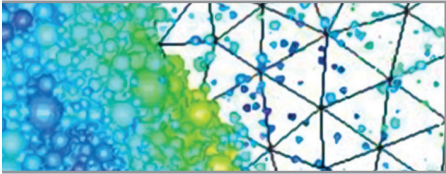


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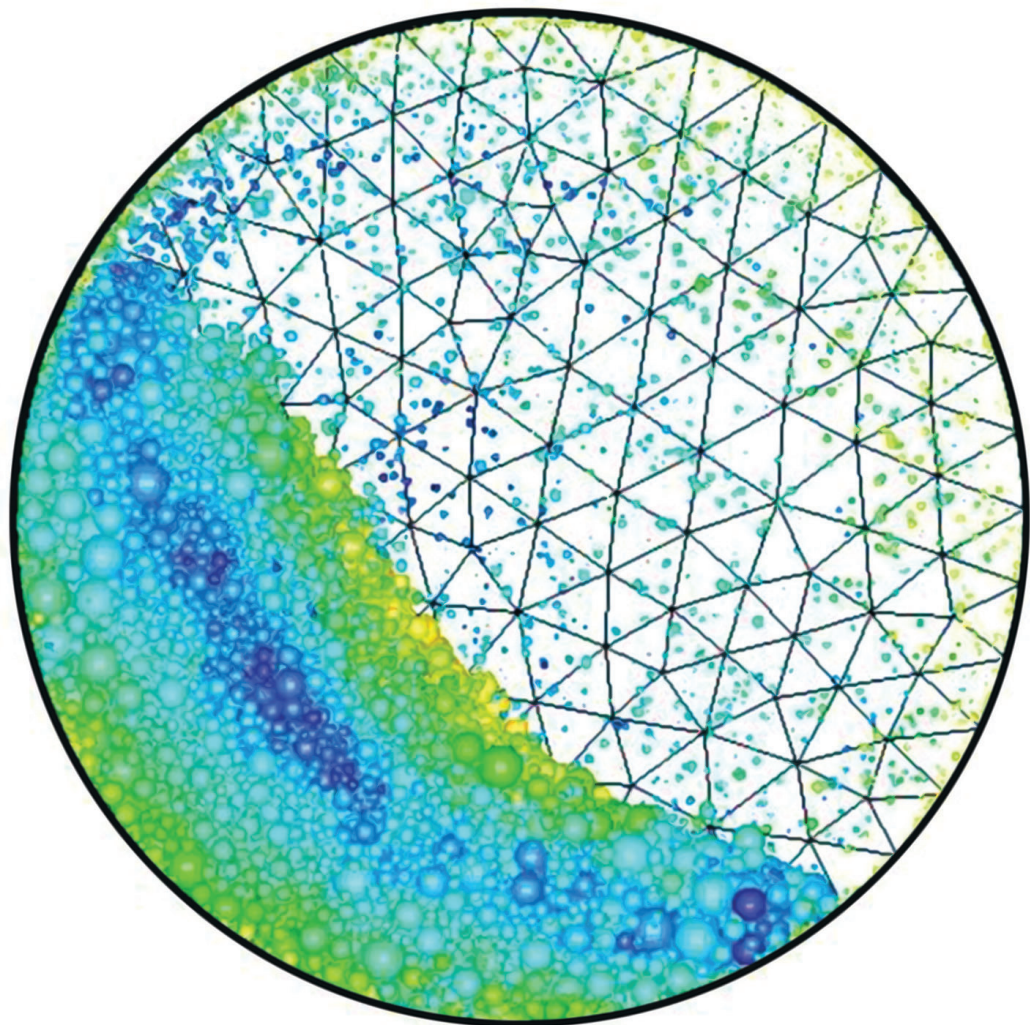
NEW DEVICES, MANUFACTURING EQUIPMENT AND MODELLING TECHNIQUES



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“Pulmonary & Nasal Delivery: New Devices, Manufacturing Equipment and Modelling Techniques”

This edition is one in the ONdrugDelivery series of publications from Frederick Furness Publishing. Each issue focuses on a specific topic within the field of drug delivery, and is supported by industry leaders in that field.

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ACHIEVING THE POTENTIAL OF NASAL DRUG DELIVERY

SNBL is developing its μco^{TM} System for nasal formulation and delivery of small-molecule and protein therapeutics, and intranasal vaccines. In this piece, Shunji Haruta, PhD, Executive Officer, SNBL Ltd, and General Manager, NDS Division, describes the development (including clinical development) of several products in the μco^{TM} System, indicating rapid, effective, safe and well tolerated delivery via the nasal mucosa.

BACKGROUND

Nasal delivery of therapeutics and vaccines has a number of compelling advantages over other routes of administration; namely its non-invasiveness, rapid attainment of therapeutically relevant concentrations to the bloodstream, no first-pass metabolism, and ease of administration.

Viable nasal delivery technologies have the potential to enable drug developers in creating innovative medicines using already approved products by delivering them through new routes

As advantageous as the 505(b)(2) pathway is, hindering technical challenges still persist for nasal delivery technologies, the most notable being mucociliary clearance. Mucociliary clearance, the continuous flow (clearance) of particles and substances from the nasal cavity into the gastro-intestinal (GI) tract, interferes with rapid and efficient absorption of nasally delivered drugs into the bloodstream. Attempts to mitigate the clearance have generally included the use of nasal mucosal permeation enhancers which unfortunately induce nasal irritation and other local toxicities.^{1,2} Additionally, the increase in absorption through the use of enhancers and other marketed nasal delivery technologies still leaves room for the achievement of consistent and high bioavailability.

"THE WATER-INSOLUBLE, MUCO-ADHESIVE POWDER CARRIER SIGNIFICANTLY INCREASES RESIDENCE TIME ON THE NASAL MUCOSA, RESULTING IN HIGHER ABSORPTION WITHOUT THE NEED FOR ENHANCERS"

of administration. Currently the US FDA offers 505(b)(2) applications to drug developers, which allow the use and reference of approved data from previous NDAs to be applied to the alternatively delivered form of the same drug. An attractive option for pharmaceutical companies, this route to approval both shortens timelines and decreases money required to bring products to market.

represents a major advance in nasal drug delivery. With the premise of eliminating the use of liquids in nasal drug delivery, μco^{TM} System's primary breakthrough came in two areas: first, the highly effective, powder formulation carrier technology; and second, the accompanying easy-to-use nasal device, delivering the powder formulation with high reproducibility. The proprietary system's water-

μCO^{TM} SYSTEM

A product of more than ten years in research and development, SNBL's μco^{TM} System



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insoluble, muco-adhesive powder carrier significantly increases a compound's residence time on the nasal mucosa, therefore resulting in higher absorption without the need for any enhancers. Higher absorption also results in a considerable decrease in variability, another issue plaguing poorly absorbed and traditional nasal delivery systems.³

Additionally, the muco-adhesive carrier is water-insoluble and is eventually cleared out of the nasal cavity into the GI tract. The carrier is otherwise inactive in the body, causing no local irritation or safety issues, as observed to date in preclinical and clinical studies.

Finally, perhaps the most compelling advantage of μco^{TM} System is the platform's ability to deliver a wide range of drug compounds, including small molecules and peptides. Its mucosal adhesion qualities also make it a promising technology for locally acting drugs and vaccines.

EXAMPLE APPLICATIONS OF μCO^{TM} SYSTEM

Granisetron

SNBL is currently using the μco^{TM} System to develop a nasally delivered granisetron (TRG). Granisetron is approved as an oral and IV drug (Kytril) indicated for the treatment of cancer patients suffering from chemotherapy-induced nausea and vomiting (CINV). Currently undergoing development in the US, TRG is designed to be the first intranasal, anti-emetic product for patients suffering from CINV.

In a Phase I study, TRG demonstrated complete absorption (100% absolute bioavailability) compared with the marketed granisetron IV injection. Absorption was rapid with maximum concentration (C_{max}) achieved by 20 minutes (70% of C_{max} reached within five minutes) post administration, with low variability observed between patients (Figure 1).

As about half of the granisetron is lost due to first-pass metabolism when given orally and absorbed through the GI tract, the fact that TRG shows 100% bioavailability suggests that nearly all of the granisetron in TRG is being absorbed in the nasal cavity and very little or none is cleared into the GI tract. TRG has been evaluated in 94 human subjects to date and has shown a safety profile comparable to that of Kytril without any observed local nasal irritation.

A preclinical study conducted using SNBL's proprietary and highly effective non-human primate nasal PK evaluation model demonstrated 70% bioavailability with a T_{max} of 30 minutes (Figure 2).

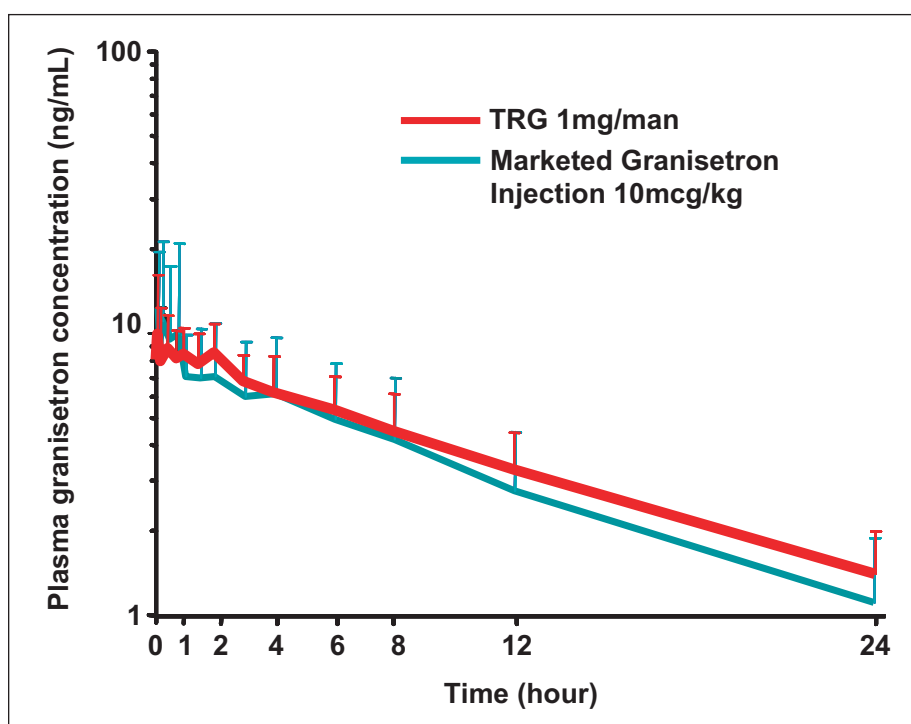


Figure 1: Plasma Granisetron Concentration in Human.

Zolmitriptan

SNBL is also using μco^{TM} System to develop a nasally delivered zolmitriptan (TRZ). Zolmitriptan is currently marketed as Zomig, an oral tablet, an oral disintegrating tablet and a liquid nasal spray, for the treatment of migraine headaches. SNBL is developing TRZ in the US, which promises to be the best-in-class intranasal form of zolmitriptan.

In a Phase I study, TRZ demonstrated higher absorption than the marketed products

(both oral and liquid nasal spray) with relative bioavailability of 136% compared with oral tablets, and 182% compared with the nasal spray. More importantly, TRG demonstrated significantly faster absorption than the existing drugs. Specifically, in the first 120 minutes after administration, relative bioavailability was 200% compared with oral tablets and 333% compared with nasal sprays. Maximum concentration was reached within 20 minutes compared with 120 minutes for the marketed

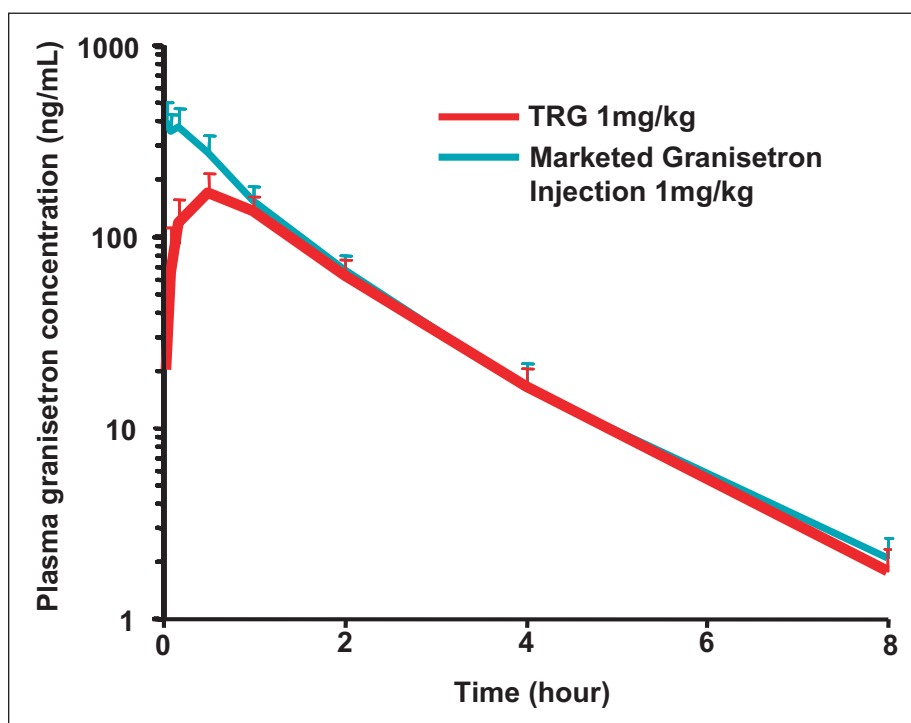


Figure 2: Plasma Granisetron Concentration in Non-Human Primate.

