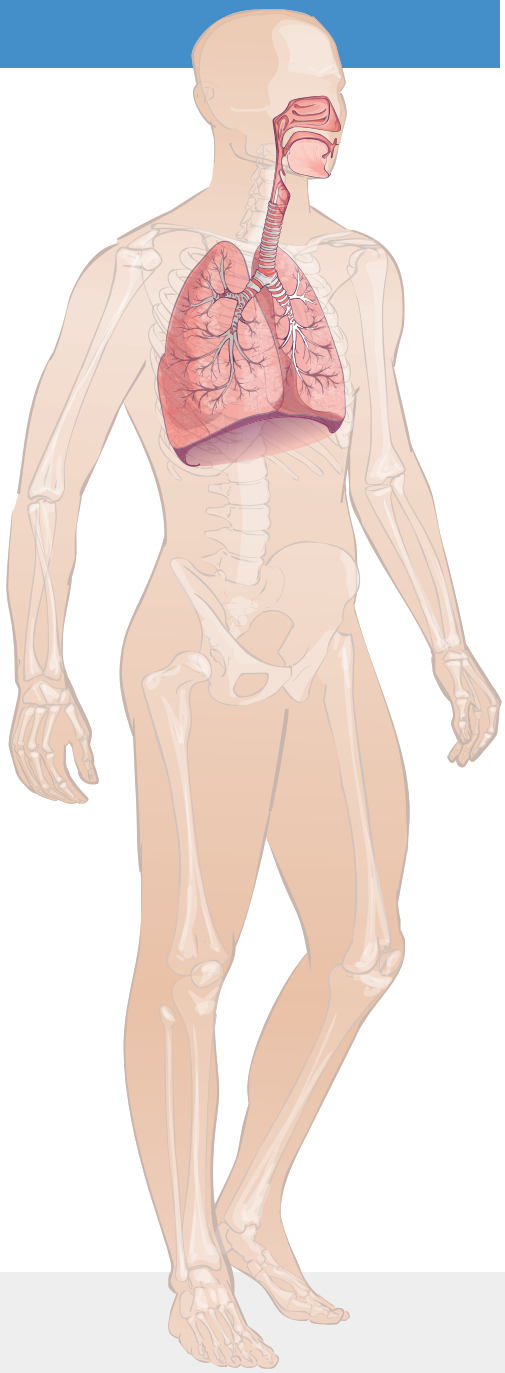
PULMONARY & NASAL DELIVERY

ON drugDELIVERY



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PULMONARY & NASAL DELIVERY

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EDITORIAL CALENDAR

Dec 2019	Connecting Drug Delivery
Jan 2020	Ophthalmic Drug Delivery
Feb	Prefilled Syringes & Injection Devices
Mar	Skin Drug Delivery: Dermal, Transdermal & Microneedles
Apr	Pulmonary & Nasal Drug Delivery
May	Injectable Drug Delivery
Jun	Connecting Drug Delivery
Jul	Novel Oral Delivery Systems
Aug	Industrialising Drug Delivery
Sep	Wearable Injectors
Oct	Prefilled Syringes & Injection Devices
Nov	Pulmonary & Nasal Drug Delivery

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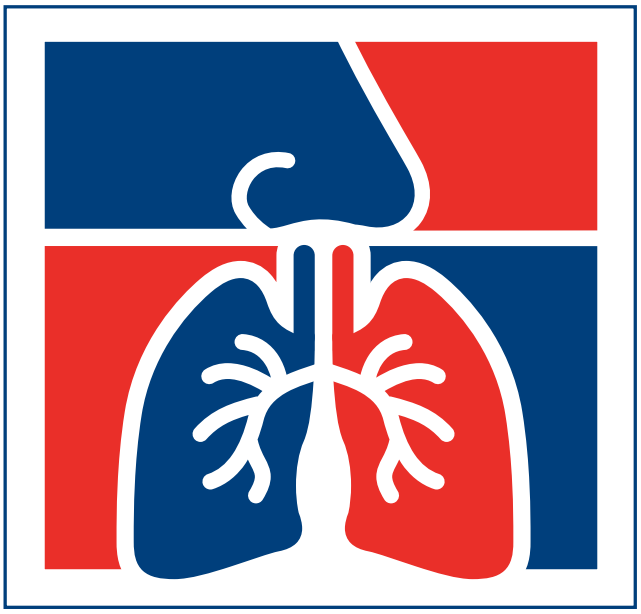
Respiratory Drug Delivery



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DRY POWDER INHALERS: TOWARDS EFFECTIVE, AFFORDABLE, SUSTAINABLE RESPIRATORY HEALTHCARE

In this article, João Ventura Fernandes, PhD, Director of Technology Development and Licensing, and Peter Villax, Chief Executive Officer, both of Hovine Technology, look at the trends shaping the development of dry powder inhalers.

Inhaled drug delivery is established as the primary choice for airway disease treatment and continues to hold high potential for systemic drug delivery. Since its invention in the 1950s, the pressurised metered dose inhaler (pMDI) has been the inhaled therapy "gold standard"[1] for airway diseases such as asthma, as a result of being easy to use, multi-dose and inexpensive to manufacture.

However, its drug delivery performance remains dependent on patient co-ordination – often leading to high drug losses – and environmental concerns have emerged with respect to the use of propellant-driven pMDI technology. Although initial chlorofluorocarbon (CFC) propellants have been discontinued due to their impact on the ozone layer, their hydrofluoroalkane (HFA) replacement propellants are unfortunately potent greenhouse gases – 2,000 times more potent than carbon dioxide.[1]

> "Currently, 100 new inhaled drugs in the pharma development pipeline have already opted for DPI technology[3] and are expected to achieve an ever-growing market share for this category of device."

> "Without major technological breakthroughs in finding alternatives which are not greenhouse gases, pharmaceutical companies may lean towards the use of alternative inhaler technologies."

The global battle against climate change arising from greenhouse gas emissions may drive regulators to subject pMDI technology to carbon emission restrictions. Without major technological breakthroughs in finding alternatives which are not greenhouse gases, pharmaceutical companies may lean towards the use of alternative inhaler technologies.

In this regard, an alternative available now is the propellant-free, breath-actuated dry powder inhaler (DPI). In terms of total lifecycle harmful gas emissions, DPIs not only produce 10 times less greenhouse gas emissions than pMDIs[2] but can also achieve lung delivery efficiencies and deliver drug loads which are beyond the reach of pMDI technology. DPI market entry occurred in the 1960s and market adoption by pharma companies has been growing steadily as a result of these advantages. The DPI product market size surpassed US$16 billion (£13 billion) in 2015 and is expected to continue growing at 5% CAGR until 2024.[3] A total of 114 inhaled products are currently being marketed,[3] delivered to patients by about 49 million DPI devices produced per year.[3]

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TRENDS SHAPING DPI DEVELOPMENT

Currently, 100 new inhaled drugs in the pharma development pipeline have already opted for DPI technology and are expected to achieve an ever-growing market share for this category of device. Looking ahead, as a result of evolving industrial and societal trends, four key requirements are expected to shape DPI developments, as shown in Figure 1:

- **Delivery efficiency.** To deliver the drug as efficiently as possible to where it needs to go in the airways remains the number one goal. Developers will continue their drive to improve drug delivery efficiency to the lung through reduction of losses in the device and the upper airways as this enhances patient treatment. Recent inhaler developments have reached lung doses between 40% and 50% as a percentage of label claim using a number of formulations: traditional carrier-based; carrier-based with force control agents; and carrier-free formulations.[4]
- **High-dose drug delivery.** There are new large molecules entering the respiratory development pipeline of large pharma and biotechs – namely proteins, oligonucleotides, antibodies and nanobodies. As a result, new DPIs may be required to deliver higher doses using drug-rich, carrier-free formulations, using large powder volumes and possibly requiring multiple patient inhalations.

