dose AUC[1]	4/6 (67%)	2/6 (33%)	2/6 (33%)	4/6 (67%)
Number and percentage of patients who had both a 6 mg and 4 mg dose, who had a lower AUC value at the 6 mg dose than a 4 mg dose AUC	4/6 (67%)	2/6 (33%)	2/6 (33%)	1/5 (20%)

1 Each patient had two measurements for each AUC time interval.

Based on these studies, it appears that the possibility exists that, in a given patient, the titrated "increase" from 2x1 mg to 1x3 mg could actually result in lower blood insulin AUC, rather than the expected increase in blood insulin. This could create a significant problem in upward titration of dose, particularly in the lower dosage ranges such as might be used in Type 1 diabetes. This problem would be magnified if the drug is used off-label for the treatment of pediatric Type 1 diabetics, who generally have lower body weights and therefore smaller initial insulin doses.

Furthermore, patients must be strongly cautioned that if they run out of 3 mg blisters, they must not substitute three 1 mg blisters for each 3 mg blister, because of the risk of severe hypoglycemia.

In order to search for a clinical correlate for these problems with dose proportionality and dose equivalence, the clinical reviewer examined all narratives for serious adverse events of hypoglycemia. A possible indication of a clinical correlate would be a finding that a disproportionate number of serious hypoglycemic events were preceded by a dose of 3x mg + 1 mg, e.g. 4 mg, 7 mg, 10 mg, etc. This could occur if the increase in insulin concentration was unexpectedly large when a patient was titrated from a dose requiring only 3 mg blisters to a dose requiring 3 mg blisters plus a one mg blister. However, doses of 4, 7 or 10 mg did not occur in a disproportionately high number of patients; such doses were given prior to the hypoglycemic event for only 7/47 episodes for which inhaled insulin dose data were available.

Table 8.1.3 Serious Hypoglycemic Adverse Events: Time of Event, Last Inhaled Insulin Dose Prior to Event, and Accompanying Related Events

Pt ID	Pt Age	Time of Day of Hypoglycemic Event	Last Inhaled Insulin Dose Prior to Event	Accompanying Related Event(s)
1009-5088-3381	7	after lunch	2 mg prelunch	fall, unresponsiveness
1009-5096-3021	10	0429	not in narrative	confusion, lethargy, possible seizure
1022-1001-0009	37	0445	3 mg at 1930 previous night	unconsciousness
1022-1015-0837	37	0430	4 mg presupper previous night	loss of consciousness
1022-1025-1424	32	0630 (prebreakfast)	not in narrative	confusion, change in affect
1022-1026-1489	22	0715 (prebreakfast)	7 mg at 1930 previous night	disorientation, motor vehicle accident
1002-1037-2136	51	0620	1 mg at 0120	loss of consciousness
1022-1029-1661	35	0530	7 mg at 2030 previous night	difficult to arouse
1022-1050-3914	46	1930 (postsupper)	3 mg at 1800 (presupper)	disorientation
		0630	7 mg presupper previous night	incoherence
		0500	8 mg at 1900 previous night	incoherence
1022-5074-3082	51	0230	12 mg presupper previous night	to ER for "hypoglycemic symptoms"
1022-5147-3376	45	0626	6 mg presupper previous night	disorientation, memory loss
		0538	6 mg presupper previous night	disorientation, memory loss
		0530-0630	6 mg presupper previous night	disorientation, memory loss
1026-1001-	50	0420	1 mg at 2310 previous night	semiconsciousness,

Table 8.1.3 Serious Hypoglycemic Adverse Events: Time of Event, Last Inhaled Insulin Dose Prior to Event, and Accompanying Related Events

Pt ID	Pt Age	Time of Day of Hypoglycemic Event	Last Inhaled Insulin Dose Prior to Event	Accompanying Related Event(s)
0017				unresponsiveness
1027-5148-1329	43	2105	6 mg presupper	loss of consciousness
1029-1059-2607	45	postbreakfast	4 mg prebreakfast	seizure
1029-1093-3854	64	2200	4 mg at 1730	unconsciousness
		2122	3 mg at 1830	unconsciousness
1029-1093-3857	62	postlunch	not in narrative	loss of consciousness
		between 1400 and 1600	not in narrative	not in narrative; EMS treated
106-5025-6592	42	postbreakfast	not in narrative	confusion, possible seizure
		0700	6 mg at 0140	convulsions
		0540	not in narrative	seizure, tongue-biting
106-5030-6883	53	0900	not in narrative	found unconscious; hypothermia
		1800	3 mg prelunch	found in car by side of road; sluggish speech
		prelunch	6 mg prebreakfast	unresponsiveness
106-5060-6966	36	early morning	not in narrative	unresponsiveness
		early morning	not in narrative	coma
107-5052-7181	19	0850	dose not in narrative; last inh ins 9.5 hrs prior to event	difficult to arouse
		0900	dose not in narrative; last inh ins 10.5 hrs prior to event	difficult to arouse
		0604	dose not in narrative; last inh ins 9 hrs prior to event	difficult to arouse
		0525	dose not in narrative; last inh ins 9 hrs prior to event	difficult to arouse
		0858	dose not in narrative; last inh ins 11.5 hrs prior to event	difficult to arouse
		0758	dose not in narrative; last inh ins 12 hrs prior to event	difficult to arouse
		0530	dose not in narrative; last inh ins 9 hrs prior to event	difficult to arouse
		0600	dose not in narrative; last inh ins 8 hrs prior to event	difficult to arouse
		0625	dose not in narrative; last inh ins 12 hrs prior to event	difficult to arouse
107-5052-7181	53	midnight	not in narrative	ran his car into a ditch
107-5083-7499	17	afternoon	1 mg prior to lunch	
107-5127-7221	30	morning	not in narrative	seizure
		2200	6 mg presupper	seizure
		after bedtime	6 mg presupper	seizure
		0400	6 mg presupper	seizure
		after bedtime	6 mg presupper	seizure
		0400	not in narrative	seizure
109-5071-0483	66	1900	6 mg at 1800	unresponsiveness
111-5017-8450	73	1630	5 mg prelunch	car crash, disorientation, confusion
111-5052-7180	34	early morning	3 mg presupper	incoherent speech, crying
111-5061-	44	1800	8 mg presupper	unconsciousness

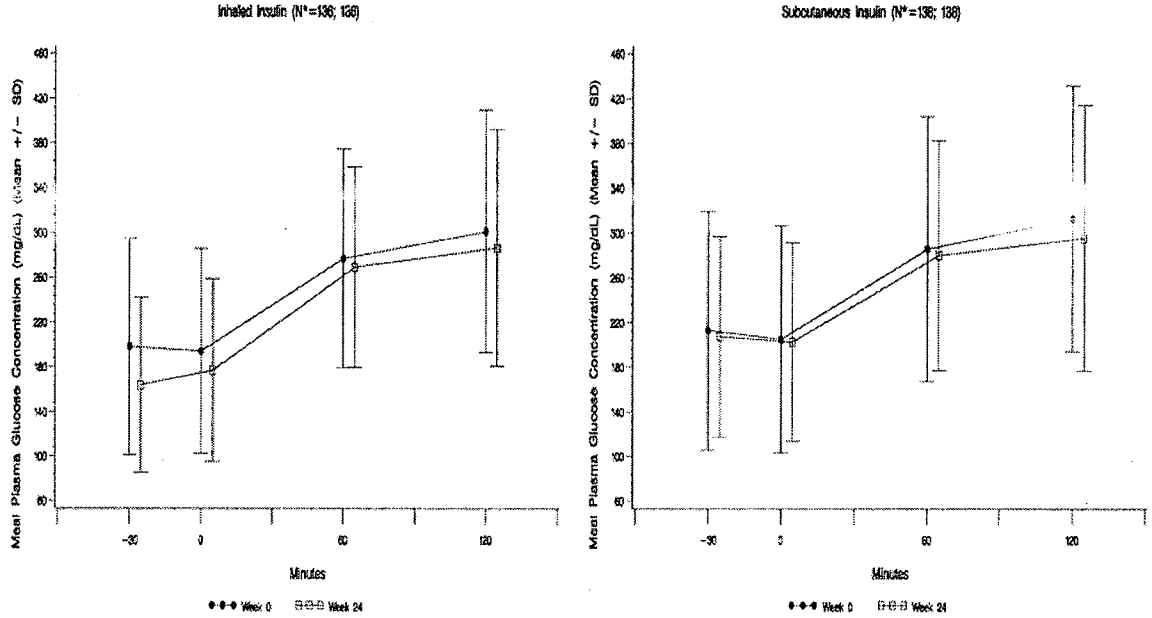
Table 8.1.3 Serious Hypoglycemic Adverse Events: Time of Event, Last Inhaled Insulin Dose Prior to Event, and Accompanying Related Events

Pt ID	Pt Age	Time of Day of Hypoglycemic Event	Last Inhaled Insulin Dose Prior to Event	Accompanying Related Event(s)
7793				
111-5061-7794	31	0200	not in narrative	unconsciousness, incontinence
		0445	1 mg at 2215 previous night	disorientation
111-5061-7797	46	0300	2 mg at bedtime previous night	unconsciousness, fall
111-5066-7741	41	0230	dose not in narrative; last inh ins 6 hr prior to event	incoherence
111-5066-7745	29	0400	not in narrative	seizure
111-5070-6896	30	prebreakfast	9 mg presupper previous night	unresponsiveness
111-5070-6898	42	0030	2 mg presupper previous night	convulsions
111-5081-6446	18	1600	dose not in narrative; presupper previous night	incoherence
111-5082-3341	11	prebreakfast	not in narrative	seizure
111-5082-3346	10	prebed	7 mg presupper	
111-5082-3347	8	1300 (prelunch)	6 mg prebreakfast (ate at 0920)	seizure
111-5082-3348	9	1800	15 mg prelunch	confusion, unilateral leg weakness
		0100	12 mg presupper previous night	unresponsiveness
		early morning	not in narrative	possible seizure
111-5087-7011	17	0900	3 mg prebreakfast	confusion, disorientation
111-5088-3384	7	0240	3 mg at 2115 previous night	seizure
111-5091-3008	11	midnight	4 mg at 2200 previous night	seizure
111-5094-7094	14	0700	3 mg at 2200 previous night	incoherence, combativeness
111-5095-3334	7	2100	not in narrative	
111-5096-3358	12	0900	3 mg at 1800 previous night	confusion
111-5096-3359	10	0500	1 mg at 2152 previous night	seizure
111-5098-3048	9	0600	3 mg at 2048 previous night	seizure
		0615	2 mg at 2005 previous night	seizure
111-5127-7224	60	1800	3 mg prelunch	unconsciousness

As discussed above, and in Sections 3.1 and 5.1, concerns exist on several levels regarding the potential for variability in delivered dose of insulin. However, significant variability in delivered dose of insulin and, more importantly, in pharmacodynamic effect, is also seen with subcutaneous insulin (Heinemann 2002). This marked variability in pharmacodynamic effect of injected insulin has been well-described in the medical literature, and represents a major barrier in efforts to achieve lower HbA1cs without undue risk of severe hypoglycemia. The relative variability of the pharmacodynamic effect for inhaled versus subcutaneous insulin can be compared using standardized meal study data from within the major trials of inhaled insulin that used subcutaneous insulin as a comparator. For example, in Study 107, patients received either

inhaled insulin or subcutaneous insulin, followed by a standard Sustacal® meal. The following figures illustrate the plasma glucose response over time:

Figure 8.1 Meal Study Plasma Glucose Concentration (mg/mL), Study 107



Source: Applicant's Figure 4.1, Study 107 report

Of note from this figure is the fact that the standard deviations for plasma glucose following administration of a standard meal are large for patients who received inhaled insulin, but the standard deviations seen for those patients who received subcutaneous insulin are at least as large as those seen with inhaled insulin. Similar findings were seen in other studies where inhaled insulin was compared to subcutaneous insulin after a standardized meal. Thus, although concern exists regarding the variability seen with inhaled insulin, it may be no worse than that seen with subcutaneous insulin.

