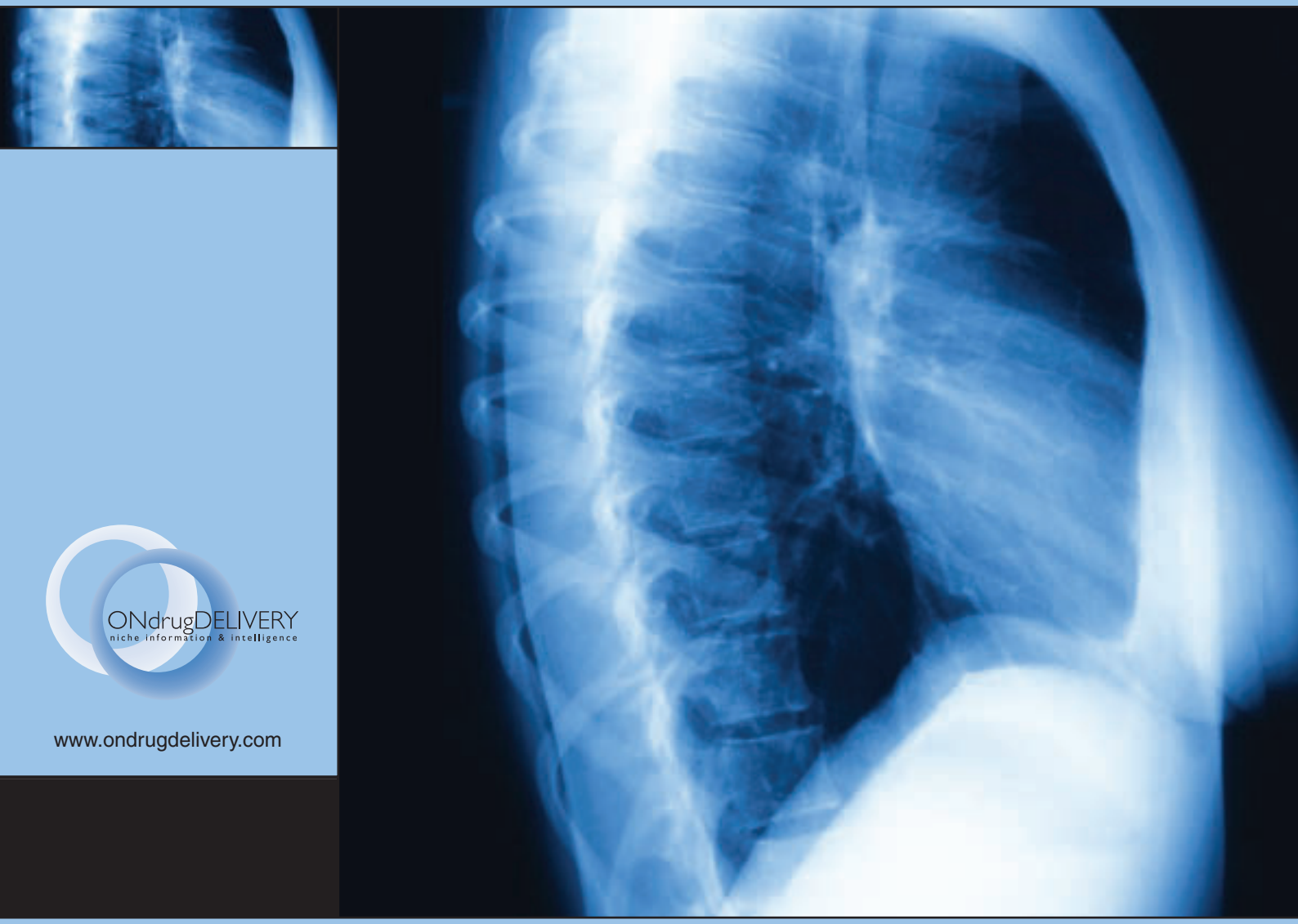
PULMONARY DRUG DELIVERY:

NEW PERSPECTIVES ON INHALERS AND INHALABLES



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CONTENTS

INTRODUCTION

PULMONARY DRUG DELIVERY: ACHIEVEMENTS, TRENDS AND OPPORTUNITIES

When being asked what field is the most up-and-coming area in today's applied pharmaceutical research I would point to pulmonary drug delivery. The reason is not because of the recent launch of inhaled insulin and the related press coverage, but the fact pulmonary delivery still offers many white areas on the map.

The more information is collected the more related question marks are surfacing covering the area of lung physiology and diseases, lung deposition, intelligent inhalation devices, delivery of biopharmaceuticals, absorption enhancement, controlled drug release in the lung and, last but not least, the topic of vaccination of the lung.

The fact that all areas of pharmaceutical research are very much interrelated and highly diversified, making pulmonary drug delivery a multidisciplinary effort, is more fascinating still.

The purpose of this introductory article is not to provide a deep and detailed evaluation of a particular subject in this broad field – that task is undertaken by the sponsors' articles that follow. Rather, this piece aims to show some achievements, trends and opportunities that the lung, as a target organ for drug delivery, can offer. Most of the information that follows is based on information to be found in the recently published book, "*Pulmonary drug delivery*"[1]

What has been achieved so far? One of the pronounced achievements is probably the recent launch of the inhalable insulin product Exubera by Nektar/Pfizer. Although, the market acceptance of the product still needs to be shown, the first regulatory approval of a larger peptide has pioneered the pathway for other pulmonary applied products containing biopharmaceutical drug compounds. Since those particular drug compounds can only be administered by injection, the lung has the potential to offer an alternative, non-invasive route of administration. Still many hurdles have to be overcome and a major challenge is the low systemic bioavailability of proteins and larger peptides, such as insulin. As shown for insulin, the bioavailability is also dependent on the individual lung condition, which varies strongly between non-smokers (about 25% bioavailability of effectively inhaled dose) and smokers (about 75% bioavailability of effectively inhaled dose)[2]. Moreover, a recent study by Henry *et al* showed that subjects with chronic asthma absorb less insulin than healthy subjects.[3] This means that each individual patient requires their own adjusted dosing regimen.

In a recent study another hydrophilic macromolecule, low-molecular-weight heparin (LMWH), was tested in clinical trials using the AKITA™ inhaler technology.[4] As a result the effect on the anti-Xa-level as a measure for anticoagulant plasma activity was about the same for 6000 IU applied by inhalation compared with 3000 IU after subcutaneous administration. However, it was observed that the peak level (C_{max}) of the inhaled heparin was delayed and the anticoagulant effect was sustained compared with the subcutaneously applied LMWH. The inter-individual variability of inhaled LMWH was comparable, if not even lower, compared with injected heparin.

From the above it can be concluded that it is indeed possible to some extend to deliver larger drug molecules such as insulin and heparin systemically up to therapeutic drug levels.

So, why has it taken so long for the first pulmonary product to reach market approval, and what can be expected in the near future?

First of all the physiology of the lung is not designed to absorb drug compounds systemically despite the very fragile and vulnerable nature of the lung epithelium. As an interface between the body's circulation and the outside air its function is to exchange only gas molecules and it has built up a strong defence against any other components that may enter the lung by accident. The defence can be by either physical by mucosal clearance or physiological by a strong presence of macrophages and enzymes. The lung can also develop immunological reactions against unwanted entities such as viruses.

A drug molecule needs to pass the physical clearance system represented by the upper airways and reach preferably the deep lung. Once deposited in the lung periphery, it should avoid the biological defence mechanism and be absorbed by the alveolar epithelium.

In order to reach the lung periphery as efficiently as possible, several state-of the art devices have been developed. The most prominent ones in the case of insulin are developed by Nektar Therapeutics (Exubera inhaler[5]) and Aradigm (AERx[6]), where a defined particle cloud is generated which can be efficiently administered through slow inhalation by the patient. Another method is utilised by Alkermes[7], where large particles are formulated that have a very low density[8] (AIR, originally developed by Advanced Inhalation Research).

For optimal lung deposition the aerodynamic diameter ($_{aer}$) should be about 2 µm. Since d_{aer} is defined to be dependent on the geometrical diameter (d_{geo}) and the density as follows: daer = $(r)^{0.5}$ * d_{geo} , the increase in the geometrical diameter can be compensated by reducing the density of the particles accordingly. The so-called large porous particles (LPP) are generated by spray-drying of polymeric and non-polymeric nanoparticles into very thin-walled macroscale structures[9]. For these particles it is also claimed that, due to their large structure compared with small, dense particles, attack by macrophage is less critical when deposited in the alveolar region of the lung.[10]

Even better lung deposition can be obtained through so-called intelligent inhalation devices, where the AKITA technology, developed by Activaero[11] (Germany) is the most advanced available device currently on the market. It can be combined with different commercially available nebulization devices such as Pari's (Germany) LC Plus [12]. The unique feature of the device is not only the generation of a well defined aerosol, but the special consideration of the patients' breathing manoeuvre for optimal lung delivery.

To deliver a drug formulation to the lung periphery the patient should breathe slowly (to avoid impaction) and as deeply as possible. Preferably, the aerosol cloud should stay for a few seconds in the lung before the patient starts to exhale so that the aerosol particles in the tiny alveolar capillaries can sink by gravitation and deposit on the alveolar surface.

Furthermore, the AKITA technology can target the drug formulation to a particular location of the lung such as the lung periphery or the bronchial region. This is achieved by a bolus of the drug aerosol that is released into the inhaled air stream at a defined time point. If the bolus is released early it will reach the alveolar region, whereas a bolus release at a later stage of the inhalation cycle will deposit in the upper airways. This concept of controlled inhalation has been confirmed in several scientific publications as recently reported by Brand *et al*[13] and Scheuch *et al*[14].

AKITA is equipped with a "smartcard" that contains the patient's physiological lung function data so that the inhalation manoeuvre can be adapted to the individual lung.

Last year a paediatric device was also introduced to the market that translates the electronically controlled features of the AKITA device very nicely by mechanical means as shown in Figure 1. The inhalation volume is defined by the size of the balloon in the device chamber and the inhalation velocity is controlled by the air-inlet valve at the back of the device. The aerosol can nebulized into the device by, for example, any commercially available MDI system that is connected to the mouthpiece of the

device. In line with the most recent EU regulations[15] that emphasise the need to design suitable application tools for children, this is to my personal opinion one of the inventive highlights of the year 2006 in the pulmonary field besides the launch of Exubera.

What other opportunities may arise from the pulmonary field? Looking to excipients the use of inulin as a non-reducing, stabilizing sugar glass could assist to formulate sensible protein and other molecular structures[16]. By means of spray-freeze-drying, inulin forms so-called solid solutions with the dispersed drug molecule and upon contact with water the amorphous sugar particle dissolves quickly and releases the drug molecule.

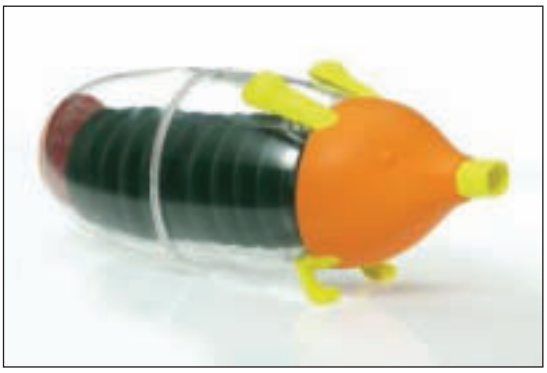

Figure 1a: Activaero's Watchhaler device for controlled lung application in children.

Also poorly soluble drug compounds can benefit from formulation into a molecular dispersed solid solution within the amorphous sugar matrix[17].

The use of controlled drug-releasing systems in the lung is a controversial issue today. Beyond academic attempts, not many commercial solutions have emerged so far. The major reason is the highly efficient physiological defence system for particulates in the lung that is difficult to overcome. As soon as a foreign particle is observed in the lung tissue a powerful macrophage reaction is launched to attack the particle. Probably, the most promising approaches involve the use of stealth approaches, such as PEGylation[18] or the use of endogenous compounds that occur in the lung such as dipalmitoylphosphatidylcholine (DPPC).

DPPC can be co-formulated into liposomes that encapsulate a drug compound for prolonged release. An interesting study based on these findings has been reported by the company Delex (acquired by YM Biosciences, Canada) using the AeroLEF system (aerosolized Liposomal Encapsulated Fentanyl). In a press release of May 2nd, 2007, it was reported that its product had reached the clinical endpoints of the clinical Phase IIb study in patients with post-operative pain[19].

Another interesting application of the pulmonary route is the delivery of vaccines. Besides providing a convenient alternative to needle injections (it should be noted that 10% of all patients suffer from severe needle phobia[20]) it also has shown to be more efficient in antibody responses than injected vaccine in a recently published article by Bennett *et al* [21].

This concept would really benefit compliance of patients that are otherwise difficult to reach. In particular, in economically less fortunate regions in the world where infectious diseases are strong threats to quality of life and one of the major causes of mortality, vaccination programs by inhalation can be regarded as a clear advantage of invasive administration. It should also be noted here that a nasal vaccine formulation against seasonal influenza has recently entered the market place, namely FluMist™ , distributed by AstraZeneca [22].

