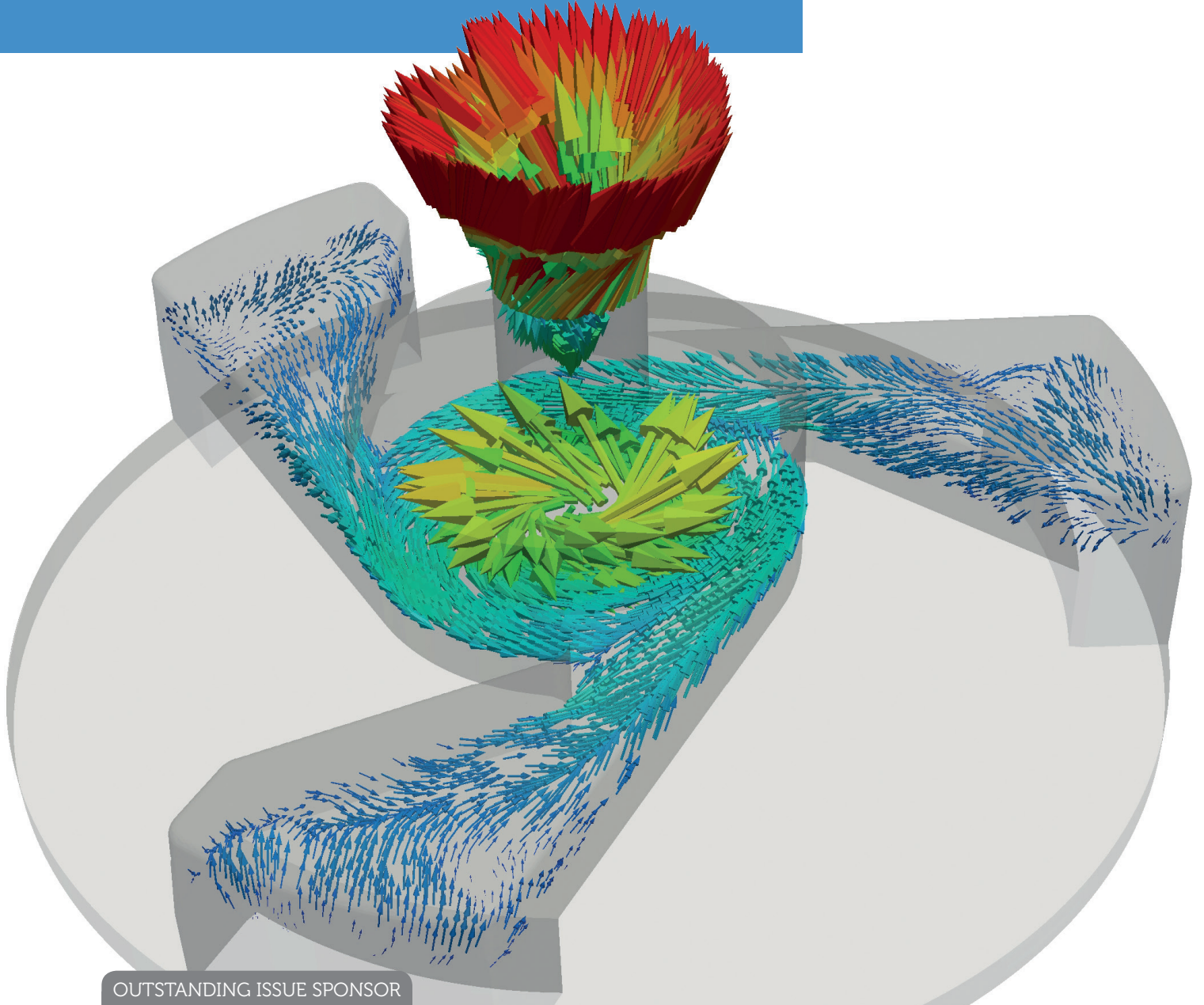
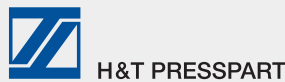


PULMONARY & NASAL DELIVERY



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PULMONARY & NASAL DELIVERY

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| Jan '18 | Ophthalmic Delivery |
| Feb | Prefilled Syringes & Injection Devices |
| Mar | Skin Drug Delivery: Dermal, Transdermal & Microneedles |
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Front cover image, 'Velocity profile of fluid passing through a nozzle, showing the swirl motion'. Copyright © 2017 Nemera. Reproduced with kind permission.

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THE SCIENCE BEHIND CAPSULE-BASED DRY POWDER INHALATION TECHNOLOGY

Here, Fernando Díez, Scientific Business Development Manager, Justin Kalafat, Business Development Manager (North America), and Jnanadeva Bhat, PhD, General Manager, Product Development & New Product Offerings, all of ACG, explain the mechanics behind cDPIs, from the scientific perspective, before looking to the future of cDPIs in the market.

INTRODUCTION

Inhalation delivery to the respiratory system has gained wide acceptance as an effective, non-invasive method for local and systemic delivery of active pharmaceutical ingredients (APIs). The unique features of the lung (i.e. large surface area, thin alveolar capillary membrane, low enzymatic activity and avoidance of first-pass metabolism¹) all contribute to the preference for this dosage form.

Legacy products in this dosage form targeted chronic obstructive pulmonary disease (COPD) and asthma, however, many new medical conditions are being explored. Parkinson's disease, pulmonary hypertension, biologics and other treatment

areas are seeing increasing development activity in the area of inhalation delivery as an alternative to more traditional dosage forms.

There are various technologies available within the inhalation category. One popular, proven and convenient system is the capsule-based dry powder inhaler (cDPI). Some examples of commercial cDPI products are shown in Table 1. cDPIs, such as that shown in Figure 1, use a hard capsule that contains a mixture of powders composing the drug which is loaded inside an inhalation device. Patients operate the device to puncture, open or cut the capsule, and then take a deep breath to inhale the powder, using air as the vector of drug displacement. Lactose, known for good

| Product | Generic Name of API | Capsule Type | Company |
|---------------|-----------------------------|--------------|------------|
| Onbrez | indacaterol maleate | gelatin | Novartis |
| Foradil | formoterol fumarate | gelatin | Novartis |
| Seebri | glycopyrronium bromide | HPMC | Novartis |
| Spiriva | tiotropium bromide | gelatin/PEG | Boehringer |
| Tobi Podhaler | tobramycin | HPMC | Novartis |
| Ultibro | glycopyrronium/ indacaterol | HPMC | Novartis |

Table 1: Commercial cDPI products.



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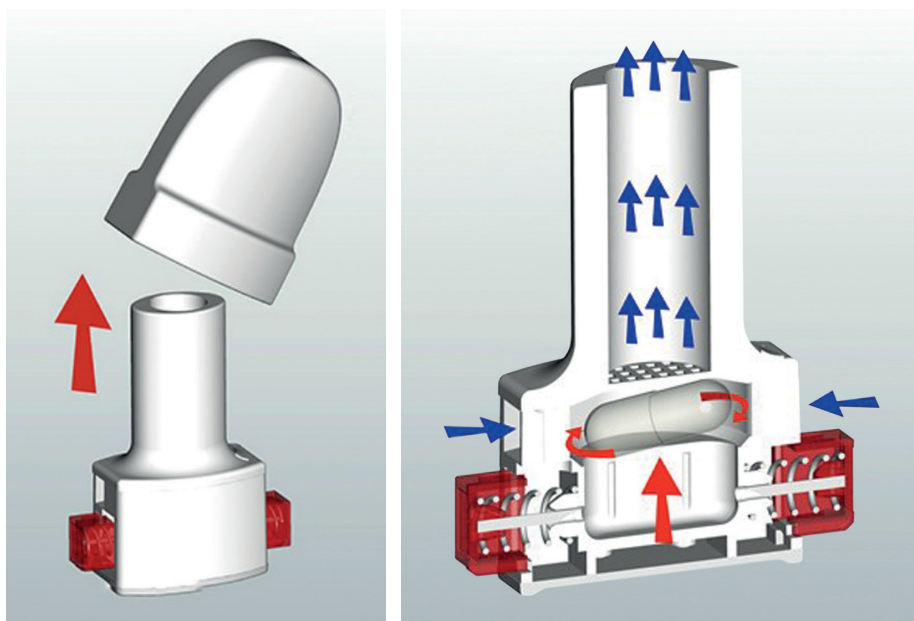


Figure 1: A cDPI (images from Plastiaple).

“The maximum force to open hard capsules is in the range of 3-5 N. To understand this order of magnitude, consider that the values for the force exerted during a keystroke whilst typing are in the range of 3.5-6.8 N. Opening a capsule is as easy as pressing a button.”

lung tolerance, is typically used as a carrier in the powder mixture along with the active ingredient to deliver drugs to the target. The system is simple, economical and eco-friendly, cDPIs have a carbon footprint 18 times lower than pressurised metered dose inhalers (MDIs).

THE FUNDAMENTAL LAWS OF INHALATION TECHNOLOGY

The inhalation dosage delivery and cDPIs in particular follow two laws:

- 1st law: The higher the quantity of powder that leaves the capsule, the higher the efficiency of the process. The parameter is measured by the emitted dose (ED).
- 2nd law: Particle size does matter, as the geometric diameter of the active ingredients within the formulation need to be in the range 1-5 μm . The parameter that measures this effect is called fine particle fraction (FPF).

To understand the need for such minute particle sizes better, it is necessary to consider how drug particles

pass through the respiratory system. The pathway through the lungs is not a straight line, in fact it's full of twists and turns (Figure 2). To reach the alveoli the particle must change direction continuously. If not, it will contact the wall of the airways

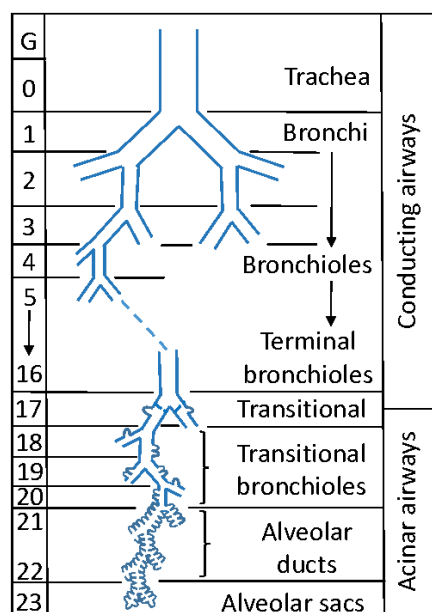


Figure 2: The way to the lung (Weibel model).³

and not reach the alveoli effectively. In fluid physics, there is a dimensionless number called the Stokes number (STK) which gives an idea of the ability of a particle to change direction with flow.² It is defined as:

$$\text{STK} = K d_p^2$$

Where K is a constant and d_p the particle diameter.

The key factor is whether the STK is greater or less than one:

- If $\text{STK} > 1$, the particle will detach from a flow, especially where the flow decelerates abruptly.
- If $\text{STK} < 1$, the particle follows fluid streamlines closely as it is able to change directions.

It then clearly follows that large particles with high velocity will not flow along the trajectory of the airways. This is due to inertia causing them to impact the wall of the bronchi and deposit there. Correlation *in vitro/in vivo* studies have shown that the limit size for a particle is 5 μm .¹ Additionally, particles whose diameter is lower than 1 μm will be exhaled.

CAPSULE-BASED DRY POWDER INHALERS

Puncturing

For hard shell capsules to function effectively as drug reservoirs in cDPIs, the capsule must be capable of being punctured efficiently. Sharpened pins or thin blades cut the capsules to release the powder medication upon inspiration, with low forces being necessary for the puncturing process. It is critical that capsule fragments do not hinder the outflow of the powder. For example, if a pin punctures the capsule, then the flap produced must stay attached and remain open, not closing or obstructing the opening.

Hard capsules fulfil these conditions. One can observe the initial linear slope of the curve (following the Young's modulus) which resists the force due to the elasticity of capsule. It reaches the threshold immediately prior to puncturing. Afterwards, there is a subsequent reduction in the force that is determined by the frictional forces between the pin and the perimeter of the punctured hole created in the capsule, including any "flap" that may be present. The force then becomes relatively constant. This is attributable to a more constant friction

Force/ Deformation for Hard Capsules

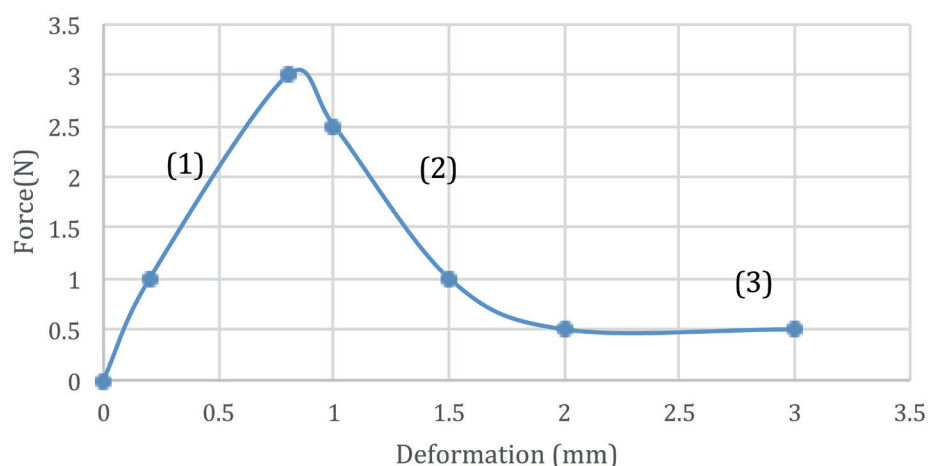


Figure 3: Standard graph of the displacement of a conical pin on a hard capsule versus the recorded force. The numerals indicate the various steps involved in the puncturing process (Redrawn from Ref 4).

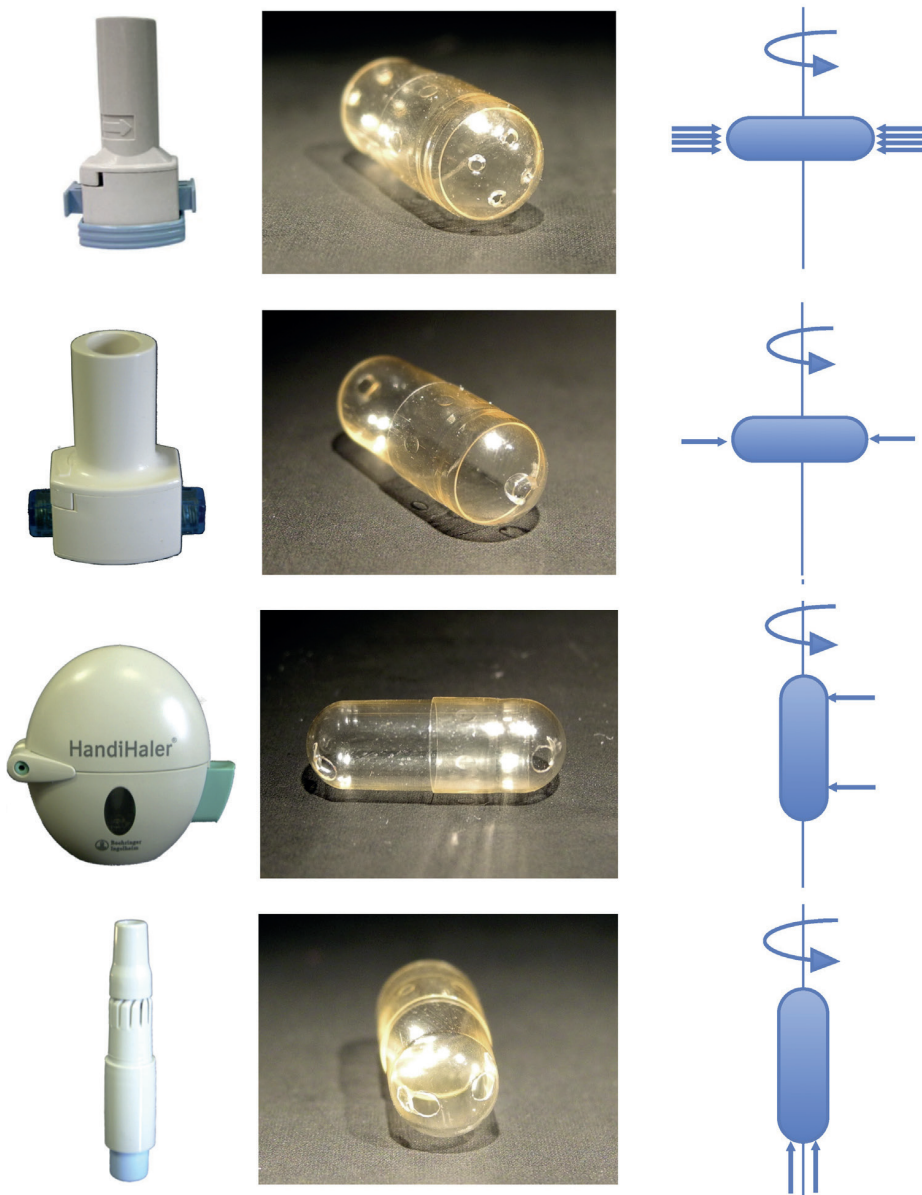


Figure 4: Capsule rotation modes for different inhalation devices.¹⁰ (Reproduced with kind permission from the International Journal of Pharmaceutics.)

force between the perimeter of the capsule puncture and the pins.⁴

The maximum force to open hard capsules is in the range of 3-5 N. To understand this order of magnitude, consider that the values for the force exerted during a keystroke whilst typing are in the range of 3.5-6.8 N.⁵ Opening a capsule is as easy as pressing a button.

The capsule profile shown in Figure 3 assures us that there are no pieces being shed and that the flap stays attached during the process. If this happens, the constant force value would drop until it reaches zero.

Aerosolisation

Powders in the range 1-5 μm are characterised by highly cohesive and adhesive properties that make processing them rather difficult. To overcome this, the micronised API is mixed with coarser excipient particles. The larger size of these carrier particles, usually in the range of 50-200 μm , improves powder flow and thereby improves powder dosing and dispensing. Additionally, the excipient acts as a diluent and increases the amount of powder that must be dosed from the microgram range, to the milligram range, a scale that makes dosing more feasible.⁶

Upon aerosolisation and inhalation of a powder, carrier particles deposit in the mouth and throat regions. It is therefore essential for drug particles that are attached to the carrier particle surface to detach from it, so that they do not deposit together with the carrier particles, instead depositing in the targeted lower respiratory airways.

This powder de-agglomeration is key to the success of the process. It depends on the fluid dynamic shear which may be enhanced by turbulence. Capsules contribute to creating this turbulence by rotating inside the inhaler device. The physical law behind this is the conservation of angular momentum.⁷ They can reach angular velocities of 2800 rpm inside the device,⁸ creating a high turbulence. For comparison, the spin speed of a washing machine is about 1600 rpm.

“Capsules contribute to creating this turbulence by rotating inside the inhaler device. They can reach angular velocities of 2800 rpm inside the device.”

Upon inhalation, the flow field generated within a cDPI acts to rotate the capsule at high speed. This ejects powder contained in the capsule through the created holes into the surrounding flow field.⁹ The break up can occur through a number of capsule-induced de-agglomeration mechanisms:

- Impact of the powder agglomerates with internal walls of the capsule.
- Forcing powder agglomerates through the small holes in the capsule, breaking up large agglomerates, preventing slugs from exiting the capsule.
- High speed impactions with the surrounding walls of the device when the particles are ejected from the capsule.
- The spinning capsule could act as a rotor to de-agglomerate ejected capsules through mechanical impaction with the external walls of the capsule.

Figure 4 shows different capsule rotation modes for four example inhalers.

Capsule Internal Surface

The capsule manufacturing process requires the use of a surface lubricant on the mould pins on which the capsules are formed. It enables the dried capsule parts (caps and bodies) to be removed from the moulds without damage. The nature and quantity of lubricant that remains in the capsule will modify the capsule surface properties. This plays a role in capsule aerosolisation performance.

