Trends-in-Medicine

September 2005
by D. Woods

Quick Pulse

Trends-in-Medicine
Stephen Snyder, Publisher
2731 N.E. Pinecrest Lakes Blvd.
Jensen Beach, FL 34957
772-334-7409 Fax 772-334-0856
www.trends-in-medicine.com

FDA Advisory Committee Recommends Approval of Inhaled Insulin

Silver Spring, MD
September 8, 2005

The FDA's Endocrine and Metabolic Drugs Advisory Committee voted 7-2 to recommend approval of Pfizer's Exubera (insulin powder, rDNA origin, for oral-pulmonary inhalation), for the treatment of Type 1 and Type 2 diabetes, despite concern about the agent's pulmonary toxicity and decline in pulmonary function.

If the FDA approves Exubera, it would be the first form of inhaled insulin available on the market. Several other drug companies have inhaled insulins in the pipeline, including Eli Lilly, Alkermes, Mannkind, and Novo Nordisk.

Pfizer is seeking FDA approval to market Exubera to adult non-smoking patients with diabetes for the control of hyperglycemia as:

- Combination therapy with intermediate/long-acting subcutaneous (SQ) insulin or oral agents.
- Monotherapy (for Type 2 diabetes).

The FDA staff described Exubera as safe and effective, although there are still some safety concerns, especially regarding smokers and people exposed to second-hand smoke. The FDA staff said that inhaled insulin is as effective as injections in controlling glucose levels. Some patients taking inhaled insulin reported coughing after inhaling, as well as a decrease in breathing capacity, but it appears breathing capacity returns to normal when inhaling is discontinued.

The Company Perspective

Pfizer's Exubera team leader told the panel that the drug is safe and effective. He said that the company's 10-year clinical development program, which looked at more than 43,000 pulmonary function test (PFT) measurements performed on more than 4,000 adults, showed that Exubera is:

- Efficacious as a short-acting SQ insulin.
- Provides long-term glycemic control.
- Preferable to most patients compared to previous therapy.
- Has a safety profile that is well-tolerated, with hypoglycemia comparable to injected insulin, and that can produce insulin antibodies as well as small, early, non-progressive, reversible declines in FEV_1 and DLCO.

The Exubera global clinical leader described the clinical pharmacology of Exubera, saying that its bioavailability is approximately 10% relative to subcutaneous insulin.

She said that 40% of the insulin, when inhaled orally, goes to alveolar spaces, 20% is deposited in the oropharynx, 10% to tracheobronchial, and 30% is retained in the blister/device. She also said that:

- Exubera is absorbed more rapidly than SQ regular insulin and as rapidly as SQ insulin lispro.
- Exubera has shown dose-separated and dose-linear exposure over 1 to 6 mg.
- Three 1 mg blisters should not be substituted for one 3 mg blister.
- Age, gender, race, and BMI have no effects on the pharmacokinetics (PK) of Exubera.
- Smoking significantly affects the absorption rate and extent.
- Bioavailability is higher in COPD patients and lower in asthmatics.
- Intra-subject variability of PK and pharmacodynamics (PD) are comparable to SQ regular insulin in diabetics.

Smokers should not use Exubera, according to the speaker, who said that the proposed labeling will note that change.

A Pfizer speaker said that Exubera is not inferior to SQ insulin in treatment of adult patients with Type 1 diabetes or insulin-using Type 2 diabetics. Results from two Phase III studies showed Exubera effective in treatment of adult patients with Type 2 diabetes when used alone, in combination with an oral agent, or in combination with a basal insulin, and efficacy was sustained over two years. The speaker said that patients also are more satisfied with Exubera than with SQ insulin.

In terms of safety, increased cough occurred noticeably more often in patients receiving Exubera, with hypoglycemia the most common serious adverse event in Type 1 diabetics and myocardial infarction (MI) the most common serious adverse event in Type 2 diabetics. There were 32 total deaths with Exubera in the clinical program, with 28 occurring ≥30 days.

