

# Inhalation Technologies – A Breath of Fresh Air

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## Introduction

The approval of Exubera® (inhaled PEGylated insulin) for the treatment of diabetes highlights the vogue for, and potential for, commercial success in reformulating existing therapies for pulmonary delivery. This article will focus on the proprietary mechanisms utilised by specialist biotechnology companies for the pulmonary delivery of reformulated insulin. In doing this, it also profiles three speciality drug-delivery companies with pulmonary delivery expertise – **Nektar Therapeutics**, **Aradigm** and **Alkermes** – and the partnering approach they have taken in commercialising their technologies. A range of pulmonary therapies are in clinical development, targeting profitable but competitive disease areas, and these are outlined in the three profiles. In the next decade we will see the launch of more drugs delivered via the pulmonary route (for non-respiratory indications) and it will be intriguing to ascertain what market share they can capture in competition with established therapies.

In January 2006, Exubera was approved for the treatment of types 1 and 2 diabetes mellitus, both in the US and in Europe. In type 1 diabetes (insulin-dependent diabetes), Exubera is indicated for use in combination with longer acting insulin, while for type 2 diabetes it can be used alone, as an alternative to rapid-acting insulin injections/oral antidiabetics, or in combination with these therapies. Sales of diabetes-related drugs exceeded US\$12 B in 2004 (Bernstein Research), with worldwide revenues expected to rise annually by 12% through to 2011; this exceeds the expected industry-wide sales growth rate of 6%.

The approval of Exubera was greeted with mixed reactions from analysts. Would this product be **Pfizer's** next blockbuster with potential peak annual sales of US\$1.5 B (Lehman market analysis), or more of a gimmick that would not supplant or even complement injectable insulin as the gold-standard treatment for diabetes?

## Profile: Nektar Therapeutics

Co-developed by Pfizer and **sanofi-aventis** (then **Aventis**), recombinant human insulin (later named Exubera) was originally supplied to Nektar Therapeutics (then **Inhale Therapeutic Systems**) in November 1996 to be developed with its proprietary deep-lung delivery system and formulation technology. Nektar developed a non-invasive, dry powder form of this insulin for use in its inhaler device. sanofi-aventis transferred the sole rights for Exubera to Pfizer in January 2006.

For successful drug delivery across the lung surface, there is a dual requirement for the active compound to be in an inhalable formulation and be accompanied by a device capable of delivering that formulation. For Exubera, the optimal size of particles for absorption is 1–3 µm. In a 1-µm aerosol particle there are 300 million insulin molecules stabilised with glass formers. This formulation is used in conjunction with Nektar's pulmonary inhaler. The inhaler injects compressed air at the speed of sound through the dry powder, converting the insulin into an aerosol cloud. The inhalation of the aerosol results in a therapeutic dose of insulin being administered to the deep lung, where it crosses into the bloodstream. It has been demonstrated that efficient pulmonary delivery

Drug (Indication)/ Partnering Company	Preclinical	Phase I	Phase II	Phase III	Launched
Exubera® – insulin (type 1 and 2 diabetes) / Pfizer	[Progress bar from Preclinical to Launched]				
Tobramycin (respiratory infections associated with cystic fibrosis) / Chiron	[Progress bar from Preclinical to Phase III]				
Dronabinol (multiple indications) / Solvay Pharmaceuticals	[Progress bar from Preclinical to Phase II]				
Cipro® – ciprofloxacin (chronic lung infections by Pseudomonas aeruginosa in cystic fibrosis) / Bayer Healthcare	[Progress bar from Preclinical to Phase I]				

Figure 1 – Pipeline for Nektar Therapeutics drugs using its proprietary technology in active development (Source: Nektar's web site).

is more effective than subcutaneous injection as a means of delivering insulin into the bloodstream. An additional advantage is the avoidance of first-pass hepatic metabolism, thus ensuring a longer systemic half-life.

The extensive range of clinical needs that may be met by inhalation technologies is exemplified in Nektar's wide-ranging product pipeline (Figure 1). Nektar is partnering with **Chiron** (now merged with **Novartis**) to develop tobramycin for lung infections in cystic fibrosis patients; this therapy is currently in Phase III clinical trials. In preclinical development, ciprofloxacin is being co-developed with **Bayer Healthcare** for chronic lung infections by *Pseudomonas aeruginosa* in cystic fibrosis. In addition to these antibacterial therapeutics, dronabinol is in Phase II clinical trials for multiple indications. Dronabinol is the active ingredient in Marinol®, capsules that are prescribed as an appetite stimulant in HIV patients and as an antiemetic for chemotherapy-induced nausea in cancer patients. This compound is being developed with **Solvay Pharmaceuticals**.