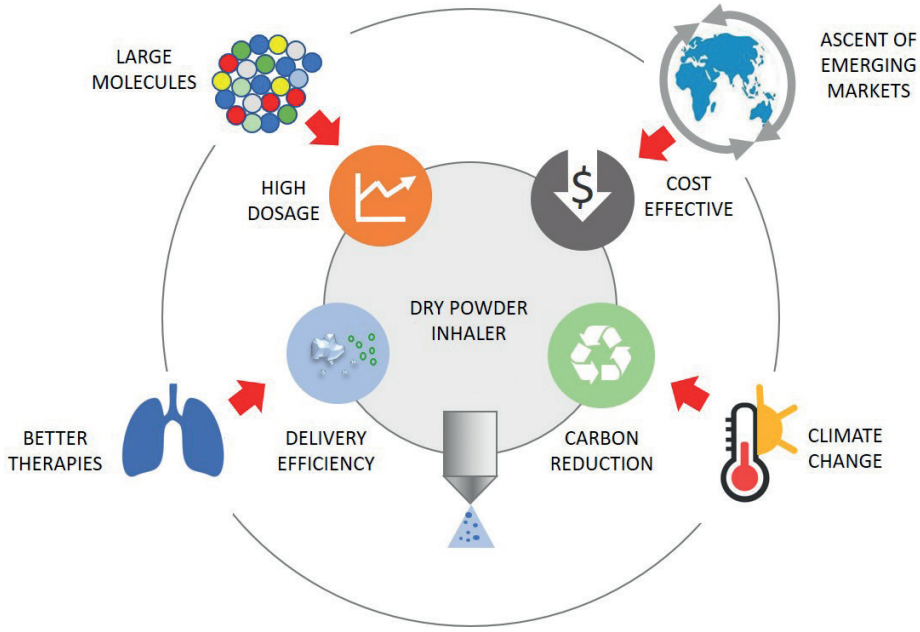


Figure 1: Trends and requirements shaping dry powder inhaler development.

- **Cost effectiveness at global scale.** It is forecasted that, by 2030, seven of the 10 largest economies by gross domestic product in purchasing power parity will be emerging markets – China, India, Indonesia, Turkey, Brazil, Egypt and Russia.[5] The ascent of these countries will provide DPI growth opportunities for cost-leader inhalers to harvest on a global scale.
- **Environmental sustainability.** Today's inhalers are contributing a significant carbon footprint,[2] and public opinion and regulatory pressure is already pushing towards environmental improvements.[6] The ideal environmentally friendly inhaler is a simple, effective, propellant-free device made of only a few recyclable-material parts, thus minimising its full environmental lifecycle cost.

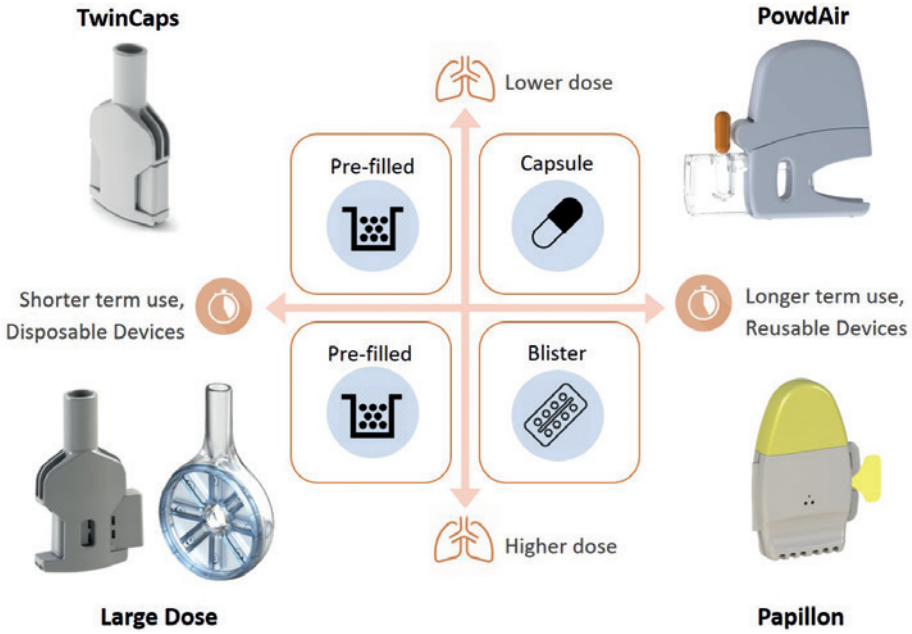


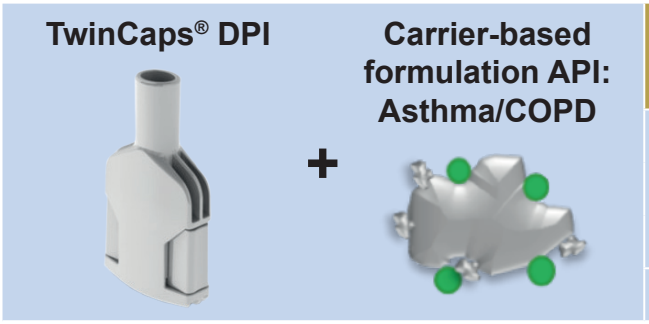
Figure 2: Hovione Technology's portfolio of innovative dry powder inhalers.

SHIFTING THE INDUSTRIAL PARADIGM

In DPI development, the innovator strategy has been to develop new, more effective molecules to treat airway diseases delivered by ever-more complex and expensive DPIs, as a means to increase development and cost barriers for generic competition. It is now common that state-of-the-art multi-dose DPIs are made from more than 20 plastic parts, which the patient uses for two months and then discards and replaces by a new unit.

Such an industrial strategy is successful in the market but results in a major consumption of primary raw materials and energy – and these account for carbon emissions and generate large quantities of plastic waste that needs further processing to avoid impacting natural ecosystems.

In fact, Figure 1 underlies the need for DPIs to be fundamentally simple to use, so that the patient is able to understand how they work and to use them correctly to achieve effective delivery – and made of only a few recyclable-material parts, so that both its environmental footprint and overall cost of goods are the lowest possible. This requires a shift in industrial strategy towards effective, globally affordable, sustainable DPIs. Hovione Technology aims to realise this paradigm shift with the portfolio of DPIs shown in Figure 2.



Inhalation Volume (L)	Flowrate (L/min)	Pressure drop (kPa)	Delivered Dose (%)	Fine Particle Fraction (%)
4	28	2	93.0	41.1
	38	4	99.6	44.2
	46	6	104.8	46.8
2	38	4	98.6	42.6

Table 1: TwinCaps DPI – delivery performance with an asthma/ COPD drug carrier-based formulation at two flow rates and two inhalation volumes.[7]

"Unlike most other medical devices, inhalers do not need to be fundamentally complex and built from many parts to achieve a high and robust performance in drug delivery to the lungs."

SIMPLE AND HIGH PERFORMING

Unlike most other medical devices, inhalers do not need to be fundamentally complex and built from many parts to achieve a high and robust performance in drug delivery to the lungs. An example is the TwinCaps DPI (Figure 2), launched in Japan in 2010 as part of Daiichi-Sankyo's Inavir (laninamivir) influenza drug product. Its extreme simplicity of operation, requiring only one step per inhalation, and its ease of manufacture – two plastic parts only – were key to its commercial success.

Inavir currently has the largest market share in the Japanese influenza market and TwinCaps has become the world's largest-selling single-use-dose disposable inhaler. In a recent study of aerodynamic performance with an asthma/ COPD carrier-based formulation, TwinCaps demonstrated high and robust drug delivery performance across different inspiratory flow rates and inhalation volumes.[7]

As shown in Table 1, the TwinCaps delivered dose of more than 90% of total dose and fine particle dose of over 40%, substantially independent from patient-generated inspiratory flow rate and inhaled volume, indicates that performance-leading DPIs can be simple in design, construction and operation.

ENABLING HIGH DOSE

When it comes to inhaled delivery of the large molecules entering the drug development pipeline – which are expected to require large lung doses – not only innovative formulations are needed but also new and effective large-dose inhalers, tailored to the specific usability and convenience needs of patients. As shown in Figure 2, Hovione Technology is developing such large-dose DPIs.

These include 8Shot, the world's first eight-dose, factory-filled DPI enabling delivery to the lungs of therapeutic doses up to 400 mg in eight inhalation manoeuvres. In use, the patient just turns a dose wheel to access the next unit dose. 8Shot provides a patient-friendly solution for high-dose delivery without the burden of instructing the patient to reload an inhaler multiple times with a capsule or blister, leading to a long, time-consuming, error-prone use sequence.

As shown in Figure 3, the 8Shot DPI is designed to allow the patient to sequentially inhale the right amount of drug or particle-engineered powder formulations, mitigating the coughing risk resulting from sudden airways exposure to a single large dose. Being manufactured from only two plastic parts turns this large-dose DPI into an economically viable option from short to long-term inhaled treatments requiring high-dose delivery.