Type 1 Diabetics: Serious Adverse Events from All Causality in Controlled Phase II/III Studies

Measurement	Exubera n=698	SQ insulin n=698
Hypoglycemia	3.6	4.8
Loss of consciousness	1.1	1.6
Myocardial infarction	0.4	0.4
Diabetic ketoacidosis	0.4	0.1
Convulsions	0.3	1.1
Depressions	0	0.7

Hypoglycemic events

In patients with Type 1 diabetes, the hypoglycemic event rate was comparable between Exubera and SQ groups at ~1 event per month. In Type 2 patients, the event rate was lower but comparable between Exubera and SQ groups. In non-insulin-using patients, the rate was lower still.

Pulmonary safety

A Pfizer speaker said that pulmonary safety was measured using respiratory adverse events, chest x-rays, and PFTs. Although Phase II studies showed little change, data from Phase III studies showed a small decrease in lung capacity. She said that "The inhaled insulin-associated decrease in FEV_1 was fully manifested at the first reassessment endpoint and did not progress in up to two years of treatment." She added that when Exubera was stopped, lung capacity was regained.

PFTs showed that Exubera-associated decreases in FEV_1:

- Occur early upon initiation of therapy.
- Are small in magnitude (~1%-1.5% change from base-line).
- Are not driven by outlier subjects with large changes.
- Are non-progressive with long-term administration.
- Resolve upon discontinuation.

Type 2 Diabetics: Serious Adverse Events from All Causality in Controlled Phase II/III Studies

Measurement	Exubera n=1,279	SQ insulin n=488	Oral agents n=644
Myocardial infarction	0.8	0.8	1.1
Chest Pain	0.5	0.2	0.6
Angina	0.4	0.3	0.8
Hypoglycemia	0.4	2.1	0.3
Coronary artery disease	0.4	0.6	0
Cellulitis	0.3	0.6	0
Loss of consciousness	0.2	1.0	0.2

Chest X-ray and High Resolution Computerized Tomography (HRCT)

No consistent pattern of Exubera-related abnormality was evident. HRCT results showed that Type 2 diabetics using insulin showed no difference from SQ groups.

Respiratory adverse events

Increased cough, increased sputum, and dyspnea were higher in Exubera patients than in SQ patients. Exubera-associated cough occurred most often during the first month and decreased with continued Exubera administration. The cough was mainly mild in severity, and 1% discontinued due to cough. Cough occurred within minutes or seconds of dosing, rarely occurred at night, and was not associated with decreases in FEV_1. The majority of dyspnea cases were mild. A Pfizer expert said, "Overall, the number of respiratory serious adverse events is low in both the inhaled insulin and comparative groups…All serious adverse events occurred in patients with Type 2 diabetes, with the exception of a single case of pneumonitis…Overall, asthma is reported infrequently

and comparably in the inhaled and SQ groups and rarely causes discontinuation. There are, however, more reports of severe asthma and of asthma causing discontinuation in patients receiving inhaled insulin. Two other relevant serious adverse events were pleural effusion and lung neoplasm."

Insulin antibodies

No clinical impact was identified for insulin antibodies, and the Pfizer expert concluded:

- Exubera is associated with higher insulin antibody levels compared to SQ insulin, more so in patients with Type 1 than Type 2 diabetes and more in women than in men.
- Mean antibody levels plateau after 6-12 months.
- Exubera-associated insulin antibodies are of the IGG class, as are SQ insulin-associated antibodies.
- Insulin antibodies are not associated with changes in HbA_{1c} hypoglycemic event rates, insulin doses, or PFTs.
- Insulin antibody levels decline after discontinuation of Exubera.

A Pfizer consultant talked about glycemic control delay complications in both Type 1 and 2 diabetics and made the case that inhaled insulin promotes greater acceptance of insulin in the diabetic population. Another Pfizer expert concluded that Exubera is safe and effective, and will be well-accepted by patients, resulting in earlier and better glycemic control. He outlined Exubera's risks and benefits and said the company is committing to a long risk management program, "We understand the need to assess…and monitor for rare pulmonary events. We understand the need to increase our knowledge in children and infants."