The capsule internal surface is not flat (see Figure 5) and it seems that low quantities of internal lubricant do not fill all the surface pores, meaning the powder occupies these points. This makes it more complicated for the drug to exit the capsule. On the other hand, if the lubricant

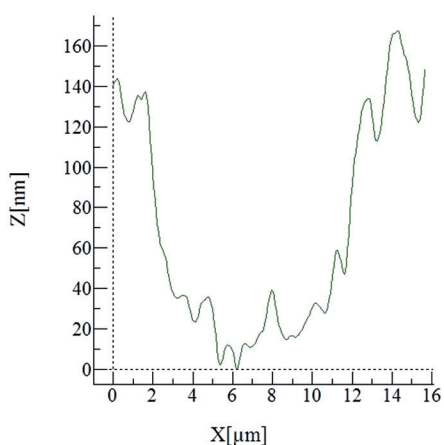


Figure 5: Capsule internal surface profile.¹¹

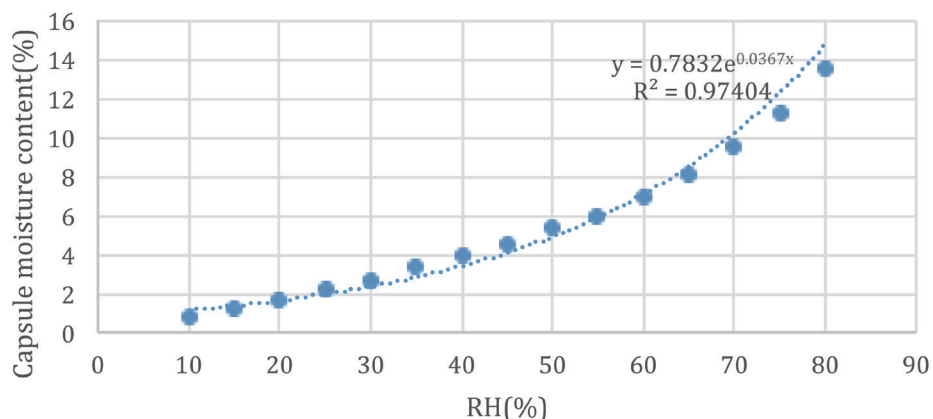


Figure 6: Correlation between HPMC capsule moisture content and RH. Exponential fitting.

content is high, adhesion between the capsule and powder may occur, reducing the process efficiency.

Stability/Moisture Content

Water is one of the enemies of inhalation drugs for the following reasons:

- Most inhalation drugs are moisture sensitive and are degraded by water.
- In presence of high relative humidity (RH), the capillary forces are significant, increasing the drug particle size. This reduces FPF and the efficiency of the process.
- Many inhalation drugs are only active in amorphous form. Amorphous solids are thermodynamically unstable, thus potentially can undergo crystallisation upon storage. The tendency to crystallise is increased with humidity, as water plasticises the solid, lowering its glass transition temperature.

Stored at RH not exceeding 65% HPMC capsules have a low moisture content of 3-8%, and these levels can be further reduced without any influence of their mechanical properties (Figure 6). These capsules do not become brittle in arid conditions, unlike gelatin capsules. A normal procedure for desiccation would be filling the capsules and storing them at low relative humidity (i.e. 11%, which corresponds to a capsule moisture content of 1%), followed by blistering and packaging.

cDPI MARKET OPPORTUNITIES AND FUTURE

cDPIs belong to the broader category of dry powder inhalers (DPIs). According to a BCC Research report¹² the CAGR for this technology is likely to be 12.5% in the period 2013-2018, while other alternatives

“Simplicity of use, flexibility of application, ease and economy of availability, proven performance and exciting new innovations in the pipeline are some of the reasons why cDPI technology has gained wide acceptance and has a promising future.”

like MDIs may grow at a more modest 4.2% CAGR. Interest in cDPI technology has increased thanks to an overall trend in favour of respiratory delivery methods and the rise of inhalable biotherapeutics.

Apart from their conventional applications in asthma and COPD, cDPIs can also be used for systematic disorders as diabetes, cancer and neurological diseases.¹³ Two good examples where inhalation capsules are used are oxytocin (peptide hormone) and levodopa (Parkinson’s disease).

There are exciting innovation projects in the development pipeline such as the use of new inhalation devices applying a magnetic field to increase the capsule rotational speed (Maxwell law) or the use of magnetic particles to increase the FPF of the delivery.¹⁴

CONCLUSION

Simplicity of use, flexibility of application, ease and economy of availability, proven performance and exciting innovations in the pipeline are some of the reasons why cDPI technology has gained wide acceptance and has a promising future.

Developing a cDPI drug involves subject specific knowledge, expertise and capable partners. One of the critical elements in the value chain is choosing the right type of hard gelatin or HPMC capsules. Several considerations are involved in this which are unlike the conventional dissolution and disintegration parameters typically associated with the capsule. Other critical elements are the choice of an appropriate device, formulation expertise, technology for precision encapsulation and optimum packaging.

An experienced partner like ACG with capabilities in integrated pharma manufacturing technologies can bring in valuable expertise and partner with customers to develop a complete solution.

The present outlook for cDPI technology is excellent, with continued advancement and a more promising future.

ABOUT THE COMPANY

ACG has been serving the pharmaceutical industry for five decades and is the second largest manufacturer of empty hard capsules in the world. The group comprises 13 companies, including subsidiaries in China, the US, Indonesia, Brazil and Europe.

ACG has a presence in over 100 countries with its products and services, employing more than 3,000 members of staff that strive to provide world-class technologies across multiple domains. It offers a complete range of solutions beginning with empty capsules, granulation and coating, capsule filling, tableting, packaging films, blister packing and carton packing, to end-of-line solutions. With over 20,000 machine installations

worldwide, it speaks volumes of the high quality standards followed at ACG, as well as compliance with major international quality certifications and legislations.

ACG is committed to a core corporate competence. Its research teams strive to develop innovative technologies in order to continually give customers the benefit of a cost competitive edge plus world-class technology. SciTech Centre, the group's R&D centre located in the heart of Mumbai, is a government recognised research institution. Especially in the last 25 years, the company has witnessed breakthroughs in development-including, controlled-release pharmaceutical engineering, dosage forms and veterinary and agricultural research, all with an emphasis on delivery systems.

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ABOUT THE AUTHORS

Fernando Díez is Scientific Business Development Manager for ACG and holds an MBA and degree in chemistry. He creates new business opportunities outside of the formal review/tender process and fosters relations with external research institutes and R&D centres. He has a wealth of experience in the pharmaceutical industry, having worked with renowned multi-national companies.

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A SIMPLE AFFORDABLE DPI: MEETING THE NEEDS OF EMERGING MARKETS

In this article, Anselm Ebert, PhD, Business Development Director, H&T Presspart, João Ventura Fernandes, PhD, Business Development Manager, Hovione Technology, Ameet Sule, Head of IPTC, H&T Presspart, and Sunita Sule, IPTC Consultant, H&T Presspart, discuss the rising need for respiratory medication in the developing world. They go on to highlight the novel challenges presented by these new markets and explain how a new DPI, PowdAir Plus™, meets those challenges, offering a solution to the increase in chronic respiratory conditions across the globe.

GROWING NEEDS FOR RESPIRATORY CARE

It is estimated that chronic respiratory diseases such as asthma and chronic obstructive pulmonary disease (COPD) may affect as many as 334 million people worldwide today,¹ with that number predicted to rise by an additional 100 million by 2025.² Whilst the prevalence of asthma and COPD has been historically estimated to be higher in developed countries,³ it is forecast that many will also become affected in developing countries, as the disease prevalence rate is expected to rise faster in these countries as a result of

urbanisation and modifications to lifestyle and the environment.² While asthma alone causes over 250,000 deaths every year, the mortality rate of chronic respiratory diseases is known to be mainly correlated with access to essential respiratory care



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“Whilst the inhalables market has previously been dominated by MDIs, DPIs have become the fastest growing segment.”

and drugs. Hence, mortality rates are currently higher in developing countries such as India, China and South Africa. Thus, there is a growing need to improve access to basic respiratory healthcare and medications in emerging markets.

THE IMPORTANCE OF THE INHALER

Improving population access to respiratory care in developing markets is both a clear, unmet medical need and a major task for manufacturers of respiratory drugs and delivery devices. As the traditional strategy followed by pharmaceutical companies in developing countries has been geared towards providing a barrier to generic competition (via complex products, customised to expensive devices), patients in developing countries have not yet been able to benefit from an industrial strategy targeted to fulfil their needs for improvement in access and treatment affordability. In this aspect, dry powder inhalers (DPIs) are a particularly well suited delivery device platform for emerging markets. In particular, capsule-based DPIs offer flexibility to deliver a wide range of drugs from a single, cost-effective device platform.

In practice, the device has become the largest portion of the final pharmaceutical package cost, making it essential to develop new, state-of-the-art device designs that maximise ease of use whilst minimising manufacturing costs. This facilitates patient access to respiratory medicines in developing markets. Market research predicts that, with key drugs and delivery devices soon to come off-patent in the asthma and COPD space, emerging markets offer considerable potential for inhaled generics.

Driven by the rapidly evolving healthcare industry, Asia Pacific is expected to display the fastest growth, having to look after an increasing patient pool in need of treatments for asthma and COPD. India, in particular, is expected to gain from the increased efforts of its government to reduce overall healthcare expenditure. Other regions such as Latin America, the Middle East and Africa are also observing improved access to healthcare, connected to a rise of the middle class with more disposable income, in turn driving an increased usage of asthma inhalers. Whilst the inhalables market has previously been dominated by metered dose inhalers (MDIs), DPIs have become the fastest growing segment. Whereas most DPIs



a) PowdAir Plus in storage position



b) Step of pushing moveable tray into the open position for loading of the pharmaceutical capsule



c) Step of closing the loaded tray, which allows the capsule to be cut open, and opening the hinged cover for inhalation

Figure 1: Usability of the PowdAir Plus capsule-based DPI: a) storage position; b) loading pharmaceutical capsule; and c) closing the loaded tray.

“Whilst the pharmaceutical industry has made extraordinary technological advances with inhalation devices, it is important in some market segments to make sure that not too much complexity is added, making the devices more difficult to use and expensive to manufacture.”

have been designed for developed markets and their economic structure, with multiple components and complex mechanics, the demand for respiratory treatments is growing rapidly in developing markets, presenting a new set of challenges. By listening to customers, a clear demand can be heard for DPIs that deliver reliable performance, are easy to use and are readily affordable. Whilst the pharmaceutical industry has made extraordinary technological advances with inhalation devices, it is important in some market segments to make sure that not too much complexity is added, making the devices more difficult to use and expensive to manufacture.

Which important issue should the design of a device tackle? A large independent study completed in 2016, summarising over 140 articles reporting on 50,000 subjects, concluded that “incorrect inhaler technique is unacceptably frequent and has not improved over the past 40 years, pointing to an urgent need for new approaches to education and drug delivery”.⁴ Furthermore, the Asthma Society of Ireland published figures showing that up to 60% of the 300,000 asthmatics in the country do not have their disease under control.⁵ In context, these numbers support the conclusion that a well-designed, easy to use inhaler might reduce the risk of errors caused by incorrect inhaler technique. Looking at developing countries, such as India, COPD deaths have increased by 65% in the last decade.

MAKING IT EASY

At the beginning of 2017 H&T Presspart teamed up with Hovione Technology and launched PowdAir Plus™ (Figure 1).

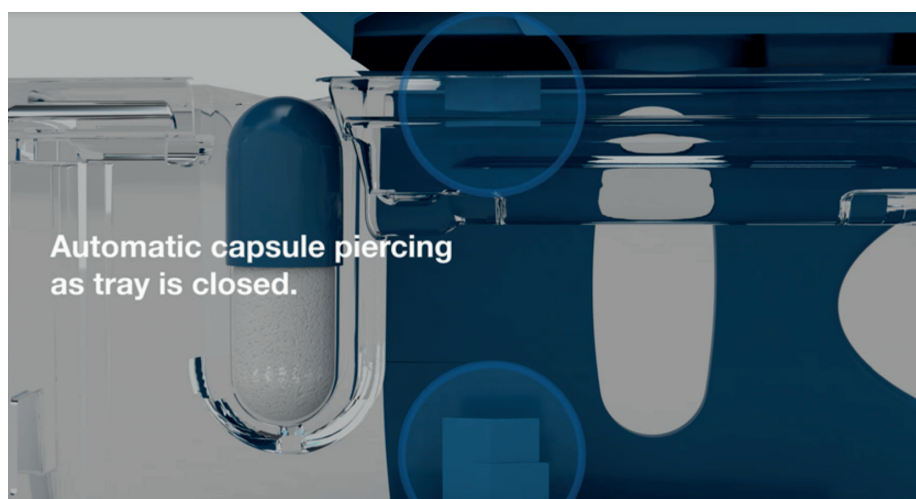


Figure 2: Easy capsule opening: automatic capsule activation as tray is closed.

PowdAir Plus, a capsule-based DPI, is designed to maximise simplicity and ease of use whilst minimising manufacturing, assembly and production costs (for example, by using no metal parts). A particularly novel design feature is the way that the device opens the capsule automatically once the tray is closed, removing the need for patients to actively pierce the capsule and reducing the number of operational steps. The device is patented with a unique blade technology (Figure 2).

As the industry becomes more customer-focused and aesthetics play a greater role, the visual and haptic design becomes a factor of utmost importance. If patients are going to keep a device on them at all times for frequent use, it must be neat, portable and robust. Most capsule-based DPI formulations are available in transparent or partially transparent capsules. The clear transparent capsule chamber in the PowdAir Plus device (compatible with all Size 3 capsule types) gives visual feedback that the complete dose has been inhaled from

the capsule, and its hinged dust lid ensures continuous protection of the mouthpiece. Incorporation of these features has made the PowdAir Plus device simple, compact and discrete.

A patient-centric methodology was followed by Hovione Technology during the design generation of this new capsule-based DPI. In an initial human factors study, a first design embodiment was evaluated and benchmarked against the market-leading capsule-based DPI by 19 COPD patients in terms of use steps, size, shape, capsule handling, mouthpiece comfort and dust cap design. This led to the discovery that patients preferred fewer use steps – in particular the automatic capsule piercing feature – and the more ergonomic shape and size of the proposed new design. However, patient feedback also indicated the need to both further facilitate loading and ejecting the capsule, and integrate a fully hinged dust cap. Based on collected patient preferences and human factors findings, a second design was proposed which integrated the desired



Figure 3: The four parts of PowdAir Plus.

“Next to the three human factors studies performed by Hovione Technology, H&T Presspart brings professional manufacturing capabilities to the table.”

design features, and was subsequently submitted to two new human factors studies with 34 additional COPD patients. The results confirmed the usability improvements and the beneficial impact of integrating patient-focused testing during inhaler device design for achieving maximum ease of use in the final PowdAir Plus DPI.

Next to the three human factors studies performed by Hovione Technology, H&T Presspart brings professional manufacturing capabilities to the table. By employing these, the possibility was opened up to fulfill the market demand for high quality devices at affordable costs (Figure 3). H&T Presspart, being one of the leading suppliers for the respiratory inhalation field, has experience producing high quality products at lean manufacturing costs.

EFFECTIVE DELIVERY

PowdAir Plus is a medium resistance device (50 L/min corr to 4 kPa) capable of delivering both lactose carrier-based and particle engineered dry powder formulations. The X-ray pictures (kindly provided by Prior PLM Medical) (Figure 4) show the effectiveness of the device. The two major positive effects of this delivery method are, firstly, a steady release of the powder during the inhalation period and, secondly, creating a vortex in the capsule itself to disperse and de-agglomerate the powder. The *in vitro* laboratory data of PowdAir Plus with a generic marketed salbutamol formulation exhibits good particle size distribution in line with currently marketed DPIs. The delivered dose data shows flow rate independency at 30, 60 and 90 L/min (Figure 5).

H&T Presspart's Inhalation Product Technology Centre (IPTC) unit collaborated with Hovione Technology's experts to combine both knowledge and experience regarding device development, powder characteristics and analysis. A joint effort was made for the functional

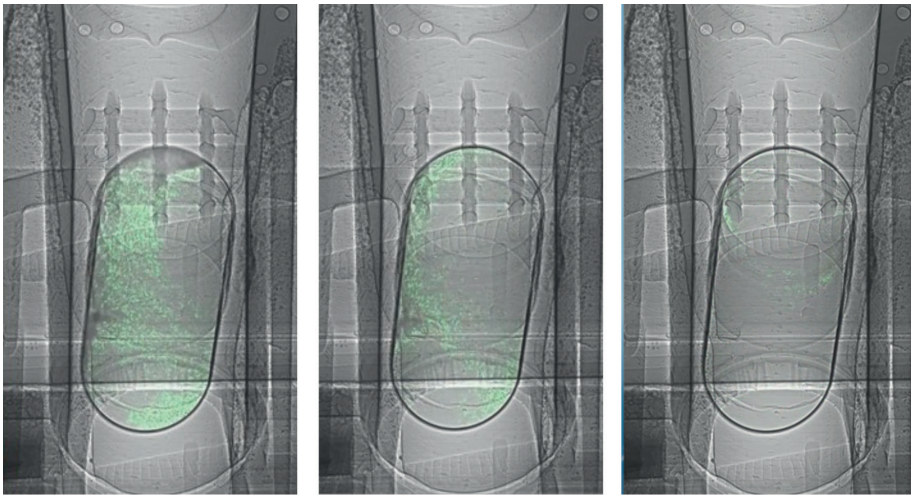


Figure 4: High speed X-ray images of the powder dispersion dynamics inside the capsule during inhalation (kindly provided by Prior PLM Medical).

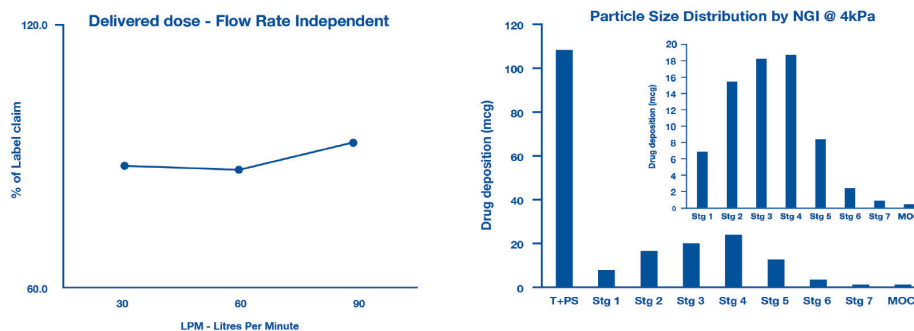


Figure 5: *In vitro* performance data of PowdAir Plus device for a marketed salbutamol capsule-based formulation.

optimisation of the device design, using techniques such as computational fluid dynamics (CFD) and X-ray analysis, leading to the PowdAir Plus DPI.

CONCLUSION

With the prevalence of asthma and COPD on the rise, increased healthcare costs in developing countries will be an undeniable consequence. To help these countries improve basic access to respiratory drugs and care whilst maintaining sustainable healthcare systems for their patients, cost effective solutions by respiratory drug and device manufacturers are needed. Human factors studies suggest that usability issues, incorrect inhalation techniques and a lack of adherence contribute to unsatisfactory treatment results.

On the other hand, as the delivery device

itself has become the largest portion of the final cost of pharmaceutical goods, it is essential to develop new, state-of-the-art device designs that maximise ease of use for improving treatment compliance whilst simultaneously minimising its manufacturing cost, meeting the requirements of emerging markets. Nowadays, both generic and originator medication are developed to meet the demand for easy to use, high quality devices, delivering high doses of medication in a reliable and repeatable fashion, for as little cost as possible.