Of potential concern for Type 1 diabetics is the fact that the lowest available blister strength (1 mg) may not allow for the fine titration that is often used for Type 1 diabetes. A 1 mg blister is roughly pharmacodynamically equivalent to 3 IU of subcutaneously injected shortacting insulin. For Type 1 diabetics, titration is often done in increments of 1 IU, and premeal "sliding scales" are often prescribed in 1 IU increments. However, this lack of fine titration capability does not seem to have had a clinical correlate in the clinical trials, either for glycemic control or hypoglycemia risk.

8.2 Drug-Drug Interactions

Study 1005 included pharmacokinetic data regarding co-administration of inhaled insulin and inhaled albuterol. While overall, inhaled insulin PK did not differ from 30 minutes pre- to 30 minutes post- albuterol, the small subset of emphysema patients (5/12 total COPD patients) had mean insulin exposure that was 46% higher post-albuterol than pre-albuterol.

No other specific drug interaction studies were reported.

8.3 Special Populations

Study 1004 was conducted in elderly (>65 years of age), obese Type 2 diabetics, and compared inhaled insulin (4 mg) PK and PD to that of SQ regular insulin (12 U) (6 mg inh ins or 18 U SQ for patients with weight ≥150 kg). The study did not include a control arm of younger patients. Inhaled insulin had an earlier insulin Tmax and a higher Cmax, but a similar exposure by AUC_{0-360}.

Table 8.3.1 Glucose Pharmacodynamics for Inhaled and Subcutaneous Insulin in Patients >Age 65 years, Study 1004

Statistical Analysis of Geometric and Arithmetic Means for Inhaled and Subcutaneous Insulin Treatment

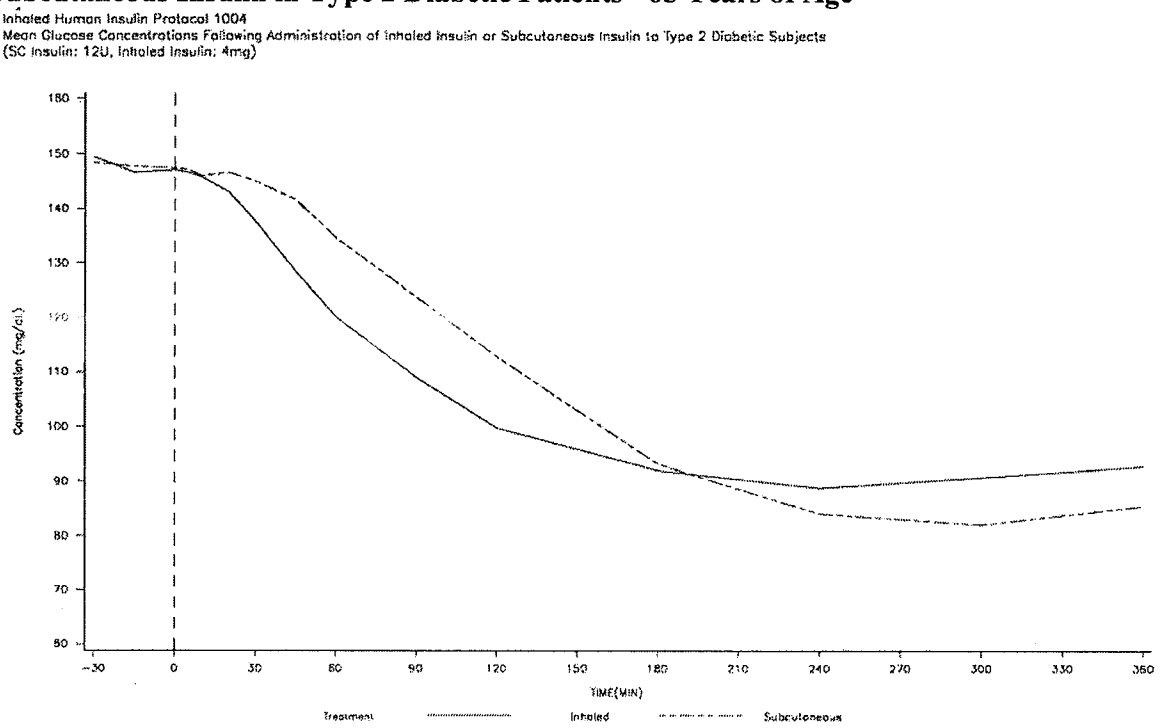
Pharmacokinetic Parameter	Adjusted Geometric Means		Ratio (%)	90 % Confidence Limits (%)
	INH	SC	(INH / SC)	
AUC_{0-120} (µU·min/mL)	3472	1852	187	(138, 255)
AUC_{0-240} (µU·min/mL)	4500	3937	114	(81, 161)
AUC_{0-360} (µU·min/mL)	4696	4823	97	(68, 139)
Cmax (µU/mL)	48.62	28.57	170	(131, 221)
	Adjusted Arithmetic Means		Difference (min)	(min)
Tmax (min)	37.6	99.6	-62.0	(-82.2, -41.8)

Source: Tables 5.3.1

Source: Applicant's Table 5.3.1, Study 1004 report

Decline in blood glucose concentrations was greater over the first 120 minutes after insulin administration for inhaled insulin than for SQ insulin.

Figure 8.3.1 Mean Glucose Concentrations Following Administration of Inhaled Insulin or Subcutaneous Insulin in Type 2 Diabetic Patients >65 Years of Age



Source: Applicant's Figure 2.1, pg 84, Study 1004 Report

The clinical reviewer was unable to find pharmacokinetic or pharmacodynamic data on the administration of equivalent mg/kg dosing of inhaled insulin to obese nonelderly Type 2 diabetics, and therefore cannot comment on the expected differences in PK/PD in elderly patients who receive inhaled insulin compared to younger patients who receive inhaled insulin. Because of the problems with nonequivalence of 1x3 mg and 3x1 mg, one cannot extrapolate PK/PD data from studies using other doses.

8.4 Pediatrics

Pediatric safety and efficacy data are presented in Sections 6 and 7 of this review. In each section, discussion of available pediatric data is presented after adult data.

8.5 Advisory Committee Meeting

This application was presented to the Endocrine and Metabolic Drugs Advisory Committee on 8 Sep 05. Please see the official transcript of that meeting for details.

The Committee recommended approval of Exubera® for control of hyperglycemia in both Types 1 and 2 diabetes in adults. The Committee expressed less concern than the clinical reviewer

regarding the evidence of efficacy for intensive management of Type 1 diabetes. However, several important safety concerns were emphasized, including:

- data are inadequate to assess safety in patients with underlying lung disease
- extensive specific postmarketing study of pulmonary safety is needed even for patients without underlying lung disease
- education of patients and providers in proper use of the inhaler will be very important, and the applicant needs to provide specific plans for how providers and patients will be trained
- specific measures beyond labeling are needed to reduce the likelihood that smokers will use the drug
- Dr. Talmadge King recommended study of the pulmonary effects of Exubera® in African Americans, stating that lung function in African Americans differs from that of other racial and ethnic groups. The clinical reviewer confirmed that African Americans have been described to have lower baseline lung function than Caucasian Americans and Mexican-Americans (Hankinson 1999).

Members of the Advisory Committee called into question the usefulness of the patient-reported outcomes data (regarding treatment satisfaction and patient preference) presented by the applicant. The Advisory Committee pointed out that it is unsurprising that these instruments would favor inhaled insulin, because patients who would be willing to try inhaled insulin were likely to have already been dissatisfied with subcutaneous insulin.

8.6 Literature Review

Literature relevant to the review is referenced throughout the review.

8.7 Postmarketing Risk Management Plan

With the original NDA submission, the applicant did not submit a postmarketing risk management plan (RMP) that included measures other than routine postmarketing adverse event surveillance. On 2 Aug 05, the applicant submitted a revised RMP; this RMP is under review by the Office of Drug Safety as of 28 Sep 05.

8.8 Other Relevant Materials

Not applicable

9 OVERALL ASSESSMENT

9.1 Conclusions

Conclusions reached in this review are the result of the clinical reviewer's evaluation of the clinical portions of the New Drug Application; nonclinical and clinical pharmacology portions are also under evaluation by reviewers with expertise in the relevant areas, and these reviews may also affect decisions made by signatory authorities regarding approvability of this application. A separate pulmonary clinical safety review is being conducted.

For each point of discussion in Section 9.1, the relevant section number for the main body of the review is included to permit ease of reference. If an entire paragraph contained information from a single section of the main body of the review, the relevant section number is included after the first sentence in the paragraph in Section 9.1.

9.1.1 Efficacy Conclusions

The applicant proposes the following language for the "Indications and Usage" section of the product label:

"EXUBERA is indicated for the treatment of adult patients with diabetes mellitus for the control of hyperglycemia. EXUBERA has an onset of action similar to rapid-acting insulin analogs and has a duration of glucose-lowering activity comparable to subcutaneously administered regular human insulin. In patients with type 1 diabetes, EXUBERA should be used in regimens that include a longer-acting insulin. In patients with type 2 diabetes, EXUBERA can be used as monotherapy or in combination with oral agents or longer-acting insulins."

Because of this proposed labeling regarding indications, the clinical reviewer considered four potential indications:

- control of hyperglycemia in Type 1 diabetics (inhaled insulin in combination with a longer-acting insulin (Section 6.1)
- control of hyperglycemia in Type 2 diabetes (inhaled insulin monotherapy) (Section 6.2)
- control of hyperglycemia in Type 2 diabetes (inhaled insulin in combination with oral agents) (Section 6.4)
- control of hyperglycemia in Type 2 diabetes (inhaled insulin in combination with longer-acting insulins) (Section 6.3)

Although the applicant does not seek an indication for the use of Exubera® in children, the clinical reviewer anticipates significant interest in the use of inhaled insulin in children, and therefore efficacy data regarding pediatric use were also considered (Section 6.5).

In general, the major Phase 3 trials met the definition of "adequate and well-controlled" studies contained in 21 CFR 314.126. One concern regarding trial design was the method of treatment

assignment (6.1.3.2). Patients were assigned to their treatment groups by block allocation within center rather than by traditional randomization. However, ordering of block sizes was random, and statistical analyses did not reveal evidence of bias related to this treatment allocation method. All studies were open label, and none used inhaler or injection placebos. Historically, clinical trials of insulin have generally not been blinded trials, due to safety, logistical, and ethical concerns.

For the most part, exclusion criteria used in Phase 2 and Phase 3 trials were unlikely to limit the general applicability of trial results. However, the following exclusion criteria could have excluded significant numbers of diabetics who might be encountered in clinical practice (Section 7.2.1.2):

- BMI >35 kg/m^2 for Type 2 diabetics
- HbA1c >12%
- Renal impairment
- Requirement of >150 units per day of subcutaneous insulin
- Signs of autonomic neuropathy, such as gastroparesis or orthostatic hypotension
- Tobacco smoking within 6 months of study or during study
- Two or more serious hypoglycemic episodes within the year prior to study
- Hospitalization or emergency room visit within the six months prior to study for poor diabetes control

Information regarding the efficacy and safety of large doses of inhaled insulin, such as that required for very obese patients, and those who have already demonstrated a high subcutaneous insulin requirement, is lacking. Significant renal impairment and autonomic neuropathy are common complications of diabetes. Although the applicant proposes in its label to exclude smokers from use of inhaled insulin, it is likely that smokers will use the drug, either because the smoking exclusion is not noted by prescribing clinicians, or because patients do not share their smoking history with their physicians.