This company official also proposed patient and physician education through labeling, call centers, healthcare professional training, and patient training support, including an instructional video, manual, and quick reference guide as well as device replacement and enhanced pharmacovigilance to increase the follow-up reporting of rare respiratory adverse events. He described a proposed long-term, multi-national pulmonary safety study of 5,000 patients over five years as well as other studies to monitor pulmonary effects, specific patient populations, such as those with COPD and asthma. A Pfizer official also pledged to restart pediatric studies after consultation with the FDA.

Pfizer experts responded to a variety of FDA panel member questions, including:

➢ ***Change in FEV_1:*** "There were 54 patients with FEV_1 changes over time. Interestingly, of these 54, 25 patients recovered their FEV_1 spontaneously while on inhaled insulin, and 44 subjects in the comparative group showed a similar pattern. Of these, 25 improved while in inhaled insulin therapy."

➢ ***Non-smokers in the COPD population:*** "I think all, if not many, of these COPD patients had been previously smokers, but it is critical that we do not have patients who are currently smokers. Past smokers, fine; current smokers, no…I believe there was a caveat that non-smokers could be admitted. As far as I know there were no smokers in the trial so far."

Panel member (pulmonary physician): "So, obviously, this was mild COPD in the entry cohort for (Study) 1030…A one-liter decline in FEV_1 is far different for one…than another."

Pfizer: "The problem for us at the moment is that this is an ongoing study. We have about 30 patients on inhaled insulin in that particular study."

➢ ***Patient satisfaction – is it an emotional issue because people don't have to take shots?:*** "We didn't do satisfaction studies in all the studies. The ones we showed you (the panel) were the three efficacy studies, and they lasted from three to six months. They were done before measurements of HbA_{1c}."

➢ ***Patient learning curve and device reliability:*** "There would be a comprehensive training program instituted to train (patients) to use the device…The device performed very robustly in the clinic. We'd periodically check on its performance. We'd pull devices back from the clinic to see how it was doing, and there was also robotic testing done to make sure that it would perform satisfactorily."

➢ ***Device failures during the studies:*** "Yes, there were device failures in the clinic in two categories. Some were self-inflicted. The pull ring had some mechanical robustness issues which were resolved. We had a button that cracked during the clinical trials. I mention that because the robotic trials didn't have finger oils, and when we repeated it, we found the button would crack…In the clinic, we reported 2.9% failures, but after those I mentioned were resolved, we only had one in 600 devices that had an issue. The call center will be available for patients who have an issue with the device."

➢ ***Study 111:*** "Two groups were treated, and then one group was withdrawn, and the other group continued with inhaled insulin. The conclusion we drew was that both groups, after time, had a reduction in lung function which came on early in the studies, and the group that stopped taking inhaled insulin had a return of approximately the same amount they had lost, whereas the group that stayed on inhaled insulin had the same reduction in lung function."

➢ ***Consequences of the IGG antibodies:*** "We have not identified clinical consequences of the antibodies."

➢ ***Effect on the lungs:*** "We're…continuing to look. We've looked at two years continuous exposure. We have some studies that have gone to three years. We're proposing looking at five- and seven-year continuous dosing. We will continue to see if there's any effect. That's about all I can say in terms of the mechanism. We'll look for the effect. We have other investigations going on to look for the mechanism. We're willing to hear suggestions."

➢ ***Define ex-smoker:*** "We defined ex-smokers as those patients who had not smoked for six months…We looked to see if there was any effect on previous smokers. We looked to see if there was any effect in rate of change of pulmonary function. The answer is there was no difference."

➢ ***Does technique matter?:*** "The technique does matter."

THE FDA PERSPECTIVE

FDA staff said that Exubera appears to be effective for patients with Type 2 diabetes, but they were uncertain whether it is a desirable drug for patients with Type 1 diabetes.