By combining the strengths of Hovione Technology and H&T Presspart, a unique unit dose, capsule-based DPI, PowdAir Plus, is now available, combining user-friendliness, functionality and affordability to provide for the unmet needs of developing countries for improved respiratory care.

ABOUT THE AUTHORS

Anselm Ebert has a PhD in Neuroscience from Edinburgh University and is Business Development Director at H&T Presspart, the leading supplier of respiratory drug delivery components. Dr Ebert previously worked as a Senior Business Consultant and before joining H&T Presspart was Director of Product Development at Hartmann AG who specialise in the manufacture of medical products.

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Ameet Sule, Director, Inhalation Product Technology Centre, H&T Presspart, is a pharmaceutical professional having worked in the industry for more than 20 years, specialising in the development of inhalation products and devices.

Sunita Sule, Inhalation Product Consultant, is a pharmaceutical professional who has over 25 years of experience in the pharmaceutical industry, with core expertise in formulation and device development of inhalation products.

ABOUT THE COMPANIES

H&T Presspart offers pharmaceutical customers high-precision injection moulded plastic components and deep drawn metal cans for respiratory drug delivery systems.



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The company has more than 45 years' experience and a worldwide reputation for competence, quality and innovation in the pharmaceutical and other industrial sectors. H&T Presspart Inhalation Product Technology Centre (IPTC) supports new product developments and strategic initiatives with its customers. Founded in 1970 and acquired by the Heitkamp and Thumann group in 2002, H&T Presspart has three European manufacturing sites in Germany, Spain and the UK, with sales offices in China, India, South America and the US.

Hovione Technology offers access to innovative, attractive and globally competitive inhalation devices that maximise simplicity of use, safety, drug delivery performance and industrial manufacturability. With more than 20 years' experience in inhalation device development and a track record for developing successfully marketed, novel and effective inhalation devices, Hovione Technology offers device development services and access to a family of disruptive, patent-granted inhalers for both acute and chronic treatments.

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THE LATEST DIGITAL TOOLS REVEAL ACTUAL PATIENT BEHAVIOUR

In this piece, Ryan Noble, Senior Drug Delivery Specialist, and Tom Lawrie-Fussey, Healthcare Digital Strategist, Cambridge Design Partnership, discuss the potential of digital innovations to improve understanding of real patient behaviour and consequently increase adherence.

The digital world is increasingly affecting our interactions with information and with each other. Value is no longer restricted to physical products – it's now also linked to the information a product creates or gives us access to. Inhalation device development very much aligns with this strategy, with many new connected devices and service organisations now established to help quantify patient adherence, and ultimately improve patient outcomes, for diseases such as chronic obstructive pulmonary disease (COPD). But is this going far enough? Is it truly patient centric? The problem is particularly acute for patient groups that typically don't shout loudly about their concerns, children and the elderly for example, from whom it's particularly hard to elicit opinions.

EFFICACY OF THERAPY DUE TO LOW ADHERENCE

We all hear a lot about adherence. But although this term is now common parlance across the industry, successful system-level implementation of product-enabled services, beyond the concept, remains far from established. We know that poor adherence leads to poor disease control and increased healthcare costs, so how are we assisting patients in optimising their therapy? Do we understand how to help them push through the barriers of remembering to take their prescription on time and in the right way? Do we enable patients to persevere and receive the clinical benefits they need?

Adherence is far from a new topic. It has been written about in the context of using technology to monitor dosing since Cramer's 1995 article on "Microelectronic systems for monitoring and enhancing patient compliance with medication regimens", in which a method of understanding

"The EU's myAirCoach project is looking into multiple factors around asthma sufferers' daily management of their therapy... it hopes to understand aspects of adherence better by using on-inhaler sensors to monitor the time of use of products."

how patients were taking their tablets is described, using special containers with a microprocessor that records the time when each dose is removed.¹

Jump forward 20 years and the EU's myAirCoach project is looking into multiple factors around asthma sufferers' daily management of their therapy,² including fluctuations in disease state and improved lung models. A key aspect of this study is how it hopes to understand aspects of adherence better by using on-inhaler sensors to monitor the time of use of products. It then sends this usage data up to a cloud-based analytics service for assessment, using the insights gleaned to help tailor personalised asthma treatment plans in the future. Whilst a fantastic step forward – and one that will surely uncover a wealth of opportunities – we should consider it as just a part of the journey, not the endpoint. There are still many other innovative ways of enhancing (and simplifying) the actual inhalation process.

WILL BETTER DEVICE DESIGN SOLVE THE ADHERENCE PROBLEM?

But surely we can solve the adherence problem by improving the real-world patient experience? Are there established links that relate adherence to inhaler design, perhaps?



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Certainly, there are many devices already on the market, such as dry-powder inhalers (DPIs) and pressurised metered-dose inhalers (pMDIs), that aim to improve quality of life in routine treatment. With design features such as multi-dose capabilities and counters, better device design improves adherence – on paper, at least. However, a recent study looked at the impact of multiple-dose versus single-dose inhaler devices on treatment via persistence.³ The study indicated that, in fact, inhaler type seems to make no difference to adherence. It is perhaps worth highlighting that these more sophisticated devices, whilst potentially superior, are still inherently disliked by patients – often not due to any design flaw but simply because the patient doesn't want to use the device in the first place.

The current industry realisation is that the true therapeutic benefits of long-term inhaled medicine may never be fully realised, due to patients failing to take their medication on time and not persevering with the right technique to get the effect they need. Indeed, in a study published earlier this year, the pMDI inhalation technique of more than 200 adults was observed, and only 23.1% were found to use their inhaler correctly.⁴

This is particularly true of those patient populations that perhaps require the greatest support but don't necessarily represent the majority – and therefore lack the loudest voice. Understanding the behaviour of the young and old may well unlock the

“How has the automotive sector managed an increased adherence to safety and better driving practices, whilst providing substantial interaction gains to the consumer, whereas adherence to inhalation methods remains stubbornly low?”

most significant innovation opportunities. Further, these behavioural observations shouldn't be restricted to the inhalation process – better understanding the day-to-day situational context is crucial to providing an improved patient experience, and ultimately better outcomes.

REGULATED INNOVATION

If we look at other regulated sectors, such as automotive, aerospace and nuclear, they have all successfully innovated without impacting on safety – indeed, they've markedly enhanced it. In those instances where safe consumer interaction is paramount (e.g. interfacing with the driver whilst they're at the wheel) innovations have rapidly evolved, with a typical dashboard now providing a plethora of safety, convenience

and infotainment feedback, often controlled by gesture alone. How has the automotive sector managed an increased adherence to safety and better driving practices, whilst providing substantial interaction gains to the consumer, whereas adherence to inhalation methods remains stubbornly low?

The route to innovation has not been driven by regulation but by competition, and also a tier-1 supplier base that is a very active development partner. Such an industry dynamic creates a never-ending rush to democratise new technology, and there is a convenient spread of product/cost to accommodate the roll-out. Whatever appears on the luxury (higher margin) fleet will typically appear on all vehicle variants within 10 years. So how can this staged roll-out and development partner ecosystem be adopted and adapted to better serve medical devices?

FOCUS ON SPECIFIC DEMOGRAPHICS

Should we start with specific demographics, where overall production volumes are low and margins high? Whilst they provide a credible commercial launchpad, asking children or the elderly what they look for in an inhalation device rarely leads to success. Similarly, monitoring them in user trials, equipped with the usual myriad of cameras, microphones and one-way glass hiding review teams, often causes the Hawthorne effect – our behaviour changes when we know we're being watched. This is true for us all but often manifests itself even



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more strongly with those demographics that are more intimidated by such a facility, don't fully grasp the fundamental aim of such work, and worry instead about what they're expected to do.

What if we could leverage development partners and access the latest remote observation technologies, so that we can observe users in their homes – without affecting their behaviour? What if we could also quantify their exact behaviour and usage interactions? With this quantitative truth, surely we'd be better placed to make informed product development decisions, where we could aim innovations squarely at those user sequences that a particular demographic most struggles with?

USER TRIAL RESULTS

Results from our recent at-home monitoring study of the use of a product over a one-month period have shown a significant drop in use after just two weeks. Whilst the logging technology was hidden from view, users were informed of the capabilities of this approach – yet still we saw clear drop-off in adherence during the study. We used miniature bolt-on logging “pucks” which are able to capture a range of user behaviours, without impacting the very use they're assessing.

Our data scientists decoded and translated this raw usage data into tangible user insights (see Figure 1). Behind the seemingly simple challenge statement lies a vast array of tasks, including initial hackspace challenge scoping, development of new caseworks, modifications of our electronic modules and, most crucially, the development and iteration of the back-end analytics service. In this instance it had to learn what “normal” looked like for each user. Once these individual characteristics were categorised, the usage classifier was then able to suggest what was normal or abnormal – or non-usage.

This trial confirmed two things – firstly, even though the respondents insisted they had continued to use the device each day, their own usage data disputed this. Secondly, after an initial increase in usage, soon after week two many respondents clearly found the immediate gains to be insufficient and usage quickly dropped off.

So what insights can we take from this? Probably most critical is that it clearly shows there is a defined point in time where users are about to reduce their adherence – in this case, soon after two weeks but likely to be different for different treatments. If this

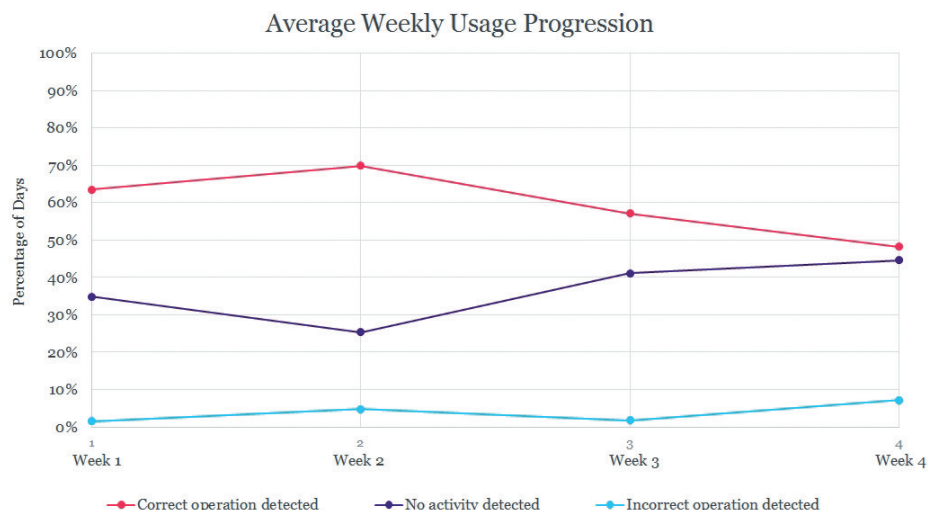


Figure 1: User trial results.

inflection point could be known, relative to when a patient started to take the treatment, additional measures could be taken (e.g. personalised incentives) to attempt to bridge the gap between initial interest and longer-term verifiable gains/results.

In the world of inhalation, for example, it may be possible to act when a patient is inhaling too quickly or storing the device the wrong way. Such actions could be measured and the user provided with the appropriate feedback, either in real time or as a reminder on a connected application. If we use technology to understand the behaviour of patients – not just in the market but during the development of the product – then we may gain access to previously unknown information that can be used to help users achieve the clinical effect of their medication.

CONCLUSION

It is understood that a certain amount of success can be achieved purely through patient engagement software such as HealthPrize, which has focused on the human psychology element in aiming to create the optimal carrot/stick incentivisation regime. It remains a difficult path to tread, however, as the aspirations of the sector continue to mature beyond monitoring to include assisting in treatment or diagnosis.

What is clear is that the base technology already exists to enable designers to improve their understanding of the needs of their patients and, in doing so, it empowers them to make the required design changes to inhalers to provide a beneficial user experience. Translating such raw usage data into quantifiable user insights is hard,

requiring large high-quality datasets, a sound grasp of the fundamentals of classic data science and (then and only then) vast amounts of computing power to drive artificial intelligence and machine learning.

So what is really stopping us? Is it the cost? Is it the regulations? Or is it simply not understanding the patient well enough?

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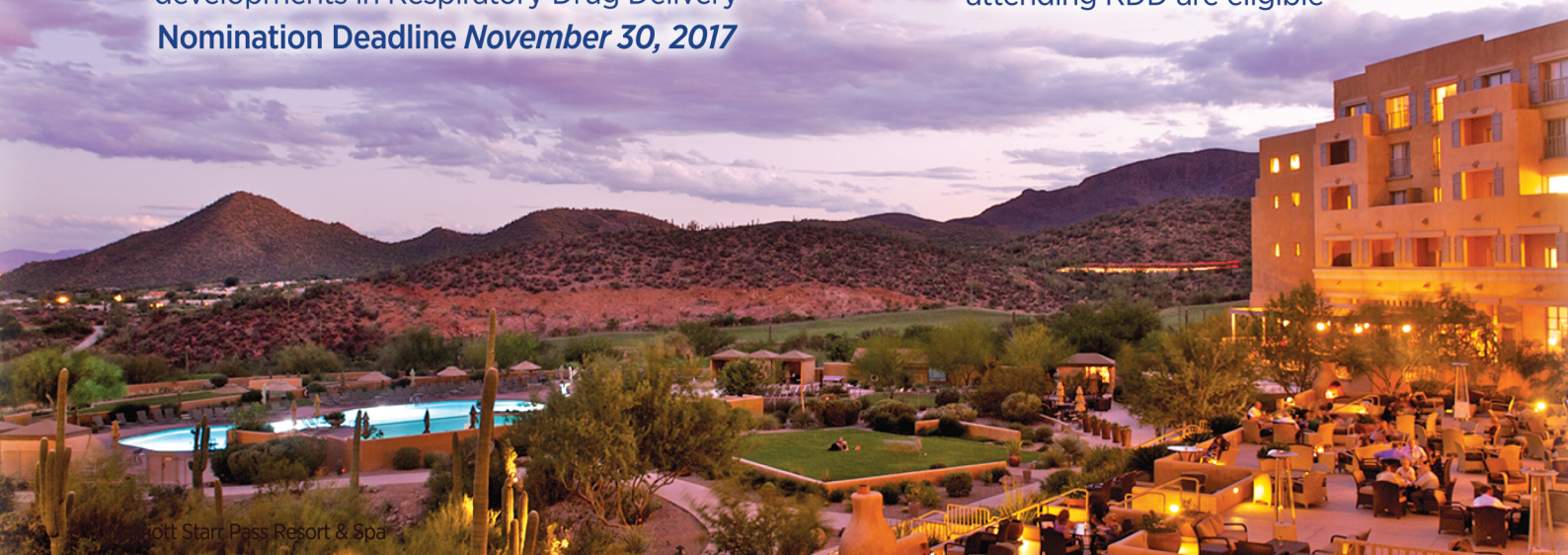
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THE DEVELOPMENT PATH TO BIOEQUIVALENCE FOR A NASAL SPRAY

In this article Pascale Farjas, Global Category Manager, ENT Products, Alain Regard, Technology Product Manager, and Céline Petitcolas, Customer Technical Support, all of Nemera, discuss the steps taken when designing a nasal spray device for the growing bioequivalence market and the key competencies, including experience with regulations and regulatory agencies in numerous geographic regions, that Nemera can offer throughout the process.

An observation of generics in the nasal spray market will reveal to the keen observer an opportunity. Whilst the overall nasal spray market is currently experiencing limited growth, the market share of generics is increasing at a much faster rate. Seeing this, Nemera has established a unique approach for developing devices in this field. This approach follows seven steps:

1. Understand the market and identify the best reference nasal sprays to target.
2. Appraise the regulation and, by isolating the most stringent requirements, use it to drive the programme.
3. Establish the identity of the device (e.g. bill of materials, performance, patient use) using a supply of the reference from different markets.
4. Develop the device, based on Nemera's pump platform, to have equivalent performance to the reference device with the reference drug formulation.
5. Test the performance, comparing the Nemera device with the reference with iso-formulation in a comprehensive study, to demonstrate bioequivalence (Figure 1).
6. Prepare the "datapack" containing robust statistical analysis to be delivered to the client, the data therein being used simultaneously to support the drug registration process and justify the device selection.
7. Repeat the study with the final drug.

UNDERSTANDING THE MARKET

The topical nasal preparations market, as per the Anatomical Therapeutic Classification (ATC), is currently estimated at a value around US\$5 billion (£3.8 billion). Well over half of this market is for corticosteroids (Figure 2), due to the fact that they remain the frontline treatment for moderate to severe allergic rhinitis (AR) as the most effective option for relieving nasal symptoms. The second thing to note is that the entire topical nasal formulations market is growing and evolving.

There are two key trends that can be observed as driving this evolution. First is increasing competition from generics. Nasonex (mometasone furoate), for example, has generic competitors with US FDA approval. Second is established brands shifting from a prescription-only to an over-the-counter (OTC)



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"Across the world there are several co-existing regulatory ecosystems, each with a different approach to bioequivalence ... When assembling the datapack further down the development pathway Nemera uses its understanding of the regulatory environment to tailor the strategy to the target geographic market."

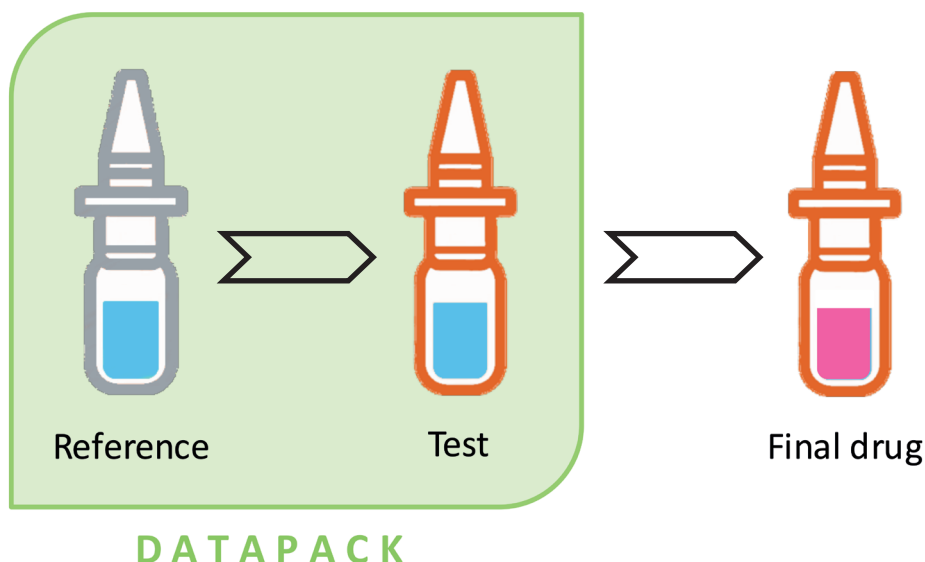


Figure 1: Nemera's device is compared to the reference with iso-formulation, in a comprehensive study to demonstrate bioequivalence, before testing with the final drug.

model, an example of this would be Sanofi's Nasacort AQ which was the first intranasal corticosteroid (ICS) in the US to make the switch, back in 2013.

Such trends are to be expected in a mature market and contribute to steady growth (1% CAGR in the period 2014-2016). However, with this observed increase in generics, the market share for generics increased from approximately \$1.4 billion in 2014 to \$1.7 billion in

2016, and improving access to healthcare, especially in developing countries, the future of this market looks to be both secure and promising. As such Nemera has selected a number of corticosteroids as part of their bioequivalence programme.

APPRAISING THE REGULATION

When looking at ICS as a global market it is important not to underestimate the

complexity of the regulatory landscape. Across the world there are several co-existing regulatory ecosystems, each with a different approach to bioequivalence. The most frequently mentioned is the US FDA, often considered to have the most stringent regulation. The FDA issues precise guidances for bioequivalence and statistical approaches. Additionally, they have drug specific guidances for generic products submitted under an ANDA. When assembling the datapack further down the development pathway Nemera uses its understanding of the regulatory environment to tailor the strategy to the target geographic market.