The proposed indication for combined use of inhaled insulin and a longer-acting insulin for the treatment of Type 1 diabetes was addressed in Studies 106 and 107 (Section 6.1). Of these, 107 was most relevant, because inhaled insulin and the comparator insulin were both administered in an "intensive" fashion, similar to that used in the landmark Diabetes Control and Complications Trial (DCCT), which demonstrated that "tight" control of HbA1c resulted in a lowered risk of diabetic complications in Type 1 patients. The standard of care for Type 1 diabetes now includes a HbA1c <7.5%, with <6.5% recommended by the American Association of Clinical Endocrinologists. In Study 107, inhaled insulin was noninferior to subcutaneous insulin with regard to the primary endpoint, change from baseline in HbA1c (Section 6.1.4.2). Mean HbA1c went from 8.0% to 7.7% at 24 weeks in the inhaled insulin group, and from 8.0% to 7.8% in the SQ group. This mean value for both groups is higher than that achieved in the intensive control group in the DCCT. Although 64% of inhaled insulin group patients achieved a HbA1c <8% by 24 weeks, only 23% achieved a HbA1c <7% (Section 6.1.4.3.1). Inhaled insulin was associated with significantly lower fasting plasma glucose at end-of-study than was subcutaneous insulin, but more patients on inhaled insulin had undesirably low fasting plasma glucoses, also (Section

6.1.4.3.2). This observation was not due to differences in evening longacting insulin doses. Rates of severe hypoglycemia were also higher in the inhaled insulin group than in the SQ group by the applicant's analysis (Section 7.1.3.3.1.1). However, the FDA Biostatistics review calls into question the statistical model used by Pfizer for comparison of hypoglycemic event rates. Review by the FDA Biostatistics reviewer is ongoing as of 25 Sep 05, but it appears that a more appropriate model may show that severe hypoglycemia event rates did not actually differ between groups. Postprandial glucose excursion was moderately numerically and statistically significantly greater in inhaled insulin group patients than in subcutaneous group patients, which is undesirable due to an epidemiologic association of postprandial glucose levels with cardiovascular risk (Section 6.1.4.3.3). Noninferiority of the inhaled insulin regimen to the subcutaneous regimen in this trial does not necessarily indicate noninferiority of this inhaled regimen to the intensive subcutaneous regimen used in the DCCT. By the best-validated surrogate endpoint available (HbA1c), intensive control of Type 1 diabetes appears possible for some patients with inhaled insulin. However, it is not clear from this trial whether the average Type 1 diabetic taking inhaled insulin can attain glycemic control commensurate with the clearly established standard. Special attention may be needed to ensure control of postprandial glucose excursion, and to avoid fasting and severe hypoglycemia.

Two major trials in Type 2 diabetics included an inhaled insulin monotherapy arm compared to oral agent(s) (Section 6.2). Study 109 enrolled patients who were poorly controlled on combination oral agent therapy, and randomized patients to one of three arms: premeal inhaled insulin monotherapy, premeal inhaled insulin plus the patient's baseline oral agents, or continued combination oral agents. Study 110 compared premeal inhaled insulin monotherapy to rosiglitazone treatment. In Study 109, inhaled insulin monotherapy was superior to continued oral agent therapy for change in HbA1c at Week 12, for this population that was failing oral agent therapy at baseline (Section 6.2.4.2.1). Inhaled insulin monotherapy was superior to continued oral agent therapy for achievement of HbA1c <8% and <7%, for this population that was failing oral agent therapy at baseline (Section 6.2.4.2.2.1). Inhaled insulin monotherapy was superior to continued oral agent therapy in reduction of fasting plasma glucose and postprandial glucose excursion in this population that was failing oral agent therapy (Section 6.2.4.2.2.2). In Study 110, inhaled insulin monotherapy was superior to rosiglitazone for the primary endpoint, percentage of patients achieving a HbA1c <8% (Section 6.2.4.3.1). A higher percentage of patients in the inhaled insulin group also achieved a HbA1c <7%. Inhaled insulin treatment resulted in a greater decline in HbA1c than that seen with rosiglitazone (Section 6.2.4.3.2.1). The difference between groups was not significant for change from baseline in FPG and postprandial glucose excursion (Section 6.2.4.3.2.2). From Study 109, it appears that inhaled insulin monotherapy is effective in achieving better glucose control (by HbA1c) for Type 2 patients who are failing combination (dual) oral agent therapy. From Study 110, inhaled insulin monotherapy appears superior to rosiglitazone in achieving HbA1c goals in Type 2 patients not previously exposed to injected insulin.

Study 108 was the major completed trial utilizing inhaled insulin in combination with a longer-acting insulin for Type 2 diabetics, and review focused on this study (Section 6.3). Study 108 was a 6 month, block-allocated, open-label, parallel group study done in Type 2 patients who had been on a stable regimen of SQ insulin for at least 2 months prior to study entry, and who had

entry HbA1cs between 6 and 11%. Patients were assigned to receive either TID premeal inhaled insulin plus bedtime Ultralente® (UL), or BID mixed SQ NPH and regular insulin. The objective was to determine if inhaled insulin administered in this regimen was at least as effective (in control of HbA1c) as BID mixed SQ insulin. The clinical reviewer had some concern regarding the lower intensity of management in the SQ group (two insulin doses per day) compared to the inhaled insulin group (four insulin doses per day). The increased attention to self-care required for a four time per day intervention might in itself result in a greater decrease in HbA1c than one could achieve with a twice daily intervention. However, a twice daily injected insulin regimen is commonly used in Type 2 diabetes, and thus permits comparison to "usual care". Likely clinical scenarios of use for inhaled insulin in Type 2 diabetics would be either one in which the patient is on a mixed BID regimen and wishes to take fewer injections per day, or one in which the clinician or patient desires tighter control, but wishes to spare the patient a four shot per day regimen. In these cases, substitution of a TID premeal inhaled insulin plus a q day basal SQ injection would be likely. It will be important in this scenario to know if one would be putting the patient at risk of more hypoglycemic episodes in general, or of more serious hypoglycemic episodes. This trial design permits exploration both of the efficacy of this premeal inhaled + q day basal SQ regimen, and of the safety of the regimen with regard to the possibility of increased hypoglycemia. Furthermore, it appears that the likely efficacy of the inhaled insulin portion of this regimen is not in question, because in Study 109 (Section 6.2.4), inhaled insulin monotherapy was effective in improving glycemic control in Type 2 diabetics who were failing dual oral agent therapy. For change from baseline in HbA1c, the premeal inhaled insulin plus hs UL regimen used in Study 108 was noninferior to the BID mixed SQ regimen (Section 6.3.4.2). A slightly higher percentage of patients in the intensively-administered inhaled insulin group achieved HbA1cs of <8% and <7% than did patients in the BID SQ group (Section 6.3.4.3.1). Fasting plasma glucose declined more in inhaled insulin group patients; there was no significant difference in the change in postprandial glucose increment (Section 6.3.4.3.2). In Study 108, a regimen of TID premeal inhaled insulin plus bedtime UL was noninferior to a regimen of BID SQ mixed regular and NPH insulin, for the control of HbA1c in Type 2 diabetics. By the applicant's analysis, rates of hypoglycemia did not differ between treatment groups; reanalysis by FDA Biostatistics is ongoing. The applicant provided an interim analysis of an ongoing study, Study 1029, which, when complete, will provide a comparison of TID premeal inhaled insulin to TID premeal SQ insulin, when both are administered with a longer-acting subcutaneous insulin (Section 6.3.6). In this study, patients in the inhaled insulin group are receiving TID premeal inhaled insulin plus hs intermediate- to long- acting insulin (UL, NPH or glargine), and patients in the SQ group are receiving TID premeal insulin (regular, aspart or lispro) and hs intermediate- to long- acting insulin (UL, NPH or glargine). A one-year interim analysis of this study indicates noninferiority of the inhaled regimen(s) to the SQ regimen(s), with changes from baseline in HbA1c of -0.53 (SE 0.05) for the inhaled insulin group and -0.60 (SE 0.05) for the SQ group.

Regarding the proposed indication for combined use of inhaled insulin and oral agents for control of hyperglycemia in Type 2 diabetes, the applicant submitted the results of Studies 109, 1001, and 1002 (Section 6.4). Study 109, which was also used to support inhaled insulin monotherapy, included an arm with TID premeal inhaled insulin plus continued combination oral hypoglycemic agents (insulin secretagogue, plus glitazone or metformin). Study 1001 combined inhaled insulin with a sulfonylurea, and Study 1002 combined inhaled insulin with

metformin. Study 1001 included patients who were already poorly controlled on sulfonylurea therapy and had HbA1cs between 8 and 12%. HbA1c strata included 8-9.5%, and >9.5-12%. Patients were assigned to one of two groups: TID premeal inhaled insulin + continued SU, or metformin (1 gm BID) + continued SU. Study 1002 included patients who were already poorly controlled on metformin (1 gm BID) and had HbA1cs between 8 and 12%. HbA1c strata included 8-9.5%, and >9.5-12%. Patients were assigned to one of two groups: TID premeal inhaled insulin + continued metformin, or glibenclamide (maximum dose 5 mg BID) + continued metformin. For Study 1001, for the primary efficacy endpoint of change from baseline in HbA1c, the 6-month data did not support superiority of the addition of inhaled insulin over the addition of sulfonylurea to failed metformin therapy (Section 6.4.4.2). For Study 1002, for the primary efficacy endpoint of change from baseline in HbA1c, the 6-month data did not support superiority of the addition of inhaled insulin over the addition of metformin to failed sulfonylurea therapy (Section 6.4.4.2). However, for both studies, the addition of inhaled insulin appeared noninferior to the addition of the comparator oral agent. In Study 109, the addition of inhaled insulin to continued failed combined (dual) oral agent therapy appeared superior to continued failed combined (dual) oral agent therapy alone for change from baseline in HbA1c at 3 months (Section 6.2.4.2.1). For both Studies 1001 and 1002, the addition of inhaled insulin resulted in a greater percentage of patients achieving HbA1cs <8% than did addition of the comparator agent (Section 6.4.4.3.1). Patients with higher HbA1cs at baseline (>9.5-12%) were more likely to achieve a HbA1c <7% with the addition of inhaled insulin than with the addition of the comparator, although the percentage of patients in either treatment group who achieved a HbA1c <7% was small. In Study 109, the addition of inhaled insulin to continued failed combined oral agent therapy appeared superior to continued failed combined oral agent therapy alone for achievement of HbA1cs <8% and <7% (Section 6.2.4.2.2.1). Overall, the addition of inhaled insulin to a failed oral agent appears at least noninferior to the addition of a second oral agent for the control of Type 2 diabetes. Addition of inhaled insulin to failed combined (dual) oral agent therapy appears superior to continued failed combined oral agent therapy alone. The combination of inhaled insulin and failed combined oral agent therapy resulted in greater favorable changes in measures of glucose control in Type 2 diabetes than did inhaled insulin monotherapy, which in turn was also superior to continued failed combined oral agent therapy alone.

Regarding Type 1 diabetic pediatric use of inhaled insulin, Studies 106 and 107 included adolescents ages 12-17 years, and Study 1009 included children ages 6-11 years (Section 6.5). No children ages 5 and under were studied. Studies 106 and 107 were described above regarding use in adult Type 1 diabetics (Section 6.1.3). Study 1009 was a 3-month study conducted in Type 1 diabetic children ages 6-11 years (Section 6.5.3). A total of 120 children (61 in inhaled insulin group) were treated with either an inhaled insulin regimen (TID premeal inhaled insulin + hs or BID UL or NPH) or a SQ regimen (BID lispro or regular + q day or BID UL or NPH). There was little difference between treatment groups for change from baseline in HbA1c in Studies 106, 107 and 1009 (Section 6.5.4.1). Neither treatment group attained "tight" control of mean HbA1c in any of these studies, with mean HbA1c remaining above 8% in all treatment groups. Inhaled insulin patients had little change from baseline in HbA1c. In Study 1009, a slightly larger percentage of children ages 6-11 achieved HbA1cs <8% and <7% in the inhaled insulin group than did children in the SQ group (Section 6.5.4.2.1). In Study 1009, mean fasting

plasma glucoses remained undesirably high in both treatment groups, with no significant difference between groups (Section 6.5.4.2.3). There was no significant difference between groups for change in postprandial glucose excursion, with small declines in both treatment groups. Studies performed in children and adolescents to date do not appear to show that the desirable level of glucose control (i.e. that associated with decreased risk for later diabetic complications) can be predictably achieved with inhaled insulin. Should Exubera® be approved for use in adults, further study in children appears warranted.

