

Post Exubera: Can New Life be Breathed Back into Inhaled Insulin?

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One of the biggest drug delivery stories of 2007 has been the spectacular flop of **Pfizer's Exubera®**, the inhaled insulin product aimed at securing a multi-billion dollar market. This article looks back over what happened and what went wrong with the launch, examines what was wrong with the product itself, and assesses the repercussions of the failure. Finally, a number of upcoming inhaled insulin therapies – and their chances of success – are considered in the light of Exubera.

Diabetes is a growing global issue, and one that is exacerbated by the increase of the prevalence of obesity. In 2007, there were around 246 million sufferers worldwide, up from only 194 million in 2003. This figure is predicted to grow to 380 million in 2025. The true figures could be much higher than these as it is estimated that 50% of people with diabetes are unaware that they have it. Type 1 diabetes normally develops in childhood as the result of the destruction of the insulin-producing beta cells of the pancreas. It must be managed using long-acting, injected insulin topped up with injections of shorter-acting insulin. Type 2 diabetes occurs when there is inadequate insulin production by the beta cells, and onset typically occurs later in life. Initially, it may be managed solely through oral hypoglycaemic preparations but, as the disease progresses, many type 2 patients also require insulin injections. Injections are invasive and, on the face of it, it seems obvious that a non-injected form of insulin would be a runaway success. In early 2006, many analysts thought that an alternative such as Exubera would surely take a large share of the then US\$22 billion diabetes market.

Exubera has a long history. In 1996, a deal between **Nektar** (then **Inhale Therapeutics**) and Pfizer was signed whereby Pfizer helped to fund Nektar's development of a powdered form of recombinant human insulin. The powder was to be delivered deep into the lungs via an inhaler that was also to be developed by Nektar. Nektar negotiated significant royalties of 20% on all product sales. Upon approval, Pfizer was to market the product. **sanofi-aventis** partnered with Pfizer for eight years to develop and promote the final product, but it handed the rights back to Pfizer in January 2006. Exubera was approved for sale in the US and EU in February 2006 having been shown in trials to be just as effective as insulin in controlling blood sugar levels.

Exubera was trumpeted as a revolutionary product that would allow millions of diabetes patients, both type 1 and type 2, to be freed from their short-acting insulin injections. In addition to appealing to those already taking insulin, it could access the fraction of patients that were unwilling to take insulin via injection, thus improving compliance and avoiding the severe affects of untreated diabetes (retinopathy, neuropathy and renal problems). Indeed, in Pfizer's clinical trials, three times as many patients chose to start on insulin therapy when the inhaled option was made available. The patient would use the inhaler before meals, and was expected to carry it around during the day. Exubera was the first approved, non-injected method of taking insulin since it was discovered in the 1920s. On account of these perceived benefits, in January 2006 analysts were predicting peak sales of US\$2 billion.

It was not long after Exubera's launch that both Pfizer and Nektar realised that something had gone, and was going, very wrong. Sales were extremely low, reaching only US\$3 million in 2006 (*Figure 1*). There were several reasons for this: a lack of education of physicians, problems with the product itself, an overestimation of the 'problem' posed by injections, marketing failures and governmental decisions. The following paragraphs discuss each of these factors in turn.

Early on, it became apparent that physicians had not been properly educated about how to use the new inhaler. There was confusion over how to achieve the correct dose. Exubera's inhaler dosed insulin in milligrams instead of the standard international units used for injected insulin. In

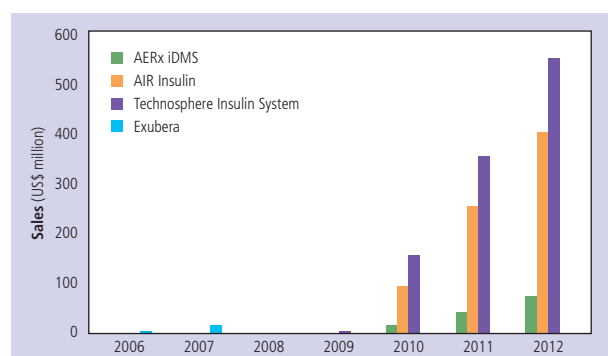


Figure 1 – Recorded sales for Exubera and predicted sales for the inhaled insulin products now in Phase III (2006–12).

the absence of hands-on demonstrations, unfavourable opinions spread amongst doctors, which compounded the situation and created a mental barrier to acceptance.

The size of the inhaler was also a key issue. At about the size of a can of hairspray or a tube of tennis balls, many felt that it was embarrassing and cumbersome – certainly not the convenient and comfortable product Pfizer had intended it to be. Additional problems with the product itself included concerns over lung function. Physicians were not happy about the lung function tests they needed to perform to check whether Exubera could be used by individual patients. Exubera is not suitable for those who smoke or have existing lung diseases. Doctors were unwilling to move away from a safe method of administration to one that might carry a risk.