Looking elsewhere, EU regulation has the nuance that each member country may have a different interpretation of the regulations and directives. In the EU, for ICS, there are generally more submissions for hybrids than generics.

Of course, differences are far more noticeable when moving to emerging markets such as China. One of the hurdles that must be leapt when getting a drug approved for the Chinese market is finding a suitable agent to assist in the filing process. Not only will an application to the CFDA need to be translated but, if the application is filed by a foreign company without a Chinese office, an agent is also a legal requirement, similar to how an agent is required as an intermediary when dealing with ANVISA in Brazil. It is also worth noting that the CFDA has, at present, no clear guidance on liquid dosage for bioequivalence. Whilst the aim seems to be to synchronise with the US FDA, CFDA regulation is still very much under construction.

As Nemera focuses on the most stringent regulation during development, here we shall use the FDA as the exemplar for how Nemera supports the registration process. Under FDA guidelines, whatever the regulatory position of the targeted reference product (i.e. prescription only or OTC not under monograph), a generic product will follow the same process for its first submission and must therefore answer to the same requirements. When modifying the dossier, that is to say when making a variation upon the first submission (e.g. to add a second source), there are two ways to go about it. The first is to repeat the same process as the first submission and the second is to use a simple equivalence of performances of the pumps, thereby bypassing the need to follow the full guidance on bioequivalence for generics.

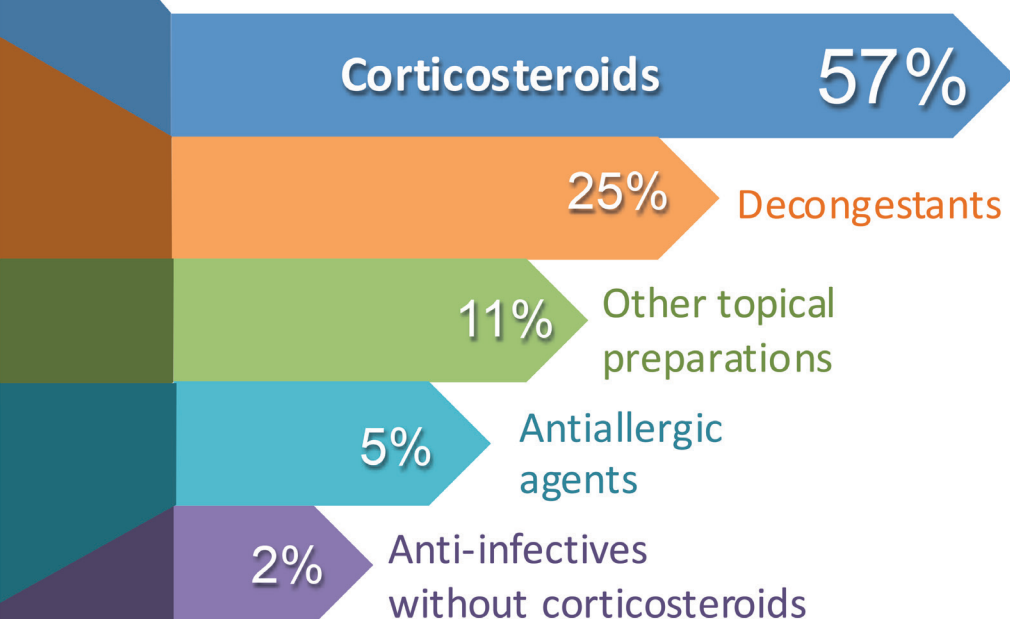


Figure 2: Worldwide intranasal market by drug type. (Source: IMS Health)

“It is noteworthy how small the dimensions of all these parts are, typically in the range of 0.2-0.4 mm, especially given the complex geometry. As such, high precision manufacturing is required to ensure that the final combination product generates a consistent spray after scale-up to industrial manufacture.”

When going through the process of registering a generic however, it may be more relevant for authorities to compare the variation directly to the reference product. A suitable analogy would be to imagine a simple door key: a copy of the master key would most likely be able to open its door, but a copy of a copy is less likely, and increasingly so the further down that rabbit hole you go. It's important to copy a key directly from the master and, likewise, it is important to test bioequivalence directly from the original reference product. Thanks to its deep experience with these processes, Nemera can strongly support a submission document with the chapters linked to the device.

ESTABLISH THE IDENTITY

In simple terms, a nasal spray is the combination of two regulated products, a drug and a device, which together make the combination product. Nemera's expertise is in the latter of these two, the spray device, but it remains crucial to acknowledge throughout the design process that the device is part of the greater combination product. The device is a major contributor to treatment efficacy, patient safety and robustness of the combination product. Nemera takes steps to ensure that the critical factor of device performance is under control at all stages of development.

A spray device has three main functions:

- Preserving drug product integrity
- Delivering an exact preset dose
- Delivering drug product to the targeted site.

In more detail, when discussing product integrity the main things to consider are ensuring that the device does not leak, that there is no weight loss (indicating an evaporation of solvent and therefore a change in the potency of the drug product) and that the extractables and leachables

profiles of the device materials are within regulatory limits. On the last point, Nemera performs studies to determine these profiles for the toxicological assessment and carefully selects the raw materials for the device.

The second two functions are both aspects of delivery. A preset dose of the API translates, at the device level, to a consistent weight of shot throughout the product's lifespan. Whilst a critical aspect of both efficacy and safety, it is perhaps the easiest of the three functions to control. The third function, delivering drug product to the nasal cavity in a consistent manner, requires consistent spray characteristics. Nasal sprays are characterised by droplet size distribution on the one hand, and spray geometry (a combination of spray pattern and plume geometry) on the other. These attributes contribute to the deposition pattern inside the nasal cavity and therefore play a role in the efficacy of the final combination product.

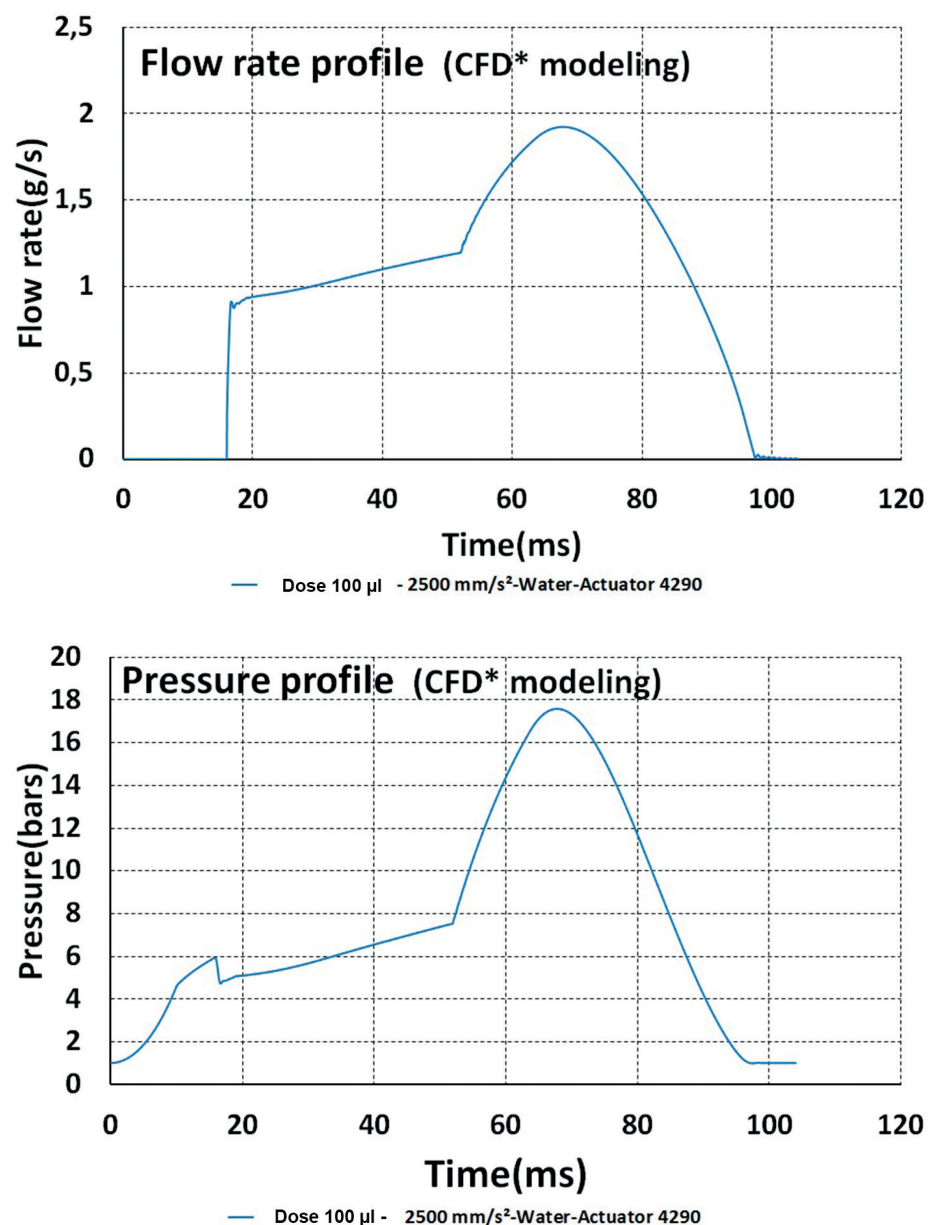


Figure 3: Flow rate profile (top) and pressure profile (bottom) from numerical modelling of a Nemera pump.

DEVELOP THE DEVICE

The discussion of device identity invariably brings us to the spray, which in point of fact is the hardest aspect to control, thus it is spray generation where the greatest effort must be expended during development of the device. With this in mind, let's turn to the heart of a nasal spray device: the pump. The pump has multiple functions, one previously touched upon is metering, ensuring the delivery of a preset dose.

Another primary function of the pump is to generate a flow and, furthermore, control flow rate and pressure level to master the generation of the spray. The flow rate and pressure profiles are dependent upon the pump technology and the actuation profile, with the nominal dose of the pump also having influence due to its impact on spray duration.

Figure 3 shows the outputs of numerical modelling of one of Nemera's pumps. The pump modelled had a dose of 100 μL , the test fluid was water and the nozzle was also a design of Nemera's. The flow rate profile shows that the dose is dispensed in under 100 ms with a flow rate of 1-2 g/s. In conjunction, the pressure profile shows that this flow rate generates an internal pressure rising to 18 bar. Such models are important to understand the physical behaviour of the pump fully, which in turn permits the prediction of outputs from the pump for given inputs.

Moving from heart to head, the next key part of the device to focus on in development is the nozzle (Figure 4), which is surprisingly

complex. Inside a nozzle tip are several vertical channels which then enter into convergent channels to move the rising liquid into a swirl chamber before exiting through the orifice at the tip of the nozzle. It is noteworthy how small the dimensions of all these parts are, typically in the range of 0.2-0.4 mm, especially given the complex geometry. As such, high precision manufacturing is required to ensure that the final combination product generates a consistent spray after scale-up to industrial manufacture.

Of the nozzle's components, the swirl chamber is perhaps the most interesting. Figure 5, a velocity profile of the fluid as it passes through the nozzle, clearly shows the swirl motion. In the swirl chamber at the centre, the fluid can be seen rotating and converging to the spray hole. The combination of the rotational and axial speeds generates an overall speed profile at the orifice that forms a rotating cone. The flow rate used in this simulation is 1.2 g/s, which is on the lower end of the flow rates for this pump, as seen previously. It is worth pointing out the magnitude of the fluid's velocity at the orifice: 48 m/s. For comparison, this is equivalent to 170 km/h or 105 mph, and the value nearly doubles when the flow rate reaches maximum.

When a fluid leaves a narrow orifice at such speed it breaks up into droplets in the first 2 mm after exit

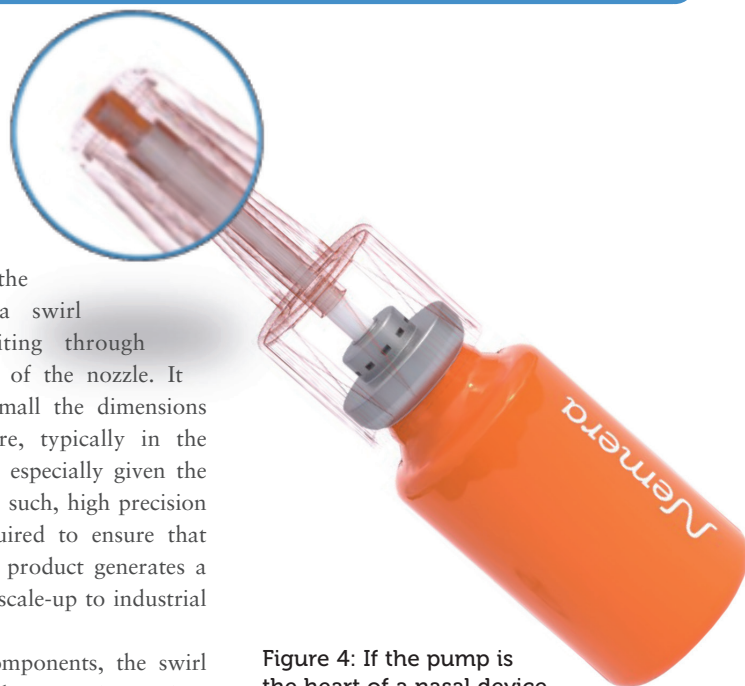


Figure 4: If the pump is the heart of a nasal device, then the nozzle is its head.

(Figure 6, see next page). These droplets form the basis for analysing how well and how consistently the device will deliver drug product inside the nasal cavity. These droplets, and hence the spray, are hugely impacted by the viscosity, and to a slightly lesser extent the surface tension, of the drug formulation. Batch-to-batch variability of viscosity can be significant and must be taken into account when designing a spray with a defined target as is the case in the bioequivalence approach. Because the impact of viscosity is so tremendous, the factors that affect viscosity, such as temperature, the delay between actuations and the fluid memory effect (i.e. whether or not the product has been shaken), must in turn be considered.

Velocity Magnitude

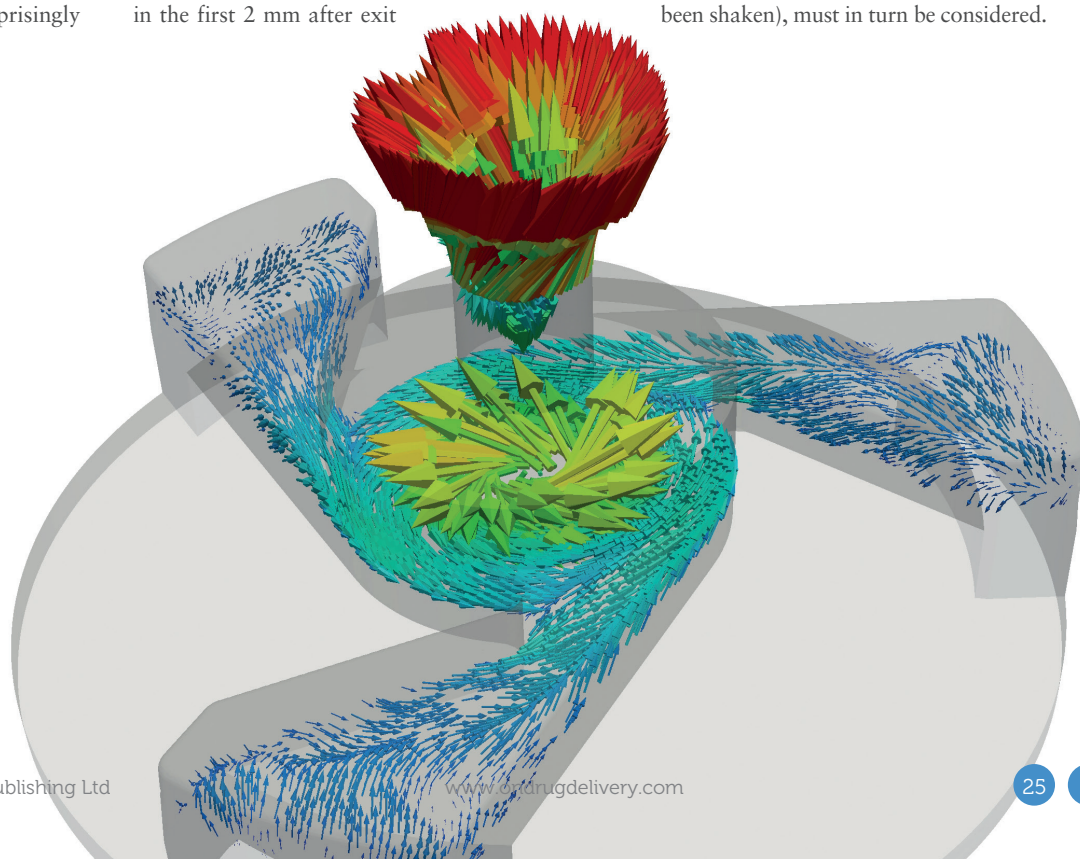
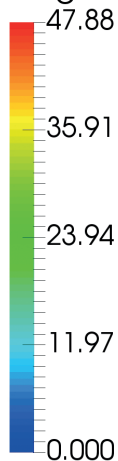


Figure 5: Velocity profile of fluid passing through the nozzle, showing the swirl motion.

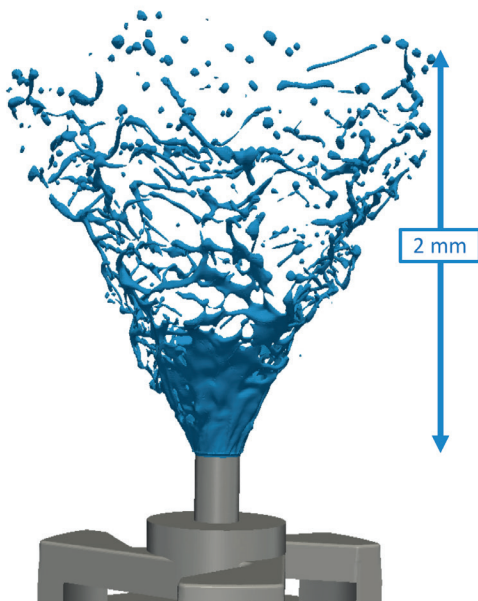


Figure 6: CFD representation of fluid break-up as it exits a nasal device.

Nemera approaches this complex development process with multiple tools:

- Experimental testing and a database of results helps track input and performance data as well as aiding in the analysis of influencing factors and trends.
- The capacity to manufacture fully functional, novel nozzles in a matter of weeks, including metrology control, enables the exploration of the design space and shorter tuning loops.
- Computational fluid dynamics (CFD) modelling allows for a richer understanding of the physics involved. CFD can also be used to run sensitivity analysis on specific parameters, as seen earlier in this article.
- Finally, mathematical modelling makes the link between input variables and output performance.

Understanding the sensitivity of the performance in the design space allows the set-up of control strategies, ensuring robust and controlled performance when it comes to mass production. And, by incorporating data analysis and mathematical modelling into development, Nemera achieves acute refinement of the design, all building to one ultimate goal: to have the spray on target.

TESTING THE PERFORMANCE

Nemera has developed its own testing laboratory using cutting-edge technology. Customised testing methods are used to cover all aspects of a nasal device from broad parameters (dosage accuracy, leakage, weight loss, etc) to in-depth spray characterisation. Tests are also performed on the component materials to establish extractables profiles. All of which can be customised to the needs of clients and partners.

Of the tests performed one of the most interesting is spray characterisation. These tests are very sensitive and use advanced, automated equipment to perform three analyses:

- Droplet size distribution, testing the size of droplets in a spray

- Spray pattern, a horizontal cross-section of the spray to show spray area, shape and homogeneity
- Plume geometry, a vertical cross-section of the spray to estimate spray angle and width.

