CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-868

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology and Biopharmaceutics Review (FINAL)

NDA: 21-868 **Date of Submission:** December 27, 2004
August 4, 2005
August 10, 2005 (Electronic)

Generic Name	Insulin rDNA
Brand Name:	EXUBERA®
Formulations:	Powder
Route of Administration:	Oral Inhalation
Indication:	Diabetes Mellitus (Type 1 and Type 2)
Type of Submission:	NDA
Sponsor:	Pfizer New London, CT
Reviewer:	Sayed (Sam) Al Habet, R.Ph., Ph.D.
Team Leader	Hae-Young Ahn, Ph.D.

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1. Executive Summary:

1.1 Recommendation:

The Office of Clinical Pharmacology and Biopharmacetuics has found this NDA acceptable, provided that the sponsor agrees to conduct an additional study as a Phase 4 commitment.

OCPB Briefing Date: August 31, 2005

Briefing Attendees: Drs. Henry Malinowski, Hae-Young Ahn, John Hunt, John Lazor, Mehul Mehta, Karen Mahoney, Emmanuel (Tayo) Fadiran, Julie Bullock, Edwin Jao, Oluchi Elekwachi, Prasad Peri, Arzu Selen, Philip Colangelo, Atiqur Rahman, and Sayed Al Habet

1.2 Phase 4 Commitments

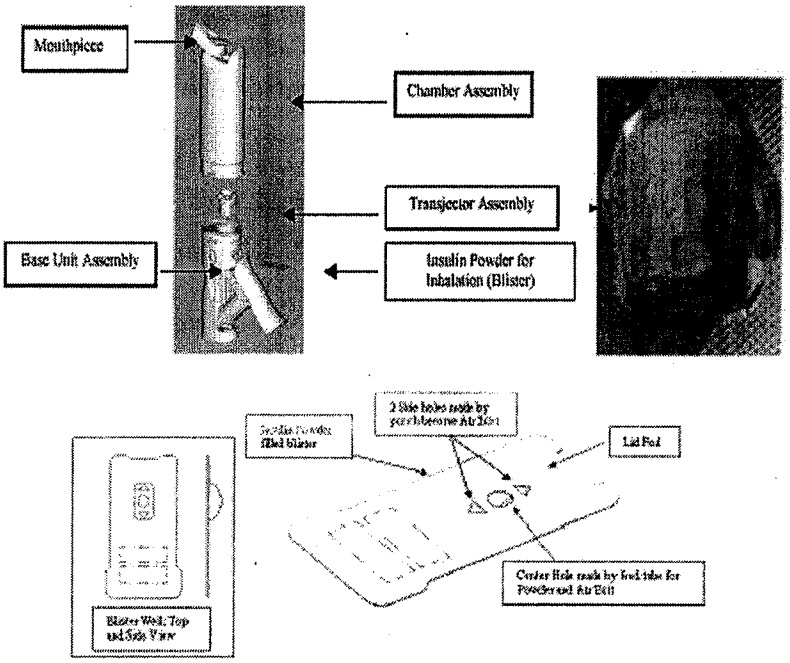
A single dose and multiple dose PK study should be incorporated into the sponsor's proposed 4 week double blind crossover study in normal controls to assess the effect of the full Exubera formulation or excipients alone on indices of lung function. The sponsor must submit a protocol for review prior to initiating the study.

1.3 Summary of Clinical Pharmacology and Biopharmacetuics Findings

1.3.1 Background:

Exubera (also referred to as INH) is a novel treatment system for Type 1 and Type 2 diabetes mellitus (DM). It combines a novel dry powder formulation of recombinant human insulin with a reusable mechanical inhaler (**Figure 1**). In Type 1 DM, Exubera should be used in regimens that also include longer-acting insulin, while in Type 2 DM it can be used either as monotherapy or in combination with other oral hypoglycemic agents or longer-acting insulin.

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



1.3.2 What is the Formulation?

The inhaled insulin formulation will be available in blisters of 1 mg and 3 mg strengths of dry powder. The most commonly anticipated dose using this product would be one or two inhalations of 1mg or 3 mg blisters. The maximum dose would be 6 mg which is the maximum dose studied in this NDA. For each inhalation, a single-dose blister filled with powdered insulin formulation is inserted into a slot on the inhaler. The blister is punctured, and the powder is dispersed into a visible forming cloud aerosol inside a holding chamber. Each blister is inhaled one at a time and each blister is considered one inhalation.

1.3.3 What is the Rationale of the Inhaled Insulin?

Frequent subcutaneous insulin injection is required to control glucose level in Diabetic patients. The inhaled insulin would markedly improve both patient's compliance and quality of life.

1.3.4 What Studies Are Submitted in this NDA?

Overall, 32 single-dose clinical pharmacology studies have been conducted in this NDA. In 15 of these studies the final to-be-marketed powder formulation [redacted] and the final inhaler version (P3) were used. The final formulation and device was also used in Phase III clinical trials.

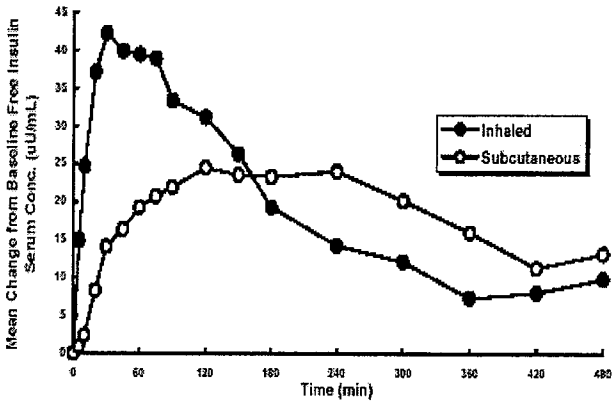
1.3.5 What are the Main Findings in this NDA?

Reviewer's Cautionary Statement: As stated above almost half of the clinical pharmacology and biopharmaceutics studies were conducted using early developmental formulations and devices (inhalers). Therefore, cross study comparison should be exercised with great caution.

Absorption and Bioavailability:

- The absorption of inhaled insulin is as rapid as subcutaneously injected (SC) rapid-acting insulin analog lispro and more rapid than regular human insulin.
- The insulin Tmax following inhalation occurs approximately 30 minutes earlier than SC regular insulin (**Figure 2**). Also, for inhaled insulin the Tmax was comparable to SC lispro (approximately 40 to 90 min inhaled vs 60 to 150 min SC). Furthermore, the Tmax appears to be shorter in Type 1 DM (~40 to 80 min) than Type 2 DM (~80 to 260 min).

Figure 2. Typical Insulin Concentration-Time Profiles following Inhaled (2 x 3 mg) and 18 U SC Regular Insulin (from study # A217-003).



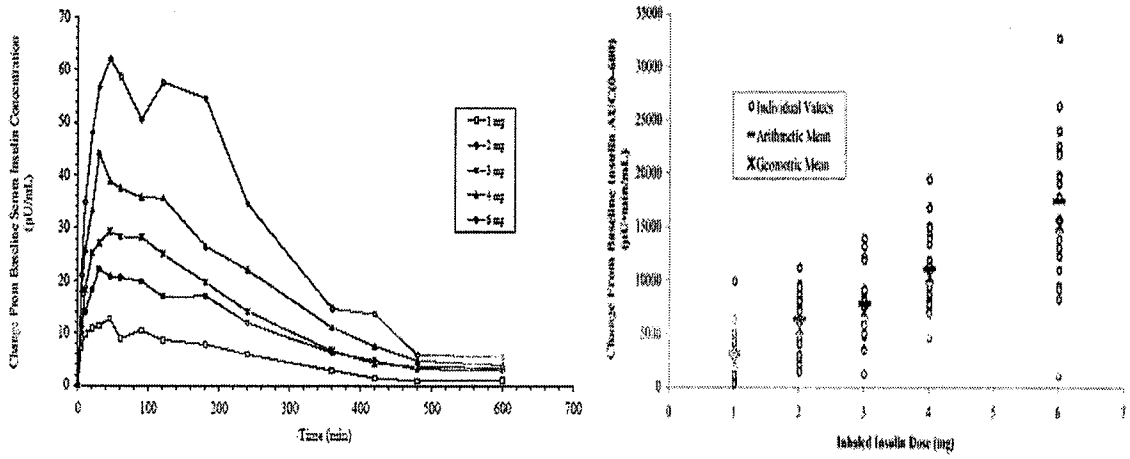
- The bioavailability of inhaled insulin relative to SC regular insulin from all studies is approximately 10%, ranging from approximately 5% to 15%. However, there are one or two exceptions with a bioavailability of about 20%.

Dose Proportionality:

- There is clear dose separation in insulin plasma levels as the dose increases from 1 mg to 6 mg, irrespective of formulation (**Figure 3**). However, due to the large variability in the data, the dose proportionality can not be confirmed with certainty at this time.

Figure 3. Summary of Dose-Proportionality Data (Study # 217-012).

A) Profiles (Mean Change from Baseline) **B) Dose vs AUC**



Bioequivalence:

- One of the most **critical** finding in this NDA is that the 3 x 1 mg and 1 x 3 mg blisters are **not bioequivalent (Table 1).** The exposure (Cmax and AUC) following 3 x 1 mg is consistently 30% to 40 % higher than 1 x 3 mg. This would make the titration process more complex and unpredictable. Therefore, the interchangeability between these strengths is not recommended.

Table 1. Overall Statistical Summary for all Treatments (Study A217-1006)

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

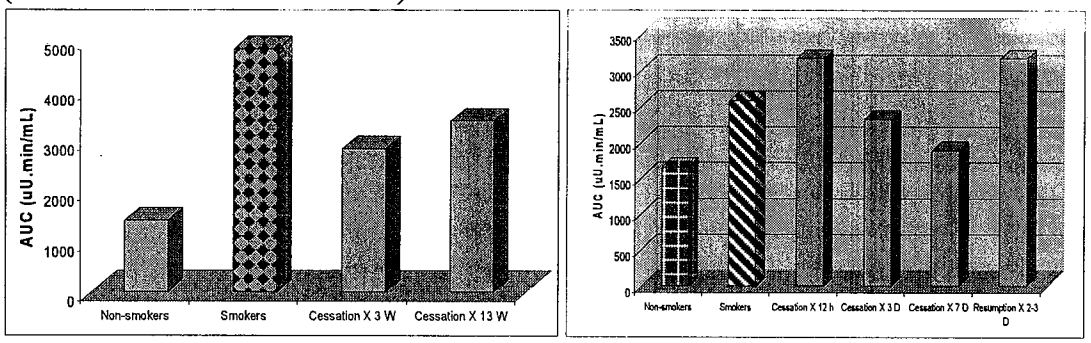
- As stated earlier, the Phase III and the to-be-marketed formulations are similar. However, at the commercial production scale, there was a difference in particle size aerodynamics parameters between the two lots that warranted BE studies. From the regulatory perspective, the 3 mg commercial scale up lot [redacted] and clinical lot [redacted] are bioequivalent. However, the commercial production lot for the 1 mg strength [redacted] is not bioequivalent to the clinical scale lot [redacted]. Based on the data, it appears that there is approximately 10% difference in exposure with 1 mg strength. The impact of this difference may not be clinically significant.

Effect of Extrinsic Factors:

Effect of Smoking:

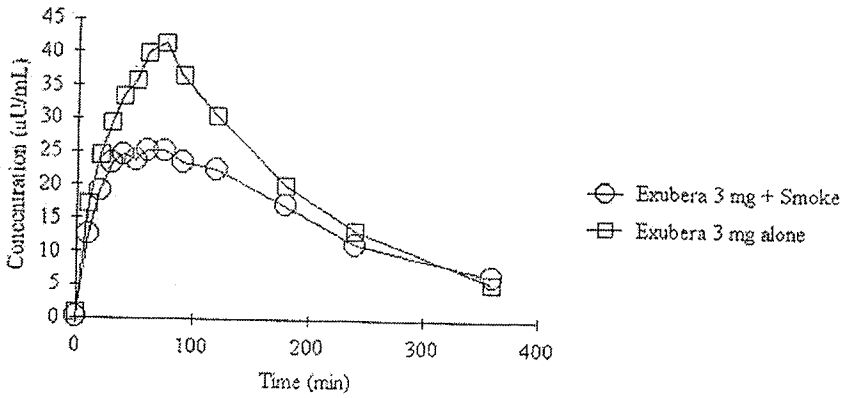
- The exposure from inhaled insulin is approximately 2 to 5 fold higher in smokers than in non-smokers. The cessation of smoking for about 24 to 48 hours appears to reduce the exposure to near the level of non-smokers. Conversely, the resumption of smoking increases the exposure back to its baseline level prior to cessation of smoking within 1-2 days (**Figure 4**).

Figure 4. Effect of Smoking, Smoking Cessation, and Smoking Resumption on Exposure (Studies 217-016 and 217-1020)



On August 10, 2005 the sponsor submitted an additional study to investigate the effect of acute passive smoking on the PK of inhaled insulin. The data show a completely different picture. Passive smoking reduces the absorption and exposure of inhaled insulin by approximately 20% to 30% (**Figure 5**).

Figure 5. Mean Insulin Concentration-Time Profile in the Presence and Absence of Passive Smoking



The reason for this difference in exposure between the chronic smokers and passive smokers is unknown. A further investigation is warranted to determine the mechanism of these conflicting exposure data between active smoke (chronic smokers) and passive smoke (secondary smokers).

Rhinovirus Infection:

The rational for this study is that patients with respiratory infection usually have excess mucous that may affect the absorption of inhaled insulin as well as they are expected to be more susceptible to external irritation such as inhaled powders.

In this study the data was inconclusive to indicate that the rhinovirus infection affects the absorption of inhaled insulin. It appears however that the exposure on Day 1 (prior to inoculation) was higher than Day 4 in both virus and saline group. It should be noted that there was a high variability in the data and the number of subjects in the control group (saline) was too small (n=4) compared to active treatment group (n=20). This unequal number of sample size makes the interpretation of the data more difficult.

Effect of Intrinsic Factors:

Obstructive Pulmonary Disease (COPD)

- Similar to the effect of smoking, the exposure appears to be greater in patients with Chronic COPD, and in particular patients with emphysema (**Figures 6 and 7**). However, the data from this study was highly variable and may need to be repeated.

Figure 6. AUC (0-60) and AUC (0-360) in Patients with COPD (Study # A217-1005)

A) AUC (0-60) **B) AUC (0-360)**

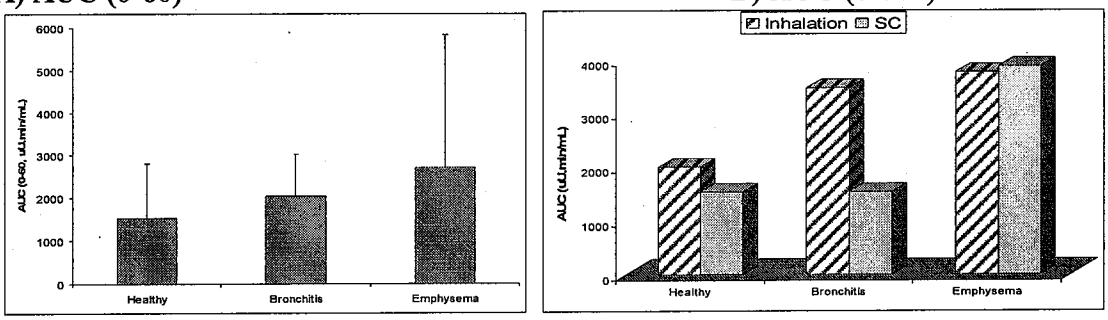
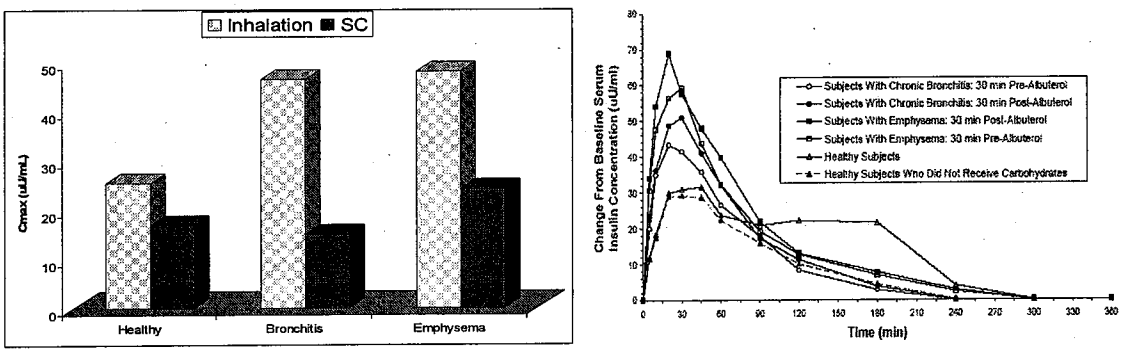


Figure 7. Effect of COPD on Cmax of Inhaled and SC Insulin (Study # A2171005)



- In contrast, the data provided by the sponsor does not show any significant increase in exposure from inhaled insulin in other respiratory diseases such as asthma. In contrary, however, the exposure in asthmatic patients was consistently lower by approximately 20% to 50% than normal.
- Due to the critical nature of the disease and mechanism of the delivery system, additional study is recommended to provide a more reliable data that can be used to establish adequate titration process in this patient population.

Effect of Other Intrinsic Factors:

- The bioavailability of inhaled insulin relative to SC insulin tends to be greater in obese subjects than in subjects with normal weight. This could be due to lower SC insulin exposure in these obese subjects.
- There appears to be no gender or race effect on the disposition of insulin following inhalation.

Drug Interactions:

On August 10, 2005 the sponsor submitted a study report on the effect of short-acting bronchodilator (albuterol) and inhaled corticosteroid (fluticasone) on the absorption of inhaled insulin in non-diabetic subjects with asthma (Study # A2171056). The data show there was 25% and 50% increase in insulin exposure when administered 30 minutes after albuterol in subjects with mild and moderate asthma, respectively (**Table 2**). However, the administration of fluticasone had no effect when it was administered 30 minutes before inhaled insulin (**Table 3**).

Table 2. Effect of Inhaled Albuterol on Inhaled Insulin (Study # A2171056).

	Group 1*				Group 2*			
	Adjusted Geometric Means				Adjusted Geometric Means			
	Test†	Reference†	Ratio	95% CI	Test†	Reference†	Ratio	95% CI
AUC0-360 (min·μU/mL)	2941.4	1953.3	150.59	(119.75, 189.38)	5052.0	4056.0	124.56	(106.15, 146.16)
Cmax (μU/mL)	29.6	20.1	146.99	(120.20, 179.75)	46.8	34.6	135.16	(115.14, 158.65)

*Group 1 = moderate asthmatic subjects; Group 2 = mild asthmatic subjects, as defined in Study Population and Criteria for Inclusion
†test = albuterol (180μg) + INH (3 mg); reference = INH (3 mg)

Table 3. Effect of Inhaled Fluticasone on Inhaled Insulin (Study A2171056)

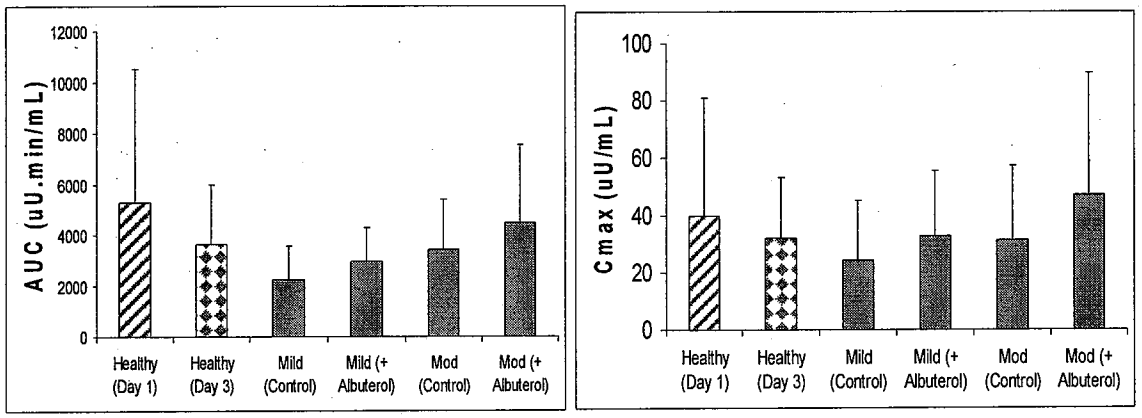
	Group 1*				Group 2*			
	Adjusted Geometric Means				Adjusted Geometric Means			
	Test†	Reference†	Ratio	95% CI	Test†	Reference†	Ratio	95% CI
AUC0-360 (min·μU/mL)	1842.5	1953.3	94.33	(74.89, 118.83)	4008.5	4056.0	98.83	(83.89, 116.43)
Cmax (μU/mL)	19.1	20.1	94.79	(77.43, 116.06)	34.2	34.6	98.78	(83.82, 116.41)

*Group 1 = moderate asthmatic subjects; Group 2 = mild asthmatic subjects, as defined in Study Population and Criteria for Inclusion
†test = fluticasone (440 μg) + INH (3 mg), reference = INH (3 mg)

Further analysis of the data reveals that the exposure in asthmatic subjects is much lower than in healthy non-asthmatic, even after albuterol administration (**Figure 8**). The data is consistent with observation made in the previous study in asthma (Study # 217-009). There was high variability in the data, irrespective of treatments. For example, the mean AUC in healthy on Day 1 was 5280 with SD of 5260 and on Day 3 was lowered to 3640 with SD of 2360. The clinical impact of these observations, in particular, the effect of albuterol, should be carefully assessed.