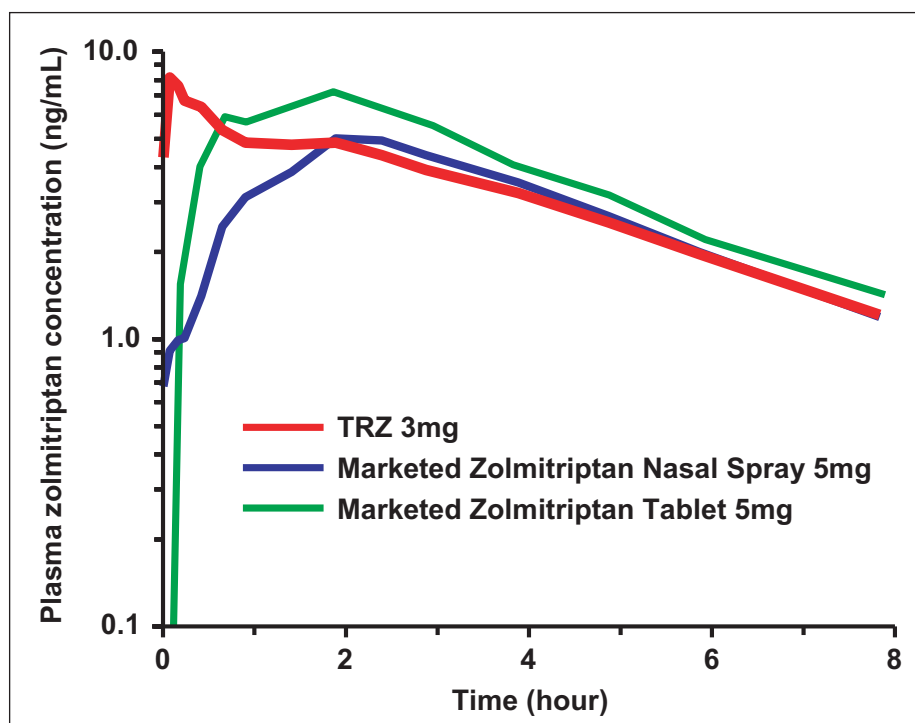


Figure 3: Plasma Zolmitriptan Concentration in Human.

products (see Figure 3). The more rapid PK properties of TRZ strongly suggest the potential for delivering faster headache relief to migraine sufferers.

TRZ is absorbed with greater efficiency and faster kinetics relative to the oral tablet which is, again, consistent with the notion that μco^{TM} System is enabling a large majority of the drug compound to be absorbed through the nasal mucosa into the bloodstream.

Calcitonin

μco^{TM} System has demonstrated high efficiency in delivering peptides into the bloodstream. One example is calcitonin, a 3,431 Dalton peptide indicated for the treatment of osteoporosis and currently available to patients as a liquid nasal spray. In a preclinical study conducted using SNBL's non-human primate PK model, calcitonin delivered by the μco^{TM} System (TRC) showed bioavailability of 17%

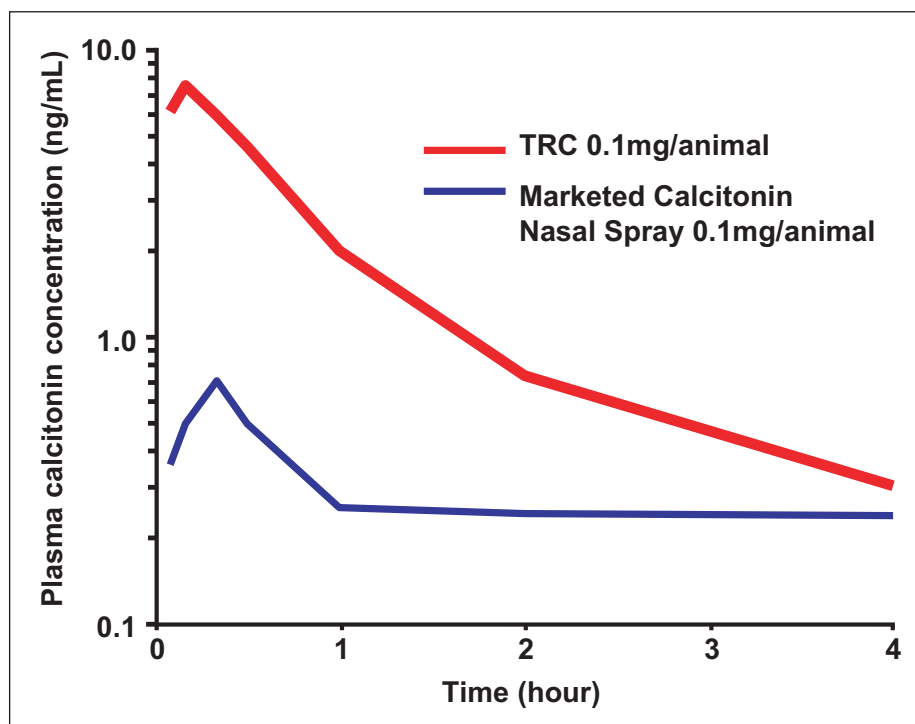


Figure 4: Plasma Calcitonin Concentration in Non-Human Primate.

SNBL'S PREDICTIVE IN VIVO PK MODEL

All too often, nasal drug candidates make it into Phase I trials, only to see a large discrepancy in efficacy between the IND trials and first-in-man. This is largely due to the inappropriate choice of animal models. Currently, dog, pig and rodent models are favoured industry-wide for preclinical testing of nasal drugs. These models, however, are not highly predictive of PK in humans. Due to the large surface area relative to bodyweight and significant differences in the nasal anatomy,^{4,5} PK evaluation in dogs, pigs and rodents may be significantly over-estimated, leading to disappointing clinical trial results and large amounts of wasted R&D money. Non-human primates are truly the best model for preclinical testing of efficacy and safety because the nasal cavity structure is far more similar to that of humans than other test models.

SNBL has developed a non-human primate nasal administration model for these reasons. But in order to create a better predictive model, SNBL has also engineered and validated a nasal administration device which monitors the breathing cycle of the animal and automatically synchronises the administration with the inhalation phase. SNBL's model also enables administration in an unanaesthetised state.

This highly effective and predictive model has important advantages. First, due to an unanaesthetised animal and full administration during the exact appropriate phase in the breathing cycle, results are likely to be more similar to those expected in humans because the model more closely mimics human self-administration of a nasal drug. Secondly, variability is greatly reduced, necessitating as little as three animals per study to obtain reliable results.

As used in the development of SNBL's own nasal products, this model enables more informed optimisation of the formulation and business decision making at a very early stage in development before committing resources to more costly and time-consuming GLP or clinical studies.

compared with IV bolus injection, whereas the marketed liquid nasal spray exhibited only 4% bioavailability compared with IV injection (Figure 4).

SUMMARY

As demonstrated by the examples described above, μco^{TM} System rapidly and effectively delivers drugs (both small molecules and peptides) via the nasal cavity into the bloodstream with consistently high efficiency. Notably, observations in clinical trials to date strongly suggest that μco^{TM} System is safe with very high tolerability.

Although this article has only described applications for delivering drugs systemically, μco^{TM} System also represents an effective platform for delivering vaccines locally to the nasal mucosa. Due to the muco-adhesive carrier's prolonged retention time, the platform

enables efficient delivery of vaccines to the nasal mucosa, resulting in the generation of an effective mucosal immune response. Given these promising properties, SNBL is using μco^{TM} System to actively pursue the development of a number of nasally-delivered vaccines.

In summary, μco^{TM} System is an effective platform to deliver drugs systemically via the nasal cavity, with promising effects for locally acting drugs as well as nasal vaccines. μco^{TM} System represents a significant advance in the field towards delivering on the long-held promises of nasal delivery. SNBL is using μco^{TM} System to develop best- and/or first-in-class therapeutics for opportunities of significant clinical unmet needs. SNBL is also actively partnering with leading pharmaceutical companies to use this platform to enable effective nasal delivery of their internally developed therapeutics and vaccines.

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Figure 5: Prefilled Single-Use Device.



Figure 6: Capsule-Loading Multiple Use Device.

SNBL'S μCO^{TM} SYSTEM

μco^{TM} System consists of two proprietary and complimentary technologies. The first is a GRAS muco-adhesive carrier which is entirely water-insoluble. The carrier effectively prolongs the retention time, allowing the API time to solubilise, permeate the membrane and transfer directly into the bloodstream. The carrier requires no absorption enhancers and causes no irritation or damage to the mucosal membrane; preclinical and clinical studies with μco^{TM} System carrier have confirmed no irritation or damage. The water-insoluble carrier is eventually cleared out of the nasal cavity by the mucociliary clearance into the GI tract; it has no other effects in the body.

The second of the complimentary technologies is a line of in-house designed nasal devices, consisting of a single-use device (Figure 5), and a multiple-use device (Figure 6). These devices provide excellent patient control over treatment as they are easy-to-use and portable, and they are designed to provide consistent and complete delivery (Figure 7) for a wide variety of patient types. The single-use device is preloaded with drug formulation and disposed of after use. The multiple use device accepts encapsulated formulations with negligible residue build-up even after high usage.

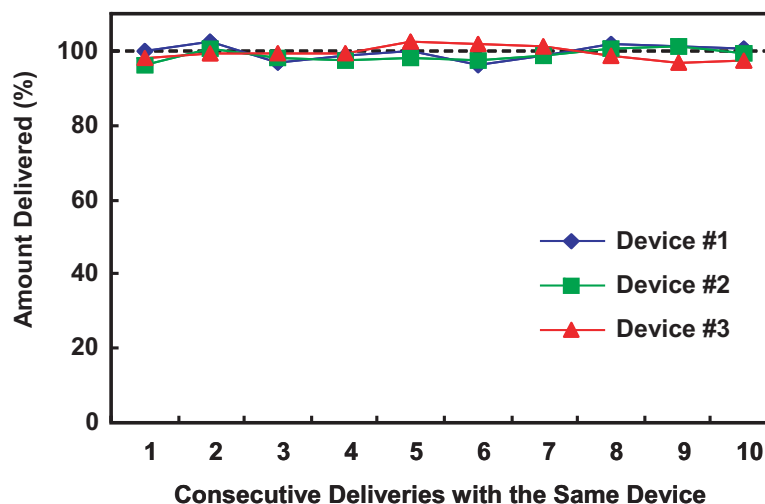


Figure 7: Amount of Formulation Delivered over Multiple Uses.

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TECHNOLOGY SHOWCASE – TWISTER™



Aptar Pharma introduces Twister™, a new versatile affordable capsule-based dry-powder inhaler (DPI), specifically targeting fast-growing markets.

It is estimated by the World Health Organization (WHO) that approximately 235 million people suffer from asthma worldwide. In keeping with the theme of this year's Asthma Day, "You can control your Asthma", the launch of Twister™, brings a cost-effective drug delivery device to pharmaceutical companies, helping them market affordable healthcare treatment to patients worldwide.

In the US and Europe, the majority of asthma drug sales are currently delivered via DPIs and pressurised Metered Dose Inhalers (pMDIs). However, in Asia and Latin America, asthma has been treated predominantly with pMDIs, which are considered to be a more cost-effective device proposition than DPIs. Healthcare reforms in these regions and other growing markets are making asthma diagnosis and medication more available to patients.

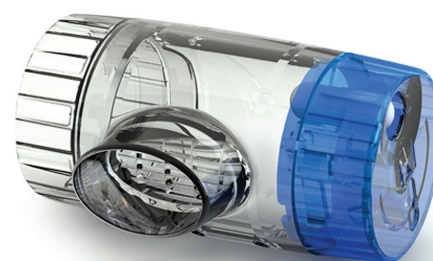
Aptar Pharma anticipates that the trend for growth in the DPI market will spread. Twister™ is by nature simple to use, and will allow a wider range of asthma sufferers to not only gain better access to medication but also become more

compliant with the treatment they receive due to its feedback design.

SENSE AND SIMPLICITY

Twister™ has been uniquely designed specifically to address unmet needs in fast-growing markets. Capsule-filling technologies are well established, cost effective and robust in all regions of the world, allowing for regional manufacturing.

During the development process, Aptar Pharma's dedicated inhalation drug formulation research team tested and collected data on various drug formulations, validating Twister™ as an off-the-shelf device, suitable for a variety of different drug compounds and formulations. Twister™ is a transparent patient-friendly device. Only three simple steps are needed



Twister™: an affordable, versatile, off-the-shelf DPI.

our customers with a wide range of delivery technologies and analytical services backed by years of proven expertise.

Aptar's main focus is on metering valves for pressurised metered-dose inhalers (MDIs), and dry-powder inhalers (DPIs);

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to operate it – Insert, Twist and Inhale – and the patient will be guided by various audible and visual feedbacks confirming that the full dose has been properly delivered.

ABOUT APTAR PHARMA

Aptar Pharma – part of the Aptargroup family of companies along with Aptar Beauty + Home and Aptar Food + Beverage – creates innovative drug delivery systems that meet the evolving needs of biotechnology, healthcare and pharmaceutical companies around the world. The company provide

and multidose pumps, single-dose devices and metering valves for nasal and sub-lingual drug delivery.

The company offers a full set of associated services to support customer speed-to-market and provide global support to customers in all geographies and in both developed and emerging markets.

Aptargroup (NYSE: ATR) is headquartered in the US and has manufacturing sites in North America, Europe, Asia and South America.

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Better by Design

INTRANASAL VACCINE DELIVERY – A PROMISING FUTURE

Needle-based injection is by far the most common route of administration for vaccines yet it has shortcomings in terms of safety and, in some cases, in terms of efficacy too. In this piece, Tim Wolfe, MD, Medical Adviser, LMA Atomization, makes the case for nasal vaccine delivery as a compelling alternative to injection and describes a nasal device that fulfills WHO requirements for vaccine delivery using single-use, auto-disable systems.

INTRODUCTION

Driven by the recent emergence of highly infectious diseases such as severe acute respiratory syndrome (SARS) and H1N1 influenza (swine flu), and by concerns regarding pandemic bird flu or a terrorist deployed weaponised pathogen, the vaccine industry has entered a time of renewed interest and growth. The current global vaccine market exceeds US\$22 billion (£14 billion) in revenue with annual growth rates predicted to be 9.7%.¹

The traditional methods of vaccination are via an oral or an injected route of delivery, with most vaccines being injected. Unfortunately, despite decades of proven efficacy and safety, injectable vaccines suffer from significant downsides that are primarily related to the injection.

Vaccine injections elicit a great fear in many patients, including medical personnel, with estimates of over 10% (probably more) of patients never obtaining immunisations due to this fear.¹⁻³ This failure to immunise such a substantial portion of the population is of concern and can greatly hamper the protective effects of herd immunity should a highly contagious infection enter a community. Highly trained medical personnel are also needed to administer the vaccine injection safely, leading to high labour costs for successful immunisation of large populations. Highly skilled medical personnel also must be immediately available to intervene if an injection leads to an anaphylactic reaction.¹ The limited availability of trained personnel is such that some poor countries are unable to provide

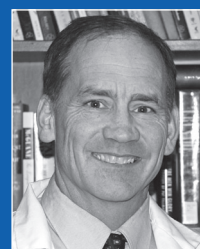
reliable immunisation programs without massive international assistance.

