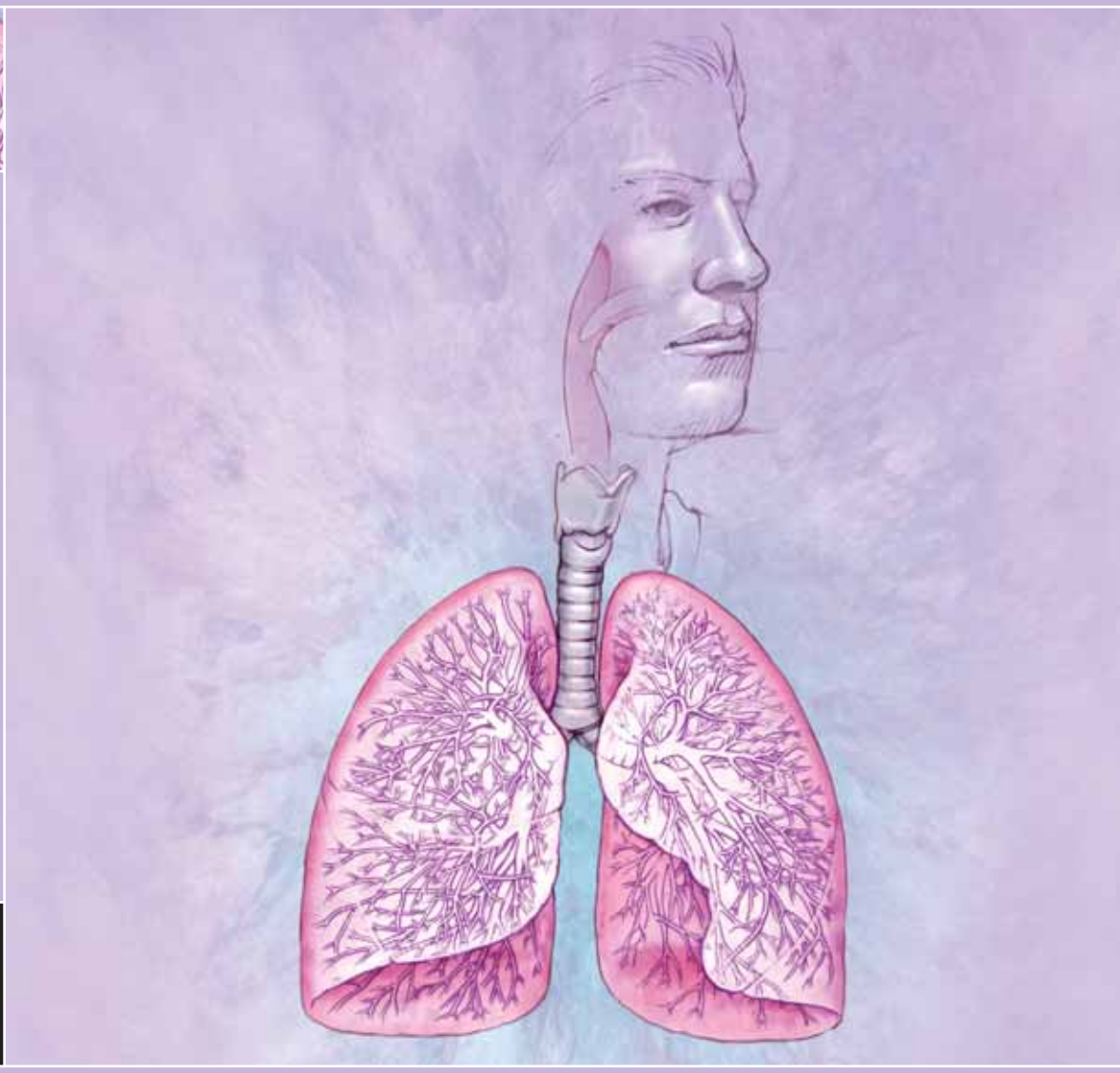
PULMONARY DELIVERY

INNOVATIVE TECHNOLOGIES BREATHING NEW LIFE INTO INHALABLE THERAPEUTICS



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VECTURA

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ARADIGM

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PULMONARY & NASAL DRUG DELIVERY

"Pulmonary delivery: innovative technologies breathing new life into inhalable therapeutics"

This edition is one in a series of sponsored themed publications from ONdrugDelivery Ltd. Each issue will focus on a specific topic within the field of drug delivery, and contain up to eight articles contributed by industry experts.

Full contact information appears alongside each article. Contributing companies would be delighted to hear from interested readers directly. ONdrugDelivery would also be very pleased to pass on to authors, or answer as appropriate, any queries you might have in relation to this publication or others in the series.

Forthcoming editions cover: needle-free injection; prefilled syringes; nasal drug delivery; oral modified release; solubilising technologies; delivering injectables; novel biomaterials for drug delivery; safer injections and transdermal delivery, among other topics. To find out more about receiving or participating with any of these issues, please contact ONdrugDelivery Ltd.

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"*Pulmonary delivery: innovative technologies breathing new life into inhalable therapeutics*"
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INTRODUCTION

It is fortuitous that just after the US and European regulatory authorities both approved Nektar/Pfizer's inhalable insulin, Exubera – the first product for systemic pulmonary delivery – ONdrugDelivery is publishing this edition, covering pulmonary drug delivery (as well as another issue dedicated to drug delivery in diabetes).

There are of course numerous inhaled products already on the market, and in development, for respiratory diseases such as asthma and COPD. More recently, inhalable formulations for treating conditions not strictly of the lung, but nonetheless affecting the lung, such as lung infections and lung cancer, have been developed.

Yet the lung – accessible, with a rich blood supply and enormous surface area – in humans, larger than the area of a tennis court – has the characteristics of an excellent route into the body for pharmaceuticals.

Exubera's approval is as much an important landmark in the drug delivery industry as it is in the treatment of diabetes. A new delivery route has opened up, not only for the other companies developing pulmonary insulin formulations, but also for the many companies aiming to deliver other drugs to the systemic circulation via the lung.

Among the companies that contribute articles to this issue, MannKind Corporation, Aradigm Corporation, Direct-Haler and Vectura are involved in systemic pulmonary drug delivery. But putting systemic pulmonary delivery to one side for a moment, it is worth mentioning at this point that most of the companies that appear on the following pages also maintain a strong presence in the respiratory field. It is important not to lose sight of the substantial opportunities that pulmonary drug delivery continues to present to the respiratory market.

Notably, while pharmaceutical companies continue the problematic task of seeking new active compounds and even new pharmacological targets, the most recent significant respiratory blockbusters have been combinations of existing compounds in novel delivery systems. The two notable examples are GlaxoSmithKline's salmeterol/fluticasone delivered via the Diskus inhaler, and AstraZeneca's budesonide/formoterol, delivered via the Turbohaler.

Dr Troels Keldmann, Managing Director of Direct-Haler said in 2004: "In addition to being an efficient means of delivering an active compound to the target organ (a pharmacological consideration), an inhaler must be acceptable to all of its stakeholders – patients (both adult and paediatric), GPs, instruction nurses, pulmonologists, consulting physicians and even the pharma representatives whose job it is to sell the device."

As the article from Team Consulting (page 4) demonstrates so plainly, the implementation of device innovations and modifications as part of a product lifecycle management in the respiratory market (among others), can bring significant advantages more quickly, less riskily and less expensively, in relation to new molecule discovery and development.

... THE NEW ERA

Entering the age of systemic pulmonary delivery, as we have done recently, catapults the potential market size for inhalation technologies to an entirely new level – spanning almost all therapeutic classes.

Each company involved in systemic pulmonary delivery has its own strengths. For example, Aradigm has three inhaler systems that serve the pulmonary delivery market at several levels, ranging from the "high-end" electronic AERx device, to the less technically complicated mechanical AERx *Essence* and the newly acquired *Seville* inhaler. Vectura's expertise, to give another example, extends deep into both inhaler device design and inhalable formulation development, allowing the company to develop a device and corresponding formulation concurrently. MannKind's Technosphere formulation system enables products such insulin and other hormones to closely mimic natural release profiles. Finally, Direct-Haler's DirectHaler Pulmonary DPI, made with only 0.6g of polypropylene and only two or three components, can be manufactured at minimal expense while, in terms of its delivery efficiency, still competing with more complex inhalers.

One common attribute of systemic pulmonary technologies is their ability to deliver consistent doses with suitable particle-size and low particle-size variability, to the deep lung. This is the entry-level requirement for systemic pulmonary delivery. Details of how these companies' technologies achieve this and, perhaps more importantly, what they offer both the systemic and local pulmonary drug delivery markets, over and above the mere entry-level, can be found in the articles that follow.

Guy Furness, Managing Director, ONdrugDelivery Ltd

DEVICES AND PACKAGING IN LIFECYCLE MANAGEMENT:

HOW PHARMA CAN REAP THE BENEFITS AND WHY NOW IS THE RIGHT TIME

Lifecycle management in pharmaceuticals, compared with the critical role it has in other industries, has always been rather restricted and, until recently, viewed as less of a priority. In this article, Mark Clements, a freelance writer working on behalf of Team Consulting, Iain Simpson, PhD, and Julian Dixon, both Senior Consultants at Team Consulting, explain how a different take on product lifecycle management has the potential to give pharmaceutical and biotechnology companies the freedom to implement strategies that generate real value and are as agile as those commonly practised in other markets.

A quiet revolution has taken place in the mainstream British press over the last year or so, but the ideas behind it were not new. Perhaps in response to the ever-growing dominance of the internet, the once familiar broadsheet presentation of newspapers has now all but disappeared, having been replaced with smaller versions. The content, however, remains the same and the editors of these publications report that readership and, crucially, sales have increased.

A number of important lessons can be learned from the move to the smaller tabloid or Berliner formats, but perhaps the most important is that this change, and the consequent increase in sales, could have been achieved before. What has been critical over the last 12 months is that someone actually took the decision to change something that had remained unchallenged for years.

These redesigns have resulted in advantages for both publishers and readers. The papers are less difficult to handle and carry, making reading easier and more enjoyable. Display and distribution, due to the smaller size, have also become easier, and new press technology has made production cheaper. All these advantages, yet the core element – the news itself – remains the same.

This revolution is perhaps a classic example of successful lifecycle management (LCM) bringing a number of benefits without changing a product's core element.

LCM is commonly applied to the consumer goods and food industries, with user groups regularly consulted on what might be a preferred presentation or variety of a product. In these industries, not only is lifecycle management a method for boosting the return on investment in a given product line or brand, but it is an absolutely essential part of the core business model and thus an inherent part of the commercialisation strategy from the outset.

