

# **Clinical Pharmacology and Biopharmaceutics Review**

## **(Executive Summary for Advisory Committee)**

---

**NDA:** 21-868                      **Date of Submission:** December 27, 2004

**Generic Name**                      Insulin rDNA

**Brand Name:**                      EXUBERA<sup>®</sup>

**Formulations:**                      Powder

**Route of Administration:**                      Oral Inhalation

**Indication:**                      Diabetes Mellitus (Type 1 and Type 2)

**Type of Submission:**                      NDA/NME

**Sponsor:**                      Pfizer  
New London, CT

**Reviewer:**                      Sayed (Sam) Al Habet, R.Ph., Ph.D.

**Team Leader**                      Hae-Young Ahn, Ph.D.

**Date of Submission:**                      December 27, 2004

**Date Received:**                      March 15, 2005

**Review Date:**                      June 15, 2005

**Final Version**                      August 10, 2005

**DFS Version**                      August 10, 2005

---

# 1. Executive Summary:

## 1.1 Recommendation:

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

## 1.2 Phase 4 Commitments

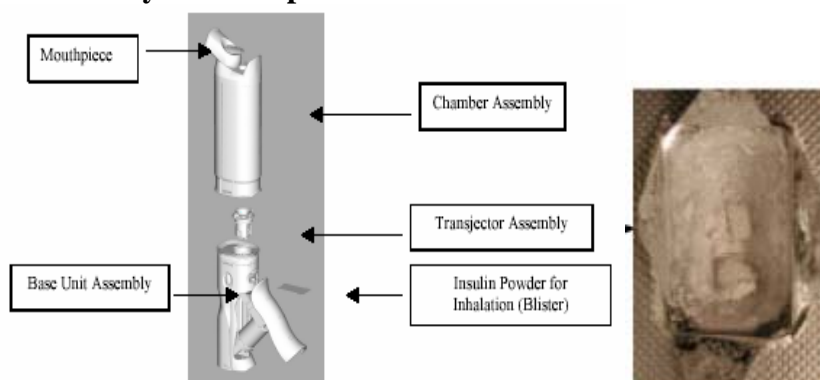
To be discussed!

## 1.3 Summary of Clinical Pharmacology and Biopharmaceutics 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 using 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 Assembly and Sample View of the 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 ( ) and the final inhaler version (P3) were used. The final formulation and device was also used in Phase III clinical trials.

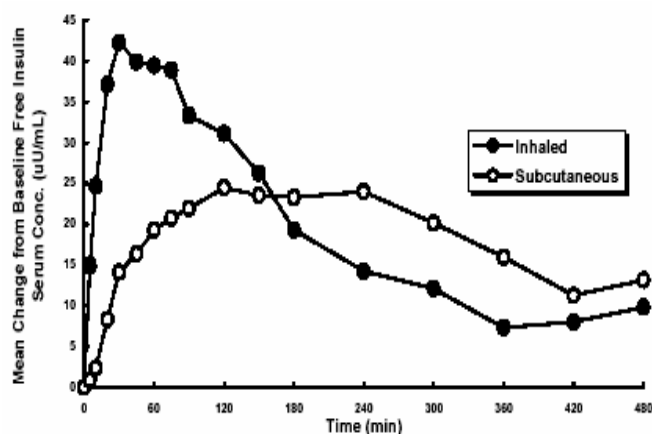
### 1.3.5 What are the Main Findings in this NDA?