Immunisation shots also fail to provide optimal immune responses to many antigens. Injected immunisations only elicit a systemic immune response, with no establishment of a mucosal immunity to block initial pathogen entry into the body.^{1,4,5} Finally, any time injections are required added costs are incurred due to infection control issues surrounding blood contaminated devices, needle-stick risk issues, prevention of reuse of the injection technology used and safe disposal of the needles and syringes.^{1,6}

AN ATTRACTIVE ALTERNATIVE

Intranasal vaccine delivery offers numerous benefits over injectable vaccines if the antigen is bioavailable across the nasal mucosa and the disease typically enters the host through the mucosal surface.¹ The most obvious advantage of intranasal vaccine delivery is the elimination of the injection. There is no needle, no needle phobia, no fear, no pain, no needle-stick risk, and easier disposal of the delivery system. Because no shot is required the vaccine can be administered by personnel with less training, or potentially even by the patients to themselves. This could be of major importance should a pandemic event require rapid administration of millions of doses of a vaccine.

Nasal vaccines also elicit a dual immune response, in both the systemic and the mucosal compartments. This mucosal immunity leads to production of secretory IgA which likely results



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in an added layer of protection against pathogens that first contact the host at the mucosal entry point.^{4,7,8} Furthermore, transmucosal delivery of antigen has been demonstrated to result in a superior immune response (higher antibody titers) with fewer side effects, significantly reduced risk of an allergic reaction and little need for sterile administration technique.^{1,6,9} Less vaccine is needed as well. The superior immune response found with mucosal vaccine delivery can be elicited with vaccine doses 75% smaller than that required for an injection, a potentially important cost savings in vaccine manufacturing.^{1,6,9}

Intranasal vaccines are not without their concerns.^{1,6,7} To be effective the antigen must be bioavailable across the nasal mucosa and it must be proven to elicit an immune response. Since the nasal mucosal ciliary activity spontaneously cleans off all contaminants the vaccine must be available for long enough to elicit an immune response. The delivery system must also be shown not to damage or destroy the vaccine to ensure the active antigen is provided in adequate concentrations on the mucosa to elicit immunity. Safety issues in terms of CNS distribution through the nose-brain pathway via the olfactory mucosa also need to be studied and addressed. Appropriate research into individual vaccines is required to ensure these issues are resolved prior to widespread adoption of a new vaccine and displacement of proven injectable vaccines. Fortunately some of that research is completed or is being done, noting the efficacy of influenza, measles and rubella vaccines delivered transmucosally.^{5,9}

WHO REQUIREMENTS FOR VACCINE DELIVERY

The cost and safety of any new vaccination technology must be addressed. The World Health Organization (WHO) has specific guidelines for manufactures, which outline all requirements the WHO deems essential for the adoption of a new immunisation delivery system.¹⁰ A primary WHO concept for any new delivery technology is that it should consist of a single-use delivery system that will auto-disable upon use: "All countries should only use auto-disable (AD) syringes for immunisation."

This auto-disable feature provides more effective infection control with less risk of cross contamination by preventing any device re-use either on another patient or for other purposes (as a child's toy, for example). The WHO and other regulatory agencies expect the medical device industry to comply with this requirement while simultaneously providing "a reliable stream of safe, affordable, high-quality devices designed to meet the needs and constraints of the developing world".¹⁰



Figure 1: The VaxINator™ spraying an atomized mist.

NASAL VACCINATION – FULFILLING THE WHO MANDATE

Nasal vaccine delivery fits nicely into the needs of the WHO and the needs of the patient. It can be safely delivered by people with minimal training with less risk of any allergic phenomenon and it elicits an adequate if not better immune response compared with injection. The delivery system does not require any needles so blood contamination is not an issue and needle disposal costs are eliminated, making waste disposal much less expensive. From a manufacturing standpoint the sterile delivery issues are eliminated and the volume of vaccine per patient is less, which can reduce drug costs per patient. Furthermore, high-quality, inexpensive nasal vaccine delivery systems exist that fulfill all the WHO needs in terms of auto-disable functions.

THE LMA VAXINATOR™ NASAL DRUG DELIVERY SYSTEM

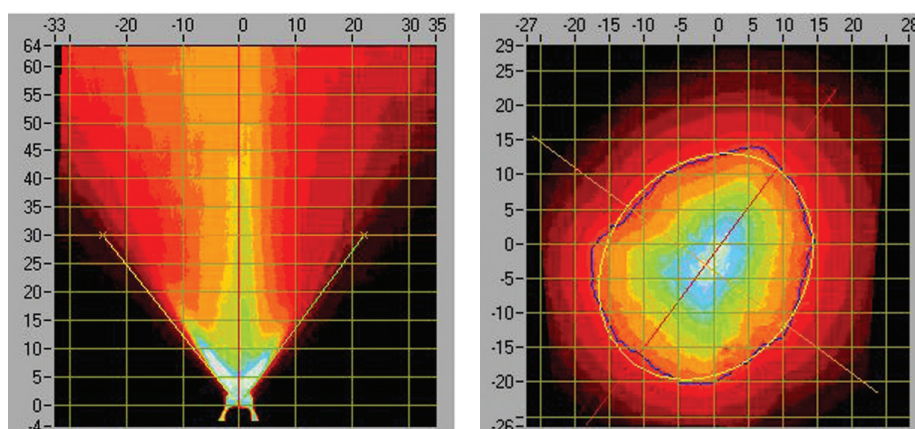
The LMA VaxINator™ is a recently introduced atomization device that fulfills the needs

of any pharmaceutical company looking for a cost-effective, single-dose intranasal vaccine or drug delivery system (Figure 1).

The VaxINator consists of a cone shaped atomizer with a luer-lock attachment that allows it to be connected to any standard luer-lock syringe. The nasal cone allows comfortable and appropriate placement of the device against the nasal opening while preventing accidental trauma should the patient move their head. The VaxINator produces an atomized mist of approximately 30-100 μm , with plume geometry and spray pattern as shown in Figure 2.

An optional addition to the system is the VaxINator auto-disable syringe. Using the auto-disable syringe results in automatic disablement of both the VaxINator and the syringe following drug delivery (see Figures 3-6).

Using the auto-disable syringe also results in a very small device dead space (less than 0.05 ml compared with 0.1 ml with a standard syringe), leading to very little medication waste. The simplicity and elegance of this device design allow high-quality, high-volume



Figures 2: LMA VaxINator™ plume geometry and spray pattern.

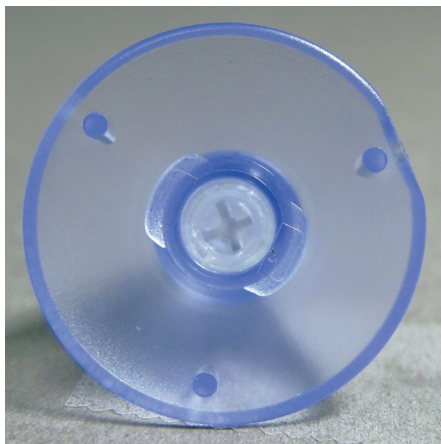


Figure 3: Cross sectional view of the base of the VaxINator atomizer. Visible inside the lumen of the device is a “latch” which grasps the “catch” portion of the syringe plunger preventing retraction of the syringe.

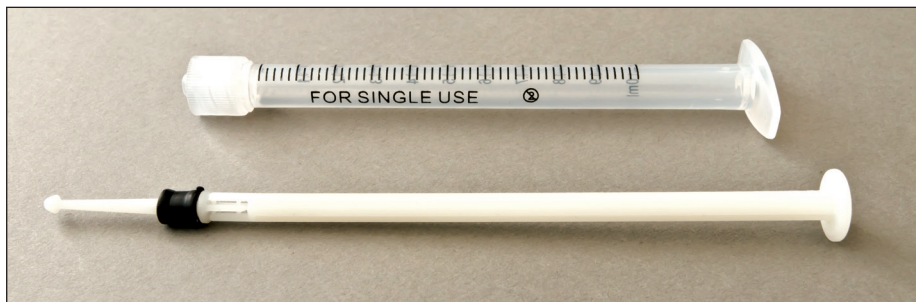


Figure 4: The VaxINator™ Auto Disable (AD) syringe. The plunger of the syringe has a “catch” which imbeds itself within the “latch” of the VaxINator atomizer upon actuation. The plunger also has a built in weak point that will break if the plunger is withdrawn, disabling both the syringe and the atomizer.

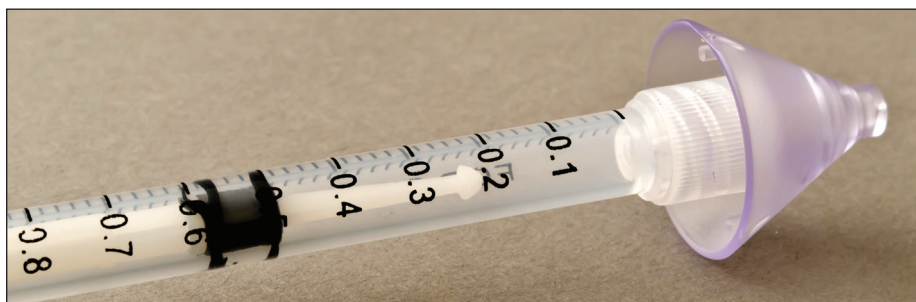


Figure 5: The VaxINator™ “catch” reduces dead space within the device.



Figure 6: An Auto-disabled VaxINator™ device. Following complete drug administration the “catch” engages within the “latch”. If the plunger is retracted it will break off, leaving the device nonfunctional. Similarly if the atomizer is twisted off, the “catch” will either pull out the center of the atomizer or break off within the device.

manufacturing making the product both reliable and affordable.

Safety is also well established. The VaxINator progenitor, the MAD Nasal™ mucosal atomization device, has seen millions of patient uses for over a decade with no real safety concerns.

CONCLUSION

Intranasal vaccine delivery is poised to take a prominent worldwide position as an effective and perhaps preferred method of immunisation. Simple, safe, affordable, high-quality auto-disable nasal vaccine delivery systems now exist.

The safety features, cost containment and logistical benefits that nasal vaccination promises to offer provide compelling rea-

sons to push this technology forward until it becomes an established standard. This may allow more patient access to rapid immunisations should pandemic infection emerge and it will provide an alternate therapy to patients who fear injections.

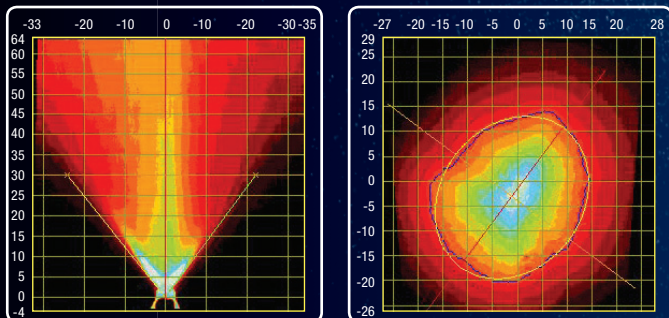
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COMPANY PROFILE TEAMTECHNIK GROUP

EFFICIENT DEVICE ASSEMBLY & TESTING FROM TRULY FLEXIBLE AUTOMATION SOLUTIONS



Medical products such as inhalers and pens make it possible for chronically sick people to live largely unrestricted lives. Inhaler systems allow asthmatics fast access to their medication, and diabetics are able to inject themselves with their daily dose of insulin quickly and safely thanks to their insulin pens.

The fact that they are so easy to use means that these devices have long been in great demand, and are produced in high volumes - and the trend is growing.

The requirement for increasingly flexible solutions to automate the manufacture of medical products from assembly to the complete packaged unit, including functional testing, is therefore also increasing. teamtechnik Group is one of the leading suppliers developing and implementing turn-key production systems for medical devices.

teamtechnik has been making intelligent and reliable automation solutions for the automotive and solar technology and for medical and pharmaceutical industries for over 35 years. With their focus on assembly and testing, the systems are distinguished by their consistently modular and standardised process-oriented structure.

teamtechnik, based in Freiberg, Germany (Figure 1), is considered an international leader in highly flexible automation technology. With a total of 700 employees throughout the world, the company achieves sales



Figure 1: teamtechnik's Facility in Freiberg, Germany.

of over €130 million (£111 million). The teamtechnik Group has production sites in Germany, Poland, China and the US.

teamtechnik develops innovative process-optimised production solutions for medical technology that meet customers' requirements right up to serial production. The systems are designed with a modular approach, a highly-flexible concept which allows the manufacturers of medical devices to adapt their production quickly and economically to changes in the market.

In the new TEAMED system, its latest sys-

tem platform, the company has brought to market a highly flexible and upgradeable linear system for assembly and testing, realising almost 80% of all customer solutions in the medical technology sector. Sophisticated process technology and 100% end-of-line testing can be integrated in the platform specifically for the assembly of medical devices and pharmaceutical products.

TEAMED (shown in Figure 2) allows production compliant with global guidelines and monitoring systems such as GAMP 5, FDA and CE and meets class 6 clean-room



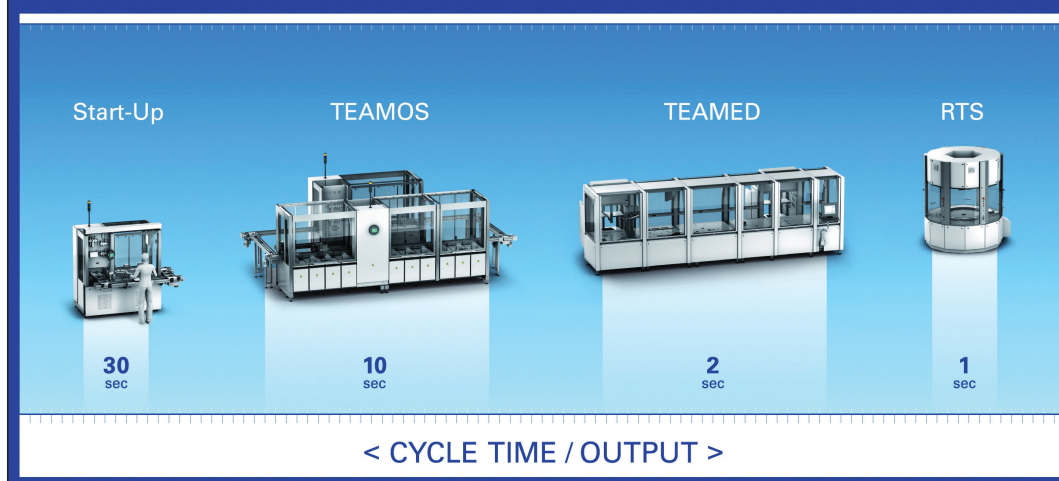
Figure 2: A TEAMED Production Line.