All of these tests can be influenced by a litany of factors, either from the environment (enclosure, lighting, calibration, manual/automatic priming, device setting, input parameters, etc) to the sample itself (shaking, temperature, alignment, etc). On top of that the selection of data for analysis is a huge part of the final result as well. In order to ensure the reproducibility and reliability of the data, measurements are taken when the spray has fully developed during its stabilisation phase, somewhere between 30 ms and 180 ms (Figure 7).

PREPARING THE DATAPACK

As previously mentioned, after testing a device with the reference product, Nemera prepares a datapack containing statistical analysis of the tests. The purpose of this is to maximise the chance of a successful application for bioequivalence across geographic regions and, as such,

“The US prefers Population Bioequivalence (PBE) and Europe prefers Average Bioequivalence (ABE). PBE is a more complex calculation than ABE, but guidance is available with detailed formal framework, whereas there is none for ABE. Nemera offers experience and expertise in both systems to assist partners and clients through these bioequivalence *in vitro* tests.”

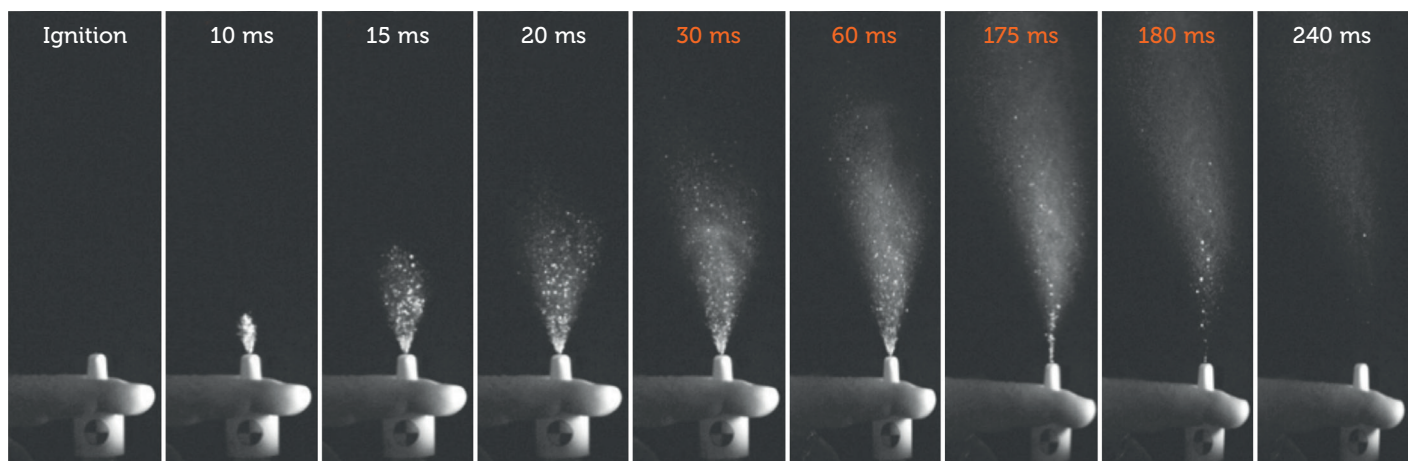


Figure 7: The stabilisation phase of a spray occurs between 30 ms and 180 ms.

highlights the main differences between regulators. One such difference is in the calculations required in the US (and those that base their regulation on FDA guidelines) and Europe. The US prefers Population Bioequivalence (PBE) and Europe prefers Average Bioequivalence

(ABE). PBE is a more complex calculation than ABE, but guidance is available with detailed formal framework, whereas there is none for ABE. Nemera offers experience and expertise in both systems to assist partners and clients through these bioequivalence *in vitro* tests.

CONCLUSION

Nemera brings great benefits to partners looking to develop a generic nasal spray, a process far more complex and involved than it may first appear, but which growing market demand worldwide shows is increasingly likely to be a worthwhile endeavour. Able to offer expertise in market understanding, regulatory affairs, device development and statistical analysis, Nemera also prides itself on being a co-operative, committed and responsive device design partner.

ABOUT THE COMPANY

Nemera is a world leader in the design, development and manufacture of drug delivery devices for the pharmaceutical, biotechnology & generics industries. Nemera's services and products cover several key delivery routes:

- Nasal, buccal, auricular (pumps, valves and actuators for sprays)
- Inhalation (pMDIs, DPIs)
- Parenteral (auto-injectors, pens, safety devices & implanters)
- Ophthalmic (multi-dose, preservative-free eyedroppers)
- Dermal and transdermal (airless & atmospheric dispensers).

Nemera always puts patients first, providing the most comprehensive range of devices in the industry, including innovative off-the-shelf systems, customised design development, and contract manufacturing.

ABOUT THE AUTHORS

Pascale Farjas is the Global Category Manager for the ear, nose, and throat (ENT) segment at Nemera. Her role encompasses understanding patient needs, and regulatory requirements, to develop and market packaging solutions that improve the patient experience. She is in charge of the market introduction of new pump platforms for nasal sprays. Ms Farjas joined Nemera in 2011 and holds a Chemical Engineering degree from the National Institute of Applied Sciences of Rouen, France, completed with a marketing-focused Masters degree from the Business Administration Institute (France). Prior to joining Nemera, Ms Farjas held various positions in strategic (market intelligence and market studies) and operational marketing in the pharmaceutical industry for international markets.

Alain Regard, Technology Product Manager, graduated with a degree in Polymer Engineering and Processing from ESP in Oyonnax, France. After a long experience in design and development in the automotive industry, he joined the company in 2010 as a product development Leader. Mr Regard, today one of the key technical experts of Nemera's Innovation Centre for Devices (ICD), leads the nasal and dermal developments. He drives some Nemera own IP projects as well as working on several customer product developments in the field of nasal and dermal applications.

Céline Petitcolas holds a Materials Engineering degree from the École Nationale Supérieure de Chimie et de Physique in Bordeaux, France. Her current position is Customer Technical Support for nasal range at Nemera. Following a first R&D experience in the automotive industry, Céline joined Nemera in 2012 to develop pharmaceutical devices, focusing especially on the nasal spray area. Her new role consists in helping and assisting customers from a technical point of view in their development of nasal sprays and more specifically in the area of bioequivalence. Ms Petitcolas is the preferred technical contact for customers as she interfaces with multiple Nemera teams (marketing, sales, technical) to bring customers and partners the support they need.



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ADDRESSING THE CHALLENGES IN NASAL DEVICE TESTING: EVALUATION OF PUMP PERFORMANCE

Heli Chauhan, Senior Applications Chemist, Proveris Scientific, details the myriad challenges facing the OINDP market, with a particular emphasis on nasal spray devices, when it comes to testing products on a mass-production scale, such as a lack of adequate testing equipment and the need to capture accurate data consistently. She goes on to offer a solution in the form of Indizo®, Proveris' automated nasal spray testing apparatus.

INTRODUCTION

The orally inhaled and nasal drug product (OINDP) market is growing rapidly and the number of nasal spray products on the market, as well as in development, has been significantly increasing in recent years. More than 150 million units of fluticasone propionate nasal spray alone are sold in the US every year.¹ Production of this magnitude generates a vital need for robust, reproducible release testing of nasal spray products.

The OINDP industry currently faces a plethora of challenges when it comes to product testing. Of the utmost importance is the need to generate accurate data consistently. This is problematic at present because reproducibility is compromised by hand actuation of pumps during testing; the forces and precise methods involved naturally vary from analyst to analyst. The second major problem is that, due to the increasing number of samples involved, testing can be a labour intensive, time consuming and error-prone process. Another challenge is posed by the absence of adequate diagnostic tools to evaluate the mechanics of a nasal spray device in case of an aberrant result. A serious issue when it comes to product release in a

"More than 150 million units of fluticasone propionate nasal spray alone are sold in the US every year. Production of this magnitude generates a vital need for robust, reproducible release testing of nasal spray products."

quality control (QC) setting is an inability to perform a proper investigation and root cause analysis of out of specification (OOS) results. With the aforementioned ramp up in manufacturing, both transitioning to more efficient workflows and maximising throughput whilst minimising analyst time required will be critical aspects of success.

Proveris Scientific's Indizo® (Figure 1) system addresses all of these challenges. The fully automated Indizo can be used to conduct a variety of the required regulatory tests in a reproducible manner while simulating human use of the product. It expedites the analysis by effectively streamlining the workflow and eliminating manual processes.

This article focuses on addressing the three main challenges faced by the OINDP industry:

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1. Reproducibility of data
2. Lack of investigative tools to evaluate pump performance during OOS
3. Increasing productivity whilst maintaining high quality of data.

MANUAL VERSUS AUTOMATED ACTUATIONS

Testing using hand actuation is neither consistent over time nor between analysts. Stroke length and velocity are known to influence nasal drug delivery, therefore any variation in the actuation profiles, for example due to manual actuation by different analysts, will influence the accuracy and reproducibility of the data. Automated, mechanical actuation using a testing profile derived from patient-use data is the ideal way to conduct OINDP testing, ensuring there is no variation in the results over time while using a humanly achievable actuation profile. It also makes it possible to avoid the human error, an occurrence made probable by a high volume of samples, operator fatigue and other sources (Table 1). This results in a significant reduction in the number of deviations/investigations attributed to analyst error, thereby increasing the efficiency of the lab.

The range of variation in hand actuations can be seen in Figure 2. The data is derived from a Proveris by Design® ergonomic study using Proveris' Ergo®, a device that measures and records human usage parameters. The figure shows the high variability in stroke length and actuation velocity as recorded from a hand study (left) compared to consistent parameters with automated actuation (right) for a multi-dose nasal spray. This could lead to variability in test results for delivered shot weight, spray pattern and droplet size distribution.

Controlling testing parameters with automated actuators throughout the testing can help maintain batch-to-batch reproducibility along with ease of regulatory submission. This is valuable when it comes to stability time points for QC analysis, where it is important to keep the testing conditions identical over time, thereby minimising the out of trend (OOT) results.

DIAGNOSTIC MEASURES OF PUMP PERFORMANCE

With manual actuation, there is no traceable data for an investigation. Root cause analysis becomes tedious which prolongs resolving a lab investigation, potentially



Figure 1: The Indizo system (left) available in two separate configurations (right).

| Description | Manual | Indizo |
|--|---|-------------------------------------|
| Shaking the device before analysis | Lack of consistent shaking for suspension products manually | Consistent shaking for every bottle |
| Recording tare weight/dose weight (metered or delivered) | Inadvertently miss to record the tare/dose weight | No issue |
| Dose Collection | Incorrect number of doses in the dose collector; improper positioning of collector causing loss of entire or part of dose | No issue |
| | Variation in dose content due to person to person differences | No issue |
| Actuation into waste collector | Ergonomic burden on the operator during larger devices (firing down 200 shots) | No issue |

Table 1: Source of error comparison between manual analysis versus Indizo for pump delivery (PD) and spray content uniformity (SCU) testing.

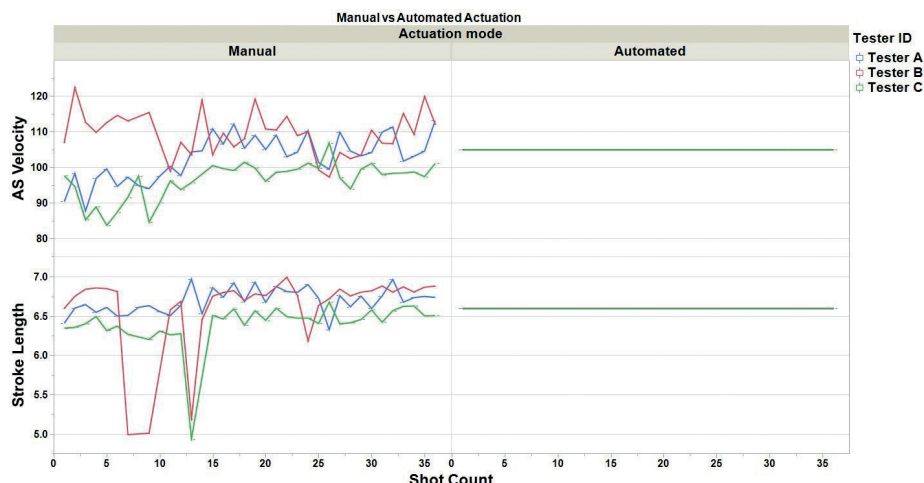


Figure 2: An example graph of data from a hand study (left) that shows the variation in actuation velocity (mm/s) and stroke length (mm) of a commercial nasal spray from three analysts, compared with the reproducibility of automated actuation (right).

delaying product release. This challenge can be addressed with the multitude of tools made available by automated actuation, such as force and intensity profiles that help analyse changes in the device over the duration of the spray, as well as life of the product. Quantitative real-time force and position feedback, obtained from the Indizo software platform Viota®, provides insight into device performance. This information, along with a fully traceable audit trail, can help resolve investigations/OOS faster in compliance with 21CFR Part 11. The result is significant savings in time and resources. Some of these applications are further discussed below.

Confirmation of Priming

It is extremely important to prime a multi-dose nasal spray pump prior to using the product. Inconsistencies in shot weights and other spray results, like spray pattern and spray content uniformity (SCU), in the beginning of life (BOL) actuations can be avoided by sufficiently priming the device. The force graphs from Indizo can provide information about the priming of the device. Figure 3 shows the force profiles (measured in kg_p) of a commercial multi-dose nasal spray device over the course of the six labelled priming actuations (Shots 1 to 6). As seen from the graph, the force value (y-axis) increases consistently from Shots 1 through 6. Initially, air is pumped out of the dip tube, leading to a lack of resistance which, in turn, results in a lower maximum force (≈2.4 kg for Shot 1). Following this a mixture of air and formulation is discharged, increasing the resistance to the pump (5 kg maximum force in Shot 4). Once the device is primed, a consistent force is observed (≈6 kg for Shots 5 and 6). This force profile analysis can be used to compare the required number of priming shots for test and reference products and detect any systematic differences between the two.

“For example, pump delivery testing for one batch of a nasal spray bottle with 240 doses takes over 6 hours when performed manually, compared to under 15 minutes of operator time with Indizo.”

“With manual actuation, there is no traceable data for an investigation. Root cause analysis becomes tedious which prolongs resolving a lab investigation, potentially delaying product release. This challenge can be addressed with the multitude of tools made available by automated actuation.”

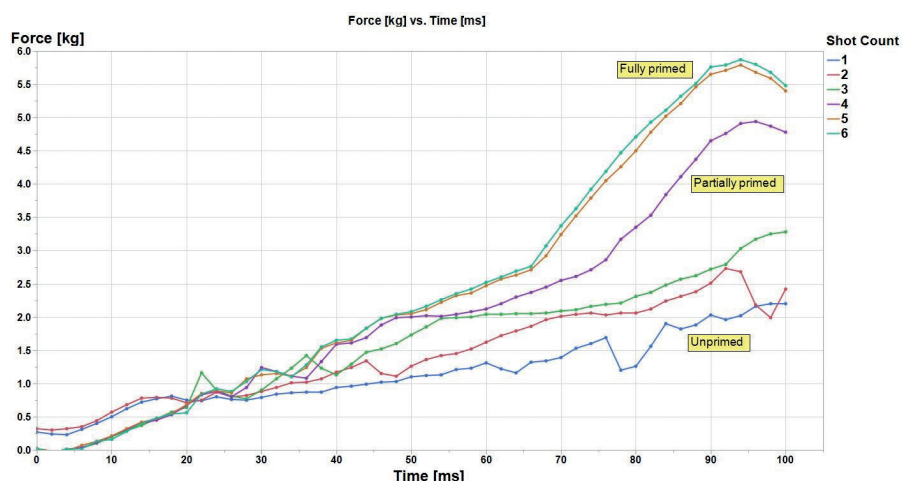


Figure 3: Changes in force profiles over the six priming shots for a commercially available multi dose nasal spray.

Priming/Re-priming in Various Orientations

A priming/re-priming study is required by the US FDA for multi-dose nasal spray drug products.^{2,3} The CMC guidance recommends to “Characterise the priming and re-priming required for the product after storage in multiple orientations (upright and inverted or upright and horizontal) and after different periods of non-use”. SCU and other pertinent parameters should be evaluated, and the following information should be established:

- The approximate interval that can pass before the drug product should be re-primed to deliver the labelled amount of medication.
- The number of sprays recommended to prime or re-priming the unit. “Multiple orientation studies should be performed with initial sprays and with sprays near the label claim number”.

Indizo can be a useful tool during this study. It not only makes it possible to test multiple conditions in a single run, but provides confirmation for priming as well. The lower force to actuate (FTA) can indicate whether or not the device requires re-priming and the force profile can confirm whether priming was achieved.

Loss of Prime (OOS Root Causes)

Root cause analysis is crucial during an out of specification (OOS) event for QC samples. When the device is actuated manually, there are no measurable metrics to distinguish between a normal and an aberrant result. The FTA data as well as the force position profile from Indizo enables the user to investigate the cause of an atypical result by comparing it to a standard force profile example. The FTA is the resistive force exhibited by a device when it begins to emit the spray. A typical force profile can be the starting point for investigation in case of an OOS shot weight or spray result. Depending on which region of the force profile is different from the typical profile, it can be determined what could be a probable reason for the failure (e.g. defect in pump, actuation or delivery).

As a proof of concept study, a commercially available multi-dose nasal spray device was used partially and then stored for 30 days (Figure 4). The label on the product states re-priming is required after 48 hours of non-use. In this way, the 30 day storage ensured the device lost prime. Following this, FTA was measured for the first five actuations. The bottom

image of Figure 4 shows the first actuation after non-use with a force to actuate of 6.64 kg. The top image is the actuation following the re-priming of the device with FTA of 9.51 kg. The lower force in the bottom image is due to loss of prime in the device. This can also be confirmed from the decrease in maximum force and distance travelled for the lower image as seen from the force versus time (green) and position versus time (red) graphs.

Tail-Off Determination

The tail-off study is part of drug product characterisation of nasal sprays. "These studies help determine if the target fill and any proposed overfill of the containers are justified, since the tail-off characteristics can vary as a function of pump design, container geometry and formulation".² Pump delivery needs to be performed for each individual spray after the last labelled dose until no more sprays are discharged from the container, a tedious and time consuming process. Indizo can carry out this analysis on multiple devices without operator intervention.

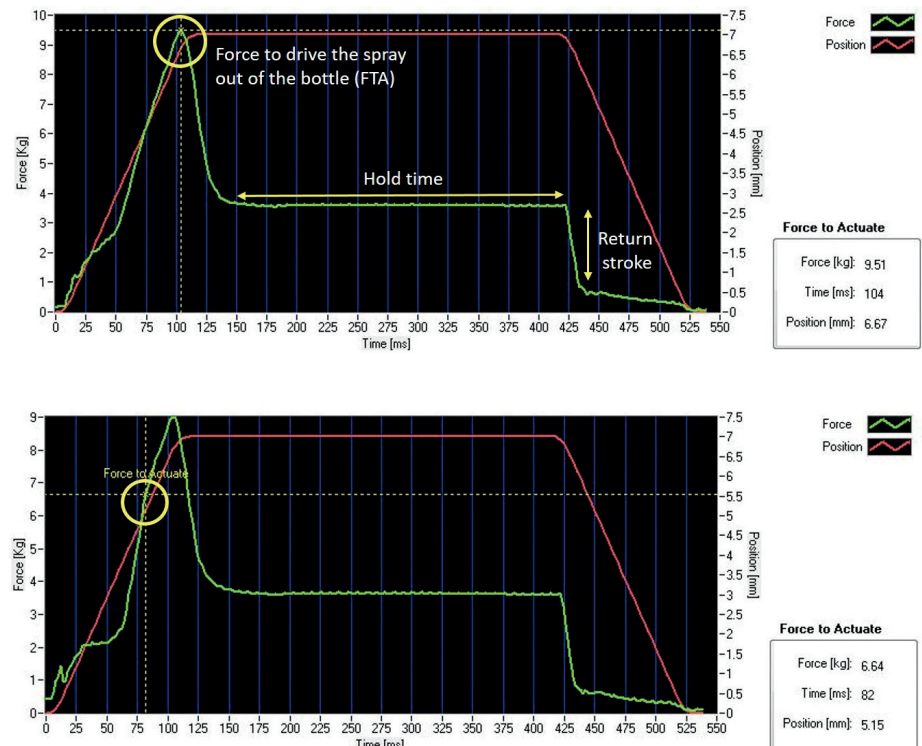


Figure 4: Example of a typical force profile of a commercial multi dose product with a FTA of 9.51 kg (top), compared with a result with a much lower force to actuate (6.64 kg) indicating loss of prime in the device (bottom).