But can the same really be said for LCM in the pharmaceutical and biotechnology industries? LCM does happen in these industries and its aim – to generate the maximum value from the pipeline while avoiding the huge investment of time and cash that is required for new product (i.e. NME) development – is similar to that of LCM in other industries.

However, in practice the strategy plays a rather restricted role in the pharma and biotech sectors. Although the intention is to overcome the heavily regulated, slow-moving, risky, costly nature of the drug development business, current pharma LCM is nonetheless still limited by these factors. Furthermore, it appears to have been difficult for the industry to find a way around the problem.

It is not through lack of trying, though. More often than not, pharma/biotech LCM concentrates on extending indications which, while quite effective, still requires costly, lengthy clinical trials.

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Many other LCM tactics are employed. Among them are prescription-only to over-the-counter (Rx-to-OTC) switching (the Tufts Center for the Study of Drug Development predicts an increase in this activity in the US in its recently published *Outlook 2006*), development of combination products, in-licensing new products, and the use of legal strategies to fend off generic competition.

Drug delivery does of course also feature as a crucial tool in many pharmaceutical companies' product lifecycle management strategies, and it has had significant success. However, usually such initiatives involve the development of novel formulations, for example to produce modified-release versions with a more suitable dosing regimen. New product approvals are still required (often an NDA or at least an ANDA must be filed in the US, for example).

... TIME TO EMBRACE A NEW WAY OF THINKING ABOUT LCM

Today, at last, something is changing in the pharma industry. In the same way as the British newspaper publishing industry has, as described above, recently taken advantage of an opportunity that it has been aware of for some time, pharmaceutical companies are beginning to consider new types of LCM strategies. Unlike those that have gone before, these strategies will allow them to implement LCM in the manner in which they have so dearly wanted to for so long, but have felt unable to because of the nature of the pharma business. Fast-moving, agile, inexpensive, low-risk, value-generating LCM projects are now a real prospect.

Drug delivery devices employed in LCM offer pharmaceutical and biotechnology companies myriad opportunities at a fraction of the cost. The expertise to exploit this route may not reside within pharma companies themselves, but it does exist. All that pharma companies need to do fully to exploit the device LCM benefits available to their portfolios, is realise that they, like the publishers of the British broadsheets, have the freedom to change, and to find the right partner to help them to do so.

Well-thought-out device-based LCM strategies can offer an intellectual property holder a number of advantages.

The Handihaler (Boehringer Ingelheim) provides a good example of device LCM. The old Inhalator device had a blocky and unattractive design and no mouthpiece cover, while the newer Handihaler offers users a more pleasing shape both to use and to see, as well as protection to the mouthpiece (see figure 1).

While recognising the success of the redesign, Team believes that further improvements could be made. The drug delivered by the

Figure 1: Before and after – Inhalator and Handihaler

Handihaler is Pfizer's Spiriva, which is used to treat chronic obstructive pulmonary disease (COPD). The COPD population is generally more elderly, and conversations with respiratory nurses have revealed that the lack of grips on the device can cause problems for some users. There is also the possibility that the user will not lock the mouthpiece down properly after inserting the capsule, or that that they will inadvertently block the air intake vents.

However, in general, opportunities for error are low, and the device provides a key component in user reassurance, which is that it gives feedback – one can hear the capsule moving during inhalation and afterwards one can see that it is empty. For patients, knowing that they have successfully taken their dose is an important factor for inhaled drugs, and capsule inhalers meet this need well.

Other examples of device-based LCM can be found by examining the traditional needle-and-syringe, for which it is easy to identify reasons for product resistance and the potential benefits of change.

Many patients requiring injected medications are nervous about using hypodermic needles, making home injection difficult. To overcome this, a patient may have to visit a healthcare provider, resulting in time and financial cost for both the patient and provider. Auto-injectors and pen injectors, however, overcome this problem, allowing the patient to self-inject in the comfort of their own surroundings. The injected substance remains the same, but the new delivery device makes the product more attractive and economical. In this case, there is also a safety element, as many self-injection devices incorporate protection against needle stick injury.

Greater understanding of a product's possible uses may also act as a driver for LCM and allow those uses to be better exploited. For example, if follow-up studies have shown that a drug is particularly effective in, for example, older patients or children, its appeal and take up will rise if presented in a way that those patient groups can easily identify with and fully use.

At a very basic level, bright colours might appeal to children, while more subdued colours might appeal to seniors. However, both of these groups might be unable to cope with a device that is overly delicate and complicated – think of how dexterity diminishes with the onset of arthritis, for example.

Redesigning a drug's delivery device or primary packaging to make it more accessible may help to capture a patient group that otherwise may not be able to completely benefit from it, and will give a product the edge over competitors.

It is important to highlight that human-factors work can be an incredibly important tool when re-examining product design, especially for self-medication. Team has developed considerable skill in carrying out such analyses.

To find out what people like, you can simply ask them. However, that is just the beginning. The real value from examining human factors comes from working out what makes a device intuitive and easy to use – and, even more importantly, almost impossible to misuse.

Powerful data can be gathered from going out to users with early-stage models and observing them interacting. Watching them, not interviewing them, is key. Backed up with rigorous task and risk analysis, the result can be a new product, which you are confident will be accepted, used correctly and perhaps even actively enjoyed – a significant benefit which could make a difference to the prescribing decision.

Clearly, it is important to remain grounded and, while being sure to realise the full potential, constantly to keep in mind that there are limits to what is possible through product improvements such as these. For example, if

TEAM WORKED WITH JOHNSON WAX PROFESSIONAL TO DEVELOP A NEW DELIVERY METHOD FOR ITS CLEANING CHEMICALS.

Johnson Wax Professional (now JohnsonDiversey) provides industrial cleaning chemicals that are diluted at point of use – thus greatly reducing transport and packaging costs. This dilution had previously been achieved through two means: either the installation of a wall-mounted dilution station from which concentrated liquid was mixed with water from the mains; or a dispenser that could be attached to the bottle and attached to the mains via a hose.

Both approaches presented drawbacks. The wall-mounted equipment was costly to install and maintain, whilst the dispenser had a relatively high cost per unit, offered no flexibility of dilution levels and required the re-attaching of the dispenser to each successive unit. All of these factors represented a barrier to market growth.

To overcome these difficulties, Team worked with Johnson Wax to identify new market opportunities and, as a result, to develop the J-Flex. The J-Flex is a low-cost, maintenance-free disposable dispensing head and bottle system. Its design has led to a 20-fold reduction in manufacturing cost compared with the existing hose/dispenser technology, as well as additional functionality, which greatly reduced barriers to adoption and opened up new market opportunities. The system's simple, intuitive design requires minimal training, which has greatly encouraged its adoption.

The J-Flex's precise mechanism is made from low-cost, mass-produced materials and manufacturing techniques, and it has created a new market segment. US and European sales have far exceeded expectations. In 2004, the J-Flex won a Starpack award for technical innovation, and a Worldstar for packaging in 2005.

one active substance is vastly more effective than another, then it will be prescribed almost no matter what the delivery device. But if the drugs are more comparable in performance, then improvements to the device and primary packaging can make the real difference; perhaps between settling for a minimal market share and taking prime position of market leader.

Team has developed its own methods for carrying out human-factors studies. Although unique to Team, they comply with the relevant US FDA guidelines ("Medical device use-safety: incorporating human-factors engineering into risk management", US FDA, July 18, 2000).

... WHAT'S REALLY NEW THOUGH?

The ideas outlined very briefly by the examples above, for developing novel delivery devices and primary packaging, and improving previous systems, will not come as a shock for readers.

However, what is novel and perhaps slightly foreign to pharma, is the concept of incorporating these types of approaches as tools for product LCM as a routine and core activity within the overall commercialisation programme for a pharmaceutical product line. And this is the subtle, yet immensely important point – the door is already open, pharmaceutical companies just need to walk through it.

A question that arises is why, if these approaches have actually existed for a while, is now the right time to begin employing them as LCM strategies? The answer is that a convergence of factors, outside and inside the pharmaceutical industry, makes the timing for LCM strategies such as these perfect.

Firstly, the pharmaceutical industry has become more pressured than ever by development costs and timelines. As reported in *Nature Reviews Drug Discovery* (January 2006, Vol 5, p 7), NME approvals by the US FDA dropped from 31 in 2004 to just 14 in 2005. Drug discovery is not as productive as it used to be, leaving gaps in pipelines that grow ever larger as existing products lose patent protection (according to *Nature Reviews Drug Discovery*, three blockbusters went off patent in 2005, but six will lose their patent protection this year). These trends strongly drive the need for new approaches that will generate additional value from the pipeline.

Secondly, healthcare is becoming more consumer-oriented at a rapidly accelerating rate. Patients, previously at arm's length from decision making processes for their healthcare, and especially purchasing decisions, are now evermore informed and involved. Their opinions now matter and the quality of their treatment experience matters too.

Thirdly, patients are, generally speaking, increasingly sophisticated when it comes to their healthcare, including medication. They are more commonly treating themselves at home, for example. So factors such as the convenience and aesthetic appeal of a medicine, which used to be viewed as albeit serious but certainly not critical factors, are now being given careful attention.

Where better to start looking for aspects of a pharmaceutical product that can be improved to address the factors above than the drug delivery device and primary packaging?

... LESSONS FROM OUTSIDE THE DRUG BUSINESS

For an insight into thinking about how LCM (of the sort practised by other industries) might now benefit pharmaceutical companies, let's consider some non-pharmaceutical, yet relevant examples.

A major shampoo manufacturer found that its products, when supplied in bottles, were too expensive to achieve significant market penetration in India. However, when supplied in smaller sachets – of the type found in hotel rooms – it fell within the reach of more of the population. This re-presentation brought the product within the financial reach of a population that otherwise would have bought an alternative. There are countless examples of populations that are in need of drugs that, in their current presentations, are priced out of the market.

There are numerous opportunities for manufacturers to increase their markets if they choose to look at the possibilities available to them. What is important is to be able to tap into the technology that is available and see how it can be adapted and applied.

The clockwork wireless radio developed by Trevor Baylis has allowed greater ownership of radios in Africa and removed the need for expensive batteries. Clockwork mechanisms had been long ignored but, in this case, their modified re-use has allowed greater radio ownership in poor countries, benefiting everyone except perhaps battery manufacturers! Spurred on by this success, a number of companies are now looking at whether clockwork technology can be applied to computers.

The pharmaceutical and biotech industries can learn from these examples. Re-examining a drug delivery method with a view to improving the device, put simply, can bring down the cost of manufacture, the cost of administration, improve safety, open up new markets, or make products more acceptable. As importantly, the LCM process is economical to perform when it is only the device or primary packaging, or perhaps just carefully chosen aspects of these, which are being modified.