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FROM LOW TO HIGH SPEED PRODUCTION



teamtechnik provides machinery equipment for assembly and test in each volume class, from proof of principle operator system to high volume industrialisation turn-key equipment.

specifications. The special feature is that TEAMED also incorporates processes from clinical Phase I and II prototype production directly in serial production, thus verifying critical processes in advance of the original configuration later on and providing the person responsible with reassurance for future serial production from the start. TEAMED-based systems can be adjusted to accommodate increasing unit numbers quickly and with little extra effort, as in the case study that follows.

FROM PROTOTYPE TO HIGH-VOLUME PRODUCTION: A DPI ON THE PATH TO MARKET SUCCESS

First Stage: Prototype Production

The assembly of a dry-powder inhaler (DPI) normally includes many complex processes which must be monitored whilst the process is underway, or else the result must be verified after the process.

To reduce time-to-market, the customer ideally needs a complete final device assembly line from the outset (Phase I clinical trials). In practice though, factors such as cost and risk used to mean this was usually impossible. However, teamtechnik – one of the leading suppliers developing and implementing turn-key production systems for medical devices – now offers exactly this option.

Having the critical processes automated in a very early phase of development is

made possible with the TEAMED platform. The machine will typically be a small, manually operated unit with only some selected processes and tests performed automatically.

In the following case study, the customer came to teamtechnik with a device still in development. We designed a TEAMED workstation for one to five operators working at the machine at the same time. The number of operators depends on the output the customer likes to get from the machine. Output is one unit per minute with one operator up to six per minute with five operators.

All parts are fed manually by the operator into the nests of the carrier or direct into the device. For a delicate assembly process the operator moves the carrier manually into the process station where the fully monitored assembly process is performed automatically. After a successful process, the operator pulls out the carrier and pushes it to the next station where minor assembly operations are done by the next (or by the same) operator(s). Before closing the device (another monitored automatic process) a camera system checks completeness and correct positions of all parts. Finally, the assembly of the lid is done automatically to avoid an operator influence after this check of completeness. The lid assembly is path force monitored also.

Next Level: Small-Volume Production

Due to flexible modular TEAMED design of the process units, teamtechnik integrates the

same process units into the next-level machine: a semi automatic assembly line with material input by one or two operators.

The process stations are connected via a flexible carrier system. The carrier still has the same design as in the first prototype machine, now with some additional nests for manual preloaded parts. Almost all assembly operations are performed by automatic stations, and the delicate process stations are still the same as in the prototype machine for Phase I clinical trial products. Output is at 20 parts per minute now, working with two or three operators.

Market Level: High-Volume Production

The next stage is a four-up fully automatic high-volume line with all parts fed by bowl feeders or palletizing systems. Output is at 120 parts per minute now, the machine is running 24/7 with one operator and one milk runner.

teamtechnik designs the carrier back to the roots of the prototype machine where only a main nest and an intermediate nest was necessary. The delicate processes have been validated at the prototype machine in the Phase I clinical trials and are still identical in design and function. This saves a lot of time in the complete path to market and due to the early market entry the time to return-on-investment (ROI) is reduced dramatically.

This has only been made possible by a very strong modular medical TEAMED design from teamtechnik. In a non-critical, high-speed assembly satellite of a pre-assembly unit teamtechnik selected a two-up PFUDERER RTS dial system with 60 cycles per minute.

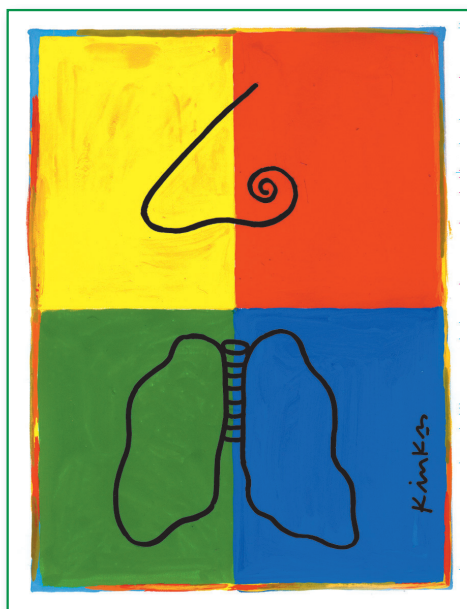
A final 100% function test with all data stored to the customers network proves the product quality before the device gets a final data matrix code by a label. The trays for the final product are also printed online by an inkjet system

An inhaler on its path to the market - a story of success - developed and manufactured by teamtechnik.

PLEASE MARK YOUR CALENDARS AND PLAN TO ATTEND!

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CONFERENCE PREVIEW - RESPIRATORY DRUG DELIVERY (RDD®) CONFERENCES & WEB SERVICES

MAY 13-17, 2012, PHOENIX, AZ, US

Here, Richard Dalby, PhD, Professor of Pharmaceutical Sciences at the University of Maryland School of Pharmacy, gives us the inside track on what the RDD team has in store for this May's Phoenix meeting.

Since starting in 1988, the Respiratory Drug Delivery Conferences (RDD®) have established themselves as the pre-eminent pulmonary and nasal international meetings focused on all aspects of drug delivery by inhalation. This success stems from an engaged and dynamic audience eager to learn from and meet scientists from regulatory agencies, industry and academia, together with enthusiastic support from an increasing number of companies wishing to share their latest developments during a combined Scientific Poster and Technology Exhibition.

RDD's dedicated team of volunteer reviewers and editors work collaboratively with experienced and emerging authors to ensure only the best and newest work is presented and archived in professionally produced bound and online versions. The

while keeping the meetings running smoothly in state-of-the art conference facilities so that participants can take advantage of almost endless networking opportunities at social events and meal breaks together with those afforded during the meeting itself.

Since 2005 RDD has partnered with Aptar Pharma (see this issue, page 16) to run meetings in Europe. The latest of these, RDD Europe 2011, took place in Berlin, Germany and attracted a record European attendance of 465 participants including 40% who had previously not attended an RDD meeting. Delegates came primarily from Europe (70%) and North America (22%) but with a healthy showing from emerging markets in Asia, the Middle East and Australia.

Pharmaceutical Aerosol Consortium on Regulation and Science (IPAC-RS), to facilitate in-depth review of the utility of efficient data analysis in inhaled product quality assessment after the RDD meeting ended. One trip – two meetings – time and money saved.

Your next opportunity to see presentations by representatives of regulatory agencies, pharmacopaeias, industry and academia in Europe will be at the Intercontinental Hotel in Berlin, Germany, when RDD Europe 2013, takes place, May 21-24. RDD will again strive to provide excellent opportunities for scientific and commercial networking during the meeting's signature Scientific Poster and Technology Exhibition and interactive Workshop sessions which allow delegates to customise their conference experience to meet their unique needs.

To be a part of this meeting please bookmark www.rddonline.com/rdd/rddeurope2013, and visit after June 1, 2012 to find deadlines for speaker nominations and poster abstract submission, together with details of how your company could present a workshop or sponsor a session.

You don't have to wait for RDD Europe 2013 if you can find your way to Arizona, May 13-17, 2012, where RDD 2012 will be held at the JW Marriott Desert Ridge Resort & Spa in Phoenix (Figure 3), and where you are likely to meet upwards of 650 like-minded scientists, business professionals and industry suppliers. All you need to know to participate in this meeting is at www.rddonline.com/rdd/rdd2012, and while you may have missed the deadline for speaking, or presenting a poster, you may still be able to attend if you register quickly.

This year's meeting is directed towards developing issues surrounding aerosol drug delivery including new therapeutic opportunities and drug design technologies, progress in drug development alongside novel *in vitro* and *in vivo* testing methods and regulatory science. The podium sessions at RDD 2012 feature much new science as well as more debates aimed at interfacing nationally known regula-



Figure 1: The RDD Online Homepage.

meeting organisers work with IT professionals to ensure an expanding library of over 1,500 papers spanning almost 25 years of aerosol know-how is searchable by keyword, title, author and organisation at www.rddonline.com/publications. The RDD onsite team has a reputation for selecting outstanding venues and excellent hospitality

The meeting was comprehensively reviewed by Guy Furness in the last edition of ONdrugDelivery Magazine (Issue N° 30, November 2011, pp 26-27).

RDD Europe 2011 marked a continuation of RDD collaborating with professional organisations, in this case the International

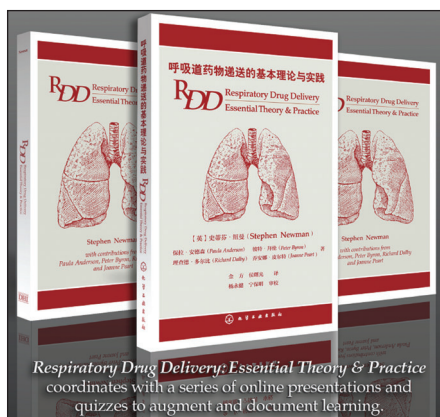


Figure 2: English and Chinese version of RDD Online's first book.

tors from the US, China and developing markets with their scientific counterparts in industry.

Generic inhalers, the needs for aerosol drug dissolution testing and potential changes to international compendia will all be featured in presentations and debates. Following the recommendation of a selection committee, RDD will also confer the 4th Charlie Thiel Award on a distinguished scientist in the inhalation science community, and showcase up-and-coming researchers and technologies during an expanded Posters on the Podium session.

RDD 2012 is the first meeting where participants can choose between a full color bound copy of the proceedings (three volumes, >1,000 pages) or electronic access to the same material during the meeting with web access once they get home.

RDD Online (see Figure 1) is available year-round, 24/7 at www.rddonline.com, providing information on past and future meetings, plus a host of additional information of interest to the pharmaceutical aerosol community.

Through RDD's education offerings, laboratory scientists and managers new to the field, as well as students, recent graduates or new hires can get convenient access to basic training in inhaled drug delivery so that they can quickly become knowledgeable and productive. RDD Online has partnered with experts in several



Figure 3: The JW Marriott Desert Ridge Resort & Spa in Phoenix, AZ, site of RDD 2012.

areas of aerosol drug delivery to create interactive Powerpoint presentations synchronised with narration. Listeners can easily navigate each presentation, and receive certificates for their training files following successful completion of a question bank driven quiz. Employees of more than 250 companies have accessed this feature and many more have reviewed highlights of debates that we recorded at RDD meetings – a service particularly popular with scientists and regulatory affairs professionals.

After RDD Europe 2011, over 1,500 full-text original works were available as RDD downloads. Individual articles can be purchased online and are delivered by email as PDF file attachments, while current RDD Online individual and institutional subscribers can instantly download and view all articles. A one-year free subscription to articles in the current year is granted to anyone who attends that year's RDD meeting. Past copies of bound proceeding are available to those who prefer paper articles.

Providing a systematic treatment of pulmonary delivery topics, discussion of the latest technologies, extensive references, and clear explanations and figures, Respiratory Drug Delivery: Essential Theory & Practice, by Stephen Newman was the first book published by RDD Online. The US FDA has been among the biggest purchasers of the English version, and of the approximately 700 copies of the translation sold in China, the Chinese government accounted for 500.

RDD plans to continue to share relevant developments of interest to a global audience by making key papers and books accessible in both languages, and by posting recordings of presentations for the benefit of individuals unable to attend our annual meetings. A good example of the latter is a presentation entitled: "Responsible Inhaler Development in Article V Countries: Navigating the Scientific, Regulatory, Political and Commercial Challenges", chaired by Ashley Woodcock, MD, and available at www.rddonline.com/education/online_presentations/rdd2010_environment/index.php.

Other online resources include a calendar of upcoming events, a searchable directory of pharma companies and service providers active in pulmonary and nasal drug delivery, and a library list of key text books, journals, organisations and regulatory guidance documents.

Recognising the tight employment situation, RDD's job posting service is now free of charge and provides an opportunity for employers to find key people in our niche market. Recently added online resources includes online calculators relevant to pharmaceutical aerosol scientists and the availability of mathematical airway models which represent adult geometries of the

COMMENTS FROM RECENT MEETING PARTICIPANTS

"The conference is the best organised of any meeting I attend, and it is a joy not to have to worry about organisational aspects for a change."

"RDD is the biggest and the best conference in the respiratory field. The way it is organised is perfect."

"This was the first RDD conference I have attended for probably eight years. It was extremely well organised and provided the attendees with everything we needed to have effective learning and interactions. I really appreciated the freely available and healthy breakfasts and lunches – time is short and it makes it all easy when the basics have been provided. Thanks for a great experience."

"We get a 'commercialised' perception from industry regarding the many delivery technologies and devices in development, so it's truly invaluable to hear directly from academics and researchers in the field."

mouth-throat region and upper tracheobronchial airways based on literature values and medical images. These models can be used to test aerosol deposition, flow field characteristics, or for the construction of computational fluid dynamics (CFD) geometries.

Year round, RDD provides services and meetings likely to be useful to anyone concerned with the study, commercialisation, regulation or clinical use of products inhaled into the nose or lungs.

RDD Europe 2013 will be held at the Intercontinental Hotel in Berlin, Germany, May 21-24, 2013.

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TECHNOLOGY SHOWCASE – DF30Plus



Aptar Pharma is the worldwide leader in aerosol metering valves for pMDIs for the treatment of Asthma and COPD. Aptar Pharma's metering valves have been selected by major branded pharmaceutical companies across the globe. Each year, several hundred million metering valves are produced in Aptar Pharma GMP ISO7 cleanrooms.

Aptar Pharma is the only metering valve supplier that designs, develops and manufactures its own elastomer formulations and rubber gaskets – a key component of the valve – within its unique in-house Elastomer Center.

DF30Plus, ULTRA-CLEAN, ROBUST AND VERSATILE

Aptar Pharma's DF30 metering valve technology platform has been the industry gold standard for more than 20 years and Aptar is constantly striving to optimise it.