In conclusion, it appears that pulmonary drug delivery is truly an emerging field that evolves on different new avenues to the market place. On the shorter time scale it will be the only non-invasive alternative to the needle to administer biopharmaceuticals into the system circulation. With Exubera the first pioneering step has been made and, independent of the commercial success of the product, further research will be applied to address the remaining challenges for pulmonary delivery.

It is also important to remember that the local administration of drugs to the lung for poorly met lung diseases such as asthma, COPD, lung cancer, community acquired pneumonia, mucoviscidosis and cystic fibrosis, is still in its infancy from a commercial point of view. However, there are several new therapeutic concepts besides the classical corticosteroids, ,-agonists and antibiotics coming through the pipeline, such as the DNAzyme concept of Sterna Biologicals (Germany) for the causal treatment of asthma[23] or the use of NFkB, MEK and caspase inhibitors for antiviral therapy as very recently published and patented by a consortium of three major academic groups in this field[24,25].

The success of the examples mentioned above as well as other new approaches will strongly depend on dose and site-efficient lung delivery technology.

Paediatric lung treatment is something often neglected and which may benefit from the coming EU regulations.

Last, but not least the application of inhaled vaccines are showing very interesting potential and I personally predict that this area will be another hot topic in the field for the coming 10 years.

Henrik L. Luessen, PhD
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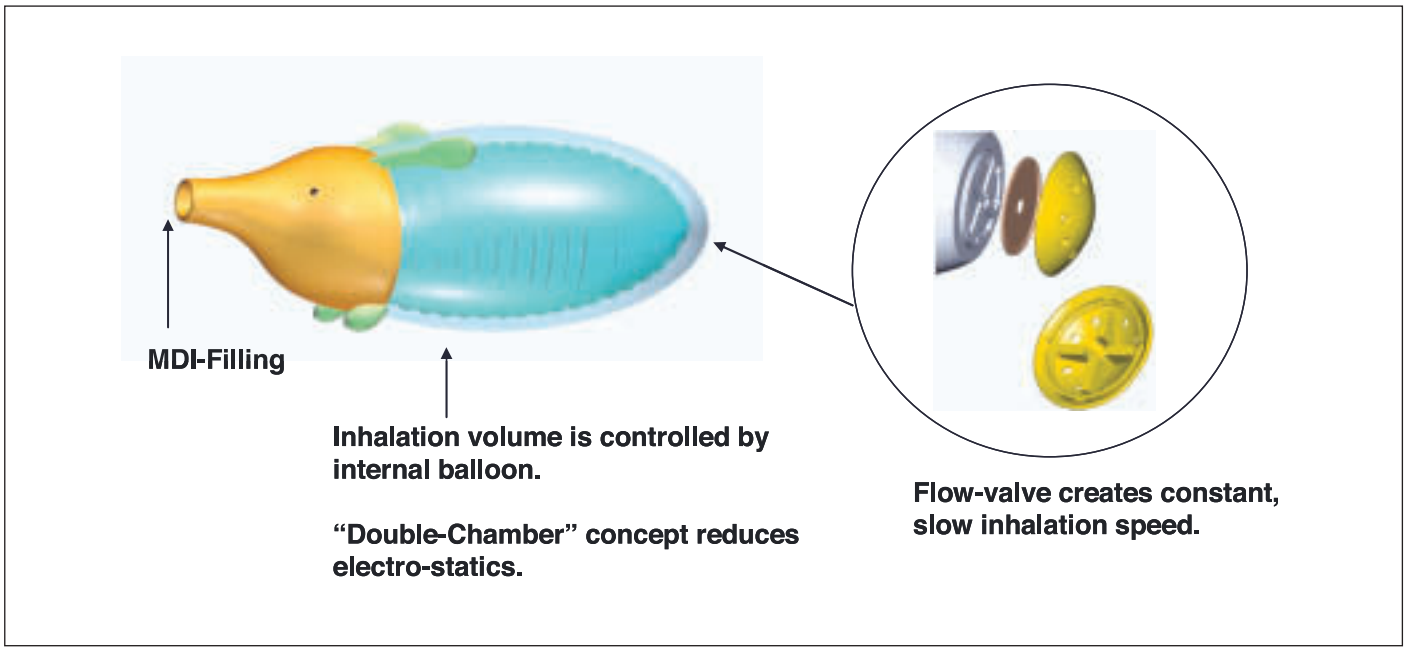

Figure 1b: Schematic drawing of the Watchhaler device and how it controls the major features for optimal lung delivery: a) volume of inhalation by the size of the inner balloon chamber and b) inhalation velocity by the flow valve at the back of the device. The aerosol is simply filled into the ballon by connecting the MDI device with the mouthpiece of the Watchhaler™

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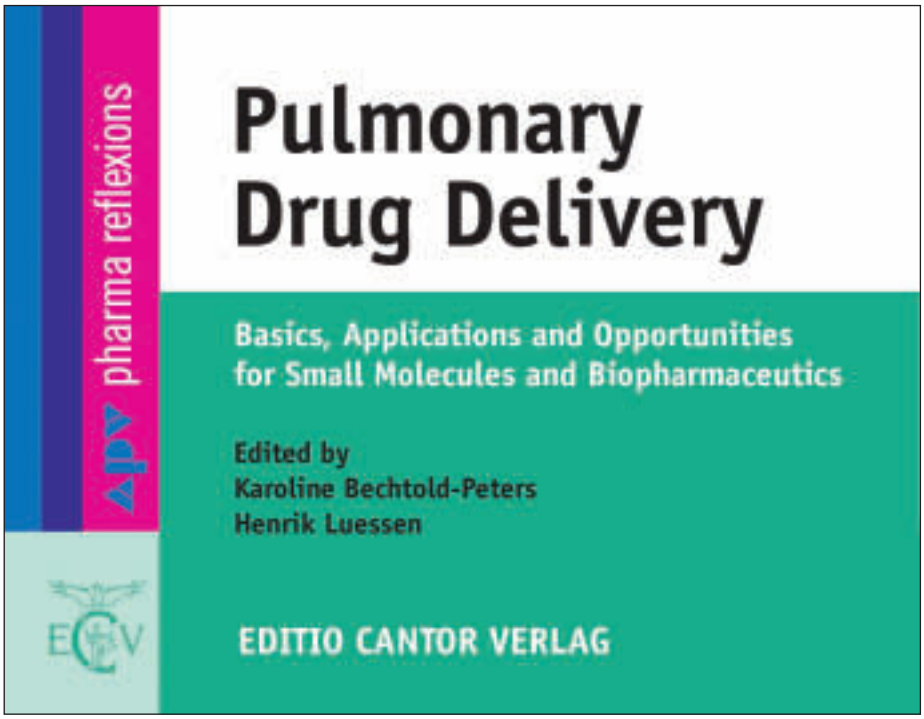

***"Pulmonary Delivery: Basics, Applications and Opportunities for Small Molecules and BioPharmaceuticals"*, published in 2007 by ECV. Available from www.ecv.de, priced €126.00**

NEXT GENERATION OF AUTOMATED PULMONARY DELIVERY TESTING SYSTEMS

In this article, Anthony Moran, Sales and Marketing Director, Automated Drug Delivery Testing, Astech Projects Ltd, outlines the features of automated pulmonary delivery testing systems, and describes how they can benefit companies developing inhalable products.

The increasing pressure to reduce pulmonary drug development times is often made more difficult by the amount of analytical testing needed for each new device design or formulation change. Stringent regulatory requirements mean that the testing of these pulmonary drug delivery devices is both labour-intensive and hence time-consuming, further adding to product release delays. Examples of regulatory tests for pulmonary products include particle size determination and dose content uniformity or emitted dose testing.

However, a solution is available to mitigate the extent of testing inefficiencies by using intelligent, automated testing platforms to automate Andersen or Next Generation Impaction (NGI) cascade impaction testing and also emitted-dose testing for dose-content uniformity. By automating these tests it is possible to greatly reduce development costs as a result of the following benefits:

1 Reduction of test variability by utilising reproducible machinery
2 Increased throughput with parallel 24 hour/day processing
3 Generation of useful data by employment of intelligent sensors
4 Reduced time to market by increasing validity of test data
5 More time for analysts to engage in value-added activities
6 Improved standards of health and safety for testing personnel

AUTOMATION: REDUCING ERRORS AND INCREASING EFFICIENCY

Using the pressurised Metered Dose Inhaler (pMDI) manual preparation shake as an example, it is widely acknowledged that varying results can be obtained from the emitted dose testing caused by the inconsistent shaking actions of the analyst between emitted doses, or from analyst to analyst across different tests. There are many reasons for these manual test inconsistencies such as shake speed, method of shaking e.g. long arc motion or short linear motion, physiology of the analyst causing stronger centrifugal forces in the shake action. These inconsistencies mount up and can be responsible for unreliable data.

Fortunately automated equipment can eliminate these variables with intelligent control and sensory feedback. With the use of intelligent electrical drives it is possible to specify the exact profile of the shake, such as the acceleration, velocity, distance and deceleration. All these parameters are consistent and valuable recorded feedback enables the analyst to interrogate the machine data to help with investigations resulting from unreliable or out-of-specification analytical results.

Another advantage realised with automation is productivity. Where operations demand high-throughput testing, it is increasingly difficult to serve those demands using analysts that only work eight hours a day, five days a week. It is not always as simple as employing more analysts due to the costs involved, for what is an essentially manual and laborious job.

Using Andersen Cascade Impaction testing as an example, it is understood that on average an analyst performs four impactions a day, two in the morning and two in the afternoon. Astech Projects' Automated Andersen product, the Xelize™, can perform approximately forty impactions per day over a 24 hour period, a ten-fold increase in productivity. Coupled with the benefits of reproducibility it is easy to appreciate the advantages that the Xelize™ can bring to this particular environment.

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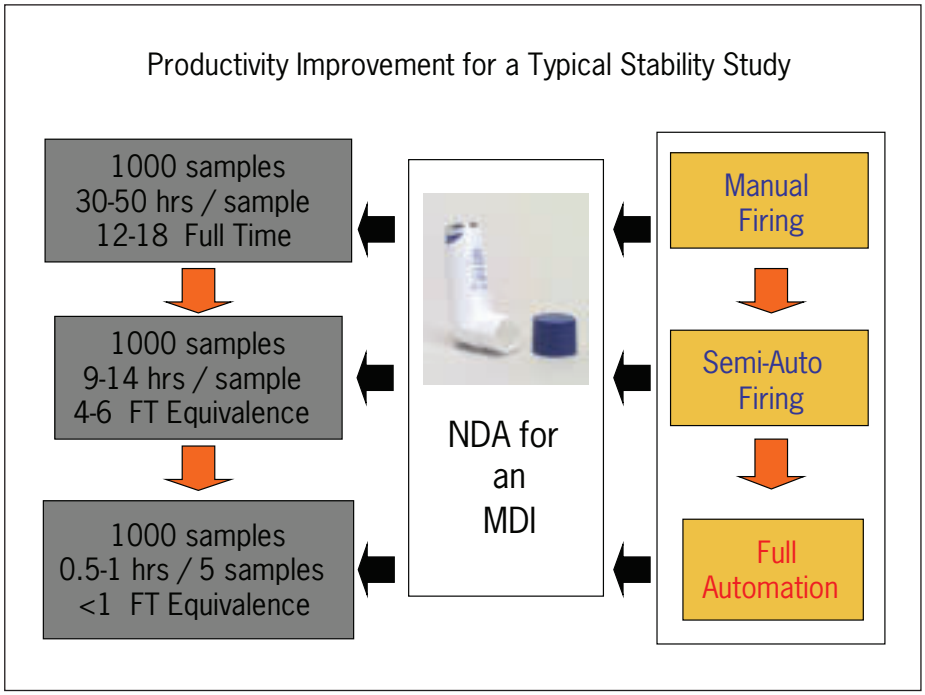

Figure 1: Productivity improvement for a typical stability study

Another example is the amount of regulatory testing required for a New Drug Application (NDA). The costs associated with outsourcing this work to a Contract Research Organisation can run into the many millions of dollars due to the number of analysts required over a long run of samples. Figure 1 provides an indication of the advantages offered by automation in terms of the productivity improvement for a typical stability study. The figures indicate a representative number of samples, the number of hours and number of employees to achieve throughput equivalence.

Whilst automation takes away some of the analyst's work, it is largely unskilled, manual work that is best suited to a machine. This of course allows the analyst to concentrate on highly skilled value-added work that benefits both the employer and the employee.

Automation also increases health and safety standards by removing hazards associated with repetitive strain injury (RSI). During the testing of pMDIs the analyst has to shake multiple devices many times over long periods, increasing the likelihood of RSI. Exposure to solvents and drug product are other hazards that can be limited with the use of automated equipment.

MODULAR SYSTEMS ALLOW CHANGES IN SPECIFICATION

Automation is not limited to finished products. As the pulmonary device design changes through the course of development, it may no longer fit within the constraints of the current testing platform, which is why Astech Projects has developed modular automation platforms that can accommodate such changes.

For example, Astech Projects' automated platforms allow the pulmonary device actuation module to be exchanged for an alternative device type module with minimal downtime. This gives the customer the ability to test multiple device designs on the same system. Another example may be the exchange of the dose collection chamber mouthpiece to suit different device mouthpiece profiles.