A third example of successful LCM from outside the pharmaceutical industry is the novel delivery system for industrial cleaning chemicals, developed by Team Consulting together with JohnsonDiversey. The J-Flex device, details of which are given in the boxed text on page 6, is of particular interest here as there are several parallels with how drug delivery devices can be used in LCM. Most notably, the project team radically improved the function and revitalised sales of an established product by modification of the delivery device only, and without any changes to the active ingredient.

Team Consulting is a product development consultancy, primarily focused on the pharmaceutical and healthcare markets. The company has established a strong reputation for medical device development, particularly in pulmonary, nasal and parenteral delivery systems. Clients range from start-up ventures to some of the world's leading pharma and contract research organisations including Sanofi-Aventis, Pfizer, Valois and Novartis.

A partner such as Team has a proven track record in drug delivery device development and, crucially, first-hand experience of LCM projects in other industries. It is well placed to bring about the change in pharmaceutical product LCM. Team has a data bank of available technologies. The change might be as simple as a packaging redesign. It could be the design and incorporation of a new component – such as a lock-out system or dose counter into an existing device – or the development of an entirely new delivery device.

Team is able carefully to identify which delivery system best suits a client's needs and then confirm this through appropriate assessments, including performance testing and user studies. Careful identification and selection of how a drug is best delivered can be key in delivering not only increased margins, but whole new revenue streams.

The door is already open, pharmaceutical companies just need to walk through it.

Most of the projects that Team Consulting conducts for pharmaceutical and biotechnology clients are carried out under strict confidentiality, making it difficult to provide detailed examples. Team is therefore keen to talk directly with readers wishing to find out more about Team's specialist pharma and biotech product design and development capabilities. Full contact details can be found on page 4.

MannKind Corporation

TECHNOSPHERE® TECHNOLOGY:

A PLATFORM FOR INHALED PROTEIN THERAPEUTICS

MannKind Corporation is developing a novel pulmonary delivery platform, Technosphere® technology. In this article, Andrea Leone-Bay, PhD, Senior Director, Chemistry and Formulations, and Marshall Grant, PhD, Director, Formulations Development, both of MannKind Corporation, describe the technology and detail its many unique characteristics that have the potential to achieve improved efficacy, higher bioavailability, and improved patient compliance.

Patients who consistently comply with their therapeutic regimens have better outcomes. In fact, patient compliance is so critical that medical and pharmaceutical communities are constantly seeking methods to simplify and optimise treatment regimens. Thus, the development of non-invasive routes for the delivery of drugs commonly administered by injection is the focus of considerable effort in the pharmaceutical industry. Numerous technologies designed to achieve this elusive objective are currently in development.

Inhalation, for example, is an efficient route for drug administration, both for targeted pulmonary therapy and for the systemic administration of macromolecular drugs (peptides and proteins). The lungs provide a large, efficient surface area for drug absorption and the non-invasive nature of pulmonary delivery has the potential to improve patient quality of life greatly. Advanced, dry-powder delivery technologies are highly efficient systems for pulmonary drug delivery. When combined with an optimised device, a fine powder can be inhaled easily with reproducible results.

TECHNOSPHERE® PARTICLES

MannKind's Technosphere® technology represents a versatile drug delivery platform that allows the pulmonary administration of therapeutics currently requiring administration by injection.

TO ENVISION THE ARCHITECTURE OF A TECHNOSPHERE® PARTICLE, IMAGINE A THREE-DIMENSIONAL SPHERE CONSTRUCTED FROM A DECK OF CARDS

The technology is based on the intermolecular self-assembly of a diketopiperazine molecule called fumaryl diketopiperazine (FDKP). The chemical structure of FDKP is shown in figure 1. FDKP is a white solid with a molecular weight of 452 Daltons that is highly soluble in water at neutral-basic pH. The pH-dependent aqueous solubility of FDKP is a consequence of the molecule's two terminal carboxylic acid groups (COOH).

During particle formation, FDKP crystallises in microcrystalline plates. Molecular modelling of the crystal structure predicts a plate-like morphology in which the carboxylic acids are

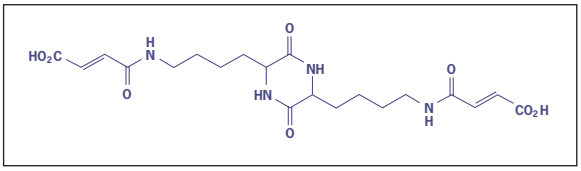

Figure 1: Chemical structure of FDKP, the raw material used to prepare Technosphere® particles

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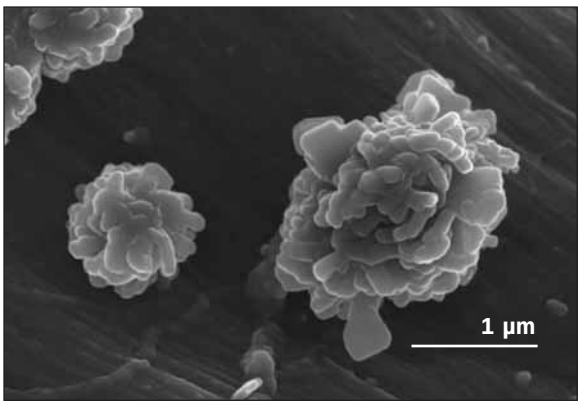

Figure 2: Scanning electron micrograph of Technosphere® particle

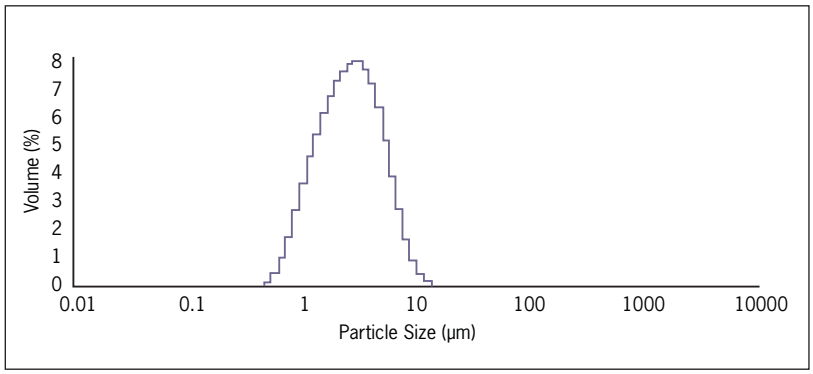

Figure 3: Particle size distribution of Technosphere®/Insulin particles measured by laser diffraction. 90% of the particles are below 5.7 µm in diameter; 50% of the particles are below 2.6 µm in diameter, 10% of the particles are below 1.1 µm in diameter.

exposed on some crystal surfaces. These crystalline plates associate into microspheres called Technosphere® particles.

Scanning electron microscopy studies of Technosphere® particles confirm that they are composed of an assembly of FDKP microcrystalline plates (figure 2). The particles have high surface area and high internal porosity (60-80%). To envision the architecture of a Technosphere® particle, imagine a three-dimensional sphere constructed from a deck of cards. Each card represents an FDKP microcrystal and the sphere constructed from the cards represents a Technosphere® particle. The back and front faces of the cards provide the sphere with a large surface area and the spaces between the cards provide the sphere with a high internal porosity.

EVEN RAPID-ACTING INSULIN ANALOGS ARE ABSORBED MORE SLOWLY THAN INSULIN ADMINISTERED AS TECHNOSPHERE®/INSULIN

TECHNOSPHERE®/INSULIN

Technosphere®/Insulin is a novel inhaled insulin that has the potential to satisfy mealtime insulin requirements for patients with diabetes. Technosphere®/Insulin particles are prepared from Technosphere® particles by precipitating insulin from solution onto preformed particles.

Under the precipitation conditions, the insulin molecules are slightly positively charged and the FDKP molecules comprising the Technosphere® particles give the surface a slight negative charge. This charge difference and the high surface area of Technosphere® particles combine to promote insulin adsorption to form Technosphere®/Insulin powder. Also, it is the insulin monomer that is deposited onto the particles. The Technosphere®/Insulin particles have a uniform size distribution as measured by laser diffraction (figure 3). More than 90% of the particles are in the respirable range defined as >0.5 μm and <5.8 μm; and the average particle diameter is 2.5 μm. Technosphere®/Insulin particle morphology essentially mirrors that of Technosphere® particles.

Technosphere®/Insulin particles are optimised for inhalation into the deep lung. They are inhaled using the MedTone™ inhaler, a passive, high-resistance, low-flow, dry-powder delivery device (shown in figure 4a).

Technosphere®/Insulin powder in 2.5-10 mg quantities is filled into single use cartridges that are inserted into the MedTone™ inhaler. The powder is discharged into the oral cavity simply by inhaling through the device mouthpiece. The inhaler does not require manual activation. Since it is activated by patient inhalation, it is not necessary to co-ordinate the timing of device activation and patient inhalation. Additionally, the MedTone™ inhaler is a small, compact device that is inconspicuous, easy to carry and use (see figure 4b).

Once inhaled, Technosphere®/Insulin powder disperses evenly throughout the deep lung. This uniform distribution is readily observed following the inhalation of radio-labelled Technosphere®/Insulin particles. Technetium-labelled Technosphere®/Insulin was inhaled by healthy volunteers and the subjects were imaged using gamma scintigraphy (figure 5).

RAPID PHARMACOKINETICS OF TECHNOSPHERE®/INSULIN

Inhaled Technosphere®/Insulin particles dissolve rapidly at the surface of the lung. This rapid dissolution is due to the combination of FDKP solubility in the interstitial fluid of the lung and the high surface area of the Technosphere® particles. FDKP is highly soluble at the near-neutral physiological pH of the lung.

Based on current data, it is likely that once the particles have dissolved, the insulin is rapidly absorbed because it is present as monomer. The monomeric state of insulin in Technosphere®/Insulin has been confirmed by analytical ultracentrifugation (AUC). This

Figure 4a: MedTone™ inhaler with single-use cartridge containing Technosphere®/Insulin powder

Figure 4b: MedTone™ inhaler in use

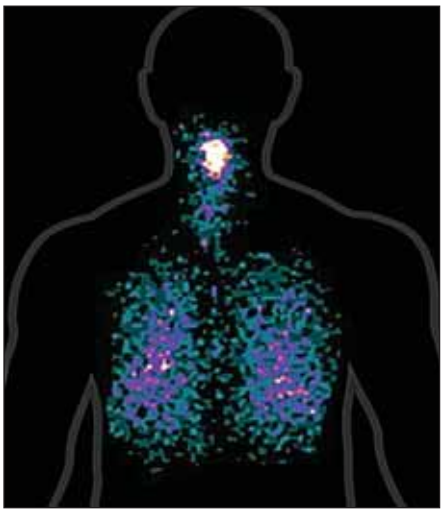

Figure 5: Representative lung image of clinical subject following inhalation of technetium-labeled Technosphere®/ Insulin particles. The particles are evenly distributed throughout both lungs. Powder can also be seen in the mouth and trachea.