**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%.
- The following conditions have no effect on the absorption of inhaled insulin:

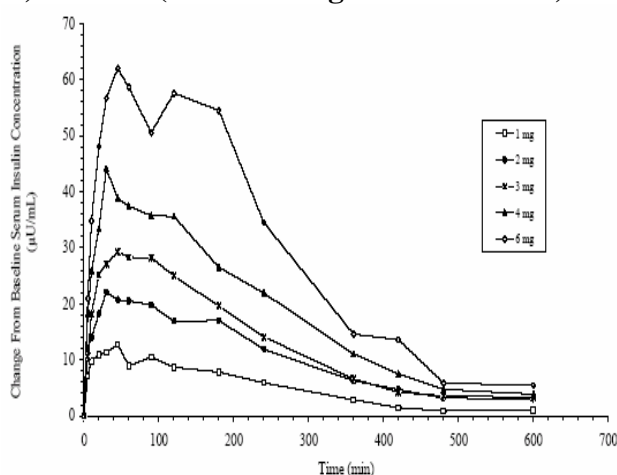
- Pregnancy (pre-gestational Type 1 or Type 2 DM)
- Ethnic difference, race, gender, and age

### Dose Proportionality:

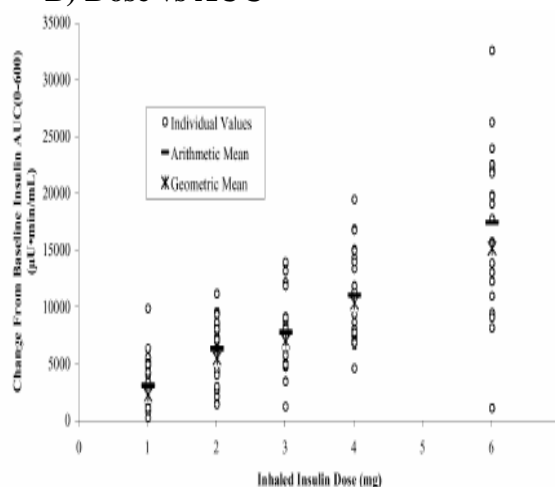
- There is clear dose separation in insulin plasma levels as the dose increase from 1 mg to 6 mg, irrespective of formulation (**Figure 3**). However, due to the large variability in the data, the dose proportionality can not be confirmed with certainty at this time.

**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 <sup>a</sup>	1x3 mg <sup>a</sup>	Ratio/Difference	90% CI
AUC <sub>0-360</sub> (μU·min/mL)	2599	1859	140%	(117%, 167%)
Cmax (μU/mL)	31.02	24.51	127%	(108%, 148%)
F (%) <sup>**</sup>	5.80	4.15	140%	(117%, 167%)
Tmax (min)	44.4	42.0	2.4	(-4.4, 9.2)

<sup>a</sup>Adjusted geometric means for AUC, Cmax, and F; adjusted arithmetic mean for Tmax

<sup>\*\*</sup>AUC<sub>inhaled</sub>/AUC<sub>sc</sub>; 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 and clinical lot are bioequivalent.

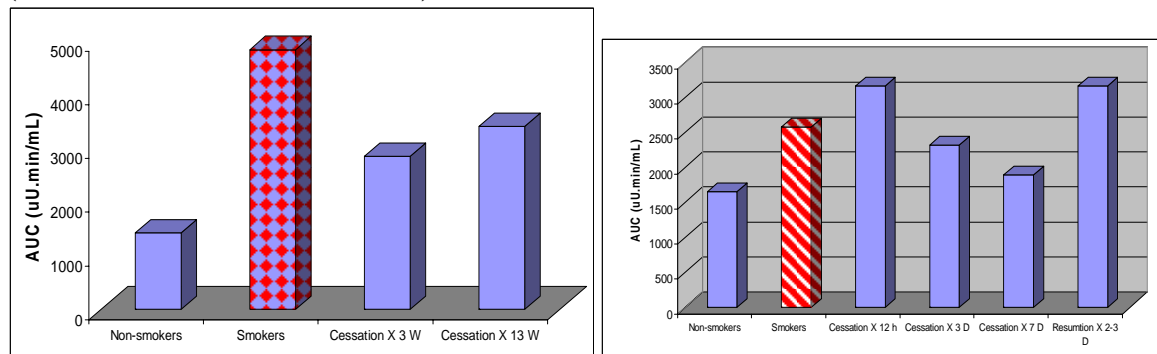
However, the commercial production lot for the 1 mg strength is not bioequivalent to the clinical scale lot. Based on the data, it appears that the difference in exposure is approximately 10% difference in exposure to 1 mg strength. The impact of this difference may not be clinically significant.