In the overall Phase 3 program, for both Type 1 and Type 2 diabetics, the mean dose of long-acting insulin for inhaled insulin group patients was somewhat lower than that for subcutaneous insulin group patients (Section 7.2.1.3). The mean dose of inhaled insulin gradually increased over time, while the dose of subcutaneous short-acting insulin increased from baseline to Month 3, and then remained stable until Month 12. It is difficult to attach particular significance to either of these observations. The mean lower dose of long-acting insulin for inhaled insulin patients implies that, on average, glycemic control was not disproportionately "carried" by the long-acting component of inhaled insulin patients' regimens. The gradual increase in inhaled insulin dose without a corresponding increase in short-acting SQ dose could indicate developing resistance to the action of inhaled insulin, or neutralization of insulin action by insulin antibodies; or it could merely represent increasing familiarity and comfort with upward titration of a novel agent. In major diabetes trials, such as UKPDS and DCCT, insulin dose tended to increase gradually over time; however, it is not clear why this occurred in the inhaled insulin group here and not in the SQ group.

9.1.2 Safety Conclusions

A total of 22 deaths occurred among 3,603 subjects (0.6%) exposed to inhaled insulin in the clinical development program, as of the safety cut-off date of 1 Sep 04 (Section 7.1.1). Of these, 21 patients were participants in the clinical development program and one was a neonate born of a mother exposed to inhaled insulin. Ten deaths, including that of the neonate, occurred during controlled Phase 2/3 trials, which included 1,975 adult patients (0.5%). Twelve deaths occurred during extension studies, which included 1,449 patients (0.8%). Five patients who received comparator drugs died, out of 1,938 comparator patients (0.3%). When taking into account the longer duration of exposure for inhaled insulin groups, there is little difference in mortality rates between inhaled insulin and comparator treatments.

Of the adult patients who died during the clinical development program, 15/21 appear to have died of cardiac causes. Most diabetics die of cardiovascular disease, and the percentage of deaths which were due to cardiovascular disease during the study of this product is consistent with the usual incidence of cardiovascular death among diabetics. Those patients who died of acute causes do not appear to have had an unusually high incidence of severe hypoglycemic events (those requiring the assistance of another person, or events with a blood sugar <36 mg/dL). However, four of these patients had histories of a large number of nonserious hypoglycemic events, and one death occurred shortly after what appears to have been a hypoglycemic episode. Overall, the deaths which occurred in inhaled insulin group patients do not seem to have a stronger association with hypoglycemia than expected in diabetics treated

with subcutaneous insulin. A total of 7/21 of the total deaths occurred in Type 1 diabetics who were taking inhaled insulin. The rate of death among Type 1 inhaled insulin patients does not exceed that found in the intensive treatment groups of large randomized trials in Type 1 diabetics. No clear difference was demonstrated between inhaled insulin and comparator patients for incidence or cause of death.

In controlled Phase 2 and Phase 3 studies in adult Type 1 patients, serious adverse events occurred at a slightly higher frequency in SQ group patients than in inhaled insulin group patients (Section 7.1.2.1.1). The most common serious adverse events among Type 1 patients were hypoglycemia and loss of consciousness. In the controlled Phase 2/3 population, these events occurred with slightly greater frequency in SQ patients than in inhaled insulin patients. In Type 1 adult patients, no pattern emerged of a single type of serious nonpulmonary adverse event, or grouping of serious nonpulmonary adverse events, that occurred with significantly greater frequency among inhaled insulin group patients than among SQ patients. Pulmonary serious adverse events will be discussed separately in Dr. Seymour's review. Event terms potentially related to hypoglycemia did not occur more frequently in Type 1 adult patients receiving inhaled insulin, and appear to have occurred less frequently numerically among inhaled insulin patients than among patients receiving SQ insulin.

In controlled Phase 2 and Phase 3 studies in Type 2 patients, serious adverse events occurred with approximately equal frequency among inhaled insulin patients and comparator patients (Section 7.1.2.1.2). Myocardial infarction, chest pain, angina and hypoglycemia were the most common SAE terms among Type 2 patients. Inhaled insulin group patients did not have a significantly higher frequency of serious nonpulmonary adverse event term groupings of interest, such as terms related to coronary artery disease, hypoglycemia, loss of consciousness, seizure, accidents, injuries, neoplastic events, or immune system disorders. Hypoglycemia adverse event terms occurred numerically more frequently among SQ patients than among inhaled insulin patients or OA patients. Pulmonary adverse event term groupings will be addressed in Dr. Seymour's pulmonary review.

Hypoglycemia reported as a serious adverse event occurred somewhat more frequently among children taking inhaled insulin than among children taking SQ insulin (Section 7.1.2.1.3). Otherwise, no single type of serious adverse event or grouping of adverse events occurred more frequently among pediatric patients taking inhaled insulin than among pediatric patients taking SQ only. Almost all serious adverse events among pediatric patients were related to hypoglycemia. Severe hypoglycemia was reported as a serious adverse event term more frequently among pediatric patients than among either adult Type 1 or Type 2 patients.

When evaluating serious hypoglycemic adverse events, the clinical reviewer also considered whether the nature of serious hypoglycemic adverse events differed between inhaled insulin and comparator patients (Section 7.1.2.3). The clinical reviewer examined all adverse event narratives provided by the applicant, and identified those hypoglycemic events which had serious accompanying events, e.g. loss of consciousness, syncope, accidents and injuries. Adult inhaled insulin group patients do not appear to have had a higher incidence of potentially dangerous accompanying events to serious hypoglycemic episodes than did comparator patients.

For further evaluation of serious adverse events, the clinical reviewer compared the event terms used by the applicant in its serious adverse event listings to the terms used by the investigators (Section 7.1.2.3). This was done in order to ascertain whether the nature of serious adverse events could have been downplayed in the inhaled insulin groups, or embellished in the comparator groups. Upon review of all serious hypoglycemic event narratives, the clinical reviewer noted some cases in which the event was reported only as hypoglycemia, and an accompanying accident or injury was not mentioned in the listing. Although the serious adverse event listings for hypoglycemic events sometimes did not include mention of an accompanying accident or injury, this reconciliation difference did not occur more frequently among inhaled insulin patients than among comparator patients. Terms used for other types of serious adverse events in the applicant's serious adverse event listings almost always reconciled closely with those found in provided event narratives.

Because diabetic ketoacidosis is the leading cause of mortality among pediatric Type 1 diabetics, it was an event of significant interest (Section 7.1.2.3). No deaths from diabetic ketoacidosis occurred in children in this development program, and no cases of cerebral edema accompanying DKA were reported. Pediatric serious adverse events of diabetic ketoacidosis did not occur more frequently among inhaled insulin patients than among SQ patients in controlled Phase 2/3 trials (one case among inhaled insulin patients, two cases among SQ patients). In the extension study 111, a total of 21 serious adverse events of ketoacidosis occurred among 17 patients. This study had a large total duration of exposure for pediatric patients, with a total of 5,801 subject-months of exposure. Comparative incidence rates for DKA were 0.04 cases of diabetic ketoacidosis per child-year for inhaled insulin patients in all Phase 2/3 trials and 0.04 cases of DKA per child-year for SQ patients in controlled Phase 2/3 trials. In the medical literature, the reported incidence of DKA (after initial diagnosis) ranges from 1-10% per year (Dunger 2003).

When considering all adverse events (serious and nonserious), in controlled Phase 2/3 studies in Type 1 diabetics, the overall incidence of adverse events was similar between inhaled insulin patients and SQ patients, with 99.4% and 98.7% of patients, respectively, experiencing some type of adverse event (Sections 7.1.5.3 and 7.1.5.4). In controlled Phase 2/3 studies in Type 2 patients, adverse events occurred with nearly equal frequency between inhaled insulin patients [93.7% with event(s)] and SQ patients [96.7% with event(s)]. Among Type 2 patients treated with oral agents, 81.7% experienced an adverse event. This lower rate among oral-agent-treated patients is due to a lower rate of hypoglycemia among these patients than among inhaled insulin or SQ patients (Section 7.1.5.4).

Hypoglycemia was the most common adverse event among Type 1 patients, and occurred with equal frequency in inhaled insulin and SQ group patients (Section 7.1.5.4). Cough was a common adverse event, and occurred with significantly greater frequency among inhaled insulin patients (196/698, 28.1%) than among SQ patients (59/705, 8.4%). Other respiratory adverse events (dyspnea, respiratory disorder) also occurred with greater frequency among inhaled insulin patients. Nasopharyngeal adverse events (epistaxis, pharyngitis, rhinitis, sinusitis) occurred at a higher frequency in inhaled insulin groups (310/698, 44.4%) than in SQ groups (220/705, 31.2%). Adverse event terms related to accidents occurred with equal frequency

between groups. The event term "allergic reaction" occurred with slightly greater numeric frequency in inhaled insulin patients (31/698, 4.4%) than among SQ patients (23/705, 3.3%).

Among Type 2 patients, hypoglycemia was the most common adverse event term, and occurred most commonly in SQ patients (360/488, 73.8%) (Section 7.1.5.4). Inhaled insulin patients had a lower rate of hypoglycemic events than did SQ patients, but had a higher rate than did OA patients [inh ins = 794/1277 (62.2%), OA = 185/644 (28.7%)]. Cough was also very common, and occurred with significantly higher frequency among inhaled insulin patients than among comparator patients (inh ins 21.0%, SQ 7.4%, OA 3.7%). Accident and injury terms occurred numerically more frequently among SQ patients than among other groups. Several respiratory events (e.g. asthma, bronchitis, dyspnea) had a somewhat higher frequency among inhaled insulin patients than among comparator patients; please see Dr. Seymour's pulmonary review for discussion. Headache and paresthesia occurred at a slightly higher numeric rate in inhaled insulin groups than in comparator groups.

Hypoglycemic event rates did not differ between pediatric inhaled insulin and SQ patients (Section 7.1.5.4). Among pediatric patients, the adverse event term seen with the greatest excess frequency for inhaled over SQ was cough. Nausea, headache and dizziness also occurred numerically more frequently in inhaled insulin patients than in SQ patients. When combining ear terms, adverse events related to the ear occurred more frequently in children in inhaled insulin groups than in children in SQ groups. The terms ear pain, ear disorder and otitis media had a combined event rate of 18/153 (11.8%) in the inhaled insulin patients vs 7/148 (4.7%) in SQ patients. This difference could be due to chance; however, the Eustachian tube in children provides an anatomically more direct route to the middle ear than does the Eustachian tube of adults. The potential mechanism of these ear events is unknown, but could be due to inflammation, or entry of oral secretions or insulin powder into the Eustachian tube related to the inhalation maneuver.

Common adverse events which seem likely to be related to inhaled insulin use include cough; nasopharyngeal adverse events such as pharyngitis, rhinitis and sinusitis; and certain respiratory adverse events such as dyspnea (Sections 7.1.5.4 and 7.1.5.5). Adverse events related to the ear seem to be related to inhaled insulin use in children (Sections 7.1.5.4 and 7.1.5.5).

There is no clear relationship between age and incidence of rhinitis or sinusitis in patients exposed to inhaled insulin, and dose-dependency was not demonstrated. Inhaled insulin patients who developed rhinitis did so sooner than SQ patients who developed rhinitis (Section 7.1.5.6).

Regarding serious but rare adverse events, the events "retinal hemorrhage" and "allergic reaction" appeared to occur more frequently per unit of patient-time over all Phase 2/3 trials than these events occurred per unit of patient time in comparator groups in the controlled Phase 2/3 trials (Section 7.1.6). Concern exists for the development of undesirable immune responses to inhaled insulin. Malignant neoplasms did not occur with greater frequency in inhaled insulin patients per unit of patient-time than in comparator patients.

Hypoglycemia reported as a serious adverse event was discussed above with other serious adverse events (Sections 7.1.2.2 and 7.1.2.3). Hypoglycemia was also evaluated in two other ways (Section 7.1.3.3.1).