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WORKFLOW IMPROVEMENT

The importance of continuous improvement in workflow to increase productivity is often overlooked. A typical OINDP testing lab faces a lot of issues, such as batch release schedules, minimising errors and increasing throughput. These issues can be resolved by small improvements in the workflow.

Introducing complete automation can be a major step forward when a large volume of samples need to be tested on a strict timeline. This is extremely useful during stability testing when there is a high number of samples, due to controlled room versus accelerated temperature storage testing and multiple orientations (i.e. upright, inverted), and a tight deadline.

Operator Hands-On Time

In a QC setting, hundreds of batches need to be tested per year owing to the high rate of manufacturing for commercial products.¹ Indizo greatly reduces the amount of operator time required for testing. To perform pump delivery for 1 batch (10 devices), with a method that includes 4 priming, 5 BOL, 86 fire-down and 5 end of life (EOL) actuations, the operator time for Indizo was found to be under fifteen minutes, whereas it was over four hours if done manually. Time saved increases with more rated doses in the product.

Although the overall testing time might be similar for manual/semi-automated workflows and those supported by Indizo for nasal spray bottles with a lower number of rated doses (i.e. 30 or 60), a significant amount of analyst time can be saved, and ergonomic burden reduced, when testing products with higher number of doses (e.g. 200 or 240). For example, pump delivery (PD) testing for one batch of a nasal spray bottle with 240 doses takes over six hours when performed manually,

compared to under fifteen minutes of operator time with Indizo. This also generates an opportunity to continue testing outside of business hours, by running Indizo overnight without any analyst oversight.

For SCU, as per the current workflow, it takes almost an entire day for dose collection and sample preparation and up to two analysts to complete the analysis for a single batch. Using Indizo can greatly reduce the dose collection time to only a couple of hours. Indizo improves the workflow and reduces the required labour from two analysts per batch to one analyst (Figure 5). Furthermore, shot weight can be combined with SCU to complete both the tests in the same run with the completely automated Indizo.

Cost Analysis

One of the main concerns when it comes to adopting automated instruments is the initial cost of investment. However, when analysed in detail, automation increases the overall efficiency and productivity of the lab and saves time and labour on individual analyses. Based on Proveris's time comparison analysis between Indizo versus manual/semi-automated analysis, for high volume manufacturing environments, tens of thousands of dollars can be saved per year whilst generating time savings equivalent to one full time analyst. The return on investment also lies in the high quality data gathered, reduced OOS results and increased ease of regulatory submission.

CONCLUSION

This article has outlined some of the many challenges in OINDP testing. The Indizo system addresses these issues, providing valuable data for troubleshooting purposes, reliably consistent testing and increased efficiency through automation.

The applications described here are not just limited to QC and can be applied to product development as well. By integrating automation as part of the workflow, Indizo increases the productivity and safety of the operators, whilst maximising use of resources. The end results are high quality data, high throughput and a better understanding of the overall performance of device.

ABOUT THE COMPANY

Proveris Scientific delivers innovative technologies, services and deep product knowledge to a worldwide customer base of branded and generic pharmaceutical companies, device manufacturers, CDO/CRO/CMOs and regulatory agencies working with orally inhaled and nasal drug products (OINDPs).

Its team of engineers, scientists and service professionals has developed a more complete understanding of the critical quality attributes affecting the performance of OINDPs, and in effectively controlling them from a testing and patient usability perspective.

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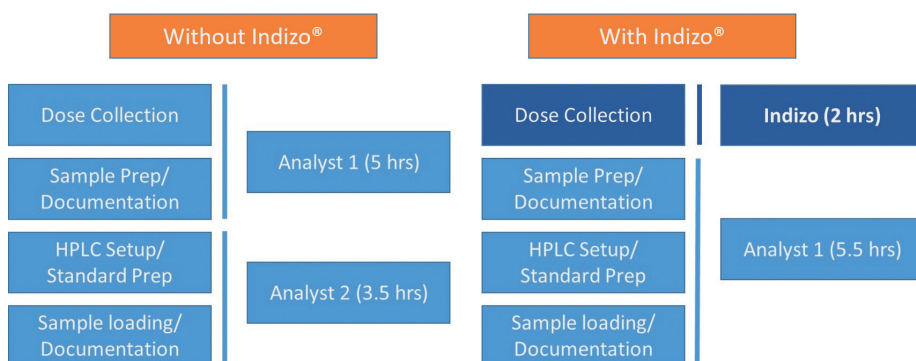


Figure 5: Workflow comparison for SCU analysis with and without Indizo.



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AN OVERVIEW OF DRY POWDER INHALATION FOR SYSTEMIC DRUG DELIVERY

In this article, Brian Jones, Scientific Advisor to Qualicaps, and Susana Ecenarro Probst, Director of Scientific Business Development, Qualicaps, discuss the growing interest in using inhaled APIs to treat systemic conditions. Furthermore, they review some of the methods used to engineer molecules to be suitable for DPI capsules and look to the possibility of administering biomolecules via the pulmonary route.

Interest is growing in the treatment of systemic diseases using active pharmaceutical ingredients (APIs) administered via inhalation, a method especially applicable to the delivery of biomolecules. Inhalation therapy in its various forms has been used for hundreds of years,¹ used mainly to treat or alleviate conditions of the lungs, asthma and chronic obstructive pulmonary disease (COPD). The advantages of pulmonary delivery over the oral route is that the APIs are not subjected to the enzymes in the gastrointestinal (GI) tract and the effects of first pass metabolism.

Originally, the principal way to avoid the GI tract was by injection or infusion of the API. The latest advancement in API development however, is based on designing biomolecules which cure disease states by interfering with biological pathways in the body. This has changed the challenges of formulation, as the complex structures of these large biomolecules are less stable than the smaller, simpler structures of their predecessors.² It has increased the need for dosage forms that avoid the GI tract and use the other oral route, the pulmonary.

It was reported in 1997 that APIs used to treat asthma will have systemic effects because they are cleared via the systemic circulation,³ thus kindling the interest in this field, which has grown significantly since. By this point, devices for delivery via the pulmonary route had already been developed: nebulisers, metered dose inhalers (MDIs) and dry powder inhalers (DPIs).^{3,4}

The former two use various solvents, both aqueous and organic, thus meaning DPIs offer the best prospect for developing a stable system. Devices for inhalation therapy must be able to aerosolise the formulation so that it is delivered deep into the lungs, where it requires a residence time sufficient for absorption before it is cleared away by the mucus cycle. To successfully arrive at the target location, particles must have both the correct size (1-5 μm) and shape.

EXCIPENTS IN INHALED FORMULATIONS

Treatment of systemic diseases using inhaled APIs is increasing in favour because it can be used with biomolecules: proteins, peptides and the new forms produced by recombinant DNA.^{1,3} The biomolecules that have been studied are shown in Table 1, along with

“An extensive review in 2005 highlighted the advantages of using a carrier based system for delivery: APIs do not innately have the necessary properties and therefore formulations with inert carriers are required for deep lung penetration.”



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their target disease states. Manufacturing protein pharmaceuticals requires processes that will not damage them. For example, spray drying in its various forms has been employed and results in products with a low moisture content, helping to improve their stability.^{4,8} Excipients (e.g. sugars and polyols such as lactose, mannitol and cyclodextrin⁴) need to be added to the formulations to produce particles with the correct aerodynamic properties⁵ and are used to reduce particle aggregation.

An extensive review in 2005 highlighted the advantages of using a carrier based system for delivery: APIs do not innately have the necessary properties and therefore formulations with inert carriers are required for deep lung penetration.³ Carriers have many advantages, enabling more API powder to reach the site of absorption, improving the *in vivo* API stability and improving product taste. The most popular type of inhalation device is the DPI with unit powder doses packaged in either blisters or hard capsules. The efficacy of this method is dependent on the patient's inspiratory flow rate, necessitating the instruction of patients in the correct mode of use.

In 2010 MannKind Corporation made a novel development that introduced a new excipient, fumaryl diketopiperazine (FDKP), a spherical, crystalline particle with a large surface area on which to adsorb the API.⁹ This product was used for Afrezza[®] insulin with a simple breath actuated inhaler. Clinical trials and patient usage showed that Afrezza[®] insulin offered glycaemic control comparable to injected insulin.¹⁰

In 2011 another disease, cystic fibrosis, which had previously been treated with an antibiotic, tobramycin (TP), from a nebuliser, was switched to a DPI with improved results.¹⁰ The formulation was a water in oil micro-emulsion containing perflubron. It was spray dried; as the water evaporates the droplets decrease in size, then the perflubron evaporates to form pores in the particles. This rapid drying process, on the scale of milliseconds, causes the TP to form as an amorphous solid. These particles, called PulmoSphere[®], contain 90-95% TP. The dose is delivered using a breath actuated T-326 Inhaler (Novartis) and powder filled

| Disease state | Protein and peptide for treatment |
|--------------------|--|
| Anaemia | Erythropoietin |
| Anticoagulant | Heparin |
| Cancer | LH-RH analogues |
| Diabetes | Insulin |
| Diabetes insipidus | 1-deaminocysteine-8-D-arginine vasopressin (dDAVP) |
| Growth deficiency | Human growth hormone |
| Multiple sclerosis | Interferon- β |
| Neutropenia | rhG-CSF |
| Osteoporosis | Calcitonin, Parathyroid hormone |
| Viral infections | Ribavirin, Interferon- α |

Table 1: Proteins and peptides proposed for inhalation delivery, redrawn from "Inhalation delivery of protein therapeutics".⁴

by inhalation grade hypromellose capsules (Qualicaps, Quali-V[®]-I). These were chosen because gelatin capsules become brittle in low relative humidity (RH) storage whereas hypromellose capsules are unaffected by these conditions. Size 3 capsules and the powder fill dose were chosen on the ability of the average paediatric patient (6-10 years) to empty a capsule in a single inhalation.

PARTICLE ENGINEERING FOR INHALATION

Particle engineering was used to improve the stability and aerosol performance of dry powder inhalation for recombinant parathyroid hormone (rPTH).¹¹ The formulation contained a non-reducing sugar, α -trehalose dihydrate (TD) and a non-ionic surfactant (NIS). Mixtures of rPTH, TD and NIS were dissolved in water and the pH adjusted to 7. Particles were formed by either spray drying or spray freeze drying. The particles were assessed using SEM images and tests to measure particle shape, chemical properties and density. Their aerodynamic properties were measured using an Anderson cascade impactor. The powder was filled in a hypromellose capsule and punctured using

a Spinhaler[®] DPI. Results showed that the formulation without NIS was the most stable.

Research was conducted on producing a heat-stable form of oxytocin (OT) aimed at making a particle size of 1-5 μ m.¹² Spray drying, either a standard or low temperature process, was the only way of making amorphous masses using excipients with high glass transition temperatures (GTT), such as lactose, trehalose and citrate salts. The resulting powders were characterised using a variety of techniques to measure their particle size, shape and density. The particles had a median size of 2 μ m and an excellent aerodynamic performance with a respirable fraction up to 70%. The dry powders were amorphous, stable and retained a greater than 90% activity after storage.

A collaboration in 2017 between the University of Parma in Italy and Qualicaps Europe studied the stability of pure spray dried insulin filled into inhalation grade hypromellose capsules (Quali-V[®]-I),⁸ using the commercial insulin product Afrezza[®] for comparison. 2 mg of powder was filled into a Size 3 capsule using a Harro Höfliger Omnidose vacuum drum filler. Capsules were blister packed using transparent PVC/PVDC films for storage trials and samples were then stored for six months at the ICH condition of 25°C, 60% RH (climatic zone II) and fridge conditions of 4°C. Respirability was measured using a Plastiapipe RS01[®] DPI in a new generation impactor. Both formulations showed good emission from the device (>90%). The Parma University formulation showed a significantly high respirability with a fine particle fraction (FPF) of 91.5% and a lower mass median

"Gelatin capsules become brittle in low relative humidity storage whereas hypromellose capsules are unaffected by these conditions."

“For pulmonary development, the product pipelines have shifted from a mix of small molecules to biologics, a significant shift from when low cost asthma and COPD APIs were the market targets.”

aerodynamic diameter. The percentage of degradation products was found to be below USP limits under both storage conditions during the six months of the study. The stability outcome has demonstrated that the formulation contained in the hypromellose capsules (Quali-V®-I) together with a PVC-PVDC blister packaging material can offer a stable therapy less dependent on cold chain storage.

DELIVERING BIOMOLECULES VIA INHALATION: PROSPECTS & CHALLENGES

The use of the pulmonary route for delivering proteins and peptides is a viable proposition, the challenges and perspectives being discussed in a review paper in 2013.¹⁴ Three available delivery devices were analysed: nebulisers, MDIs and DPIs, with the fact that only DPIs did not use liquid formulations being highlighted. The particle size and shape requirements for dry powders were related to the anatomical features of the lungs. The use of DPIs relies on the patients' inspiratory efforts to provide the energy to disperse the powder particles, which involves fluidisation, then de-agglomeration

to form a fine, respirable aerosol cloud. DPIs have design features to aid this process.

The formulated powders must maintain the integrity of the protein and avoid degradation during processing and storage. The formulation and manufacturing processes are related to potential problems. The excipients used to stabilise formulations and their regulatory status were explained, being used to modify lung clearance mechanisms and improve systemic bioavailability. Absorption mechanisms have different pathways related to API molecular mass. The regulatory status of applications for approvals were listed with their safety aspects. The history of marketed inhaled insulin products was discussed, particularly the problems surrounding Exubera® insulin (Nektar, Pfizer) and its subsequent withdrawal from the market after one year due to unexpectedly low sales, most notably its cumbersome and difficult to use inhaler.

Another, more recent paper summarised the challenges and prospects for the delivery of biologicals.¹⁵ Three routes were given, oral mucosal, pulmonary and transdermal with details of the product formulation requirements. For pulmonary development,

the product pipelines have shifted from a mix of small molecules to biologics, a significant shift from when low cost asthma and COPD APIs were the market targets. The key factor for inhalation and deep penetration into the lungs is the aerodynamic particle size of the formulation. Only particles with aerodynamic diameters of less than 3 µm will reach deep into the lungs and be absorbed into the blood stream to treat systemic diseases. Progress requires a combination of particle engineering and device design to achieve this goal. Currently over 30 APIs are at various stages in the development process, either in preclinical testing or in Phase I and II trials.

ABOUT THE COMPANY

Qualicaps, a wholly owned subsidiary of Mitsubishi Chemical Holding Corporation, has over a century of experience in manufacturing hard capsules and a strong record of pioneering in new forms of drug administration. Qualicaps is responsible for several milestones in the history of two-piece hard capsule development, having introduced features so widely accepted and trusted that they have since become industry standards.

As a company dedicated to capsules, Qualicaps has a unique perspective on how to contribute to health, delivering pharmaceutical-grade capsules together with a comprehensive service along the drug product lifecycle, through a global team of commercial, scientific and technical services. Geared toward quality and functionality, they deliver on being “Engineered to perform” by offering not only exceptional performance from their capsules, but also from their team, made up of subject matter experts who partner with customers on optimising dosage form development and operational effectiveness in encapsulation during drug product manufacturing.

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ABOUT THE AUTHORS

Brian Jones has extensive experience in the field of hard capsules, both in their manufacture and usage. He has visited pharmaceutical companies in the US, Europe, Africa and Asia to give lectures and to assist in problem solving for this particular dosage form. He has been involved with hard capsules and their use and performance in dry powder inhalers since their introduction to the market in the 1960s. Mr Jones has Bachelor's and Master's degrees in Pharmacy from the University of Wales and is a Fellow of the Royal Pharmaceutical Society of Great Britain. He is an honorary senior lecturer in the Welsh School of Pharmacy and Pharmaceutical Sciences, Cardiff University, UK.

Susana Ecenarro Probst supports R&D centres within the pharmaceutical industry in new drug developments by providing scientific and technical expertise, as well as promoting collaborations with European universities and third parties that focus on the application of state-of-the-art capsule technologies. Prior to Qualicaps, she worked for Schering AG for 18 years, working in diverse QA positions and covering several functions, including analytical development, process validations, technology transfer, and operational excellence projects, amongst others, followed by five years of experience leading an analytical R&D unit of a Bayer Healthcare facility. Ms Ecenarro Probst holds a MBA and a Bachelor's degree in Pharmacy.

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DEVELOPING EFFECTIVE TRAINING DEVICES FOR THE PULMONARY HEALTHCARE MARKET

Pulmonary drug delivery is an effective route of pharmaceutical administration but research has shown that a large majority of patients fail to use their devices properly. To address this problem, training devices can help patients learn how to administer the drugs correctly. Joe Reynolds, research manager at Noble looks at the design challenges that need to be addressed as well as some of the latest features that can be incorporated to develop optimal training devices for patients.

Over the years, many industry stakeholders and pharmaceutical manufacturers have come to realise the importance of training and the role it has on promoting healthy patient outcomes and effective disease management. Many studies suggest that without proper training during the onboarding process, or the first 30 to 90 days of treatment, patients are more likely to drop off from therapy or incorrectly use drug delivery devices, such as metered dose inhalers (MDIs), dry powder inhalers (DPIs) and other forms of self-administration.

Designed primarily for at-home use, pulmonary drug delivery is an effective route of administration for localised and systemic uptake of pharmaceutical products. As a result, pulmonary administration is a viable alternative to more invasive routes, with future growth potential across new therapeutic areas. These products are often marketed as combination therapies,

consisting of active pharmaceutical ingredients and drug delivery devices.

DRAWBACKS OF PULMONARY DRUG DELIVERY DEVICES

When properly used by patients, these devices are effective in delivering a prescribed dose to the lungs; however, user errors can result in, partial delivery and suboptimal therapeutic outcomes for patients.

According to a study conducted by the University of Texas Medical Branch at Galveston (UTMB), US,¹ 93% of MDI patients failed to use their devices properly, with more than half missing three or more steps.

The most common mistakes patients made were:

- Failing to prime
- Exhaling
- Coordinating actuation with the necessary timing, force and duration of inhalation.

In addition to traditional instructions and package inserts, healthcare providers are often leveraged as learned intermediaries to onboard patients and provide access to training and education. While these training strategies can be very effective, research suggests that there is often a great deal of variability and inconsistency both with these training methods and patients' ability to retain this information and

“Further research demonstrates that many patients are looking for increased access to education and support for self-administration.”



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apply it successfully to the use of their delivery system.

Further research demonstrates that many patients are looking for increased access to education and support for self-administration. A study, conducted by Noble, surveyed patients and examined the impact of device training solutions on patients using MDIs. The study examined five different training solutions, ranging from the common Instructions for Use (IFU) to smart error-correcting training, in an effort to better understand how training technology can reduce device errors.

The survey showed that 82% of users said they would feel most confident when training with a device that detects errors. Additionally, 76% of users prefer some form of error detection to help overcome anxiety about administering treatment. For example, one device that was tested included IFU and would whistle if used incorrectly.

To address the common gaps in patient onboarding, training devices often use novel technologies and mechanisms that fully simulate the mechanical aspects of the drug delivery experience. While these devices appear to be fairly simple at first glance, there are numerous design and engineering challenges that need to be met.