An FDA medical officer described Exubera's clinical efficacy and non-pulmonary safety review. She said the agency wanted to know if Exubera can be used to effectively manage Type 1 and 2 diabetics, if the risk of hypoglycemia or other adverse events with inhaled insulin are different from that for comparators (given comparable HbA_{1c}), and if there is a pulmonary risk associated with Exubera. She said, "It appears that Exubera is effective in Type 2 diabetes. For a Type 1 diabetic, however, I might say that I'm not sure."

Type 1 diabetes. The medical officer said that questions remain about whether Type 1 diabetics can expect to achieve "tight control" with Exubera: "I'm not sure that a Type 1 diabetic would achieve a DCCT-level, but is it even reasonable to expect DCCT-level control? Is 28% achieving HbA_{1c} <7% good enough?"

For patients with Type 1 diabetes, inhaled insulin was described as non-inferior to SQ for change from baseline in HbA_{1c}, but:

- Neither treatment group achieved DCCT-level mean HbA_{1c}.
- Only 28% of adults in the inhaled insulin group achieved HbA_{1c} <7%.
- Post-prandial glucose excursion increased from baseline to 24 weeks with inhaled insulin.

Pediatric use. The reviewer added that pediatric efficacy is not clear and may warrant further study. She noted that Pfizer has not asked for a pediatric indication, but she said the FDA anticipates significant interest in Exubera's potential for use in children. She added that pediatric patients' mean HbA_{1c} levels did not change much in three studies of 180 adolescents aged 12-17.

Safety. The FDA reviewer found:

- No clear differences were seen between treatment groups for deaths and serious adverse events.
- Hypoglycemia was the most common event and did not appear to occur more frequently in either patients using SQ insulin or patients inhaling insulin.
- Type 1 diabetics using inhaled insulin had more non-serious nasopharyngeal adverse events than SQ patients.
- Inhaled insulin was associated with greater insulin antibody response than comparators, but no apparent clinical correlation was found.

The incidence of deaths was similar to that seen in large diabetes trials, and most deaths were from cardiovascular causes. There was no difference in causes of death between inhaled insulin and comparator groups, and no pediatric trial participants died.

The frequency of serious adverse events was comparable between inhaled insulin and comparator patients, according to the FDA speaker. Serious hypoglycemia was the most common serious adverse event, and inhaled insulin patients were not more likely to have an accident or injury with hypoglycemia. There was little difference between treatment groups for incidence of other serious adverse events. Serious hypoglycemic adverse events were more frequent for inhaled insulin pediatric patients than for SQ patients.

The most common adverse event was hypoglycemia. Nasopharyngeal adverse events and allergic reactions were more frequent or slightly higher in the inhaled insulin group of Type 1 diabetics. There was little difference between the groups for accidents or malignancies. For pediatric patients, ear adverse events were more frequent with inhaled insulin. The most common respiratory adverse event for Type 1 diabetics was respiratory tract infection (in both inhaled users and SQ patients), followed by cough in inhaled insulin users, but an FDA expert was unable to draw conclusions about respiratory adverse events.

An FDA statistician said that hypoglycemic events are similar in quality and characteristics between inhaled insulin-taking patients and SQ-treated patients. However, she warned that rates of hypoglycemia should not be summarized and analyzed based on total events without carefully examining the distribution of events across patients, saying that "outliers" may grossly skew the estimates of risk. The statistician criticized the company's study model because it did not take into account the incidence of multiple events in one patient and said that, for example, several patients had multiple events in a short period of time.

Antibodies. Patients on inhaled insulin had greater increases in serum insulin binding activity, which led to concerns about the possible clinical consequences of insulin antibody formation with inhaled insulin, according to the FDA expert. Insulin antibody seroconversion occurred in 88% of inhaled insulin Type 1 diabetics compared to 23% of SQ patients. For Type 2 diabetics, insulin antibody seroconversion occurred in 71% of inhaled insulin patients and 6% of comparator patients.