GLOBALLY AFFORDABLE, SUSTAINABLE CARE

When aiming to fulfil the need for readily accessible and affordable treatments across world regions and delivering environmental gains, the DPI developer faces a question – is it worth spending tens of millions scaling up a 20-part DPI device only used for a few months or is it preferable to choose a device that costs at

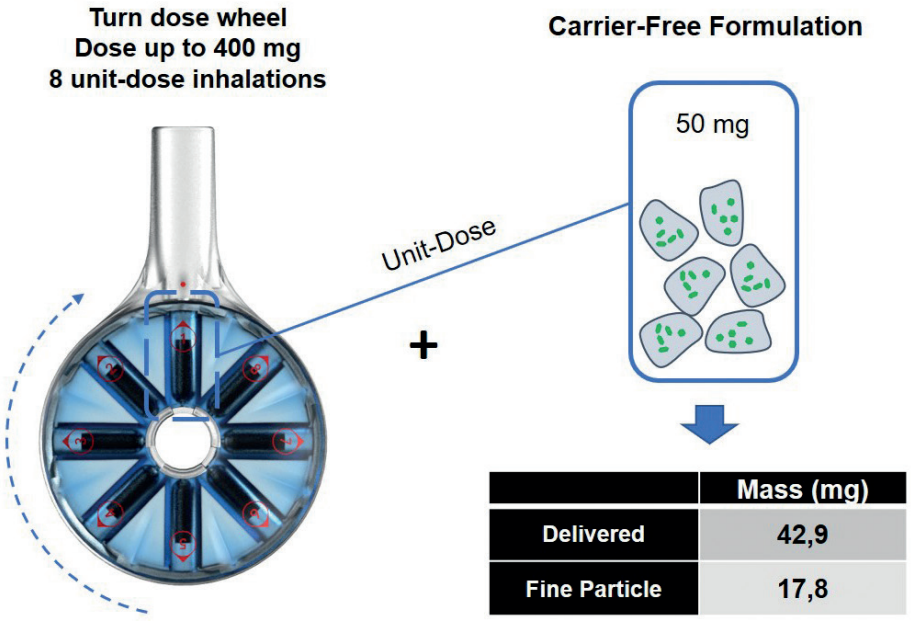


Figure 3: The 8Shot DPI, the world's first eight-dose factory-filed inhaler – enabling high-dose drug delivery to the lungs. In this example, up to 140 mg of carrier-free drug powder may be deposited in the lung.

least 10 times less to bring to production, with less environmental impact and without compromising delivery performance?

The Papillon DPI (Figure 2), Hovione Technology's new single-dose, reusable blister-based DPI, unlocks a paradigm shift for pharma companies developing inhaled drugs. On account of it being made from a single, reusable plastic part, as shown in Figure 4, Papillon can achieve unit dose costs competitive to multi-dose inhalers at a fraction of the development cost and risk associated with complex 20-part inhalers.

The Papillon inhaler delivers extreme ease of use: the patient loads the blister, closes the device and inhales the dose. Papillon may then be reused for the remaining doses provided (Figure 4). Its patented system for automatically piercing the loaded blister enables the single-part DPI construction. Furthermore, it features a large blister size for accommodating a wide range of inhaled drug doses. Papillon is designed for global, industry-leading inhaler affordability across emerging and established markets.

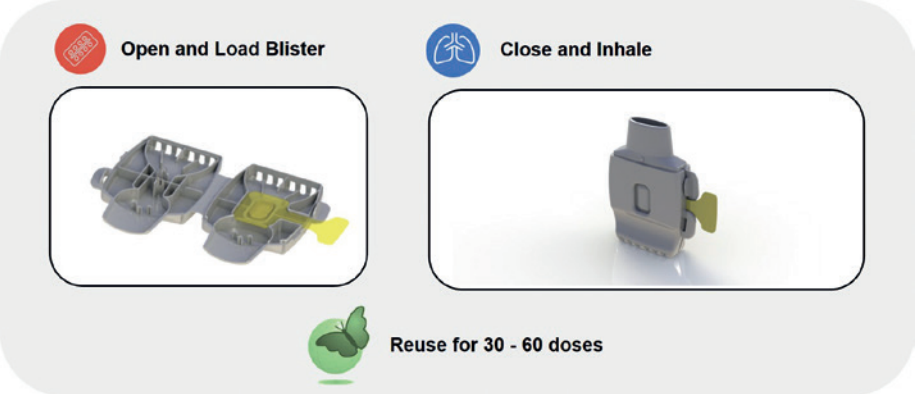


Figure 4: The Papillon DPI – a single-dose, reusable blister-based DPI built from a single part.

CONCLUSION

We have presented the case for simple, inexpensive DPIs with a reduced number of parts. A growing preference from pharma companies for DPIs delivering new drugs under development is supported by their delivery efficacy and ease of use – and, in the case of the devices presented in this article, large-dose capability, ease of manufacturing and better environmental sustainability. Hovione Technology's portfolio of DPIs – disposable, capsule-based, blister-based and large-dose inhalers – addresses the need for effective, globally affordable and increasingly more sustainable inhaler technologies.

ABOUT THE COMPANY

Hovione Technology offers access to a complete portfolio of innovative, globally affordable dry powder inhalation devices – disposable, capsule-based, blister-based and large-dose DPIs. With more than 20 years of expertise developing inhaler technology, Hovione Technology's team has been behind the first market-approved disposable dry powder inhaler for influenza treatment in Japan – the TwinCaps. Millions of patients are being treated every year with Hovione Technology's innovative inhaler technology.

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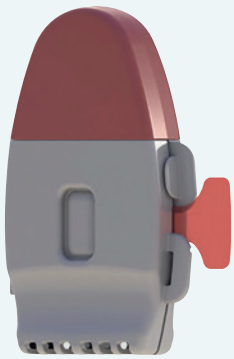
ABOUT THE AUTHORS

João Ventura Fernandes is Director of Technology Development and Licensing at Hovione Technology. He is a mechanical engineer, holds a PhD in Engineering Design and is an inventor and patent holder. He has acquired significant experience in product development across the aerospace and pharmaceutical industries. He has previously worked in jet-engine design at Volvo Aero and Rolls-Royce and joined Hovione in 2014, becoming a developer of inhaler technology and a licensor of intellectual property. He has taken a leading role in developing, licensing and marketing the new PowdAir capsule-based inhaler and in the expansion and promotion of Hovione Technology's product portfolio.

Peter Villax is Chief Executive Officer at Hovione Technology. He joined Hovione in 1982 as a computer programmer and led Hovione's computerisation, then switched to pharmaceutical development in 1990 and soon became interested in pulmonary delivery. He is an inventor of all generations of dry powder inhalers at Hovione. His disposable dry powder inhaler TwinCaps, licensed to Daiichi Sankyo for the delivery of influenza drug Inavir, continues to be the only commercial device of its kind in the world, and has helped Daiichi Sankyo become the market leader in influenza products in Japan. He has significant experience as an inventor of devices, a patent holder and a licensor of technology patents.

Hovione Technology

Dry Power Inhalers

PowdAir	8Shot	Papillon	TwinCaps
			
CAPSULE BASED	LARGE DOSE 8 x 50 mg	BLISTER BASED	DISPOSABLE 2 x 50 mg

Innovative, effective and globally affordable DPIs

Hovione Technology, a specialist in innovative inhalation device technology, has developed a complete portfolio of effective and globally affordable dry powder inhalers – disposable, capsule-based, blister-based and large dose DPIs. Featuring easy-to-use, attractive designs that are precision built from few plastic parts for maximum affordability and minimum environmental impact, all our inhalers are available for development, supply and licensing. With over 20 years of expertise developing innovative inhalers, our team was behind the first approved disposable inhaler, the TwinCaps DPI, marketed in Japan for influenza. Millions of patients are being treated every year with Hovione Technology's inhalers.

- Innovative, patents to 2038
- Easy to use, attractive
- Effective, market proven
- Precision built, few parts
- Affordable, at global scale

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EXPLORING A FASTER, MORE COST-EFFECTIVE ALTERNATIVE TO GENERIC BIOEQUIVALENCE

Jag Shur, PhD, Chief Executive Officer of Nanopharm, an Aptar Pharma company, explores the challenges companies face in bringing generic respiratory and nasal therapies to market – and how some organisations have proactively addressed the challenge and developed services to integrate the device and the formulation, introducing the Aptar Pharma Services offering.

Whether you are a large pharmaceutical company with access to knowledge space at every point of the drug development cycle, or a smaller company with a particular specialism, time to market will be a key driver.

The challenge is how to accelerate development time, while at the same time de-risking the opportunity. And, of course, ensuring that costs don't escalate. This challenge is particularly evident in the respiratory and nasal therapeutic areas where the complexity of the development and regulatory approval process places a significant financial and regulatory burden – especially on those developing generic formulations.