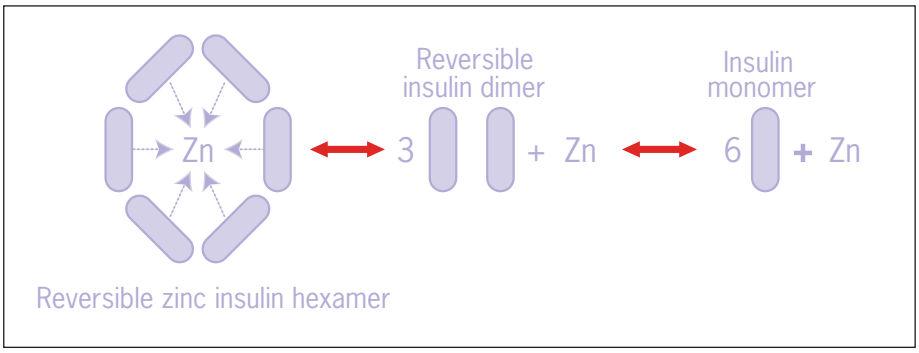

Figure 6: Schematic representation of hexameric zinc insulin dissociation into readily absorbable monomers.

biomolecular research technique is widely used to determine both the molecular weights and molecular interactions of proteins.[1]

In AUC studies, insulin dimers and monomers are the primary species observed both in insulin solutions used to prepare Technosphere®/Insulin and in the insulin released upon dissolution of Technosphere®/Insulin particles.

Diffusion rate decreases with molecular weight, so oligomers of insulin diffuse more slowly than monomer. In most pharmaceutical dosage forms, regular human insulin exists as a reversible zinc hexamer that must dissociate into dimers and monomers (figure 6) following administration.[2]

The rate of this dissociation is one of the parameters that control the rate of insulin absorption after dosing. While insulin hexamers do not provide the most rapid absorption, they tend to be more stable than dimers and monomers. However, the dry-powder Technosphere®/Insulin formulation tends to stabilise monomeric insulin, providing a delivery advantage without compromising stability.

Following inhalation of Technosphere®/ Insulin, systemic insulin concentrations are seen almost immediately. The shape of the insulin pharmacokinetic curve (figure 7) closely resembles that observed following insulin infusion (figure 8). Compared with injection of subcutaneous (sc) regular human insulin, Technosphere®/Insulin provides a more rapid delivery of insulin to patients with diabetes with timing that closely mimics normal physiology.

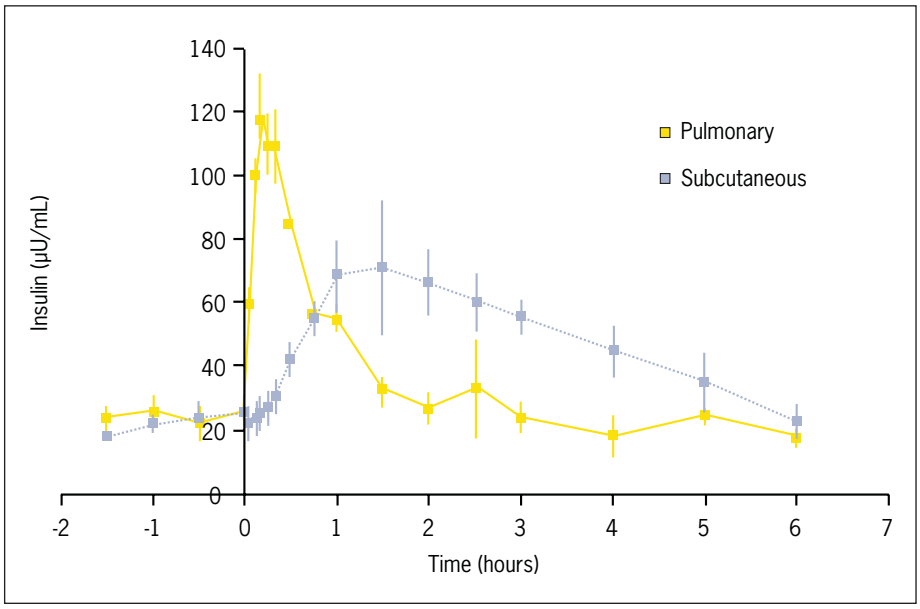

Figure 7: Pharmacokinetic profiles of regular human insulin inhaled as Technosphere®/Insulin or injected subcutaneously. The orange line represents circulating insulin concentrations following Technosphere®/Insulin inhalation and the purple line represents circulating insulin concentrations following subcutaneous injection of insulin. This study was conducted in healthy volunteers.

These data support previous observations that insulin that dissociates rapidly into monomers and dimers is absorbed faster than slowly dissociating insulin.[3] Indeed, this concept represents the foundation for the design of rapid acting insulin analogs such as Novo Nordisk's Insulin Aspart® and Lilly's insulin Lispro®. Upon injection, both of these rapid-acting insulin analogs become monomeric at a faster rate than regular human insulin. The result is a more rapid absorption. However, even these rapid-acting insulin analogs are absorbed more slowly than insulin administered as Technosphere®/Insulin.

OTHER TECHNOSPHERE® PROTEIN FORMULATIONS

In addition to insulin, the Technosphere® technology platform has also been used to deliver salmon calcitonin (sCT) and parathyroid hormone (PTH) by inhalation in healthy volunteers. Both of these peptide drugs are approved for the treatment of osteoporosis, a disease that affects an estimated 10 million Americans and remains a threat for 55% of people over the age of 50 years.

Most sCT products are injectables, but one nasal product, Miacalcin®, is also currently available. One sc PTH product, Forteo® is currently marketed. Clearly, the ability to administer these drugs by inhalation would enhance patient compliance and contribute to an improved quality of life. Additionally, the rapid-onset pharmacokinetic profile observed with Technosphere®/Insulin is expected to be ideal for the delivery of both sCT [4] and PTH [5] (see figure 9).

In a clinical pharmacokinetic study, Technosphere®/PTH powder was administered to 11 healthy volunteers using the MedTone™ inhaler. Each subject received three doses of Technosphere®/PTH (400,800, and 1600 IU) and an sc injection of PTH alone as a control.

Systemic PTH concentrations were measured over a period of five hours. Two of the three test groups (800 and 1600 IU PTH) demonstrated significant peak PTH plasma levels that were above those required to achieve clinical efficacy.[5]

The relative bioavailability of inhaled PTH compared with sc injection was 48%.

SUMMARY

The Technosphere® technology platform is a novel inhalation system for the non-invasive administration of peptide therapeutics that currently require injection. Formulations using this system, including Technosphere®/Insulin and Technosphere®/PTH, have the potential to offer patients freedom from injections and an enhanced quality of life.

A sharp peak in the pharmacokinetic profile that mimics endogenous plasma levels is certainly beneficial in the delivery of insulin, and is also likely to be beneficial in the delivery of other therapeutic proteins and hormones.

However, the application of Technosphere® technology is not limited to proteins and peptides. Initial research has indicated that formulations of small-molecule therapeutics for the treatment of pain and nausea, among other indications, could be effective in delivering rapid relief.

Furthermore, while the focus is pulmonary delivery, research has also demonstrated that proteins (including insulin) can be stabilised against degradation when formulated with Technosphere® particles. This property may prove invaluable in the development of fragile protein or vaccine therapeutics that would not otherwise be feasible.

Together, the assets associated with Technosphere® technology have the potential to provide impressive drug delivery solutions across a wide variety of therapeutic areas encompassing a number of diverse disease states.

REFERENCES

1. Cole JL and Hansen CJ, "Analytical ultra-centrifugation as a contemporary biomolecular research tool". J Biomol Tech, 1999, Vol 10, pp 163-176.

2. Brange J, Whittingham J, Edwards D, Zhang Y-S, Wollmer A, Brandenburg D, Dodson G, and Finch J., "Insulin structure and diabetes treatment". Curr Sci, 1997, Vol 72, pp 470-476.

3. Brange J and Volund A, "Insulin analogues with improved pharmacokinetic profiles". Adv Drug Delivery Rev, 1999, Vol 35, pp 307-335.

4. Azria M, "Treatment with calcitonin for osteoporosis". Ann Rheum Dis, 1996, Vol 55, pp 700-714.

5. Frolik CA, Black EC, Cain RL, Satterwhite JH, Brown-Augsburger PL, Sato M, and Hock JM "Anabolic and catabolic bone effects of human parathyroid hormone (1-34) are predicted by duration of hormone exposure". Bone, 2003, Vol 33, pp 372-379.

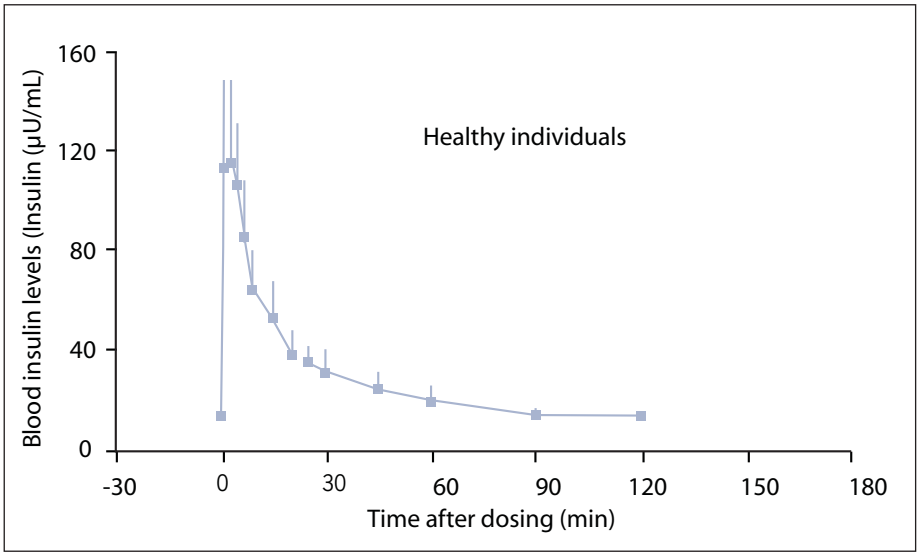

Figure 8: Insulin release in healthy individuals following artificial stimulation by a bolus infusion of glucose