Figure 8. Compiled Cmax and AUC Data in Healthy and Asthamtic (Mild and Moderate) Subjects Before and After Albuterol (Study # A217-056) (Day 1= before inoculation and Day 3 = post-inoculation)

A) AUC **B) Cmax**



Variability:

- The PK profile of insulin following inhalation is highly variable. Many factors contribute to the variability of absorption of inhaled insulin. These factors are inherent to the quality of formulation, the inhaler, subjects, and the inhalation techniques.

- For example, in the dose proportionality study (# A217-1012), the AUC ranged form as low as 45 to as high as 32400 over a dose range of 1 to 6 mg doses as follows:

Dose (mg)	Blister Strengths	Range (µU.min/mL)	Difference	Ratio (Max/Min)
1	1 x 1 mg	45-9730	9685	216.2
2	2 x 1 mg	1270-11000	9730	8.66
3	1 x 3 mg	1070-13800	12630	12.89
4	1 x 1 mg + 1 x 3 mg	4440-19300	14860	4.34
6	2 x 3 mg	934-32400	31466	34.68

It should be noted that each dose was administered in replicates in each subject. Therefore, the above table represents all subjects and all treatments.

For comparison to SC administration, the following table was similarly compiled for AUC from the pivotal bioequivalence study for the 1 and 3 mg strengths (study # 1006):

Dose	Blister Strengths	Range (µU.min/mL)	Difference	Ratio (Max/Min)
1 mg	1 x 1 mg	109-6660	6551	61.10
3 mg	1 x 3 mg	377-11600	11223	30.76
9 U	**SC injection**	**2330-8420**	**6090**	**3.61**

From the above table, it can clearly be seen that SC administration has much lower variability compare to inhalation within the same study and the same subjects.

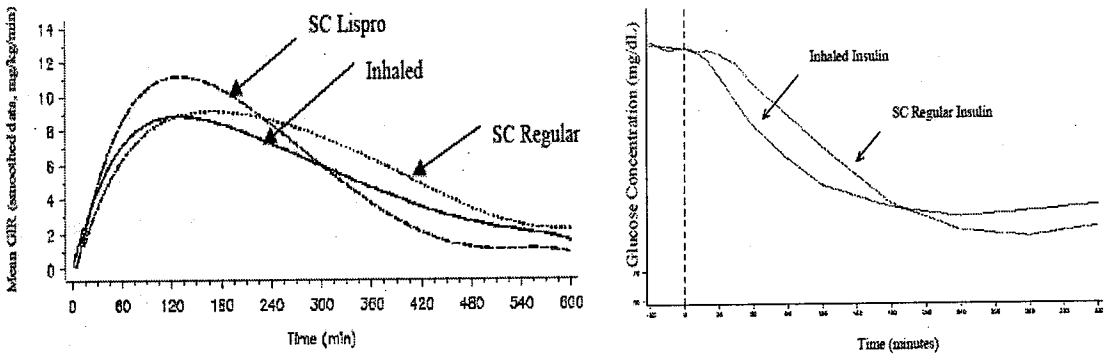
- Overall, the inter- and intra-subject variability in PK of inhaled insulin is generally high. From the entire NDA, the % CV, on average is expected to be >50%.
- The within-subject variability of glucose-lowering activity of inhaled insulin is generally comparable to that of SC regular insulin in subjects with Type 1 or Type 2 DM.

Pharmacodynamics (Duration of Action)

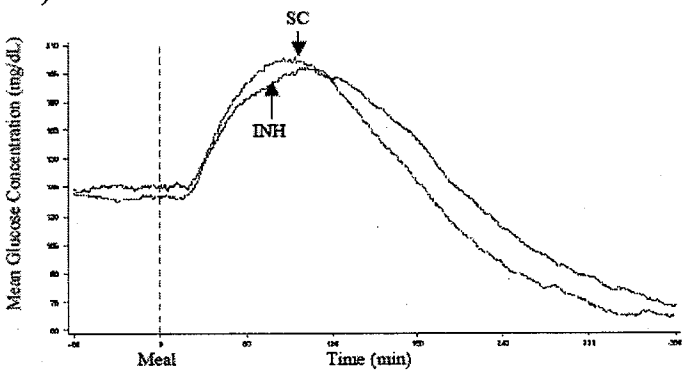
- Consistent with the PK profile, the onset of action of inhaled insulin is as rapid as SC insulin lispro and more rapid than SC regular insulin (**Figure 9A**).
- The duration of action of inhaled insulin is longer than SC insulin lispro and comparable to SC regular insulin (**Figure 9 A & B**).
- There is an immediate relationship between insulin exposure and response in terms of glucose control (**Figure 9A-C**).

Figure 9 (A-C) . Pharmacodynamic of Inhaled Insulin (Glucose Parameters):
A) Mean Change in Baseline GIR (Glucose infusion Rate) After Inhaled Insulin (2 x 3 mg) and 18 U SC Regular or Lispro Insulin in Healthy Subjects (Study # 217-017)
B) Mean Glucose Concentrations After 4 mg of Inhaled Insulin or 12 U SC Regular Insulin in Type 2 DM Patients (Study 217-1004)

A) **B)**



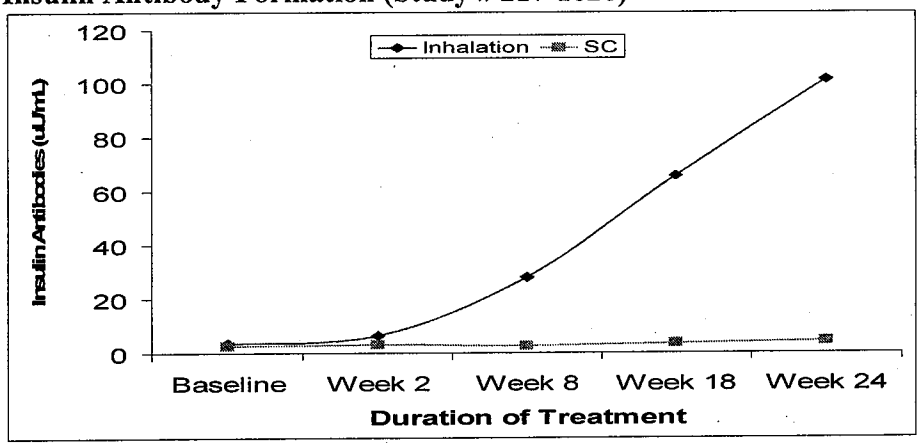
C). Mean Postprandial Glucose Concentrations in Subjects with Type 1 DM (Study # 217-021) C)



Antibody Formation:

- Inhaled insulin has been shown to be associated with approximately **30 fold** increase in antibody over 6-months treatment. By contrast, SC administration virtually did not show any antibody formation (**Figure** 10). According to the sponsor, no apparent glucose intolerance or loss of glycemic control associated with insulin resistance with neutralizing antibodies were observed over 24 weeks treatment with either inhaled or SC insulin (Study # 217-1026).

Figure 10. Insulin Antibody Formation (Study # 217-1026)



Effect of Particle Size Aerodynamics:

- Fine particle dose (FPD) less than) was shown to be better predictor of clinical performance than any other aerodynamic metrics so far tested in this NDA.

- Two studies were conducted specifically to address the effect of particle size on the bioavailability of insulin powder formulation. Two formulations for 1 mg strength in these two studies were used). The Mass Median Aerodynamic Diameter (**MMAD**) used in these two studies ranged from approximately Across these two studies, the data

1 Page(s) Withheld

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

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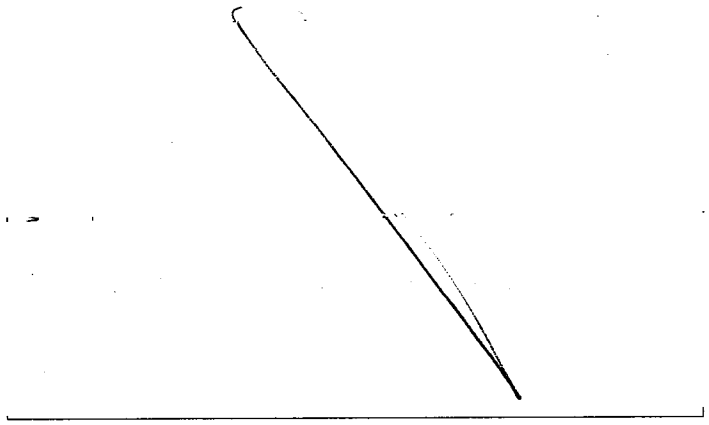
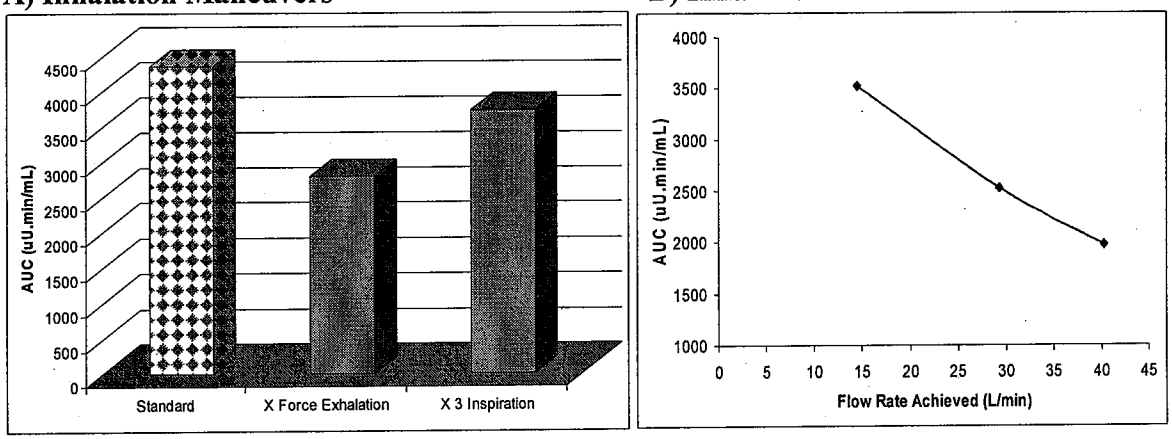


Effect of Inhalation Techniques:

- The standard inhalation technique produced optimal delivery, irrespective of all other tested techniques/maneuvers (**Figure 14**). In addition, insulin delivery is greater with slow inhalation rate (e.g., 10 L/min) than fast inhalation (>35 L/min)

Figure 14. Effect of Inhalation Techniques and Flow Rate on Exposure (Study #217-002)

A) Inhalation Maneuvers **B) Inhalation rate**



Safety Note:

- The major of safety related issues in all clinical pharmacology studies as well as Phase III studies was hypoglycemia. According to the sponsor's analysis, the incidence of hypoglycemia in all clinical pharmacology studies was 40.1% for inhaled insulin and 29.5% for SC insulin.
- Other safety related adverse events (AE) noted with greater rate following inhaled insulin compared to SC insulin are headache, dizziness, and cough. Six severe AE events occurred in inhaled insulin group in clinical pharmacology studies. These were headache (n=4),

myocardial infarction, and dizziness. According to the sponsor, these latter six cases were considered not related to treatment.

- The discontinuation from the study due to adverse events was greater in inhalation than SC treated subjects. The most common adverse events that resulted in discontinuation from the study are cough, hypoglycemia, and dyspnea.
- There was some decline in FEV_1 and carbon monoxide diffusion capacity (DLco) in this program. These were observed more commonly in inhalation than SC group.

Note on Efficacy:

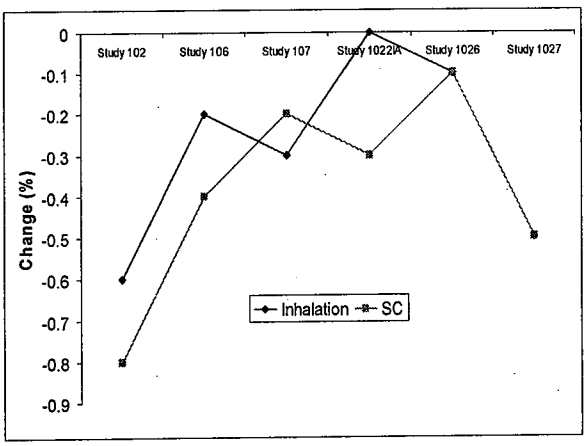
- There was some separation between inhaled and SC insulin in terms of the effect on the primary clinical endpoint, **HbA_{1c}**, and the secondary endpoint, glucose response (**Figure 15 A & B).**

These graphs were constructed based on the summary data provided by the sponsor from different studies as noted in each graph. Within a given study, there was clear difference in the % change in HbA_{1c}, between inhaled and SC insulin, with inhaled demonstrating higher trend in all studies, except study # 10221A. In terms of fasting blood sugar, three studies clearly show marked separation in fasting blood sugar between inhaled and SC insulin (**Figure 15 B).** In addition, according to the sponsor, glycemic control was maintained over 12 months in the ongoing study # 1022. For more details and updated information, please see the Medical Officers review.

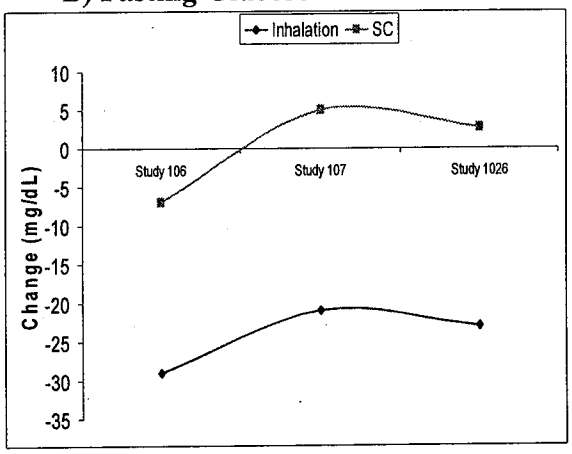
Figure 15. Efficacy Data

A) Change from Baseline in Glycosylated Hemoglobin (HbA_{1c}, %) in Type 1 Diabetes (Source: Module 2.7.3, page 32, Table 12)
B) Change from Baseline in Fasting Plasma Glucose in Type 1 DM (Source: Module 2.7.3, page 33, Table 14)

A) HBA_{1c} (% Change)



B) Fasting Glucose

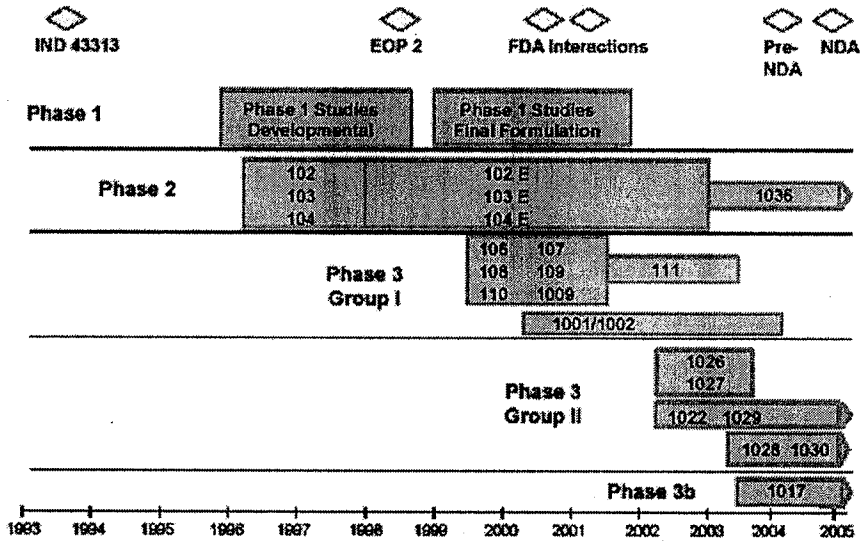


2.0
Clinical Pharmacology and Biopharmaceutics Review (Question Based Review-QBR)

2.1 What are the General Attributes of Exubera®?

From the clinical pharmacology and biopharmaceutics perspective, Exubera represents a novel delivery system for insulin, a drug that has been administered by injection (SC or IV infusin) for many decades since its discovery early in the last century. The sponsor have undertaken a lengthy developmental program to improve the performance of the formulation and the device in the treatment of patients with Type 1 and Type 2 diabetes mellitus (DM). This program started more than 15 years ago with IND submitted back in 1993 (**Figure 2.1.1**).

Figure 2.1.1. Phase 2/3 Clinical Development Program of Exubera



EOP = end of Phase 2

To the clinical pharmacologist, Exubera is considered a complicated "unit" consisting of a novel dry powder formulation of a recombinant human insulin and a mechanical inhaler. The complication of this "unit" does not end at this point as the powder packaging, the process of the mechanical piercing of the blister shell and delivery of the powder to holding chamber of the inhaler plays an important role in the performance and acceptability of the unit.

2.1.1 What are the Proposed Dosage?

Exubera will be available as dry powder unit dose foil blisters of two strengths: 1 mg and 3 mg. The maximum proposed dose is 6 mg via oral inhalation which will be titrated according to the patient's needs. In patients with Type 2 DM, the product may be used as monotherapy or in

combination with oral agents or longer-acting insulin. According to the data the use of 3 x 1 mg blisters may result in greater insulin exposure than 1 x 3 mg blister. Therefore, 3 x 1 mg doses should not be substituted for 1 x 3 mg dose.

2.1.2 What is the Rationale of the Inhaled Insulin?

Frequent subcutaneous insulin injection is required to control glucose level in Diabetic patients. The inhaled insulin would markedly improve both patient's compliance and quality of life.

The pulmonary delivery of large peptides such as insulin is very challenging and requires fine tuning between the physiochemical characteristics of the molecule, the formulation, and the physiology of the lungs. The airway epithelium is suitable to transport such large molecules due to the large lung surface area (50-140 m^2) and well perfused absorptive surface (~ 5 L blood/min) in addition to other lung physiological characteristics that allow rapid absorption of insulin-like peptides into the systemic circulation.

2.1.3 What is the Mechanism of Alveolar Deposition?

According to the sponsor, the proposed inhaled insulin product is designed to optimize alveolar deposition of drug powder, while minimizing its deposition of drug powder in the mouth and other upper respiratory airways. Mechanistically, it is believed that the inhalation product would produce an aerosol cloud that contains drug particles with the appropriate size for alveolar deposition.

2.1.4 What is the Mechanism of the Inhaler?

According to the sponsor, the inhaler is designed to deliver dry powder aerosol cloud into a holding chamber and then to the patient. This generation of the aerosolized cloud should be independent of the patient's strength of inhalation and/or actuation. In other words, the powder's delivery rate should be consistent in all patients as it is controlled by the inhaler and the particle size.

The device and the characteristics of the powder together were developed to allow deep deposition of insulin into the lung. The device is purely mechanical in that it does not require batteries, electronics or external power source.

The inhaler must be primed with compressed air before use. This priming step is necessary for the powder aerosolization and for piercing the blister. For each inhalation one blister will be inserted at a time into the inhaler slot. On actuation the inhaler disperses the powder and produces aerosol cloud in the holding chamber. During inhalation ambient air is pulled into the chamber thereby displacing aerosol out of the chamber so that it can be inhaled by the patient. Each blister dose is inhaled using one slow deep inhalation. Doses requiring multiple blisters are administered by repeating the blister procedure multiple times.