DEVELOPMENT OF TRAINING DEVICES

Pulmonary smart training devices are designed to monitor patient behaviours and provide corrective feedback during the onboarding experience, which are the early stages of the learning process.

Engineering these devices for manufacturability and repeatability is a delicate balance. Fully understanding device development and mechanical design is one of the first steps in creating robust solutions.

Throughout the design process, human factors are taken into consideration to ensure that training devices align with the physical, cognitive and emotional needs of users. Thus, when designing a device it's important to understand the sequence of steps patients go through and the risk of error associated with each (Table 1).

While there are many variables that influence the deposition of pulmonary therapeutics (e.g. timing, force, volume and muscle memory), trainers should be developed to support patients in establishing motor and muscle skills, along with the appropriate level of force required to use inhalers effectively. How the patient

| Step | Description | Risk of error |
|------|--|---------------|
| 1 | Prepare device | Low |
| 2 | Remove mouthpiece | Low |
| 3 | Inspect the mouth piece for obstructions | High |
| 4 | Prepare dose | Medium |
| 6 | Exhale, away from the device | High |
| 7 | Place device in mouth | Medium |
| 8 | Actuate dose | High |
| 9 | Inhale with the appropriate force, duration & sequence | High |
| 10 | Hold breath (as specified in IFU) | Medium |
| 11 | Repeat dose as prescribed | Medium |
| 12 | Clean and store device as prescribed | Medium |

Table 1: Use steps of a MDI and their associated risk of error.

interfaces with the delivery device plays an important role in drug deposition and full absorption.

In addition to understanding user needs, Noble has analysed a variety of on-market delivery systems to understand their handling requirements and critical functions. Though in some cases mechanisms similar to commercial devices are used, ground-up mechanical design is usually employed to integrate all necessary functions in a resettable and reusable training device. This means that the trainer will look the same on the outside; however, internally it will be vastly different.

EXTERNAL AND INTERNAL DESIGN OF THE TRAINING DEVICE

The exterior of the device should emulate the real drug delivery device so that patients become familiar with key features and physical characteristics such as the look, feel and weight of their commercial delivery devices. Characteristics of the inhaler such as the shape, mouthpiece, size and shape of the canister and dose indicators all need to be accurately matched.

Although making the device look like the real product externally may appear simple, it does present its own challenges. For example, if the trainer looks exactly like the real device one may mistakenly use a trainer in an emergency or *vice-versa*. This is typically addressed with optimised packaging, labelling and graphical training instructions. Trainers usually have large

“Pharmaceutical companies that prioritise the patient experience, using training technology to help these patients properly use their devices, will continue to benefit through competitive advantages and the value they create within the industry.”

labels which read “Trainer, This Device Contains No Drug”. Though in every other regard, the trainer appears exactly the same: size, shape, textures and Pantone-matched colour schemes (or complimentary colours to denote that it is a trainer).

Other considerations that must be prioritised include ancillary training features like augmented auditory and/or video-based training instructions. Many of the trainers currently in development include some form of collateral training like talking packaging, sensor-based error-correction, smart device application or a combination of these features.

The interior design of the devices needs to be meticulously engineered to provide a proper training experience. It also needs additional mechanisms to allow the device to be used multiple times.

QUALITY CONTROL PROCESS

Quality design standards are paramount when designing training devices in order to ensure that every patient has a consistent and accurate training experience. Noble conducts rigorous device testing, taking into consideration each brand's specified requirements.

One of the keys to success is utilising optimised standard operating procedures (SOPs) and standard inspection procedures (SIPs) in the assembly process at the factory. Many manual and semi-automated tests and inspections are integrated throughout the process to verify targets will be met on the final assembly stage, thus reducing scrap rate and ensuring a high quality product.

Critical functions like activation forces and the auditory feedback of calibrated whistles are tested at several points during design, development and manufacturing. During pilot runs, many other tests are also performed to evaluate the function and

conformance of trainers with specifications and other design inputs. Some of these include environmental, accelerated ageing/life, shipping, drop-testing and materials compliance. Though not a formally regulated device category, Noble treats the design and manufacturing of trainers much like a regulated product to ensure the highest final quality product.

CONCLUSION

In order for training devices to work efficiently, it is necessary that devices are tested to stringent standards. As training technology becomes more prevalent in the pharmaceutical industry, the design and capabilities of these devices will continue to advance, requiring a more complex engineering process. These advancements are necessary as they will allow patients to become more confident in their treatments, overcome treatment barriers and ultimately lead healthier lives.

Patients need to familiarise themselves with a device in order to learn and anticipate the steps necessary for proper drug administration. This requires training devices to replicate the ergonomics, interaction and required forces of the actual device accurately.

A growing number of patients are being prescribed self-administered treatments. Pharmaceutical companies that prioritise the patient experience, using training technology to help these patients properly use their devices, will continue to benefit through competitive advantages and the value they create within the industry.

ABOUT THE COMPANY

Noble is a full-service, user-centered advanced drug delivery training device and patient onboarding company. Noble works closely with the world's leading drug delivery device original equipment manufacturers and pharmaceutical companies to develop educational and training solutions designed to provide positive patient onboarding experiences, reduce errors and improve patient outcomes.

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Joe Reynolds is Research Manager at Noble, where he leverages his knowledge and experience to develop and implement strategies that improve the patient experience and maximise value for stakeholders. His experiences include commercial, managed care and product development initiatives with leading medical device, pharmaceutical and biopharmaceutical manufacturers. Mr Reynolds earned his Bachelor of Science in Business Administration from the University of Central Florida, a Master of Science in Marketing from the University of South Florida, and a Master of Science in Pharmacy and Master Certificate in Drug Regulatory Affairs from the University of Florida.

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KEY CONSIDERATIONS FOR NON-CLINICAL SAFETY ASSESSMENT OF INHALED BIOPHARMACEUTICALS

In this article Simon Moore, PhD, Kirsty Harper, PhD, and Sylwia Marshall, PhD, all of Envigo, highlight some of the key considerations for the development of inhaled biopharmaceuticals, including non-clinical safety assessment.

Inhalation is the route of choice for the delivery of numerous small molecule drugs, especially for the treatment of respiratory diseases, as it has a number of advantages over parenteral routes. These include faster onset of action due to the large surface area (80–120 m²) and good vascularisation of the lung, improved therapeutic index due to targeted delivery requiring lower doses and improved patient compliance.

Historically, the development of biopharmaceuticals for inhalation has been hindered by challenges such as high drug requirement, manufacturing costs and stability issues. However, technological advances addressing these concerns are now facilitating the development of such modalities. One of the earliest marketed inhaled biopharmaceuticals was Pulmozyme®, which was approved in 1993 for cystic fibrosis. The field has continued to grow since then, and there are an extensive number of inhaled biopharmaceuticals in early development.

The percentage of biopharmaceuticals in the global pipeline has grown from 30% in 2010 to 42% in 2017, and total revenues from their sales increased from 17% of all prescription drugs to 26% over the same period, with the figures expected to reach 30% by 2022.¹ It is highly likely that inhaled biologics will contribute to this projected growth, having already been evaluated for numerous indications (Figure 1).

NON-CLINICAL SAFETY ASSESSMENT OF INHALED BIOPHARMACEUTICALS: GENERAL APPROACH

There are of course numerous differences between biologics and new chemical entities (NCEs) and these heavily influence the development strategy, including non-clinical safety assessment.

Biologics are a heterogeneous group of medicinal products that are generated or derived from biological sources and include biopharmaceuticals (proteins including monoclonal antibodies, peptides and oligonucleotides), vaccines and advanced therapies (gene/cell therapies). Each of these product types has specific features as well as specific biology that must be considered when designing non-clinical safety assessment programmes. Biopharmaceuticals are generally much larger than NCEs with many having complex structures, including secondary and tertiary structures, which are intrinsically linked with their function. Therefore, the physicochemical properties of these products must be taken into consideration when designing delivery systems.

The general approach to safety assessment of biopharmaceuticals is described in the ICH S6 (R1) guideline, “Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals”, where the basic principles of safety assessment in pharmacologically relevant species, and inclusion of appropriate pharmacodynamic (PD) endpoints wherever possible, are specified. This approach translates for assessment of biopharmaceuticals delivered by all routes of administration, inhalation included, and will likely determine the required programme of work for an inhaled biopharmaceutical.

Biopharmaceuticals exert their activities through specific interaction with their targets in the recipient patient, and it is therefore essential that all safety assessment studies replicate the clinical situation as far as possible with regard to target expression, binding and subsequent downstream biology. A comprehensive understanding of the pharmacology of the biomolecule in both humans and the candidate preclinical safety species is therefore required, and studies should only be performed in



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Figure 1: Various indications for which biotherapeutics have been evaluated using the inhalation route.

appropriate species. This may mean that a single species approach is sufficient and there are examples of biopharmaceuticals that received subsequent clinical approval following evaluation in a single species.

Due to the strong emphasis on pharmacology, non-clinical safety programmes are product specific and, unless the biopharmaceutical has a chemical modification, may omit some studies that are routinely found in NCE preclinical safety work packages, such as genetic toxicology studies.

Further, for most biopharmaceuticals, safety pharmacology endpoints are undertaken on a risk-based approach and are often incorporated into the design of pivotal repeat dose toxicity studies, with investigations in a single species commonly being acceptable. Depending on the mechanism of action of the biopharmaceutical, respiratory safety pharmacology may need to be supplemented with investigations of other systems which

may be targeted, such as the central nervous system. The feasibility of such investigations needs to be carefully considered, especially with reference to the selected pharmacologically relevant species.

INHALED BIOPHARMACEUTICAL FORMULATIONS & DEVICES

Inhaled drugs tend to be either liquid formulations administered via a nebuliser in a hospital environment or with the assistance of an experienced carer, or are self-administered as either aerosols or dry powders via handheld inhalers, which are generally acknowledged to be more efficient, stable and convenient for patients.

In general, most biopharmaceuticals show good aqueous solubility, and in the case of repurposing of existing products, a solution formulation is likely to already exist. For powders, however, more novel manufacturing techniques (lyophilisation, spray drying or vacuum foam drying) are

more likely to be used than traditional manufacturing techniques, such as micronisation, as they tend to provide greater stability and ensure structural integrity of the biopharmaceutical. In addition, powders can accommodate the inclusion of various excipients.

There are a number of device types, each associated with their own advantages and disadvantages, that may be used to deliver biopharmaceuticals. Nebulisers can operate with many liquid formulations and are capable of delivering large quantities of drug, which may be needed to ensure sufficient clinical overages for toxicity assessment in the non-clinical setting. Nonetheless, liquid formulations can have limits with viscosity, ionic strength and surface tension which will impact output and drug concentration.

Pressurised metered dose inhalers (pMDIs) are not easily compatible with biopharmaceutical drugs due to the inherent temperature, pressure and excipient aspects, although in some cases there may be viable approaches to stabilise the drug product. An alternative approach to nebulisers and pMDIs are soft-mist devices which provide a pMDI-like dosing experience with an aqueous solution product. However, drawbacks include the requirement for high concentrations and the forces involved in delivering the formulation, which may prove incompatible for drug products where large doses are needed.

In contrast to pMDIs, which require the patient to co-ordinate breathing in with actuating the device by hand, dry powder inhalers (DPIs) generally require little to no hand-breath co-ordination, and they can deliver quite high payloads with a quicker dosing time than nebulisers. However, additional pre-formulation, formulation and device screening is necessary for DPI-based products, to address some of the dry powder formulation and stability characteristics.

AEROSOL SAMPLING & ANALYTICAL METHODOLOGY

Confirmation of the amount of the dosed test material is not only good scientific practice but also a regulatory requirement. To verify the concentration of the delivered dose, samples are collected directly from

the exposure system from locations that are representative of the breathing zone for the animals (generally a facemask or restraint tube attachment position) using methodology that provides optimal trapping of the drug and permits chemical analysis of the active component. For most liquid formulations, this comprises a glass sintered sampling trap using an appropriate trapping solvent. For powder or suspension formulations, a quartz fibre filter is used rather than the standard glass fibre filters for NCEs. This is used in conjunction with silanizing analytical glassware prior to use.

For aerosol concentration and particle size assessment, standard Ultra Performance Liquid Chromatography (UPLC) analysis is normally employed. However, alternative methodology may have to be used depending on the biopharmaceutical. As mentioned earlier, biopharmaceuticals have complex structures and in many cases their activity depends on correct folding and subsequent tertiary structure. The shear forces exerted during the process of aerosol generation can impact the structure and therefore alter the bioactivity of the drug substance, with the worst-case scenario being loss of potency. For feasibility studies, one should consider the inclusion of not only a binding assay, but also a cell-based potency assay, where the pharmacological activity of the test material may be evaluated and any change in potency following aerosolisation noted. Since such assays tend to be product-specific, early dialogue with the selected non-clinical CRO partner is encouraged to ensure smooth transition from exploratory studies to regulatory GLP safety assessment.

BIOANALYTICAL AND BIOMARKER CONSIDERATIONS

Non-clinical safety studies with biopharmaceuticals intended for inhaled delivery have a number of additional considerations that are unique to this method of administration. Although confirmation of drug exposure by comprehensive pharmacokinetic/toxicokinetic (PK/TK) evaluation is expected in all biopharmaceutical safety assessment packages, it is important to consider that for inhaled products systemic exposure may not always be achievable or indeed desired. For instance, there may be limited transport of the delivered biopharmaceutical due to its size (molecules larger than 50 kDa display reduced bioavailability^{2,3}) or targeted delivery, and binding to

“Shear forces exerted during the process of aerosol generation can impact the structure and therefore alter bioactivity, with the worst-case scenario being loss of potency. For feasibility studies, one should consider the inclusion of not only a binding assay, but also a cell based potency assay, where the pharmacological activity of the test material may be evaluated and any change in potency following aerosolisation noted.”

a receptor in the lung or a specific cell population may lead to retention of the drug in the lung.

Therefore, sampling of the local environment by bronchoalveolar lavage (BAL) to confirm that the intended delivery has been achieved as well as establishing systemic exposure should be considered.

The feasibility of obtaining BAL measurements requires careful consideration as, although possible, in-life sampling carries an inherent risk to the animal. For this reason strict sampling limits are imposed and it is highly likely that a full lung TK profile will not be possible in non-rodent species, with rodent studies requiring additional animals for such assessments.

The analytical approaches required for TK assessment of biopharmaceuticals may differ to those more commonly employed for NCEs, with immunoassays based on ligand binding assessment often required, although liquid chromatography-mass spectrometry (LC-MS) or MS based assays can still be utilised if a signature peptide has been identified, or for smaller products such as oligonucleotides.

As mentioned earlier, the safety profile of a biopharmaceutical can only be adequately assessed in a pharmacologically relevant species, ideally where the intended clinical biology can be replicated. As a result, markers to confirm PD activity should be included in safety assessment studies wherever possible. Appropriate markers should be identified based on the expected pharmacological effect and assessment performed at timepoints relevant to its induction.

A detailed understanding of the intended biology is therefore required and this should include any downstream effects in addition to the direct effect of the drug interacting with its target. The relationship of this biology in the non-clinical species to the clinical situation should also be thoroughly investigated so that any differences in the

level or distribution of the target expression can be understood and interpreted.

In addition to PD endpoints, safety biomarkers can also be incorporated into the non-clinical safety studies. These can include markers of immune activation (CRP, cytokines, immune cell activation and/or mobilisation), immunogenicity assessment (discussed later), as well as assessment of “off-target” pathways that have been identified for certain classes of drugs. For example, prolonged coagulation and complement activation have long been associated with oligonucleotides, especially those with a phosphorothioate backbone or products with lipid based formulations.^{4,5} The exact parameters required for analysis are selected based on the biology and risk specific to the individual product, and if this risk is unknown or theoretical it can be assessed in preliminary studies to determine whether further follow up in pivotal studies is required.

IMMUNOGENICITY

One of the considerations specific to biopharmaceuticals is the development of immunogenicity. Administration of a human protein to an animal species can induce an immune response specific to the drug following delivery by any of the main routes of administration. The lung is predisposed to remove foreign material, and populations of the immune system, such as macrophages, specifically support this, so the potential for immunogenicity responses should be explored.

Although it is accepted that immunogenicity in an animal model is not predictive of immunogenicity in the clinical setting, the recognised consequences warrant at least the collection of samples. Blood samples should be collected prior to treatment and following completion of dose administration to assess the presence of systemic anti-

drug antibodies (ADA), should there be any change to the PK/PD relationship during the study. This may be followed-up by more detailed investigations such as assessment of the functionality of the ADAs in neutralising antibody assay and/or immunohistochemistry staining for the presence of immune complexes. Such in depth characterisation is not often needed at the preclinical stage but it should be considered for inclusion in clinical studies.

CONCLUSION

Drug delivery via inhalation is an exciting and growing field of drug development. Despite the additional considerations associated with the inhalation route in the context of biopharmaceuticals, there is considerable research activity in this field. A detailed understanding of the pharmacology and biology of the biopharmaceutical product and careful execution of appropriately designed

non-clinical safety studies, combined with selection of the most appropriate delivery method, can ensure a successful transition from non-clinical to clinical assessment.

ABOUT THE COMPANY

Envigo provides essential products and research services for pharmaceutical, crop protection and chemical companies, as well as universities, governments and other research organisations. With more than 3,300 employees across over 50 locations worldwide, Envigo is committed to helping customers realise the full potential of their research and products, working together to build a healthier and safer world.

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ABOUT THE AUTHORS

Simon Moore, PhD, joined Envigo in 1999 and is now the Director of Inhalation Science and Engineering and Toxicology Operations Inhalation Team Leader. In this role, Dr Moore is responsible for all aerosol technology aspects including the overall interpretation and reporting of the inhalation studies including safety pharmacology and ADME. In addition, he also leads a team of inhalation engineers who design, prototype and manufacture custom inhalation equipment for nonclinical safety assessment studies conducted at Envigo.

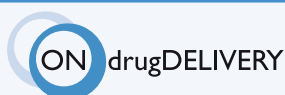
Dr Moore obtained a Chemistry degree from the University of Dundee (UK) in 1996 and gained his PhD in Heterogeneous Catalysis from the University of Glasgow (UK) in 2000 using high-pressure gas flow and chromatography. He lectures at the University of Surrey (UK) as part of the MSc Toxicology course on inhalation dosing, techniques and methodology and is a committee member of the Association of Inhalation Toxicologists and the British Standard Institution on Nanotechnologies.

Kirsty Harper, PhD, joined Envigo in June 2013 in her current role to design safety studies and non-clinical development programmes for biologics in response to customer requests as well as to provide scientific support and advice. Prior to this, she was employed as Principal Scientist at Oxford Immunotec Ltd, where she was responsible for pipeline product development projects and the provision of immunological advice and expertise.

Dr Harper obtained her PhD in Immunology from the University of Bristol (UK) in 2005, after which she completed a post-doctoral position investigating peptide therapy as potential treatment for autoimmune disease. Prior to this she obtained her BSc and MSc in Microbiology at Massey University (New Zealand) and worked at the Malaghan Institute (New Zealand) where she conducted basic research in autoimmune disease.

Sylwia Marshall, PhD, joined Envigo in July 2014 as Director of Biopharmaceutical Development and is responsible for designing safety studies and nonclinical development programmes for biologics, and providing scientific support and advice. Prior to joining Envigo, Dr Marshall held a senior research position at Novartis, where she lead multi-disciplinary biologics projects from early discovery through to clinical development working with external collaborators and CROs.

Dr Marshall received her undergraduate degree (BSc Biomedical Sciences) from the University of Durham (UK) and completed her PhD at University of Manchester (UK) in 2005 where she researched peritoneal wound healing and fibrosis. She then took on post-doctoral research positions at University College London and The Lung Institute of Western Australia which investigated biological processes involved in the development of fibrosis and inflammation.