Adverse events associated with insulin antibodies included a slightly higher incidence of allergic reaction among Type 1 inhaled insulin patients (4.4% versus 3.3%). This did not correlate with the degree of insulin binding activity or occur more frequently among patients with very high binding activity. There was no correlation between the degree of insulin binding activity and frequency nor severity of hypoglycemic events. Insulin antibodies began to decline within two weeks after discontinuation of inhaled insulin and declined by about 70% by 12 weeks.

Pharmacology. An FDA senior clinical pharmacologist who reviewed Exubera told the panel that the pathology of the lung, as well as other exogenous factors, play a critical role in the absorption, delivery, and systemic exposure of inhaled insulin. These conditions affect the exposure of inhaled insulin:

- Smoking – increases absorption ~2-5 fold. He warned that non-smokers who start smoking should stop using Exubera immediately.
- Passive smoking – decreases absorption by 20%-30%.
- COPD – increases absorption by ~50%.
- Asthma – decreases absorption by 20%-30%.
- Rhinovirus infection.

Dosages. The FDA pharmacologist also talked about the lack of dosage form equivalency between the 1 mg and 3 mg strengths, saying that it was problematic in terms of the titration process. He said that inhaled insulin is highly variable. The percentage coefficient of variation (CV) can be in the range of 50% to 100%. In some studies, % of CV is >100%, and in almost all studies the % of CV is >50%.

Long term issues. An FDA pulmonary expert explained why clinical pulmonary safety is a concern (novel substance and chronic administration) and talked about inhaled insulin's potential long-term effects on the lungs. She also said she is concerned about tissue growth, including tumors.

Comparing PFTs, the FDA speaker said that the Type 1 diabetic group taking inhaled insulin had a greater decline in pulmonary function compared to the SQ group in the one study that followed patients out to two years. In two years, 40 mL decline in FEV_1 from baseline compared to the SQ group. The speaker said that this is not clinically significant.

Lung function changes. As for Pfizer's claims that the drop in pulmonary function can be reversed in inhaled insulin users, an FDA expert said the company's data are not conclusive for Type 1 diabetics. She said, "The increase is not sustained; essen-tially the results are not much different, so it's difficult to note a reversal of the effect when there was little reversal effect at 12 weeks." However, she said there was a suggestion of a reversal in Type 2 diabetics.

She looked at inhaled insulin and DLCO for Type 1 diabetics and found:

- Inhaled insulin associated with greater decline in DLCO than comparator.
- Effect noted within first few weeks.
- Treatment group difference of ~0.5-0.6 mL/min/mmHg did not progress out to two years.
- Data from Study 1027 suggest reversal of the effect of inhaled insulin on DLCO after short term (12-week) exposure.

For Type 2 diabetes patients she found:

- Both treatment groups demonstrated similar decline in DLCO at two years.
- Maximum treatment group difference was ~0.5mL/min /mmHg during treatment.

More significant chest x-ray changes were noted by the FDA reviewer in the inhaled insulin group compared to the SQ group. These changes included nodular density, opacity, nodule, atelectasis, and cardiomegaly. Two year HRCT data did not suggest an increase in abnormal findings associated with inhaled insulin use. The reviewer looked at underlying lung disease data and found:

- Limited data at 52 weeks.
- On asthma: There was a separation of treatment groups for FEV_1 and DLCO after Week 39, favoring the comparator.
- On COPD: There was a 30 mL greater decline in FEV_1 with inhaled insulin at 52 weeks, and there was an increase in DLCO at 52 weeks with inhaled insulin.

Serious Adverse Events in Asthmatics and COPD Patients

Condition	Exubera	SQ insulin
Asthma		
Cough	14%	3%
Respiratory tract infection	43%	33%
Discontinuations due to respiratory adverse events	3 patients	0
Exacerbation of non-severe and severe asthma	More common with Exubera	
COPD		
Cough	8.6%	3.1%
Dyspnea	11.4%	6.3%
Discontinuation due to respiratory adverse events	1 patient	0
COPD exacerbation	1 patient	0
Non-severe COPD exacerbation	10 patients (with 14 events)	4 patients (with 9 events)
Severe COPD exacerbation	1 patient	0

THE PANEL DISCUSSION

The panel chair asked about DCCT target data. A panel member (biostatistician) asked if DCCT targets should be higher than other standards and said he didn't have that much concern about Study 107.