2.2 Overview of the Clinical Pharmacology Program:

The sponsor undertook extensive clinical pharmacology and biophatrmaceutics program over a period of more than 15 years in the development of this product. The sponsor had to overcome many challenges, including but not limited to the following: Insulin production, powder size, aerodynamic metrics of the powder, and the mechanism (s) of the device (inhaler) to provide optimal delivery/deposition of insulin powder into the lung. These challenges were apparent as almost half of the clinical pharmacology studies alone were conducted using early formulation in addition to other studies using different inhaler prototypes as well as two different insulin sources. Therefore, the sponsor had to make a link across all these variants.

2.2.1 What Studies are submitted in the Current NDA?

Overall, 32 single-dose clinical pharmacology studies have been conducted. In 15 of these as well as in Phase 3 trials the final to be-marketed formulation (# [redacted]) and inhaler version (P3) were used. Four of these studies evaluated the bioequivalence of the clinical/commercial formulation, dose proportionality, and dose strength equivalence (Study # A2171014, A2171015, A2171012, A2171006). One additional study (# A2171026) was conducted to evaluate the pharmacodynamic (PD) response to inhaled insulin in subjects with type 1 DM after a 24-week dosing period.

Seventeen studies which were conducted during the early development stage used early powder formulation and inhaler versions. Five of these early studies (217-05, 06, 007, 009, and 010) were conducted to explore the absorption of inhaled insulin in special populations. Furthermore, an exploratory scintigraphy study (# 217-008) was conducted to investigate the deposition of inhaled insulin. Another Phase II study is 217-101 which was designed to investigate the postprandial PK and PD of inhaled insulin in over 800 patients with type 2 DM.

Due to the complexity of the clinical pharmacology and the clinical trial programs and the inter-relationship among various studies, all efforts were made to review the most relevant studies (if not all) irrespective of the formulation used.

2.2.2 What are the Monitoring Endpoints in this NDA?

From the clinical pharmacology perspective, the most important end point in this program is insulin exposure following inhalation. This is critical as glucose response is directly controlled by the concentration of insulin in the systemic circulation. Any small changes in insulin exposure may have dramatic effect on glucose response and intimately may result in either hyperglycemia or hypoglycemia. As potent as insulin is, it can be considered the most sensitive direct model for PK/PD relationship. In other word, glucose response is as rapid as the insulin appears in the blood.

2.2.3 What are the key Components of the Clinical Pharmacology Studies Designes?

The sponsor designed all studies based on the concept of insulin-glucose response relationship. Therefore, most of the clinical pharmacology studies were designed as follows:

A) Postprandial Studies:

The majority of the clinical pharmacology studies were conducted in fasting subjects. However, as stated above, food and in particular, carbohydrate rich food plays critical role in this program. The reason is that administration of carbohydrate rich food will affect the baseline of endogenous insulin production in certain population and in particular in healthy subjects. For example, accidental ingestion of carbohydrate rich food was noted in four subjects in one study (# A217-1005, COPD study). This resulted in their exclusion from the final analysis.

Postprandial studies were conducted after single dose administration in subjects with Type 1 DM (Study # 217-021), Type 2 DM (Study # 217-018, 101), and in Phase 3 study following chronic administration in Type 1 DM (A217-1026).

In these studies, inhaled insulin and/or SC regular insulin was administered prior to a standardized meal. There was some slight variation among study designs relative to timing in insulin administration. In general, subjects stopped their intermediate or long-acting insulin and oral hypoglycemic agents and replaced it with multiple short-acting insulin 24 hours before dosing. All meals were standardized, including dinner a night before the study. In addition to their usual nightly SC doses, all Type 1 subjects received IV infusion of regular insulin overnight (Study 217-021 and 018) or variable glucose infusion (Study 217-021). Insulin treatments (inhaled or SC) were administered in the morning within 10 minutes before breakfast.

B) Glucose Clamp Technique:

The objective of the clamp technique is to reduce the risk of hypoglycemia and to minimize the counter-regulatory effect in fasted subjects. This technique was used in several clinical pharmacology studies (217-017, A217-1003, 1012, 1016, and 1026).

This technique allows blood glucose concentrations to be maintained at a constant level by adjustment of the Glucose Infusion Rate (**GIR**). This is a critical PD parameter as it regulates the metabolic activity of insulin. The GIR time profile reflects the PD time action profile of administered insulin. In all these studies, regular insulin was constantly infused at a rate of 10 to 15 μU/mL (60 to 90 pmol/L) to maintain blood glucose level at about 90 mg/dL (5.0 mmol/L).

Therefore, from the clinical pharmacology perspective, the PK/PD endpoints are the following:

1) Insulin plasma level
2) Glucose blood profiles
3) GIR (Glucose Infusion Rate)

It should be noted, however, that glucose parameters are also consider "surrogate" end points from the clinical perspective. The primary endpoint in **Phase III** studies, however, is the change from baseline in glycosylated hemoglobin (**HbA_{1c}**) in patients with Type 1 and Type 2 DM. Therefore, beside **HbA_{1c}**, the entire NDA is focused on glucose response as PD parameter.

Safety Parameters:

From the safety perspective, the following parameters were monitored in all clinical pharmacology program and all Phase III studies:

1) Incidence of hypoglycemia
2) Pulmonary function tests (e.g., FEV_1)
3) General vital signs

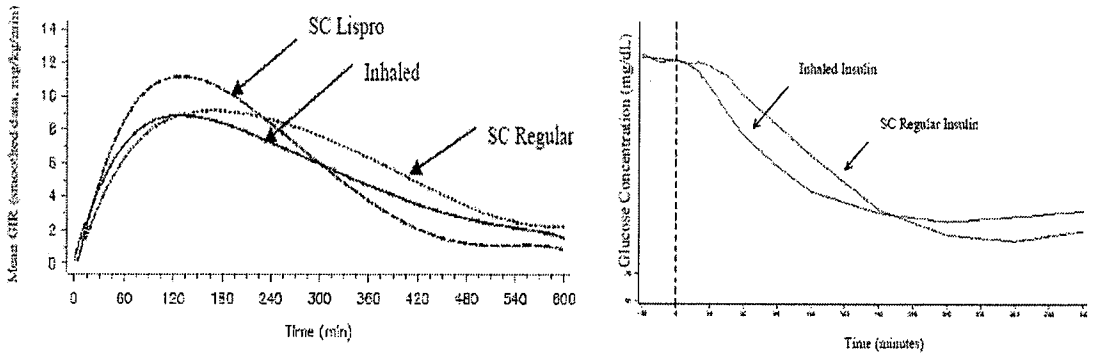
Other safety parameters were also monitored. For details, please see Medical Officer's reviews.

2.2.4. Is There a Relationship Between Exposure and Response?

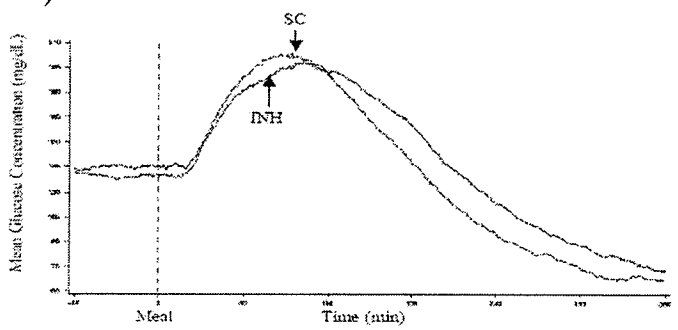
As stated above, there is an immediate relationship between insulin exposure and response in terms of glucose control. In this NDA, the sponsor has repeatedly established this relationship for inhaled insulin in almost all studies as exemplified in **Figures 2.2.1 (A, B, and C)**

Figure A-C . Pharmacodynamic of Inhaled Insulin (Glucose Parameters):
A) Mean Change in Baseline GIR (Glucose infusion Rate) After Inhaled Insulin (2 x 3 mg) and 18 U SC Regular or Lispro Insulin in Healthy Subjects (Study # 217-017)
B) Mean Glucose Concentrations After 4 mg of Inhaled Insulin or 12 U SC Regular Insulin in Type 2 DM Patients (Study 217-1004)

A) **B)**



C). Mean Postprandial Glucose Concentrations in Subjects with Type 1 DM (Study # 217-021) **C)**



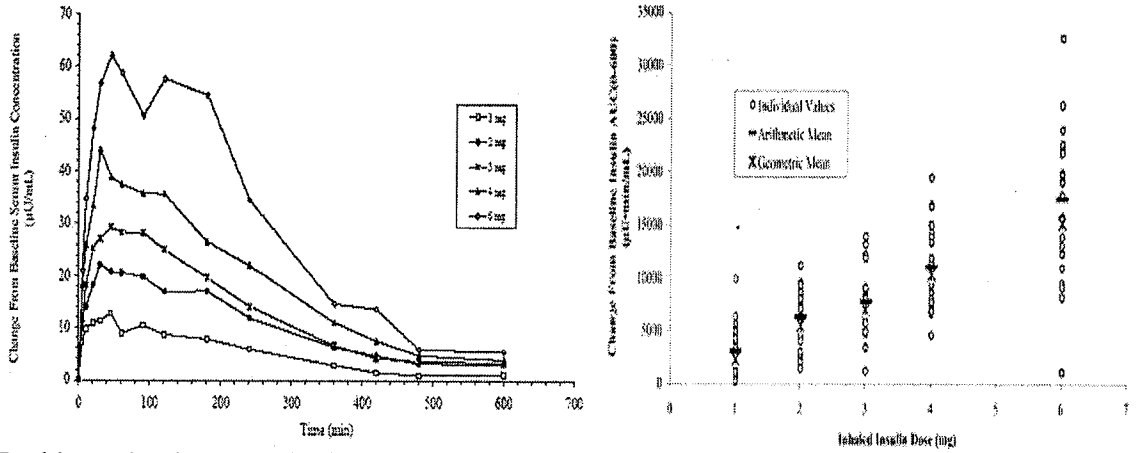
2.2.5 Is There Dose Proportionality in Insulin Exposure?

This question was addressed by the sponsor in one study over a dose range of 1 mg to 6 mg with specific objective to establish dose proportionality over the recommended dose range of inhaled insulin (Study # A217-1012). This was 6-peroid crossover study in healthy subjects using euglycemeic clamp techniques. There were five dose levels: 1, 2, 3, 4, and 6 mg given as 1 x 1 mg, 2 x 1 mg, 1 x 3 mg, 1 + 3 mg, and 2 x 3 mg, respectively. The study was conducted in replicate at each dose level (i.e., each subject received the same treatment twice).

Although there was a trend in increase in insulin level with increase in dose, the pre-determined dose proportionality criteria (base on BE criteria) were not met. However, considering all the variability factors including the number of subjects at each dose level, it can be concluded that there is clear dose-separation at each dose level (**Figure 2.2.2 AB**).

Figure 2.2.2. Summary of Dose-Proportionality Data (Study # 217-012).

A) Profiles (Mean Change from Baseline) **B) Dose vs AUC**



In this study, there was high inter-and intra subject variability in the data at all dose levels. For example, the AUC after 1 mg dose in one subject was 45 μU.min/ml in first period and 3870 μU.min/ml in second period. The same trend was noted in a different subject at a dose of 6 mg where the AUC was 934 μU.min/ml in the first period and 8020 μU.min/ml in the second period. In all subjects following all treatments, the exposure (AUC) ranged from as low as 45 μU.min/ml in one subject at a dose of 1 mg to as high as 32400 μU.min/ml in another at a dose of 6 mg (**Table 2.2.5.1**).

Table 2.2.5.1. AUC Range in Dose Proportionality Study at Each Dose Level in all Treatments (Study # 217-012)

Dose (mg)	Blister Strengths	Range (μU.min/mL)	Difference	Ratio (Max/Min)
1	1 x 1 mg	45-9730	9685	216.2
2	2 x 1 mg	1270-11000	9730	8.66
3	1 x 3 mg	1070-13800	12630	12.89
4	1 x 1 mg + 1 x 3 mg	4440-19300	14860	4.34
6	2 x 3 mg	934-32400	31466	34.68

It should be noted that each dose was administered in replicates in each subject. This high variability and unpredictability in exposure are of major concern from the safety perspective as well as efficacy.

For comparison to SC administration, the following table was similarly compiled for AUC from the bioequivalence study for the 1 and 3 mg strengths (study # 1006):

Table 2.2.5.2. AUC Range in Compiled from the Bioequivalence Study (Study # 1006)

Dose	Blister Strengths	Range (µU.min/mL)	Difference	Ratio (Max/Min)
1 mg	1 x 1 mg	109-6660	6551	61.10
3 mg	1 x 3 mg	377-11600	11223	30.76
9 U	**SC injection**	**2330-8420**	**6090**	**3.61**

From the above examples, it can be concluded that the variability in exposure following inhalation is much higher than that after SC administration. Overall, the % CV in AUC or Cmax following inhaled insulin is expected to be in the range of 50%-100%.

Reviewer's Comments:

Careful examination of the individual data reveals that the exposure is unpredictable over the recommended dose range of 1 mg to 6 mg. However, there is some evidence of separation in exposure with increasing dose. Thus, it can clearly be seen from the entire clinical pharmacology program that the variability in the data plays a major safety concerns for inhaled insulin. For inhaled insulin, there are several sources of variability which include but not limited to: patients lung's condition, inhalation techniques, formulation and device related, and even the process of shipping and handling. All of these sources of variability that affect exposure will be discussed in the following sections and throughout this review.

Furthermore, based on the dose proportionality data it can be speculated that the absorption of insulin from the lung may not be barrier mediated process. The reasons for this assumption are that the lungs have large surface area, highly permeable, and highly perfused tissues. This can further be explained by the fact that the absorption was rapid at all doses with a mean Tmax ranging from 45 min to 75 min at all doses (**Figure 2.2.2**).

2.3 Are there any Intrinsic Factors that Affect Exposure?

There are several intrinsic factors that may affect the performance of this product, including but not limited to the following:

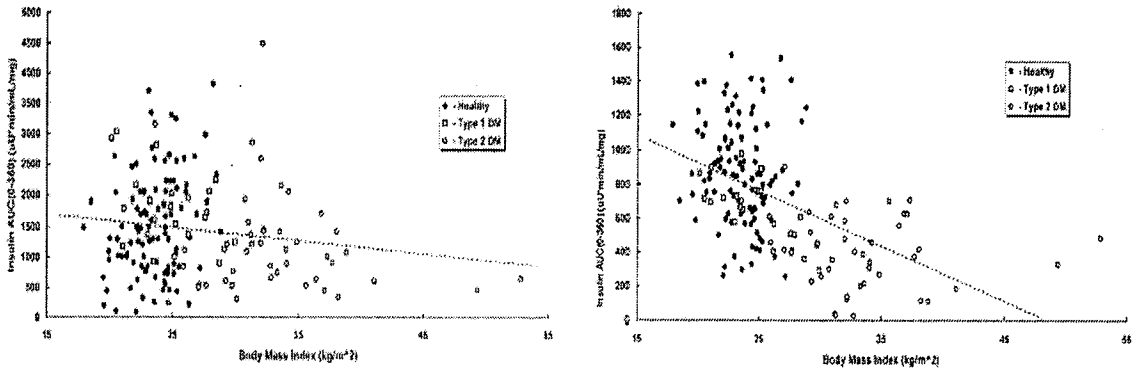
- Age, weight (Body mass Index), gender, and race/Ethnicity
- Pregnancy/gestational diabetes
- Diseases
    - Respiratory disease (e.g., COPD, asthma…etc).
    - Renal impairment
    - Liver impairment

Except for renal and liver impairment, all of the above intrinsic factors have been investigated in several overlapping studies. The effect of each of these factors will be briefly summarized in this review. For clarity and simplicity, only those studies with clinically significant data will be referenced in this review.

Effect of Weight (Obesity): For inhaled insulin, obesity had no effect on either Cmax or AUC. However, for SC insulin, the exposure in obese subjects was about 40% lower than control subjects (Studies A217-1004, A217-1003, 217-007, 217-007). This suggests that the absorption of SC insulin is decreased in obese subjects. Across studies meta analysis conducted by the sponsor for the relationship between insulin exposure and Body Mass Index (BMI) showed a dramatic effect of BMI on insulin exposure following SC injection compared to inhaled insulin (**Figures 2.3.1**).

Figure 2.3.1. Dose Normalized Insulin AUC and Body Mass in Healthy Subjects, Type 1 and Type 2 DM Patients Following Inhaled and SC Insulin (Source: sponsor's summary, Page 32)

A. Inhaled Insulin **B. SC Insulin**



Effect of Age:

It is not clear if the age has any effect on the absorption of inhaled insulin. The sponsor did not conduct stand alone study of the effect of age study with appropriate doses and study design, but rather performed cross study comparisons. Two main studies were used in the sponsor's analysis. The first was conducted in Type 1 DM pediatric patients between ages of 6-17 years (Study # 217-018) and the second in elderly patients with Type 2 DM of age range from 63-80 years (Study # A217-004). Two other supportive studies were used in the sponsor's analysis of the data in patients with type 1 DM with age range 23-43 (Study # 217-021) and patients with Type 2 DM of age range from 43-68 years (Study # A217-1003).

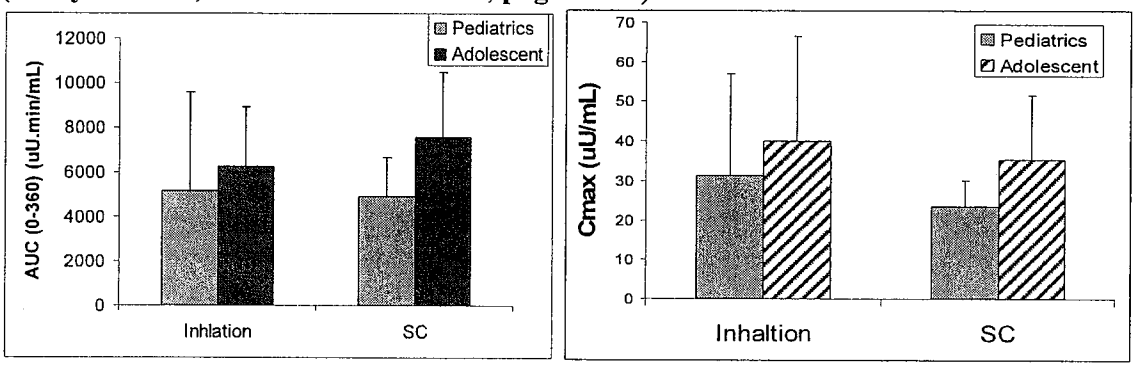
The reason for lack of clarity in these data is that the doses of inhaled insulin were different in each study as they ranged from 1 mg to 6 mg (**Table 2.3.1**). Therefore, it is difficult to make a meaningful interpretation of the data.

Table 2.3.1. Effect of Age on the PK of Inhaled Insulin

Study	Age (y) (mean)	N	Dose INH (mg)	Dose SC (U)	AUC0-360[a] (µU.min/mL) INH	AUC0-360[a] (µU.min/mL) SC	Cmax[a] (µU/mL) INH	Cmax[a] (µU/mL) SC	Tmax (min) INH	Tmax (min) SC	F (%)
217-018[m]	6-11 (8.8)	10	1, 2, or 3	3, 6, or 9	3760[c]	4590[c]	27.1[c]	22.9[c]	68	134	8.4[d]
	12-17 (14.2)	12	2, 3, or 4	6, 9, or 12	5730[c]	6880[c]	32.8[c]	31.9[c]	78	107	8.8[d]
217-021	23-43 (32.4)	22	3, 4, or 6	9, 12, or 18	6140	7340	35.2	32.9	61	136	8.2-10.7[d]
A2171003[g]	43-68 (55.6)	14	6	18	6770[f]	6420[f]	49.2	26.5	60	258	11[f]
A2171004[g]	63-80 (71.6)	20	4	12	4700	4820	48.6	28.6	38	100	11[d]

It should be noted, however, that the analysis of the data from study # 217-018 shows that the exposure of inhaled and also SC insulin appears to be higher in adolescent compared to pediatric subjects (**Figures 2.3.2**).

Figure 2.3.2. Mean AUC (0-360) and Cmax (SD) in Adolescents and Pediatrics Subjects (Study 217-018, Source Tables 5.2.1-2, page 56-61).