## Delivering Diabetes Treatment

Although Nektar Therapeutics and Pfizer were pioneers for inhaled insulin, 'fast followers' are looking to capture their market share. Aradigm (in collaboration with **Novo Nordisk**) and Alkermes (in collaboration with **Eli Lilly**) both have inhalable formulations of insulin in clinical development; these will be discussed in the following profiles.

Other products in development include **MannKind's** Technosphere® drug delivery technology. In the US, in March 2006, this product entered Phase III development for both types of diabetes. The company's proprietary Technosphere technology consists of diketopiperazine derivatives of proteins that self-assemble into an ordered lattice at a low pH. The insulin formulation is pH sensitive, and turns to liquid on the lung surface, thus allowing for quicker absorption. This formulation is delivered with MannKind's MedTone™ inhaler.

**Kos Pharmaceuticals** has an inhaled insulin formulation in Phase II development for which it anticipates approval in 2010. Kos' formulation is excipient-free and is a mixture of crystalline recombinant insulin containing only water and a non-CFC propellant. The clinical development of insulin has stagnated as Kos seeks a partner with whom to commercialise this product.

In collaboration with **Quadrant** (which was acquired by, and merged into, **Innovata** in August 2005), **MicroDose Technologies** is developing fast-acting insulin for pulmonary delivery. This development benefited from a brief spell with **Bristol Myers Squibb**, which licensed the compound for 2 years, driving forward development of the therapy into Phase I, before returning the rights to the Innovata/MicroDose partnership in December 2005. Innovata/MicroDose are now completing preparations for an IND submission. This collaboration exploits Innovata's formulation and particle-engineering expertise to produce dry-powder formulations. These methodologies

include micronisation, blending, spray drying and polyol stabilisation. Controlled and sustained release can be achieved using either sugar derivatives or hyaluronic acid. The delivery device is MicroDose's electronic dry-powder inhaler that uses piezo-electronics to deliver a broad range of compounds efficiently and independently of patient inhalation flow rate.

**Coremed** is a US-based, privately funded biotech company founded in 1994. It has developed an inhalable form of insulin, Alveair™, now in Phase I development, which is based on a proprietary new platform for drug delivery. Coremed cites Alveair's advantage over other inhaled formulations of insulin in development as the high level of bioavailability (near 100%) of the compound. This is the result of the company's development of a novel polymer/bio-adhesive drug delivery platform that allows drug delivery without modifications to the three-dimensional structure of molecules. Coremed's insulin formulation is completely soluble in water, vaporised before inhalation and delivered in a generic hand-held device. The company is partnering with two large Chinese companies – **Fosun Pharmaceutical** and **Wanbang Biochemistry** – in a tripartite agreement to develop Alveair.

The product in the earliest stage of development is **BioSante's** inhaled insulin; currently in the preclinical development. Using BioSante's proprietary calcium phosphate nanoparticulate (CAP) delivery system, BioAir™, a suspension of CAP, polyethylene glycol (PEG) and insulin is generated for pulmonary delivery. It appears that this therapy is not being actively developed at the current time.

## Profile: Aradigm

The competitiveness of the 'pulmonary delivery' interest area is emphasised when you compare Nektar's pipeline (Figure 1), with Aradigm's pipeline (Figure 2), and view the overlap in compounds in clinical development. Aradigm's proprietary technology to reformulate drugs for pulmonary delivery is AERx®. The AERx system is composed of a Strip™ dosage form and inhalation device. The Strip is the central element of Aradigm's system and contains a disposable nozzle to ensure performance every time the patient inhales medication. The nozzle's patented design can be adjusted for various formulation characteristics and treatment requirements so that the particle size and thus the primary deposition area of the therapy are regulated. The nozzle is used in conjunction with Aradigm's second-generation of inhaler Essence™, which uses a piston mechanism to expel formulation from the Strip.

Likely to be launched as the next diabetes drug after Exubera is Aradigm's AERx insulin Diabetes Management System (iDMS), currently in Phase III clinical trials. Aradigm has partnered with Novo Nordisk to commercialise iDMS since 1998. In contrast to Pfizer's Exubera dry powder formulation, Aradigm's formulation is liquid.