The new optimised **DF30Plus** offers several key benefits, including:

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- Excellent pressure filling capability

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www.aptar.com/pharma/prescription-division

On the unveiling of **DF30Plus** at the DDL22 Conference in Edinburgh, Scotland, last December, Chris Baron, Associate Director, Business Development for Aptar Pharma's Prescription Division, said: "We are extremely pleased to announce the launch of this new optimised metering valve. **DF30Plus** is the result of innovation and continuous improvement to the DF30 technology platform range and provides several new benefits. After 20 years of leading the industry in the supply of metering valves for pMDIs, we still continue to improve our high quality devices and anticipate our customers' future needs and expectations."

ABOUT APTAR PHARMA

Aptar Pharma – part of the Aptargroup family of companies along with Aptar Beauty + Home and Aptar Food + Beverage – creates innovative drug delivery systems that meet the evolving needs of biotechnology, healthcare and pharmaceutical companies around the world. The company provides its customers with a wide range of delivery technologies and analytical services backed by years of proven expertise.

Aptar's main focus is on metering valves for pressurised metered-dose inhalers (MDIs), and dry-powder inhalers (DPIs); and multidose pumps, single-dose devices and metering valves for nasal and sublingual drug delivery.

The company offers a full set of associated services to support customer speed-to-market and provide global support to customers in all geographies and in both developed and emerging markets.

Aptargroup (NYSE: ATR) is headquartered in the US and has manufacturing sites in North America, Europe, Asia and South America.



DF30Plus crimped on a pMDI canister

The Forefront of Delivery Science and Technology

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FILLING DRY-POWDER INHALERS: A PARADIGM SHIFT WITH "FILL2WEIGHT"

Traditionally, dry-powder inhaler dosage's are regulated by weight, yet manufactured volumetrically. Controlling the weight of each dose of medicament to the required limits is technically challenging. The advent of high-speed weighing systems has enabled viable commercial powder dispensing technology using gravimetric systems. These fill by weight, providing 100% feedback of the weight of every dispensed dose. Higher accuracies and more flexibility are possible. This article from Tom Bailey, Managing Director, and Dave Seaward, PhD, Projects Director, both of 3P Innovation, explains why filling DPI's is so challenging and provides an overview of conventional filling systems, before describing in detail a novel and scalable gravimetric system.

CHALLENGES OF DISPENSING POWDER ACCURATELY INTO DPIs

Since the 1950's the delivery of aerosolised drugs via inhalation has become a well-established means of treating diseases associated with the lungs such as asthma and chronic obstructive pulmonary disease (COPD). There has also been increasing interest in the lungs as a delivery site for other diseases; small molecules can be delivered for systemic delivery with a very rapid action and high bioavailability, whilst large molecules can be delivered without the need for injection. The authors

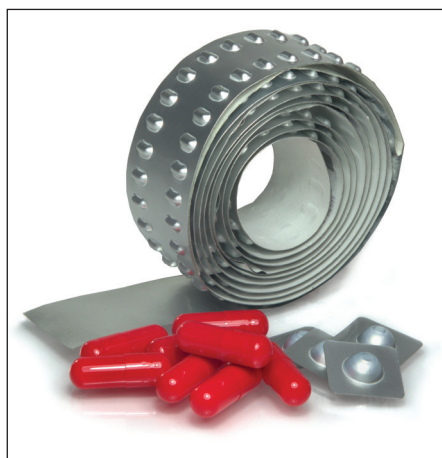


Figure 1: DPI receptacles include capsules, single blisters & blister strips.

have identified over 70 different DPI's which are currently in various levels of development.

Early devices stored powder in reservoirs, the powder being automatically metered by the device for each medication. More recently the trend has been towards pre-metered dry-powder inhalers (DPIs) where each medication is pre-dispensed into a receptacle (either single or multiple dose). The pre-metered powder receptacle is usually provided with a foil covering to minimise moisture ingress, and can take many different forms:

- traditional hard capsules (gelatine or HPMC),
- individual thermoformed foil blisters,
- thermoformed blister strips,
- thermoformed arrays of blisters
- injection mouldings with foil coverings

Three examples are shown in Figure 1.

Reservoir devices typically contain 500-2000 mg, whilst single doses can range from 1-50 mg. Although there are applications with pure active pharmaceutical ingredients (APIs), inhalation blends of powder often have the API together with a carrier excipient (usually lactose). Unlike solid oral dose applications, which are manufactured on a range of standard equipment, inhalation applications necessitate the commissioning of both customised assembly and customised powder-filling equipment.

The complex nature of powders, and inhalation powders in particular,² means that accurately



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Figure 2: A typical powder bowl with ploughs and rakes to condition and aerate the powder.

dispensing very small amounts of powder from a bulk supply into the device's receptacles is a significant technical challenge. Pharmaceutical powders typically have true densities around 1.4-1.6 g/cm³, with the bulk density of 0.4-0.8 g/cm³. This means that between 50-75% of the volume of the material to be dispensed is air, which acts as a lubricant. Changes in the amount of air entrained within a powder will significantly alter both the powder's density and its flow properties.

Powders are usually non-uniform materials and uniquely have "dynamic" physical properties as they constantly aerate or settle and cake: they can behave like solids, or like liquids (and occasionally like gases). The nature of the small particle size required for inhalation applications means that these powders are naturally very cohesive and tend to agglomerate. This does not suit many standard filling technologies and the fine particle size can cause build-up and then seizure of any sliding mechanical parts within the dispensing machinery. One of the common methods of improving dose-to-dose repeatability is to compress the powder into a fixed volume prior to dispensing which removes inconsistent voids of air: powder compression can, however, adversely impact bio-availability in inhaled applications. Furthermore many formulations are very sensitive to static electricity, or are hygroscopic. This requires processing in a low-humidity environment, which exacerbates static sensitivity.

The final challenge is that often the receptacles are either small, and/or very close together and/or of a similar volume to the dispensed volume of the powder: this means that mechanical tolerances of both the product and the assembly machinery need to be very carefully considered to ensure an efficient process.

TRADITIONAL POWDER DISPENSING TECHNOLOGIES

One of the most common styles of powder dispensing technology is the dosator which can typically dose 10-500mg. The majority of exist-

ing commercially available dosators operate using the same basic technology. Powder is fed into a vessel which is usually a rotating bowl (Figure 2). This has ploughs and a doctor blade which "conditions" the powder by aerating it, and provides a smooth surface and a constant height to the powder. A thin walled tube with a central plunger is then introduced into the powder. A plunger is positioned within the tube such that the defined space within the tube is equivalent to the required dose of powder.

The system dispenses powder volumetrically and the weight of powder dispensed is a function of the defined volume and the powder density. Inserting the dosator deeper within the powder bed can create an element of powder compression or densification, which reduces dispensed weight variability.

The central plunger face, initially just above the face of the powder can descend slightly. This action causes a small degree of compaction sufficient to lock the dose within the dosator. The dosator sleeve and plunger are now retracted. The dosator can be moved over the final required pocket/receptacle and the powder deposited by actuating the plunger downward.

Dosator's are popular as they are relatively low-cost devices and they are widely used to fill capsules in solid oral dose applications. They are also used in inhalation applications but have a limited range both in terms of dose weight that can be dispensed and in the types of powders that can be accurately handled. Cohesive powders tend to have voids that create poor weight consistency. Very free flowing powders do not adequately "lock" within the dosator tube such that powder can fall out before the dispense position. In addition, the fines from inhalation blends can build up between the tube and the pin leading to seizure of the mechanical components. It should also be noted that the dispensed powder must be compressed, which can adversely impact bio-availability for inhaled applications.

Despite the narrow operating range dosators remain a popular first choice of powder dispenser due to the wide range of equipment available from many vendors. Understanding and minimising the risks highlighted above is important in order to avoid costly mistakes and reduce time to market.

To address this uncertainty, 3P markets a fully instrumented laboratory dosator. With a minimum of powder (essential for early clinical development) the "LabDosator" (see Figure 3) can be used to screen formulations for suitability for commercial scale dosator applications. This ensures that the formulation and equipment can be optimised during early phase development, in the knowledge that the same

parameters can then be applied to commercial scale manufacturing equipment.

The instrumentation enhances any Quality by Design (QbD) initiative with the ability to run formal design of experiments. Figures 4 and 5, show typical traces from the LabDosator for three different formulations: the process understanding generated by LabDosator can be used to develop formulations for dosator based applications.

The deficiencies with dosators led to the development of alternative powder dispensers, many of which are fully customised for DPIs. One of the more widely used systems is the vacuum dosator which is loosely based upon a standard dosator. In these systems, vacuum is applied to the base of the pocket into which the powder is placed. This removes air from powder which improves the dispensed weight consistency. However, it also compacts the powder, which can adversely impact bioavailability.

The vacuum also aids retention of the powder within the pocket such that vacuum dosators are able to process free flowing powders that would fall out from conventional dosators. Vacuum dosators can be built into drums (if the final doses are arranged linearly) or on flat platens as shown in Figure 6. 3P's lab dosator can be fitted with conventional or vacuum platen dosators.

As might be expected, one of the most advanced filling systems is that used by the market leader, GlaxoSmithKline, for their Advair/Seretide Diskus (fluticasone + salmeterol) inhaler. This pre-metered DPI uses a linear thermoformed blister strip with pockets filled with powder (Figure 1). In order to overcome the issues associated with standard powder



Figure 3: 3P Innovation's LabDosator used to screen formulations and produce early clinical supplies.

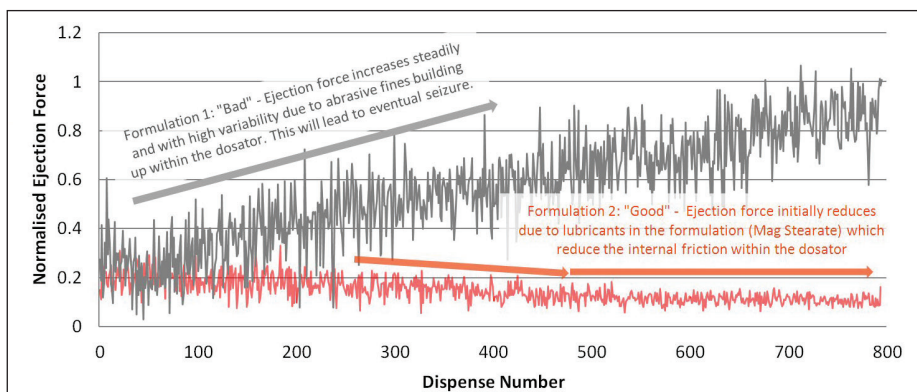


Figure 4: 3P Innovation's LabDosator measures ejection force which can be used to identify formulations that will run commercially.

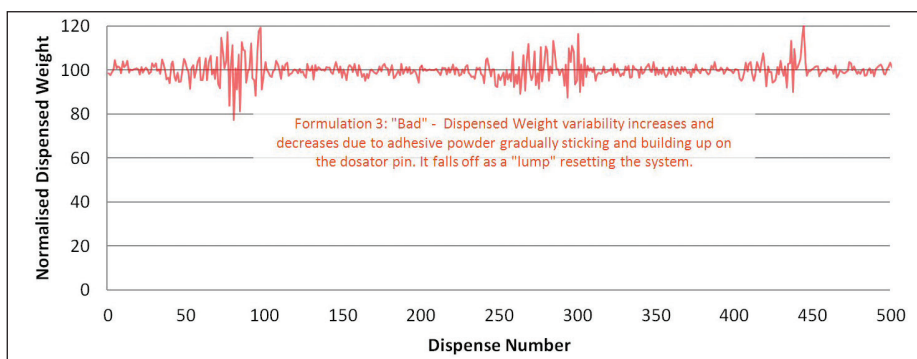


Figure 5: 3P Innovation's LabDosator measures dispensed weight which can be used to identify formulations that will run commercially.

dispensing systems fully custom solutions were commissioned (indeed, one of this article's authors is named as inventor on one of the associated patents).¹

A PARADIGM SHIFT?

Most liquid-dispensed medicinal products are regulated by volume and therefore dispensed by volume, whereas most powder based products are regulated by weight and yet dispensed by volume. It is stranger still when one considers that powders, by their very nature, have "dynamic" physical properties such that density varies with time. This fundamentally limits performance and this compromise is a result of the inability to dispense powders by weight at

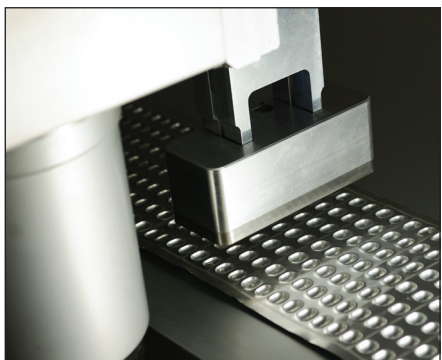


Figure 6: A 3P platen dosator over a blister strip.

required commercial rates when compared with volumetric dispensing methods.

Commercial pressures for high outputs and tradition have led to the vast majority of powder dispensing systems using volumetric methods with a statistical process control (SPC) check of actual weights. These checks are often destructive which is costly in addition to any reject batches.

Significant effort is expended by the pharmaceutical industry to formulate powders such that they have the appropriate flow characteristics for volumetric filling systems. This can be via unusual processing of the powder or by adding flow enhancing excipients. 3P's range of instrumented laboratory powder dispensers are used to derive such formulations via process understanding.

Would it not be more logical to dispense a weight of powder by weight? This is known as gravimetric dispensing. The concept is simple: link the input to a powder flow control device (a valve) to the output of a weighing system. Such systems have been available for many years but until recently the inherent slow response of weighing systems meant such systems were limited to use in laboratory settings. They typically take 10-30 seconds to carry out a single dispense which is adequate for laboratory and clinical supply applications, but inadequate for a high-volume DPI manufacture where each device may contain 60 doses.

Over the past five years the increased speed in microprocessors has enabled a new generation of sub-milligram-resolution, accurate, stable and fast weighing systems to be produced. In turn, this enables high-speed gravimetric filling of powders. 3P Innovation's Fill2Weight system is one such system. It is a gravimetric powder dispensing system whereby 100% of all dispensed weights can be recorded.

Fill2Weight uses the latest high-speed weighing technology combined with a high-performance powder flow valve designed to dispense very cohesive to very free flowing powders without any requirement to change parts. The computer control necessary to link the valve and weighing technologies also enables the ability for the system to self-tune and "learn" optimum settings for given powders and to compensate automatically for the "dynamic" changes in the powder's physical properties.

By design, both the powder dispensing and the weighing system have a narrow form factor which ensures systems can be stacked in a very small space for commercial applications. It is therefore possible to use a single head for pre-clinical and clinical trials and to scale the same process for commercial applications: the traditional project delays associated with scale-up are therefore eliminated.