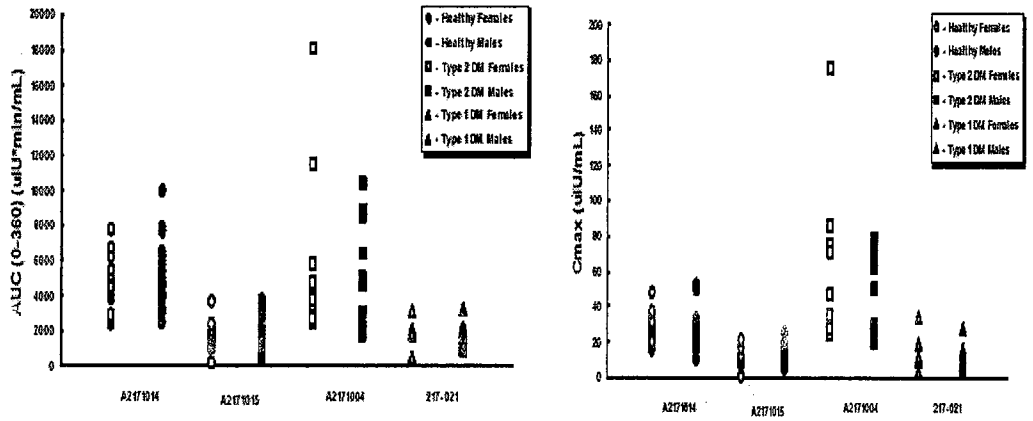


Effect of Gender:

The sponsor did not conduct a stand alone study of the gender effect study but relied on pooled analysis of the data from different PK studies (**Figures 2.3.3**). Overall, based on the review of all relevant studies it can be concluded that there is no apparent difference between males and females in terms of insulin exposure and PD effects.

Figure 2.3.3 Insulin Exposure by Gender (Poled Data from Different Studies)

A) AUC **B) Cmax**



Effect of Race and Ethnicity:

The information available, thus far, is limited to Japanese population. Cross study analysis reveals that there is some difference in exposure following inhaled insulin between Japanese and Caucasian population (Study # A217-1016 and 217-023). Both of these studies are small in size ranging from 12 to 16 subjects.

In study 217-023, the exposure in Caucasian appears to be approximately 30% higher than Japanese at 2 mg dose, but comparable at 1 mg dose (**Figures 2.3.4 and 2.3.5**). It should be noted that the exposure in Caucasian was more than doubled after 2 mg compared to 1 mg in both population. However, in study # A217-1016, the exposure was dose proportional in Japanese subjects (**Figures 2.3.6 and 2.3.7**). No Caucasians were included in study #1016. The bioavailability of inhaled insulin in both studies ranged from approximately 6% to 9% following all treatments. This is consistent within the range of values found in other studies.

Overall, it appears that the variability in PK data plays important role in the interpretation of the data. Therefore, it would be fair to conclude that the exposure, overall, in Japanese and Caucasian is comparable.

Figure 2.3.4. Exposure in Japanese and Caucasian Population (Study # 217-023). Data Mean (± SD)

AUC **Cmax**

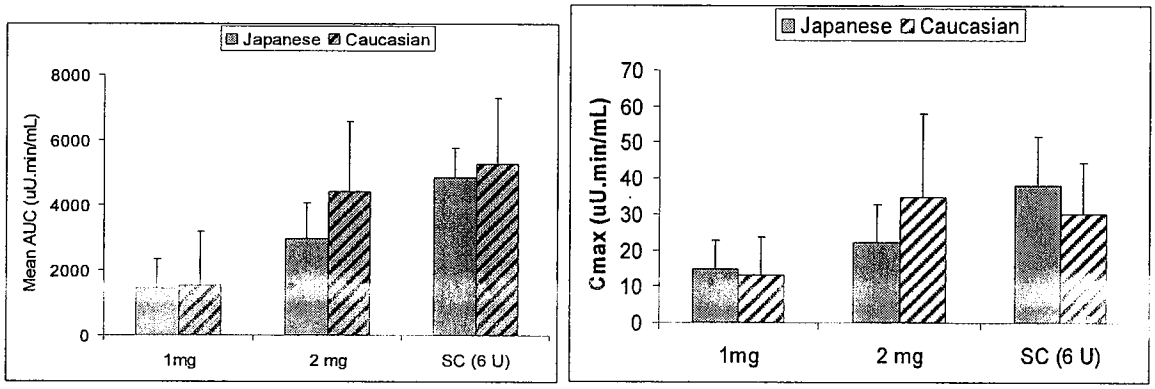


Figure 2.3.5. Insulin Plasma Profiles in Japanese and Caucasian (Study # 217-023)

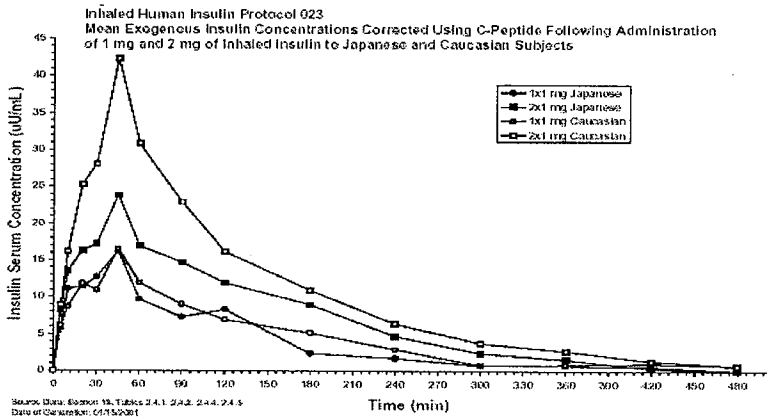


Figure 2.3.6. Insulin Plasma Profiles in Japanese (Study # A217-1016)

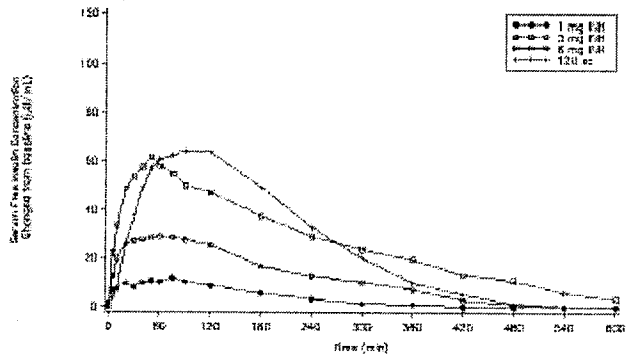
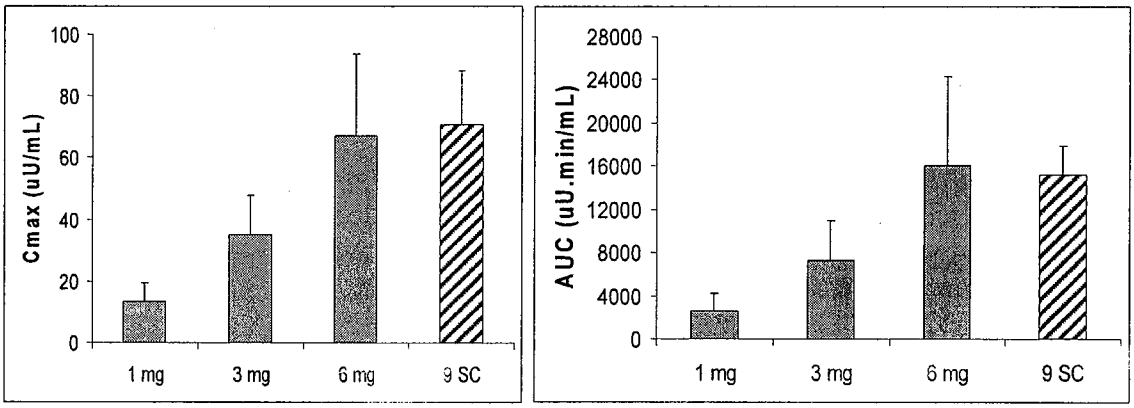


Figure 2.3.7. Exposure and Dose Proportionality in Japanese Population (Study # A217-1016)



Effect of Pregnancy/Gestational Diabetes:

A study was designed to investigate the PK of inhaled and SC insulin in 13 females with gestational diabetes mellitus (GDM) or pregestational Type 2 DM (pregnant subjects with preexisting Type 2 DM). In these patients, the exposure from inhaled and SC insulin was within the range of that observed in all other studies in this NDA following 3 mg (1 x 3 mg) inhaled dose and 9 U SC insulin (Study # A217-1007). Therefore, it can be concluded that pregnancy has no effect on the absorption and/or disposition of inhaled or systemic insulin (**Table 2.3.2**)

Figure 2.3.2. Insulin PK Parameters in all Subjects (Mean and %CV)

Parameter	INH (1 x 3 mg)	SC (9 U)	Ratio/Difference	95% CI
AUC 0-360* μU·min/mL)	2435 (50)	2630 (57)	93%	(55%, 155%)
Cmax (μU/mL) *	39.0 (57)	21.3 (97)	183%	(116%, 290%)
Tmax (min) **	45.8 (39)	82.9 (63)	-37.1	(-75.1, 1.0)

*Adjusted geometric means
**Adjusted arithmetic means
CV% derived from arithmetic means

Patients with Respiratory Condition:

The lung function is the most critical for the absorption and systemic delivery of the inhaled insulin. Because of its importance, the discussion of these conditions/factors will be undertaken in a relatively greater length than the previous factors discussed above. Although, these respiratory diseases are considered intrinsic factors, other sources that affect lung functions such as smoking and rhinovirus infection will be discussed in a separate section under extrinsic factors.

Patients with Chronic Obstructive Pulmonary Disease (COPD):

The general notion is that the absorption of the drug would be reduced in dysfunctional cell membranes. In contrary, the absorption of inhaled insulin was enhanced in patients with COPD

and most surprisingly by 2-3 folds increase in smokers compared to non-smokers (this will be discussed in under extrinsic factors).

The PK and PD of inhaled insulin were investigated in patients with COPD, who are no longer smokers (Study # A217-1005). The study was conducted in patients with emphysema and chronic bronchitis following either 3 mg oral inhaled insulin or 9 units of SC regular insulin. COPD patients were also given 2 puffs of albuterol 30 min before or 30 min after both inhaled and SC insulin administration. This study consisted of 12 healthy subjects, acting as control, and 12 patients with COPD.

Although, the variability in the data was too high to make a meaningful conclusion, the overall impression is that the exposure of inhaled insulin in patients with COPD, and in particular patients with emphysema, was higher than in healthy subjects (**Figures 2.3.8 and 2.3.9**). This increase in exposure was more noticeable with Cmax and during the initial 60 minutes of inhalation.

Figure 2.3.8. AUC (0-60) and AUC (0-360) in Patients with COPD (Study # A217-1005)
A) AUC (0-60) **B) AUC (0-360)**

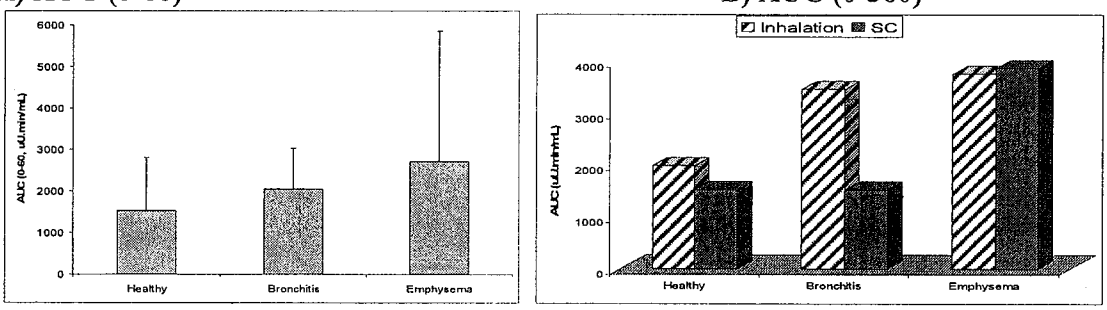
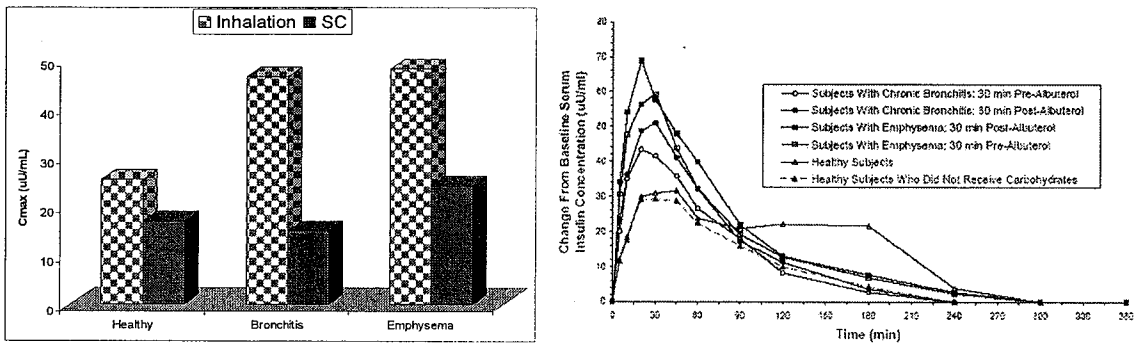


Figure 2.3.9. Effect of COPD on Cmax of Inhaled and SC Insulin (Study # A2171005)



The use of albuterol inhaler had no effect on the PK or PD. In addition, four healthy subjects were excluded from the analysis as they received carbohydrates during inhalation treatment which increased the baseline of insulin concentrations. Furthermore, two patients were considered outliers by the sponsor as the individual relative bioavailability to SC was **615%** in one subject and **683%** in another subject. The sponsor's explanation is that these two subjects had abnormally low exposure following SC administration.

In terms of safety, two patients with COPD suffered myocardial infarctions during the study: one at approximately 13 hours post inhalation arm with albuterol and the other on Day 3 after SC injection. According to the sponsor, these events were not related to the study treatments.

Conclusions:

Although the excessive mucus production in COPD and the loss of alveolar surface area in emphysema and/or smokers are expected to impair the absorption of drugs from the lung, the results obtained from this study indicates that the insulin absorption appears to either enhanced and/or did not changed. This is an interesting observation (s) that deserves further investigation.

Therefore, based on the uncertainty in the data and the critical safety issues in this patient's population, it is recommended that the study be repeated with sufficient power at the highest recommended inhaled insulin dose (i.e., 6 mg).

Patients with Asthma (Study 217-009):

The data from patients with asthma are in sharp contrast with the data from COPD patients for the following two main reasons:

1) The data is more consistent than that of COPD
2) There is a clear trend in decrease in exposure in asthmatic patients, rather than increase as shown in COPD patients (**Figure 2.3.10 and Table 2.3.3**)

Figure 2.3.10 Exposure in Asthmatic Patients (Study # 217-009)

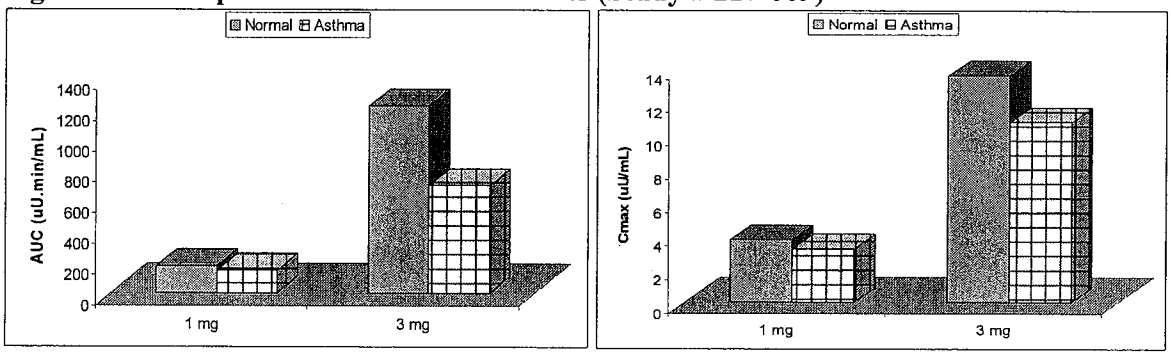


Table 2.3.3. Summary of PK data in Asthma (Study # 217-009)

Parameter	Asthmatic	Normal	Ratio (%) or Difference	95% CI
$AUC_{0\text{-}360}$ Inhaled 1 mg (μU·min/mL)	146	175	83%	(35%, 200%)
$AUC_{0\text{-}360}$ Inhaled 3 mg (μU·min/mL)	701	1220	58%	(26%, 129%)
$AUC_{0\text{-}360}$ SC (μU·min/mL)	3720	3530	105%	(81%, 136%)
F* (1 mg/SC)	0.01	0.02	82%	(33%, 206%)
F* (3 mg/SC)	0.02	0.04	54%	(23%, 126%)
Cmax Inhaled 1 mg (μU/mL)	3.21	3.76	85%	(48%, 151%)
Cmax Inhaled 3 mg (μU/mL)	10.8	13.6	80%	(47%, 133%)
Cmax SC (μU/mL)	23.2	19.9	117%	(82%, 166%)
Tmax Inhaled 1 mg (min)	31	31	-1	(-18, 16)
Tmax Inhaled 3 mg (min)	36	47	-11	(-35, 13)
Tmax SC (min)	83	76	7	(-35, 49)

* AUC values were dose-standardized prior to calculation of F (Inhaled AUC/SC AUC)

Renal and Liver Impairment study:

Since no formal study was conducted in these patients and based on the historical data and the clinical experience with insulin, the sponsor recommended careful glucose monitoring and dose adjustment of inhaled insulin in patients with renal impairment and liver impairment. A language to this effect was included in the Clinical Pharmacology and Precaution sections of the labeling. This language will be reviewed and revised accordingly.

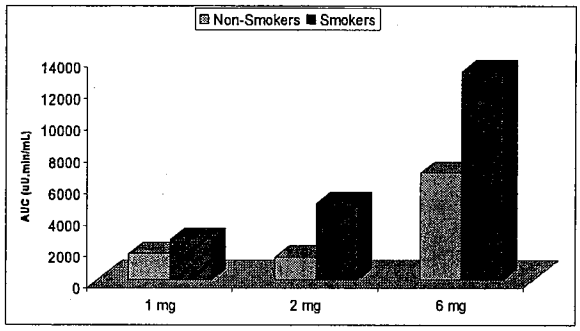
2.4 Are there any Extrinsic Factors?

The most striking extrinsic factor is the effect of smoking on the absorption of inhaled insulin. The sponsor conducted four separate studies to investigate the effect of smoking on the absorption of inhaled insulin (Study # 217-005, 217-016, A217-1003, and A217-1020). From all these studies, the following conclusions can be made:

- The exposure (Cmax and AUC) increased by about 2-3 folds in smokers compared to non-smokers (**Figures 2.4.1-3**).
- The absorption of inhaled insulin is approximately 30 min faster in smokers than non-smokers (i.e., Tmax was reduced by 30 min).
- Smoking cessation for 2-3 days results in a rapid decrease in exposure to a level comparable to that of non-smokers (**Figure 2.4.2**). Conversely, the resumption of smoking for 2-3 days returns the exposure to the baseline level as was prior to the smoking cessation (**Figure 2.4.3**).
- As expected, glucose level was consistent with insulin levels, being low in smokers as the exposure to insulin was high and being high in non-smokers and at the time of smoking cessation as insulin level was low.