A CHANGING REGULATORY LANDSCAPE

The US FDA requires comparative clinical endpoint bioequivalence (BE) studies in its weight-of-evidence approach for an abbreviated new drug application (ANDA) of all orally inhaled and nasal drug products (OINDPs). This requires a lengthy and costly clinical trial, with often unpredictable results.

In fact, Datamonitor suggests it costs more than $100 million (£79 million) to bring any AB rated (drugs that have been proven to meet the necessary bioequivalence requirements through *in vivo* and/or *in vitro* testing compared with a reference standard that is currently approved) inhaled drug to the US market. The cost of a single, 900+ person clinical endpoint BE study is circa $45 million. These studies typically have high variability and low sensitivity, and cannot detect any formulation differences between test and reference products. They really only confirm local equivalence.

For this reason (in its own words) "even though there is a current, clear regulatory pathway utilising the weight-of-evidence approach for BE assessment of OINDPs", the US FDA's Office of Generic Drugs (OGD) continues to explore new methods to make development and BE assessment of OINDPs more cost and time effective in the future.

In May 2019, the FDA provided an alternative pathway for an ANDA submission of a solution metered dose inhaler (MDI). This alternative will decrease programme costs by about 45% and increase the net present value of respiratory generic

> "We are witnessing an escalation in the complexity of the registration process and a heightened focus on device technology and patient safety."

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products. Currently there are 26 FDA product specific guidances for OINDPs. Removing clinical endpoint BE studies for OINDPs could save $5 billion over time.

THE VALUE OF AN INTEGRATED APPROACH

We are witnessing an escalation in the complexity of the registration process and a heightened focus on device technology and patient safety from regulatory bodies. This, coupled with the loss of technical skills in some large pharma, and the lack of expertise in smaller pharma companies, has resulted in a gap in the analytical capabilities required to accelerate and de-risk drug development.

There is a growing desire to develop both new and generic OINDPs, and so the need for pharma partners to be able to support customers during the entire life cycle of the drug product and deliver them a complete solution is clear. In response to our partners' needs, we have developed Aptar Pharma Services. This offer builds on Aptar Pharma's established credentials of >25 years of manufacturing excellence and a wide portfolio of solutions and services, now complemented with the expertise of Aptar-acquired Nanopharm, Next Breath and Gateway Analytical, to provide that complete solution.

The Aptar Pharma Services model is a novel example of how partners are responding to the market need for accelerated device and finished drug product development, while at the same time mitigating risk and reducing cost. Consisting of four complementary, value-added and differentiated analytical, testing and development services, the model enables Aptar Pharma to collaborate earlier with customers to support their complex drug formulations and delivery requirements at all stages of drug development and commercialisation.

The four components are:

- Aptar Pharma – a global provider of drug delivery systems and services
- Next Breath – a full-service cGMP lab specialising in analytical testing of drug delivery systems
- Gateway Analytical – a leader in the testing of injectable drugs, providing particulate detection and predictive analytical services
- Nanopharm – a provider of orally inhaled and nasal drug product design and development services.

> "The key element... is to find an alternative BE clinical endpoint approach for OINDPs."

WHAT ALTERNATIVES ARE AVAILABLE TO FAST TRACK GENERIC BE STUDIES?

So far, we have established that the challenge is how to accelerate development time, while at the same time de-risking the opportunity for failure and managing cost. The key element in that trifecta of challenges is to find an alternative BE clinical endpoint approach for OINDPs.

One option is Nanopharm's SmartTrack™ process, which combines the recording of inspiratory breath profiles with realistic aerodynamic particle size distribution performance testing. Using representative mouth-throat models, *in vitro* dissolution and morphology directed particle sizing, chemical imaging of a representative lung dose and regional deposition modelling, together with physiologically based pharmacokinetic models for predicting local and systemic exposure, SmartTrack provides the critical elements required to meet the alternative requirements and eliminate clinical endpoint BE studies.

ACCELERATING AND DE-RISKING GENERIC PRODUCT DEVELOPMENT

SmartTrack uses methodologies to bridge *in vitro* measurements and *in vivo* performance of OINDPs through clinically relevant mouth-throat models, dissolution, advanced *in silico* modelling and simulation tools. Using its proprietary aerosol collection apparatus (UniDose), Nanopharm investigates the *in vitro* dissolution, formulation microstructure and realistic aerodynamic particle size distribution performance of generic and reference products with representative mouth-throat models. These data, with realistic breathing profiles, are employed in an *in silico* regional deposition model with physiologically based pharmacokinetic simulation of local and systemic exposure.

Such novel *in vitro* techniques have been used to predict the local extent and rate to which the active drug from OINDPs is absorbed and becomes available at the site of therapeutic action. SmartTrack has proved indispensable in guiding product development programmes, local bioavailability and BE assessment of OINDPs, as well as in supporting regulatory decision making.

ACCELERATING OINDP DEVELOPMENT

When predicting clinical outcomes, aerosol delivery – including emitted dose, fine particle mass and aerodynamic particle size distribution – from a dry powder inhaler (DPI) is largely determined by the interaction between the device, formulation and inhalation manoeuvre.

The SmartTrack process with an inhalation flow profile (NIP) device enables real-time measurement of patients' inspiratory flow profiles – and measurements of their initial acceleration at the beginning of inhalation, peak inspiratory flow, total inhaled volume and airpower. These profiles, with clinically relevant mouth-throat and nasal models, show good *in vivo* correlations in predicting regional drug deposition and systemic exposure.

With real-time feedback, NIP has been successful in clinical PK studies, training patients and gathering inhalation profile data of patients during different arms of a longitudinal, crossover clinical trial for soft mist inhalers, MDIs and DPIs.

Nanopharm has pioneered the concept of structural Q3 equivalence for OINDPs. This approach is vital for the industry. SmartTrack is guiding alternatives for inter-product comparisons that support clinical endpoint biowaivers for OINPD development programmes, bringing cost-effective generic medications more quickly to market (Figure 1).

WHAT BENEFITS ARE THERE FROM THIS ALTERNATIVE APPROACH?

For pharma companies, this delivers a unique, holistic approach to predicting clinical outcomes, at a fraction of the time and cost of conventional approaches. It enables experts to speak to experts, creating a partner approach that is committed to good outcomes. It also provides for a backstop in the event internal resource becomes an issue. Finally, it provides choice and an awareness of delivery options that may not be available in-house.

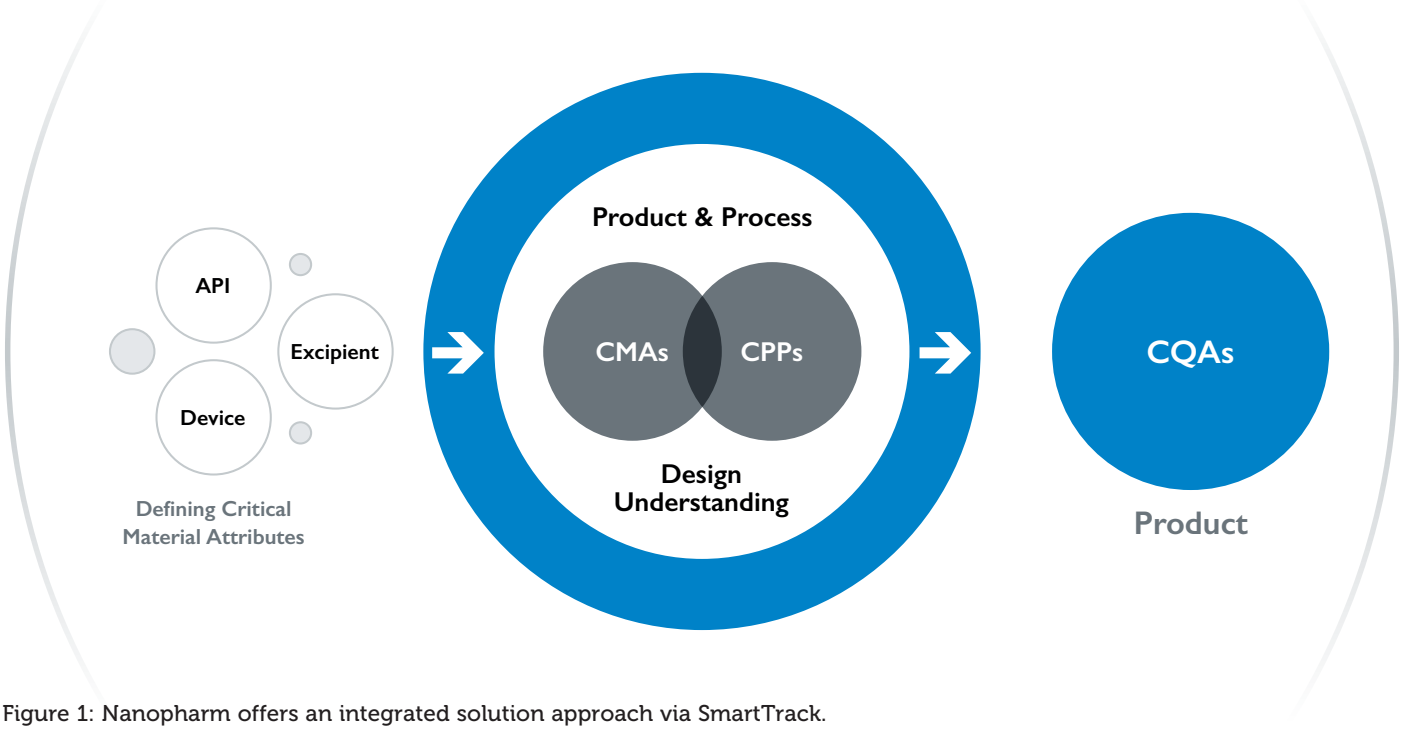

Figure 1: Nanopharm offers an integrated solution approach via SmartTrack.