Committee members asked questions about rare events such as lung cancer, variability of the studies, patient training to use the device, effects of second-hand smoke on patients, the cough response to Exubera, the estimated percentage of drug that would go to the lungs, how patients and doctors would be trained, how the device is cleaned, how long will the device last, patients with underlying lung disease, and post-prandial glucose measurements.

- **Smoking and malignancies:**

Panel member (biostatistician): "There were four neoplasms. Have you given thought to what kind of study sizes would be necessary to discriminate? Do you have some sense of the kinds of studies that would be necessary to elucidate the lung cancer rate going forward and what would be the power and the size? There seems to be conflicting data about the signal…I would think it would have to be a huge study, so realistically I don't see how we could do it."

Pfizer expert: "We did conduct a study to study the effects of passive smoke. Subjects were exposed for two hours at a level of smoke, and then we administered the inhaled insulin dose and measured. We didn't measure chronic cigarette exposure."

FDA expert: "On the smoking issue, to the extent that the effects of smoke, active smokers, and passive smoking were in exactly the opposite direction, at what point does passive smoke exposure become like smoking? At what point are you exposed to so much passive smoke that you have to wonder about over-exposure? I know you don't know the answer, but I wanted to qualify the question."

Pfizer expert: "We have a proposed 12-year study looking at lung cancer mortality between inhaled insulin-treated and non-inhaled insulin-treated diabetic patients. It will use the THIN electronic medical record database in the U.K. (around 57,000 patients). We will also develop a smoking questionnaire to collect smoking history data. We should be able to calculate a relative risk of about 1.5. It will compare those exposed to those not exposed."

Panel member (biostatistician): "I'm befuddled by the difference between active and passive smoking."

Pfizer expert: "I think it's a difference between irritation and inflammation."

- **Variability:**

Panel member (endocrinologist): "Are the variabilities greater with inhaled insulin rather than SQ insulin? That's one of the downsides of SQ. By the time the person is really good at using it (inhaled insulin), are we able to diminish that variability?"

FDA staff: "We don't have data to say that if the patient continues to use it that it will have lower variability."

Pfizer expert: "We have data that variability does improve, and bear in mind what we're comparing is a completely new entity against SQ being injected by people who know how to do it and have known how to do it for a very long time."

- **Patient training:**

Panel member (endocrinologist): "What is the learning curve – two weeks, four weeks, two months?"

Pfizer expert: "I did the studies with the variability of SQ on some preparations, and I can tell you we see a broad variability which is within the range you quoted."

Consumer representative: "Were there tests as to who could or could not use the device? Some people can't use inhalers. Will there be labeling to see if someone is tested to see if they can take a deep breath?"

Pfizer: "In terms of lung function screening…our estimation might be 10% screened failed because of PFTs."

Consumer representative: "The siren call of that (inhaled insulin) is almost irresistible. My question would be the practicality of it. It's highly regrettable that you didn't bring a device for us to see. My concern is – I'd like to know how big the device is, as far as portability goes."

Pfizer: "It's bigger than a pen (holds hands about six-seven inches apart)."

Consumer representative: "It's easy to carry around a pen. It might be easy for me, as someone who carries a purse, but a little more difficult for male patients. I think people will be getting multiple devices as well. My biggest concern goes back to the training level because this is really novel."

Panel member (biostatistician): "I was wondering if you collected statistics on the number of times people wanted to use the device and the number of times they were successful. What was the failure rate? Some statistics like that might help concerns about the robustness of the device."

- **Cough:**

Panel member (endocrinologist): "My guess is that the first time is going to result in cough response. If someone is inhaling something, they're more likely to be queried about cough. Is there a learning curve for cough?"

