

# The Promise of Pulmonary Drug Delivery

■ John S Patton, PhD, Founder and Chief Scientific Officer, Nektar Therapeutics

## Summary

Delivering drugs to the lungs has evolved from the simple asthma inhalers of the 1950s as technologies invented in the 1990s open new applications for systemic and local lung therapy. As inhaled molecules move quickly through the lungs into the bloodstream, pulmonary drug delivery is becoming an attractive alternative to injections. Recent advances in technology facilitating the delivery of large doses directly to the lung make pulmonary delivery feasible for treating a growing number of lung indications. As a result, pharmaceutical developers now realise that inhalation offers unique advantages for a range of therapeutics, potentially replacing oral or injectable delivery in many cases. They are now investigating pulmonary drug delivery as:

- Targeted treatments for all lung disorders;
- A non-invasive alternative to injection for peptides and some proteins;
- An attractive delivery mode for drugs requiring fast onset of action; and
- Patient-friendly vaccines.

## A Brief History of Pulmonary Delivery

The first metered dose inhalers (MDIs), developed in the 1950s for asthma, delivered potent drugs with large therapeutic windows (e.g. corticosteroids and bronchodilators) to the airway. These compact devices dispense controlled doses of medication, reducing the dose needed and thus side effects, compared with delivery by mouth or injection. This approach has been very successful; in 2002, **3M Corporation** estimated that 80% of asthma patients use MDIs to take their medications. Today, second-generation devices (advanced MDIs, liquid jet and ultrasonic nebulisers) offer closer dose control and better replicability, and can deliver a wider range of compounds.

The 1990s saw increasing interest in pulmonary delivery of drugs to treat systemic diseases. Spurred by biotechnology, the rising proportion of biotherapeutics in development compelled pharmaceutical firms to seek alternatives to injections for these proteins and peptides (which are not orally bioavailable). While the lungs' expanse of alveolar surface was an attractive portal, existing technology could not deliver large and consistent doses of drugs to the deep lung. Capital poured into companies inventing new pulmonary delivery technologies, among them **Aerogen** (founded in 1991 as Fluid Propulsion Technologies), **Alkermes** (1986), **Aradigm** (1991) and **Nektar Therapeutics** (as Inhale Therapeutic Systems in 1990). The R&D investment needed was greater than expected; companies spent hundreds of millions of dollars along the way. The technical and regulatory

challenges conspired with the collapsing investment bubble to winnow down the number of competitors in this field.

Today, the industry leaders are leveraging their multiple technology platforms to develop products through collaborations with pharmaceutical partners as well as through their own programmes. This has raised barriers to entry even as pulmonary drug delivery becomes more attractive to the market.

## Pulmonary Delivery Today

Oral medications remain the first choice of patients and physicians. However, pulmonary delivery has long attracted interest, since the lungs move molecules quickly into the bloodstream across the large surface area of the alveoli. Technological advances have led to a growing body of clinical data and experience supporting the efficacy and safety of inhaled drugs. New products cluster in four main pharmaceutical categories: drugs to treat local lung indications such as lung infections, respiratory and systemic diseases; non-invasive delivery of peptides and some proteins; drugs for systemic diseases where fast onset is advantageous; and vaccines for respiratory and systemic diseases.

## Targeted Treatment of Lung Disorders

Asthma was the original target for airway delivery. However, not all lung diseases are treatable using the original airway delivery technologies. These systems work best delivering drugs with wide therapeutic windows where patients simply dose themselves until symptoms subside. Drugs with narrower dosage windows, and of course, macromolecules, do not work in these systems because they must reach the deep lung.