3P Innovation has a team of engineers with over 100 combined man-years of powder-dispensing experience drawn from a wide range of industries. This experience has been put to good use in the flexible design of Fill2Weight.



Figure 7: A single Fill2Weight Head used for Clinical supply fitted to a laboratory workstation which can be multi-tracked for commercial applications to provide a scalable solution.

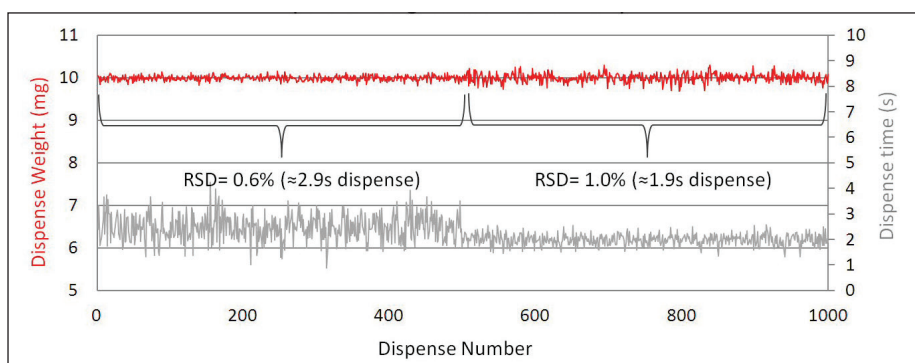


Figure 8: Typical Fill2Weight dispensing performance at a 10 mg dose with a free-flowing powder (Lactose – Inhalac 230). Note how the weight variability can be adjusted in software by altering the dispense time.

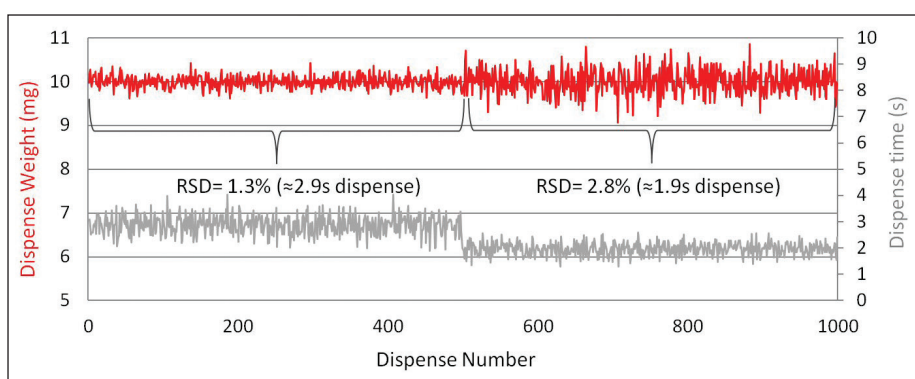


Figure 9: Typical Fill2Weight dispensing performance at a 10 mg dose with a cohesive powder (Lactose – Sorbalac 400). Note how the weight variability can be adjusted in software by altering the dispense time.

It can fill the widest range of powders from very free-flowing to highly cohesive and from 1 mg to 20,000 mg without change parts.

The system has a wide variety of software-configurable features which may or may not be required for a given application. Target-weight and product change is managed via software, such that its control algorithms continually optimise internal settings. These also compensate for changes in powder physical properties between batches and within a batch. In theory every consecutive dose, if required, could be controlled to be a different weight. Every dose is weighed and internal control parameters recorded, so that a very detailed batch record can be produced.

The system delivers true Quality by Design (QbD) including many of the features required for parametric or real-time release. By setting reject levels 100% of production can be guaranteed to be within pre-determined weight tolerances.

The powder dispensing valve or “nozzle” with an integrated hopper conveniently clips on and off the drive module. The integrated nozzle and hopper can therefore be easily removed for cleaning. Alternatively the low-cost moulded hopper can be considered a disposable item to eliminate cleaning costs. At the base of the hopper is an orifice which can be automatically closed to allow more or

less powder to flow, via a high-performance servo system. Free flowing powders as their name suggests will flow freely from such an orifice. Cohesive powders, however, will tend to bridge over the small orifices required to control the required low flow rates (the system can control below one milligram per second).

Additional automatically controlled vibration and bridge-breaking features have been integrated into the flexible design to deal with normally “troublesome” highly cohesive powders. The system does not need to compact the powder to improve dispensing accuracy. This is done through software. Fill2Weight therefore has zero powder compaction which improves bioavailability in inhaled applications.

Typical dispensing accuracy for inhaled grades of free-flowing and cohesive powders are shown in figures 8 and 9 respectively. Uniquely for any given powder, the dispense repeatability (normally expressed as relative standard deviation (RSD)) can be tuned by adjusting the dispense time, and the mean weight is adjusted in real time.

CONCLUSION

This article outlines the technical challenges associated with dispensing small amounts of inhaled formulations into DPIs. A brief review

WHO ARE 3P INNOVATION?



3P Innovation Ltd is a successful engineering automation and consultancy company based in the UK. 3P is focused on the supply of bespoke machinery and production solutions to an array of industry sectors.

3P's services range from product to production development including design for manufacture input, test rig development, bespoke, batch or low-volume assembly equipment, test and evaluation expertise and scalable powder handling solutions.

3P takes a holistic view of all technical challenges, looking for opportunities to enhance the product, enable efficient process and thereby support commercially viable production.

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of traditional volumetric methods describe their fundamental limitations. A novel and flexible gravimetric system has been introduced which dispenses the widest range of powder types and which scales from early phase clinical supply through to commercial manufacture. The weight can be dialled-in via the control system and 100% of all weights are recorded.

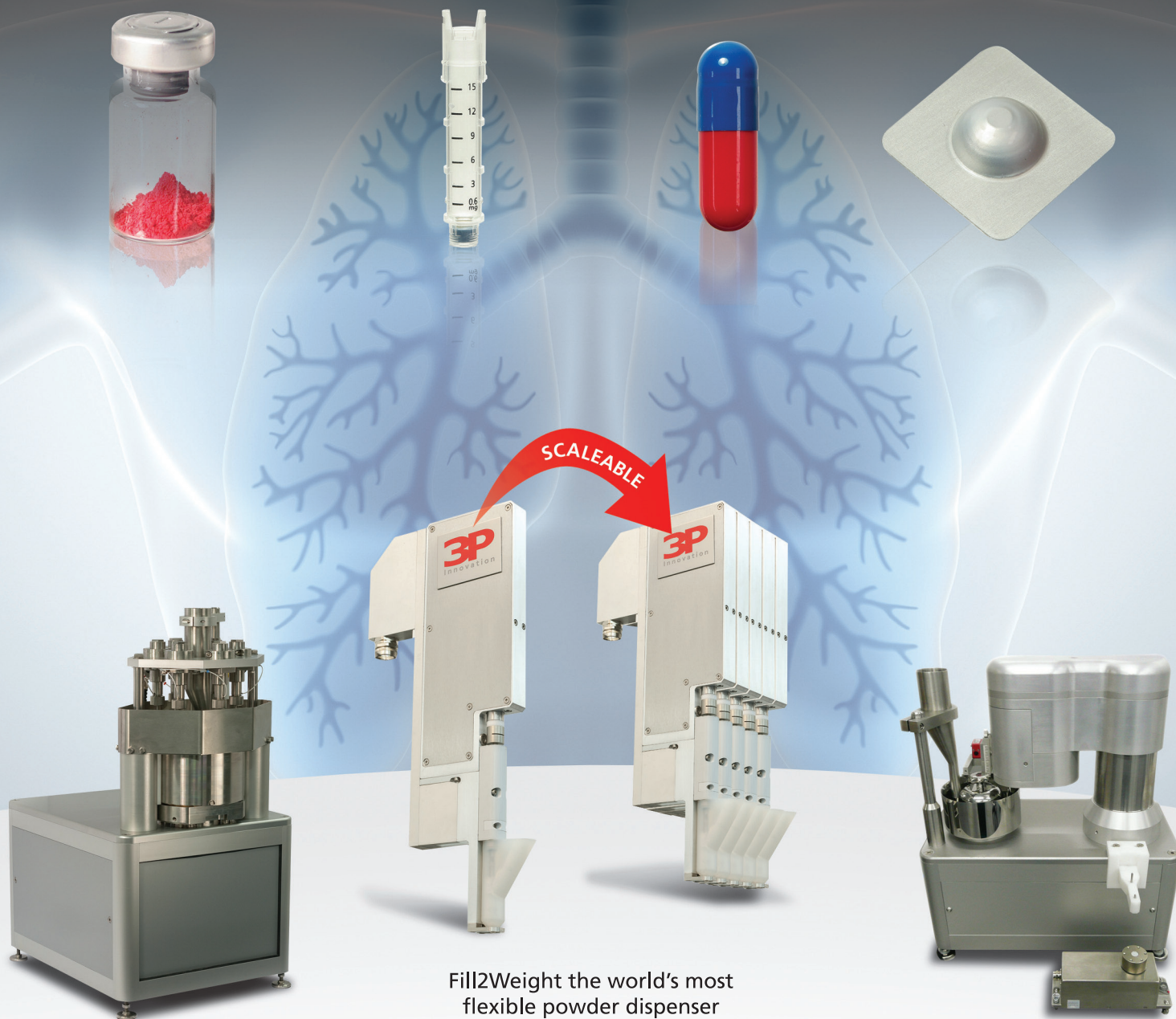
The trend towards powders which are increasingly challenging to process, with traditional volumetric systems, continues. If you currently dispense inhaled powders into DPIs, or are working on a new product, is it time to de-risk your product development by using a flexible gravimetric system?

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CONFERENCE REPORT

DRUG DELIVERY TO THE LUNGS 22 (DDL 22)

DECEMBER 7-9, 2011, EDINBURGH, SCOTLAND, UK

Drug Delivery to the Lungs 22 (DDL 22) was held in Edinburgh, Scotland, UK on December 7-9, 2011. Guy Furness, Publisher of ONdrugDelivery, attended the meeting and here he reports some of the highlights.

The *Drug Delivery to the Lungs* conference, organised by a voluntary sub-committee of the Aerosol Society, takes place over three days each December at the Edinburgh International Conference Centre (EICC), in the Scottish capital. It is established as a major event in the pulmonary and nasal drug delivery industry calendar; an event where one gets the feeling that the key people in almost the entire inhalable drug delivery community are present.

I attend DDL regularly and, for me, what sets this event apart is the way in which the conference programme consistently reflects the fact that pharma industry, and perhaps particularly the inhalable delivery field, is powered by cutting-edge science being done by first-class scientists both in industrial and academic research labs around the world. These are the people I saw presenting at DDL 22, and one gets a real sense of a thriving and healthy working relationship between industry and academia in the field of inhaled drug delivery.

A balance was struck at DDL 22 whereby even the most academic of academics, whilst presenting the very latest, pioneering scientific techniques, discoveries and developments in the field, always related his or her talk back to unmet clinical needs or opportunities for industry; and, likewise, even the most commercially-minded businessperson presenting never talked purely on “partnering” or “marketing”. These factors came up regularly at DDL 22, but never without being presented in the context of science; fully grounded in the scientific research that underpins the product or technology that is to be partnered or marketed.

In addition to this sense of striking the right science-commerce balance – or perhaps as a result of it – I was also very aware at DDL 22 that this conference really was bang up to date. In fact, on hearing from one presenter why he had had to make some frantic changes to his slides minutes before he took to the stage, I jotted down in my notes: “You know a conference is at the cutting edge when speakers in the after-

noon are having to update their slides in light of what they heard that morning!”

Another attractive characteristic of the DDL conferences is that there is just one track of talks all running consecutively in one presentation hall. For attendees, this makes following the proceedings simple and somehow more relaxed, with no parallel sessions and no resultant rushing to and fro between different rooms. A single track in one hall allows more time and space to listen to and digest the content of every presentation. This is precisely what I did, and here is a summary of a few of my key DDL 22 observations and highlights.

The conference opened with The DDL Lecture, entitled “New Drugs and Targets for COPD”, given by Peter Barnes, FRS, FMedSci, Professor of Thoracic Medicine and Head of Airway Disease at the National Heart and Lung Institute, Imperial College (London, UK). Professor Barnes provided some stark facts about COPD – which he said would soon be the third-commonest cause of death worldwide, with incidence in women increasing rapidly of late to equal that in men. COPD now kills more women than breast cancer in the UK.

He described the particularly unpleasant nature of the disease’s slow progression and its terrible effect on the lives of patients, against which there is no treatment. The disease pathology relates directly to symptoms, Barnes said, and current treatment is for symptoms, the mainstay of drug therapy being long-acting bronchodilators, which are generally either long-acting β -agonists (LABAs) or long-acting muscurinic antagonists (LAMAs).

Improvements in LABA and LAMA therapies included the development of new molecules with longer durations of action, and the development of LABA + LAMA combinations was the most exciting, he said, highlighting QVA-149, an indacaterol + glycopyrronium bromide combination under development by Novartis, which had performed very well in clinical trials. A triple combination inhaler,

TrioHale (tiotropium + formoterol + ciclesonide) from Cipla, was on the market, he added.

The focus of Professor Barnes’ research is on understanding the cellular and molecular mechanisms of COPD in order to enable novel therapeutic approaches in the future, importantly including drugs that prevent disease progression. He said that many mediators are involved and so drugs that block these individually are unlikely to work. Possibly promising active molecules mentioned by Professor Barnes and in early development were: neutrophil chemokine receptor (CXCR2) blockers; selective matrix metalloproteinase 9 (MMP9) inhibitors; and phosphodiesterase 4 (PDE4) inhibitors. An important target he mentioned was nuclear factor erythroid-derived 2-related factor 2 (Nrf2). Activation of the Nrf2 pathway turns on anti-oxidant genes.

In terms of drug delivery challenges in COPD, Professor Barnes pointed out that new treatments for COPD – both bronchodilators and anti-inflammatories – would likely need to be given by inhalation to reduce systemic toxicity. Delivery to the peripheral airways and lung parenchyma was difficult in the presence of airway obstructions of the sort common in COPD and more attention needed to be focused on this challenge he said. Deposition studies in COPD were extremely rare. He could only find one study when he searched, he said, and described this specific area of research as having been neglected.

In addition to respiratory diseases such as COPD and of course asthma, applications of inhalable drug delivery technologies in other indications featured prominently at the meeting. The main focus stayed on diseases of the lung such as respiratory infection and lung cancer though, rather than systemic delivery via the lung.