Inhalers are becoming ever more sophisticated with the inclusion of advanced design features such as lid opening mechanisms, dose counters, firing mechanisms and dose extraction options such as breath-actuated devices. These modifications often add complexity in automated device handling and thus, device performance checks and extensive system suitability checks are required before use or during the firing of each dose. Therefore, an important design criterion of any automated system is the utilisation of modular parts to adapt the system to iterations in device design.

SCALE-UP SYSTEMS WITH ADDITIONAL MODULES

In addition, the modular concept allows the analytical development or testing teams to gain confidence in automation step-by-step, by utilising Astech's single module workstations such as the device handling module being integrated with the recovery module or the sample preparation module.

This approach has been adopted by several major pharmaceutical companies. Over time, additional modules can be added to form a fully integrated automation platform.

A useful starting point for dose content uniformity testing may be the automated dose recovery module. In this example, the user would place a single actuated device into the device carriage which would closely align with the dose collection chamber's inlet. The dose recovery system would automatically extract the dose onto the dose collection chamber filter ready for automated recovery of the drug product for analysis. As development of the device progresses and the geometry becomes fixed, device storage, handling and actuation modules can be introduced. Automated device actuation is an important step in reducing the variation caused by manual handling and actuation.

With automation the device can be automatically actuated to a precise and repeatable torque which is recorded and presented to the device elastomeric mouthpiece adapter at a force defined in the user method. Once in position, the system vacuum will apply a flow rate according to the method parameters set and with the specified rise time. Data such as position, force, torque, temperature, humidity, rise time and flow can all be recorded and stored in a system database for generating reports. The same data can be used to suspend device testing at the point of failure with the use of intelligent real-time data monitoring. For example if the desired flow rate is not achieved the software will flag an alarm which can be used to prevent the test being carried out.

Astech Projects' Automated Emitted Dose system, Xelair™ can achieve higher throughput emitted dose collections, of up to 200 per day, through minimising solvent usage and advances in automated handling of the pulmonary device. Dose actuation parameters are controlled through software. These include: number of doses, number of waste doses, device weighing option (or example, never weigh; weigh before and after every shot; or weigh before and after every dose shot), duration between shots, actuation speed, actuation hold time and actuation torque.

Software-controlled dose-firing parameters, including dose collection airflow rate, dose collection airflow duration and mouthpiece to inlet sealing force can be incorporated into the Xelair™. Device performance checks such as air-flow resistance, chamber leak testing and check weighing modules posed particular tech-

nical challenges. Modifications to the air flow channel and the use of current automated valve technology alongside intelligent closed-loop control instrumentation allowed for control-enabled leak testing at the appropriate vacuum pressures.

Other design features include waste fire collection, device tracking with the use of Radio Frequency Identification (RFID) and air flow resistance testing through the device. In addition, with current high-speed metering pumps, dispensing to the dose recovery module can be achieved with sample data accuracies and precision of 0.3% at 50ml/min. If required, greater dispensing accuracies can be achieved at lower throughput.

Sample collection includes an emitted dose collection chamber that can recover drug product in as little as 25ml solvent with rinsing, due to its reduced internal volume and ability to agitate through rotation and high pressure recirculation. A fully automated HPLC vial collection module with capacity for up to 400 HPLC vial collections is another important feature of Astech's Xelair™ system.

QUALITY AS STANDARD

It is essential that quality is built into automation systems during their design and development. Once a system is installed and operating, the opportunity to improve quality cost-effectively has gone.[1] As the development of automated systems may take many months, quality has to be integral to each phase of the project lifecycle, from user requirements specification to system commissioning. Implementing Good Automated Manufacturing Process (GAMP) 5 guidelines can assist in delivering quality automation.

Software is fundamental to the successful operation of automation systems. Poor quality software can severely affect efficiency and reliability. To meet customers' quality expectations, software suppliers, including in-house developers, need to define and implement a quality system which covers all the essential business processes in the product lifecycle. The software quality standards body, TickIT, guides the developer to achieve this objective within the framework of ISO 9001.[2]

Next-generation automated pulmonary testing systems have to comply with 21 CFR Part 11 as laid down by the US FDA rule relating to the use of Electronic Records and Electronic Signatures. The biggest issue facing the automation industry is understanding and implementing the regulations in a timely cost-efficient manner. To this end, Astech Projects fully complies with Good Practice and Compliance for Electronic Records and Signatures, Part 2 – Complying with 21 CFR Part 11, Electronic Records and Electronic Signatures which aims to provide industry and its suppliers with practical guidance on how to comply with the rule, while dealing with common issues of concern.[3]

Figure 2: The Astech Xelair™ 5 Series for Dose Content Uniformity of the Emitted Dose

IN-LINE TESTING IMPROVES MANUFACTURING EFFICIENCY

Astech Projects' automated systems have been developed for both R&D and manufacturing quality control. Traditionally testing has been performed in batches as a separate function, mostly in a separate location from the manufacturing environment. Astech Projects' automation technology enables systems to allow in-line process testing with the use of sophisticated control software and advanced handling systems. Simplistically, the device is picked from the production line and placed into the storage area of the automated pulmonary delivery testing systems. Results are processed by the information systems and the process can be stopped, if necessary, before the full batch is produced, thereby reducing manufacturing downtime and increasing profitability.

This article highlights the features and advantages of Astech Projects' automated pulmonary delivery testing systems. The importance of designing automation systems to be modular and scalable is emphasised to promote and encourage the adoption of automation within the laboratory and the production environment without committing large amounts of capital.

Automation quality and cost has improved dramatically over the past decade and industry leaders have to be innovative if they are to realise the overall cost benefits that automation brings. As pressure increases on Western pharmaceutical companies to become increasingly lean and efficient, measures have to be taken if those companies are to prosper as global competition intensifies. As a trusted manufacturer of automation products and bespoke systems, Astech Projects is able to offer the automated platforms that increasing efficiency requires.

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REVIEW OF PRODUCT CHARACTERISATION REQUIREMENTS FOR AEROSOL PRODUCTS

Interest in the development of inhalable products is mounting throughout the industry. However, products for pulmonary delivery are amongst the most complicated to develop, especially in terms of characterisation for regulatory review. Here, Christopher Shelton, Laboratory Manager, Tim Stephens, Associate Group Leader, Derek Wood, Laboratory Manager and Steven Pilewski, Director, Inhalation Products & Medical Devices, all of PPD Inc, highlight some of the discussion points for product characterisation studies and emphasise some of the resource requirements that are unique to inhalable products.

INTRODUCTION

The development of any pharmaceutical product represents a significant investment on the part of the sponsor company both to demonstrate clinical efficacy of the pharmaceutical ingredient as well as to prepare the product dossier for regulatory submission.

Pharmaceutical products intended for local or systemic delivery to the lung, specifically pressurised metered dose inhalers (pMDI) and dry powder inhalers (DPI), are among the most complex products where interactions between the formulation and delivery device create additional factors to be understood and monitored. In addition, while most regulating authorities have prepared guidances to industry outlining recommendations for product characterisation studies and product specifications, the expectations of these agencies can vary considerably.

Over the past ten years, several significant documents have been issued that have profoundly affected the approaches to conducting both characterisation studies as well as stability studies for aerosol products. Among these reference documents are the US FDA draft guidance for metered-dose and dry-powder inhaler products (1998), the FDA Guidance for Nasal Sprays (2002) and the joint European and Canadian guideline published in 2006.[1-3]

During this time several technical groups have been organised by industry to establish dialogue with the regulating agencies during the development of these guidance documents. These groups include IPAC-RS, EPAG, AAPS-ITFG and PQRI (Product Quality Research Institute), which have facilitated discussion between industry and the agencies by recommending best practices to industry and providing science-based, data-driven responses to the regulatory agencies.[4]

To companies or individuals new to this area of pharmaceutical dosage forms, the differences between territories and unresolved issues related to these products can be difficult to uncover.

Due to the complexity of inhalation dosage forms and the individuality of each product, either by functional design or mechanism of aerosolisation, more studies may be required to fully characterise a product for regulatory submission, specifically related to device robustness, that are not detailed in any guidance document. Therefore, this article will be limited to the recommended studies for dry-powder and pressurised metered-dose inhalers that would be applicable to the majority of products in development.

PRODUCT CHARACTERISATION STUDIES

Product characterisation studies for pMDI and DPI products include studies conducted to support product labelling and performance claims as well as to establish product stability storage conditions. A list of recommended studies for product characterisation is presented in Table 1.

Many of these studies are similar between the US and European agencies, as identified in the table. However, as the FDA has outlined some additional product characterisation studies to be performed prior to regulatory submission, it is important for European and Asian companies to be aware of these requirements if considering submitting an application within the

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MDI	DPI
Determination of Storage Conditions[1,3]	Determination of Storage Conditions[1,3]
Accessory Drug Deposition[1,3]	Accessory Drug Deposition[3]
Cleaning Instructions[1,3]	Cleaning Instructions[1]
Microbial Challenge[1]	Microbial Challenge[1]
Dose Proportionality[1]	Dose Proportionality[1]
Plume Geometry[1]	Effect of Orientation[1]
Performance After Temperature Cycling[1,3]	Effect of Moisture[1]
Resting Time, Priming, Re-priming[1,3]	Effect of Patient Use[1]
Tail-off Profile[1,3]	Fill Weight[1,3]
Effect of Varying Flow Rates[1]	Device Robustness[1,3]
Low Temperature Performance[3]	Effect of Varying Flow Rates[1]
	Dose Buildup and Flow Resistance[1]
	Tail-off Profile (device metered) [1,3]
	Priming[1]

Table 1: Characterisation Studies for pMDI and DPI Products

US. Of the studies listed in Table 1, the authors are not aware of any significant differences or ambiguity between regulatory authorities except in the case of temperature cycling studies for pMDI products. In this case, the EMEA guidance requires temperature cycling conditions over a ten-day evaluation period while the FDA states this study should extend up to six weeks.

Analytical methods used to set product specifications are listed in Table 2. The first six of these methods, which assess the purity and mass of the active components and excipients, are not specific to aerosol products. Extensive review of the other analytical methodologies listed in Table 1 for testing both pMDI and DPI dosage forms have been reviewed previously.[5] While attributes assessing purity and potency of active and excipient ingredients are approached similarly between regulating agencies, other tests for evaluating the container closure system and the product aerosol performance remain in debate.

Approaches for testing foreign particulate matter have been discussed in a review produced by members of the IPAC-RS working group.[6] Foreign particulate matter testing commonly uses a variety of techniques to quantify and analyse the material that is not part of the formulation. These techniques include light obscuration, optical microscopy, scanning electron microscopy/energy dispersive X-ray (SEM/EDX), Fourier-Transform Infrared Microscopy and Raman Microprobe.

The benefit of the microscopic techniques is that information about the size, shape and species of the particulate matter can be collected. However, the techniques are time consuming and the enumeration of the particles is imprecise due to the sampling and subjectivity imparted to the system by the operator. Automated microscopic image analysis systems are available to accelerate the particle enumeration process and remove operator subjectivity, but subsequent particle identification may still require extensive analysis and expertise.

Light obscuration techniques have been developed for particulate analyses that also rapidly enumerate particles. These systems are advantageous since larger sampling can be accommodated that may better represent the particulates present in the product. In addition, the increased sample throughput from these instruments also allows larger data sets to be generated that can be treated statistically for the evaluation of any stability indicating trends. However, the cost of improved efficiency is the trade-off that no data are generated regarding particle morphology or species since the technique assumes a spherical shape for all particles and cannot differentiate between substances (plastic and metal, for example). While the microscopic techniques can be used individually or in combination to characterise the particulate matter profile, light obscuration's relative speed and reproducibility make it more attractive to accommodate the large scope of routine testing required for registration stability studies.

Recommendations from the FDA draft guidance are generally more detailed than offered by other agencies, specifically in regard to the extent of product characterisation and the resolution of test procedures. In the case of leachables testing, the EMEA guidance proposes leachables characterisation for pMDI products whereas the FDA document specifies leachables characterisation for both pMDI and DPI products. Additionally, a PQRI Working Group for Leachables and Extractables prepared a document to the FDA recommending a Safety Concern Threshold (SCT) value for leachables of 0.15 mg/day, which is based on a more conservatively applied evaluation of toxicity database information.[7]

In general, leachables testing requires a thorough prior evaluation of the critical device components, and then conducting exhaustive, controlled extraction studies with separate extract analyses for volatile, semi-volatile and non-volatile extractable profile evaluations (utilising headspace-GC/MS, direct-injection GC/MS and LC/MS instrumentation).

A toxicological evaluation of the extractables data is performed following the controlled extraction study, and a justification is made for which extractables are to be monitored as potential leachables in the drug product. Then development and validation of leachables methods are conducted, as the leachables methods are used to monitor leachables for the product on stability extending throughout the expected shelf life of the product.

Aerosol performance characterisation requirements for both pMDI and DPI products have been an area of extensive discussion over the past few years and again demonstrated the prescriptive approach taken by the FDA. This is particularly apparent in dose content uniformity testing, both in study design and in specifications, where significant differences remain between regulatory agencies both in the approach to assessing dosing performance and the acceptance criteria for this test.

The FDA study design outlines a dosing regime comprised of individual collections at beginning, middle and end dosage units for three canisters to assess through container life dosing, whereas the EMEA design comprises ten collections across beginning, middle and end dosage units to assess through container life dosing. The FDA expectation for dosing specification is within 20 percent of the nominal dose, but the EMEA allows for wider specifications based on the applicable pharmacopoeia. Depending on the targeted market for a product in development, bridging these differences can add significant burden on the product sponsor if both European and US submissions are desired.