Deep lung delivery offers unique advantages for treating lung diseases such as infections, emphysema and cancer. The primary advantage is obvious: the treatment goes immediately to the disease site. Injections and infusions also bypass first-pass metabolism by the gastrointestinal (GI) system and liver, but the cardiovascular system is a less efficient gateway to the lung than inhalation. Delivering small amounts of drug directly to diseased lungs may improve efficacy and reduce or eliminate side effects of oral therapies caused by delivering high levels of drug to the whole body. For these reasons, directly treating the lung means less drug is needed, offering cost improvements as well. The initial hurdles have been technical, so advances in delivery technology are opening new opportunities to treat lung diseases. Moreover, development, regulatory and market risks for lung disease therapies may be more manageable than for products targeting systemic indications. For some therapeutics and vaccines, there are also cost, margin and product life cycle advantages.

Lung diseases are a leading cause of morbidity and mortality worldwide, with many unmet medical needs. Respiratory infections are a large and growing concern for infants, the elderly, the immunocompromised and people with predisposing conditions (e.g. cystic fibrosis, asthma). Lung, bronchial and interstitial infections by bacteria, fungi and viruses present growing opportunities, especially for diseases such as TB and pneumonia, where antibiotic resistance demands new treatment approaches. Inhaled antibiotics deliver concentrated active drug to the infection site and may reduce pathogen resistance by sparing the GI microbial population, reducing the dosage of antibiotic needed and clearing the infection more quickly.

One of the first inhaled lung infection treatments was developed by **Pathogenesis** and marketed in 1998 by **Chiron**. TOBI® is a liquid tobramycin product to treat *Pseudomonas aeruginosa* infections in cystic fibrosis patients. Chiron and Nektar are collaborating on a next-generation inhaled, dry-powder tobramycin product. A powdered version of tobramycin has the potential to improve delivery efficiency to the lung. A 12-person trial indicated that doses of Nektar inhaleable tobramycin delivered the tobramycin to the lung with an efficiency 3.5 times higher than from a liquid solution via nebulisation: 44% for the inhaled powdered dose compared with 12.5% for the nebulised solution. Moreover, the powdered version was delivered in less than 1/10th the time required for the nebulised dose.

Chronic lung diseases are natural targets for pulmonary delivery, including therapies for congenital emphysema, Chronic Obstructive Pulmonary Disease (COPD), cystic fibrosis and primary pulmonary hypertension. Cancer is another large market. Pulmonary delivery could enable precise delivery of smaller doses of chemotherapies to primary lung cancers as well as to lung metastases from other primary sites. Pain medications and adjunct therapies such as blood cell growth factors are also excellent candidates for pulmonary delivery. Further out, gene therapies and cancer vaccines may offer future opportunities.

Returning full circle to immunological diseases of the respiratory system, such as asthma, allergies and anaphylactic reaction, advanced pulmonary delivery has more to offer than ever. Technical advances in delivery devices, such as advanced MDIs, dry powder inhalers (DPIs) and nebulisers, are joining improved molecules, particles and formulations to improve efficacy and patient convenience while reducing side effects. A number of companies are developing various second-generation MDI systems to deliver medications for asthma and COPD.

## Non-Invasive Alternative to Injection for Peptides and Proteins

As the population ages, many chronic diseases with inadequate current treatments are becoming more prevalent, offering growing market opportunities. For many of these diseases, the most effective treatments

are monoclonal antibodies, proteins and peptides, or gene therapies. The entire biotechnology industry was founded to create such macromolecule therapeutics, and innovations in drug discovery are continually increasing their numbers. Biopharmaceuticals are the fastest growing segment of the therapeutics development effort, with some 85 such products currently approved for US sale and perhaps 350 more in clinical development.

Large molecules such as unmodified proteins and peptides cannot be delivered orally. The GI tract breaks down proteins as if they were food and renders them pharmacologically inactive. Moreover, therapeutic quantities of most macromolecules cannot pass easily through the skin or mucous membranes without penetration enhancers like detergents or electrical impulses, increasing the likelihood of irritation or other side effects. Therefore, although less desirable for patients and practitioners, injections and infusions perforce have been the primary mode for administering large molecule drugs. This has confined biologicals to indications where the need to treat trumps the associated costs and inconvenience.