Even the very basis for developing Exubera was questioned: are injections really that bad? There may be an initial reluctance to inject oneself, but experts report that this is usually easily conquered. The number of patients for whom a fear of needles continues to be a prohibitive issue is in fact a minority. In addition, most patients using Exubera would still need to administer additional insulin by injection.

Nektar became increasingly concerned when direct-to-consumer advertising campaigns failed to materialise. Nektar felt it had received insufficient contact with Pfizer's marketing team, and so instigated weekly meetings with the team. Nektar suggested airing television adverts, but by the time they were aired in July 2007 it was too little too late. Exubera managed only US\$14 million in sales in the whole of 2007.

On top of all these issues, it seems governments may be unwilling to pay for a new therapy that they see as offering little benefit over an existing one. This was the stance of the UK's **National Institute for Health and Clinical Excellence**, which advised in a draft guidance that the National Health Service should not pay for Exubera, which at around £1,100 per year costs twice as much as injected insulin. It rejected the alleged benefits on the grounds that people would still need to use needles to inject insulin and/or monitor blood sugar levels. This guidance was subsequently relaxed, and Exubera was to be made available to patients that had 'a proven injection phobia diagnosed by a psychiatrist or psychologist'. Pfizer retorted that this would stigmatise and discourage patients from choosing Exubera, but the policy still stands.

As news of Exubera's staggering underperformance got out, knock-on effects on all parties concerned became apparent. Without the expected influx of cash, Nektar needed to cut spending and make 350 of its employees redundant in early 2007. At the end of the first quarter of 2007, Pfizer reported that its profits had fallen by 17.5%, partly due to Exubera's poor performance. **Consort Medical**, the makers of Exubera's inhaler, had been benefiting from large orders for the inhalers and a rising share price before Exubera's launch. Post-launch, its shares sank from 840p in March to 643.5p in September, as uncertainties over Exubera grew further.

It therefore came as no surprise to many when Pfizer announced on 18 October 2007 that it would no longer make Exubera, saying that it had made this decision 'because too few patients' were taking it. Nektar immediately issued its own press release, stating that they 'first learned of Pfizer's decision to walk away from Exubera from [Pfizer's] press release.' It added that 'Nektar has been very disappointed in Pfizer's performance in marketing Exubera.' Nektar's share price took a knock, falling some 20% from US\$8.08 to US\$6.67 on the day of the announcement (*Figure 2*). The biggest loser in financial terms was clearly Pfizer, however, which reported the same day that it had suffered a 77% fall in profits, with net income standing at US\$761 million for the third quarter of 2007 – down from US\$3.4 billion for the same period in 2006. Pfizer's CFO estimated the total cost of Exubera to be US\$2.8 billion, including some US\$900 million on research alone. On 13 November 2007 it was announced that Nektar and Pfizer had resolved all outstanding contractual issues concerning Exubera, including a payment to Nektar of US\$135 million.

Writing off such a huge sum of money will hurt Pfizer, especially as sales of Lipitor® (atorvastatin calcium), its multi-billion dollar cholesterol-lowering drug, have been falling since 2006. Perhaps a more far-reaching consequence will be the damage to Pfizer's reputation as the industry's top marketing partner. As internal innovation falls, Pfizer cannot afford to alienate potential biotech licensors. Pfizer has publicly admitted that it made a lot of mistakes with Exubera. Time will tell whether Pfizer can redeem itself and once again win the trust of its future partners.

As for Nektar, the situation may not be quite as disastrous as it might first appear. The product is innovative, has been launched, is selling and has so far found to be safe. It is therefore rather a safe bet in comparison with therapies still in development. Nektar has also done deals with **Novartis** and **Bayer** concerning other products, thus proving their ability to lure in the heavy hitters. For these reasons, Nektar may in fact find a new marketing partner for Exubera quite easily. Nektar is also developing Next Generation Inhaled insulin (NGI). Currently in Phase I trials, this new wave of therapy should also help Nektar to attract a partner.