In individual studies, the applicant defined severe hypoglycemic events as those in which all three of the following criteria were met:

- the patient was unable to self-treat
- the patient exhibited at least one of the following- memory loss, confusion, uncontrollable behavior, irrational behavior, unusual difficulty in awakening, suspected seizure, loss of consciousness
- measured blood glucose was ≤ 49 mg/dL; or if no blood glucose was measured, clinical manifestations were reversed by oral carbohydrates, subcutaneous glucagon, or intravenous glucose.

For the overall safety review, severe hypoglycemia was defined as an event in which the subject had a measured blood glucose of ≤ 36 mg/dL and/or required assistance. The specified blood glucose was requested by a previous FDA clinical reviewer.

For adult Type 1 patients overall, inhaled insulin was not associated with a higher rate of severe hypoglycemia (BG ≤ 36 mg/dL or required assistance) than was SQ insulin (Section 7.1.3.3.1.1). However, in Study 107, the "intensive control" study in Type 1 diabetics, severe hypoglycemic events (by the applicant's study definition) did appear to occur more frequently in the inhaled insulin group than in the SQ only group (Section 7.1.3.3.1.1), by the applicant's analysis. This could be an important finding, because intensive control is now the standard of care for Type 1 diabetics, and severe hypoglycemia tends to be the limiting factor in achieving tight control. However, it should be noted that FDA Biostatistics review calls into question the statistical model used by Pfizer for comparison of hypoglycemic event rates. Review by the FDA Biostatistics reviewer is ongoing as of 25 Sep 05, but it appears that a more appropriate model may show that severe hypoglycemia event rates did not actually differ between treatment groups.

Among Type 1 diabetics overall, in both the inhaled insulin and SQ groups, overall hypoglycemic (severe and nonsevere) event rates declined over time, with similar rates of decline between groups (Section 7.1.3.3.1.1). This could indicate an initial period of adjustment to the study regimen, with declining incidence of severe hypoglycemic events as the study progressed, or a decline in reporting of clinical events. Although there was an apparent decline over time in controlled Phase 2/3 studies, severe hypoglycemic adverse events continued to occur in extension studies; the occurrence of severe hypoglycemic adverse events cannot be entirely attributed to an initial learning period for inhaled insulin (Appendix 10.5).

Among Type 1 diabetics, inhaled insulin group patients tended to have higher hypoglycemic event rates in the early morning than did SQ group patients, while the converse was true for midday (Section 7.1.3.3.1.1). This was observed for the overall pattern in Phase 2 and Phase 3 trials, and held true across most studies. The reason for this consistent pattern of prebreakfast hypoglycemia in inhaled insulin group patients is unclear. One would expect prebreakfast hypoglycemia to be related to evening dosing of longacting insulin, rather than to the patient's

short-acting insulin. However, in Study 107, the intensive control study in Type 1 diabetics, mean dose of longacting insulin was actually somewhat lower for inhaled insulin group patients, both for the evening dose and for the total daily dose (Section 6.1.4.3.2). Study 1026 was the only study in which 0200 blood sugars were routinely measured (Section 6.1.4.3.2). In this study, hypoglycemia was more common at 0200 for inhaled insulin group patients than for SQ patients. For the overall population of Type 1 diabetics in all Phase 2/3 studies, the majority of hypoglycemic episodes reported as serious adverse events among inhaled insulin patients occurred in the early morning hours (for those patients for whom serious adverse event narratives were provided).

Overall, severe hypoglycemic events were less common among patients with Type 2 diabetes compared to patients with Type 1 diabetes (Section 7.1.3.3.1.2). Inhaled insulin group patients were not more likely to experience severe hypoglycemic events than SQ group patients, in studies of Type 2 patients who were using insulin at baseline. However, inhaled insulin group patients were more likely to experience severe hypoglycemia than were patients in oral agent comparator groups in studies of patients who were not insulin-using at baseline. Control of glycemia was in general better with inhaled insulin than with oral agents, and thus a higher rate of hypoglycemia would be expected. In Studies 104, 109 and 110, all severe hypoglycemic events occurred in inhaled insulin group patients. The FDA Biostatistics reviewer is reanalyzing these hypoglycemic data in the same manner as the reanalyses for Type 1 diabetic patients.

In studies of Type 2 diabetics where SQ was used as a comparator, rates of hypoglycemia declined over time for both SQ and inhaled insulin patients (Section 7.1.3.3.1.2). In studies of Type 2 diabetics where oral agents were used as a comparator, event rates were too low to distinguish a time trend. The applicant provided data regarding time of day of hypoglycemic events for Type 2 patients, but the number of events was too low to discern a trend for any particular time of day.

In Studies 106 and 1009, children and adolescents who were treated with inhaled insulin were somewhat less likely to experience protocol-defined hypoglycemia (severe or nonsevere) than patients who were taking SQ insulin (Section 7.1.3.3.1.3). In Study 107, there was no demonstrated difference between groups. Protocol-defined severe hypoglycemic events did not occur more frequently among pediatric inhaled insulin patients in Studies 106 and 1009. In Study 107, there were 16 events of severe hypoglycemia in the inhaled insulin group, and 10 events in the SQ group. Although the risk ratio was 1.62 for occurrence of severe hypoglycemia for inhaled insulin-treated adolescents vs SQ-treated adolescents, the limits of the confidence interval fell on either side of 1, and therefore the difference between groups was not statistically significant. Overall, protocol-defined hypoglycemia, and protocol-defined severe hypoglycemia, did not appear to occur statistically significantly more frequently in pediatric patients treated with inhaled insulin compared to those treated with SQ alone. Biostatistics reanalysis of hypoglycemic event data is ongoing.

Dose dependency of adverse events was explored (Sections 7.4.2.1 and 7.1.5.6). Among Type 1 diabetics, increased sputum production may be dose-related. When one examines the overall incidence of accidents and fractures, these events occurred at a higher numerical rate in patients

on higher doses. For serious adverse events of accident and injury, the applicant specifically examined each event to look for a relationship to hypoglycemia; no difference was noted between treatment groups for incidence of hypoglycemia-related serious accidents and injuries.

Among Type 2 diabetics, the incidence of dyspnea appeared to be dose-related (Section 7.4.2.1). Several respiratory events occurred with lower frequency in patients who were taking <10 mg/day of inhaled insulin than in those taking ≥ 10 mg/day, but with roughly equal frequency between patients taking 10-20 mg/day and those taking >20 mg/day. These events included total respiratory events, bronchitis, respiratory tract infection, and rhinitis. The overall incidence of cardiovascular events appeared to be dose-related, although no one type of event predominated. Accidental injury and fracture also appeared to be dose-related. Retinal disorders appear to be dose-related. The overall incidence of malignant neoplasms does not appear to be dose-related, nor does the incidence of any single malignancy. While the possible dose-relatedness of some of these events is concerning, these findings must be interpreted with caution. As Type 2 diabetes progresses, beta cell failure occurs with progressive loss of endogenous insulin secretion and increasing requirement for drug therapy, and eventually with increasing insulin requirement. A higher insulin requirement may be a reflection of duration of disease, which is in turn associated with aging; either duration of disease or aging could be associated with an increased incidence of many adverse events.

Time dependency of adverse events was also explored (Section 7.4.2.2). Among Type 1 patients, for respiratory events in general, and for some specific respiratory events (cough, respiratory tract infection, rhinitis, sputum increased, epistaxis), the time interval in which these adverse events were more likely to be reported (per patient) was during the first 6 months of inhaled insulin treatment. Decreased reporting of these events in subsequent treatment time intervals could be due to a true decrease in the occurrence of the event, to dropout due to the event, or to nonreporting by patients who felt they had already brought the event to the attention of investigators, and therefore did not report it again. For Type 1 patients, accidental injury, motor vehicle accidents, and accidental fractures were more likely to be reported (per patient) during the time interval beyond 24 months. This could be due to a true increase in the incidence of the events, or to longer per-patient exposure during this time period. Among Type 1 patients, hyperglycemia and hypoglycemia were more likely to be reported as adverse events (per patient) in the time interval of 0-6 months of inhaled insulin treatment. This may be due to the learning process involved in instituting a novel treatment. As with respiratory adverse events, decreased reporting of these metabolic events in subsequent treatment time intervals could be due to a true decrease in the occurrence of the event, to dropout due to the event, or to nonreporting by patients who felt they had already brought the event to the attention of investigators, and therefore did not report it again. For Type 1 patients, retinal disorders were more likely to be reported (per patient) during the time interval beyond 24 months. This could be due to a true increase in the incidence of the events, or to longer per-patient exposure during this time period.

Among Type 2 patients, for respiratory events in general, and for some specific respiratory events (cough, respiratory tract infection, epistaxis), the time interval in which these adverse events were more likely to be reported (per patient) was during the first 6 months of inhaled insulin treatment (Section 7.4.2.2). Accidental injuries and fractures were more likely to be

reported (per patient) during the time interval beyond 24 months. Hypoglycemia was more likely to be reported as an adverse event (per patient) in the time interval of 0-6 months of inhaled insulin treatment. This may be due to the learning process involved in instituting a novel treatment. No clear temporal pattern emerged among Type 2 patients for malignant neoplasms in general or for any particular neoplasm. For Type 2 patients, retinal disorders were more likely to be reported (per patient) during the time interval beyond 24 months.

Demographic interactions for adverse events were also explored (Section 7.4.2.3). A summary of the observations for demographic differences for adverse events includes:

- Numbers of non-Caucasian patients were too small to permit meaningful comparisons between treatment groups.
- For Type 1 patients, the event "sputum increased" had a higher incidence in older patients and in males for inhaled insulin patients, than it had in SQ patients.
- For Type 1 patients in the SQ group, overall respiratory events occurred with decreasing frequency by age group, but in inhaled insulin patients, overall respiratory events occurred with approximately equal frequency between age groups. For patients age 18 and older, overall respiratory events occurred more frequently among inhaled insulin group patients than among SQ patients.
- For Type 1 diabetic children, otitis media occurred more frequently in inhaled insulin group children than in SQ group children. Otitis media occurred with low and approximately equal frequency in adult Type 1 patients in both treatment groups.
- For Type 1 patients, the events "allergic reaction" and "diarrhea" occurred with higher frequency among males than among females in the inhaled insulin group. This gender difference was not apparent in comparator groups.
- For Type 2 patients, the event "dry mouth" appeared to decrease in incidence with age in inhaled and oral agent groups, but not in the SQ group.
- For Type 2 patients, for all treatment groups, women were more likely to experience cough than men; for both genders, cough occurred much more frequently in inhaled insulin group patients than in comparator patients.
- For Type 2 patients, the incidence of bronchitis increased by age group for inhaled insulin patients, but not for comparator patients.
- For Type 2 patients, accidental injury, hypoglycemia, and respiratory tract infection occurred more frequently in men than in women in the inhaled insulin group. This gender difference was not observed in the comparator groups.
- For Type 2 patients, paresthesia occurred more frequently in women than in men in the inhaled insulin group. This gender difference was not observed in the comparator groups.

Among these observations, those most likely to have clinical significance include:

- Otitis media in children appears related to inhaled insulin treatment.
- The incidence of bronchitis appears to increase by age group for inhaled insulin patients, but not for comparator patients.
- For Type 2 patients, accidental injury and hypoglycemia appear to occur more frequently in men than in women taking inhaled insulin. This gender difference was not observed in the comparator groups.

- The lack of data for non-Caucasians is of concern. African Americans have lower baseline lung function than Caucasian Americans and Mexican-Americans. Pulmonary safety of Exubera® requires further study in African Americans.