While hospital and clinic-administered injections are expensive and inconvenient, many patients find self-injections difficult. Especially in chronic diseases, such as diabetes, lack of compliance increases complications and disease management costs. Even when injected, unmodified proteins may have limited effectiveness if they are too quickly cleared from the bloodstream, degraded by enzymes in the body, or if they trigger an immune response. Any of these factors can make protein drugs less effective or necessitate frequent dosing, decreasing compliance and increasing costs. Over the past decade, the growing numbers of biologicals in development have prompted pharmaceutical firms to seek alternative delivery modes. Inhalation appeals to patients as less painful and invasive, and to practitioners as a less costly outpatient modality.

The lungs offer an even more attractive portal for large molecules than for small ones. In addition to their large surface area, the alveolar epithelium naturally absorbs proteins and peptides without enhancers. The lungs are robust and can handle large quantities of powders on an ongoing basis. According to the American Conference of Governmental Industrial Hygienists, a person can inhale up to 30 mg of nuisance dusts daily for years in industrial settings without effect. All this makes pulmonary delivery potentially superior to oral, intranasal and transdermal alternatives for macromolecules.

## Products in Development - Inhaled Insulin

Some 3 million Americans with diabetes could benefit from insulin but refuse to inject it. Many diabetics who do inject insulin do not inject as often as needed, leading to suboptimal disease management. Given the growing diabetes market, quite a few alternative delivery systems for insulin are in development, including pens, pumps,

advanced oral preparations and inhaleable systems.

Several pulmonary insulin products are now in late stages of human clinical testing. The AIR system, in Phase II clinical testing, was developed by Alkermes and applied to insulin for **Eli Lilly**. This technology is based on relatively large, low-density drug particles that can be inhaled deep into the lungs using a simple, small inhaler. In Aradigm's iDMS, insulin Diabetes Management System, the AERx inhaler electronically synchronizes the user's breathing with the device and converts a liquid insulin formulation into fine aerosolized particles delivered deep into the lungs.

**BioSante Pharmaceuticals** is developing its BioAir™ system that uses a calcium phosphate nanoparticle-based delivery system. QDose (a joint venture between **MicroDose Technologies** and **Quadrant Drug Delivery**) is developing a system for **Bristol-Myers Squibb**. This system delivers dry powder particles engineered by Quadrant deep into the lung through an inhaler developed by MicroDose.

The most advanced product in this field is Exubera®, developed by Nektar for **Aventis** and **Pfizer**, whose marketing authorization application (MAA) filing was accepted by the European Medicines Evaluation Agency in March 2004. This dry powder system incorporates novel technologies engineered specifically for inhaled insulin, but applicable to other drugs as well. Technical innovations included formulation, dry powder processing, custom packaging and devising a durable and easy-to-use inhaler. In this case, a proprietary particle engineering process produces consistent, optimally sized and rapid-dissolving dry particles in a room temperature-stable formulation. The inhalation device was engineered to be portable and easy to use to deliver dry powder deeply and consistently into the lung.

## Other Peptides and Proteins in Development

Initial development efforts for large molecules for systemic diseases have focused on chronic disorders. Nektar is working with an inhaled LHRH (leuprolide) for endometriosis with **Enzon**, Alkermes on an inhaled human growth hormone product with Eli Lilly.

Other peptides and proteins under investigation for pulmonary delivery include: heparin (blood clotting), interferons (multiple sclerosis and hepatitis B and C), calcitonin and other hormones (osteoporosis, infertility), and monoclonal antibodies (cancer, autoimmune diseases). The growing number of antibody drugs for chronic diseases such as psoriasis and rheumatoid arthritis offer particularly attractive opportunities. Looking further ahead, inhalation could be used to administer gene therapy for tissue and organ targeting.

## Drugs that Need Faster Onset of Action

For many molecules, there is no faster way into the blood stream than through the lungs. Beyond avoiding first-pass GI effects, the pharmacokinetic profile of many

small molecules is better when delivered through the lungs than through oral dosage forms. Fast onset is a key consideration for the treatment of pain, nausea, anxiety, anaphylactic shock, hypertensive crises, cardiovascular conditions (arrhythmia, strokes), Parkinson's 'lock-up' and seizures.