Figure 2.4.1. Effect of Smoking on Insulin AUC and Cmax Pooled from Three Different Studies Following Inhaled Insulin (Study # A2171—3, 217-016, and A2171020)

A) AUC



B) Cmax

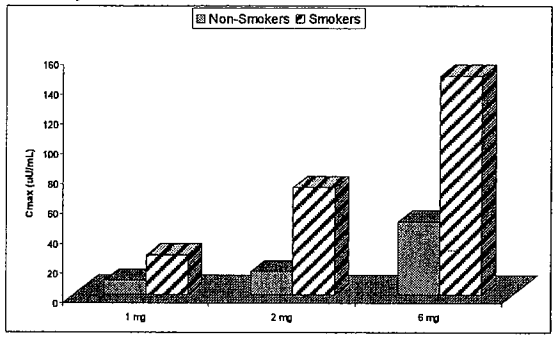
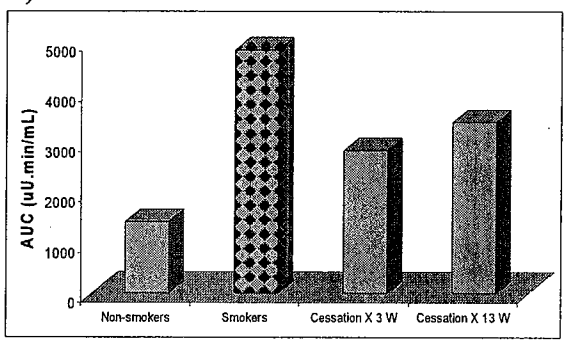


Figure 2.4.2. Effect of Smoking Cessation on AUC and Cmax Following Inhaled Insulin (Study 217-016)

A) AUC



B) Cmax

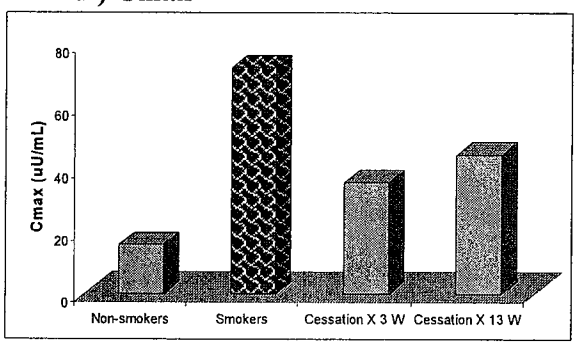
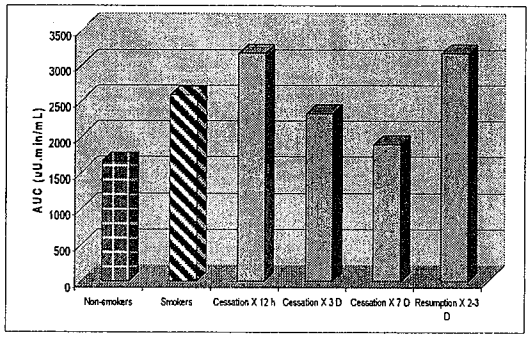
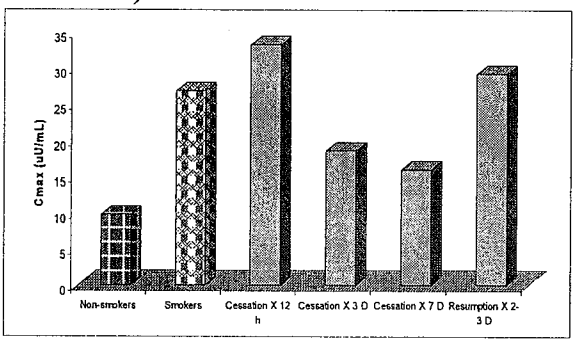


Figure 2.4.3. Effect of Smoking Cessation on Insulin AUC and Cmax Following Insulin Inhalation (Study 2171020)

A) AUC



B) Cmax



2.4.1 What is the Possible Mechanism(s) of Effect of Smoking?

The sponsor has not provided clear explanation for the enhancement of insulin absorption in smokers. The sponsor's only explanation is a possible increase in insulin permeability in smoker's lungs. However, the actual mechanism has not been illustrated.

Based on our literature review, the *in vivo* transendothelial transport of insulin appears to be a non- saturable process as shown in one study (Steil, GM, J.Clin. Invest., 97, 1297-1503, 1996). This suggests that insulin transport through lungs is not receptor mediated. Therefore, the increase in transport efficiency in smokers is most likely due to an increase in *diffusionary* capacity resulting from capillary dilation.

The above speculative mechanism is in part supported by the fact that smoking had no effect on SC data as discussed above. Thus smoking had no effect on the disposition and/or elimination of insulin and the only reasonable explanation is that smoking affects the permeability and transport of inhaled insulin into the systemic circulation.

Additional speculation is that smoking may cause either damage to the cell membranes to allow the transport of peptides such as insulin and/or the induction of unknown carrier mechanism to transport insulin through the cell and into the blood stream. The reason for this assumption is that the absorption of inhaled insulin appears to also be enhanced in patients with COPD. These have dysfunctional lungs.

2.4.2 Effect of Passive Smoking:

On August 10, 2005 the sponsor submitted additional study to investigate the effect of acute passive smoking on the PK of inhaled insulin. The study was conducted in 28 healthy non-smokers subjects in crossover design as follows:

Period 1	Washout Period	Period 2
Inhaled Insulin 3 mg + Passive Smoke Exposure (N = 14)	At least 2 weeks	Inhaled Insulin 3 mg in the Absence of Passive Smoke Exposure (N = 14)
Inhaled Insulin 3 mg in the Absence of Passive Smoke Exposure (N = 14)	At least 2 weeks	Inhaled Insulin 3 mg + Passive Smoke Exposure (N = 14)

All subjects received 3 mg inhaled insulin in the absence and in the presence of passive smoking of approximately 2 hours duration.

The data show a completely different picture. Passive smoking reduces the absorption and exposure of inhaled insulin by approximately 20% to 30% (**Figure 2.4.4 and Table 2.4.1 2.4.2**).

Figure 2.4.4. Mean Insulin Concentration-Time Profile in the Presence and Absence of Passive Smoking

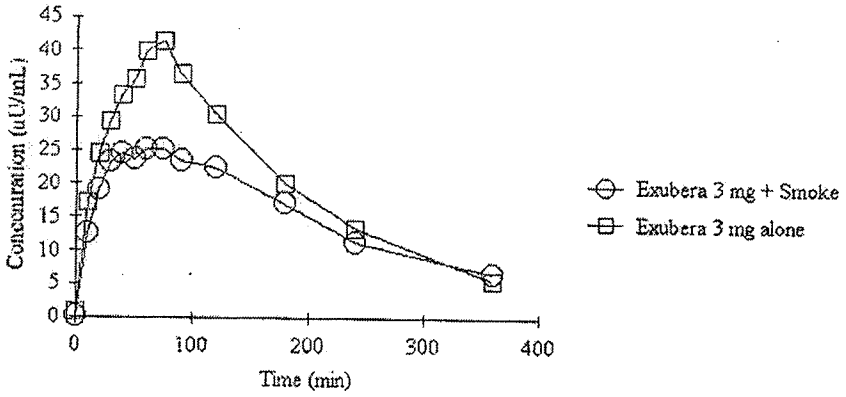


Table 2.4.1. Mean (± SD) PK Parameters of Inhaled Insulin in the Presence and Absence of Passive Smoke Exposure

Parameter	Exubera 3 mg Alone (N = 28)	Exubera 3 mg + Passive Smoke (N = 30)
AUC0-360 (min·µU/mL)	7280 (3100)	5610 (2200)
AUC0-240 (min·µU/mL)	6240 (2680)	4600 (1750)
AUC0-120 (min·µU/mL)	3790 (1670)	2590 (1010)
Cmax (µU/mL)	48.7 (28.8)	30.1 (9.94)
Tmax (min)*	60 (20 – 120)	75 (20 – 360)

*Median (Range)

Table 2.4.2. Summary of Statistical Analysis of PK Parameters in of Inhaled Insulin in the Presence and Absence of Passive Smoke Exposure

Parameter	Treatment		Adjusted Geometric Means		Ratio (%) [T/R]	95% Confidence Interval
	Test	Ref	Test	Ref		
AUC0-360 (min·µU/mL)	B	A	4718	5703	82.73	(68.78, 99.50)
Cmax (µU/mL)	B	A	28.9	41.0	70.52	(59.83, 83.13)

Treatment A = Exubera 3 mg Alone
Treatment B = Exubera 3 mg + Passive Smoke
Ref = reference; Ratio [T/R] = Test/Reference

Reviewer's Comments:

The data from this study is surprising as well as the reasons for this difference. Whatever, the mechanism may be, this unexpected data may have no clinical consequences or impact. However, it will fairly be stated that the reason for the marked difference in insulin exposure following inhalation between the chronic smokers and passive smokers remains to be unknown.

2.4.3 Rhinovirus Infection:

One study was conducted by the sponsor with the objective to investigate the effects of rhinovirus infection on the absorption of inhaled insulin. The rational for this study is that patients with respiratory infection usually have excess mucous that may affect the absorption of inhaled insulin as well as they are expected to be more susceptible to external irritation such as inhaled powders.

The information from this study is limited due to the unequal small number of subjects completed the study (n=20 active and n=4 control). Therefore, the data should be interpreted with great caution. Considering the mean data and the high variability, the rhinovirus infection appears to have no significantly effect on the absorption of inhaled insulin. It should be noted that the exposure on Day 1 (prior to inoculation) was higher than Day 4 in virus and saline group, respectively (**Figure 2.4.5 and Table 2.4.3**).

Figure 2.4.5. Mean (± SD) For Insulin PK Parameters With and Without Rhinovirus Infection (Study # 217-010)

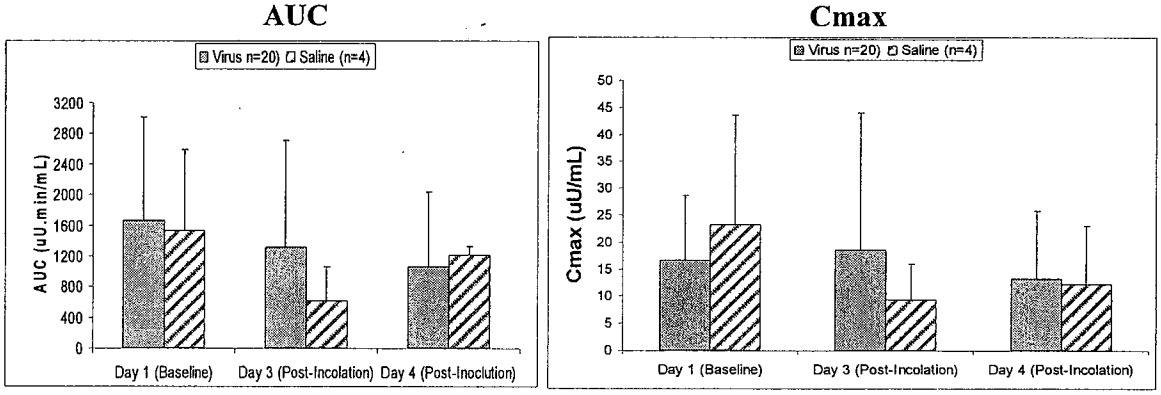


Table 2.4.3. Mean (CV%) of Insulin PK Parameters (Study 217-010)

	Virus (N=20)			Saline (N=4)		
	Day 1	Day 3	Day 4	Day 1	Day 3	Day 4
$AUC_{0\text{-}360}$ (μU·min/mL)	1663 (81)	1306 (107)	1051 (94)	1530 (69)	617 (71)	1210 (107)
Cmax (μU/mL)	16.6 (73)	18.5 (138)	13.2 (91)	23.3 (86)	9.3 (73)	12.2 (89)
Tmax (min)	45.0 (38)	37.5 (51)	48.3 (35)	30.0 (0)	33.8 (22)	22.5 (43)

Day 1: Before inoculation, Days 3 and 4: Post-inoculation

From these data, it can be concluded that the data is limited to be a definitive conclusion. Therefore, appropriate language should be included in the label accordingly.

2.4.4 Drug Interactions:

On August 10, 2005 the sponsor submitted one additional study report on the effect of short-acting bronchodilator (ß-agonist, albuterol) and inhaled corticosteroid (fluticasone) on the absorption of inhaled insulin in non-diabetic subjects with asthma (Study # A2171056).

The study was conducted as four treatments (in 48 subjects with mild or moderate asthma) and 2 treatments (in 12 healthy subjects) in crossover design. All subjects received a training 3 mg dose of inhaled insulin on Days -3 and -1. Non-asthmatic subjects received inhaled a single 3 mg dose of inhaled insulin on Days 1 and 3. The study design is summarized in the following table:

	Day –3	Day –1	Day 1	Day 3	Day 5	Day 7
Healthy Subjects	INH 3 mg training	INH 3 mg training	A	A	NA	NA
Asthmatic Subjects	INH 3 mg training	INH 3 mg training	A	B	C	D
			B	A	D	C
			C	D	A	B
			D	C	B	A

A = INH (3 mg) alone
B = Albuterol (180 µg) followed by INH (3 mg) 30 minutes later
C = INH (3 mg) followed by albuterol (180 µg) 10 minutes later
D = Fluticasone (440 µg) followed by INH (3 mg) 30 minutes later

The data show approximately 30% to 50% increase in insulin exposure when administered 30 minutes after albuterol in subjects with mild and moderate asthma, respectively (**Tables 2.4.4 and 2.4.5 and Figure 2.4.6**). In comparison to healthy no-asthmatic patients, the exposure was about twice lower in asthmatic patients prior of either albuterol or fluticasone (**Table 2.4.8**).

Table 2.4.4. Mean (± SD) PK Parameters 3 mg Insulin When Administered 30 minutes After Albuterol Inhalation (Study # A2171056).

	Group 1*		Group 2*	
	INH 3 mg	Albuterol + INH 3 mg	INH 3 mg	Albuterol + INH 3 mg
AUC0-360 (min·µU/mL)	2220 (1330)	2950 (1330)	3430 (1960)	4480 (3040)
Cmax (µU/mL)	24.3 (20.9)	32.8 (23.1)	31.5 (26.1)	47.2 (42.5)
tmax (min)	29.5 (19.7)	31.4 (14.1)	36.7 (13.6)	43.2 (18.7)

*moderate asthmatic subjects (Group 1) and mild asthmatic subjects (Group 2) as defined in Section 5.3..

Table 2.4.5. Summary of Statistical Analysis of Inhaled Insulin PK Parameters When Administered 30 minutes After Albuterol Inhalation (Study # A2171056).

	Group 1*				Group 2*			
	Adjusted Geometric Means				Adjusted Geometric Means			
	Test†	Reference†	Ratio	95% CI	Test†	Reference†	Ratio	95% CI
AUC0-360 (min·µU/mL)	2941.4	1953.3	150.59	(119.75, 189.38)	5052.0	4056.0	124.56	(106.15, 146.16)
Cmax (µU/mL)	29.6	20.1	146.99	(120.20, 179.75)	46.8	34.6	135.16	(115.14, 158.65)

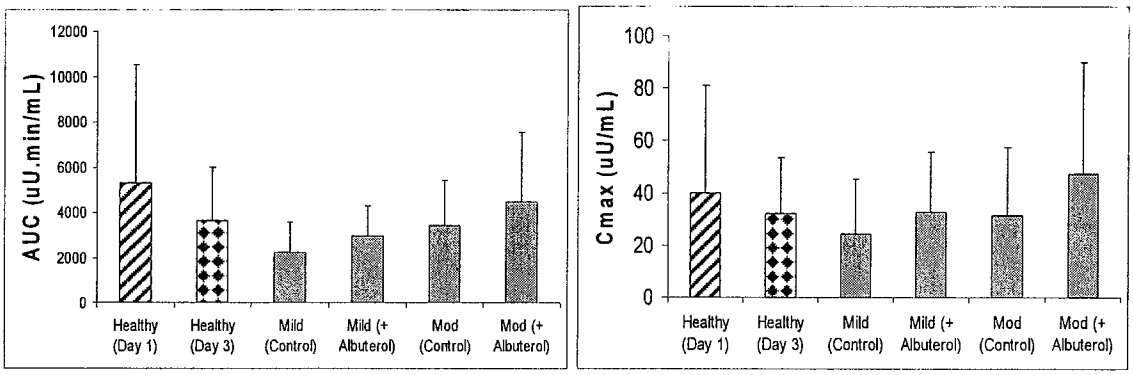
*Group 1 = moderate asthmatic subjects; Group 2 = mild asthmatic subjects, as defined in Study Population and Criteria for Inclusion

†test = albuterol (180µg) + INH (3 mg), reference = INH (3 mg)

Table 2.4.8. Mean (± SD) PK Parameters in non-Asthmatic Healthy Subjects After 3 mg Inhaled Insulin alone.

Parameter	Period 1	Period 3
AUC0-360 (min-μU/mL)	5280 (5260)	3640 (2360)
Cmax (μU/mL)	40.0 (41.0)	32.0 (21.5)
Tmax (min)	70.0 (66.2)	60.8 (90.5)

Figure 2.4.6. Complied Data on the Effect of Albuterol on Inhaled Insulin (Study # A217-1056)



In contrast albuterol, the administration of fluticasone had no effect when it was administered 30 minutes before inhaled insulin (**Table 2.4.6 and 2.4.7**).

Table 2.4.6. Mean (±SD) of PK Parameters for the Effect of Inhaled Fluticasone on Inhaled Insulin (Study A2171056)

	Group 1*		Group 2*	
	INH 3 mg	Fluticasone + INH 3 mg	INH 3 mg	Fluticasone + INH 3 mg
AUC0-360 (min-μU/mL)	2220 (1330)	2140 (1300)	3430 (1960)	3400 (1830)
Cmax (μU/mL)	24.3 (20.9)	21.5 (12.2)	31.5 (26.1)	31.0 (22.2)
Tmax (min)	29.5 (19.7)	34.3 (17.4)	36.7 (13.6)	38.3 (14.2)

*moderate asthmatic subjects (Group 1) and mild asthmatic subjects (Group 2) as defined in Section 5.3.

Table 2.4.7. Summary of Statistical Analysis for the Effect of Inhaled Fluticasone on Inhaled Insulin (Study A2171056)

	Group 1*				Group 2*			
	Adjusted Geometric Means				Adjusted Geometric Means			
	Test†	Reference†	Ratio	95% CI	Test†	Reference†	Ratio	95% CI
AUC0-360 (min·μU/mL)	1842.5	1953.3	94.33	(74.89, 118.83)	4008.5	4056.0	98.83	(83.89, 116.43)
Cmax (μU/mL)	19.1	20.1	94.79	(77.43, 116.06)	34.2	34.6	98.78	(83.82, 116.41)

*Group 1 = moderate asthmatic subjects; Group 2 = mild asthmatic subjects, as defined in Study Population and Criteria for Inclusion
†test = fluticasone (440 μg) + INH (3 mg), reference = INH (3 mg)

Reviewers Comments:

From the above data, the following comments can be made:

1) The exposure in asthmatic subjects is much lower than in healthy non-asthmatic, even after albuterol administration (**Figure 2.4.6**). However, the data is consistent with observation made in the previous study in asthma (Study # 217-009). The cause and or the mechanism of low exposure in asthmatic subjects relative to healthy subjects are of great interest and deserve further evaluation.
2) There was high variability in the data, irrespective of treatments. For example, the mean AUC in healthy on Day 1 was 5280 with SD of 5260 and on Day 3 was lowered to 3640 with SD of 2360 (**Table 2.4.8**).
3) The clinical impact of these observations, in particular, the effect of albuterol, should be carefully assessed.

2.4.5 Other Extrinsic factors:

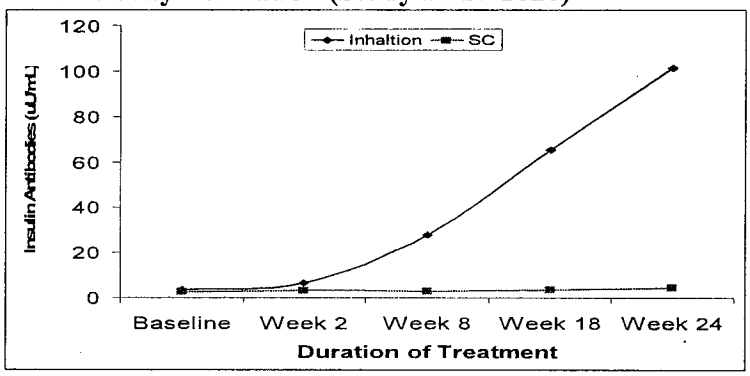
Base on the long history of insulin use, the sponsor has not conducted any additional studies. It is well known that many other factors affect insulin exposure and its pharmacological actions. For example, some conditions and/or drugs that may affecting glucose metabolism.

2.4.6 What is the Effect of Long Term Administration on PK and PD?
a) Is there Any Effect on Insulin Antibodies Formation?
b) Is There Any Evidence of Tolerance to Insulin?

In an exploratory study for 24 weeks, the sponsor investigated the effect of inhaled and SC administration on the PK and PD profiles (Study # A217-1026). The primary objective of this study was to investigate postprandial glucose after 24 weeks of daily administration in Type 1 DM patients. In addition to this objective, the sponsor provided plethora of relevant information related to PK and PD profiles including but not limited to the following: longitudinal effects, duration of insulin action, PK profiles, postprandial glucose tolerance, insulin antibody binding capacity and/or binding affinity. The study was conducted in about 24 subjects in each arm in parallel group design. Below is the summary of the observations from this study:

- There was no apparent effect of antibody formation on glucose parameters on week 24 when corrected for baseline on week 0. When corrected for the baseline, the ratio for Cmax and AUC was 1.04 and 1.10 at week 12 and 0.99 and 0.97 for week 24, respectively. The same trend was observed for GIR (Glucose infusion rate), indicating no changes in glucose response over the study period.
- However, there was a dramatic increase in antibody formation following inhaled insulin compared to SC insulin (**Figure 2.4.6**). For inhaled insulin, the level of insulin antibody increased from the baseline of 3.5 to 101 μU/mL at week 24. By sharp contrast there was virtually no change in antibody level for SC as it increased only from a baseline level of 2.62 to 4.30 μU/mL at week 24.