Across the development program, greater increases occurred in insulin antibody levels, as reflected by insulin binding activity, for patients taking inhaled insulin than for patients taking either subcutaneous insulin alone or oral agents alone (Section 7.1.3.3.2). This observation led to concerns about potential clinical consequences of this antibody formation. The following points can be synthesized from extensive data regarding insulin antibodies associated with inhaled insulin use, and the potential clinical consequences of these antibodies:

- Seroconversion rates were higher among inhaled insulin patients than among comparator patients (Section 7.1.3.3.2.1). In studies in which a quantitative insulin binding activity assay was used, 75% of all inhaled insulin patients who had undetectable insulin binding activity at baseline had measurable insulin binding activity at end of study or last measurement, while only 10% of comparator patients seroconverted. Seroconversion rates for inhaled insulin patients were higher among Type 1 patients than among Type 2 patients, and were higher among children than among adults.
- For both Type 1 and Type 2 patients, inhaled insulin was associated with higher end-of-study insulin binding activity, and with greater change from baseline, than was SQ insulin (Section 7.1.3.3.2.2).
- Among Type 1 inhaled insulin patients, pediatric patients had higher end-of-study insulin binding activity and greater changes from baseline than did patients ≥ age 18 years (Section 7.1.3.3.2.2). Among Type 1 inhaled insulin patients, female patients had higher end-of-study insulin binding activity and greater changes from baseline than did male patients.
- Among Type 2 patients, patients who had been using injected insulin prior to study enrollment had higher insulin binding activity at end of study, and greater changes from baseline, than did patients who had not been using injected insulin prior to study (Section 7.1.3.3.2.2). Among Type 2 patients using inhaled insulin, the degree of insulin binding activity appeared to correlate with age.
- Insulin antibodies were predominantly IgG for both inhaled insulin patients and comparator patients (Section 7.1.3.3.2.3). Binding profile was consistent with low affinity, high binding capacity antibodies.
- In general, adverse events of an allergic nature tended to occur with similar frequency between inhaled insulin and SQ group patients (Section 7.1.3.3.2.4). For Type 1 patients, the event terms "allergic reaction" and "rhinitis" occurred somewhat more frequently among inhaled insulin patients than among SQ patients (Sections 7.1.3.3.2.4.1 and 7.1.3.3.2.4.2).
- There were no apparent associations between insulin binding activity and incidence of hypoglycemic events (Section 7.1.3.3.2.4.2). In controlled Phase 2/3 trials, patients who had severe specifically-defined hypoglycemic events did not tend to have higher insulin binding activity than patients who did not have severe hypoglycemic events.
- When examining those patients who had the highest insulin binding activity (>2,000 μU/mL), 33/37 were Type 1 diabetics, and 11 were children (Section 7.1.3.3.2.5). Three of these 33 patients experienced adverse events of a potentially allergic nature (allergic bronchiolitis, dermatitis of face and arms, bilateral eyelid swelling). Among the Type 1

patients with high insulin binding activity, 9 patients experienced a total of 67 severe hypoglycemic events. These 9 patients represent 27% of the total Type 1 study population of patients with high insulin binding activity; in the overall controlled Phase 2/3 population, 17% of inhaled insulin patients experienced a severe hypoglycemic event. However, when one considers duration of exposure, patients with high insulin binding activity did not experience severe hypoglycemic events more frequently than did the population of Type 1 patients in all Phase 2/3 trials.

- The applicant made extensive attempts to [redacted], but was unable to do so (Section 7.1.3.3.2.6). Development of neutralizing insulin antibodies might be associated with increasing insulin requirements or worsening indices of glycemic control. However, there was no association between degree of insulin binding activity and HbA1c, postprandial glucose, fasting glucose or insulin requirement.
- The actual drug substance used [redacted] insulin, Aventis) did not exhibit inherent immunogenicity in Aventis Study 3002, in which 476 insulin-naïve Type 2 patients were randomized to receive either [redacted] or SQ Huminsulin® (Eli Lilly human insulin) for one year (Section 7.1.10). Rates of insulin binding activity did not differ between groups.
- Discontinuation of inhaled insulin resulted in a decline in insulin binding activity, although levels did not return to baseline by 12 weeks of followup (Section 7.1.3.3.2.8).

Overall, it appears that although inhaled insulin patients demonstrate a brisk increase in insulin antibody formation, studies to date do not demonstrate a clinical correlate of this finding.

Observations of note regarding reasons for discontinuation among Type 1 diabetics include (Section 7.1.3.1):

- In controlled trials, discontinuations due to adverse events were more common among inhaled insulin patients than among SQ patients.
- A large number of inhaled insulin patients withdrew consent during uncontrolled portions of Phase 2 and Phase 3 trials

Observations of note regarding reasons for discontinuation among Type 2 diabetics include (Section 7.1.3.1):

- Discontinuations due to adverse events occurred slightly numerically more frequently among inhaled insulin patients than among SQ patients, but occurred with equal frequency between inhaled insulin patients and patients in oral agent groups.
- As noted with Type 1 patients, a large number of patients were discontinued from study for "withdrawn consent" in the uncontrolled portions of Phase 2 and Phase 3 trials.

In controlled Phase 2 and Phase 3 studies in Type 1 diabetics, the most common category of events leading to discontinuation was respiratory, and all discontinuations due to respiratory adverse events occurred in inhaled insulin group patients (Section 7.1.3.2). When considering all Phase 2 and Phase 3 trials, both controlled and uncontrolled, respiratory events were again the most common category of adverse events leading to discontinuation, with a total of 21 (2.3%) of inhaled insulin group patients discontinuing due to respiratory AEs. Cough was the most

common AE leading to discontinuation, accounting for 10 discontinuations (1.1% of all Ph 2/3 Type 1 patients).

In controlled Phase 2 and Phase 3 studies in Type 2 diabetics, the most common category of events leading to discontinuation was respiratory, and 26/28 discontinuations due to respiratory adverse events occurred in inhaled insulin group patients (Section 7.1.3.2). When considering all Phase 2 and Phase 3 trials, both controlled and uncontrolled, respiratory events were again the most common category of adverse events leading to discontinuation, with a total of 42 (3.9%) of inhaled insulin group patients discontinuing due to respiratory AEs. Cough was the most common AE leading to discontinuation, accounting for 26 discontinuations (1.6% of all Ph 2/3 Type 2 patients). Three events of oropharyngeal irritation (glossitis, gingivitis, pharyngitis) resulted in discontinuation in controlled Phase 2/3 trials in inhaled insulin patients, with one additional discontinuation due to pharyngitis in extension trials. No discontinuations due to oropharyngeal irritation occurred in SQ or oral agent control patients. In controlled Phase 2 and Phase 3 trials in Type 2 diabetics, discontinuations due to neoplasia did not occur more frequently among inhaled insulin group patients than among control patients.

The large number of patients for whom consent was withdrawn was of concern to the clinical reviewer, because it raised the question of whether some of these patients actually dropped out for adverse events, tolerability issues, device use problems, or other noteworthy reasons (Section 7.1.3.1). Upon request, the applicant submitted further information regarding the actual wording that the patient or investigator gave as the reason for those discontinuations that were listed as due to "withdrawn consent", "patient no longer willing to participate in study" or "other". This information was not available for all patients. Most of these stated reasons did not relate to adverse events, tolerability issues, or device problems, but some did. When considering the group of those studies for which revised data for reasons for discontinuation were available, the apparently more frequent misclassification of discontinuation reasons among inhaled insulin patients than among comparator patients led to greater differences between groups in the rates of discontinuation for:

- adverse events (greater difference in frequency for both Type 1 and Type 2)
- insufficient clinical response (greater difference in frequency for Type 1)

If investigators were unclear on how reasons for discontinuation should have been classified, one would expect that they would have misclassified reasons with approximately equal frequency in inhaled insulin and control groups. However, discontinuations due to adverse events and insufficient clinical response appear to have been misclassified more frequently for inhaled insulin patients than for comparator patients in the controlled Phase 2/3 population (Section 7.1.3.1). This disparity in rates of apparent misclassification of reasons for discontinuation is unexplained, but raises a question of investigator reporting bias in this open-label development program.

On 23 Aug 05, in an email from Mr. Brian Green of Pfizer to Dr. Elekwachi Oluchi, DMEDP Project Manager, Pfizer provided details of continuing efforts they have made to improve the accuracy of reporting of reasons for discontinuation.

Temporary discontinuations due to adverse events were more common among Type 1 inhaled insulin patients than among Type 1 patients in SQ groups (Section 7.1.3.1). For adult Type 1 patients in controlled Phase 2 and Phase 3 trials, 4.7% of inhaled insulin patients had temporary discontinuations due to adverse events, compared to 1.3% of SQ patients. The most common category of adverse events leading to temporary discontinuation among Type 1 diabetic inhaled insulin patients was respiratory, with 16 such events among inhaled insulin patients vs 1 such event in the SQ groups.

Temporary discontinuations due to adverse events were more common among Type 2 inhaled insulin patients (5.6% of patients) compared to Type 2 SQ group patients (1.6% of patients), but occurred with comparable frequency in patients in oral agent groups (6.8%) (Section 7.1.3.1). Again, the most common category of event leading to temporary discontinuation was respiratory, with 24 Type 2 subjects (1.9%) temporarily discontinuing inhaled insulin for respiratory reasons, vs 1 respiratory temporary discontinuation among SQ patients, and zero among oral agent patients. Temporary discontinuations due to hypoglycemia were also more common among Type 2 inhaled insulin patients, with 14 patients (1.1%) temporarily discontinuing due to hypoglycemia, vs 3 (0.6%) and 3 (0.5%) of SQ and oral agent patients, respectively. Temporary discontinuations due to digestive events, particularly diarrhea, occurred more frequently among Type 2 oral agent group patients.

The incidences of new or worsening laboratory abnormalities did not appear to differ between inhaled insulin group patients and comparator patients (Section 7.1.7).

An intensive QTc study was not performed. From routine electrocardiograms from those studies for which postbaseline ECGs were obtained, mean changes in QTc were not significantly different between inhaled insulin and comparator patients in controlled Phase 2 and Phase 3 studies (Section 7.1.7.5.2). From routine electrocardiograms, outlier abnormalities of the QTc interval did not occur more frequently among inhaled insulin patients than among comparator patients in controlled Phase 2 and Phase 3 studies. Among adult Type 1 and Type 2 diabetics, there was little difference between groups for mean ECG changes in heart rate, PR interval or QRS width (Section 7.1.9.3).

Mean pulse and blood pressure did not change substantially from baseline to last observation for adult patients, and there were no significant differences between treatment groups (Section 7.1.8.3).

Type 2 patients who were insulin-using at study entry did not gain more weight with inhaled insulin than with comparator; in Study 108, SQ patients actually gained statistically significantly more weight (1.28 kg, 95% CI 0.6-1.96). However, inhaled insulin patients who were not using insulin at study entry did have statistically significantly greater weight gain than comparator patients in several studies (Section 7.1.8.3.1). The difference in weight gain was most evident in Study 1001, in which add-on inhaled insulin was compared to add-on metformin.

Study 1007 was a clinical pharmacokinetic and pharmacodynamic study conducted in 10 gestational and 3 pregestational diabetic women (Section 7.1.14). It was an open-label,

randomized, two-period, two-treatment, crossover study. Each subject received a single morning fasting dose of either 9 U regular SQ insulin or 1 puff of 3 mg inhaled insulin, then no study insulin for 14 days (with continued usual management of their diabetes), then a single dose of cross-over study medication. Insulin Tmax was earlier with inhaled insulin administration than with regular SQ insulin. Cmax was 83% higher with inhaled insulin than with regular SQ. AUC_{0-360} was similar for both treatments. Insulin Tmax in this study was similar to that seen in nonpregnant diabetics in other studies, where Tmax ranged from 38-78 minutes. Fasting insulin Cmax in these women was also similar to fasting insulin Cmax seen in nonpregnant diabetics. Bioavailability of inhaled insulin relative to SQ was 10% based on geometric mean; this relative bioavailability is similar to that seen in nonpregnant women. Time to maximum decline in glucose was somewhat shorter for pregnant inhaled insulin patients in this study (210 minutes) than for nonpregnant Type 2 diabetics receiving inhaled insulin in Study 1004, where the time to maximum decline in glucose was 248 minutes. The maximum decline in glucose concentration was less in these pregnant diabetics exposed to inhaled insulin than it was in nonpregnant Type 2 diabetics in study 1004, but significant differences in baseline glucose levels limit the interpretability of this observation.