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A NOVEL POWDER FILLING TECHNOLOGY TO REDUCE DEVELOPMENT COSTS & TIMELINES

In this article, Simon Strothers, Director, and Dave Seaward, PhD, Projects Director, both of 3P Innovation, discuss the evolution of filling technology in the inhaled world, including a new technology and approach to filling which offers significant advantages over conventional filling systems.

The inhaled market place is in the midst of major new exploration and development of new therapies for a much broader range of indications compared with the well-established treatments for asthma and COPD. Inhalation is now seen as a viable alternative drug delivery route for a wide variety of drug groups, including vaccines, gene therapies, insulin, cannabinoids and antibiotics.

In this mix of new drug formulations, many are in dry powder form, but produced using advanced manufacturing methods, such as spray-drying, to create “engineered powders”. These give a number of advantages including improved lung deposition, more potent dosing, greater

drug efficacy and improved drug stability. However, this new generation of powders also brings a new set of challenges, which demand advanced manufacturing solutions for handling and filling of the powders.

In the early days of an inhalation product development programme, the target inhaler device may not be defined, so the powder is filled into standard capsules to satisfy preclinical and early clinical manufacturing. As a project progresses, however, pharma companies may wish to use specific inhaler devices for individual drugs and indications.

The challenge becomes sourcing scalable, highly flexible powder handling and filling processes that can satisfy the total lifecycle of a new drug, from preclinical to clinical to commercial production. Technologies like this, which help to shorten development and manufacturing lead-times, reduce costs and enable faster product launch.

OLD WORLD FILLING

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 are still dispensed by volume.



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“Commercial pressures for high outputs, combined with tradition, have led to the vast majority of powder dispensing systems using inaccurate volumetric methods with a statistical process control check of actual weights. These checks are often counterintuitive as the actual weights are out of sync with the required weights.”

| DOSATOR | TAMPING DISK | VACUUM | CAPILLARY | AUGER | GRAVIMETRIC | |
|---------|--------------|--------|-----------|-------|-------------|-----------------------------|
| | | • | • | | • | 1mg to 5mg |
| • | • | • | • | | • | 5mg to 50mg |
| • | • | • | | • | • | 50mg + |
| • | • | • | • | • | • | Free flowing Powders |
| • | | • | • | • | • | Cohesive Powders |
| | | | | | • | Very cohesive powders / api |
| | | • | • | • | • | Low Compaction |
| | | | | | • | 100% weight Inspection |
| • | • | • | • | • | • | Low Speed 10s / minute |
| • | • | • | | | | High Speed 100s / minute |
| • | • | | | | | High Speed 1000s / minute |

Table 1: Matrix comparison of different types of filling system.

Powders by their very nature have dynamic physical properties and their density varies over time. Dispensing powder by volume does not deliver a truly accurate weight, neither at a development nor at a commercial level.

Commercial pressures for high outputs, combined with tradition, have led to the vast majority of powder dispensing systems using inaccurate volumetric methods with a statistical process control (SPC) check of actual weights. These checks are often counterintuitive as the actual weights are out of sync with the required weights due to fluctuations in powder density.

One of the most common styles of volumetric powder dispensing technology is the dosator which can typically dose 10-500 mg. The majority of existing commercially available dosators operate using the same basic technology.

Dosators 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 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 bioavailability for inhaled applications.

Such deficiencies with dosators led to

the development of alternative powder dispensers, many of which are fully customised for dry powder inhalers (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 the powder, which improves the dispensed weight consistency. However, it also compacts the powder, which can adversely impact bioavailability.

Broadly speaking, the formulation of powders via volumetric filling systems can sometimes be the business of guesswork. Often pharmaceutical firms improve flow characteristics via inventive methods of processing the powder or by adding flow-enhancing excipients.

Table 1 compares some of the key features of different types of filling system.

A MORE LOGICAL APPROACH...

3P's approach is to dispense powder by weight, rather than volume (i.e. by gravimetric means).

Gravimetric systems, in their purest form, have been available for several years, and until recently, the inherent slow response of weighing systems has restricted their use to lab and clinical supply applications. Xcellodose® (Capsugel, Morristown, NJ, US) and Quantos® (Mettler Toledo, Columbus, OH, US) are examples of low-speed, lab-scale, gravimetric filling systems.

3P has addressed this problem by creating the world-leading Fill2Weight technology (Figure 1) that reduces single dispense time to just a few seconds, making it suitable for high volume DPI manufacture.

Fill2Weight improves on the accuracy of volumetric systems by measuring, controlling and recording the weight of

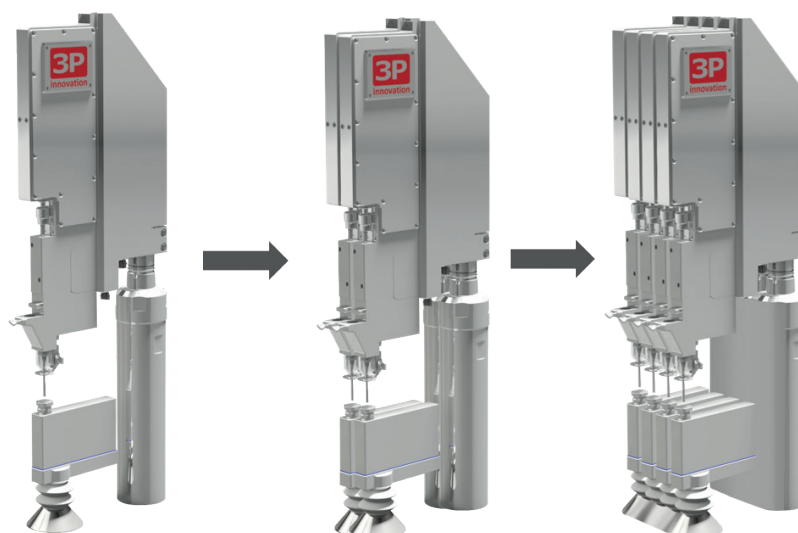


Figure 1: Fill2Weight is scalable and flexible, measuring, controlling and recording the weight of every dose, rather than dispensing a fixed volume.

every dose, rather than dispensing a fixed volume. This allows for compensation to changes in powder properties, such as density, in real-time, and without user intervention and re-calibration. Fill2Weight handles and fills a wide range of powders, including pure API, blended and spray-dried powders, engineered particles, biologics and lyophilised powders.

The benefits of the Fill2Weight gravimetric filling system are summarised in Box 1.

BOX 1: BENEFITS OF FILL2WEIGHT GRAVIMETRIC FILLING SYSTEM

- Highly versatile and independent of powder properties
- Easily scaled up for commercial manufacture
- Infinitely variable dose weight without tooling change
- No powder compaction and no particle shear
- 100% dose verification
- Tolerant to variations in powder properties
- Ideally suited to pure API

MEETING COMMERCIAL DEMANDS

In recent years, several big-name pharmaceutical product patents have expired, hitting large pharmaceutical firms hard and further accentuating the need to remain innovative and agile with new drug development.

These pressures are not restricted to medium and large pharma companies. Firms of all sizes, from SMEs to multinationals, are under increased obligation to speed up the clinical trials phase and reduce the overall time to market. Then, once in the market, agreed commercial volumes have to be consistently realised without deviation.

At 3P, our *raison d'être* is to help meet the above challenges for our clients and make them profitable while doing so. It's these commitments that have provided the blueprint for our latest R500 (Figure 2) and R1000 filling system derivatives.

Integrating the novel and powerful Fill2Weight dispensing technology and in response to market demands, 3P has now

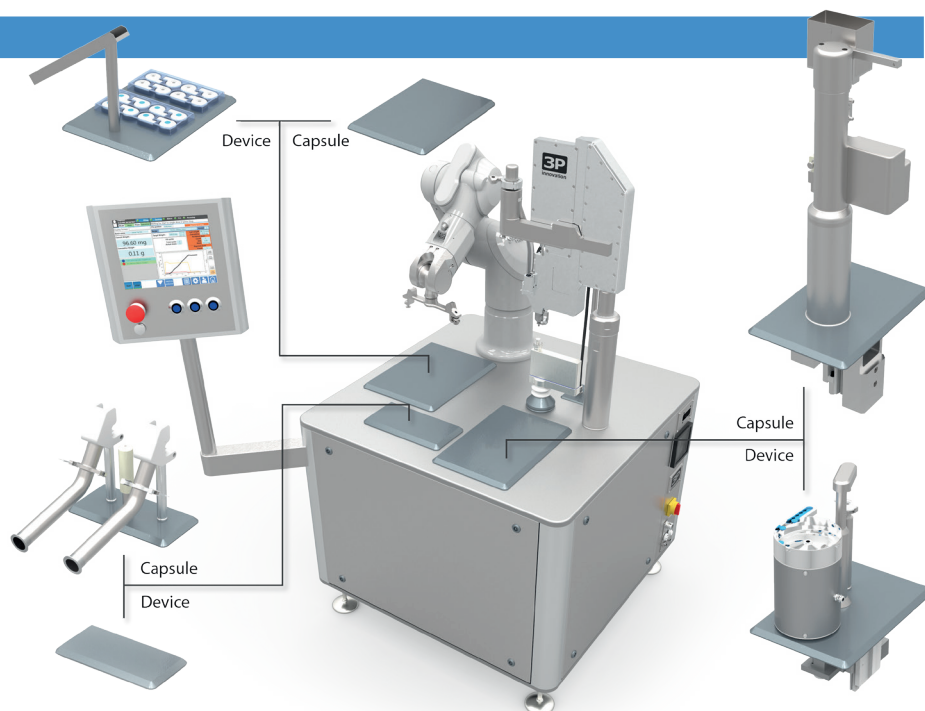


Figure 2: R500 – modular design for rapid changeover.

developed the R500 and R1000, the world's fastest gravimetric, fully automated powder micro-dosing machines. Our ongoing investment in gravimetric R&D has been driven by the evolving needs of the industry – not least the pressure on pharmaceuticals to reduce time-to-market.

R500 and R1000 machines can now fill bespoke inhaler devices and other containers as well as capsules on the same machine. The machine achieves this high level of flexibility and minimum changeover times through the use of modular design principles combined with well-proven robotic automation methods.

WHY R500 / R1000?

Reduce Preclinical – Fast-Track to Phase III

During formulation development, additional processing steps are often required to achieve a powder form suitable for correct drug distribution, solubility, measuring and dosing (e.g. achieving flowability, fillability etc). Example processes include dry granulation, blending, roller compaction, micronisation etc.

Fill2Weight can handle and fill challenging formulations such as sticky, cohesive and fluffy powders, and offers the potential to simplify formulation by eliminating the need for additional “formulation for filling” steps. This reduces development time and associated costs and helps accelerate achievement of clinical Phase I and the first time in human (FTIH) milestone.

Not only does R500/R1000 support faster achievement of Phase I, the fact that reduced formulation for filling is

required may also mean that costly and time-consuming stability trials necessary to evaluate these additional processes are reduced accordingly.

The system is highly flexible – system parameters can be quickly and easily adjusted to suit different powders, varying environments and varying bulk properties between batches. The settings are captured as “recipes” which are stored and can be quickly called up for future batches.

Meet Regulatory Challenges: PAT, Online Inspection & Feedback

Powders possess inherently variable properties, such as bulk and tapped densities, which can vary both throughout a batch and from one batch to another. The Fill2Weight system incorporated in R500 / R1000 is a dynamic system that compensates for this unstable, changing nature of powders and provides 100% real-time process control.

Fill2Weight also provides 100% verification of dosed drug weight and fill parameters. Every dose is recorded, including actual fill weight and fill time. This makes it suitable for continuous processing applications; for example, feeding powders into a processing vessel. As closed-loop weighing is used, so the system will fill until the target weight is achieved. If powder properties change, the system will adapt to this, modifying settings as necessary to maintain control of the process between defined limits. Changes and trends are recorded so a full history of the production parameters is maintained. This is adaptive, real-time control of the process.

ABOUT THE AUTHORS

Simon Strothers, MSc, joined as a Director of 3P innovation in 2013 and is responsible for Business Development and Marketing. His background is in mechanical engineering. He qualified with a Bachelor's degree in Mechanical Engineering at the University of Manchester (UK) and has a Masters Degree in Business Management from Warwick University (UK). Mr Strothers' career started with Lucas Aerospace, where he worked as Design Engineer, Systems Engineer and Programme Manager, responsible for flight control and engine actuation systems for aircraft. He then worked as a management consultant for four years, driving business improvement projects across a wide variety of industries including paper making, railways and aerospace. For the past 14 years he has worked in the field of custom automation and engineering consultancy for the life sciences and FMCG sectors, initially as senior project manager and since 2006 as business development director.

Dave Seaward, a founding director of 3P, is a chartered engineer with a first degree in joint electrical and mechanical engineering and a control theory PhD. His PhD focused on the application of servo motors to packaging machinery. This early work has led to a career spanning 30 years associated with the development of custom automation for a variety of industries. These include the pharmaceutical and medical device sectors. Many of his projects have included advanced powder or liquid dispensing. Seaward is named inventor on multiple patents. He has worked on 14 dry powder inhaler programmes and nine different injectable drug delivery and auto-injector projects. At 3P, he developed high speed gravimetric powder dispensing technology capable of dosing pure API including biologics into devices and capsules for inhaled and injectable applications. More recently he has helped develop the processes to manufacture a number of drug eluting polymer/modified release products.

Manage Potent Drugs

The trend towards smaller, higher-concentration doses and more potent NCEs is being driven by both the demand for more targeted treatments (and hence fewer side-effects) and less-frequent administration to patients. This trend is driving pharma companies to explore dose forms comprising pure API or higher concentrations of API, with either no, or more limited, excipient. Non-uniform particle morphology (shape), triboelectric charge and small particle size are some of the challenges associated with pure API that present powder-handling and -dosing challenges. In addition, filling pure API often means lower dose weights (<5 mg). Fill2Weight is designed to meet these challenges and provide a flexible, versatile tool to support next-generation powders and formulations of the future.

Support Biological Drug Development

Fill2Weight is designed to handle and fill delicate, spray-dried and freeze-dried (lyophilised) powders without damaging powder particles. The technology also offers the opportunity to pharma manufacturers to fill tray (or bulk) lyophilised powders that can reduce the overall costs associated with in-vial lyophilisation, and which opens up a whole new world of choice with regard to container or device type.

R500 / R1000

Suitable for all clinical phases and commercial production, R500 combines fully automatic functionality with high speed gravimetric filling, with the aim of reducing preclinical development and clinical production time, costs and risk.

The enhanced scalability of the R500 enables drug manufacturers to double production with the simple addition of a second Fill2Weight head. The twin-head configuration, known as the R1000, incorporates duplex tooling on the robot to double the machine output from 500 capsules per hour (CPH) to 1000 CPH.

The R500 and R1000 are the fastest and most flexible gravimetric powder fillers for capsules available. At 1000 CPH, 100% weight verification and 21CFR11 compliant, this system represents a highly competitive package across the lifecycle of a product, from lab R&D to cGMP Clinical Manufacturing to commercial-volume production.

The R500 / R1000 can be supplied in a number of formats:

1. Capsule filling only
2. Device filling only
3. Combined capsule and device filling.

For the combined capsule and device

system, changeover between formats is achieved quickly and easily through swap-out of modules. The Fill2Weight module and robot remain in place as common modules for all applications. Figure 2 illustrates how the system is configured for each format. For device or container filling, a Transfer Isolator is available for loading and marshalling devices in and out of the machine. This enables higher throughput whilst maintaining operator safety.

Full environmental control is available if required, including air extraction, humidity (RH) and temperature control.

R500 / R1000 is also designed for sterile filling if required and can withstand hydrogen peroxide vapour (HPV) sterilisation, and Wash in Place (WIP) and Clean in Place (CIP) processes using a variety of cleaning agents.

CONCLUSION

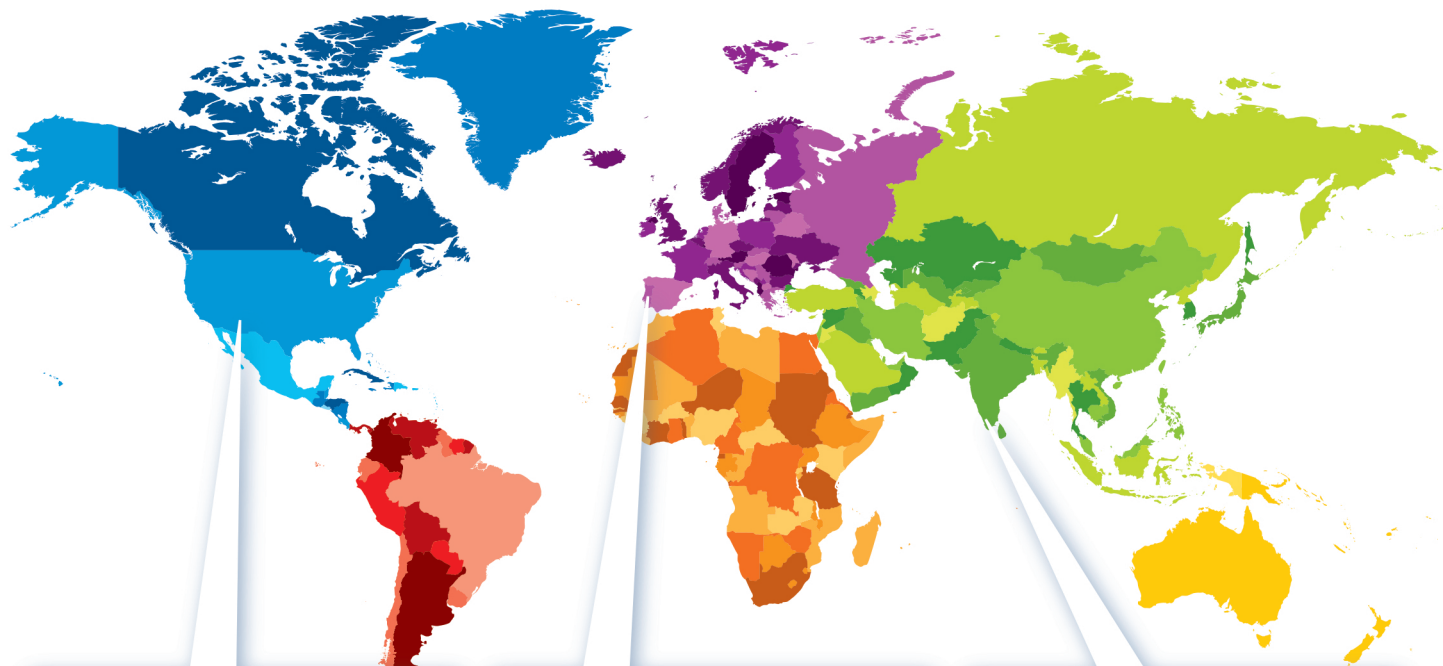
This article has summarised how the challenges of dispensing small and exact amounts of inhaled formulations into DPI devices and capsules are being overcome by technology. Volumetric systems are becoming less viable when it comes to dispensing complex powders accurately and efficiently at both clinical development and commercial production phase.

The R500 and R1000 provide automated, high-speed and accurate gravimetric filling solutions which enable critical clinical trial data to be obtained without the need for costly "formulation for filling" iterations. The technology is available now, to de-risk and cut out much of the inflated cost and time involved with dispensing new and current inhaled powders into DPIs.

ABOUT THE COMPANY

3P innovation, the home for **P**roduct, **P**rocess and **P**roduction Innovation, is a successful engineering company with a reputation for delivering innovative solutions to major pharmaceutical, medical and fast-moving consumer goods companies. The company develops custom automation, usually associated with product launches. Its approach ensures robust products are manufactured on efficient machines. From low speed laboratory equipment to high speed assembly lines 3P can develop an appropriate custom solution. It also has a range of standard machines, products and technologies. All 3P's standard systems have been designed to reduce the time to market associated with new product developments.

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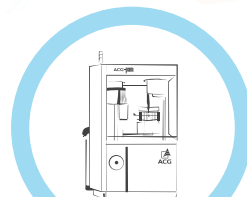
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