RESOURCE REQUIREMENTS

Analytical testing of pMDI and DPI products requires significant investment of space and manpower during stability analysis. This fact is often overlooked during the planning phase in preparation for later phase studies. While specific product packaging size does vary depend-

ing on specific device design, a typical pMDI package, with dimensions of (3.8 x 6.35 x 10.2 cm) would require a minimum of 1.6 m^3 to accommodate three lots of drug product for a registration stability study.

This assumption is based on three lots stored in two orientations at three standard conditions for a study lasting three years, but does not include overages or Tier 2 testing. It is also noted that the volume number given above is absolute displacement, not actual space consumed considering additional volume required for storage containers and air flow allowances in stability chambers.

In addition to the space requirements, staffing required to complete testing for the largest stability time points (three, six and 12 months) could easily approach 10-15 people. These large staff requirements are mainly due to the aerosol performance tests, which are recognised as very labour intensive. Preparation for this level of staffing commitment requires significant effort to train and qualify the analysts participating in the programme.

As the measured aerosol performance of many aerosol products depends on the skill of the analyst, the aspect of training can often be underestimated by the R&D analytical team, which may be comprised of a limited group of analysts who have worked with the product over the course of early development and scale-up. Since later phase studies may be conducted by another group, either in manufacturing or a contract laboratory, successful transfer of the analytical methodologies can be dependent upon the training provided to the receiving facility to understand the critical variables impacting testing of the product.

Prior to monitoring leachables on product stability samples, much time and effort are required to derive the container/closure system extractables profiles for volatile, semi-volatile and non-volatile extractables, using high-level mass spectrometric detection instrumentation methods. These controlled extraction studies are followed by a toxicological assessment of the extractables data and then methods are developed to monitor specific compounds as potential leachables in the product sample matrix. The leachable methods require ICH method validation prior to submission.

In addition, routine methods to monitor raw materials are typically required for quality control purposes and these methods in addition must be developed and validated. This work requires the work of high-level scientific staff with experience in materials science.

Developing this resource and expertise internally can be very challenging for any company, especially so where multiple programs may be competing for the same staff within a department. Due to these constraints, many companies often look to outsource these types of studies to qualified laboratories. In this case, it is important to carefully evaluate whether the contract facility possesses the expertise, qualified staff, stability storage capacity, redundant instrumentation and required quality systems to complete the testing requirements, especially with the more technically challenging methodologies such as aerodynamic particle-size distribution testing.

MDI Products	DPI Products
Identification[1,3]	Identification[1,3]
Assay (Total Contents) [1,3]	Assay (Total Contents) [1,3]
Impurities & Degradation Products[1,3]	Impurities & Degradation Products[1,3]
Moisture Content[1,3]	Moisture Content[1,3]
Alcohol[1,3]	Microbial Limits[1,3]
Foreign Particulate Matter[1]	Foreign Particulate Matter
Microbial Limits[1,3]	Leachables[1]
Leachables[1,3]	Emitted Dose Uniformity[1,3]
Shot Weight and Total Actuations[1,3]	Emitted Dose Uniformity (thru life) [1,3]
Leak Rate/ Weight Loss[1,3]	Particle Size Distribution[1,3]
Emitted Dose Uniformity (and thru life) [1,3]	
Particle Size Distribution[1,3]	
Spray Pattern[1]	

Table 2: Analytical Test Methods for pMDI and DPI Products

CONCLUSION

Testing of inhalation products has proven to be more complex than most other dosage forms. With the increasing interest in developing therapeutics in this area, it is important for any company entering the field to understand and prepare for the level of resource commitment necessary to complete the registration testing package required for submission to the regulatory agencies effectively. Careful preparation can enable a sponsor to achieve the program milestones for product development and launch successfully.

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HIGH DOSE-RATE AEROSOL DELIVERY OF BIOLOGICS AND MACROMOLECULES

BioTechPlex is developing a new aerosol delivery platform for high dose-rate delivery of macromolecules and biologics. In this article Donovan Yeates, Chief Executive Officer, and Lid Wong, Chief Scientific Officer, outline the problems related to the aerosolisation of these agents, describe the approach BioTechPlex is taking to resolve these issues, and illustrate applications of this SUPRAER™ technology in the delivery of surfactant, an antibiotic, alpha-1 antitrypsin and siRNA.

DELIVERY OF BIOLOGICS AND MACROMOLECULES

It has been estimated that 16% of new drugs will be delivered via the respiratory tract for the treatment of both respiratory and non-respiratory diseases. Whereas there are excellent nebulizers for the delivery of microgram quantities of many small molecules, efficient and effective aerosol delivery of many biologics and macromolecules present new challenges for aerosol delivery systems. These agents include proteins, peptides, surfactants, liposomes, antibiotics, biologics, mucokinetics, DNA and RNA viral vectors, immunoglobins, antisense, oligonucleotides, small interference RNA as well as vaccines and anticancer agents.

Delivery of large-molecular-weight compounds in many cases requires the aerosolisation and efficient delivery of 10-100 mg or more. Presently the delivery of such high doses requires inhalation times of 20-30 minutes. In addition, the agent may have to be administered several times a day. It has been estimated that patients with cystic fibrosis and COPD may spend up to two hours daily taking their medication.[1] This is a major barrier to "acceptable" aerosol delivery.

The physicochemical properties of some of these agents in solutions may change the viscosity and surface properties of the solution, thus making them more difficult to aerosolise. In some cases, the compounds may undergo shear degradation while in the reservoir as well as during the nebulization process.[2] Confounding these factors is the variation in the particle size on inhalation due to the evaporation of the aerosol with the entrained room air.[3]

The need to reduce CFC in aerosols while delivering higher masses of agents led to the development of dry powder inhalers. However the difficulty in dispersing fine powers into small respirable particles is legend. This has led to the use of low-surface-energy excipients. Inclusion of these excipients decreases the drug load while potentially increasing the risk of adverse actions through increases of osmolarity and/or irritant effects. For instance, Exubera blisters contain either 1 mg or 3 mg of insulin. Each blister contains about an additional 70% excipients. Thus, Nektar's DPI delivers insulin along with the excipients, sodium citrate, mannitol and glycine. The fine particle dose is 40% of the total insulin dose (NDA 21868). Not surprisingly, given these excipients, inhalation of Exubera causes coughing in some patients.

THE SOLUTION PROVIDED BY SUPRAER™

To address these issues, BioTechPlex created the technology for high dose-rate aerosol drug delivery. The goal of SUPRAER™ is to generate large particles from aqueous solutions of the agent of interest, rapidly dry them, concentrate them and deliver a solid respirable aerosol of "pure" agent to the patient on demand. SUPRAER™ is portable but not pocket-sized. US and PCT patent applications have been filed.

The goals of a SUPRAER™ -drug combination for high dose-rate aerosol delivery system are to:

- Target the drug directly to the diseased lungs
- Enable home treatment
- Reduce the total dose administered compared with oral or IV
- Reduce the potential side-effects and complications with long term IV administration

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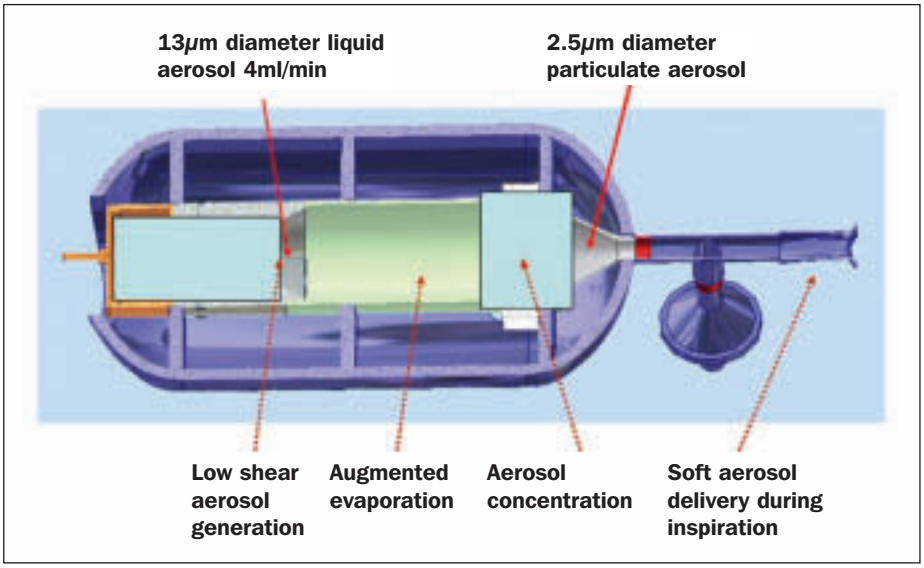

Figure 1: A schematic representation of the processes whereby SUPRAER delivers a high dose-rate respirable aerosol

- Reduce the cost of the drug and its administration
- Increase patient and physician acceptance and compliance
- Produce an expected improvement in therapeutic outcome

To maximise the mass of drug being delivered to the lungs, the particle size should be as large as possible. However, large particles (6-10 μm) deposit predominantly on the delivery tubing, mouth and larynx with only a small fraction reaching the alveoli. The maximum efficiency for alveolar deposition of inhaled particles in healthy humans during "normal" breathing is about 4 μm in diameter.[4] Particle deposition of this size, and larger, is more affected by breathing pattern than that of smaller particles. This issue becomes especially evident in patients with airway diseases.

The mass increases as the cube of the radius of the particle. Thus, we have chosen a "compromise" particle size of 3 μm aerodynamic diameter for delivery.

SUPRAER™ generates large aqueous particles which are rapidly dried and concentrated and delivered as a "soft" respirable aerosol of pure drug to the patient (see figure 1).

As SUPRAER creates large aqueous particles, the energy and the shear forces are reduced. The energy required to create the surface area of a 3 μm diameter aqueous aerosol is five times greater than that required to create a 15 micron diameter aerosol from an equal volume of fluid. Particles generated with a diameter of 13.9 μm are 100 times the volume of 3 μm particles and thus can carry 100 times the mass of active agent.

The task at hand is to generate relatively large aqueous particles (12-20 μm) with a relatively narrow size distribution at aqueous fluid flow rates up to 5 ml per minute. The size of the residual particle can be controlled through either a) the concentration of the agent in solution or b) the aerosol generation process. For instance, in the above case, a 1% protein solution aerosolised at 5ml/min would result in a maximum output of 50 mg/min of 3 μm diameter protein particles; thus providing the potential for high dose-rate drug delivery.

It is also notable that SUPRAER™ can deliver high concentrations of sparsely soluble agents. The aerosol processing technology used in SUPRAER™ can be adapted to accommodate a number of aerosol generating "orifices". This provides flexibility in creating a specific drug-device combination suitable for premarket approval (PMA) regulatory processes of the US FDA.

SUPRAER™ augments the drying of the aqueous aerosol and concentrates the resultant aerosol which is then delivered to the patient by a breathing control unit. SUPRAER™ is designed to deliver the aerosol on demand and to ensure the patient slowly inhales a soft aerosol throughout the entire breath, thus maximising the dose delivered per breath and the reliability and reproducibility of the deposition of the inspired aerosol.

ADVANTAGES OF SUPRAER™

- Markedly reduces inhalation times
- Avoids the problems of dry powder dispersion
- Obviates the physicochemical problems of generating respirable aerosols of high-concentration protein and macromolecular solutions.
- Delivers an optimum and stable size aerosol tailored to both the drug and target site.
- Eliminates particle-size variability due to evaporation of aqueous aerosols during breathing
- Eliminates the use of potentially irritating excipients.
- Minimises shear-induced molecular degradation by single-pass generation of large particles
- Delivers aerosols of sparsely soluble agents.
- Delivers surfactants, antibiotics, proteins, oligonucleotides, liposomes, viral vectors and mucokinetics.
- Aerosol size tailored for deposition at the desired target site.
- Aerosol generation does not require large negative pressures, rapid inhalation or hand-breath co-ordination.
- Inhalation rate of the "soft" aerosol is either continuous or self-regulated via visual feedback
- The dose delivered is indicated.

APPLICATIONS

Aerosol Delivery of Surfactant

In addition to the need for aerosolised surfactant for the treatment of respiratory distress the delivery of surfactant is likely to become an efficacious treatment for obstructive lung diseases. Respiratory distress syndrome, RDS, affects 2 million babies worldwide with 270,000 occurring in the developed world. Of this only 100,000 are estimated to receive surfactant therapy. Also, some 50,000 infants develop broncho-pulmonary dysplasia, BPD. The cost of treating BPD in the US and Europe can approach $250,000. Adult respiratory distress syndrome impacts 150,000 to 200,000 adults in the US with similar numbers in Europe. Surfactant deficiency has been implicated in the pathogenesis of COPD.[5] This patient population includes patients with chronic bronchitis and emphysema.

THE GOAL OF SUPRAER™ IS TO DELIVER A SOLID RESPIRABLE AEROSOL OF PURE AGENT TO THE PATIENT ON DEMAND

Aerosol Delivery of Antibiotics

The demand for high-dose drug delivery, particularly for antimicrobials, where the industry has so far failed efficiently and reproducibly to deliver drugs in a short time is evident. For instance, Tobramycin is an aminoglycoside antibiotic. It has a molecular weight of 467.5, a specific gravity of 1.0, and is water soluble.