Figure 2.4.6. Insulin Antibody Formation (Study # 217-1026)



- According to the sponsor, PK samples for month 3 and month 6 were inadvertently not collected. The only data available is for week 0 which shows wide inter-subject variability. Therefore, no new or useful information was noted for the PK perspective in this study.

Conclusions:

- For inhaled insulin, antibody level increased from the baseline by about **30 fold** at week 24. However, there was virtually no change in antibody level following SC injection. The mechanism of such increase in antibody with inhaled insulin is unknown and worth further investigation.
- According to the sponsor's, no evidence of glucose intolerance as a result of antibody formation over 6 month's treatment with either inhaled or SC insulin.

2.4.7 Does this Drug Prolong QT or QTc Interval?

As an endogenous substance and as a product of a recombinant technology, insulin has been used for many decades in lowering blood sugar in diabetic patients. All of its pharmacological and safety profiles have been well established. Its effect on heart, heart rates, and QT intervals are well established.

2.5 Biopharmaceutics Issues

In this section, the focus will be on product performance in relation to its bioavailability, bioequivalence within dosage strengths and SC administration, dose proportionality, and reproducibility (variability). The most important aspect of this section of the review will focus on the effect of particle size distribution and other aerodynamic metrics and characteristics. It should be noted that some discussion will overlap among different sections of this review and in particular those associated with changes in the source of drug substance (i.e., insulin), formulation, and inhalers.

Overall, the data from this section can be summarized as follows:

- The bioavailability of oral inhaled insulin compared to SC was approximately 10%.
- Although the sponsor believes that the variability in inhaled insulin is comparable to that of SC, the data is questionable as it was obtained under rigorous and strict study guidelines.
- Due to this high variability, the dose proportionality is somehow questionable over the dose range of 1 mg to 6 mg. However, the data appears to indicate that there is a trend for increase in exposure over this dose range as well as clear separation between doses.
- Based on rigorous *in vitro* aerosol studies related to particle size metrics and characteristics, the sponsor concluded that the Fine Particle Dose (FPD) less that —— (FPD < —— is the primary performance metric for the scale up formulation.

2.5.1 What is the Drug Product/Formulation?

Background:

As a product, Exubera, consists of two main components: the dry powder formulation (the drug) and a device (the inhaler). The two components are inseparable as the optimal performance of the product (Exubera) depends on the fine tuning of the formulation (the powder) and the mechanistic process of the delivery system (the inhaler). Therefore, in this section the critical interrelationship between the powder formulation, the source of insulin production (*the drug substance*), and the mechanism of deliver via the inhaler will be discussed in some details as it pertains to the clinical pharmacology and in particular to the biopharmaceutics aspect of the product.

Drug Substances:

There were two sources of insulin inhalation powder that were used in this NDA; one supplied by Eli Lilly and the other by Aventis. This product is known to be jointly developed by Pfizer and Aventis. The early developmental studies including but not limited to toxicology, Phase I, IIa and IIb studies were conducted using Lilly's insulin, whereas Phase III study was conducted using the insulin supplied by Aventis (Formerly know as Hoechst Marion Roussel or **HMR**). According to the sponsor, the chemical, physical, and structural analysis of the two insulin sources were similar (**CMC review**). In addition, a BE study was conducted to establish the link between two different sources of insulin (Study # 217-012).

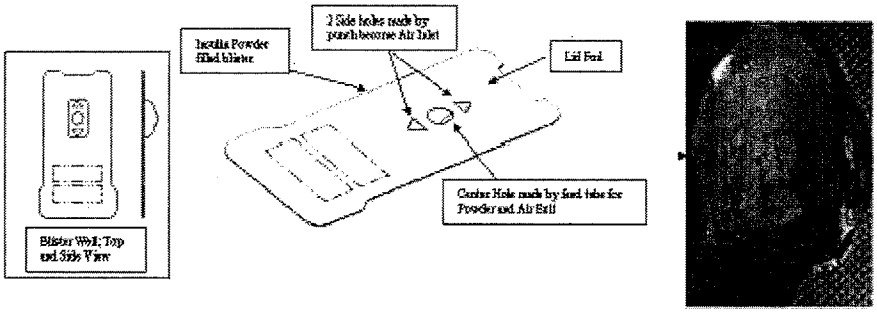
Drug Products:

The drug product will be available in ——— foil/PVC unit dose perforated blisters in two strengths, 1 mg and 3 mg.

Appears This Way
On Original

Appears This Way
On Original

Scheme: Sample of Dissected Blister and Blister's Assembly



These dosage forms are compositionally proportional. The 60% formulation was used in all Phase III studies and is to-be-marketed formulation (**batch #** [redacted]. The same formulation containing the same excipients with different composition was used in early development, including Phase II, with insulin loading of only 20% (**Table 2.5.1**). Another important difference between the two strengths is that the fill mass being 1.7 mg and 5.1 mg for 1 mg and 3 mg strength blisters, respectively. As a result of these changes, the systemic delivery from the 1 mg was more efficient than the 3 mg strength (see later discussion). Thus the two formulations were not bioequivalent (i.e., 3 x 1 mg vs 1 x 3 mg).

These major differences in formulation strengths and product performance are among the most challenging issues in the clinical pharmacology and biopharmaceutics program for this product and in this review. Not to mention, also the changes in inhalers along the way from version P 1 to P3. Thus making cross studies analysis and comparison is very difficult and unacceptable in certain situations.

Although the Phase III formulation is to-be-marketed formulation, the sponsor conducted two BE studies to establish bioequivalency between the clinical batch (1.5 Kg) and the scale up batch (15 Kg). The main reason for this study was due to the differences observed in particle size aerodynamic parameters between the 1 mg and 3 mg strengths. These studies will be discussed in later in this section of the review.

Table 2.5.1. Formulation Used Early Development and Phase II Studies

Formulation Identity	[redacted] Commercial and Phase I-3	I-004 Phase 1 and Phase 2	I-005 Phase 1 only	I-033 Phase 1 only
% Insulin	60%	20%	60%	90%
Component	% w/w	% w/w	% w/w	% w/w
Insulin	60.00	20.0	60.00	90.00
Mannitol	[redacted]			
Glycine				
Sodium Hydroxide				
Sodium Citrate				
Citric Acid				
Total	100.00	100.0	100.00	100.00

What are the Critical Components for Formulation Stability?

It was noted that the ratio of mannitol:sodium citrate is a key stability parameters in all formulations. In addition, the % of insulin loading is critical component for formulation stability.

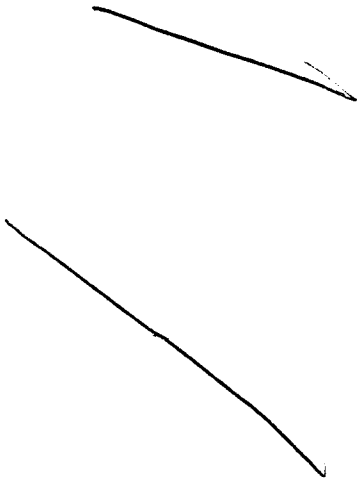
2 Page(s) Withheld

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

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Clin Pharm/Bio-_____



2.5.1.2 Was there a link Between Early Formulation and Final Formulation?

The sponsor did not conduct a formal study to establish the link between the early and Phase III formulations. However, based on cross studies comparison the bioavailability of the early formulation and the Phase III formulation relative to SC administration was within 5% to 8% for both formulations (Studies # 217-001 and 217-012, **Table 2.5.5**).

Table 2.5.5. Mean Relative Bioavailability of Early Formulations (Study # 217-001)

Study	Formulation FID	Treatment INH	Treatment SC	F (%)	95% CI (%)
217-001		3x1 mg	0.15 U/kg	8	(7, 10)
		1x3 mg		8	(7, 11)
217-012		3 mg/P2	10 U	5	(4, 7)
		3 mg/P3		7	(5, 9)

2.5.1.3 What is the Effect of Particle Size on the Product Performance?

Two studies were conducted specifically to address the effect of particle size on the bioavailability on insulin powder formulation (Studies # 217-014 and 217-019). The Mass Median Aerodynamic Diameter (**MMAD**) used in these two studies ranged from approximately [redacted] Across these two studies, the data show clear inverse relationship between particle size and exposure with no effect on Tmax (**Figure 2.5.3 and Table 2.5.7**).

Figure 2.5.3. Effect of Particle Size on Exposure (Studies # 217-014 and 217-019)

A) AUC **B) Cmax**

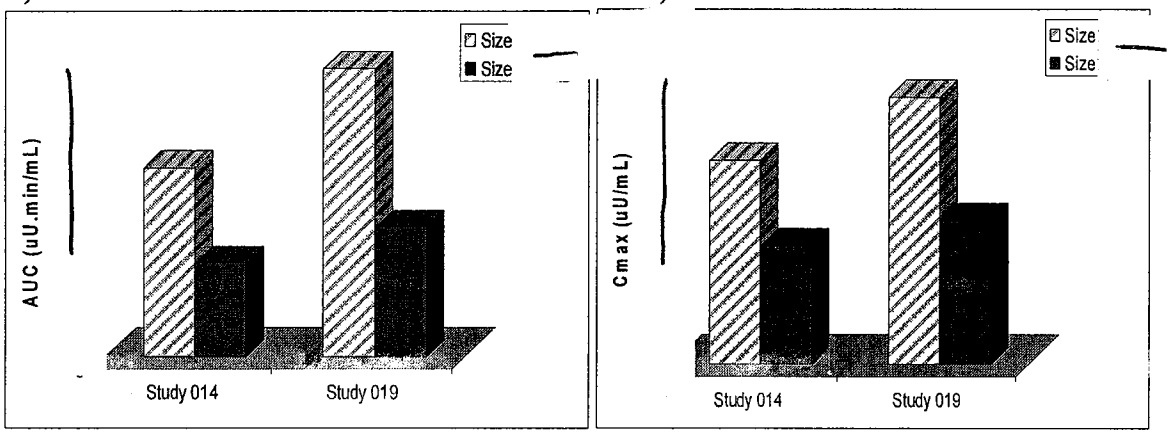


Table 2.5.7. Effect of Particle Size on Insulin PK (Studies # 217-014 and 217-019)

Study 217-	Dose (mg)	FID #	MMAD µm	N	AUC0-360* (µU·min/mL)	Cmax* (µU/mL)	Tmax (min)
014	2x1			24	948	11.4	38
				24	1910	19.6	47
019	2x1			24	1310	13.8	42
				24	2910	25.6	43

2.5.1.4 Is Particle Size Distribution in the Clinical and Commercial Scale Products Similar?

Although the clinical and the commercial scale up products have similar FPD — the commercial powder — clinical batch. This difference may be explain the — in emitted mass with commercial powder. Therefore a BE study was necessary (Studies # A217-014 and A217-015). The data from these studies will be discussed in a separate section later.

2.5.1.5 What is the Effect of Fill Mass and Particle Size Characteristic on the PK of Inhalation?

In the early product development, the blisters for both 1 mg and 3 mg were filled with a total of — powder containing 20% or 60% insulin, respectively. A BE study was conducted and showed comparable profiles between 3 x 1 mg and 1 x 3 mg strengths (Study # 217-001). However, the formulation used in this study was found to have stability problems (Formulation # I-004). Thus, a new formulation was developed —. The formulation issues have not been completely resolved as the new formulation produced higher bioavailability for 3 x 1 mg than 1 x 3 mg. In addition, the two strengths were not bioequivalent (Pivotal BE Study # A217-006). This was consistent with particle size metrics and specifically with the differences in FPD — the Cmax and AUC for 1 x 3 mg blister were 30% to 40% higher than 1 x 3 mg blister.

Another study was conducted comparing the old formulation with high fill weight (# I-004) and the modified low fill weight formulation used in Phase 3 studies (formulation # —

The low fill weight formulation composed of 1.7 mg powder/blister and 60% insulin while the high fill weight composed of 5 mg powder/blister and 20% insulin. The study was conducted only for 1 mg strengths. The two formulations were not bioequivalent (Study # 217-015).

From the pivotal BE study it was concluded that the 3 x 1 mg blister is not equivalent to 1 x 3 mg with 30% to 40% higher exposure (**Table 2.5.8,** study # A217-1006). In this study, the fill mass was 1.7 and 5.1 mg insulin for 1 and 3 mg strengths, respectively.

Table 2.5.8. BE Parameters (Study # A217-1006).

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

Based on i*n vitro* data, the emitted dose were similar for each strength. However, the dose normalized values of FPD [redacted] was higher for the 1 mg compared to 3 mg strength (**Table 2.5.9**). The difference in the bioavailability between the two strengths is attributed by the differences in the fill masses. Thus, the lower the fill mass the better the aerosol performance as reflected in the higher FPD values for the 1 mg blister with lower fill mass compared with the 3 mg blister with higher fill mass (**Table 2.5.9**). Furthermore, the difference in clinical performance for the two dose strengths with different fill masses was not reflected in the emitted dose (ED) ratio for the two blisters. Therefore, it can be concluded that FPD [redacted] be considered to be more predictive of the insulin absorption following inhalation than ED.

Table 2.5.9. Aerosol metrics and Clinical PK data (Study # A217-1006)

	$AUC_{0\text{-}360}$	Ratio AUC (A/B)	ED* (mg)	Ratio ED (A/B)	FPD < [redacted] (mg)	Ratio FPD [redacted] (A/B)	MMAD* (µm)
3x1mg (A)	2600	[redacted]					
1x3mg (B)	1860						

Overall Summary of Particle Size Effect on the Product Performance:

- Based on *in vitro/in vivo* analysis of the PK data, a higher FPD [redacted] could be associated with product delivery problems.
- Therefore, FPD [redacted] is optimal powder for delivery of insulin via inhalation. The sponsor is proposing to use this metric in the labeling to measure the "delivered dose" of insulin inhalation product.
- The amount of powder (or fill weight) in the blister is an additional factor that affects the aerosolized particle size distribution. As fill weight is reduced, more compressed air energy from the inhaler will be available per mg of powder to aerosolize the powder. The relationship between the fill weight and product performance were investigated in several studies (#A217-006, 012, 014, 015, and 019). These studies have demonstrated that the differences in fill weight result in differences in FPD among the formulations.

2.5.2 What is the Relative Bioavailability of the Proposed to-be-Marketed Formulation Following a Single Dose Administration Compared to the Clinical Products?

As indicated in the previous section, the sponsor conducted two studies to establish bioequivalency between the formulation used in Phase 3 and to-be-marketed (Study # A217-1014 and A217-1015). The main reason of these studies was due to the observed difference in the particle size aerodynamic parameters between the clinical batch of [redacted] and the commercial batch of [redacted] **(Figures 2.5.2.1 and 2.5.2.2)**.

Figure 2.5.2.1 Particle Size Distribution of Clinical Batch ([redacted]) and Commercial Batch [redacted]

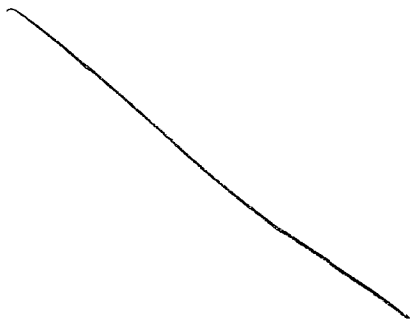
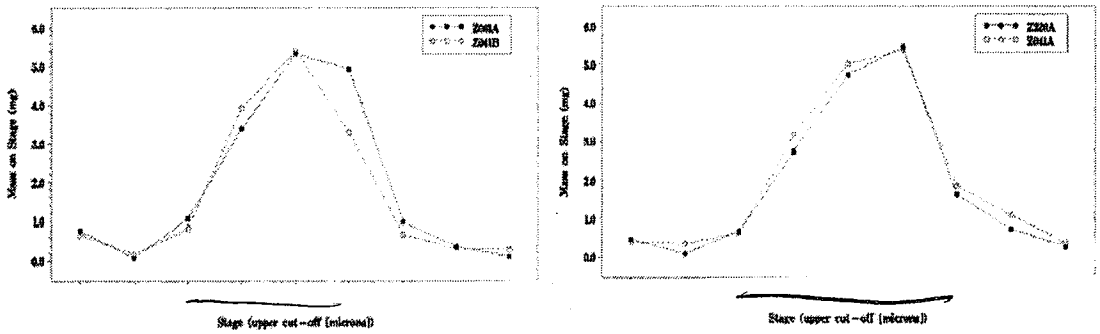


Figure 2.5.2.2. Particle Size distribution for 1 mg and 3 mg Clinical and Commercial Strengths

A) 1 mg Strength **B) 3 mg Strength**



Z001A is Clinical Scale
Z041B is Commercial Scale

Z220A is Clinical Scale
Z041A is Commercial Scale

Based on *in vitro* aerodynamic data, the particle size distribution for the commercial and clinical products are slightly different as shown in **Figures 2.5.2.1 and 2.5.2.2**. Thus, based on this *in vitro* data a similar *in vivo* performance would be expected. Thus the sponsor conducted two studies, one for the 1 mg strength (Study # A217-1015) and the other for the 3 mg strength (A217-1014) blisters. Both of these BE studies were conducted using crossover design with three treatments arms as follows:

Treatment A (**replicate**): 1 mg or 3 mg of clinical formulation
Treatment B (**replicate**): 1 mg or 3 mg to-be-marketed formulation
Treatment C: 9 U SC insulin for the 3 mg strength in study # 014 or 3 U for the 1 mg strength in study #015.

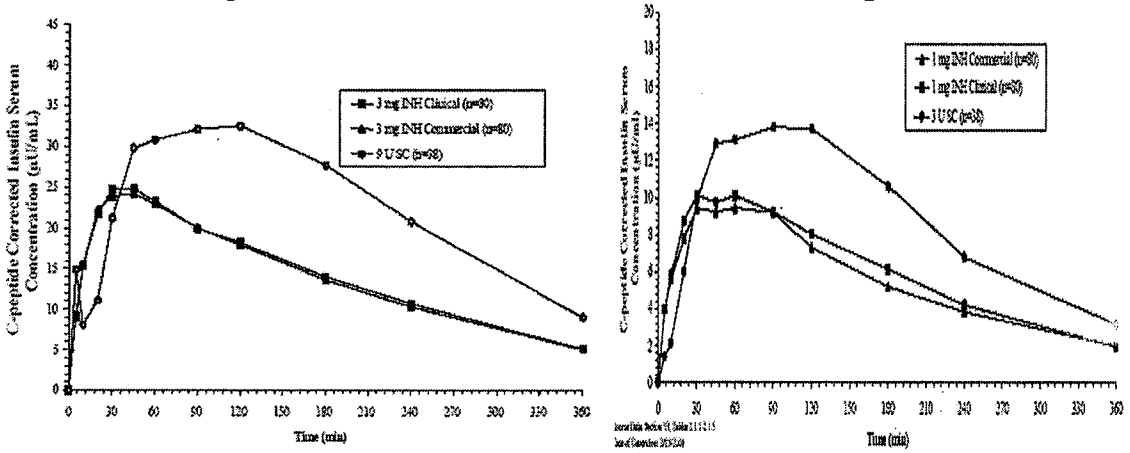
Based on the data from these two studies, it can be concluded that the 3 mg strengths were equivalent, but not for 1 mg strengths (**Table 2.5.2.1**). The 90% CI for AUC for 1 mg strength was just below the regulatory acceptance limit of 80% (i.e., **78.8%**). The plasma concentration-time profiles for insulin were very similar (**Figure 2.5.2.3**).

Table 2.5.2.1. Summary of BE Analysis (Study # A217-1014 and A217-1015)

Parameter	N	COM	CLN		
A2171014 (3 mg blister)	40	Adjusted Geometric Means		Ratio (%)	90% CI
AUC_{0-360} (µU. min/ mL)		4620	4750.	97.2	91.7, 103
Cmax (µU/ mL)		25.5	25.9	98.7	93.1, 105
		Adjusted Arithmetic Means		Difference	
Tmax (min)		45	51	-6	-14, 2
A2171015 (1 mg blister)	40	Adjusted Geometric Means		Ratio (%)	
AUC_{0-360} (µU. min/ mL)		1610	1780	90.7	78.8, 104
Cmax (µU/ mL)		10.6	11.4	93.3	84.9, 103
		Adjusted Arithmetic Means		Difference	
Tmax (min)		65	63	3	-10, 15

Figure 2.5.2.3. Mean Insulin Profiles Following 1 or 3 mg Strengths for Clinical and to-be-marketed formulations (Study # A217-1014 and 1015)

1 mg **3 mg**



Conclusion:

From OCPB and regulatory perspectives, the clinical and commercial batches for the 3 mg strength are equivalence, but **not** for the 1 mg strength. However, from the clinical perspective and impact, this small difference in the CI may be considered insignificant.