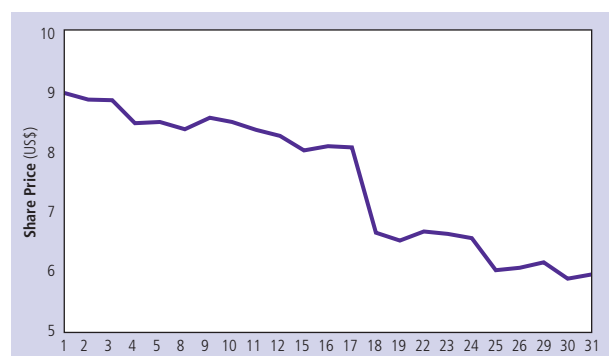


Figure 2 – Nektar's closing share prices for each day in October 2007.

| Principal Company | Partnering Company | Product | Launch Date | Inhaler Description |
|-------------------|--------------------|-----------------------------|-------------|------------------------|
| MannKind | None | Technosphere Insulin System | 2009/2010 | 'Medtone', palm-sized |
| Alkermes | Eli Lilly | AIR Insulin | 2010 | Size of a highlighter |
| Aradigm | Novo Nordisk | AERx iDMS | 2010 | Size of a mobile phone |

Table 1 – Comparison of the three inhaled insulin products currently in Phase III.

An obvious question arising from the Exubera debacle is whether the other inhaled insulin products currently in clinical trials have a chance of success. There are three such products in Phase III: **MannKind's** Technosphere® Insulin System, **Eli Lilly** and **Alkermes' AIR®** Insulin and **Novo Nordisk** and **Aradigm's** AERx insulin Diabetes Management System (AERx iDMS) (Table 1).

MannKind's Technosphere Insulin System encapsulates a unique approach. A powder made of pH-sensitive carrier particles loaded with insulin is administered deep into the lungs via an inhaler. When the particles contact the pH-neutral lining of the lungs, they dissolve instantly and rapidly pass into the bloodstream. The inhaler device, Medtone®, is palm-sized, a factor that MannKind views as a significant advantage over Exubera. MannKind has only a limited marketing capacity itself, and it does not have a marketing partner, but it claims to be in discussions with a number of big pharma companies. MannKind hopes to launch the product in 2009 or 2010. With expected sales of over US\$500 million by 2012, the Technosphere Insulin System is the most promising of the inhaled insulin products in development.

Alkermes chose Eli Lilly as its partner to develop and market AIR Insulin in 2001. The breath-activated device allows a powder of low-density particles carrying insulin plus a lung surfactant (a natural phospholipid) to be carried into the lungs. Like MannKind, Alkermes and Lilly are progressing undeterred by Exubera's flop. Lilly is funding a multi-million dollar expansion of Alkermes' drug plant in Chelsea, near Boston, to produce commercial quantities of insulin. There are plans to take on 100 more employees there in 2008. Alkermes views its chances of success as being higher than Exubera's for two reasons: the inhaler for AIR Insulin is the size of a highlighter, thus making it very discreet, and Lilly has experience in the diabetes market as it already sells insulin. Pfizer had little experience in this market before Exubera. It is expected to submit AIR Insulin for approval in 2009, and sales are predicted to reach almost US\$400 million by 2012.

Novo Nordisk partnered with Aradigm in 1998 to develop AERx iDMS. This is the only Phase III inhaled insulin product that has insulin in a liquid form for dosing. Liquid containing insulin is drawn through 1µm diameter holes in the mobile phone-sized inhaler to create a fine mist. Furthermore, it is easy to set the correct dose. Novo Nordisk admits that Exubera has caused it to re-evaluate its assumptions about the market for AERx, but it is

still confident that there is a market for insulin inhalers. Aradigm is certainly happy to have the world's biggest supplier of insulin as its marketing partner. The two companies expect to receive regulatory approval in 2010.

Whoever reaches the market first will have a hard task creating demand and changing opinions in the wake of Exubera. It was originally been intended that the above products would step into Exubera's market and take a share of it, but that market must now be created once more. Furthermore, the regulatory bodies will be watching closely to ensure there are no negative pulmonary side-effects from using the inhalers.

Other inhaled insulin products in development include **Kos Pharmaceuticals'** (now a subsidiary of **Abbott**) KI 02 212. This formulation is excipient free and delivered to the lungs using the patient's breath via the breath-actuated inhaler, which looks like an asthma inhaler. It is currently in Phase II trials. Also in the clinic is **Baxter Healthcare's** Recombinant Human Insulin Inhaled Powder (RHIP), which has now successfully completed two Phase I trials. RHIP uses PROMAXX™ technology, a water-based, protein microsphere matrix system. The insulin-carrying microspheres are administered as a dry powder via an inhaler.

In summary, Exubera's failure is unlikely to mean that there is no market for inhaled insulin. Lessons have been learned and assumptions about the market (such as exactly how unwanted injections are) are being rechecked. Action has already been taken with respect to the inhaler device's size. It is now apparent that such a product will not sell itself, and that considerable attention must be paid to the education of physicians should another inhaled insulin product be launched. Well-targeted advertising campaigns will be needed to undo some of the negative press Exubera received and to create a receptive market. If these things are done correctly, there is clearly still hope for inhaled insulin, even if the market size may, in reality, turn out not to be quite as big as Pfizer and Nektar had once hoped.