FDA staff: "In a few of the studies, the sponsor utilized a cough questionnaire. In that data, it does look like, as time goes on, there is less reporting of cough. So it may be associated early on with the initial use of it, and as time goes on there is less reported."

Panel member (pediatric endocrinologist): "How intense is the cough? Can it be subsided by drinking water?"

FDA staffer: "In the majority it was mild."

Pfizer expert: "Much of the cough that was reported or classified as cough was essentially throat clearing…One thing to keep in mind is the particular breathing pattern that is used. For normal breathing, you might expect the opposite. But the patient is directed to hold the breath. We're not sure it's all in the alveolar space. We do know that for aerosols, deep lung deposition can be as high as 60% or 70% with a deep slow breath hold. So, it depends on the breathing pattern used. This device, particle, and pattern have been optimized for deep lung deposition."

➢ **Glucose:**

Panel member (pediatric endocrinologist): "I wonder if the sponsors have data on glucose monitoring."

Pfizer expert: "We measured post-prandial glucose in two ways obtained from patients in the last week of the study. We did not see significant differences between the two groups. We also designed a study that looked specifically at post-prandial glucose control over six months. Over time, there is no difference from baseline in either treatment group…We would expect to see good control of post-prandial glucose…In a liquid meal challenge test, we found that post-prandial glucose concentration is comparable between inhaled and non-inhaled insulin."

FDA staffer: "The question of post-prandial glucose may be relevant; however, the FDA doesn't label drugs with regard to specific claims of efficacy related to post-prandial glucose. We accept HbA_{1c}."

➢ **Longevity of device:**

Panel member (endocrinologist): "If someone uses this device three times a day for a year, how many, if any, device failures would be expected? Would the device failures be evident at the time? And would it be affordable for patients to be encouraged to have a backup?"

Pfizer expert: "The device is designed to work for a year without failing…The trials are running for at least a year and then we replace the device…The design allows a cloud visualization so any kind of failure – the patient would not see the cloud…There should be one spare chamber. Another backup system is the 24-hour call system so that a patient can have one very, very quickly."

➢ **Non-inferiority:**

Panel member (endocrinologist): "My question is the non-inferiority claim and why you weren't looking for superiority. Weren't you anticipating better glucose numbers with the inhaled insulin especially with its quicker onset, and how were you titrating these levels up? Were you less aggressive than you should have been and what were the goals?"

Pfizer: "We set up our studies on non-inferiority in terms of HbA_{1c} control."

➢ **X-rays:**

Pfizer: "It is true that when we took our controlled Phase III database and looked at the x-rays that there was a difference between inhaled and non-inhaled insulin. We couldn't find any causes. Most of these resolved spontaneously while on inhaled insulin. We saw 29 abnormalities and had follow-up imaging on 25. Twenty-two of those patients resolved, and 18 of the 22 resolved while still on inhaled insulin."

THE PANEL VOTES

The panel chair defended the use of open label, unblinded, active control trials, but he raised issues with the drug: "The prospect of being able to use insulin while avoiding some or all of the...injections…appeals to many patients, family members, and physicians. It is therefore essential that we and they understand the risks associated…with Exubera." The salient issues in his mind were:

- Pulmonary safety in patients with and without existing pulmonary disease.
- Utility of Exubera as a short-acting insulin, dose titration, and insulin switching.
- Safety regarding hyperglycemia, particularly in patients engaged in intensive regimens.
- Use by patients with underlying pulmonary disease or patients who smoke.
- Use by young children with Type 1 diabetes.

Question 1: *Has the efficacy of Exubera been adequately assessed in patients with Type 1 diabetes? Specifically, is there sufficient clinical trial evidence that Exubera can be effectively applied to an "intensive" glycemic control regimen?* **YES by a vote of 8-1**

Question 2: *Has the efficacy of Exubera been adequately assessed in patients with Type 2 diabetes?*
Unanimously YES

Question 3: Has the safety of Exubera regarding hypoglycemia been adequately assessed in:

a. *Type 1 diabetes in "intensive" control regimens?* **YES by a vote of 7-2**

b. *Type 2 diabetes?* **Unanimously YES**

Question 4a: *Pulmonary effects. Have the effects of respiratory infection, asthma, and smoking on the kinetics of Exubera inhaled insulin been adequately assessed?* **Unanimously YES**

Question 4b: *Are there sufficient data to assess the pulmonary safety of Exubera in patients without underlying lung disease?* **NO by a vote of 5 to 4**

If no, what additional information is needed?