It is sold in doses of 300 mg in 5ml capsules. This solution is inhaled in about 200 breaths over a 30-minute period twice a day. Clearly, if this time could be reduced to 2-3 minutes, the procedure would be more tolerable for the patient, and would likely increase patient compliance. The need extends beyond those patients with cystic fibrosis to COPD and bronchiectasis.[6]

Aerosol Delivery of Alpha-1 Antitrypsin (ATT)

Of the 19.3 million people with COPD it has been estimated that 9.5% of these (over 1.8 million) carry phenotypes, PiMZ, PiZZ or PiSZ. These phenotypes are related to increased risk of severe emphysema in later life.[7] Persons who have genetic deficiency of the enzyme inhibitor, alpha-1 antitrypisin (AAT), have an absence or marked reduction in protection against neutrophil elastase. Many of these AAT-deficient patients will suffer from emphysema following the 4th and 5th decades of life.

In people with emphysema, neutrophils are twice as abundant compared with healthy persons, thus exacerbating the loss of gas-exchanging alveoli in these people. Furthermore, life expectancy is reduced by 20 years for AAT-deficient smokers.

There is no cure for this disease. Disease management involves the augmentation of AAT through weekly intravenous infusion of human plasma-derived alpha-1 antitrypsin. This intravenous infusion process is administered in a clinical setting and requires 15-40 minutes. Although the delivery of alpha-1 antitrypsin by aerosol was advocated by Crystal and colleagues in 1989 [8,9], it is still not an approved form of therapy. This has been, in part, due to the inadequacy of the methods for aerosol delivery of 100-250 mg of AAT.

Presently, approved augmentation therapy with AAT consists of once weekly clinically supervised intravenous infusion of a dose of 60 mg/kg[10] of either, a) 1000 mg/50 ml of AAT for 37.5 minutes (Aralast), b) 1000 mg/40ml over 30 minutes (Prolastin) or c) 1000 mg/20 ml over 15 min (Zemaira). Long term administration of IV AAT is not well accepted by patients.[10]

SUPRAER™ will enable the delivery of AAT directly into the airspaces of the lungs and thus provide better protection in the lungs than IV administration.[8] SUPRAER™ will reduce the delivery time of 100 mg AAT to a few minutes compared with some 20-30 minutes with the presently proposed aerosol delivery systems. The self administration of AAT with SUPRAER™ will take place in the home, thus reducing medical costs and avoiding the long term complications of multiple intravenous administrations. As administration of AAT is not required on an emergency basis, its administration in the privacy of the home should meet with wide patient acceptance, especially considering the IV alternative.

SUPRAER™ HAS THE POTENTIAL TO PROVIDE A NEW THERAPEUTIC MODALITY FOR TREATING PATIENTS WITH COPD, CYSTIC FIBROSIS AND LUNG CANCER

Alpha-1 antitrysin, AAT, by aerosol may not only be beneficial to people with homozygous alleles of AAT deficiency but also in persons with other inflammatory lungs diseases, including COPD, asthma and cystic fibrosis. In addition, a reduction in alpha-1 antitrypsin defence mechanism has been implicated in the pathogenesis of diabetes and HIV.

Aerosol Delivery of siRNA

The very recent discovery of siRNA, a naturally occurring gene regulation mechanism found in all plant and animal cells, turns out to be an exceptional drug target discovery and identification tool. siRNA is particularly appealing to those "non-druggable" therapeutic targets that are not accessible by conventional small chemical entities and molecules, proteins and monoclonial antibodies. Thus, siRNA has considerable therapeutic potential to silence genes that are involved with the pathogenesis of disease.

At present, there are no known in vivo delivery methods and formulation of siRNAs to the targeted cells/organs that minimises toxicity and non-specific inflammatory responses, while maintaining the integrity, stability and functionality of the siRNA. The capability of SUPRAER™ in delivering high dose rate of aerosolised, formulated siRNA to the targeted pulmonary diseased epithelia has the potential to provide a new therapeutic modality for treating patients with COPD, cystic fibrosis and lung cancer that were previously deemed to be "undruggable" targets.

BioTechPlex is seeking pharmaceutical and biotechnological partners for the SUPRAER™ - drug co-development for high dose-rate aerosol of their specific agent.

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BioTechPlex is an emerging drug discovery, development and delivery company focusing on the treatment of diseases of the airways, including emphysema, asthma, COPD, and cystic fibrosis.

Cell-based target site identification, physiology, pharmacology and toxicology
BioTechPlex has developed new tools, advanced technologies, assays, genetically engineered cell lines and inflammation-dependent anti-asthma target sites. Through the measurement of the intracellular dynamics of 3 independent, but coupled, target site-activated molecular species simultaneously, BioTechPlex derives from these fluorescent-based high content assays, the specificity of the target site, its cellular signal transduction physiology, the dose response and the toxicity profile.

Tissue-based Validation
Tissue-based assays include ciliary activity, transepithelial water transport and electrophysiology.

Safety Pharmacology
Safety pharmacology assays include: respiratory, cardiac and autonomic neural function can be assessed in conjunction with our Small Animal Respiratory Exposure System (SARES).

Products
CardioDataPad®, for the evaluation of cardiac autonomic function.
CiliaScope® for the evaluation of ciliary beat frequency and metachronal wave frequency

Services
BioTechPlex provides access to the above technologies on a fee-for-service basis.

Partners
BioTechPlex is seeking partners for:

a) Development of novel agents for its inflammation activated, siRNA-linked target for the treatment of asthma and
b) High dose-rate aerosol delivery of specific agents for which the high dose-rate aerosol delivery technology of SUPRAER™ provides a competitive advantage for their specific agent.

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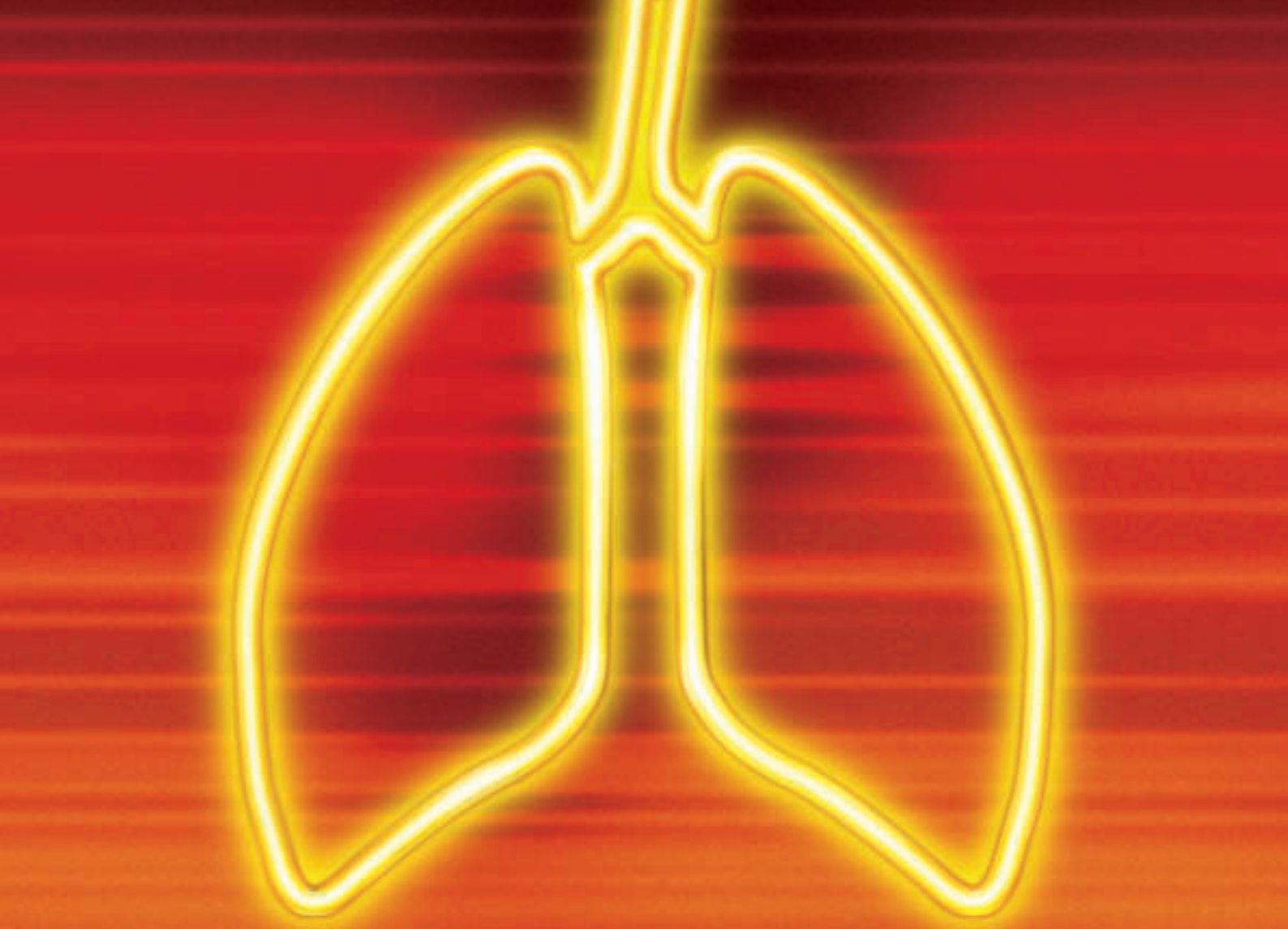

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EFFICIENT PULMONARY DELIVERY OF BIOLOGICAL MOLECULES AS PROMAXX MICROSPHERES

In this article, Julia Rashba-Step, PhD, Director, Research, Epic Therapeutics (a Wholly-Owned Subsidiary of Baxter) presents robust scientific data combined with a candid account of some of their internal procedures and company culture, as evidence that when it comes to the development of inhalable biologics, the PROMAXX microsphere delivery technology is capable of yielding a suitable inhalable formulation, and that Epic is a company with the necessary credentials to deliver a commercial product.

Since they first emerged as therapeutic products, the delivery of proteins, peptides, nucleotides, antibodies and other biologics has been almost exclusively the preserve of the injectable route. However, in recent years, developments in the pulmonary administration of biologics have gathered pace. Today, local delivery to the lung and systemic delivery through the lung both represent viable, proven delivery options for biological therapeutics.

Technologically speaking, the key to delivering biological molecules to and through the lung successfully is the ability to produce a suitable dry-powder formulation which meets precise specifications using a simple, robust and cost-effective process. In terms of delivering the successful commercial product, it is equally important that the company developing and carrying out that formulation process has the right credentials to affect an efficient, mutually rewarding and long lasting working relationship with its drug partner.

FORMULATION CHARACTERISTICS

PROMAXX microspheres are produced via a controlled phase separation process, most commonly involving cooling a super-saturated solution of aqueous protein and aqueous polymer under controlled conditions. The conditions - including ionic strength, pH, polymer concentration, protein concentration, rate of cooling, among others – may all affect formation of PROMAXX microspheres and can be varied to produce precisely the required results. PROMAXX microsphere formation takes place in an aqueous system and at mild temperatures, yet it is highly versatile, meaning that in addition to proteins and peptides, it is also applicable to other classes of biological therapeutic molecules including: nucleic acids, siRNA and small molecules.

Among the attributes that differentiate the PROMAXX process from other pulmonary powder production techniques such as spray drying are that:

- process yields homogenous particles within tightly specified size ranges, so no sieving is required;
- although it is possible to incorporate excipients into PROMAXX formulations, there is not a requirement for excipients, meaning that microspheres consisting of essentially only active molecule can be produced. High dose loading, comfortably above 90%, means that less powder mass need be delivered to achieve the desired pharmacological effect.

Epic Therapeutics has produced and characterized multiple PROMAXX microsphere formulations for pulmonary delivery. Here we discuss in detail two examples of PROMAXX formulations of human growth hormone (hGH), alpha-1 anti-trypsin (AAT) and insulin. The results demonstrate how PROMAXX microspheres measure up against the criteria that a successful inhalable dry-powder formulation must meet.

