Errata Sheet (dated 8/31/05)  
FDA Background Package  
September 8, 2005  
Endocrinologic and Metabolic Advisory Committee Meeting  
Exubera®, (insulin[rDNA origin] powder for inhalation)  
NDA 21-868

Section 1: Background and Summary

On Page 2, second paragraph under **Principle Objectives of the Exubera program**, the underlined word in the following phrase:

…associated with the large quantities of insulin powder (along with the **lactose** excipient)…

should read

(along with the mannitol, glycine, sodium citrate and sodium hydroxide excipients)…

Section 3: Clinical Pharmacology and Biopharmaceutics Review

On Page 2, replace the picture of the dissected blister with this picture:

![Dissected blister diagram](image)

Section 4: Pharmacology and Toxicology

According to the sponsor, the pulmonary data for the 6-month monkey toxicology study was amended on Oct 23, 2000 (serial #137). Since the reviewer had used the pulmonary data in the original submission (IND 43,313, Sept 16 1998) and the new amended data was numerically different, the lung compliance statement was revised to represent the amended data. Thus, the statements regarding the lung compliance in the 6-month monkey study on page 4 and 103 were changed to “In the 6-month monkey study, the slightly lower lung compliance in males treated with inhalation insulin dose of 0.64 mg/kg/d (2.87±0.27 ml/cm H2O) was not statistically significantly different from the males in the air control males (4.3±1.14 ml/cm H2O)”.

The Division is in agreement with the sponsor that there was no statistically significant change in lung compliance in 6-month monkey study.
Section 5: Clinical Efficacy Statistics

1. On Page 6, in Table 1.2.1.1, for Studies 1026 and 1027 it states that there is no data in the EDR.

Correction:

There is data for studies 1026 and 1027 in the EDR.

2. On Page 7, at the top, is the following statement: “No study report was provided for Study 1026 but information was provided in clinical summaries.”

Correction:

There was a clinical study report provided for Study 1026 in the initial NDA submission. This study was a clinical pharmacology study and can be found under the human pharmacology and biopharmaceutics section

3.  
   a. On Page 8, in Table 1.2.2.1, it states that Studies 103 and 104 had no data in the EDR.

Correction:

Efficacy data from Studies 103 and 104 were not included in the original submission of the NDA.

   b. Also, this table states that Study 108 had a 12 week randomized treatment period.

Correction:

Study 108 had a 24 week randomized treatment period.

4. On Page 18, in the paragraph above Table 3.1.1.6, it states “For the subgroups, the most notable differences are…treatment difference of 20% (p=0.07, Fisher’s exact test) in favor of INH in Study 107 for patients with baseline values less than 7%.”

Correction:

sentence should end with “…values greater than or equal to 8%”.

5. On Page 51, in the last paragraph, last line states “…Report was 39 or less…”

Correction:

This should state “…Report was 36 or less…”
Section 6: Pulmonary Safety Statistics

1. On page 19, in Figure 1, the title should indicate the percentage of subjects with respiratory events (versus the total percentage of respiratory events). In addition, the values in the x-axis should be multiplied by 100 (the percentage of subjects is being provided).

2. On page 23 (and other pages related to t1 DM pulmonary results), the statement: "Note that since most of the data in the pooled studies after week 24 are from Study 1022, the results from the Pooled analysis and from Study 1022 are fairly consistent."

   Now reads:
   "Note that since all of the data in the pooled studies after week 24 are from Study 1022, the results from the Pooled analysis and from Study 1022 are fairly consistent”

3. a. On page 42, in Figure 16, the title indicates the percentage of subjects with respiratory events

   Should indicate:
   The total percentage of respiratory events

   b. The values in the x-axis should be multiplied by 100 (the percentage of subjects is being provided).

4. On page 47, the first sentence of the second paragraph under Forced Expiratory Volume in 1 second (FEV1) reads: "In the pooled dataset, similar treatment group differences in mean change from baseline in FEV1 favoring comparator therapy are apparent among adult subjects with type 1 after 3 months of therapy."

   Should read:
   "...subjects with type 2 after 3 months of therapy."

5. On page 47 (and other pages related to t2 DM pulmonary results), it states: "Note that since most of the data in the pooled studies after week 48 are from the combined studies 1001 and 1002, the results from the Pooled analysis and from the combined studies 1001 and 1002 are fairly consistent."

   Should read:
   "Note that since all of the data in the pooled studies after week 48 are from the combined studies 1001 and 1002, the results from the Pooled analysis and from the combined studies 1001 and 1002 are fairly consistent."
Section 7: Clinical Efficacy Review

Page 49, Section 6.3.3, first paragraph, first sentence; and page 214, Section 9.1, first complete paragraph, second sentence: “between 8 and 11%” should read “between 6 and 11%”.

Page 140, Table 7.1.6.2, row for “carcinoma of lung”, comparator column. This cell should read “1 (0.06)”.

Page 140, after Table 7.1.6.2, add the following paragraph: “On 23 Aug 05, the applicant provided information indicating that an artifact of their data collection technology may have contributed to over counting of numbers of certain events. The clinical reviewer had noted this possibility, which is what led to the inclusion of Table 7.1.6.2. The clinical reviewer will work with the applicant to further refine this table.”

Page 176, fourth full paragraph. Delete fourth and fifth sentences.

Page 211, Section 8.7. Although the NDA did not include a post marketing risk management plan with measures beyond routine post marketing surveillance at the time of submission on 27 Dec 04, the applicant did submit a more comprehensive risk management plan on 2 Aug 05. This submission occurred after primary reviews for the briefing document were due.

Section 8: Clinical Pulmonary Safety

1. On page 35, the table at the top of the page and Reviewer’s Comment should be changed to the following. The changes are noted in **bold face**.

<table>
<thead>
<tr>
<th>Source System Organ Class SAEs</th>
<th>Inhaled Insulin</th>
<th>SC Insulin</th>
<th>Oral Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Respiratory, Thoracic, and Mediastinal Disorders</strong></td>
<td>10</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td><strong>Infections and Infestations (bronchitis, bronchopneumonia, pneumonia, pneumocystis carinii pneumonia)</strong></td>
<td>6</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td><strong>Neoplasms – Lung adenocarcinoma, lung neoplasm malignant, metastatic bronchial carcinoma</strong></td>
<td>2</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>18</strong></td>
<td><strong>8</strong></td>
<td><strong>4</strong></td>
</tr>
</tbody>
</table>


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

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

2. In Table 24 on page 59 and Table 31 on page 73, the studies listed in parentheses in the title should be Studies 106, 107, and 111.
3. On page 80, in the first paragraph under Section 5.1.8.3, Study 102 should not be listed because Study 102 is a study in type 1 diabetes.

4. On page 89 in Table 38, the studies listed in parentheses in the title should be Studies 108, 109, 110, and 111.

5. In the Reviewer’s Comment at the top of page 114, the second sentence should be changed to the following. “However, it should be noted that Study 1029 is ongoing and a final study report has not been submitted.”