Clinically apparent spontaneous abortions occur in insulin-requiring diabetic women at a rate roughly twice that of the normal population of pregnant women (29.5% vs 10-15%) (Miodovnik 1988). In the Exubera® development program, 4/10 women who became pregnant while taking inhaled insulin had a spontaneous abortion (Section 7.1.14). In Studies 106 and 107, mean end-of-study insulin antibody levels for Type 1 nonpregnant diabetic women were 32.6% binding (SD 22.46) for the semiquantitative Mayo assay, and 435.0 μU/mL (SD 1194.2) for the quantitative Esoterix® assay. None of the women in the development program who had adverse pregnancy outcomes had known insulin antibody levels higher than these means.

The information obtained about human reproductive risk of Exubera® is not substantial enough at this time to conclude that Exubera® can cause fetal harm, and thus Pregnancy Categories D or X are not warranted. The clinical reviewer concurs with the assignment of Pregnancy Category C for Exubera®.

Study 1004 was conducted in elderly (>65 years of age), obese Type 2 diabetics, and compared inhaled insulin (4 mg) PK and PD to that of SQ regular insulin (12 U) (6 mg inh ins or 18 U SQ for patients with weight ≥ 150 kg) (Section 8.3). The study did not include a control arm of younger patients. Inhaled insulin had an earlier insulin Tmax and a higher Cmax, but a similar exposure by AUC_{0-360}.

Data are insufficient for conclusions regarding the potential effect of Exubera® on growth.

Pharmacokinetic studies of inhaled insulin in hepatic and renal impairment were not submitted by the applicant.

Some data were submitted to characterize the use of inhaled insulin in COPD patients (Section 7.4.2.4). Study 1005 compared inhaled insulin PK between healthy patients and those with COPD. Following administration of 3 mg of inhaled insulin, Cmax was greater (by up to 50%)

in COPD patients than in healthy subjects. Tmax occurred 25-50 minutes earlier in COPD patients compared to normal subjects. Overall insulin exposure (AUC_{0-360}) was greater in COPD patients than in healthy subjects (by approximately 15%). Bioavailability of inhaled insulin was 11% in healthy controls compared to 23-25% in COPD patients.

As of 1 Sep 04, four patients with COPD had died; one of these was taking inhaled insulin and died of metastatic colon cancer (Section 7.4.2.4). No asthma patients had died as of 1 Sep 04.

Hypoglycemia event rates did not differ between underlying lung disease patients (with COPD or asthma), and those without these disorders, for either inhaled insulin or comparator patients (Section 7.4.2.4). Patients with either asthma or COPD who were taking inhaled insulin appeared to experience asthenia more frequently than comparator patients (with or without underlying lung disease), and more frequently than inhaled insulin patients without underlying lung disease. Otherwise, the small number of each type of event within the underlying lung disease groups precludes meaningful conclusions regarding other types of events.

Declines in FEV1 and DLco occurred more frequently among inhaled insulin patients than among control patients in the controlled Phase 2/3 population, and are further discussed in Dr. Seymour's pulmonary review. The clinical reviewer examined nonpulmonary adverse events in those patients who had significant declines in PFTs, defined as declines from baseline to last observation of ≥15% in FEV1, TLC or FVC, and/or ≥20% decline in DLco (Section 7.4.2.4). Hypoglycemia rates (by study definition of requirement for assistance, or BG value <36 mg/dL) were similar between patients who had significant PFT declines and those who did not, for both inhaled insulin and comparator patients. Hypoglycemia rates among patients who had declines in PFTs were similar between inhaled insulin and comparator patients. Reported adverse events of hypoglycemia occurred more commonly in inhaled insulin patients who had significant declines in PFTs than in comparator patients who had significant declines in PFTs [154/218 (70.6%) vs 86/154 (55.8%)], but at an equal rate to that seen in comparator patients who did not have significant declines in PFTs (1069/1512, 70.7%). Total cardiovascular events occurred at a higher rate in inhaled insulin patients who had a significant decline in PFTs (45/218, 20.6%) than in comparator patients who had a significant decline in PFTs (26/154, 16.9%) and comparator patients who did not have a significant decline in PFTs (202/1512, 13.4%). No single cardiovascular event occurred at a significantly higher rate among inhaled insulin patients who had significant declines in PFTs.

Tobacco smoking within six months prior to randomization was an exclusion criterion for Phase 2/3 studies. In clinical pharmacology studies (005, 016, 1003, 1020), inhaled insulin pharmacokinetics and pharmacodynamics were significantly different in smokers (Section 7.4.2.4). In nondiabetic and Type 2 diabetic smokers, Cmax, Tmax and AUC of inhaled insulin were 2-5 fold higher than those of nonsmokers. Smoking cessation led to a decline in insulin exposure within 3 days of abstinence, with further attenuation over time; by 7 days, insulin exposure was near that seen in nonsmokers. Resumption of smoking after abstinence resulted, within 2-3 days, in increased exposure similar to that seen prior to smoking cessation. The applicant is concerned about these findings, and considers the potential for rapid changes in systemic insulin exposure to be a prohibitive risk associated with cigarette smoking. The

applicant recommends that patients should abstain from smoking for at least 6 months before inhaled insulin treatment, and should remain abstinent during inhaled insulin treatment. However, in order to reduce the likelihood that smokers will use inhaled insulin, specific education of patients and providers may be needed, with enhanced emphasis on the risk. Physicians may overlook the smoking statement in a long product label, and patients sometimes do not share their smoking history with their physicians.

Study 1005 included pharmacokinetic data regarding co-administration of inhaled insulin and inhaled albuterol (Section 7.4.2.5). While overall, inhaled insulin PK did not differ from 30 minutes pre- to 30 minutes post- albuterol, the small subset of emphysema patients (5/12 total COPD patients) had mean insulin exposure that was 46% higher post-albuterol than pre-albuterol.

Animal carcinogenicity and reproductive toxicity studies were not performed (Section 3.2). The lack of carcinogenicity data is a potential concern; insulin is a growth factor, and inhaled insulin appears to be a clinical lung irritant. Although no difference was noted between inhaled insulin and comparator groups for the incidence of lung carcinoma, the duration of study was shorter than the usual duration of time needed from an initial lung insult to the development of a malignancy. However, Dr. Alavi, the animal toxicology reviewer, states that it is unlikely that animal carcinogenicity studies would have resolved questions regarding human carcinogenic potential, due to problems administering the drug chronically via inhalation to rodents, and due to a potential nonrelevant tumorigenic response in rodents, which have insulin receptors in the lung.

9.1.3 Conclusions Regarding Dosage and Administration, Dose Equivalence, and Dose Proportionality

In the DOSAGE AND ADMINISTRATION section of the proposed product label, the applicant proposes a similar regimen to that used in clinical trials (Section 8.1). Administration 10 minutes prior to meals is proposed. Calculation of initial dosage based on body weight is proposed, with a formula: body weight (kg) x 0.05 mg, rounded down to nearest whole mg, = premeal dose, assuming 3 meals/day. The applicant does not propose instructions for transitioning from subcutaneous premeal insulin to inhaled insulin, based on the patient's current premeal subcutaneous insulin dose. However, in a subsequent version of the label submitted 26 Sep 05 via email to Dr. Elekwachi, the applicant proposes to include a table with information regarding equivalent doses of inhaled insulin in mg and subcutaneous shortacting insulin in IU. No formula is presented for dosing by carbohydrate exchanges, and there are no recommendations for calculation of bedtime snack doses. The label does not include recommendations for titration increments. Mention is made of the fact that three 1 mg unit dose blisters cause greater insulin exposure than one 3 mg dose blister. The dosage and administration section does not mention a need for close monitoring by the patient and physician during initiation of inhaled insulin.

Initial dosage based on body weight is a reasonable approach. However, numerous patient factors may affect initial inhaled insulin requirement, including the patient's particular degree of

insulin resistance, current glycemic control, hypoglycemia history, et al. These factors could result in significant under- or over- dosing if initial dose is based on weight alone. The proposed label makes mention of the need for consideration of factors other than weight in determining starting dose, but does not provide specific guidance. The potential consequences of initial under- or over- dosing could likely be managed by intensive monitoring by the patient and physician in the first few weeks of initiation of inhaled insulin; the clinical reviewer recommends the addition of this recommendation to the product label.

The applicant's proposed label states, in the DOSAGE AND ADMINISTRATION section, that Exubera® may be used during intercurrent respiratory illness, e.g. bronchitis, upper respiratory infection, and rhinitis. However, some differences in inhaled insulin pharmacokinetics and glucose pharmacodynamics were seen with rhinoviral challenge (Section 7.4.2.4). Analysis of the effect of acute bronchitis on insulin pharmacokinetics and post-inhaled-insulin glucose pharmacodynamics was not provided. The clinical reviewer recommends that the label state that the effect of intercurrent respiratory illness, such as acute bronchitis, upper respiratory infection, and rhinitis, has not been fully evaluated, and that careful monitoring of blood glucose during intercurrent respiratory illness is recommended. The clinical reviewer also recommends that patients be advised to have subcutaneous insulin and needles available for use during intercurrent respiratory illness, in case glucose control proves difficult with inhaled insulin during that time.

Dose proportionality and dose equivalence were not demonstrated for Exubera® (Sections 5.1 and 8.1).

In Study A2171012, dose proportionality was not demonstrated over a range of doses (Sections 5.1 and 8.1). In this study, dose proportionality of several dosages was compared, including doses of 1 mg (1x1 mg), 2 mg (2x1 mg), 3 mg (1x3 mg), 4 mg (1x3 mg + 1x1 mg) and 6 mg (2x3 mg). None of the 90% confidence intervals for any AUC comparison fell within the applicant's prespecified bioequivalence boundaries (80-125%).

When examining the actual individual subject data from the trial, one notes that multiple samples obtained for insulin Cmax and AUC for 3 mg dosing had lower values than the mean seen for 2 mg dosing (Section 8.1). For Cmax, 10/29 samples obtained for Cmax at the 3 mg dose fell below the mean Cmax for the 2 mg dose. In this study, each patient generally only received 3 of the 5 dose combinations. A total of 6 patients received both the 2 mg dose and the 3 mg dose (doses given at different times during study). Among these 6 patients (each of whom had 2 Cmax values recorded for each dose), 4/6 had a Cmax value for the 3 mg dose that was lower than a Cmax value for the 2 mg dose. A total of 6/26 samples for the 6 mg dose had lower Cmax values than the mean for the 4 mg dose, and 2/6 patients who received both the 4 mg dose and the 6 mg dose had a Cmax value for the 6 mg dose that was lower than a Cmax value for the 4 mg dose. Similar findings were noted for AUC at each time interval, as illustrated in Table 8.1.2.

Based on this study (and Study 1006 described below), it appears that the possibility exists that, in a given patient, the titrated "increase" from 2x1 mg to 1x3 mg could actually result in lower blood insulin AUC, rather than the expected increase in blood insulin (Sections 5.1 and 8.1).

This could create a significant problem in upward titration of dose, particularly in the lower dosage ranges such as might be used in Type 1 diabetes. This problem would be magnified if the drug is used off-label for the treatment of pediatric Type 1 diabetics, who generally have lower body weights and therefore smaller initial insulin doses.

Dose equivalence was also not demonstrated for three 1 mg blisters and one 3 mg blister (Sections 5.1 and 8.1). In Study 1006, the AUC_{0-360} for 3 inhalations of 1 mg was approximately 40% higher than that for 1 inhalation of 3 mg, and Cmax was approximately 30% higher. This difference appears to be related in part (but not entirely) to a problem with the inhaler; it is much more efficient in breaking up the powder in blisters of a lower fill mass. Although the overall percent emitted mass is fairly similar for 3x1 mg and 1x3 mg, the 1 mg strength emits a higher proportion of particles < [redacted], which the applicant asserts is the particle size most capable of reaching the deep lung, and the particle size associated with optimal systemic absorption. However, the relative difference in fine particle dose for the 1 mg blister vs the 3 mg blister does not entirely account for the dose nonequivalence. In addition to the potential problems noted above with titration, patients must be instructed not to substitute three 1 mg inhalations for one 3 mg inhalation if they run out of their 3 mg blisters. This could result in greater insulin exposure and risk for hypoglycemia.