2.5.3 Are the 1 mg (3 x 1 mg) and 3 mg (1 x 3 mg) Blisters Bioequivalent? (i.e., is there Dosage Strength Equivalence?)

From the clinical pharmacology and biopharmceutics perspective, this is the most critical question related to the equivalency of the 1 and 3 mg blister strengths. The reason for its importance is that they will be used in combination for patient's titration.

Study A217-1006 was conducted to answer this question. It was crossover study with three arms as follows: A) 3 x 1 mg, B) 1 x 3 mg, and C) 9 U SC regular insulin. Treatments A and B were done in replicates.

The data from this study was showed that the two strengths were **not bioequivalent (Table 2.5.2.1, 2.5.2.2 and Figure 2.5.2.3)**. The exposure following 3 x 1 mg blisters was approximately 30 to 40% higher than 1 x 3 mg blisters. Both Cmax and AUC were outside the 90% CI limits of 80 to 125%. However, Tmax were similar.

Table 2.5.2.1. Mean (% CV) of PK Parameters for Each Treatment (Study A217-1006)

	3x1 mg		1x3 mg		SC
Parameter	INH1	INH2	INH1	INH2	
AUC0-360 (µU.min/mL)	3619 (71)	2950 (72)	2560 (49)	2150 (75)	5220 (35)
F (%)	9.0 (81)	6.8 (76)	6.4 (70)	5.3 (91)	--
Cmax (µU/mL)	43.8 (69)	32.0 (63)	31.5 (66)	29.7 (87)	31.0 (35)
Tmax (min)	43 (36)	45 (40)	45 (41)	39 (35)	79.6 (50)

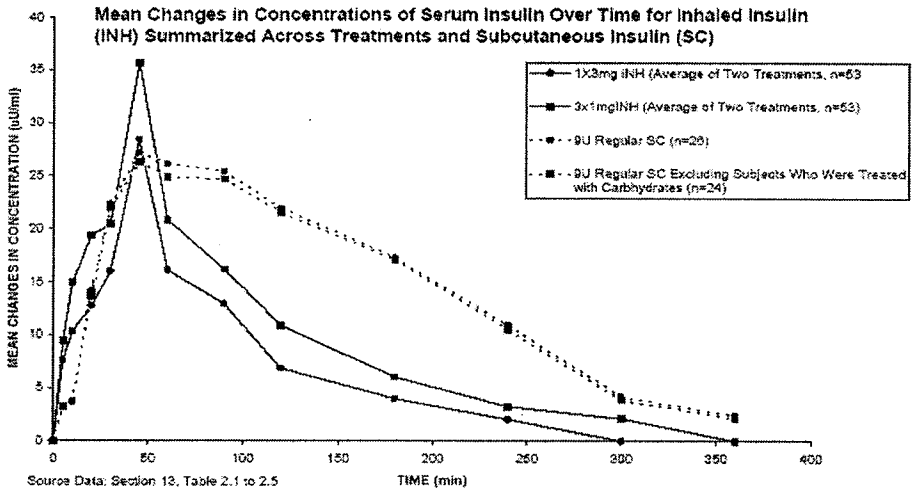
INH1: Administration of the first dose of the designated inhaled insulin treatment
INH2: Administration of the second dose of the designated inhaled insulin treatment
*For subjects who completed all five treatment periods

Table 2.5.2.2. Overall Statistical Summary for all Treatment (Study A217-1006)

Parameter	3x1 mg*	1x3 mg*	Ratio/Difference	90% CI
AUC0-inf (µU.min/mL)	2595	1859	140%	(117%, 167%)
Cmax (µU/mL)	31.02	24.51	127%	(108%, 149%)
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

Figure 2.5.2.3. Insulin Profiles (Study # A217-1006)



The sponsor believes that the lack of equivalency between the two blisters is attributed to the difference in the fine particle dose (FPD). The mean FPD values less than [redacted] micron (FPD [redacted] or FPD [redacted]) for the 3 mg strength were [redacted] mg and [redacted] mg, respectively. In comparison, the values for the 1 mg strength were higher; FPD < [redacted] 1.2 mg; FPD < [redacted] mg. According to the sponsor, the increased amount of fine particles with the 1 mg strength likely resulted in a greater delivery to the peripheral lung with a concomitant increase in systemic insulin levels (AUC and Cmax) than those achieved with the 3 mg strength.

Conclusions:

The main conclusions are the two strengths are not equivalent nor interchangeable. Specifically, if the patient is being stabilized on 1 x 3 mg blister, the use of 3 x 1 mg blisters as a substitute may have clinical implications. The sponsor's proposed language in the labeling will be reviewed and revised, if necessary

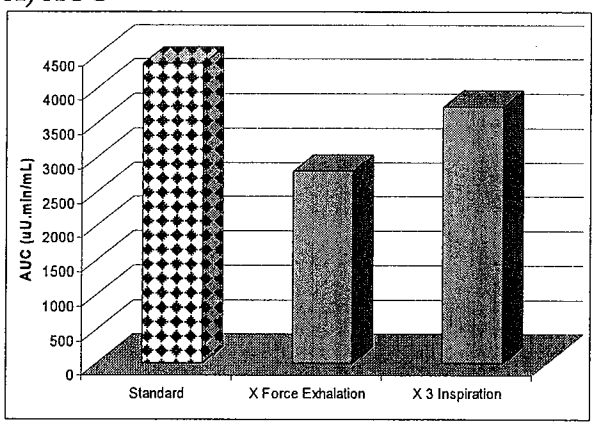
2.5.4 What are the Effects of Inhalation Techniques and Inhalation Rate on Insulin Exposure?

This is an important question that deserves a clear answer as it pertains to patient's experience, efficiency of inhaler and the mechanism of delivery. As stands, it is hard to separate the two inter-dependent components; patient-inhaler interaction.

To answer this question the sponsor conducted five studies: three studies to investigate the inhalation techniques (Study # 217-002, 217-004, and 217-014) and two studies to investigate the inhalation rate (Study # 217-011 and 217-019). Overall, from all these studies it can fairly be stated that the standard inhalation techniques and the slower inhalation rates appear to produce maximum insulin delivery (**Figures 2.5.2.4-6, and Table 2.5.2.3.**).

Figure 2.5.2.4. Effect of Inhalation Techniques/Maneuvers on Insulin Exposure (Study 217-002)

A) AUC



B) Cmax

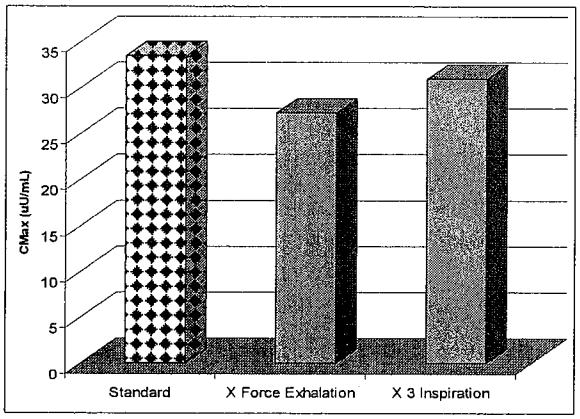
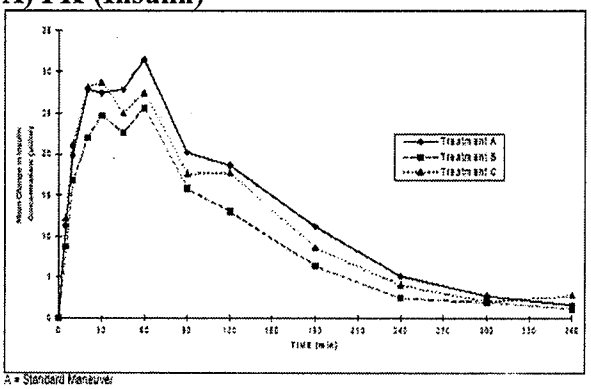
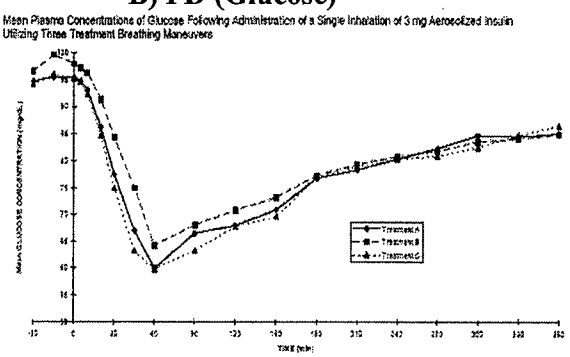


Figure 2.5.2.5. Effect of Inhalation Techniques on PK/PD Profiles (Study 217-002)

A) PK (Insulin) **B) PD (Glucose)**



A = Standard Maneuver
B = Standard Maneuver Preceded by Forced Exhalation
C = Standard Maneuver Preceded by Forced Exhalation and Followed by Three Maximum Inspirations



A = Standard Maneuver
B = Standard Maneuver Preceded by Forced Exhalation
C = Standard Maneuver Preceded by Forced Exhalation and Followed by Three Maximum Inspirations

Figure 2.5.2.6. Effect of Inhalation of Breath holding on PK/PD (Study # 217-014)

Treatment A µm Particle size using the standard inhalation

Treatment B µm Particle size using the standard inhalation

Treatment C. µm Particle size using the standard inhalation **without breath hold**

A) PK (Insulin) **PD (Glucose)**

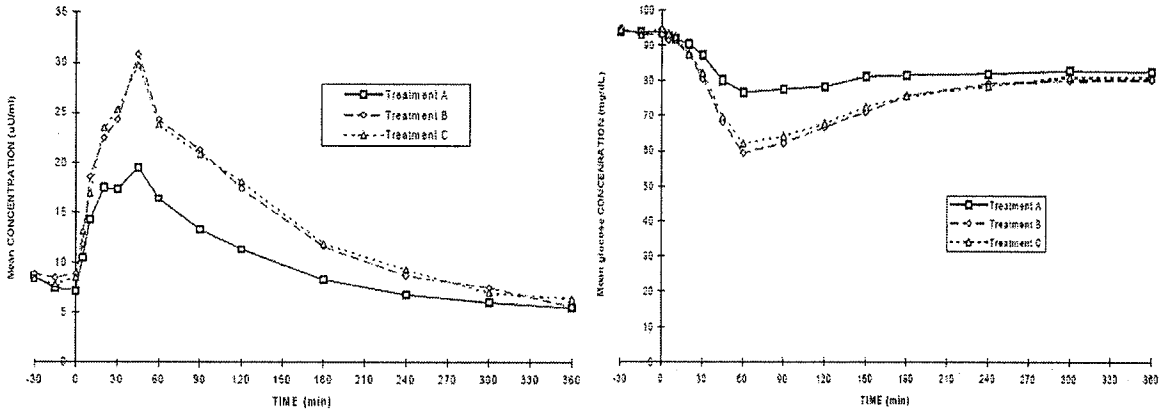
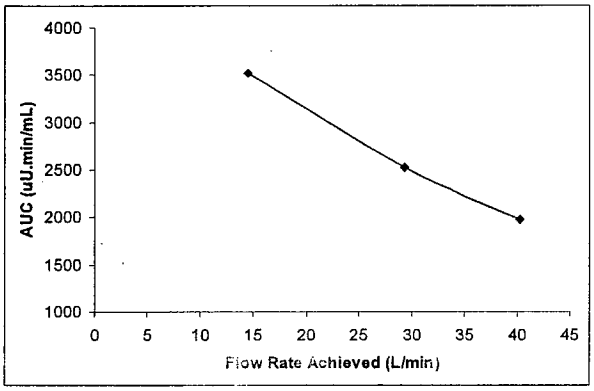


Table 2.5.2.3. Summary of Insulin Exposure Data Using Different Inhalation Techniques (B: Standard proceeded by forced exhalation, C= Maneuver B followed by three maximum inspirations)

Study 217-	Inhalation Maneuver	Dose	N	AUC0-360* (µU·min/mL)	Cmax* (µU/mL)	Tmax (min)
002†	Standard	1x3 mg	11	4360	33.5	42
	B	1x3 mg	12	2790	27.3	43
	C	1x3 mg	11	3730	31.0	38
004	Standard	1x3 mg	19	4450	35.5	38
	No breath hold	1x3 mg	19	4610	38.1	42
014‡	Standard	2x1 mg	24	1910	19.6	47
	No breath hold	2x1 mg	23	1970	21.0	39

Figure 2.5.2.7. Effect of Inhalation Rate on Insulin Exposure (Study # 217-011)

A) AUC



B) Cmax

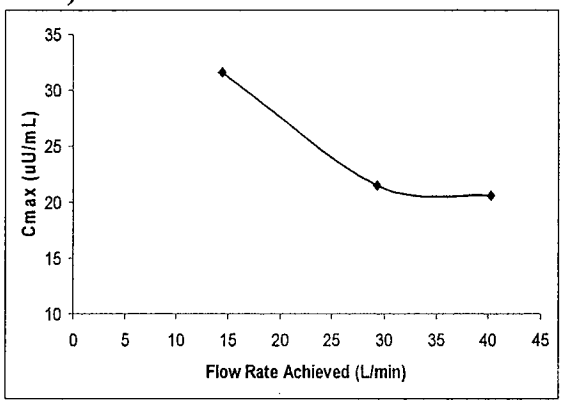
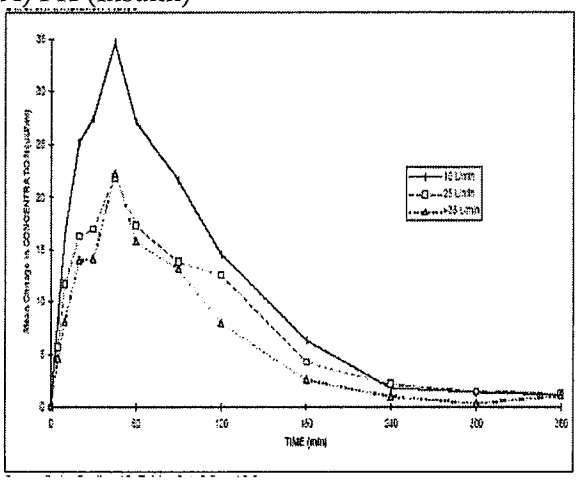


Figure 2.5.2.8. Effect of Flow Rate on PK/PD Profiles of Insulin (Study 217-011)

A) PK (Insulin)



B) PD (Glucose)

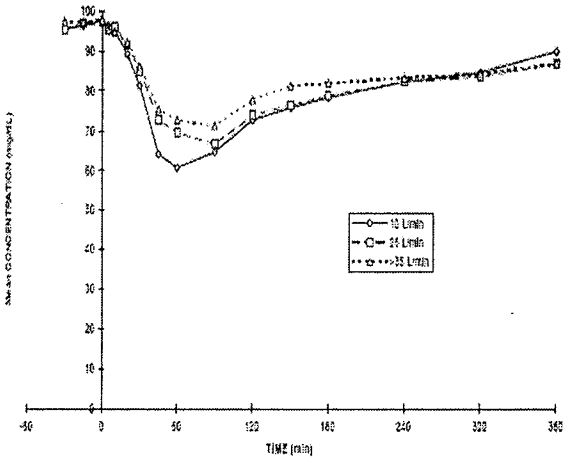


Table 2.5.2.4. Effect of Inhalation Rate on Insulin Exposure

Study 217-	Dose (mg)	Target Inhalation rate (L/min)	Flow Rate achieved[1] (L/min)	N	AUC0-360* (µU·min/mL)	Cmax* (µU/mL)	Tmax (min)
217-011	3	10	14.5	12	3520	31.6	42
		25	29.3	12	2530	21.5	46
		>35	40.26	12	1980	20.6	49
217-019	2	10	8.8	24	1310	13.8	42
		25	14.1	24	1330	14.5	46

Conclusions:

The following conclusions can be made from the above studies in reference to inhalation techniques/maneuver and inhalation rates:

- The standard inhalation technique appears to be robust and consistent. According to the sponsor, this involves the following steps: normal exhalation, dispersion of aerosolized insulin to the inhaler chamber, steady and deep inhalation, breath holding for 5 seconds, and gentle exhalation.
- Whatever the mechanism may be, the lower inhalation rate appears to enhance insulin delivery.
- Study 217-014 further confirms the significant effect of powder particle size on the pulmonary delivery of insulin (**Figure 2.5.2.6**). The smaller the size, the more efficient is the delivery of the powder.

2.5.5 Variability in the Data

Overview:

It is evident from the entire NDA that there is high variability in the PK data from inhaled insulin. In some studies the % CV is >100% and it is almost >50%. For example, in the dose proportionality study (# A217-1012), the AUC ranged form as low as 45 to as high as 32400 over a dose range of 1 to 6 mg doses as show as follows:

Dose (mg)	Blister Strengths	Range (μU.min/mL)	Difference	Ratio (Max/Min)
1	1 x 1 mg	45-9730	9685	216.2
2	2 x 1 mg	1270-11000	9730	8.66
3	1 x 3 mg	1070-13800	12630	12.89
4	1 x 1 mg + 1 x 3 mg	4440-19300	14860	4.34
6	2 x 3 mg	934-32400	31466	34.68

It should be noted that each dose was administered in replicates in each subject. Therefore, the above table represents all subjects and all treatments.

For comparison to SC administration, the following table was similarly compiled for AUC form from the pivotal bioequivalence study for the 1 and 3 mg strengths (study # 1006):

Dose	Blister Strengths	Range (μU.min/mL)	Difference	Ratio (Max/Min)
1 mg	1 x 1 mg	109-6660	6551	61.10
3 mg	1 x 3 mg	377-11600	11223	30.76
9 U	**SC injection**	**2330-8420**	**6090**	**3.61**

From the above table, it can clearly be seen that SC administration has much lower variability compare to inhalation within the same study and the same subjects.

In addition, in the most recent study report submitted in August 10, 2005, the mean AUC after 3 mg inhaled insulin was 5280 with SD of 5260 μU.min/ml (% CV = 9.6%) in healthy subjects (Study # A217-1056). When the same dose was repeated in the same subjects three days later, the AUC dropped 3640 with SD of 2360 μU.min/ml (%CV = 64.8%).

Specific Variability Studies/Analysis:

The sponsor performed specific study and cross study analysis to investigate the variability and reproducibility in the PK data following inhalation and SC administration.

By analyzing the %CV from several relevant clinical pharmacology and biopharamacetics studies, the conclusions listed below can be made relative to inter and intra-subject variability. It should be noted that all the data were re-produced from the sponsor's summary tables located in section 2.7 (Tables 14-18) and section 2.7.1 (Appendix A).

A) Inter-Subject Variability:

- For inhaled insulin: The %CV for AUC data ranges from 14% in study # 217-021 to 103% in study # A217-1005. The %CV for Cmax from 18% to 123% in study # 217-021.
- For SC insulin: The %CV for AUC data ranges from 23% in study # 217-0017 to 84% in study # A217-1005. For Cmax it ranged from 31% in study # 217-021 to 148% in study A217-1014.