### **Effect of Extrinsic Factors:**

#### **Effect of Smoking:**

- The exposure from inhaled insulin is approximately 2 to 3 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)**



### **Effect of Intrinsic Factors:**

#### **Rhinovirus Infection:**

The rationale 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.

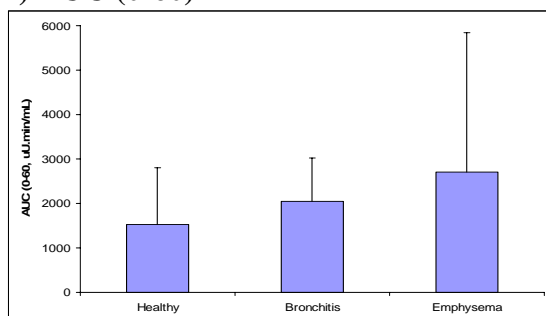
In this study the data was inconclusive to indicate that the rhinovirus infection affects the absorption of inhaled insulin. It appears however that the exposure on Day 1 (prior to inoculation) was higher than Day 4 in both virus and saline group. It should be noted that there was a high variability 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).

## Obstructive Pulmonary Disease (COPD)

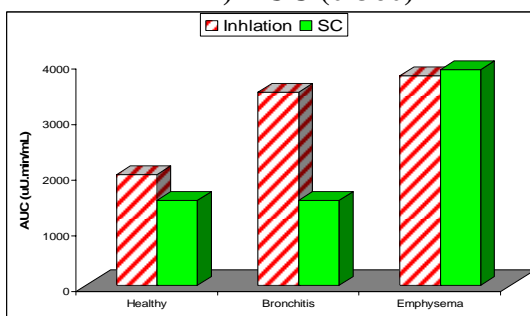
- Similar to the effect of smoking, the exposure appears to be greater in patients with Chronic COPD, and in particular patients with emphysema (**Figures 5 and 6**). However, the data from this single study is highly variable and lacking of adequate power (n= 6-12). Therefore, the data is unreliable and the study may need to be repeated.

**Figure 5. AUC (0-60) and AUC (0-360) in Patients with COPD (Study # A217-1005)**

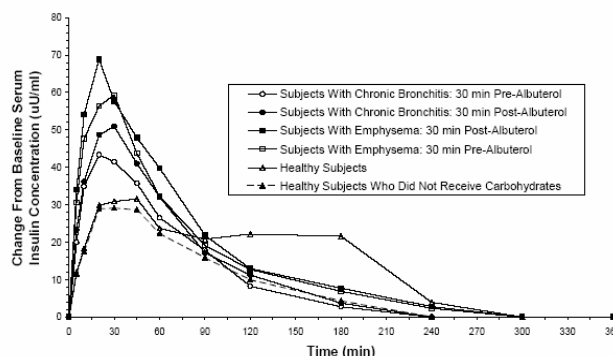
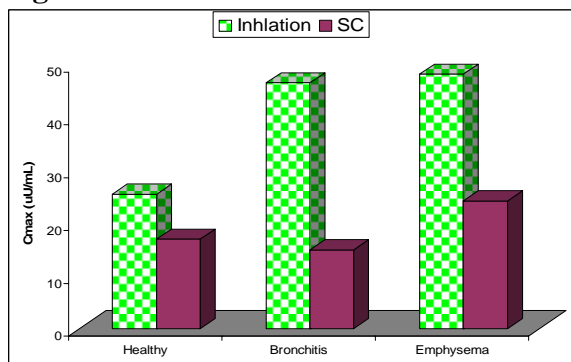
**A) AUC (0-60)**



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



**Figure 6. 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.

## **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. Furthermore, shipping and handling of the final blister products was found to affect the *in vivo* performance and introducing further source of variability into the system.
- 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.
- 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%.