A particularly powerful presentation on the threat from TB came from David Barros Aguirre, PhD, of the GSK Tres Cantos Medicines Development Campus (Madrid Spain). My notes on his delivery read: “If I was

Mycobacterium tuberculosis, I would not want to be up against this passionate scientist.”

Dr Barros Aguirre described a formidable enemy. He outlined the serious nature of the global TB epidemic (the bacterium infects a third of the world’s population and kills 1.7 million people per year). He described the complex lifecycle of the mycobacterium, the emergence of multi-drug resistance (MDR), and then extensive drug resistance (XDR), and the resulting current treatment strategies, which often included expensive, complex and increasingly toxic regimens of 6-8 drugs, some injected. Other obstacles to the development of effective treatments include the high incidence of co-infection of TB with HIV because the two infections are synergistic and TB drugs interact significantly with HIV drugs.

The size and complexity of the problem, and the severe unmet need for a solution, mean that all of the large pharma companies have established major anti-TB R&D programmes, GSK included. Barros Aguirre described GSK’s TB pipeline and how the company – well aware that one organisation has no chance of defeating TB on its own – is pursuing a collaborative strategy, including an open-innovation approach, and the establishment of the Tres Cantos Open Lab Foundation with funding and lab space for visiting scientists and mechanisms for sharing IP and dividing royalties.

It was in this context that he discussed a rationale for the pulmonary delivery of TB treatments, listing the various benefits (including the possibility of inhaled therapeutics being taken up by infected macrophages and rescuing them from alternative activation) as well as disadvantages (poorly aerated areas of the tubercular lung provide poor access for inhaled medicines) that the route has in this indication.

One problem, explained Dr Barros Aguirre, was that GSK’s drug discovery efforts are focused on generating once-daily oral medications but this strategy is falling down due to

human dosing projections of >1g. This was a key challenge that pulmonary drug delivery could perhaps provide a solution for. He ended his dramatic talk with a simple question for the pulmonary delivery scientists that filled the DDL hall: “Can you help us?”

Systemic drug delivery via the lung was the topic of only one talk at DDL22, perhaps

has received a “Complete Response” letter from the FDA which raised issues relating to CMC, a facility inspection, and its review of inhaler usability information. The company, which has a meeting with the FDA scheduled for the second quarter of this year, noted that neither clinical efficacy nor clinical safety were cited in the Agency’s letter.

“IN ADDITION TO RESPIRATORY DISEASES SUCH AS COPD AND OF COURSE ASTHMA, APPLICATIONS OF INHALABLE DRUG DELIVERY TECHNOLOGIES IN OTHER INDICATIONS FEATURED PROMINENTLY AT THE MEETING.”

indicating that this exciting area of R&D, which has had its setbacks over the past decades, is yet to re-emerge as a major, confident force in the drug delivery business.

Donald Kellerman, PharmD, Vice-President of Clinical Development at MAP Pharmaceuticals (Mountain View, CA, US), reported results from pivotal Phase III clinical trials of LEVADEX, the company’s inhalation aerosol formulation of dihydroergotamine mesylate for the treatment of migraine. The trial included a double-blind, placebo-controlled efficacy portion in 794 migraine sufferers, and an open-label, long-term pulmonary safety extension in 638 patients. In the efficacy portion, LEVADEX met all four primary endpoints (pain relief at 2hrs; photophobia free at 2hrs; phonophobia free at 2hrs; nausea free at 2hrs), and was well tolerated. The pulmonary safety section of the trial revealed no clinically meaningful effect on lung function.

At the time of DDL22, MAP Pharma had recently submitted an NDA to the US FDA for LEVADEX. Since the conference, the company

The above report represents only a selection of the material that was presented at DDL 22, which also included a number of presentations tackling human factors and the development of patient-centric devices, and various presentations covering inhalable drug delivery in paediatrics. Other talks of note included: an interesting and entertaining presentation of “*The Case for DPIs*” from David Harris, PhD, Principle Consultant at Team Consulting (Cambridge, UK); and the intriguingly titled talk, “*Tappiwhacky and the Golden Device*”, from James Tibbats, PhD, Managing Director of Concept Flow (Cambridge, UK).

DDL 22 was attended by around 450 delegates who were treated to a total of 36 oral presentations and 65 posters. Additionally, there were 70 companies exhibiting at the event.

The next conference, Drug Delivery to the Lungs 23 (DDL 23) takes place at the EICC, Edinburgh, Scotland, UK, December 5-7, 2012.

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COMPUTATIONAL MODELLING FOR DRY-POWDER INHALERS

Computational fluid dynamics (CFD) is a simulation tool used for modelling powder flow through inhalers to allow optimisation both of device design and drug powder. Here, Ralf Kröger, Consulting Senior CFD Engineer, ANSYS Germany GmbH; Marc Horner, Lead Technical Services Engineer, Healthcare, ANSYS, Inc; Robert Woolhouse, Senior CFD Engineer, ANSYS UK, Ltd; Michael Becker, PhD Student, and Herbert Wachtel, Senior Principal Scientist, both of Boehringer Ingelheim Pharma GmbH & Co KG; and Anne De Boer, Research Leader Inhalation, University of Groningen, Groningen, The Netherlands, describe in detail how CFD was used in the optimisation of the Twincer™ dry-powder inhaler, extensions of current particle modelling physics to account for particle-particle interactions, and the benefits of this approach in product development.

INTRODUCTION

After the Montreal Protocol¹ banned the use of chlorofluorocarbon (CFC) propellants in metered-dose inhalers (MDIs), the pharmaceutical industry now has provided suitable alternatives, one of which is the dry-powder inhaler (DPI). A DPI is a device in which small doses of drug powder are delivered to the lung. The inhaled dose consists of drug particles attached to carrier particles. The drug particles are typically smaller than 6 μm in diameter and the carrier particles are 20-200 μm in diameter. Carrier particles make the powder “flowable” and manageable inside the inhaler and prevent the powder from sticking. However, carrier particles have too great an inertia and tend to impact on the back of the throat rather than go down into the lung. Therefore, drug particles must de-agglomerate (break away) from their carrier particle before inhalation. The de-agglomeration step is one of the most challenging aspects of DPI design.

Powder engineering provides many opportunities to tune the physical properties of indi-

vidual particles, example manufacturing processes include spray drying, mechanofusion and processing in supercritical media.²⁻⁴ However, the large number of parameters governing the interaction of the particles with the device (and with each other) makes the product development task very complex. Simulation tools provide the unique ability to predict the effects of individual forces on the delivery and to separate them from the data scatter inevitably connected with real-world powder experiments.

Computational fluid dynamics (CFD) is the most common simulation tool used for DPI development because it can model the flow of air and suspended particles through the device and into patient anatomy or other geometry.

To give a brief introduction to the CFD process, the domain of interest is broken down into smaller control volumes, called cells, collectively termed a grid (or mesh). Specifying the material properties of the fluid and boundary conditions (for example, inlet velocity) on external boundaries of the domain completes the problem description. The fluid flow equations

are then solved iteratively to calculate the flow patterns. Additional equations can be solved to include the effects of turbulence, species transport, reactions and heat transfer, amongst others. The motion of a discrete (particle) phase can also be calculated; particles may be passive tracers that follow the flow or there can be two-way coupling between the fluid-flow and particulate phase.

The rest of this article describes two situations where CFD is currently being used in the development of DPIs. The first section summarises a flow analysis of the Twincer™ DPI. This device was originally designed to deliver colistimethate sodium to cystic fibrosis patients, replacing nebulizer therapy with a faster and more effective delivery method. Building on its initial success, the Twincer™ is currently being redesigned to deliver many more drugs, such as antibiotics for tuberculosis therapy. The second half of the article summarises our recent development efforts in the area of particle modelling, with a focus on enhancing our ability to predict de-agglomeration more accurately.



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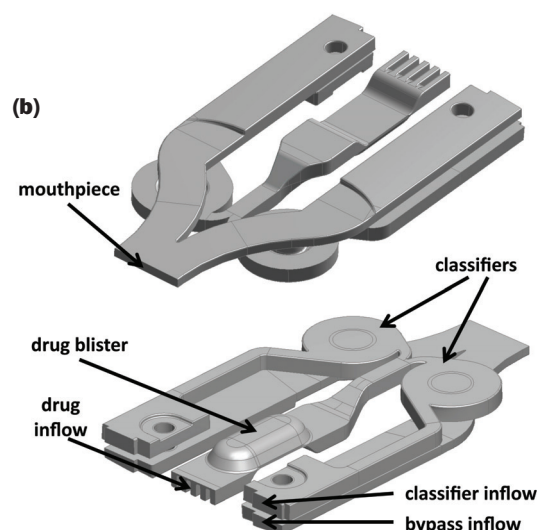


Figure 1: (a) External view of the Twincer™ DPI device (b) fluid flow volumes and identification of operational zones.

FLOW SIMULATION BENEFITS PRODUCT DEVELOPMENT

Many of the DPI's in service today are designed to administer a regular, and relatively small, dose of drug to the lung. The Twincer™ DPI is unique in that the primary goal of this device is to deliver high drug dosages as a dry powder into the lungs via inhalation. This has the benefit that materials can be stored as a dry powder rather than a liquid. This section summarises a recent CFD analysis of the Twincer™ DPI, illustrating the various ways simulation tools can help guide the product development process.

The Twincer™ device, shown in Figure 1, consists of a mouthpiece, five air inlets, and two classifier sections. Operation of the device is such that upon inhalation the entire dose is entrained from the dose compartment into the flowing air and divided over two parallel classifiers. Of the five air inlets; one of the air supply channels passes through the dose compartment and then splits into the cylindrical classifier chambers. Particle agglomerates circulate inside the classifiers, impacting with the classifier walls and each other until they are small enough to exit through two small holes in the centre of the classifier chambers. These holes discharge the aerosol into two channels which merge into the mouthpiece channel. To minimise drug retention in these channels, the air velocity is increased by adding a bypass flow across the classifier discharge holes. The amount of bypass air can be tuned to control inhaler resistance and therefore total airflow.

CFD was utilised as a way to help understand the flow fields and particle trajectories through the

device's air passages. Performance criteria were a combination of flow and particle analyses.

One of the key design criteria for any DPI is that sufficient, but not too high, air flow is available for a given suction and that some of the flow energy is used to disperse the drug. The design therefore must balance the split between the dispersion air (which tends to incur a higher pressure loss due to swirl) with bypass air (lower pressure loss, but also does not mobilise the drug) to ensure both criteria are met.

Another problem specific to high dosage DPI's is ensuring that smaller drug particles are detached from each other and are de-agglomerated in the event of sticking together. The Twincer's novel swirl chamber was designed to achieve good drug particle separation. The following paragraphs provide a brief overview of the model set-up and summarise some of our key findings. More details on the set-up and results are reported in deBoer *et al.*⁵

The following inputs are required to construct a CFD model of particulate flow in a DPI:

- geometry of the fluid domain
- material properties of the fluid and suspended particles
- boundary conditions mimicking device operation

The air-flow domain shown in Figure 1(b) was extracted from a CAD file of the Twincer™ device. Device actuation was modelled as a suction pressure applied to the mouth piece, allowing the air flow to balance itself against the resistance of the five flow channels. The flow rate of air coming in through each of the inlets was therefore an output of the model. Turbulence was accounted for using the realisable k-ε model and standard air material properties were used. The drug (and sweeper) particles were modelled using the Discrete Phase Model (DPM), the standard particle tracking model implemented in the CFD package ANSYS Fluent (ANSYS, Inc, Canonsburg, PA, US). Finally, it was assumed that the solids loading was low enough that the particles do not influence the air flow, i.e. there was a one-way coupling between the flowing air and drug/carrier particles.

This approach allowed for rapid assessment of multiple particle sizes and densities based on a single solution of the air flow patterns in the device.

As shown in Figure 2, the total pressure losses from the CFD calculations compared very well with experiment over the full range of operating flow rates. The CFD model also provided the flow splits to each section (16% to initially mobilise the drug, 24% directly to the classifier and 60% bypass), and showed that these were roughly constant over the operating range of the device. The latter was a highly valuable result as it was initially expected that the losses over the classifier chambers would significantly vary with flow rate. This meant that the device would perform consistently under a variety of patient conditions.

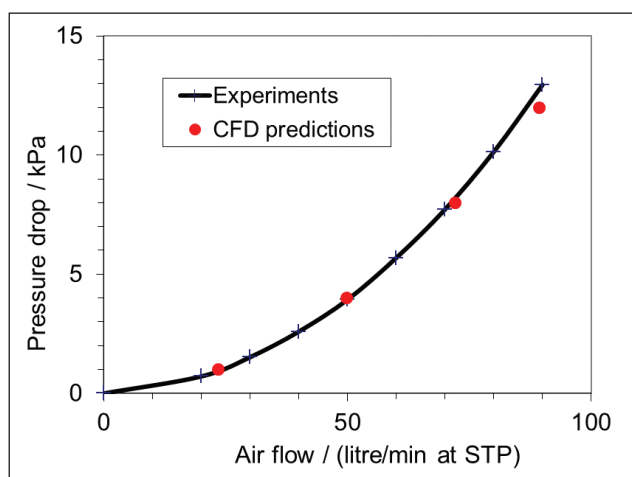


Figure 2: Comparison of experimental and computational results for pressure drop through the device as a function of flow rate.