Similarly, the marketing advantages of fast-onset medicines for acute conditions such as migraine and panic attacks are obvious. Development and marketing risks for pulmonary delivery of small molecules may be smaller than for large molecules (e.g. immunogenicity). Delivered through the lung, small molecule systemic anti-infectives may provoke less pathogen resistance than oral or IV administration. The technical challenges for moving small molecules through the lung are no greater than for large molecules, and companies with a strong toolkit for macromolecule delivery have a head start.

Small molecule products in development using pulmonary delivery for fast onset include Aradigm's AERx system to deliver controlled doses of morphine or fentanyl for acute or breakthrough pain control, and Alkermes' inhaled epinephrine for anaphylaxis. Other products include the Marinol™ Inhaled Dronabinol (THC) system in development by **Unimed Pharmaceuticals/Solvay Pharmaceuticals** and Nektar for multiple indications.

Pulmonary delivery of peptides and proteins for fast-onset treatment is focused in areas such as hormones and pain relief. Alkermes has an inhaleable human growth hormone product in clinical testing. Nektar is working with Enzon on a pulmonary system to deliver leuprolide acetate (a peptide hormone analogue) for endometriosis. Aradigm is developing an inhaled testosterone product for female androgen insufficiency.

## Vaccines

Inhaled vaccines are of growing interest to pharmaceutical developers. Of the currently approved vaccines, 53 address respiratory diseases (e.g. pneumonia, influenza). Today, nearly all are injected. The first intranasal flu vaccine was commercialised only after years of study in thousands of patients, and then only approved for low-risk age groups. Community-acquired pneumonia remains a major cause of death in the elderly, despite the wide availability of injected vaccines. Inhaled vaccines could greatly improve vaccination rates among the many who shun injections.

Few inhaled vaccines for systemic diseases are under development beyond a measles vaccine in clinical testing in Mexico. Yet pulmonary delivery offers benefits such as no needles and improved efficacy through stimulating mucosal, as well as humoral, immunity, helping to stop infections at their port of entry.

## Future Prospects

The markets for pulmonary-delivered therapeutics are sizeable and growing. In addition to local lung diseases, biologicals, drugs requiring rapid onset and vaccines present attractive opportunities. Technical, regulatory and

clinical hurdles have been higher than expected, but the number of drugs in development for pulmonary delivery continues to grow. The approval of the first inhaled insulin product will encourage further interest and investment in pulmonary delivery technologies. As technologies continue to improve, and as clinical experience regarding the safety and efficacy of these products grows, they will command an increasing proportion of the drug delivery marketplace.

#### **Further Reading**

**Adjei** AL, Gupta PK (eds), 1997. *Inhalation delivery of therapeutic peptides and proteins*. New York, US: Marcel Dekker, Inc..

**Duddu** SP, Sisk SA, Walter YH, Tarara TE, Trimble KR, Clark AR, Eldon A, Elton RC, Pickford M, Hirst PH, Newman SP, Weers JG, 2002. *Pharmaceutical Research*, **19**(5):689-695.

**Patton** JS, Bukar J, Nagarajan S, 1999. *Advanced Drug Delivery Reviews*, **35**:235-247.

**Skyler** JS, Cefalu W, Kourides IA, Landschulz WA, Balagtas CC, Cheng SL, Gelfand RA, 2001. For the Inhaled Insulin Phase II Study Group. *The Lancet*, **357** (9253 February 3): 331-335.

**Skyler** JS, Cefalu W, Kourides IA, Landschulz WA, Balagtas CC, Cheng SL, Gelfand RA, 2001. For the Inhaled Insulin Phase II Study Group. *Annals of Internal Medicine*, **134** (3 February 6):203-207.

If you have found this article of interest and would like copies for promotional purposes, please contact:

Mel Hemamda

Tel: +44 (0) 1865 784 177

Fax: +44 (0) 1865 784 178

E-mail: mel.hemamda@pharmaventures.com