## **Pharmacodynamics (Duration of Action)**

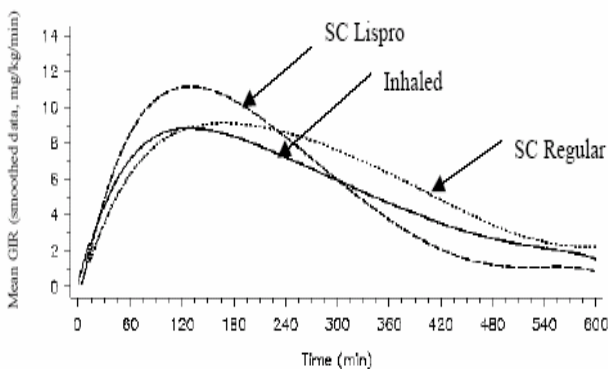
- Consistent with the PK profile, the onset of action of inhaled insulin is as rapid as SC insulin lispro and more rapid than SC regular insulin (**Figure 7A**).
- The duration of action of inhaled insulin is longer than SC insulin lispro and comparable to SC regular insulin (**Figure 7 A & B**).
- There is an immediate relationship between insulin exposure and response in terms of glucose control (**Figure 7 A-C**).

### **Figure 7 (A-C) . Pharmacodynamic of Inhaled Insulin (Glucose Parameters):**

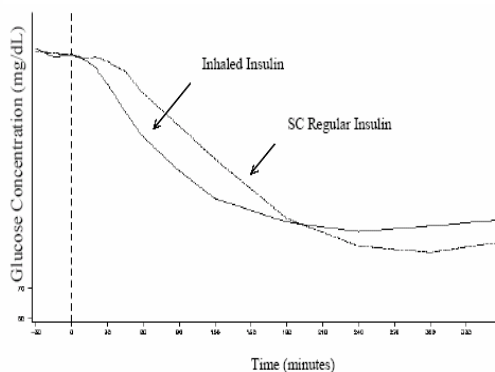
**A) Mean Change in Baseline GIR (Glucose infusion Rate) After Inhaled Insulin (2 x 3 mg) and 18 U SC Regular or Lispro Insulin in Healthy Subjects (Study # 217-017)**

**B) Mean Glucose Concentrations After 4 mg of Inhaled Insulin or 12 U SC Regular Insulin in Type 2 DM Patients (Study 217-1004)**

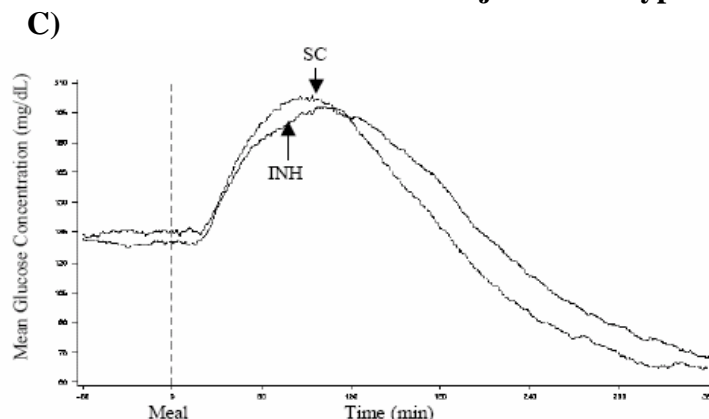
**A)**



**B)**



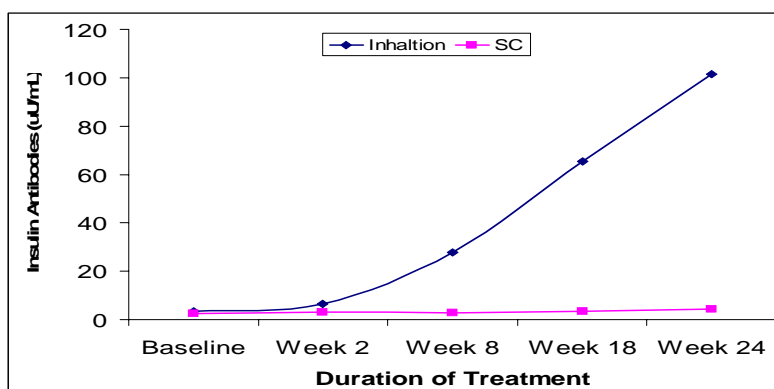
**C). Mean Postprandial Glucose Concentrations in Subjects with Type 1 DM (Study # 217-021)**