This particular drug-device combination exhibits marked variability in emitted mass of dry powder insulin; this variability significantly exceeds previously established limits for dry pulmonary inhalers (Section 3.1). This variability in delivered dose is concerning, because it may result in an increased risk for hypoglycemia when doses significantly above the mean are delivered.

While variability in delivery of insulin with Exubera® is a concern, it is noteworthy that marked variability in absorbed dose of insulin, and pharmacodynamic response, is also a major concern with subcutaneous insulin, and is well-described in the medical literature. Within this development program, significant variability in pharmacodynamic (glucose) response was seen for both inhaled and subcutaneous insulin, and the variability was comparable in standardized meal studies (Section 8.1).

Of potential concern for Type 1 diabetics is the fact that the lowest available blister strength (1 mg) may not allow for the fine titration that is often used for Type 1 diabetes. A 1 mg blister is roughly pharmacodynamically equivalent to 3 IU of subcutaneously injected shortacting insulin. For Type 1 diabetics, titration is often done in increments of 1 IU, and premeal "sliding scales" are often prescribed in 1 IU increments. However, this lack of fine titration capability does not seem to have had a clinical correlate in the clinical trials, either for glycemic control or hypoglycemia risk.

9.2 Recommendation on Regulatory Action

The clinical reviewer recommends approval of Exubera® for control of hyperglycemia in Type 2 adult patients. In Type 2 patients, Exubera® may be administered as monotherapy, in combination with a longer-acting insulin, or in combination with oral agent(s). The clinical

reviewer also recommends the approval of Exubera® for control of hyperglycemia in Type 1 diabetics, albeit with some reservations. While Exubera® exhibited similar efficacy to subcutaneous insulin in Type 1 diabetics in clinical trials, it is not clear whether the average Type 1 patient can be expected to achieve the degree of glycemic control that has been shown to reduce the incidence of microvascular complications of diabetes.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

As of 28 Sep 05, the Office of Drug Safety is reviewing a Risk Management Plan proposed by the applicant. The Office of Drug Safety, and other reviewers, may have additional recommendations for postmarketing actions.

In addition to routine postmarketing pharmacovigilance activities, the applicant proposes the following risk management activities:

- 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. A protocol for this trial has not been submitted.
- Completion of Studies 1022 and 1029, in Types 1 and 2 diabetes respectively, to obtain data regarding changes in FEV1 over 5 continuous years of Exubera® exposure.

- 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 DLco, control of diabetes and underlying lung disease, and frequency and severity of exacerbations of underlying lung disease.

The clinical reviewer agrees that these proposed investigations will provide useful data regarding outstanding questions about the safety of Exubera®. In addition to the above, the clinical reviewer recommends the following:

- Study of the pulmonary safety of Exubera® in African American diabetics. African Americans have been described to have lower baseline lung function than Caucasian Americans and Mexican-Americans.
- Study of the pharmacokinetics and pharmacodynamics of Exubera® in persons chronically exposed to cigarette smoke who are not themselves smokers. This could include workers in bars or restaurants in which smoking is permitted, or family members in a household occupied by a smoker.
- Provision of detailed plans from the applicant regarding how they plan to provide education to physicians, allied health care professionals, and patients on the correct use of the inhaler. A patients Medication Guide is recommended.
- Implementation of an active education program to reduce the likelihood that smokers will receive the drug.

9.3.2 Required Phase 4 Commitments

The clinical reviewer proposes that all of the above risk management activities be included as Phase 4 commitments, except for further pediatric studies, which may be the subject of a future Written Request for Pediatric Study after further adult safety data are obtained.

9.3.3 Other Phase 4 Requests

Due to the very high rate of insulin antibody formation seen in inhaled insulin group patients, the clinical reviewer recommends that the applicant also use the proposed

9.4 Labeling Review

On 26 Sep 05, the applicant submitted a revised product label via email to Dr. Elekwachi. The following suggested revisions are based on that version of the label. Please see Appendix 10.3 for a discussion of the proposed tradename. A proposed patient information leaflet and patient instructions for use were included with the original NDA submission and are also reviewed here.

9.4.1 Suggested Revisions to Proposed Product Label

3 Page(s) Withheld

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

__X__ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Table 9.4.1 Suggested Revisions to Proposed Product Label

Location in Proposed Label (Word® Version)	Applicant's Proposed Text or Content	Suggested Revision(s)	Comment

The Division of Medication Errors and Technical Support had many comments and recommendations regarding labeling and container issues (see DFS). The clinical reviewer has no objections to any of these comments, provided they do not conflict with the requirements of Chemistry or other review disciplines.

Ms. Mele of Biostatistics had several labeling recommendations (see DFS). The clinical reviewer has no objections to any of these comments, but feels that it is better to keep the dosing of Exubera® expressed as mg rather than IU, and to clarify the difference in relative pharmacodynamic effect (i.e. 1 mg inhaled roughly equal to 3 IU injected).

9.4.2 Suggested Revisions to Proposed Patient Information Leaflet

The clinical reviewer recommends the development of a formal patient Medication Guide, rather than merely a Patient Information Leaflet (PIL). If a PIL is included, the following changes are recommended.

Table 9.4.2 Suggested Revisions to Proposed Patient Information Leaflet (PIL)

Location in Proposed PIL	Current Wording	Suggested Revision(s)	Comment

9.4.3 Suggested Revisions to Proposed Patient Instructions for Use

Please see comments from DMETS.

9.5 Comments to Applicant

Additional comments may be added when other disciplines have completed their reviews.

The following recommended comments are for inclusion in a possible "Approval" letter to the applicant. The clinical reviewer recommends that the applicant submit a patient Medication Guide for complete review prior to approval.

"Extensive postmarketing evaluation will be needed for Exubera®. Your proposed risk management plan gives basic outlines for several risk management activities. In addition to routine postmarketing pharmacovigilance activities, you proposed the following risk management activities:

- 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.
- Completion of Studies 1022 and 1029, in Types 1 and 2 diabetes respectively, to obtain data regarding changes in FEV1 over 5 continuous years of Exubera® exposure.

- 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 DLco, control of diabetes and underlying lung disease, and frequency and severity of exacerbations of underlying lung disease.

The Agency agrees that these proposed investigations could provide useful data regarding outstanding questions about the safety of Exubera®. However, you will need to provide detailed

study protocols for review by the Agency, and for agreement on study design. In addition to the above, the Agency also requires the following:

- Development of a patient Medication Guide to be distributed to all patients for whom Exubera® is prescribed.
- Study of the pulmonary safety of Exubera® in African American diabetics. African Americans have been described to have lower normative values for baseline lung function than do Caucasian Americans and Mexican-Americans.
- Study of the pharmacokinetics and pharmacodynamics of Exubera® in persons chronically exposed to cigarette smoke who are not themselves smokers. This could include workers in bars or restaurants in which smoking is permitted, and/or family members in a household occupied by a smoker.
- Use of your proposed large simple trial, [redacted] to obtain information on possible immune-mediated adverse events, given the marked increases in insulin antibody levels seen with Exubera®.
- Implementation of an active education program to reduce the likelihood that smokers will receive the drug.
- A detailed plan for how you will ensure that physicians, allied health professionals, and patients will be educated in proper use of the Exubera® inhaler."

APPEARS THIS WAY ON ORIGINAL

10 APPENDICES

10.1 Review of Individual Study Reports

Not applicable; see Section 6.

10.2 Line-by-Line Labeling Review

See Section 9.4.

10.3 DMEDP Response to DDMAC Tradename Objection

The following memo was entered into the DFS archive on 13 May 05 in response to an objection by the Division of Drug Marketing and Advertising to the applicant's proposed tradename:

MEMORANDUM TO FILE

6 May 05
To: David Orloff, MD, Division Director, Division of Metabolic and Endocrine Drug Products
From: Karen Murry Mahoney MD, Medical Officer, Division of Metabolic and Endocrine Drug Products (DMEDP)
Re: NDA 21868 Exubera® inhaled insulin, DMEDP response to request by Division of Drug Marketing and Advertising (DDMAC) for comment on DDMAC tradename objection

Pfizer has submitted a New Drug Application for their inhaled insulin product, for which they plan to use the tradename "Exubera®". DDMAC recently notified Pfizer of an objection by DDMAC to the name, as "overly fanciful and promotional". Mr. Brian Green of Pfizer Regulatory Affairs notified Dr. Oluchi Elekwachi, DMEDP Project Manager for Exubera®, that Pfizer plans to challenge the DDMAC objection. DDMAC has asked DMEDP to comment on whether DMEDP agrees with DDMAC's objection to the tradename. This memorandum documents the DMEDP Medical Officer Reviewer's opinion regarding the tradename objection, using the regulation upon which the DDMAC objection is based [21 CFR § 202.1(a)(3)].

The pertinent regulation, accessed via the Tarius United States Code of Federal Regulations database on 6 May 05, reads as follows:
"§ 202.1 Prescription-drug advertisements.
(a)...
(3) The advertisement shall not employ a fanciful proprietary name for the drug or any ingredient in such a manner as to imply that the drug or ingredient has some unique effectiveness or composition, when, in fact, the drug or ingredient is a common substance, the limitations of which are readily recognized when the drug or ingredient is listed by its established name.
..."

The medical officer can understand DDMAC's concern, in that the "fanciful" name implies an "exuberant" response. However, the medical officer can also see that Pfizer could reasonably argue that the remainder of the regulatory statement limits the objectionability of a fanciful name to those circumstances in which the drug is not substantially different from other products containing the same active ingredient. While Exubera® contains insulin, a common drug, its characteristics are not limited to those seen with injected insulin. If it is approved, its different route of administration, and the painfree nature of that administration route, will make this product substantially different

from injected insulin. The fact that Exubera® contains insulin will not be hidden, either in labeling or promotion. The applicant would have no reason at all to create confusion about the fact that Exubera® contains insulin. Additionally, Pfizer specifically asked the Agency about the acceptability of the name years ago (17 Dec 99), and in writing, was notified on 4 Oct 00 that the Office of Postmarketing Risk Assessment expressed no objection to the proposed tradename Exubera®. Thus, Pfizer tried long ago to make sure that FDA found the name acceptable before Pfizer progressed further.

The medical officer is not familiar with how the "overly fanciful" clause has been applied by DDMAC in the past, and realizes that FDA has to apply interpretation of this clause fairly across all companies' drug naming plans. However, to the medical officer's reading of the regulation, the name of this particular drug does not seem objectionable enough to require the company to expend time and resources to change the name and marketing campaign plans. Additionally, the applicant made a good faith effort years ago to seek the Agency's input regarding the proposed tradename.

In summary, the DMEDP medical officer's opinion is that the proposed tradename Exubera® does not violate 21 CFR § 202.1(a)(3), and the medical officer's lack of objection to the proposed tradename is further supported by the applicant's previous good faith efforts to seek Agency input regarding the acceptability of the tradename.

10.4 Serious Adverse Event Listings by Patient

The following tables list serious adverse events by patient. Separate tables are provided for adult Type 1, adult Type 2, and pediatric patients. Separate tables are also provided by treatment group. In constructing these tables of serious adverse events by patient, the clinical reviewer extracted data from the applicant's Table 6.3.1.1 from the applicant's Summary of Clinical Safety, pages 1903-2296. This table did not assign an organ system for events, and therefore organ systems were assigned by the clinical reviewer and may differ from what the applicant would have assigned. When a patient was reported to have had a severe hypoglycemic event with possibly related events that occurred at the same time, such as seizures or injury, the clinical reviewer assigned the organ system as "Metabolic". In reviewing these events, the clinical reviewer also noted some dates of adverse events that could not be reconciled with the length of studies, e.g. SAEs occurring at >2 years for a 6 month study. This was brought to the attention of the applicant, and corrected data were provided for 45 events. The tables below include the corrected data. If the reader attempts to compare the following tables to the applicant's original table, dates of adverse events may differ due to this later correction by the applicant. These tables relate to Section 7.1.2 of the review, and are numbered accordingly.