ALPHA-1 ANTI-TRYPSIN (AAT)

The physiological function of AAT is to control the levels of the neutrophil elastase enzyme. In patients with AAT deficiency, a serious hereditary disorder, inadequate levels of the protein can cause liver damage and destruction of the

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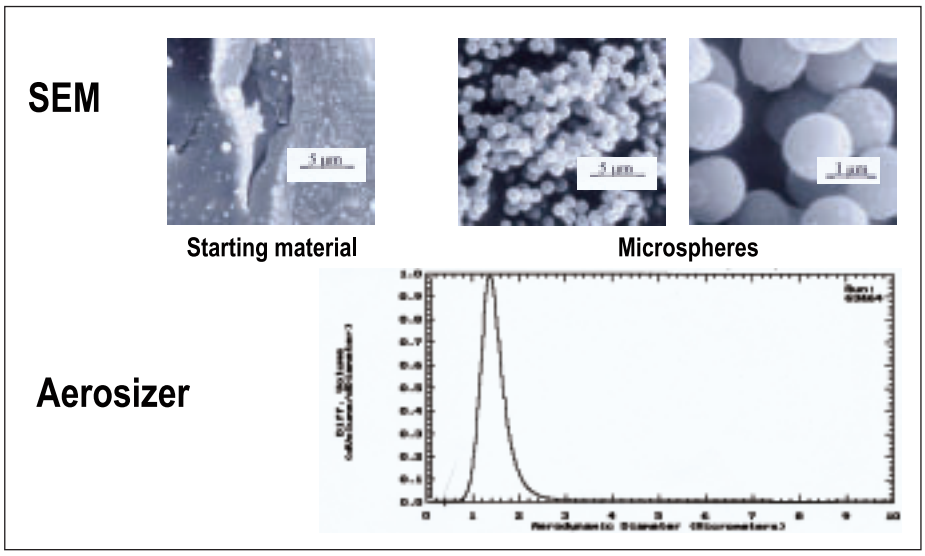

Figure 1: SEM images of AAT starting material and PROMAXX particles, and Aerosizer particle-size range data

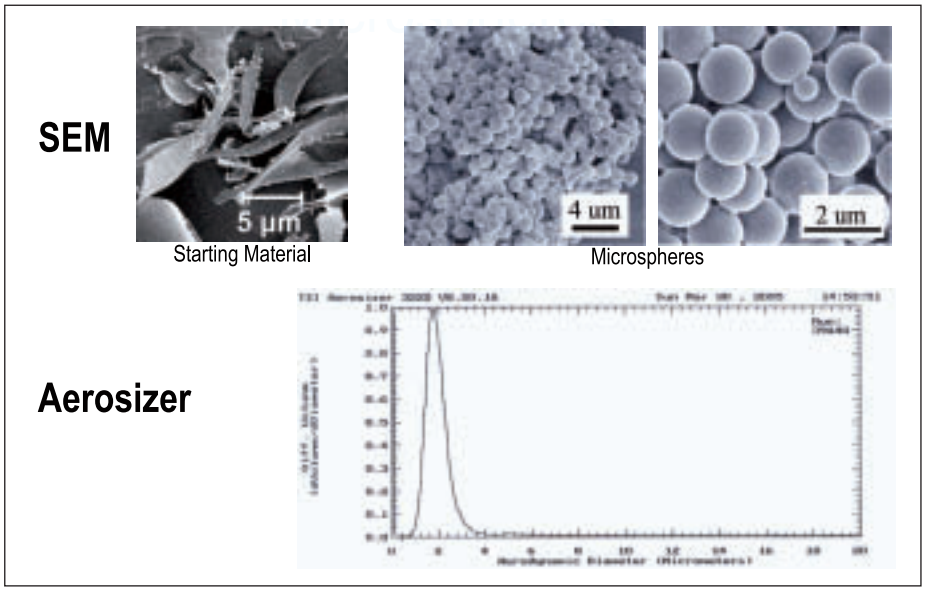

Figure 2: SEM images of hGH starting material and PROMAXX particles, and Aerosizer particle-size range data

alveolar tissue. The condition is traditionally treated with intravenous AAT augmentation but a pulmonary formulation allows administration directly to the site of action. Also delivery to the lung can solve the challenge of limited availability of AAT.

Particles within the target size range of 1-3 µm are essential if AAT is to be delivered to its site of action in the deep lung. Time-of-flight measurements made using a TSI Aerosizer and scanning electron microscopy (SEM) showed that the PROMAXX process generated AAT microspheres within the required size range and very narrow particle size distribution (see Figure 1).

Andersen Cascade Impactor studies showed that high respirable fraction (73%) of AAT protein particles were delivered to stages 2 to F, with an emitted dose of 86% from a Cyclohaler™, a simple, pocket-sized dry-powder inhaler developed by Pharmachemie, The Netherlands. These excellent aerodynamic properties were reproducible across different lots of microspheres.

Another critical test of a pulmonary dry powder production process is the retention of activity after the process, compared with activity before the process. AAT is a labile protein prone to aggregation and oxidation. An *in vitro* AAT activity assay quantifying the level of elastase inhibition showed that PROMAXX AAT retained at least 95% of its activity compared with the starting material.

Finally, shelf stability studies carried out at 4°C and at room temperature for 12 months showed no difference in activity loss between AAT PROMAXX microspheres and a lyophilized control drug.

HUMAN GROWTH HORMONE (hGH)

Human growth hormone, currently administered by daily subcutaneous injection to children with growth hormone deficiency, is a promising candidate for formulation for inhalable delivery. Not only would convenience and comfort be significantly enhanced compared with injection, but therapeutic efficacy is also likely to be improved. The protein is relatively small at 22 kDa, meaning that high bioavailability in the lungs is likely. Furthermore, using inhalation it may be possible to mimic the pulsatile nature of endogenous release.

The PROMAXX microsphere formulation of hGH yields particle sizes in the range 1-5 µm with an MMAD of 3.0 µm. As with AAT, the microspheres consisted essentially of active protein since no excipients are needed, and there was a narrow particle size distribution (see Figure 2). Andersen Cascade Impactor analysis showed the emitted dose from the Cyclohaler was 62.8% and the respirable fraction was 67.4%. SEC and RP-HPLC showed that, compared with starting material, after the PROMAXX formulation process, at least 95% of hGH activity was retained.

Systemic delivery of hGH PROMAXX microspheres to dogs via pulmonary administration resulted in very high serum concentrations of hGH and bioavailabilities of 30-50% relative to subcutaneous injections. Pulmonary administration of hGH resulted in a considerably lengthened pharmacodynamic response relative to that of subcutaneous administration as measured by IGF-1 (insulin-like growth factor 1) serum concentrations versus time post administration.

INSULIN

Inhalable insulin has perhaps the highest profile amongst all of the biological molecules under development for pulmonary administration, with one pulmonary insulin product having reached the market last year.

Like AAT and hGH, the PROMAXX formulation process has yielded positive results when applied to insulin. Particle size distribution studies have revealed that 95% of particles fall within the range 0.95-2.1 µm, and greater then 80% of the emitted dose of the formulation was delivered to stages two to F of the Andersen Cascade Impactor. Figure 3 shows that PROMAXX insulin powder retained its aerodynamic stability over 10 months, with little variation in Andersen Cascade Impactor data over

the time period.

One investigator commented: "The deposition of the radiolabeled insulin into the peripheral lung was superior to any aerosolized product this investigator has seen."

Preclinical studies in dogs have revealed pharmacokinetic and pharmacodynamic profiles of PROMAXX insulin comparable with subcutaneous injection. Specifically, serum insulin levels following inhalation of 0.44 mg of PROMAXX insulin were comparable with levels obtained following 0.12 mg delivered subcutaneous (SC). Figure 4 shows that the effect on serum glucose levels following 0.44 mg PROMAXX pulmonary insulin mirrored that of the subcutaneous dose very closely.

A Phase I clinical trial of PROMAXX insulin delivered using a simple DPI was recently completed. A total of 30 subjects participated in the randomized, two way crossover study conducted in Germany. The trial showed the product to be safe and well tolerated in healthy volunteers. The bioavailbility relative to SC was more than 12%. No coughing or shortness of breath was observed following inhalation. PROMAXX insulin has performed very well thus far through its development. Baxter recently presented the Phase I data at the Respiratory Drug Delivery Europe 2007 Conference in Paris.

FROM SAMPLE API TO CGMP FORMULATION SCALE-UP

The following few paragraphs are intended to give an account of the various stages that a biological molecule from the partner might go through on its journey towards full-scale manufacture as an inhalable PROMAXX formulation.

The process usually begins with Epic being supplied with a small quantity of the molecule by a company interested in finding out whether it is suitable for formulation using PROMAXX technology. A go/no go decision is usually reached within eight weeks following rapid screening studies at the >1 mL scale. These investigations will include solubility profiling, generating phase diagrams for the formation of solid precipitate, and identification of process boundaries.

There are two important points to note at this initial stage. Firstly, due to the complex and expensive nature of producing many biological molecules, it is common that only a very small amount of the candidate molecule is made available for Epic to assess. This presents no problem since only a tiny quantity is required for initial studies to assess whether the PROMAXX technology can be effectively applied to a molecule of interest; a far smaller amount than would be required for a similar initial assessment for a spray dried formulation, for example.

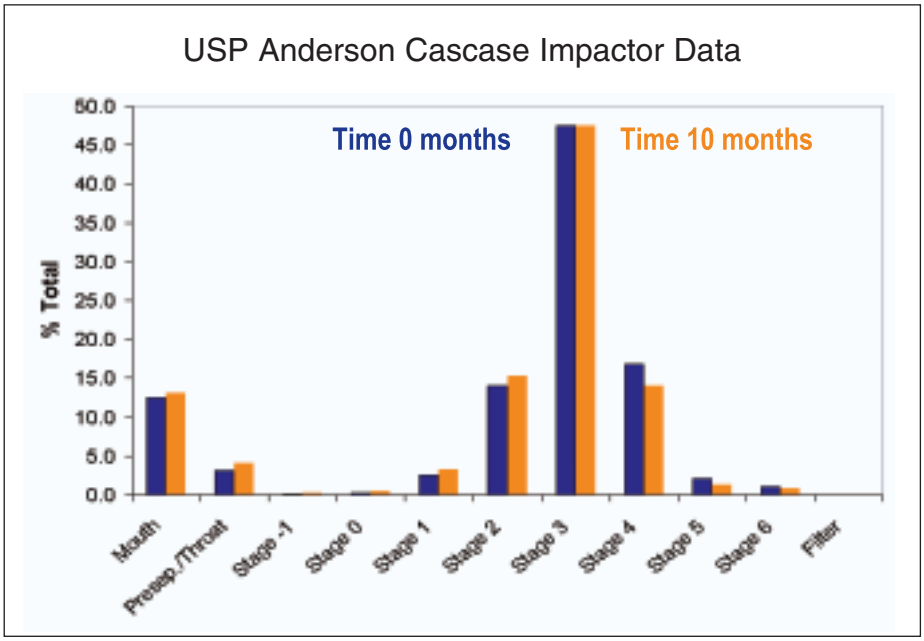

Figure 3: Aerodynamic Stability of PROMAXX Insulin measured by USP Andersen Cascade Impactor

The second point to note is about the context and the likely events leading up to the initiation of studies to explore the potential of the molecule with PROMAXX technology for pulmonary delivery. In many cases, companies will approach Epic because they have a problem formulating their molecule in-house using their own approaches. Thus for Epic, the starting point, as it first takes delivery of the test quantity of API, is often to resolve an existing problem. Epic's team of problem solvers work diligently to create a viable formulation.

After the initial go/no-go decision is made, preliminary formulation work can begin in 1-40 mL reactors. A biophysical characterization of the formulation, molecular integrity, microparticle morphology and yield analyses are often conducted. Informal pharmacokinetics (PK) studies can be conducted at this stage before fine tuning the formulation after which the project moves to process development for scale-up.

Figure 5 outlines the complex web of relationships between the key process parameters. Empirical approach for formulation development is possible but is time and labor intensive. A high throughput screening approach using DOE rapidly increases efficiency of formulation process and identifies optimal formulation conditions.

The final formulation is developed and pro-

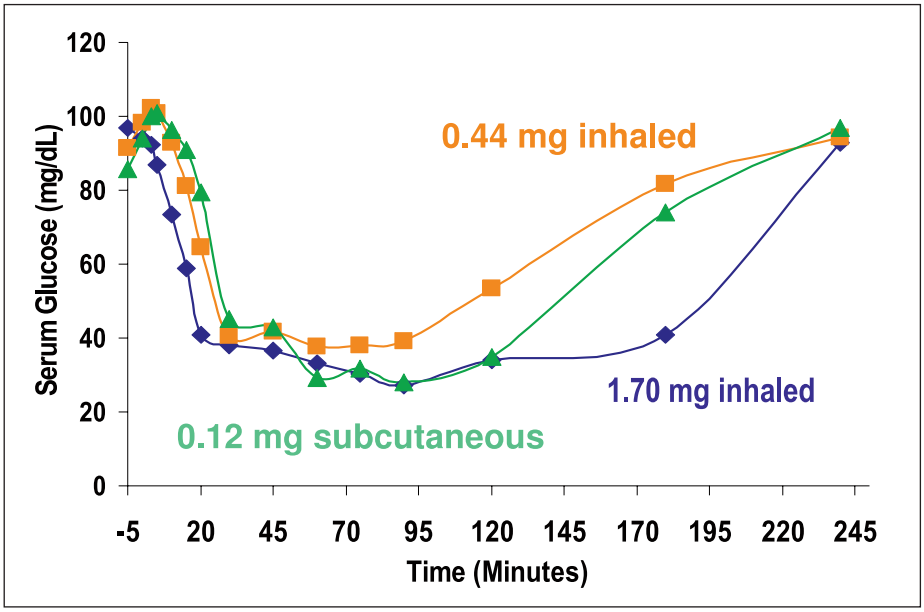

Figure 4: PROMAXX insulin pharmacodynamics (n = 5 dogs at each time point)

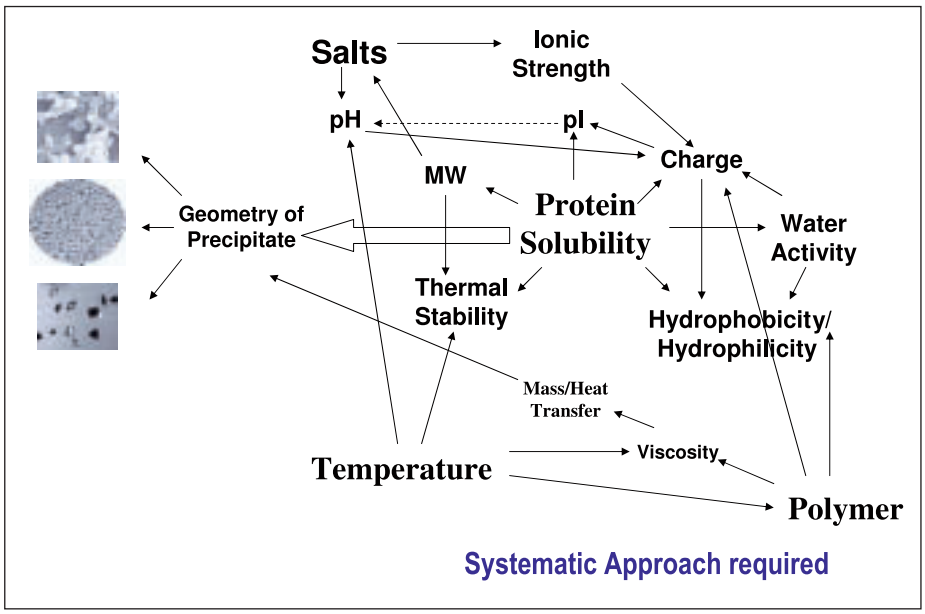

Figure 5: Process Parameters. Interrelation of the Key Factors

duced in 50-500 mL reactors. Process characterization and control is carried out at this stage using online monitoring and data collection. Molecular integrity, microparticle morphology and yield analysis are conducted as well as *in vitro* and *in vivo* aerodynamic performance studies.