Rationally, the benefits are wide ranging. An alternative to clinical endpoint BE dramatically decreases programme costs by up to 45% and increases the net present value of respiratory generic products. It provides significant opportunities for the FDA and generic sponsors to realise the efficient approval of OINDP generics. Ultimately, reduced development time and cost inevitably provides companies with a clear and compelling competitive advantage over those who pursue the conventional BE study route.

This approach also means access to more affordable medicines, faster for many more patients.

CONCLUSION

Companies need to spend in excess of $100 million to bring any generic (AB rated) inhaled drug to the US market. The cost of a clinical endpoint BE study could be up to $45 million – with little valuable data at the end of it. The time (up to six months per study) and cost required to follow the FDA's weight-of-evidence approach for an ANDA of all OINDPs could preclude many generic respiratory, oral or nasal therapies ever reaching the market.

> "An alternative to clinical endpoint BE dramatically decreases programme costs by up to 45% and increases the net present value of respiratory generic products."

But there is a smarter, faster, cheaper, quicker, approved way. Offers such as SmartTrack, from Nanopharm, provide the critical elements required to meet the alternative requirements and eliminate clinical endpoint BE studies, accelerating and de-risking generic product development.

The outcome for organisations is a clear competitive advantage over rival companies. The outcome for patients and public health organisations is access to therapies faster and at a reduced cost.

As with all innovation, the job doesn't stop there. There are many novel developments in compliance and adherence that are being considered for this smart way of studying efficacy. And the scientists at Nanopharm are already working on alternative bioequivalence studies for delivery to the lung and nose systems for systemic delivery of higher payloads.

This journey is fascinating, exciting and full of opportunity.

ABOUT THE COMPANY

For pharma customers worldwide, Aptar Pharma is the go-to drug delivery expert, providing innovative drug delivery systems, components and active packaging solutions across the widest range of delivery routes, including nasal, pulmonary, ophthalmic, dermal and injectables. Aptar Pharma Services provides early-stage to commercialisation support to accelerate and de-risk the development journey. With a strong focus on innovation, Aptar Pharma is leading the way in developing connected devices to deliver digital medicines. With a global manufacturing footprint of 14 GMP sites, Aptar Pharma provides security-of-supply and local support to customers. Aptar Pharma is part of AptarGroup, Inc.

ABOUT THE AUTHOR

Jag Shur is the Chief Executive Officer of Nanopharm, an Aptar Pharma company. His main area of research is investigation of the bioequivalence of OINDPs. The key theme of his research has been the development and application of novel tools to understand and quantify the microstructure of OINDPs. He began his career with Profile Drug Delivery (now Philips Respironics) where he developed liquid dose drug delivery systems for cystic fibrosis patients, and later went on to work for GlaxoSmithKline. Dr Shur holds a BSc (Hons) in Chemistry, and completed his PhD at Portsmouth School of Pharmacy (UK). Following this, he was a post-doctoral fellow at the London School of Pharmacy (UK), investigating the fabrication of microparticles for vaccine delivery using supercritical fluid technology.

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HOW A DIGITAL APPROACH CAN UNPICK CLINICAL TRIAL CHALLENGES AND IMPROVE OUTCOMES

In this article, Matt Ash, PhD, Consultant Electronics Engineer, Tom Lawrie-Fussey, Digital Services Specialist, and Bastiaan De Leeuw, Head of Business Development, Drug Delivery, all of Cambridge Design Partnership, look at the role digital technology can play in the development of drug-device combination products.

Clinical studies of drug and device combinations form a critical part of drug development programmes, yet significant uncertainties can be introduced from errors related to patient use. Billions of dollars are invested each year in clinical studies for new pharmaceutical products – either new molecular entities or reformulations of existing products to address additional indications. Yet for drug-device combinations in particular, if patients have difficulty effectively administering the drug, they may not receive the therapeutic benefit.

Inhalers, for example, are notoriously difficult to use. The perception that "it seems to be a simple device to use" can mask underlying mismatches between the patient's mental use model and the actual device operation – which can result in subtle errors that have a significant effect on drug performance.

Even in closely monitored studies, such as human factors usability studies, only a qualitative assessment of correct technique is possible. And in Phase III studies, which are often unsupervised, the only chance to explain any spurious or outlying trial result is what has been recorded on the case report forms. Consequently, it is common for a number of participants to be removed from clinical trials without truly understanding how the drug was administered – and whether issues have been caused by difficulties in drug delivery device use or lack of efficacy of the drug product.

Currently within the capsule-based dry power inhaler (cDPI) space, many (early-stage) clinical study results are marred by the presence of anomalous data points. These issues, which arise because of, for example, use-related error and/or delivery variation – or at least the inefficient collection or lack of collection of data – ultimately obfuscate the true efficacy of the new drug-device combination.

A number of papers have set out the prevalence of use error across almost all inhalers, including DPIs. For capsule inhalers with similar user steps and modes of operation – such as the RS01, Aerolizer and HandiHaler – a range of specific failure modes has been identified. Some of the more significant of these are:

- Failure to insert and pierce the capsule (27% of COPD users, n=205 and 41% of asthma users, n=124)
- Failure to exhale away from the device prior to inhalation (73.2% of COPD users and 71.8% of asthma users)
- Failure to follow the correct inhalation profile (45.4% of COPD users and 53.8% of asthma users)
- Failure to hold the breath following inhalation (19.5% of COPD users and 33.3% of asthma users).[1-3]

The increased emphasis on human factors in the device regulatory pathway has given rise to enhanced levels of understanding of the interaction between patient usage and drug administration – but significant issues remain. However, new digital tools

> "The increased emphasis on human factors in the device regulatory pathway has given rise to enhanced levels of understanding of the interaction between patient usage and drug administration – but significant issues remain."

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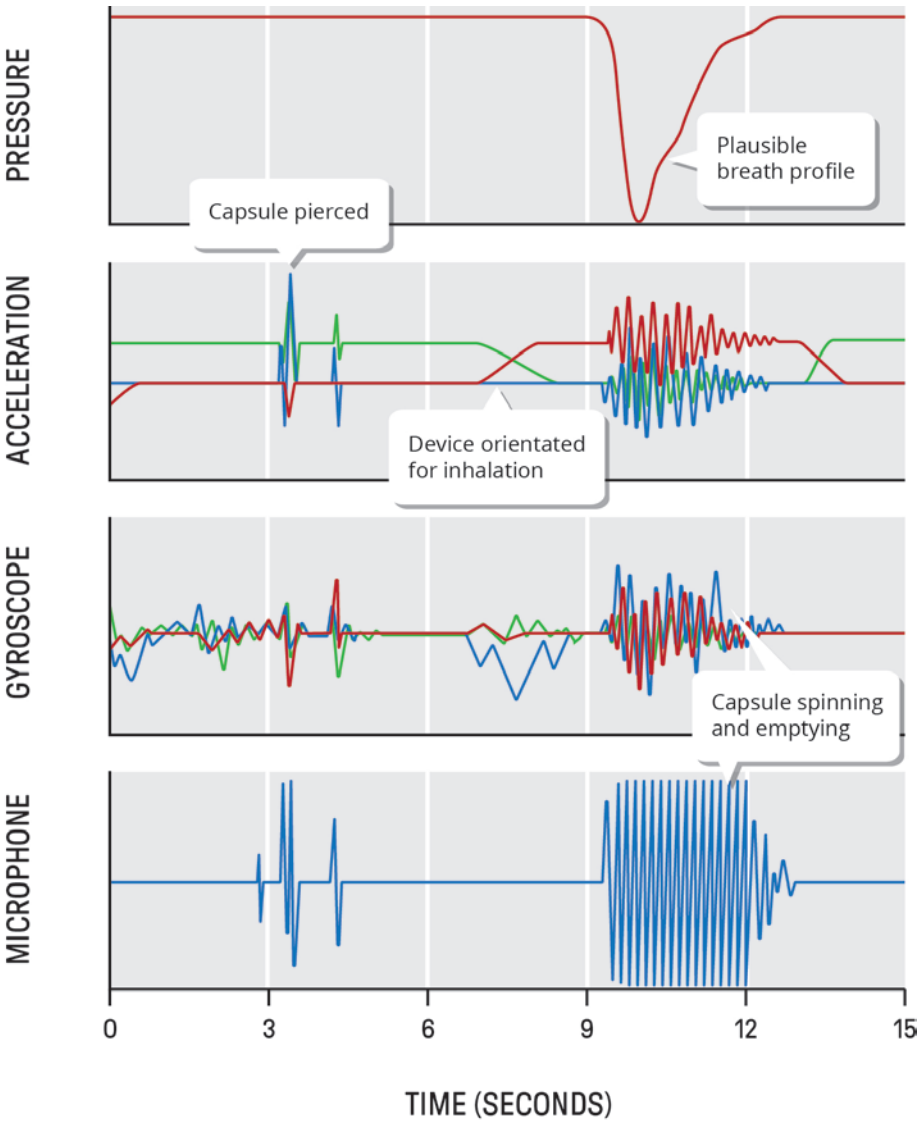