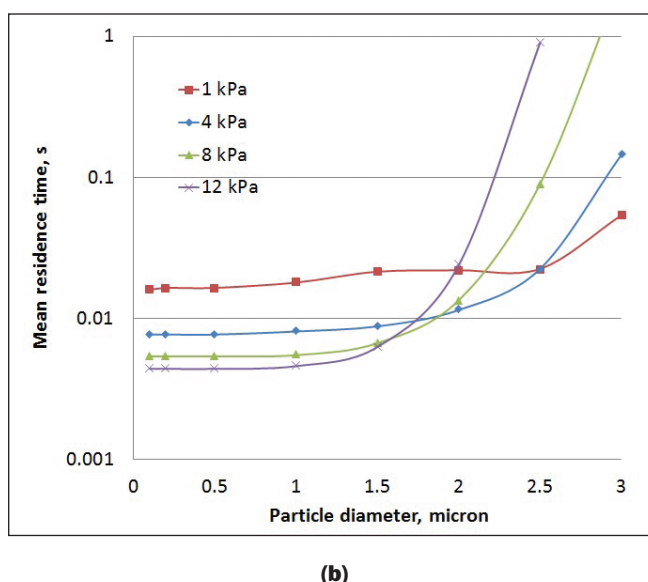
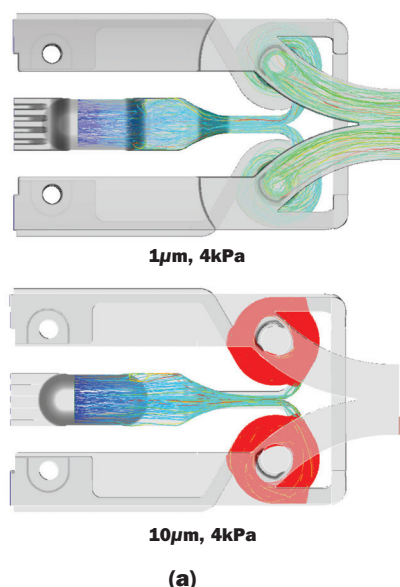


Figure 3: (a) Simulation of drug particles (top) and carrier particles (bottom) in the Twincer™ device. (b) Particle cut-off plots illustrate the relationship between particle diameter and residence time as a function of pressure drop.

The model also identified a number of areas where flow path alterations might improve performance, either through the removal of dead flow regions or by smoothing of channels to reduce pressure losses. The first area of note was the classifier channel, which was not adequately fed by the bypass inlet due to the relative pressure and channel position, the suggestion being that removing this channel entirely would simplify construction and cleaning with minimal effect on the flow to the classifiers. A second area of interest was a small recirculation zone within the drug blister region. The concern was that sticky drug may be retained within the blister rather than being mobilised. However, as not all dry powders tend to be sticky and blister shapes are standardised, it was decided that this issue did not require immediate attention.

Figure 3(a) shows a comparison of particle trajectories for two particle diameters, one representative of drug particles and the other representative of carrier particles. The CFD analyses and experimental data are in agreement that drug leaves the device and the carrier is retained. The CFD model provides additional data about how long the drug remains in the device as well as the diameter of particles that will not be inhaled (see Figure 3b). The residence time decreases with increases in pressure for particles that are predicted to escape, but the cut-off diameter decreases as pressure drop increases because of the increased classifier swirl (and thus increased centripetal force).

Overall the base design of the Twincer™ is very good at delivering smaller drug particles to the respiratory

system within a short period of time whilst retaining larger carrier within the classifier chamber. Minor modifications have been proposed and these are currently being investigated alongside other changes to the blister and drug channel.

ADVANCED POWDER MODELLING

The Twincer™ example utilised the standard particle tracking formulation in Fluent to model the motion of drug and carrier particles, which does not account for particle collisions in the flow channel. If we additionally want to simulate how the resting powder pile in the blister of a device is taken away by the air flow, we have to include the physics of particle-particle interactions.

ANSYS and Boehringer Ingelheim are working together to extend the standard suite of particle modelling capabilities in Fluent to be

able to predict agglomeration and de-agglomeration inside the DPI and to describe the transition from a resting powder pile of agglomerates to a fully dispersed inhalable aerosol.

The advanced powder model calculates air flow and particle motion using a two-way coupling between the particles and flowing air. To account for high particle volume fractions and the physics of particle-particle interactions in a discrete element manner, the model was extended by implementing user-defined (custom) functions in Fluent. A special algorithm was also implemented to detect all particle-particle and particle-wall collisions using a soft sphere approach.⁶ Because of the model character, not all

properties of aerosol particles can be considered. Many experimental methods provide information on the (equivalent) diameter of the powder particles and their number or mass within defined size classes. Therefore, our model is restricted to spherical particles and their geometric diameter.

To describe the blocking of the air flow by the powder particles, the fluid domain is treated as a porous structure with a local porosity defined by the number and size of the particles at that location. Slipstream effects are implemented to model the motion of small particles behind big particles. The collision of two particles is described with a spring-damper model which uses a virtual overlap (of the virtual sphere) with a spring co-efficient and a co-efficient of restitution. Adhesive effects, namely Coulomb and Van der Waals forces, are also implemented. Static, dynamic and rolling friction co-efficients were introduced to account for friction forces: thus the magnitudes of the different friction forces depend on the individual normal forces, the corresponding friction co-efficient, and on the contact condition between the particle surfaces, which can be sticking, sliding or rolling. The rotation of each particle is tracked and depends on the friction forces and surrounding shear flow.

Real surface roughness and other deviations from the ideal spherical particle can be taken into account by using effective friction co-efficients. The difficulty of course lies in the gathering of the right friction co-efficients for each powder. Three different experiments (one for each friction co-efficient) were designed: static friction is represented by the angle of repose in a resting powder

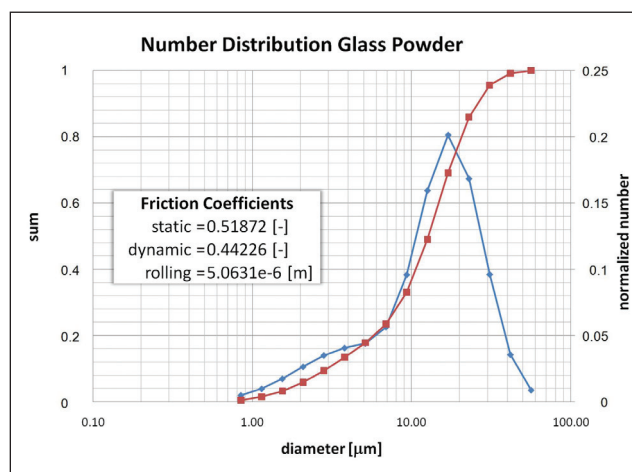


Figure 4: Glass powder properties. Size distribution from automated microscopy measurements and measured average friction co-efficients.

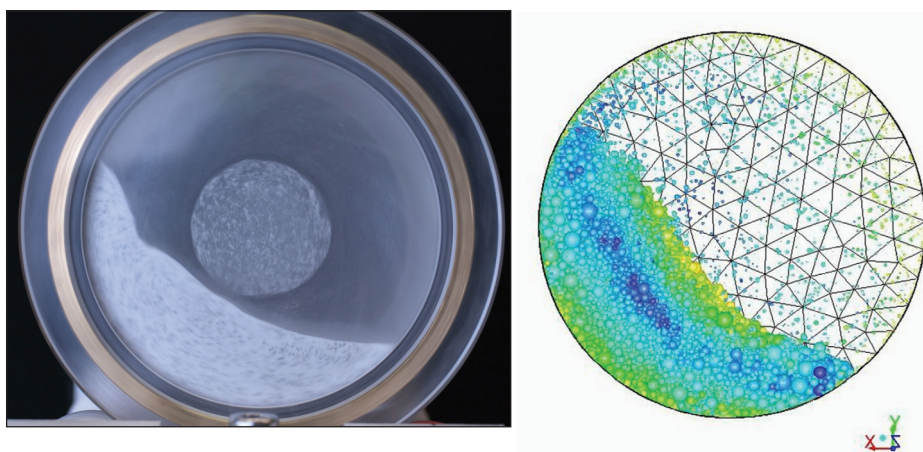


Figure 5: Comparison of rotating drum experiment (left) and simulation (right).

pile; dynamic friction can be measured from the turning momentum in a shear cell for powders; and average rolling friction can be determined from the slope angle at which a powder pile starts rolling down as an avalanche.⁷ The resulting friction co-efficients of these experiments are shown in Figure 4 for a glass powder (diameters of 0.7-57 μm) together with the size distribution.

Rotating drum and lift-off experiments were performed to validate the particle-particle interactions predicted by the modified particle tracking model. The rotating drum experiment, shown in Figure 5, was carried out to validate the particle-particle friction effects. The resulting slope of the avalanche in the drum compared quite well with the simulation results.

The lift-off experiment of a glass powder pile in a free air flow, shown in Figure 6, validates the two-way coupling between fluid flow and particle movement and the agglomeration forces.⁸ Detached agglomerates could be detected and compared with simulations with strong particle-fluid coupling, as shown in Figure 7.

The enhanced particle model is a valuable tool for parametric studies of the different adhesion and de-agglomeration mechanisms and also advances the understanding of different de-agglomeration principles.

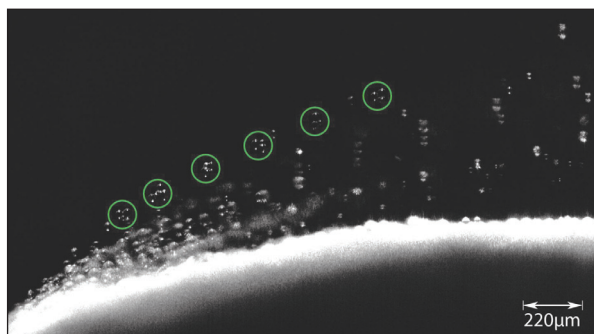


Figure 6: Lift-off experiment in free air flow. Air enters from the left side of the image. 6-fold multiple exposure allowed tracing of the path and velocity of particles and agglomerates. Time difference between the light pulses was 0.2 ms.

CONCLUSIONS

The Twincer™ modelling work shows that the use of simulation tools for the development of DPIs is playing a major role in design optimisation, and advanced particle modelling in a DPI can help with the optimisation of air duct design and in tuning the properties of powder formulations to address agglomeration effects. Future work in this area is directed at enhancing the particle model with additional particle-particle forces and applying these more recent developments to the Twincer™, further improving the accuracy of those simulations.

Finally, this article illustrated the benefits of simulation for one class of medical devices. It is now established that development processes that embrace simulation help many innovative products go to market faster while complying with product development goals⁹ and even strict medical regulations. This trend is expected to continue as improvements to simulation tools and ease of use allow users to leverage design optimisation tools to drive advanced multi-physics and systems-level models of their product all in a collaborative working environment, enhancing productivity at all levels of product development.

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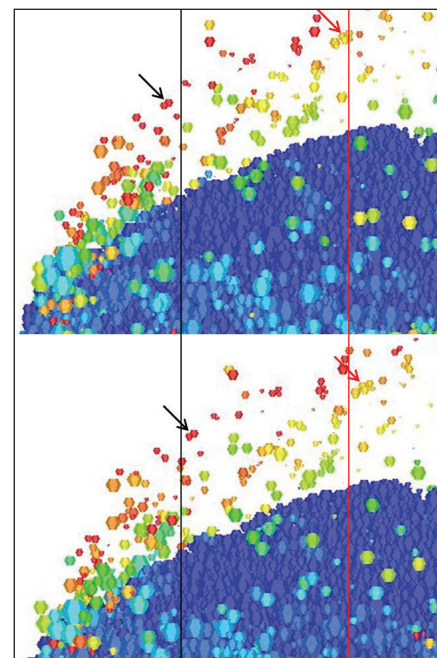


Figure 7: Computational model of the lift-off experiment. Agglomerates (highlighted with arrows) are carried by the air flowing from left to right. The lower picture is 0.5 ms after the upper. Note that the vertical lines are a reference for visualising agglomerate motion.



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- Insulin pens (Figure 2)
- Primary pharma packaging (Figure 3)
- Blood glucose meters

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Figure 1: Single-dose dry-powder inhaler for e.g. asthma & COPD therapy.



Figure 2: Injector pen (dose injector) for insulin dosage.



Figure 3: Sub-contracting drug delivery devices & primary pharma packaging.

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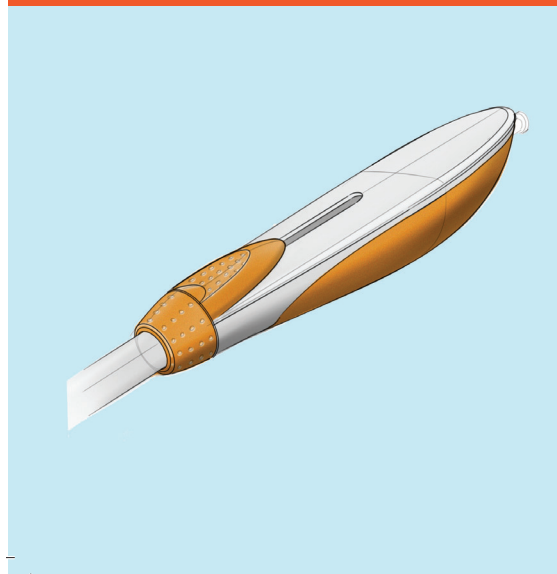
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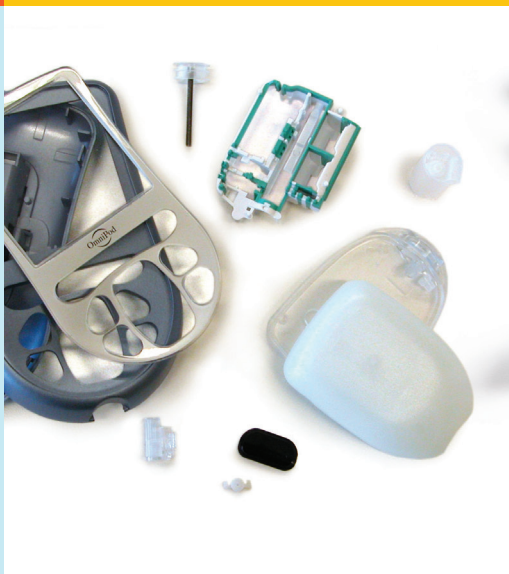
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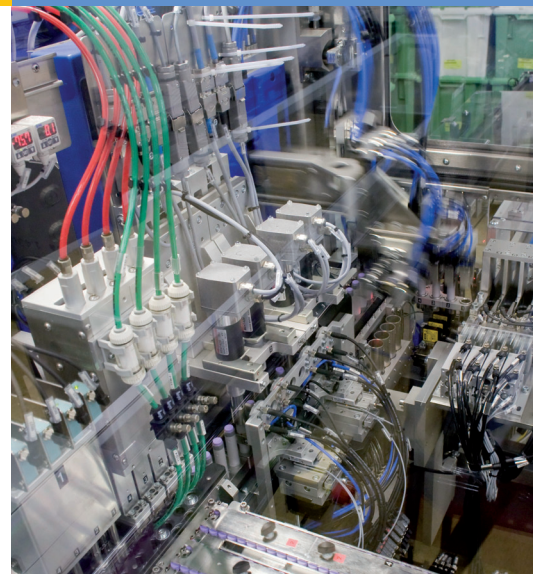
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