**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 8**). 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 8. Insulin Antibody Formation (Study # 217-1026)**



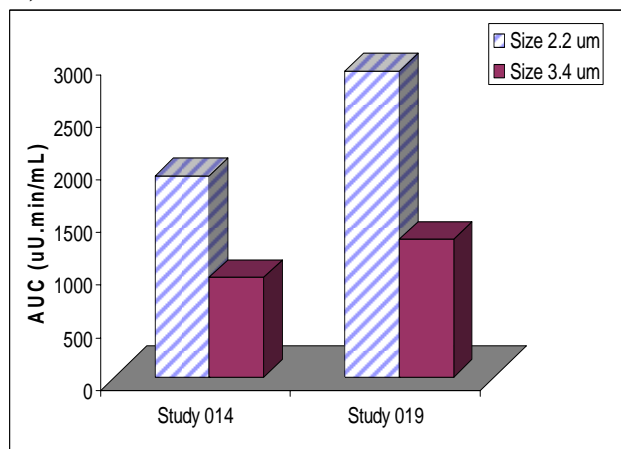
**Effect of Particle Size Aerodynamics:**

- Fine particle dose 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, . Across these two studies, the data in these proximately . show clear inverse relationship between d exposure with no effect on Tmax (**Figure 9**).

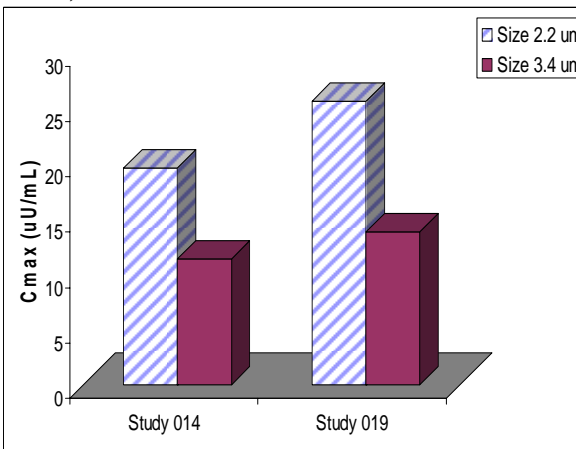


**Figure 9. Effect of Particle Size on Exposure (Studies # 217-014 and 217-019)**

**A) AUC**



**B) Cmax**



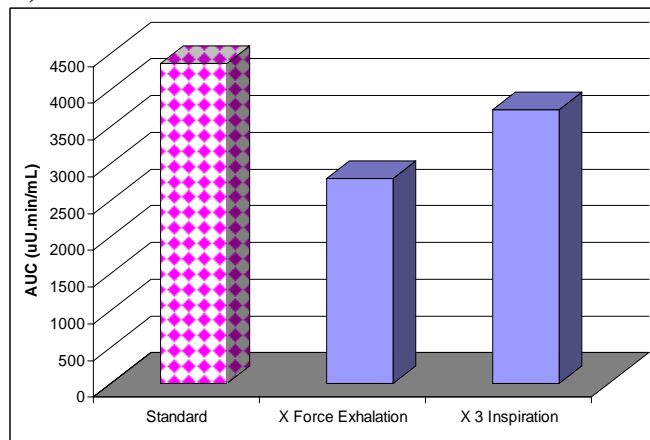
From the above data, it can be concluded that the smaller the particle size, the higher the exposure.

**Effect of Inhalation Techniques:**

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

**Figure 10. Effect of Inhalation Techniques and Flow Rate on Exposure (Study #217-002)**

**A) Inhalation Maneuvers**



**B) Inhalation rate**