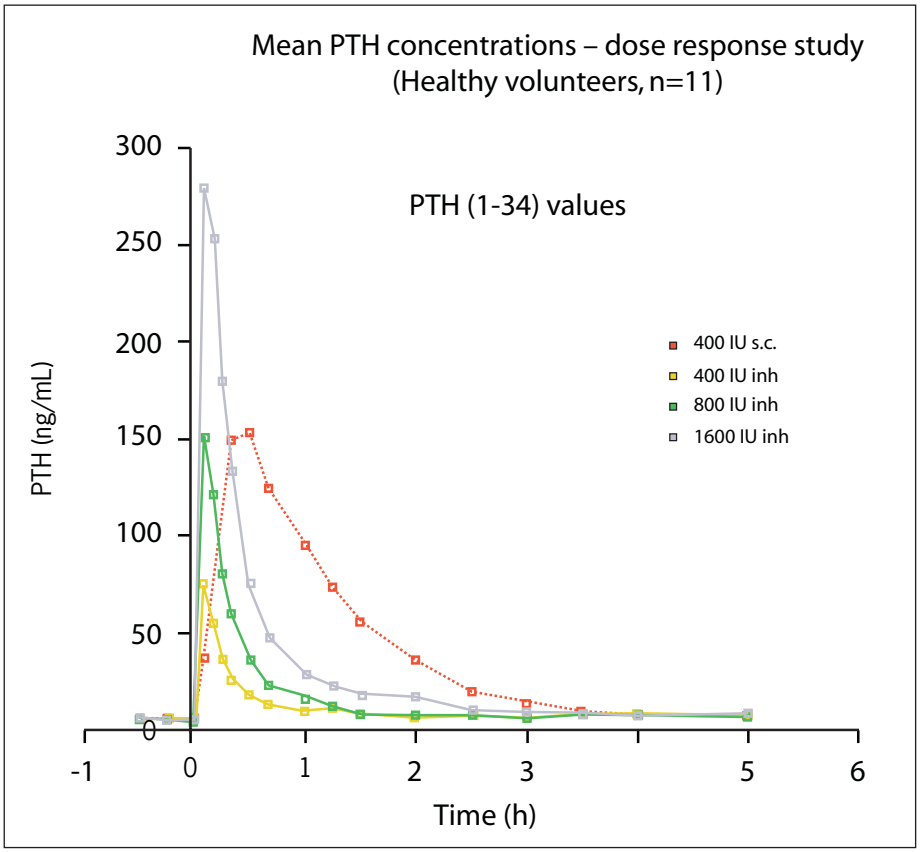

Figure 9: Plasma PTH concentrations following inhalation of Technosphere®/PTH or subcutaneous administration of PTH alone. The solid blue line represents the response following inhalation of 1600 IU Technosphere®/PTH. The solid green line represents the response following inhalation of 800 IU Technosphere®/PTH. The solid yellow line represents the response following inhalation of 400 IU Technosphere®/PTH. The dotted red line represents the response following subcutaneous injection of 400 IU PTH alone.

SYSTEMIC PULMONARY DELIVERY:

SUCCESS THROUGH INTEGRATED FORMULATION AND DEVICE DEVELOPMENT

The many advantages of delivering to the systemic circulation via the lung are all too often kept out of reach by technical obstacles. In this article, Professor John Staniforth, Chief Scientific Officer, and Dr David Morton, Head of IP and Technology, both of Vectura Group plc, explain how success can been achieved through combining, from the earliest opportunity, the development of the dry-powder formulation technology with that of the delivery device.

INTRODUCTION

Inhalation represents an attractive, rapid and patient-friendly route for the delivery of systemically acting drugs, as well as for drugs that are designed to act locally on the lungs themselves. This concept is especially exciting now that the concept of an inhaled systemic macromolecule, in the form of Exubera insulin, has been approved in Europe and the US.

Vectura has specialised in developing innovative formulation and device technologies for delivering drugs to the lungs in a predictable and reproducible manner. In particular, Vectura has pioneered the development of small-molecule drugs for systemic delivery, creating the concept ROSAT: rapid onset systemic aerosol therapies.

One of the key factors for success in this area is the ability to control the combined powder and device properties. This is essential for the development of dry-powder inhaler (DPI) products, yet remains a major technical hurdle to those wishing to succeed with this route and exploit the product opportunities arising from the numerous market drivers:

- Rapid onset of action
- Improving patient acceptance and compliance for a non-invasive systemic route
- Reduction of side effects
- Differentiation of new product and competitive brand opportunities
- Expedition of regulatory approval through improved consistency of delivery and product stability
- Product lifecycle enhancement
- New forms of inhaled therapeutics often requiring high doses and/or greater efficiency and accuracy
- Attractive device form with convenient and easy operation and delivery

This has been the motivation behind Vectura's combined study of particle science and device technology.

TECHNICAL CHALLENGES

Developing an efficient and effective portable inhalation system for medicinal use provides a greater challenge than most other drug delivery forms, requiring a complex integration of formulation and device technologies. In the case of DPI systems, the art and science required to produce high quality aerosols, repeatedly and reproducibly, arguably reach their zenith. Creating an aerosol cloud that is almost entirely composed of particles smaller than 5 μm (or even less for systemic use), using a conveniently small, simple-to-use and reliable device certainly represents a significant technical and commercial challenge.

DRY-POWDER INHALERS

Interest in DPIs as an effective, efficient and environmentally friendly way of delivering drugs to the lung has accelerated in recent years. A fundamental difficulty with developing solid-state aerosols, or DPIs, is managing both the ubiquitous and the transient forces contained in powder beds.

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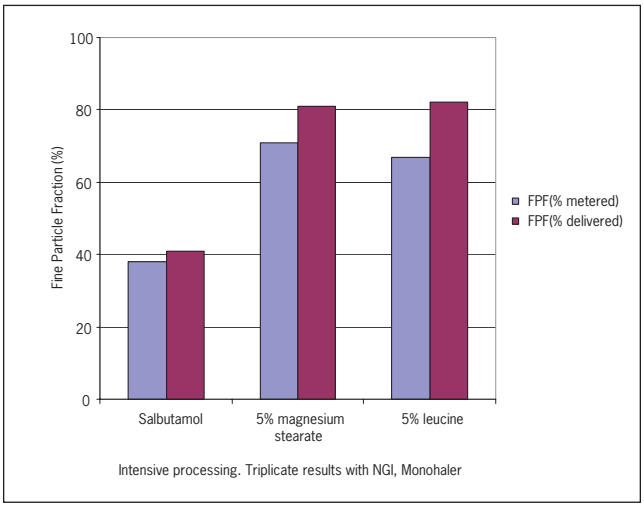

Figure 1: Effect of two Force Control Agents on salbutamol fine particle fractions

Indeed, managing such particulate forces, for example via particle engineering techniques, is now considered central to successful DPI formulation and production (Begat P, Morton D A V, Staniforth J N and Price R, "The cohesive-adhesive balances in dry-powder inhaler formulations II: influence on fine particle delivery characteristics", Pharm Res 2004, Vol 21, No 10, pp 1826-1833). In consequence, much attention is currently focused on producing "smart" formulations, where it may be possible to achieve excellent powder flow and low cohesive forces. However, having an efficient and robust formulation technology in the laboratory is only a start on the road to producing a successful DPI product.

Pharmaceutical scientists all too frequently meet major obstacles when they engage in the world of DPI product design – not least because of the further complications of this area resulting from the plethora of DPI device designs. There is tremendous variation in the methods used to store and meter powders and to generate the aerosol cloud (Ashhurst I, Malton A, Prime D and Sumby B, "Latest advances in the development of dry-powder inhalers", PSTT 2000, Vol 3, No 7, pp 246-256). In the case of DPI aerosol generation, there is a great deal of variation between different types of device, in the fluid dynamic and electrostatic environment that the powder formulation experiences.

Too often, it has been claimed that innovators in the field of DPI device or formulation design have produced a new system that will suit all. Our experience shows that there is no such thing as either a device or formulation that can be regarded in isolation as the solution to all DPI aerosol development requirements. Only when DPI device design and formulation design are harnessed as a joint endeavour, can the solid state aerosol product developer really move towards a truly efficient and effective system that is going to progress from the laboratory to manufacturing and on into the hands of the patient in a timely and economical manner.

IN SUMMARY:

1. There can be no assumption that a powder that worked well in one device or in one specific test will always perform similarly in another device or environment.
2. Development of any new DPI formulation should be conducted in parallel with the identified device as early in the development stage as possible.

POWDERHALE FORMULATION TECHNOLOGY

The PowderHale formulation concept arose from the philosophy of producing particles where the inherent chemical and physical variability of exposed powder surfaces was minimised by providing a well-engineered nano-coating of a single additive. This additive, termed a force control agent (FCA), should mask the underlying surface properties of each new drug compound, and instead provide a stable uniform surface of known properties.

A number of lung-friendly compounds have shown themselves to be ideal for this role. Further, Vectura has developed proprietary intensive co-processing methods, which are simple, practical and uniquely effective. As a net result, we have demonstrated significantly improved aerosolisation performance.

An example is provided in figure 1, which illustrates a model system where salbutamol is transformed from a cohesive pure powder, by co-processing with low levels of FCA (magnesium stearate in one instance, and leucine in the other) into an easily dispersible powder, as measured by firing from a conventional inhaler.

A strong formulation technology is only the start on the road to a successful DPI product. While it may be possible to achieve excellent powder flow and dispersibility, significant problems can still be encountered when designing systems to match the selected inhaler device. This is a stumbling block for many product programmes, and Vectura recognises the importance of developing any new formulation in parallel with the identified device as early in the development stage as possible.

A powder which works well in one device may provide insurmountable problems in another. The outcome is often difficult to predict, due to the infinite complexity of interaction of a powder with the fluid dynamic and electrostatics characteristics of a device.

AN INTEGRATED APPROACH

Vectura is addressing such challenges from both directions. In addition to applying its significant knowledge and experience to solving the demands of formulation technology, from its deep knowledge and experience, it has developed its own device systems. These have been designed to address key issues such as stability, metering and dispersion as well as the inspiratory action of the patient.

VECTURA'S DPI DEVICES INCLUDE:

GyroHaler®, a contemporary blister-based multi-unit dose "passive" inhaler for delivery primarily of drugs for treatment of local respiratory conditions

Aspirair®, a high-performance, multi-use, breath-activated "active" device for the highly reproducible delivery of drugs via the lungs for systemic activity (see figure 2).

The requirements of each specific product are assessed as part of an integrated formulation-device approach where the interaction of the powder and delivery system is considered and adapted in light of Vectura's know-how of powder technology, device engineering, pharmaceutical product development and user demands.

DEVICE TECHNOLOGY:

• GyroHaler

The GyroHaler is a novel, cost-effective, multi unit-dose DPI device that has been designed to deliver formulations that act locally in the lung. The GyroHaler is designed to target the market occupied by the latest generation of multi-dose inhalers, such as GlaxoSmithKline's Diskus®, which are capable of storing and delivering up to 60 doses.