Panel members said that long-term studies are needed. A panel member (pulmonary physician) said, "I'm very concerned about patients with other diseases." The panel chair commented, "It's fair to say that the pulmonologists have more concern than endocrinologists, and that's not surprising."

Question 5a: *Comment on clinical concerns and recommendations about the use of Exubera in the setting pulmonary pathology or exogenous factors affecting pulmonary function in viral upper respiratory infections, asthma, COPD, and smoking.*

Panel comments included:

Panel chair: "I am very concerned about viral upper respiratory – influenza."

Pulmonary physician: "In terms of asthma, I've…expressed my concern. The question of response to smoking, particularly passive smoking, was not addressed."

Another pulmonary physician: "I concur. There needs to be a study of passive smoking. This poses a threat to the effectiveness of this drug, not withstanding the efficacy issues. One of the other issues that would bear more attention would be the real world use of this device."

Consumer representative: "I have a concern about spirometry in the office – whether the skills are there to do the test."

Question 5b: *Comment on clinical concerns and recommendations regarding dose adjustment (titration) and switching between inhaled and SQ insulin.*

Panel comments included:

Patient representative: "I'd like to see the sponsor do the calculations instead of making the patient do the calculations…In the real world, the plan is the first casualty, and it's going to be used very differently, especially in a population where patients will have to make the adjustments themselves. My concerns about the doses, the equivalencies, are why are three 1s not equal to one 3?"

Endocrinologist: "Patients need to do more frequent monitoring, so just educate the patient."

Pulmonary physician: "One of the things we find extremely difficult is healthcare literacy. Physicians have a difficult time instructing patients. This is a big problem, and we haven't figured out a way to resolve it. I think this is easier, but I think there is going to be a substantial education problem, and we haven't heard much about how this will be addressed."

Question 5c: *Other issues.*

Panel members had a few other comments of interest:

Pulmonary physician: "We've heard ambitious plans and it would be reassuring to have a specific plan about the post-marketing events that would trigger a post-marketing review of those events. It would be helpful to have that articulated. At what point is it seriously re-examined?"

Panel chair: "I'm not sure that the company has thought out how to train people who are insulin-naïve. The call center is a good idea, but it doesn't take the place of someone there holding hands. I would like to see the sponsor demonstrate a substantial training program that mirrors real life. The other thing that we haven't discussed at all is that inhaled insulin doesn't mean that diabetics can throw away their needle and syringe. And that needs to be emphasized more."

Another pulmonary physician: "I think the device is a problem. It's hard enough to get our asthma patients to take (carry) their devices with them. This is actually a fairly large device, and I understand that metrosexuals are carrying purses *(laughter)*, so it's a lot easier for them, but I think it's still a big problem that people will not carry it with them, and they will leave them (the devices)."

Patient representative: "The practicality of it cannot be over-emphasized. One of the problems you have with compliance is practicality. It's got to be easy. There's still a stigma about using your medication in public, and you have to use it if you're going to be out or at work. To pull out a device calls attention to you, and that affects patient compliance. The training issue, again, I agree, to me is your Mount Everest if you're going to get this off the ground. People don't want to take a shot if they don't have to. A lot of people resist insulin because they're afraid of the needles. You have to look at how this is going to be used and make it attractive not only in theory but realistically."

Question 6: *Should Exubera be approved for the proposed indications:*

a. *Type 1 diabetes?* **YES by a vote of 7 to 2**

b. *Type 2 diabetes as monotherapy, in combination with basal insulin, in combination with oral agents?* **YES by a vote of 7 to 2**

♦