Figure 1: Readings from four different sensor types from DPI capsule loading through to completion of inhalation.

for data capture can potentially shine a light on remaining errors and provide a new opportunity to increase performance to new heights. Digital systems not only help us understand the performance of basic devices *per se* but – when used through the whole device development process – they can deliver better therapy and clinical outcomes.

"Whilst each sensor alone can provide some insight, when combined in a time-synchronised, multi-vector suite, the overall fidelity of the system is greatly enhanced."

Regulators such as the US FDA are encouraging the use of new technology to help patients use devices more effectively – for example, by providing better training and monitoring adherence. There are also opportunities to monitor supply chain performance to ensure quality and efficacy. Taken together, these innovations can certainly benefit the healthcare industry as a whole.

Connected drug delivery devices using Bluetooth Low Energy (BLE) to communicate with apps are becoming common digital solutions. But although this approach addresses some opportunities, a more holistic approach is needed to fully exploit the opportunities that digital connectivity can provide. If the "digital journey" starts by using technology to understand the patient experience better, it can then be focused on monitoring clinical trials before being refined again

"New digital tools for data capture can potentially shine a light on remaining errors and provide a new opportunity to increase performance to new heights."

in the final device. This approach has the benefit of ensuring that only the most effective digital enhancements find their way into the final product, whilst the clinical trials are supported with a new level of digital monitoring.

This opportunity involves adapting the latest, ever-growing suite of miniature low-cost sensors and device connectivity options that have been developed for the wearable devices industry, to gain a more detailed understanding of actual patient use of devices. Such quantified user insights provide an invaluable additional perspective over conventional human factors approaches.

Simply adding an array of the latest sensors is not enough. Usually more is gained from a data fusion approach. By equipping the device with a carefully chosen combination of sensors – probably more than would ever be included in a final commercial product – it is possible to create a much more accurate and robust assessment of actual patient use. For example, Figure 1 shows readings from four different sensor types through the complete patient experience of a DPI, from capsule loading through to completion of inhalation. Whilst each sensor alone can provide some insight, when combined in a time-synchronised, multi-vector suite, the overall fidelity of the system is greatly enhanced.

With suitably equipped devices, formative user studies can be used to assess potential devices and make minor modifications to optimise performance within time and budget constraints.

Once a well-informed device choice is made and the key points of weakness are identified, a subset of sensors can be carried over into clinical trials to identify those patient datasets where it is clear they were unable to self-administer the drug successfully. Although these sensing techniques do not solve the issues of patients who are unable to use the device, the

approach does enable a more informed conclusion with regards to drug efficacy, where patient outcomes can be linked back to successful administration procedures.

It's important to remember, though, that in trials the stakes are high. The instrumented devices must, of course, be reliable and behave exactly like the native device, such that they don't introduce new and unforeseen errors in patient interaction, technique or device misfunction – and regulators will need proof that this is the case. Creating a technology solution that captures and measures the complete sequence of events enables a far more granular and detailed picture of patient usage to be analysed. Also, by using a multitude of different sensor types, the conclusions drawn from a trial can be shown to be robust.

By this stage in development, the digital approach will have facilitated a much more detailed understanding of how patients interact with and use a device and how this influences drug performance. This creates a clear view of the value of digital aids in the final device offer, be they for training, monitoring or avoiding user errors.

A development programme that starts with comprehensive monitoring of formative testing enables a better understanding of patient device interaction and ensures that costly clinical trials are more informed and can be better designed. A subset of sensors can then be used to monitor the clinical trials devices to build additional knowledge and to ensure the data collected is due to the drug effect and not impaired by poor patient compliance or administration.

A small number of sensors may remain in the final device that goes to market. These will then have proven value in assisting the patient and the healthcare team to deliver the most effective therapy possible – maximising the value of a new drug launch and ensuring new lifesaving therapies make it into the hand of patients who need them.

ABOUT THE AUTHORS

Matt Ash is an experienced electronics engineer with proven cross-sector design experience, including medical, consumer and transport. In previous roles, he has delivered RF sensor and analogue electronics designs, and associated signal processing algorithms to enable clients to bring world-leading products to market. Coupled with experience in designing safety critical medical devices to meet ISO 60601 standards, Dr Ash is uniquely positioned to help clients deliver the next generation of disruptive electronic devices. He holds a PhD in Electronic Engineering, specifically on the topic of high-resolution phased array radar. An expert in his field, he has over 20 journal publications, and is a reviewer for the Institute of Electrical and Electronics Engineers (IEEE) journal, Sensors.

Tom Lawrie-Fussey has more than 15 years' product development experience and is a Chartered Engineer with a master's degree. After graduating, he worked for a major automotive company, specialising in developing innovative, real-time modelling techniques to enable dynamic testing of vehicle electrical systems. Since moving into a consultancy role, Mr Lawrie-Fussey has worked with a variety of global automotive, aerospace and motorsport clients. He now focuses on connectivity innovation for consumer, healthcare and industrial applications – creating patents involving low-cost, power-smart, ubiquitous devices. He has led the commercialisation of these ideas – culminating in a number of trials and licence agreements.

Bastiaan De Leeuw has been active in the field of drug delivery for the last 20 years. He has led projects covering dry-powder formulation development, inhaler design and development, and autoinjector design and development, as well as the associated stages of clinical and regulatory evaluations. In addition, he led the initial clinical evaluation of urologic diagnostic tests at NovioGendix (now MDxHealth) and has worked at Focus Inhalation, Akela Pharma, Oval Medical and Bespak. Mr De Leeuw has a degree in biopharmaceutical sciences, focusing on polymeric drug delivery systems for formulation of proteins and peptides. His research combined pharmaceutical technology and pharmacology in industry-sponsored projects.

ABOUT THE COMPANY

Cambridge Design Partnership is an independent innovation partner that designs and engineers drug delivery systems, as well as diagnostics, surgical equipment and other health-related products. It has completed more than 1,000 product development assignments for businesses around the world.

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PATIENT SAFETY: KEY DRIVER TO PRESERVATIVE-FREE NASAL SPRAY DEVELOPMENT

In this article, Benoît Guillard, Product Development Leader, Pascale Farjas, Global Category Manager – ENT, and Audrey Chandra, Global Category Manager – Inhalation and Dermal, all of Nemera, look at the effects of preservatives in nasal sprays, and the challenges and advantages of delivering preservative-free nasal spray drugs.

Current challenges in treating patients who suffer from chronic diseases have encouraged pharmaceutical companies to continue innovating to tackle the problems encountered by patients. The quality of life of these patients depends highly on their clinical outcomes, which are based on their adherence to the prescribed treatment as well as on the efficacy of their treatment.

The adverse effects of treatment may affect patient compliance. For example, the use of preservatives in a nasal spray may affect patient adherence due to its risks and possible side effects. Innovation in nasal delivery therefore becomes a crucial need for patient safety. By using a preservative-free nasal spray on a daily basis, patients should worry less about the adverse effects of their treatment – which therefore encourages better patient compliance.