GyroHaler is compact and easy to use and with a small number of moulded parts in order to allow short device development times and competitive manufacturing costs. The device is intended to be disposable after one month and is designed to have aerosolisation characteristics competitive with existing marketed devices. In addition the GyroHaler device offers aluminium foil blistered drug protection from moisture, oxygen and light.

GyroHaler technology could be used to deliver a range of locally acting products in an efficient, cost-effective and patient-friendly manner. The GyroHaler concept was created with the key market drivers for these products in mind, not only to facilitate development of Vectura's own product pipeline, but also to license the technology to third parties for the development of other leading respiratory products. In this respect, Vectura's engineers and scientists have experience in working in close collaboration with partners further to adapt the device design and formulation attributes to meet the potential branding and performance requirements for specific products, while building on a common foundation of core technology, intellectual property and know-how.

• Aspirair

Aspirair is a high-delivery-efficiency, user-friendly "active" DPI, which delivers drugs via the lung to the systemic circulation in an efficient and effective manner. Typically purpose-formulated powders deliver around 70% or greater fine particle dose (% of MD) from Aspirair. Unusual among DPIs is Aspirair's capability of delivering high ultra-fine particle doses (UFPD <3μm) coupled with minimal deposition in the oropharynx.

Aspirair is an "active" DPI powered using mechanically pressurised air that acts as an energy source for powder de-aggregation using a miniature cyclone dispersion chamber. To Aspirair, the patient inserts a foil blister containing the dry-powder dose into the device, which pierces the blister. A charge of air is then compressed by the patient using a low torque, corkscrew-type manual pump. Finally the patient inhales through the mouthpiece, triggering release of the charge of air, which passes through the blister, entraining the powder. The dose then flows into a vortex nozzle where shear and turbulent forces disperse the powder and slow down the air stream, so that a 'soft' aerosol emerges from the mouthpiece that is matched with the patient's inspiratory manoeuvre.

These characteristics together with other attributes such as: precise dose-to-dose repeatability and low variability of delivered dose; high payload capability for small (and large) molecules; robust and cost-effective construction; convenient small size; simple operation; delivery independent of inspiratory flow rate with slow aerosol velocity; performance approaching full dispersion of the primary particles; and excellent dose stability (from foil blisters), all make Aspirair an attractive proposition for the delivery of small-molecule drugs for systemic delivery. The device is also highly appropriate of course in macromolecule delivery, and for lung diseases where a high degree of control is required.

POWDERHALE APOMORPHINE

A small-molecule drug, apomorphine hydrochloride, has been identified as capable of rapid systemic therapeutic action when delivered via the lungs. Vectura blended apomorphine with a PowderHale formulation system. In order to achieve optimum levels of consistent ultra fine particle delivery in the hands of the patient, a highly efficient, effective and user-friendly device/formulation combination is essential.

We have published elsewhere (Morton DAV, Staniforth JN, "The challenge of the new: device-formulation matching in dry powder inhaler systems", Pharm Manuf & Pkg Sourc 2005, Spring, pp 80-83) a description of Vectura's device and formulation technology and characteristics. The key point to highlight here is that the two technologies were developed interactively and iteratively by device design engineers and formulation technology development scientists working together as a team in a single organisation.

Inhaler performance was evaluated in a Next Generation Impactor (NGI) at a flow rate of 60 l/min. The *in vitro* dispersion characteristics of apomorphine formulations are shown in figure 3. The exquisite performance achieved by these formulations can be summarised by two key performance criteria: (a) more than 90% delivered dose (DD) and (b) throat deposition of less than 5%. Most of the particles emitted are collected in stages three and four of the NGI, giving a mode for the aerosol particle cloud of 1.7μm.

Figure 4 compares the primary particle distribution in both wet and dry dispersions with the delivered aerosol. The data suggests that Aspirair closely simulates the primary particle size distribution of the active as discrete particles in the delivered aerosol cloud.

The results in figure 4 illustrate how an integrated approach to DPI system design can combine formulation and "active" device technology to create a high-performance dry-powder aerosol delivery system. By creating an aerosol whose physical properties approach those of the individual primary particles, such a system can achieve the levels of accuracy, consistency and ultra-fine particle dose so desirable for systemic pulmonary delivery, and has led to reported very high efficiency product performances in excess of 90% FPF.

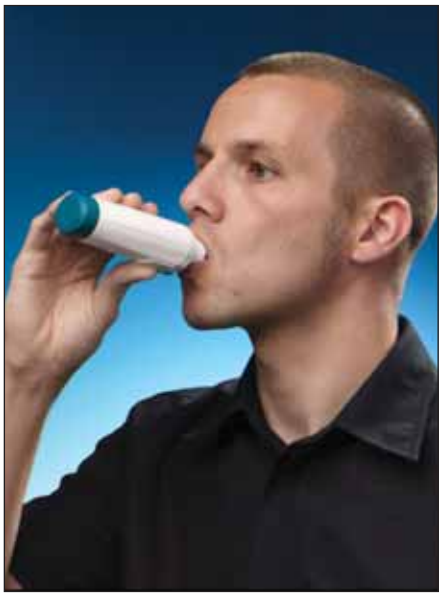

Figure 2: Vectura's Aspirair DPI device in use

ROSAT CLINICAL STUDIES

A summary of early clinical studies using apomorphine hydrochloride particles in a non-FCA PowderHale formulation delivered from the Aspirair device is given below. These studies involved 50 subjects exposed to apomorphine doses of 600-1200 μg.

In vitro performance characteristics of formulation for use in the clinical study include a delivered dose ≤ 5 μm in the range 70-75% as determined using Andersen Cascade Impactor (ACI) analysis. The clinical study formulation

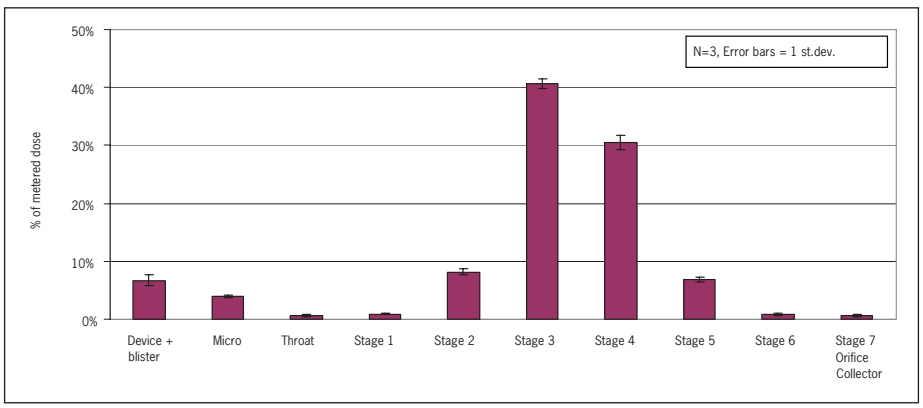

Figure 3: NGI performance of a DPI formulation containing 400µg apomorphine hydrochloride in a 2mg formulation, delivered from the Aspirair active DPI device.

	d50 (µm)	% < 5µm	% <3µm
Primary particle distribution:			
Wet dispersion Malvern	1.50	99%	94%
Dry dispersion Sympatec	1.73	99%	81%
	MMAD (µm)	***FPF <5µm**	****UFPF <3µm**
Aspirair aerosol (NGI at 601min^{-1})	1.66	94% of DD	89% of DD

** Fine Particle Fraction as percent of Delivered Dose (DD).*
*** Ultra-fine Particle Fraction as percent of Delivered Dose (DD).*

Figure 4: Comparison of aerosol characteristics, summarised by MMAD, and measures of fine (<5µm) and ultrafine (<3µm) particle generation

also showed low deposition on upper ACI stages. Taken together the *in vitro* data suggested an attractive combination of minimal oral deposition with potential for rapid systemic absorption

Safety and tolerability studies identified no serious adverse events. Onset of any reported adverse events occurred approximately ten minutes post-dose and such events were generally transient. No clinically relevant ECG changes and no clinically relevant FEV1 changes were reported.

The clinical PK of this inhaled apomorphine formulation can be summarised as follows:

- C_{max} 1-3 minutes post dosing
- Correlation between t_{max} and onset of clinical response
- C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ dose proportionality
- Rapid $t_{1/2}$ (60 minutes) and dose independent
- Essentially cleared from plasma after four hours

By comparison with the rapid onset times shown to be achievable using Ventura's high efficiency device/formulation technology for inhaled apomorphine, other erectile dysfunction (ED) treatment onset times appear very prolonged. Based on published data for different potential ED treatments, the inhaled form of apomorphine has the fastest median onset of action at approximately eight minutes. By comparison, sublingual apomorphine (Uprima) is more than twice as slow, with a median action onset time of approximately 18 minutes.

The other treatments, Levitra®, Cialis® and Viagra®, are all oral and have action onset times ranging from 25 to 60 minutes.

In a separate ROSAT product development, a different small molecule for an undisclosed indication has been formulated using PowderHale technology for delivery via the lung to the systemic circulation using Aspirair.

The first clinical data for this new product development shows that, as with apomorphine, very rapid drug absorption occurs that also shows linear dose dependency. Plasma concentration versus time profiles show IV-type kinetics with a linear dose relationship over the range 1-6 mg. Data from this clinical study show that mean tmax occurs less than two minutes post-inhalation.

These data reinforce our message that by achieving an optimum pulmonary dry-powder drug delivery system, one can offer the most rapid bioavailability for small molecules to the systemic circulation, as well as a more patient-friendly concept than the needle.

CONCLUSION

In conclusion, with market expansion in DPIs, our combined understanding of the key performance factors continues to grow, and improves with new expertise for engineering critical phenomena at the nano-scale.

With the PowderHale approach, Ventura has achieved high dispersion efficiency as well as improved delivery uniformity over large numbers of doses. This is achieved via simple, practical methods. However, each new system presents new challenges. Each and every aspect of formulation and device needs to be well aligned with patient demands and the market drivers to ensure product success.

This comprehensive approach is central to Ventura's product development philosophy. For example, by matching PowderHale formulations to the Ventura Aspirair inhaler we have consistently achieved dispersion efficiencies greater than 70% of the metered dose.

The family of Ventura technologies has been applied to a wide range of compounds, doses, formulations and device systems for DPI products. Ventura has worked together with its partners and clients to create practical formulation solutions that have been applied to marketed and development products.

Only by using the most complete and practical understanding of the relationship between powder formulations and DPI device, can a truly efficient and reproducible DPI product be developed that properly realises the rich potential of these inhalation systems.