The last stage is manufacturing scale-up, conducted in 1-10 liter reactors under "clean" conditions.

Epic is keen to stress that although it benefits from experience, and there are precedents to use as guides, there is no rigid, standard procedure to follow as a project progresses. The project design is highly versatile and succeeds because it is readily tailored to the particular needs of each individual formulation and, crucially, to each individual partner's requirements and specifications.

For example, two key factors shaping the design of the project are the amount of test substance made available to Epic, and the partner's time requirements. Indeed planning the timing of the project carefully and meeting the specified timelines are paramount.

STEPS OF A TYPICAL PARTNERSHIP

In the same way that the structure and timing of the various practical/technical development stages of each project are unique to that project, the commercial and legal structure of every individual project is tailored to that particular project's needs.

Typically, a partner comes to Epic needing to enable or enhance the continued development of their molecule. An initial non-confidential discussion reveals a likely fit and then, under a Confidential Disclosure Agreement, Epic and its partner may share data on the molecule, the project, the objectives and the PROMAXX technology.

It is important to note that while Epic might be approached by a company with PROMAXX technology in mind, it could be that one of Baxter's many other drug delivery technologies are appropriate. Partners approaching Epic will have all of Baxter's technologies and services available to them as potential solutions. If the initial assessments indicate that the PROMAXX technology can address the project requirements, a work plan is generated outlining the scope of the project, the metrics to judge progress and the API requirements to complete the work. Additionally an estimate of the time and resources required to conduct the study is prepared.

Once the work plan has been agreed upon, a feasibility study agreement is signed and the study is conducted.

Throughout the study, Epic communicates with the partner constantly. There is typically a face-to-face project "kick-off" meeting, and face-to-face meetings are arranged whenever needed. In between, a continual exchange of information and feedback is maintained. Stages of the project are defined in the agreement, each stage normally culminating in at least one report summarizing results.

Once the necessary data are available and the results support further development, the parties may execute a license and supply agreement.

A broad patent estate surrounds the PROMAXX technology, and Epic's partners can therefore benefit from the enhanced value this strong IP protection provides.

CONCLUSION

Multiple biological molecules, including AAT, hGH and insulin, have been successfully formulated using the PROMAXX microsphere delivery technology, as viable products with excellent characteristics for pulmonary drug delivery using a simple DPI. In addition to proteins and peptides, the technology is being developed for nucleic acids pulmonary delivery.

Epic's team is a team of problem solvers who can use the PROMAXX technology to create innovative solutions to its partners' problems. Epic benefits from the creativity and attention to detail that it can give to projects through its innovative, dedicated and agile team, and from its ability to draw on the infrastructure and resources of its parent organization, Baxter Healthcare Corporation.

Based on an article that appeared in Drug Delivery Technology, 2007 Volume 7 Number 6

AEROLEF™

FREE AND LIPOSOME-ENCAPSULATED FENTANYL: LEVERAGING PULMONARY DELIVERY FOR PERSONALISED PAIN MANAGEMENT

YM BioSciences Inc. is an oncology company that identifies, develops and commercialises differentiated products for patients worldwide. YM is advancing AeroLEF™, a novel, proprietary inhalation formulation of free and liposome-encapsulated fentanyl intended to provide rapid, extended and personalised analgesia for patients experiencing acute pain episodes.

ACUTE PAIN IS UNPREDICTABLE AND HIGHLY VARIABLE

Moderate to severe acute pain (Figure 1) is associated with numerous conditions including post-surgical pain, trauma pain, procedural pain and breakthrough pain experienced by cancer patients and chronic pain patients.

Common features of these various acute pain episodes are rapid onset of pain characterised by unpredictable intensity and highly variable analgesic needs. The delayed onset and fixed dose formats of currently available oral, transmucosal and transdermal routes of drug delivery have hampered efforts to provide rapid and safe titration to effective analgesic doses. Pulmonary drug delivery of AeroLEF™ is designed to overcome the limitations of existing drug delivery strategies.

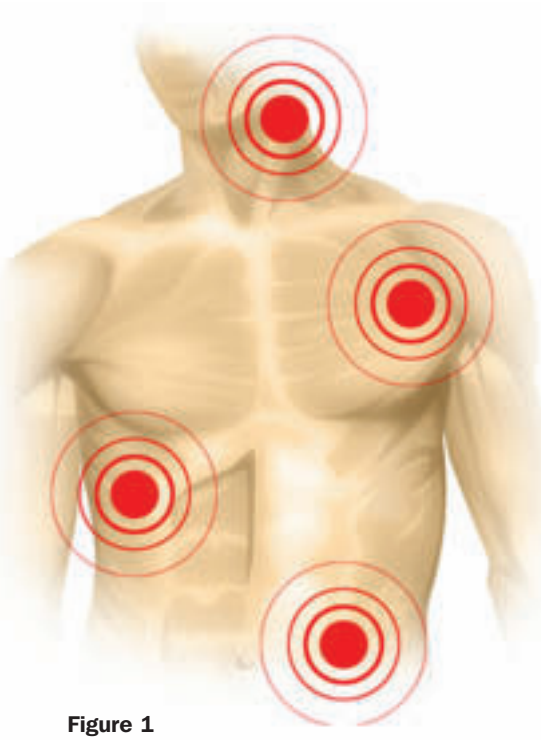

Figure 1

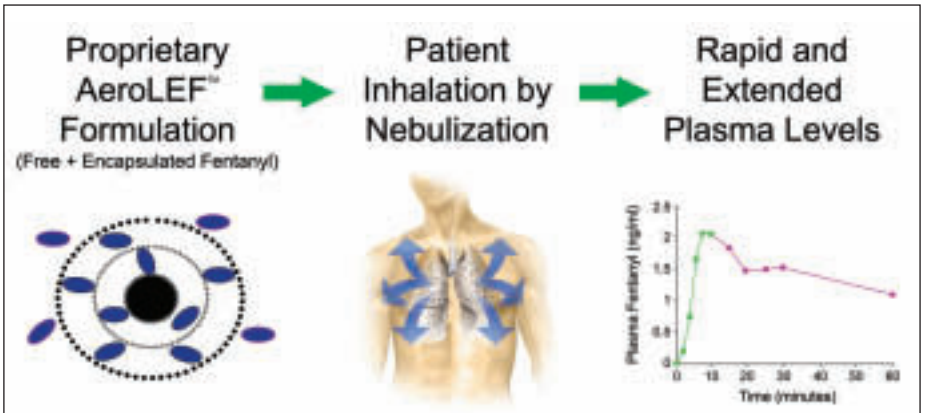

Figure 2

AEROLEF™: DESIGNED TO OFFER HIGHLY-INDIVIDUALISED, EPISODE-SPECIFIC PAIN RELIEF

AeroLEF™ is administered via oral inhalation (Figure 2) using a breath-actuated nebulizer and offers the following potential benefits as a method of analgesic drug administration:

(1) simple and non-invasive route of administration;
(2) rapid onset of analgesia from rapid pulmonary absorption of free fentanyl;
(3) extended analgesia from continued release of liposome entrapped fentanyl; and
(4) personalised, self-titratable dosing.

Pharmacokinetic studies in human clinical trials revealed the close coupling of the maximum plasma concentration with the plasma concentration realised at the end of inhalation dosing. This coupling offers the potential for the patient to individualise the consumed dose of AeroLEF™ matched to their perception of meaningful analgesia during dosing.

AeroLEF™ is an investigational drug in late stage clinical development. YM BioSciences has recently completed a randomised, placebo-controlled Phase IIb trial of AeroLEF™ in opioid naïve patients with post-operative pain following orthopedic surgery. AeroLEF™ met the primary endpoint of the study, showing a statistically significant difference in SPRID4 (sum of combined changes in pain relief and pain intensity reported over the first 4 hours following initiation of dosing) from placebo ($p<0.02$).

All of the products in the YM BioSciences portfolio are available for out-licensing and co-development proposals.

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MICRODOSE TECHNOLOGIES

FLEXIBLE, SMART AND LOW COST: THE MICRODOSE DPI, A TRUE PLATFORM INHALER

MicroDose Technologies is developing what could be the first electronic dry-powder inhaler to reach the market. Here, F. Scott Fleming, the company's Senior Vice-President, Sales and Marketing, explains how to retain all the advantages of electronics while keeping the cost down.

Let us begin by busting a myth. When it comes to inhaler design, incorporating electronics equates to high cost. That's the myth, but the truth is using electronics to create a "smart" inhaler does not have to result in an expensive device. MicroDose Technologies has developed a next-generation electronic dry powder inhaler (DPI) which utilises a piezo vibrator to deaggregate and aerosolise drug powders packaged in sealed blisters. This inhaler has a simple design, has a surprisingly low estimated cost to manufacture on the order of USD $10.00, and is reusable for up to six months or longer. The MicroDose DPI, because it is re-usable, is a cost effective alternative to lower-cost, but disposable DPIs such as GSK's Diskus, which provides one month of use.

How can it be so inexpensive? The answer is simple. It is a fair assumption to say that it would be costly to develop and manufacture speciality electronic components for an inhaler from scratch. However, MicroDose has realised that it is also completely unnecessary to do so. The electronics industry manufactures a vast range of highly advanced components for the mass consumer market, and due to the high volumes and rapid development cycles, can offer them quite inexpensively. MicroDose has simply and effectively leveraged a technology transfer, and designed its inhaler around the use of these everyday components. Not only this, but it has also built a robust patent estate around its system based on the technology's specific applications in pulmonary delivery.

With the outdated ideas about electronics and expense debunked, we are now free to move on to examine the rich benefits that an electronic DPI can bring. These benefits are not of the incremental kind. Much more than merely giving a "slight edge" over alternative inhaler formats, the benefits MicroDose's electronic inhaler brings are both significant and manifold, having a positive impact on almost every aspect of the device including pharmaceutical, therapeutic, commercial and regulatory considerations.

HOW IT WORKS

Before examining what the inhaler can do, let us take a brief look at the device itself and then discuss how it works.

The MicroDose DPI is highly design flexible. Figure 1 shows just one possible iteration of the design for the purposes of identifying the main parts. The example device shown has a multi-unit dose design and incorporates a dose counter window. The MicroDose DPI can be designed to be reusable, accepting either single dose or multi-unit dose disposable cartridges.

Figure 2 demonstrates the four simple steps for using the inhaler, which are the same steps involved in using any standard DPI: open cap; advance dose; inhale; close cap. One crucial difference is that, unlike standard mechanical DPIs, patients can be directed by indicator lights and/or other feedback stimuli. The "Inhale Now" light tells the user that the device is ready to use and that they are inhaling properly. The "Dosing Done" light indicates that the dose has been correctly delivered and that the user can stop inhaling. MicroDose's inhaler is the only DPI which gives patients active feedback during administration in this way. Moreover, because the DPI is electronic, the type of feedback and the way the feedback is delivered (light or sound for example) are easily adapted.

The device uses a piezoelectric vibrator to deaggregate the drug powder packaged in either moisture-resistant aluminium or plastic blisters. The blisters are pierced with small needles prior to dosing to creating openings into the flow channel of the device. The device is breath-activated, i.e. the piezo is activated when an inhalation sensor detects a threshold level of the patient's inspirato-

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ry airflow. The flow sensor is directional, meaning that the inhaler is activated only upon inhalation, and not if the user exhales into the device.