THE EFFECTS OF PRESERVATIVES IN NASAL SPRAY

If we take a closer look at nasal drug products delivered through a device for chronic diseases, it mainly concerns locally acting drugs for allergic patients – i.e. nasal sprays. The nasal mucosa plays an important role in mediating immune responses to allergens and infectious particles which enter the nose. It helps prevent allergens and infections from invading the nasal cavity and spreading to other body structures – for example, the lungs.

The nose cavity is lined with a type of epithelium where cells arrange themselves in columns and project tiny hairs called cilia which contain mucus-producing cells (goblet cells). Different types of preservative found in nasal sprays may have different undesirable side effects on the physiology of the nose cavity, which are observed in various studies.

However, the use of preservatives in nasal sprays has become controversial. Some argue that a certain amount is well tolerated by patients, whereas others state that they might increase the risk of adverse events for patients. For instance, an *in vitro* study shows that benzalkonium chloride (BAC) can cause ciliotoxicity (impaired ciliary activity) of the nasal mucosa – and therefore nasal irritation.[1]

In a wide range of clinical trials, which used mostly nasal sprays containing BAC, various adverse effects have been observed. These side effects include increased mucosal swelling and nasal hyper-reactivity, type IV hypersensitivity, decrease of mucociliary clearance, and nasal mucosa dysplasia. On the other hand, some clinical studies claim no effect on ciliostatic and no toxic effect.

> "Different types of preservative found in nasal sprays may have different undesirable side effects on the physiology of the nose cavity."

Although the use of preservatives in nasal sprays is debatable, risks have

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been reported by different studies and, consequently, the European Medicine Agency (EMA) recommends zero BAC in nasal sprays. In fact, the German Federal Institute for Drugs and Medicinal Devices (BfArm) has proposed that BAC is removed from intranasal products in Germany because of concerns about mucociliary effects.[2] Keeping in step with the regulatory trend, and applying the precautionary principle for patients, Nemera has developed preservative free approaches.

KEY BENEFITS OF ADVANCIA® PF WITH PUREFLOW TECHNOLOGY

Driven by the regulatory recommendations for preservative-free formulations in nasal sprays, as well as the desire to protect patients from adverse events, a technology breakthrough is a fundamental requirement when designing a preservative-free drug delivery device. Instead of using preservatives, an alternative way of keeping a nasal spray sterile is by preventing bacteria entering and contaminating the drug formulation.

Nasal sprays can be contaminated through their drug delivery orifices, with bacterial contamination coming from the external environment or the patient. A mechanical closing tip ensures that no contamination can be introduced in the nasal spray orifice after the spray has been dispensed.

To prevent contamination via air entering the device, most commercialised nasal sprays use a filter system which stops the entry of bacteria into the container. Airborne bacteria are typically around 0.3 µm. However, other smaller bacteria are present.[3] Furthermore, recent studies have demonstrated that bacterial transfer through the membrane structure takes place during filtration operations, even if the pore size is significantly smaller than the bacteria size.[4]

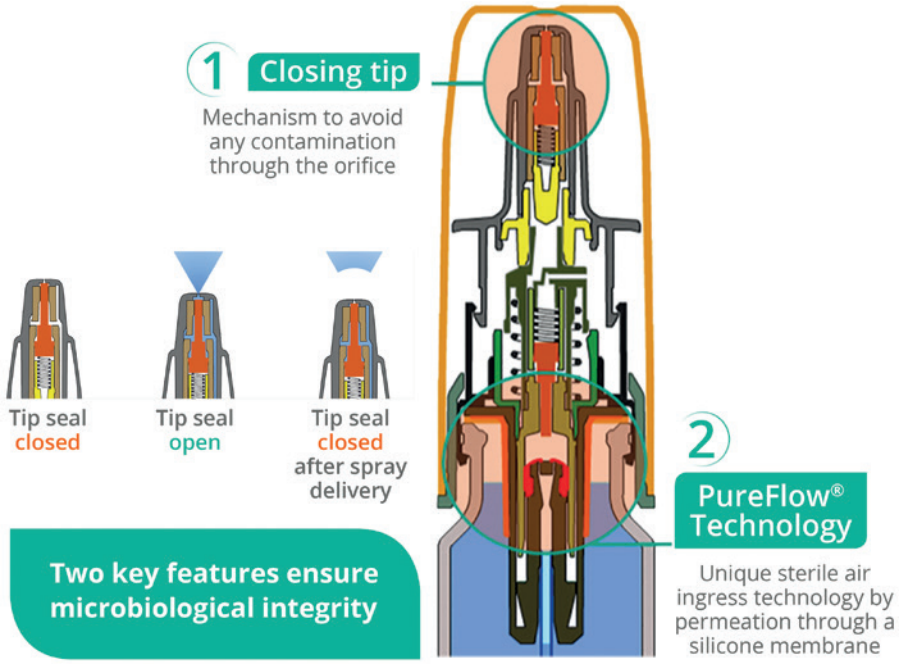

Figure 1: Advancia® PF illustration.

> "Recent studies have demonstrated that bacterial transfer through the membrane structure takes place during filtration operations, even if the pore size is significantly smaller than the bacteria size."

Nemera has introduced an alternative to filters for the Advancia® PF (Figure 1) nasal spray – using a silicone membrane to filter the returning air. The intake of air into the dispenser takes place via a venting system with a silicone membrane called PureFlow technology (Figure 2). This patented technology has a continuous barrier of homogenous material which allows air to diffuse through the silicone, which acts as a permeable membrane. Consequently, the continuous barrier guarantees the microbial integrity of the drug.

The venting system filters the intake of air using a very fine membrane manufactured from silicone polymer. The silicone membrane is a solid, non-porous material. As it is homogenous and does not contain any holes, it can be precisely engineered. The membrane's intermolecular distance is of the order of nanometres – allowing the passage of air through the membrane but completely preventing the passage of any liquid or solid particle, including bacteria, due to the silicone membrane structure where the size is smaller than 0.3 µm.

The function of the silicone membrane can be compared to an inflated balloon. The balloon is a continuous, waterproof material yet gas slowly passes through the wall of the balloon until the pressures inside and outside reach equilibrium. Devices that use this technology can be

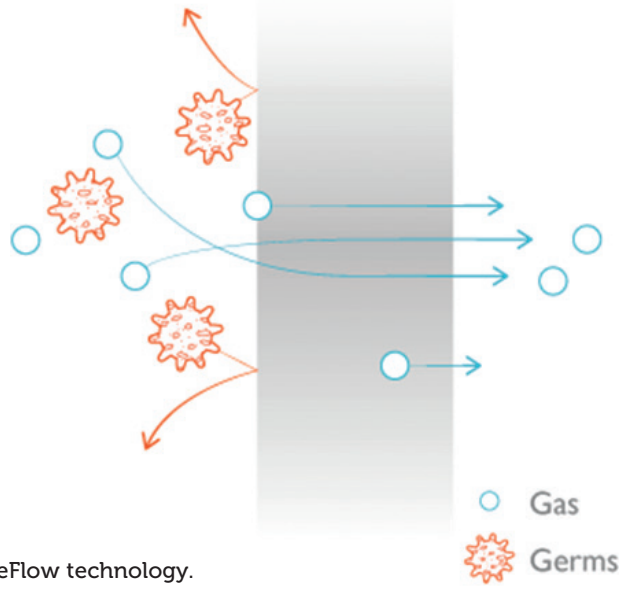

Figure 2: PureFlow technology.

tested individually in-line as a consistent part of the manufacturing process to ensure robust quality standards. This provides an even greater assurance of safety for patients.

Moreover, Advancia® PF offers a patented anti-clogging actuator in the upper part of the system, called closing tip. This mechanism ensures that no contamination can enter through the actuator orifice, which therefore provides protection from crystallisation and clogging issues, and avoids evaporation to guarantee good prime retention.

PERFORMANCE EVALUATION OF ADVANCIA® PF

To assess the performance of Advancia® PF, the microbial integrity has to be evaluated by two common practice methods.[5,6] The first standard contamination test is done by immersing the applicator inside a contaminated petri dish. The second test uses a contaminated air suspension which contains bacteria. These tests are used to verify the performance of the nasal spray; to prove whether or not the formulation inside the nasal spray is contaminated after repeated spray actuations.

The closure venting integrity test (Figure 3) is done by using *Bacillus subtilis* with a concentration between 10^8 and 10^9 CFU/g on an anti-static spherical aerosol size of a few µm. The test protocol requires nutritious sterile solution and the test has to be done on 20 samples.