**APT Pharmaceutical's** formulation of hydroxychloroquine (HCQ) is being developed for delivery in conjunction with Aradigm using the AERx system, and entered into Phase II clinical trials in July 2005 for asthma

Drug (Indication)/ Partnering Company	Preclinical	Phase I	Phase II	Phase III	Launched
Insulin (type 1 and 2 diabetes) / Novo Nordisk	→				
Hydroxychloroquine (asthma/chronic obstructive pulmonary disease –COPD) / APT Pharmaceuticals	→				
Unknown (Respiratory) / Undisclosed	→				
Liposomal ciprofloxacin (respiratory indications in cystic fibrosis) / Unpartnered	→				
Liposomal ciprofloxacin (bioterrorism) / Defence R&D Canada	→				
Nicotine (smoking cessation) / Undisclosed	→				
Treprostinil (pulmonary arterial hypertension) / United Therapeutics	→				

Figure 2 – Pipeline for Aradigm drugs using AERx® technology in active development (Source: Aradigm's website).

and chronic obstructive pulmonary disease (COPD). Also in Phase I development is an AERx formulation of a compound for an undisclosed respiratory indication with an undisclosed partner. In late 2005, Aradigm signed two preclinical alliances for the pulmonary delivery of drugs using AERx: with an undisclosed pharmaceutical company for the delivery of nicotine for the treatment of tobacco dependency; and with **United Therapeutics** for the delivery of treprostinil for treating pulmonary arterial hypertension.

From Aradigm's internal development programme, an application has been made for Orphan Drug Status for a pulmonary-delivered liposomal ciprofloxacin formulation. The company is developing a liposomal-encapsulated formulation of ciprofloxacin, utilising the AERx system, as a prophylactic for serious respiratory infections, such as those associated with cystic fibrosis. Ciprofloxacin entered preclinical development in December 2004.

## Profile: Alkermes

Alkermes' proprietary pulmonary delivery technology, AIR®, was developed by **Advanced Inhalation Research (AIR)**, a private company that was acquired by Alkermes. AIR technology is based on research showing that relatively large, low-density drug particles can be inhaled into the lungs with high efficiency and can, therefore, be used for the systemic delivery of small molecules, peptides, proteins and other macromolecules. The AIR delivery system is an inhaler that can deliver a broad range of doses. The system can provide local or systemic sustained release of drugs.

Looking at Alkermes' product pipeline (Figure 3), the inhaled therapy that is in furthest stage of development is an AIR formulation of insulin. This product is being co-

developed with Eli Lilly in an alliance that started in April 2001. The AIR pulmonary drug delivery system is a breath-activated device that will deliver a powdered formulation of insulin plus a lung surfactant – a natural phospholipid already present in the lung. The inhaled formulation is currently in extensive worldwide Phase III clinical trials. Altogether, Lilly is partnering with Alkermes in four of the latter's AIR formulation development programmes.

Lilly invested in Alkermes' large-scale commercial production facility for AIR-based inhaled pharmaceuticals in February 2002, following the already successful insulin collaboration. Targeting the US\$17 B US market for osteoporosis, Lilly and Alkermes next signed a deal in January 2006 for an inhaled formulation of parathyroid hormone (PTH) for the treatment of osteoporosis, to be based on Forteo® (teriparatide), which is already launched as an injected formulation. For the new inhaled formulation, currently in preclinical development, Alkermes will receive research and development funding, an upfront fee and milestone payments. Lilly will have the worldwide rights to the product and will pay royalties based on product sales. Much earlier, in February 2000, the companies agreed to develop an AIR formulation of human growth hormone (somatotrophin); this is presently in Phase I development. Also in Phase I development, but unpartnered, is an inhaled formulation of adrenaline for treating anaphylactic shock.

With the current investment in pulmonary delivery, it seems likely that some of these inhaled therapies will be set for success within the next decade. As pulmonary delivery has proven to be both efficacious and safe for systemic distribution, it is interesting to muse on whether injectables for chronic conditions may have had their day.

Drug (Indication)/ Partnering Company	Preclinical	Phase I	Phase II	Phase III	Launched
Insulin (type 1 and 2 diabetes) / Eli Lilly	→				
Somatropin (somatotrophin (growth hormone) deficiency) / Eli Lilly	→				
Adrenaline (anaphylaxis) / Unpartnered	→				
Parathyroid hormone (osteoporosis) / Eli Lilly	→				

Figure 3 – Pipeline for Alkermes drugs using AIR® technology in active development (Source: Alkermes's website).