The piezo transducer converts electrical energy to mechanical energy (vibration), which is transferred through the blister into the powder. This mechanical energy levitates and disperses the powder, and creates air pressure at the small holes in the top of the blister. These pressure pulses create high velocity jets that provide the mechanism by which the powder is both finely deaggregated and evacuated from the blister (see figure 3). Fine powder emitted from the blister is entrained in the patient's inspiratory airflow and inhaled into the lungs. Since the piezo operates at an ultrasonic frequency, vibrating tens of thousands of times a second, the powder is jetted from the blister very rapidly and in what appears to be a continuous "smoke-like" stream. The designed intent is to deliver the dose in a single inhalation.

Because the piezo vibrator generates the energy needed to deaggregate and aerosolise the powder efficiently, the need for high and forceful inspiratory flow to assure drug delivery is eliminated.

The inhaler and its related blister packaging are protected by 6 issued US patents together with multiple foreign patents and patents pending.

ELECTRONIC ADVANTAGES

Before discussing specific advantages, it is important to emphasise that MicroDose's digital format allows it to take advantage of the dramatic breakthroughs taking place in consumer electronics, where size, processing, storage, and interconnectivity are advancing at a staggering rate.

We shall stay with patient air-flow as we begin to explore the benefits and advantages – many of them unique – which the MicroDose inhaler brings. One of the Holy Grails of inhaler design is flow rate independence, and MicroDose's DPI achieves this challenging objective, with flow-rate having little to no effect on the inhaler's performance within normal inter- and intra-patient variability. Data from studies testing the delivery of a spray-dried peptide from the DPI at three different flow rates is presented in figure 4.

The MicroDose inhaler also achieves a second Holy Grail for inhalers, that of orientation independence. With the MicroDose DPI, the dose delivered remains the same whether the device is held vertical (with the mouthpiece pointing either up or down) or horizontal (with the intended "top" side of the device facing up or down), or anywhere in between (See figure 5). This is not the case with pMDIs and many of the marketed DPIs.

Because it is breath actuated, the potential performance variability introduced by varying patient co-ordination is also avoided.

The attributes described above are all exam-

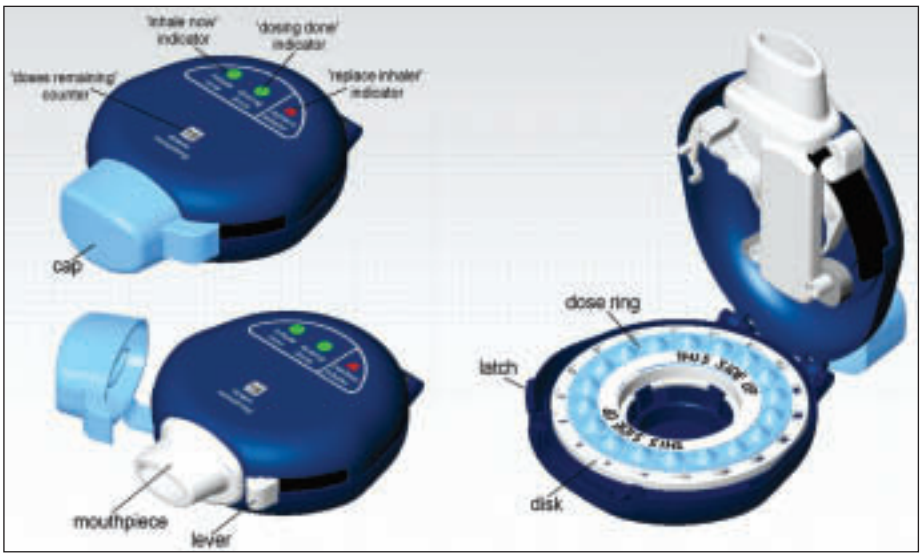

Figure 1: A view of one design iteration, to show the core components

Figure 2: Intuitive, four-step procedure for use

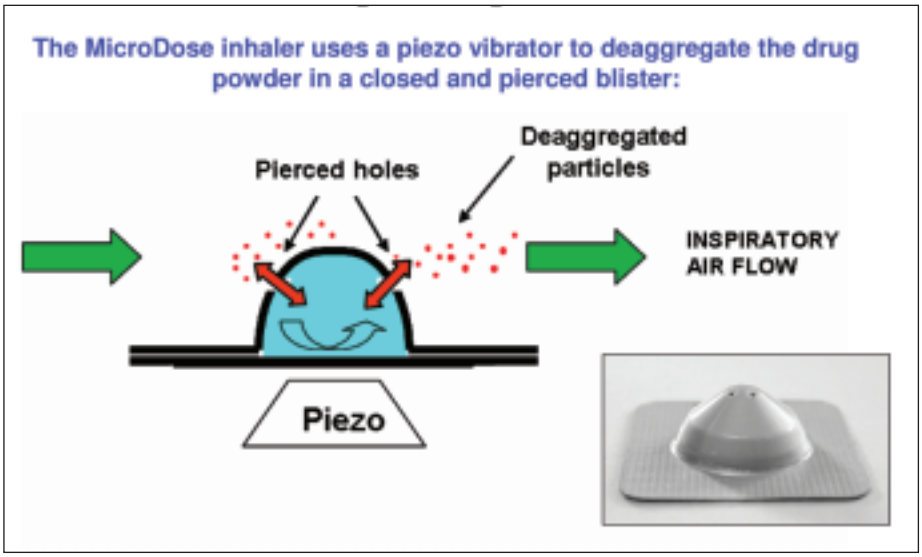

Figure 3: Principle of operation

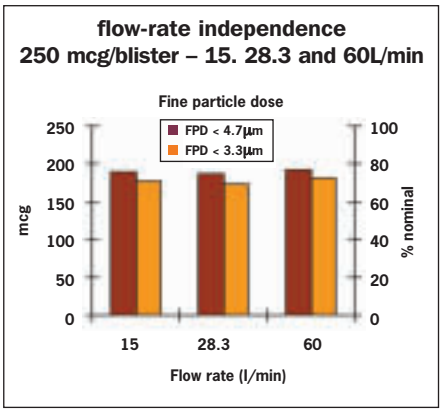

Figure 4: Graph showing constant performance, independent of variable flow rates

ples of the robustness of the MicroDose DPI's design, where the inhaler's function and performance are not compromised by the many variable factors that inhalation devices may encounter in real use. Attributes such as flow-rate and orientation independence, proper dosing feedbacks, etc. make the device easier for the patient to use correctly, whilst the efficiency of the core technology yields significant benefits in in vitro aerosol performance which should help to meet the increasingly higher performance standards established by regulatory agencies worldwide.

However, while an inhaler has to be constant and robust, it must also be flexible and readily adaptable in other ways in order to accommodate a variety of uses and users as well as the varying needs of the market.

A TRUE PLATFORM FOR PULMONARY DELIVERY

Perhaps one of the most important advantages is the fact that the MicroDose DPI is readily adaptable to different drug compounds and formulations, making it a true platform technology applicable across a broad product pipeline. This platform capability translates to reduced risk, time and cost for those companies with multiple candidate compounds who otherwise might have to identify and develop multiple technologies in order to bring its products to market.

The majority of DPIs on the market today have been developed for a specific compound and optimised for a particular formulation. They are efficient at delivering their intended product but if the developer decides to try using it for another compound in the pipeline, complete and fundamental device re-engineering might be required. Sometimes the device must be stripped back to the extent that the journey to the new optimised configuration is so long that it is more appropriate and less complicated to start over by sourcing an entirely new device more suited to the new job.

The MicroDose DPI, in contrast, exhibits unparalleled flexibility, often requiring nothing more than simple adjustment of the piezo transducer drive circuitry in order to optimise it for delivering a new compound. Thus a company licensing-in the MicroDose inhaler can think farther and wider about applications throughout its current and future pipeline. The cost, risk, timeline and strategic advantages are clear.

The MicroDose inhaler has been tested successfully with more than 30 different compounds for both local and systemic delivery, including small molecules such as corticosteroids, long- and short-acting beta agonists and anticholinergics, as well as proteins and peptides, including insulin. The DPI is also capable of delivering formulations produced by a wide variety of processing techniques including: jet-milled pure drug, jet-milled pure drug blended with lactose; spray-dried pure drug; co-spray dried drug and excipients; super critical fluid-processed powders; and combination products.

Across most of these compounds and formulations, the DPI has maintained:

- high efficiency of emitted dose (>90%)
- high fine particle fractions (from 50 to as high as 95% as a percentage of emitted dose, less than 5.8 microns, depending on formulation type and mean particle size of the powder)
- excellent dose-to-dose reproducibility (~2-4% RSD)

DESIGN FLEXIBLE

While the ability to maintain excellent technical performance across the product pipeline is an essential foundation for a true platform technology, the inhaler must also fit with the various clinical indications for which the compounds it delivers are being developed. Crucially, it must furthermore be versatile enough to suit the different patient populations that will be using the device.

The small packaging of the micro-electronics making up the core functioning elements in the MicroDose DPI allows for tremendous design flexibility of the housing or body of the inhaler. This enables the shape of the device and (as mentioned previously) the nature of the dose feedbacks, to be readily modified to suit, for example, geriatric and paediatric populations, or specific diseases. Design features for reasons of aesthetics, product differentiation and branding can be easily added. Additional features such as security codes and lockouts to prevent overdose and/or misuse are also readily incorporated.

Importantly, while these surface modifications have a significant impact on the therapeutic and commercial success of the device, the "nuts and bolts" of the device, the pharmaceutical delivery technology within, is not disturbed. The upshot of this is that the marketing team and those responsible for designing the look and feel

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Figure 5: Graph showing constant emitted dose at various device orientations (% dose emitted ex-device, 28.3 L/minute)

and strengthening the brand need not be forced to reach a compromise with the R&D team, which is concerned with maintaining performance standards such as high emitted dose and fine particle fraction in order to ensure therapeutic efficacy.

PRODUCT DEVELOPMENT UNDERWAY

The MicroDose DPI is certainly a next-generation inhaler. However, it is by no means still at the concept phase. The most advanced product successfully completed its second Phase I clinical trial with inhaled insulin earlier this year with results to be announced shortly.

MicroDose Technologies has a two-fold business strategy. One part is to create improved partnered products by combining proprietary drug delivery technologies with pharmaceutical and biotechnology company compounds.

The other is to develop pharmaceutical products in-house using our proprietary delivery technologies with generic drug substances, for late-stage partnering, co-marketing or sale. These include respiratory compounds, products for diabetes and pain, and proteins and peptides.

MicroDose's partnered programmes include; a multi-product development and licensing agreement with Novartis for its proprietary respiratory compounds, the development of an inhaled insulin product through QDose, its joint venture with Vectura, and also an inhaler for the systemic delivery of a nerve agent antidote for the US Department of Defense, in co-development with the University of Pittsburgh, which will enter clinical trials later this year.

Pulmonary drug delivery is not MicroDose's sole area of focus. The company also has a fixed-dose-combination oral dosage technology, PolyCap™ , which allows two or more drugs to be combined in a single capsule, but separated by a physical barrier. Internal development programmess utlilising the PolyCap™ technology are underway in the areas of diabetes, hypertension and hyperlipidaemia. MicroDose also has proprietary battery-operated, electromechanical needle-free system patents. MicroDose, located just North of Princeton, New Jersey, US, is privately held and has been funded by institutional and angel investors since it was founded in 1998.

SUMMARY

This article describes a highly versatile, flexible, second-generation inhaler. It is an inhaler that makes a material contribution to ensuring the development success not just of one or two carefully picked compounds that meet the criteria to fit, but of entire broad pipelines of products for local and systemic pulmonary delivery, for which it can be readily adapted.

It is on target to reach the market within the timeframe MicroDose planned and, if successful, should be the first electronic dry-powder inhaler available. The MicroDose inhaler achieves the Holy Grails of orientation and inspiratory flow-rate independence, and it is the only DPI with active dose feedbacks to patients. It is highly efficient, and exhibits excellent dose reproducibility. It is portable, pocket-sized and discreet, and readily customisable for a varying range of patient populations. It is a cost-competitive, re-usable device.

MicroDose Technologies is a financially independent and well established drug delivery leader with three platform technologies protected by a broad and robust global patent estate. It has a proven track record as a winning partner with leading pharmaceutical, biotechnology and drug delivery companies, academic institutions and government bodies. MicroDose is keen to develop new relationships with industry.

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CONTROLLED DEPOSITION

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- Individualized for each Drug and each Patient by Smart Card Technology
- Different Electronic Nebulizers

AKITA is the first inhalation device that controls the inspiration phase of the patient electronically resulting in high drug deposition (over 80% of the emitted dose) and less variability both intra and inter patient. The AKITA is individually programmed for control of the inhalation and aerosolization timing to reduce drug usage and minimize treatment time. The special way in which AKITA works creates a new drug delivery perspective. To discuss the benefits of AKITA, contact:

AKITA²

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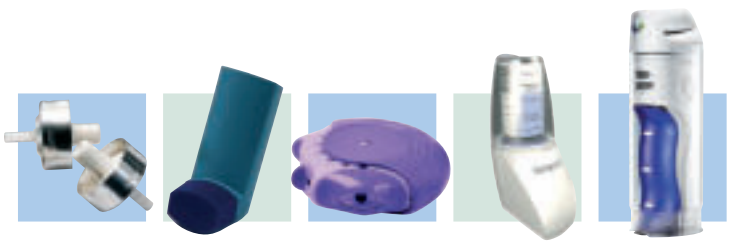

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