There are many claims for DPI devices, old and new – "active" and "passive", that offer the prospect of better aerosols tomorrow. However, it may be as well to remember that a DPI device without a coupled formulation is like a poor inhalation - just a short intake of breath, without true inspiration!

Ventura is an emerging pharmaceutical company developing a range of inhaled drugs for the treatment of respiratory and non-respiratory diseases. In addition to its own pipeline of pharmaceutical products, Ventura also actively licenses out its inhalation device and formulation technologies for product applications for other pharmaceutical companies. It also operates a well-established contract pharmaceutical development service with many years experience of successful product development.

The rapid expansion and success of the company has resulted in an international reputation as a leader in the field of inhaled drug delivery. It has developed relationships with many companies looking for a partner with the technical solutions, project know-how or resources required to capitalise on the potential of this growing market.

Ventura continues to offer its expertise and resources to support the application of the PowderHale technology as well as its Aspirair and GyroHaler DPI device technologies to pharmaceutical companies seeking to enable or optimise the delivery of new inhaled products.

In addition to the application of advanced formulation and device technologies, Ventura is able to support inhaled product development for partners and clients from early feasibility studies through to manufacture of clinical trials supplies in its GMP area. Operating from its new purpose-built development facility for inhaled products at Chippenham, approximately 1½ hours west of London, Ventura has expanded to respond to the increasing need for specialist services, expertise and technology required to create tomorrow's leading inhaled drug products. This market growth is being driven not only by increasing treatment demands but also by increased recognition of the wider benefits and technical possibilities of inhaled delivery.

For further information on Ventura and its DPI formulation and device technologies, please visit the company website: www.ventura.com.

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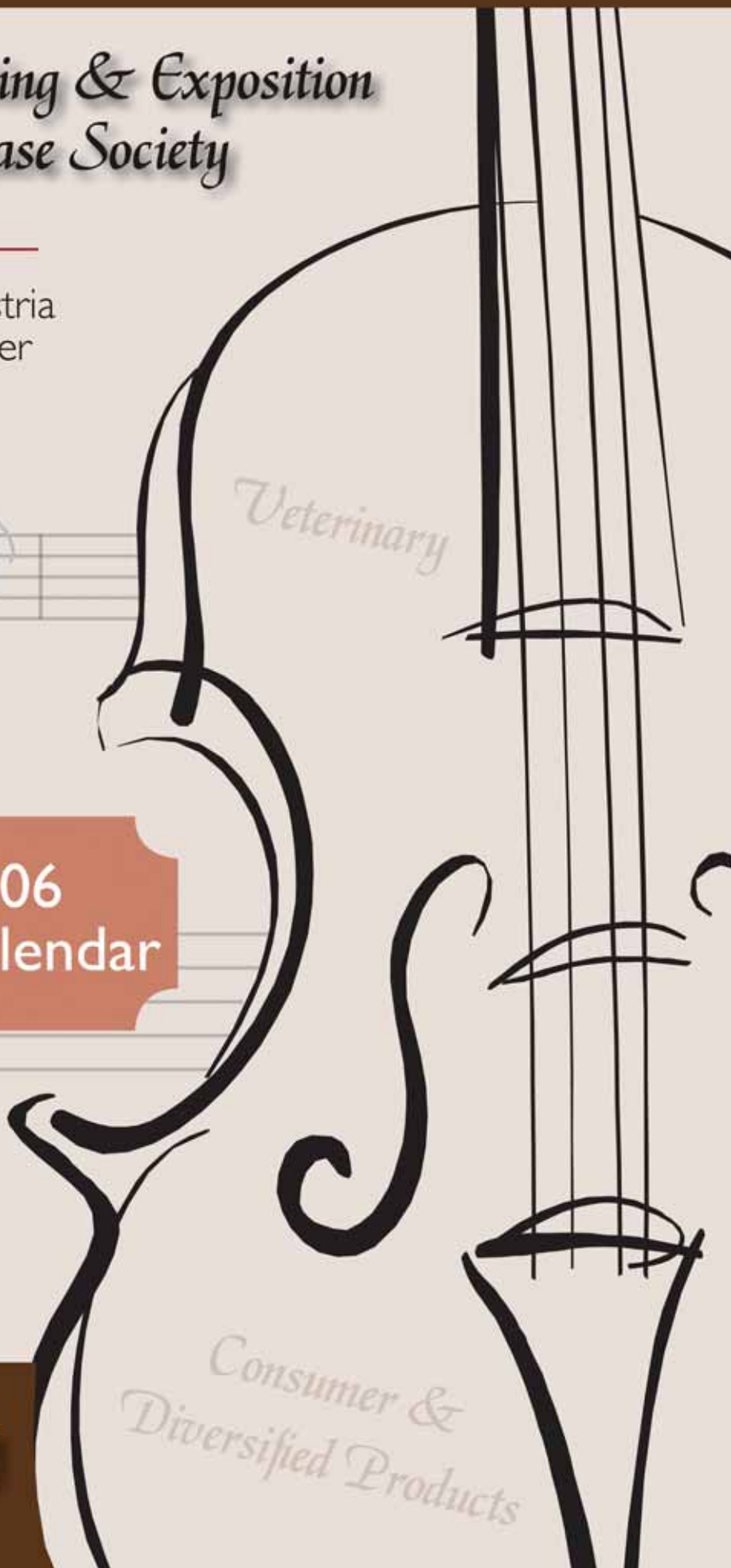

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ARADIGM

TECHNOLOGICAL ADVANCES FOR SUCCESS:

PRODUCT PIPELINE IN TARGETED PULMONARY DELIVERY

While pulmonary delivery is not a new approach to delivering drugs, technological advances have heightened the ability to utilise the lung as a transport mechanism for systemic drug delivery more efficiently. Many of the methods available in the early 1990s, such as metered-dose inhalers (MDIs), dry-powder inhalers (DPIs) and nebulisers, offered some advantages. However, standard inhalers are still not viewed as optimal in terms of both convenience and delivery. To address a number of these systems' shortcomings, Aradigm's scientists have developed the AERx® platform. Jonathan Rigby, Senior Director, Business Development at Aradigm, gives a detailed insight.

In transitioning from a technology-based company into a product-oriented company, Aradigm has executed on a strategy to leverage its pulmonary franchise with a focus on targeted respiratory care. By combining advanced, patent-protected platforms with novel formulations, we have succeeded in building a broad and extensive portfolio of products that encompass both first- and second-generation systems.

AERx is a high-performance system that delivers liquid formulations to and through the lung, for respiratory and systemic applications. It offers completely non-invasive therapy for small molecules and proteins that require frequent and/or long-term self-administration.

The AERx system consists of a disposable prefilled AERx Strip with an integral nozzle, from which drug is aerosolised via one of several delivery device options. As seen in figure 1, the devices range from electromechanical versions (AERx) with precise dose titration and data management capabilities, to all-mechanical versions (AERx *Essence*®) that deliver a pre-set dose in a single breath.

AERx is in Phase III clinical trials for the delivery of insulin, under development in collaboration with Novo Nordisk. This system has several unique features ideal for diabetics and their physicians, including single-unit dosing increments and data capture for compliance and dosing.

Aradigm has developed a second-generation system, AERx *Essence*, as a smaller and simpler approach to treating a different set of diseases (see figure 2). AERx *Essence* has many of the features of AERx in a smaller and less expensive package. Encouraging results have been achieved in recently completed in vitro and user-preference studies using fully functional, handheld AERx *Essence* prototypes. Results from a recent user study involving the AERx *Essence* showed that more than 90% of subjects responded favourably to the simplicity and usability of the AERx *Essence* device, providing a preliminary validation of the feature set of the system and the overall design.

As detailed in figure 3, Aradigm has both partnered and self- initiated programmes. Current programmes in development that would utilise the AERx *Essence* platform include AERx HCQ, AERx Liposomal Treprostinil and AERx Smoking Cessation.

Delivery efficiency is critical for accurate and repeatable lung delivery and affects the bioavailability of drugs delivered to the lung for systemic absorption. As seen in figure 4, AERx delivers more of the loaded drug dose to the lung, even for proteins, than most nebulisers, MDIs and DPIs. The combination of breath control and consistent generation of fine-particle aerosols minimises inter- and intra-subject variability.

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AERx Essence:
Small, simple, lightweight, accurate and efficient

AERx:
Sophistication to meet patient, disease and drug needs

AERx Strip
Pre-filled sterile liquid dosage form

Figure 1: AERx delivery platforms

DELIVERY THROUGH OPTIMAL FORMULATIONS

Aradigm has leveraged novel formulations to enhance the efficiency and reproducibility of drugs delivered via the AERx platform. Many drugs possess good solubility and stability in aqueous formulations and hydroxychloroquine, which is potentially useful in treating asthma patients, formulated at 100 mg/mL, has demonstrated exceptional stability and aerosol performance in AERx. For drugs with limited solubility in aqueous solution, Aradigm has demonstrated the capability to deliver ethanolic formulations, nanosuspension formulations and formulations containing cyclodextrans. Liposome drug delivery has played a significant role in the formulation of potent compounds to improve the release kinetics of various products.

Currently, most of these liposome formulations are designed to reduce toxicity and, to some extent, increase accumulation at the target site(s) in a number of clinical applications. Aradigm intends to exploit this formulation technology in two clinical programmes: the delivery of ciprofloxacin and treprostinil to target diseases that would benefit from its sustained-release capabilities and possibly reduced the number of administrations.

COLLABORATIONS AND PIPELINE

Aradigm has an impressive track record of securing partner-funded programmes, a number of which have been made public.

A summary of current key programmes can be seen below:

AERx insulin Diabetes Management System:
AERx Insulin Diabetes Management System (AERx iDMS) is in pivotal trials in collaboration with Novo Nordisk. Following the restructuring of the partnership with Novo Nordisk, completed in January 2005, Aradigm received an escalating royalty starting at 6.0% of sales from the AERx inhaled insulin product. Product launch is estimated by equity research analysts to occur in 2009. Aradigm has no further funding obligations nor will it incur any expenses associated with the royalty – the royalty will be 100% profit. Aradigm retains rights to all manufacturing designs, processes and other know-how, including rights to any related know-how or manufacturing IP developed by Novo Nordisk subsequent to the partnership's restructuring.

AERx HCQ:
Aradigm and APT Pharmaceuticals Inc, a privately held biotechnology company, are studying the delivery of aerosolised hydroxychloroquine (HCQ) for the treatment of asthma.

The AERx HCQ Phase I safety study in healthy volunteers showed that aerosolised HCQ was safe and well tolerated, with minimal oral and upper airway deposition, while exhibiting an excellent pharmacokinetic (PK) profile.