Further analysis of the data was performed by plotting the %CV from all studies for AUC and Cmax shows that overall the %CV is higher for inhaled insulin compared to SC (**Figures 2.5.1 and 2.5.2**). The residual plots (i.e, the difference between inhaled and SC %CVs) clearly show the trend, especially for AUC. It should be noted that this analysis and the plots should be interpreted carefully as the number of data set were not equal for inhaled and SC insulin. *Also, it should be noted that each data point (set) represent one study.*

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Figure 2.5.1. %CV of Inhaled and SC Insulin for AUC (Pooled Data from Several Studies in the NDA) (each data point/set represent one study)

A) % CV (Inhaled vs SC) **B) Residual Plot (Difference of Inhaled-SC)**

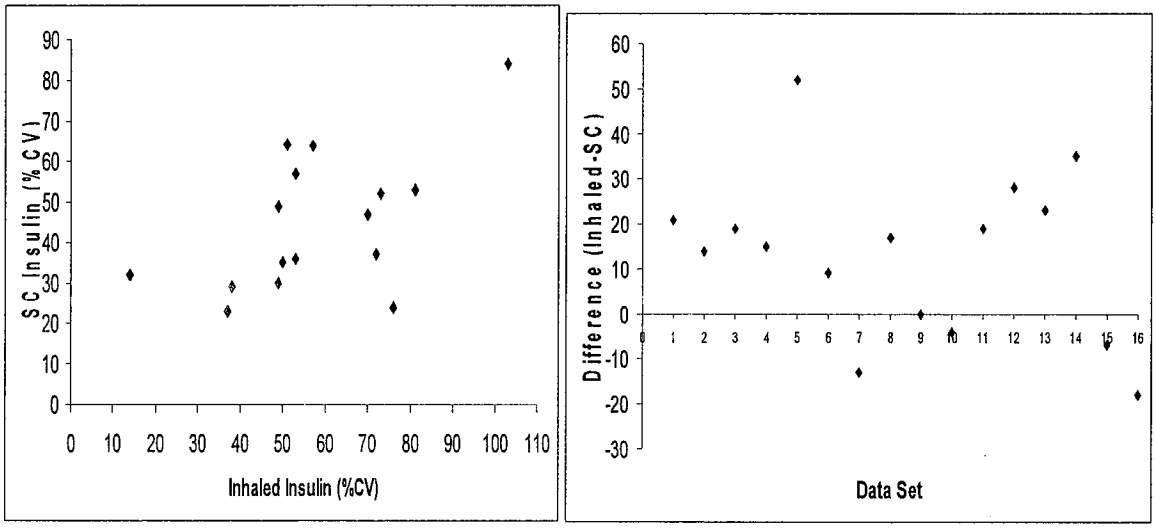
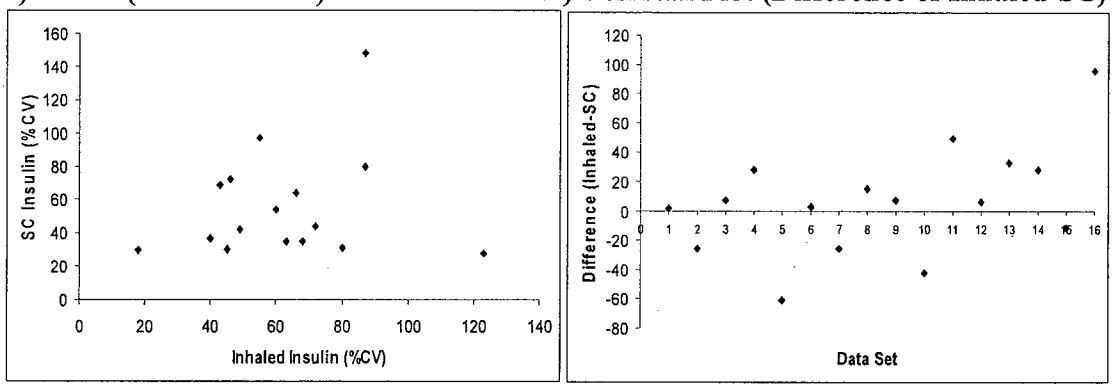


Figure 2.5.2. %CV of Inhaled and SC Insulin for Cmax (Pooled Data from Several Studies in the NDA) (each data point/set represent one study).

A) % CV (Inhaled vs SC) **B) Residual Plot (Difference of Inhaled-SC)**



Furthermore, in one of the effect of smoking study, the inter-subject variability was about 2-3 fold higher in smokers compared to non-smokers (study # A217-1003). For example, the %CV of Cmax and AUC was 110% and 96% for smokers and 37% and 61% for non-smokers, respectively.

Conclusions:

Depending on patient's experience in the use of the inhaler, the level of patient's education, and lung conditions, the high inter-subject variability in inhaled insulin is unavoidable. Therefore, careful titration process and patients' education is a must prior to initiating therapy with inhaled insulin.

B) Intra-Subject Variability:

The intra-subject variability is more of a concern than inter-subject variability. Based on ANOVA analysis, the sponsor reported the intra-subject variability in terms of CVw % (CVw = within subjects CV) ranges from about 20% to 60% for AUC and Cmax. The CVw is ANOVA analysis parameters using similar statistical approach of bioequivalence. The sponsor provided summary data for selected studies as in healthy subjects and DM patients as shown in **Tables 2.5.1-3.**

Table 2.5.1. Intrasubject CV (%) in Healthy Subjects (Source Section 2.7.1, Pagew 47, Table 16).

	Parameter	Comparison	CVw(%)	Ratio(%)	90% CI(%)
A2171014 (3 mg)					
	AUC_{0-360}	COM vs CLN	22.4 vs 22.1	101	77, 133
	Cmax	COM vs CLN	22.7 vs 21.6	105	80, 137
	Tmax	COM vs CLN	18 vs 36*	51	39, 67
A2171015 (1 mg)					
	AUC_{0-360}	COM vs CLN	60.5 vs 45.7	132	101, 173
	Cmax	COM vs CLN	37.9 vs 30.9	123	94, 161
	Tmax	COM vs CLN	40 vs 37*	110	84, 144
A2171006 (1mg, 3 mg)					
	AUC_{0-360}	3x1 mg vs 1x3 mg	50.4 vs 56.9	89	59, 133
	Cmax	3x1 mg vs 1x3 mg	35.5 vs 50.0	71	47, 107
	Tmax	3x1 mg vs 1x3 mg	16 vs 16 *	102	68, 154

COM = Commercial Batch, and CLN = Clinical Batch

Table 2.5.2. Intra-subject CV (%) in DM Patients (Source Section 2.7.1, Page 49, Table 17)

	CVw (%)							SDw		
	AUC_{0-120}			AUC_{0-360}			Cmax			Tmax		
Study	INH CVw	SC CVw	Ratio SDw (90% CI) (%)	INH CVw	SC CVw	Ratio SDw (90% CI) (%)	INH CVw	SC CVw	Ratio SDw (90% CI) (%)	INH SDw	SC SDw	Ratio SDw (90% CI) (%)
A2171004*	22.9	46.8	49 (33, 73)	30.6	43.1	71 (48, 106)	26.9	36.2	74 (50, 111)	15	75	20 (14, 30)
217-021[$]	36.4	41.2	88 (59, 131)	31.8	26.2	122 (82, 181)	50.2	24.6	204 (137, 304)	31	42	74 (49, 109)

Furthermore, the sponsor conducted a separate study to investigate the intra-subject variability of inhaled and SC insulin after self administration (Study # 217-021). This study was also briefly discussed earlier in dose proportionality section. Patients underwent extensive training and education on the use of inhaler and SC injection. Therefore, the data is believed to be biased due to this rigorous training to show low variability in both inhaled and SC insulin (**Table 2.5.3**).

Table 2.5.3. Within Subject Variability in PK Data (Study 217-021)

	Inhaled	SC		
Parameter	**CVw* (%)**	**CVw* (%)**	**Ratio (%)**	**90% CI**
Log AUC0-120 (μU·min/mL)	36.4	41.2	88	(59%, 131%)
Log AUC0-360 (μU·min/mL)	31.8	26.2	122	(82%, 181%)
Log Cmax (μU/mL)	50.2	24.6	204	(137%, 304%)
	SDw†	**SDw†**		
Tmax (min)	31.21	42.46	74	(49%, 109%)

* CVw = within-subject coefficient of variation. CVw on the raw scale is approximated as 100 X (SDw on the log scale).
†SDw = within-subject standard deviation.

From the data shown in the above tables, the % CV is comparable for inhaled and SC insulin under these tight study conditions. However, many other studies showed high intra-subject variability, especially for 1 mg strength. For example, in study # A217-1012, the % CV for 1 mg dose (1 x 1 mg) was 96.5% compared to 29.1% for 6 mg dose (2 x 3 mg) and for Cmax was 57.0% for 1 mg and 46.1% for 6 mg. This indicates that that the variability following 1 mg will always be expected to be high. This is inherent to 1 mg formulation. It should be noted, however, that the % CV for 2 X 1 mg dose was 45% and 33% for AUC and Cmax, respectively. This lower variability at 2 x 1 mg dose may indicate that the high variability observed after 1 x 1 mg could be associated with combination of factors such as variability in baseline of endogenous insulin and analytical issues.

Conclusions:

The intra-subject variability in inhaled insulin is of a major concern. Under strict study guidelines, involving rigorous training, the variability is expected to be low and even lower than for SC. However, in the real life situations, the intra-subject variability would be expected to be higher than was reported in this NDA. Therefore, it is highly recommended that every patient must undergo extensive training in the use of the inhaler prior to introduction of therapy. A language to this effect should be included in appropriate sections of the label, and in particular under Dosage and Administration as well as in the Clinical Pharmacology section of the label.

D) Variability Associated with ———

Although these are CMC issues, it is pertinent to mention it here as these affect the ———

3 Page(s) Withheld

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_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Clin Pharm/Bio-_____

2.6 Are There any Analytical Issues?

The general perception is that the assays for the determination of insulin and glucose in plasma were well established and validated. Therefore, no analytical issues were identified.

In the clinical pharmacology program two assay methods were used for the determination of insulin in plasma. These are immunoenzymometric assay (IEZA) and radioimmunoassay (RIA). Both assays were highly sensitive with a dynamic range of [redacted]) for IEZA and [redacted] for RIA.

One minor data conversion problem was discovered related to the potency of insulin calibrator value in IEZA that resulted in [redacted] higher values in 4 studies (217-012, 014, 015, 019). Since this [redacted] bias was consistent across all data within these studies, the conclusion from each study should not be affected. However, cross study comparison with other studies will not be valid and should be interpreted carefully.

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Overall Summary of Clinical Pharmacology and Biopharmaceutics Studies:

General Clinical Pharmacology Studies

- Inhaled insulin is absorbed more rapidly than SC regular insulin and as rapidly as SC insulin lispro.
- The onset of action of inhaled insulin appears to be faster than both lispro and SC regular human insulin. Tmax for inhaled insulin is approximately 30 min earlier than SC. Also, for inhaled insulin the Tmax was comparable to SC lispro (approximately 40 to 90 min inhaled vs 60 to 150 min SC). Furthermore, the Tmax appears to be shorter in Type 1 DM (~40 to 80 min) than Type 2 DM (~80 to 260 min).
- The data for patients with COPD is inconclusive, yet very critical. Based on the limited data, it can be concluded that the exposure increased in patients with COPD and in particular patients with emphysema. Due to the critical nature of the disease and mechanism of the delivery system, additional study is recommended to provide a more reliable data that can be used to establish adequate titration process in this patient population.
- In contrast to COPD, the exposure in asthmatic patients appear to reduced rather than increased. The recent report submitted by the sponsor in August 10, 2005 confirms these observations.
- The data provided by the sponsor does not show any significant changes in exposure from inhaled insulin in other upper respiratory diseases such as asthma or in patients infected with Rhinovirus.
- Smoking has been shown to dramatically enhance exposure to inhaled insulin by approximately 2 to 3 folds or higher, compared to non smokers. Cessation and resumption of smoking quickly (within days) alters inhaled insulin absorption. However, recent data submitted in August 10, 2005 showed that passive smoking has opposite effect on the exposure as compared to active smoking. In other words, the exposure from inhaled insulin is reduced rather than increased in subjects exposed to passive smoke.
- Inhaled albuterol, but not fluticasone, increase the exposure of inhaled insulin as reported in the recent study submitted by the sponsor on August 10, 2005.
- The following conditions have no effect on the absorption of inhaled insulin:

    - Pregnancy (pre-gestational Type 1 or Type 2 DM)
    - Ethnic difference, race, gender, and age

- Inhaled insulin has been shown to be associated with approximately **30 fold** increase in antibody over 6-months treatment. By contrast, SC administration virtually did not show any antibody formation.
- No glucose intolerance was noted over 24 weeks treatment with either inhaled or SC insulin.

General Biopharmaceutics Studies:

- Fine particle dose (FPD) less than [redacted] (FPD< [redacted]) was shown to be a better predictor of clinical performance than any other aerodynamic metrics so far tested in this NDA.
- Relative to SC regular insulin, the mean bioavailability of inhaled insulin (F) is approximately 10% ranging from 5 to 15 % in most of the study in the entire NDA.

- The inter- and intra-subject variability of inhaled insulin is generally high. From the entire NDA, the % CV, on average was >50%.
- There is clear dose separation in insulin plasma level as the dose increased from 1 mg to 6 mg, irrespective of formulation. However, due to the large variability in the data, the dose proportionality can not be established.
- The combination of 1 mg blister strength will always produce higher exposure than 3 mg blisters, irrespective of dose. On average, the exposure from 3 x 1 mg blister will be approximately 30% to 40% higher than that from 1 x 3 mg blister. Thus, the 3 x 1 mg doses/blisters may not be substituted for one 1 x 3 mg dose/blister
- From the regulatory perspective, the 3 mg commercial and clinical products are bioequivalent. However, the 1 mg strength is not.
- The standard inhalation technique produced optimal delivery, irrespective of all other tested techniques/maneuvers. Therefore, it is should be recommended as a method of inhalation.
- Insulin delivery is greater with slow inhalation rate (e.g., 10 L/min) than fast rate (>35 L/min).
-

Safety:

- The major safety related issues in all clinical pharmacology studies as well as Phase III studies was hypoglycemia. According to the sponsor's analysis, the incidence of hypoglycemia in all clinical pharmacology studies was 40.1% for inhaled insulin and 29.5% for SC insulin. This rate is comparable to that found in Phase III studies. However, these rates have not been verified by OCPB as they will be part of the comprehensive safety review by the Medical Officer.
- Other safety related adverse events noted with greater rate following inhaled insulin compared to SC insulin are headache, dizziness, and cough. Six severe AE events occurred in inhaled insulin group in clinical pharmacology studies. These were headache (n=4), myocardial infarction, and dizziness. According to the sponsor, these latter six cases were considered not related to treatment.
- The discontinuation from the study due to adverse events was greater in inhalation than SC treated subjects. The most common adverse events that resulted in discontinuation from the study are cough, hypoglycemia, and dyspnea.
- There was some decline in FEV_1 and carbon monoxide diffusion capacity (DLco) have been observed more commonly in inhalation than SC group. The magnitude of this decline will be reported more precisely by the Medical officer review.

Efficacy:

The interpretation of efficacy data is beyond the scope of this review. However, for completion some data from selected studies were plotted to give snap shots comparison between inhaled and SC insulin (**Figures A and B**). This is specifically presented here for OCPB briefing attendees and in no way meant to present the full picture of the efficacy data. No further discussion or

analysis of the data is needed here. Therefore, for further details, please refer to the Medical Officer's Review.

There was some separation between inhaled and SC insulin in terms of the effect on the primary clinical endpoint, **HbA_{1c}**, and the secondary endpoint, glucose response (**Figure A & B).**

These graphs were constructed based on the summary data provided by the sponsor from different studies as noted in each graph. Within a given study, there was clear difference in the % change in HbA_{1c}, between inhaled and SC insulin, with inhaled demonstrating higher trend in all studies, except study # 10221A.

In terms of fasting blood sugar, three studies clearly show marked separation in fasting blood sugar between inhaled and SC insulin **(Figure B).** In addition, according to the sponsor, glycemic control was maintained over 12 months in the ongoing study # 1022. For more details and updated information, please see the Medical Officers review.

Figure A. Change from Baseline in Glycosylated Hemoglobin (HbA_{1c}, %) in Type 1 Diabetes (Source: Module 2.7.3, page 32, Table 12)

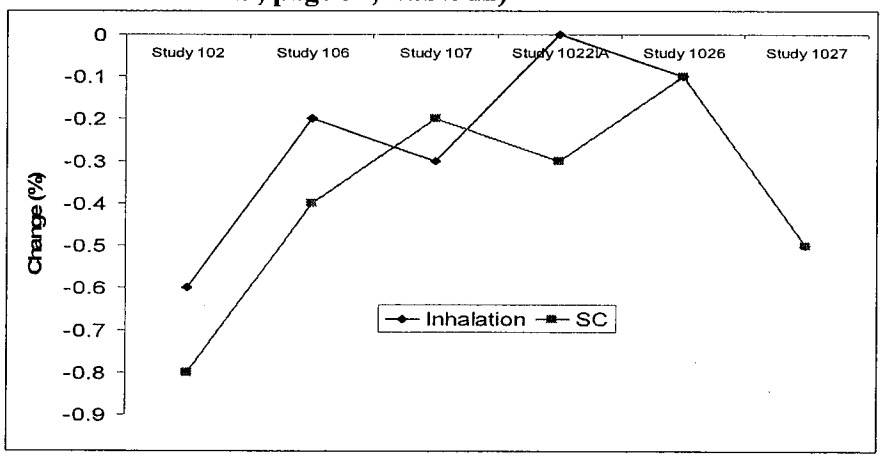
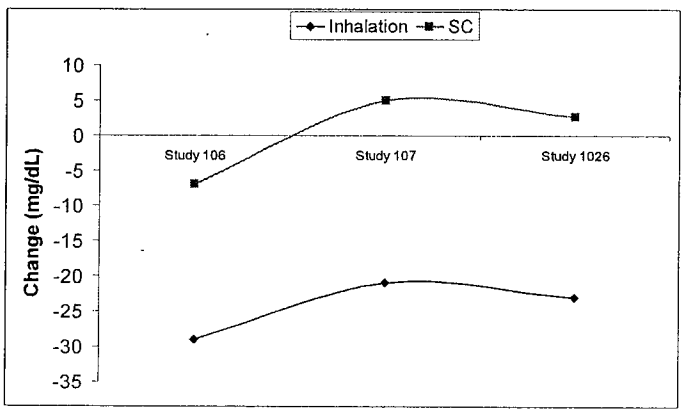


Figure B. Change from Baseline in Fasting Plasma Glucose in Type 1 DM (Source: Module 2.7.3, page 33, Table 14)



3. Detailed Labeling Recommendation

All labeling comments were made directly into the sponsor's proposed label after being discussed internally with other members of the review team and also at the Office of Clinical Pharmacology and Biopharmaceutics NDA briefing.

The major labeling issues were related to the titration process in patients with respiratory diseases such as COPD and smoking. The second major issue is the interchangeability between the two strengths (1 mg and 3 mg) across the recommended dose range. An appropriate language was included to reflect these concerns directly into the proposed label among other minor language changes related to the clinical pharmacology and biopharmaceutics issues.

19 Page(s) Withheld

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

Y § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Clin Pharm/Bio-_____

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

NDA Number	**21-868**	**Brand Name**	**Exubera®**
OCPB Division (I, II, III)	**DPE II**	**Generic Name**	**Insulin (rDNA origin) powder for oral inhalation**
Medical Division	**HFD-510**	**Drug Class**	**insulin**
OCPB Reviewer	**Xiaoxiong (Jim) Wei**	**Indication(s)**	**Type 1 & Type 2 Adult Diabetes Mellitus**
OCPB Team Leader	**Hae-Young Ahn**	**Dosage Form**	**1 mg, 3 mg Blisters**
		Dosing Regimen	**Individual titration**
Date of Submission	**12-27-04**	**Route of Administration**	**Oral inhalation with Exubera inhaler**
Estimated Due Date of OCPB Review	**07-30-05**	**Sponsor**	**Pfizer**
PDUFA Due Date	**10-27-05**	**Priority Classification**	**S1**
Division Due Date	**07-30-05**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	20		
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:	X	1		
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:	X	1		

gender:				
pediatrics:	X	1		
geriatrics:	X	1		
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:	X	5		
Phase 3 clinical trial:	X	1		
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -	X			
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	X	3		
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		33		

Filability and QBR comments		
	"X" if yes	Comments
Application filable?	**YES**	
Comments sent to firm?	**NO**	

Briefing in Content:

EXUBERA is a novel treatment system for diabetes mellitus (DM) developed by Pfizer Inc. in partnership with Aventis and Nektar (formerly Inhale Therapeutic Systems, Inc.).

EXUBERA combines a novel dry powder formulation of recombinant human insulin with a customized inhaler and was designed to permit the easy and reproducible delivery of insulin for the control of hyperglycemia in patients with DM. The pulmonary inhaler is novel, reusable and it is purely mechanical, and requires no batteries, electronics or external power source.

The proposed indication for EXUBERA® (insulin [rDNA origin] powder for oral inhalation) is for the treatment of adult patients with diabetes mellitus for the control of hyperglycemia.

EXUBERA has duration of glucose-lowering activity comparable to subcutaneously injected regular human insulin and longer than rapid-acting insulin. EXUBERA doses should be administered within 10 minutes prior to meals.

The commercial formulation is identical to the one used in pivotal clinical trials.

Two dosage forms of EXUBERA 1 mg and 3 mg unit dose blisters have been developed to support the NDA. However, these two dosage forms are not equivalent. In Study A217106 where the dosage form of three 1 mg blisters was compared with one 3 mg blister, Cmax and AUC of inhaling three 1 mg blisters were approximately 27% and 40% greater, respectively, than that of inhaling one 3 mg blister.

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
Source: Table 5.3.1

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/s/

Sayed Al-Habet
1/4/2006 03:57:52 PM
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Hae-Young Ahn
1/5/2006 02:37:20 PM
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