After positive data generated in the Phase I studies due to the enabling value of AERx, the development programme is currently progressing into Phase II clinical studies. Aradigm will be responsible for sourcing the active pharmaceutical ingredient, developing the liquid formulation of the drug product, manufacturing clinical supplies and executing on clinical and regulatory development matters.

AERx Liposomal Ciprofloxacin:
At the end of 2004, Aradigm licensed IP from INEX Pharmaceuticals relating to the manufacture of liposomal formulations of ciprofloxacin. Simultaneously, Aradigm signed a preclinical development agreement with Defense R&D Canada to investigate the potential of liposomal ciprofloxacin as an inhaled therapy to treat inhalation anthrax.

Ongoing preclinical and formulation development work is investigating the efficacy of

Figure 2: AERx Essence delivery system

liposomal ciprofloxacin to treat chromic lung infections associated with diseases such as cystic fibrosis and chronic obstructive pulmonary disease (COPD). The programme is expected to enter clinical trials in 2006.

AERx Smoking Cessation:
Aradigm has strong issued patents that relate to smoking cessation. Current therapies such as patches and gums are limited in their efficacy due to the fact that they do not mimic the PK profile of nicotine inhaled from a cigarette. Pulmonary nicotine, delivered via AERx, is expected to create this equivalent PK profile without the associated risks of smoking. This will satisfy a huge unmet need in the smoking cessation market.

Aradigm has been awarded a Small Business Innovation Research (SBIR) grant from the US National Institutes of Health (NIH) to develop a suitable inhaled formulation, and work is underway. There is significant interest from a global consumer healthcare / pharmaceutical company in return for commercialisation rights in licensing and funding development of this programme.

AERx Liposomal Treprostinil:
The dose accuracy and deep-lung delivery provided by AERx confer significant benefits to the inhalation needs of patients using potent prostacyclins to treat pulmonary arterial hypertension (PAH). Having successfully completed a feasibility study in collaboration with United Therapeutics which currently actively markets iv and sc products for PAH, Aradigm and United Therapeutics recently announced a commercial partnership focused on entering this market with a differentiated product that meets disease and patient needs.

SEVILLE – THE FUTURE OF INHALATION TECHNOLOGY

Licensed to Aradigm, the *Seville* technology was invented at the University of Seville, Spain. It is a novel and patent protected aerosol generation technology. Air and liquid simultaneously flow through a single orifice, causing the formation of aerosols that are significantly smaller than the orifice dimensions, ensuring that the nozzle does not become blocked. Compared with existing liquid technologies, the aerosolised drug output per inhalation should be considerably higher – about ten times that of most nebulisers.

Unlike AERx technologies, the *Seville* technology will be developed with a multi-dose reservoir, allowing many dose deliveries before having to reload or discard the device.

The Aradigm *Seville* technology is in early development but has the potential to improve significantly on the performance of traditional MDIs whilst simultaneously being price competitive.

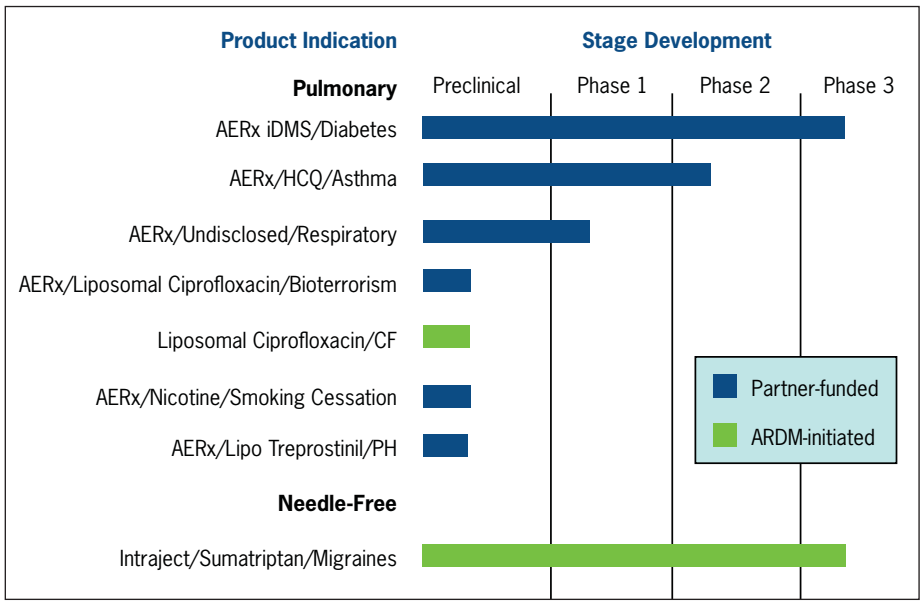

Figure 3: Aradigm's clinical development pipeline

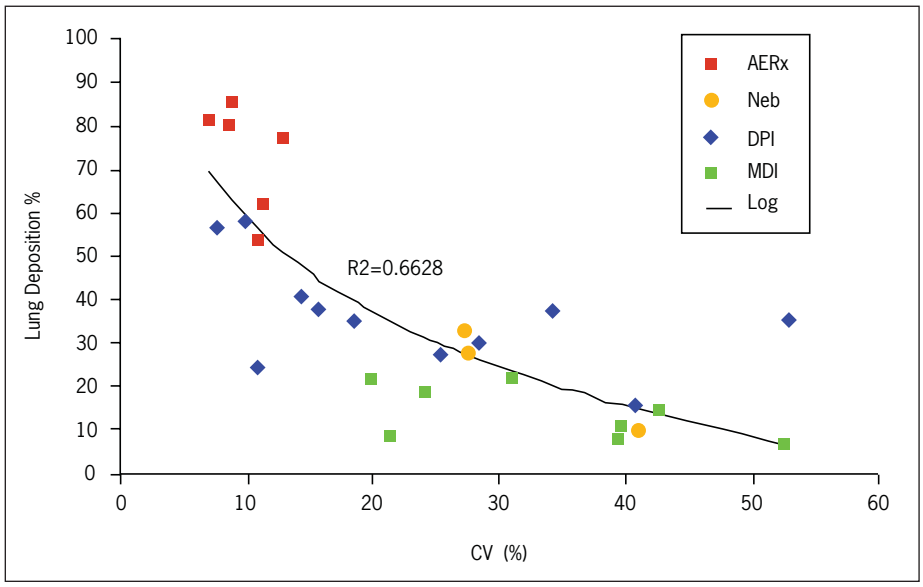

Figure 4: Lung deposition graph (source G. Taylor 2003)

BROAD CAPABILITIES

Aradigm's strength across a broad range of capabilities including device engineering, formulation, and clinical and regulatory development allows us to customise the right drug to the right system. The ability of the AERx Systems is leveraged by optimal formulations to ensure the appropriate dose is delivered at the right time. We see the AERx as exploiting the natural abilities of the lung and revolutionising pulmonary delivery.

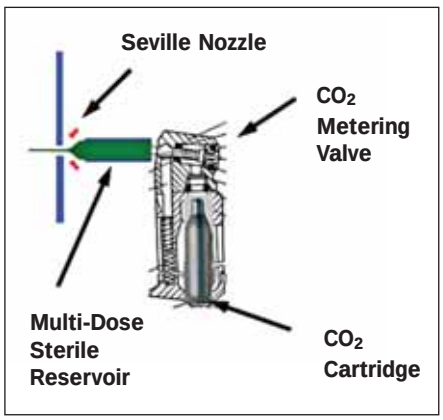

Figure 5: Aradigm's Seville Technology

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DIRECT HALER
PULMONARY & NASAL DRUG DELIVERY

DirectHaler™ Pulmonary

DirectHaler™ Pulmonary: straightforward device innovation

Unequalled ease-of-use and manufacturability – without compromising delivery performance; this was the ambition when creating DirectHaler™ Pulmonary. The successful result is confirmed in clinical trials. The device is the first advanced pulmonary delivery device enabling pharmaceutical companies to manage own device manufacture, filling and packing. The device is protected by issued patents worldwide.

Each pre-metered, prefilled pulmonary dose has its own DirectHaler™ Pulmonary device. The device is hygienically disposable, and is made of only 0.6 g of polypropylene. DirectHaler™ Pulmonary offers effective, accurate and repeatable dosing in an intuitively easy-to-use device format. Acceptability has been confirmed in the US, Europe and India.

DirectHaler™ Nasal

DirectHaler™ Nasal: innovation of device and delivery method

When air is being blown out of the mouth against a resistance, the airway passage between the oral and nasal cavities automatically closes. This anatomical feature is activated when the patient uses DirectHaler™ Nasal for blowing their nasal dry-powder dose into their nostril. Our patent protected nasal delivery method improves delivery effectiveness and patient acceptability.

Nasal anatomy/delivery experts claim further advantages of our nasal delivery method. The closed nasal/oral passage opens the connection between the two nostrils – hereby the dose blow provides deposition in both nostrils; so-called "bi-directional" delivery.

The single-use, disposable DirectHaler™ Nasal is for both mono- and bi-dose dry-powder delivery, in a pre-metered, prefilled dose format. The technology offers advanced nasal delivery characteristics, in a straightforward, worldwide patent-protected and cost-effective device with proven performance.

Dose sealed inside cap

Accommodating sensitive powders and special applications

Active substances and their formulations often have variable sensitivities to moisture, light, and mechanical impact. The DirectHaler™ devices can accommodate such needs for protection.

The powder dose is sealed inside the cap with a laminate foil strip, which is easily torn off for dose-loading into the PowderWhirl chamber, before removing the cap and delivering the dose.

Some therapeutic applications require delivery of two doses. DirectHaler™ Pulmonary and DirectHaler™ Nasal can be supplied with caps for bi-dose storage, and dose encapsulation, along with customised device appearance – both designed for optimal ease of use.

Laminate foil seal is removed

Dose released into PowderWhirl Chamber

The cap is removed

Dose ready to be delivered

LIQUID THERAPY.

SOLID ANSWERS.

The **AERx®** **Liquid Pulmonary Drug Delivery System** lets you build your brand on a stronger foundation. Its **noninvasive, rapid and precise**, offering something other inhalation technologies simply can't: a more efficient delivery method. Plus, the customized breath-control design and fine aerosol generation of the AERx system support both local and systemic delivery of large and small molecules - with **unsurpassed consistency and reproducibility**. You can count on full support from Aradigm, too. With broad capabilities across all levels of product development, our experienced team can offer the answers to best leverage your pipeline. So contact us today for more information. The therapy is liquid. But our commitment is firm.

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Some words just won't do

You would think that with over 40 years experience, more pMDI valves with HFA formulations marketed and more DPI's industrialised than any other manufacturer, we could afford to sit back and relax.

Quite the opposite.

In our business, *okay* simply isn't good enough. Our strive to improve operational excellence touches every aspect of the design, development and manufacture of our specialty medical devices.

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