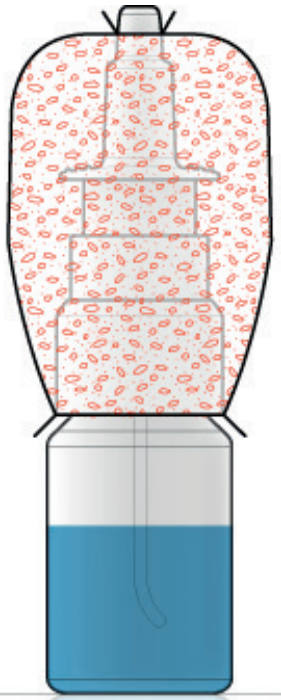

Figure 3: Closure venting integrity test.

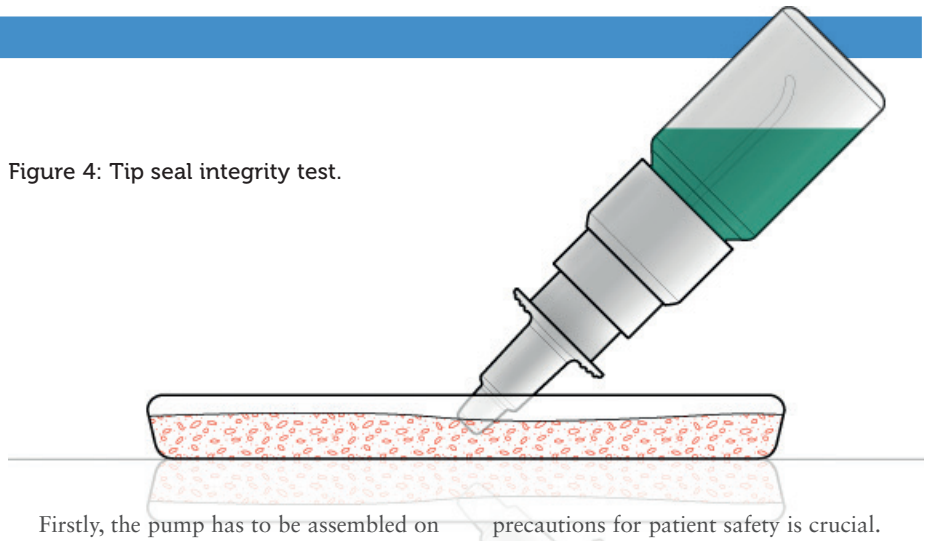

Figure 4: Tip seal integrity test.

Firstly, the pump has to be assembled on a bottle. Then, the sterility of the assembly must be checked after the assembly of the device, before exposure to the bacteria, with an incubation conducted for several days at more than 30˚C. Finally, an elastomeric sleeve has to be put around the pump and vial, and the gap between the pump and the vial is filled with the contaminated powder. The sleeve is sealed to the pump and vial. The pumps are actuated a number of times and the sterility of the nutritious solution is checked, with incubation for several days at more than 30°C. The test will therefore show whether the solution is contaminated or not.

The second contamination test is called a tip seal integrity test (Figure 4) and uses *Pseudomonas aerugiosa* with a concentration of 10^7 CFU/ml in a sterile peptone water solution inside a petri dish. The test is also done on 20 samples. The pump is assembled on a bottle filled with peptone water and incubated for several days at more than 30˚C to check the microbial contamination of the device following assembly and before exposure to the bacteria. Over the course of eight days, the pumps are actuated a number of times – with the orifice tip of the nasal spray immersed in a contaminated solution – and some sprays are collected in a petri dish to evaluate contamination of the spray. This test is done to check if the spray has any microbial load.

All 20 pumps of Advancia® PF with PureFlow technology passed both the tests – the closure venting integrity test and the tip seal integrity test – since no bacterial ingress in the container or on the tip was observed.

ENSURING PATIENT SAFETY THROUGH ADVANCIA® PF

Patients should be the key driver for innovation breakthroughs as patient safety should be the number one priority. Understanding what are the pain points for the patient is an important element in nasal spray development. Implementing different precautions for patient safety is crucial.

In the case of patients using nasal sprays daily over several weeks – for instance, to relieve allergy symptoms – it makes sense to keep preservatives away from the formulation to avoid adverse effects such as nose irritation. Applying this precautionary principle for patients, Nemera has therefore developed Advancia® PF to deliver preservative-free nasal spray drugs, as well as to keep up with the regulatory trend.

ABOUT THE COMPANY

Nemera is one of the world's leading designers, developers and manufacturers of drug delivery devices for the pharmaceutical, biotechnology and generics industries. It uses different types of business model including full solution development, pure contract manufacturing and customised solutions.

Nemera's areas of expertise include numerous modes of delivery: parenteral, nasal, buccal, auricular, ophthalmic, pulmonary, dermal and transdermal. The company has more than 150 engineers working in development, sales in 47 countries, over one billion devices produced yearly, and more than 1,950 employees.

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ABOUT THE AUTHORS

Benoît Guillard graduated at the National Institute of Applied Sciences of Lyon (France) and studied at the Trinity College of Dublin (Ireland). He holds a double master degree in mechanical engineering and in biomechanics. After several experiences with product development leadership role in the medical and pharmaceutical industry, he joined Nemera in 2014, where today he leads teams of engineers for the development of new nasal drug administration systems, within Nemera's Insight Innovation Center. In his role he contributed to the commercial launch of Advancia® and he is now focused on Nemera nasal product line extension and customer product developments. He has a successful track record of marketed drug delivery systems and medical devices, and an in-depth knowledge of these high technology product development, their large-scale production and the associated pharmaceutical industry regulation.

Pascale Farjas is the Global Category Manager for the ENT (ear, nose, and throat) segment at Nemera. Her role encompasses understanding patients' 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 Master 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.

Audrey Pamila Chandra joined Nemera in February 2019 as the Patient Media Watch Analyst and has now become the Global Category Manager for the Inhalation and Dermal segment in Nemera. She believes that the ease of use of the device plays an important role in patient quality of life. She is in charge of identifying the pain points and the unmet needs of the patients, and also accompanying product development in parallel. Ms Chandra graduated from the Faculty of Medicine in Indonesia and she pursued her Master studies in Strategy and Business Development in Toulouse School of Management, France.

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CounterAct

WHEN EVERY SECOND COUNTS...

In this article, Todd Pizitz, PhD, and Donald Mealing, Co-Founders of CounterAct, look at efforts to reduce the number of opioid-related deaths in the United States.

In emergency medicine, seconds can be the difference between life and death. The average response time for emergency medical responders is estimated to fall between eight and 14 minutes, with rural areas having longer wait times.[1] When first responders are not emergency medical personnel, having immediate access to rescue medication becomes a necessity to reverse the effects of an opioid overdose.

> "Mishandling, or easy access to opioids in a household, have led to an increase in overdose reactions."

According to the US Centers for Disease Control and Prevention (CDC), more than 47,000 people died from opioid-related deaths in the US in 2017. The estimated death rate of 130 people daily due to opioid overdoses continues without much relief. In fact, accidental ingestion of opioid medication resulting in an overdose death accounts for an estimated 40% of all the opioid overdose deaths.[2] This includes family members of a patient with an opioid prescription.

Mishandling, or easy access to opioids in a household, have led to an increase in overdose reactions. Khan, Bateman and Landon[3] found that individuals with family members who had been prescribed opioid medication were nearly three times more likely to report an opioid overdose that resulted in a hospitalisation compared with individuals whose family members were not receiving any sort of opioid prescriptions.

> "Efforts to reduce the opioid crisis have included reducing the number of opioid prescriptions written, educating the public about the dangers of opioid, and increasing the availability of opioid reversal medication."

The CDC calculates that nearly 200 million opioid prescriptions are written annually and that number has been slowly decreasing. Efforts to reduce the opioid crisis have included reducing the number of opioid prescriptions written, educating the public about the dangers of opioids, and increasing the availability of opioid reversal medication Naloxone. The US Surgeon General even recommended the public carry naloxone to help reduce the deaths associated with opioids.

Naloxone is marketed as a generic medication to treat opioid overdoses, and brand names such as Narcan and Evizo have emerged as US FDA-approved naloxone-based medications to counter the effects of an opioid overdose. Unfortunately, although these two FDA-approved formulations of naloxone are available for public use, the overdose death rate from opioid overdoses has not significantly declined.

Efforts to make naloxone more available have emerged from the US legislative arena, with lawmakers pushing for co-prescription laws mandating prescribers who write opioid medications to also consider prescribing naloxone formulations and

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Figure 1: The CounterAct Cap.

mandating the co-prescription if any of the three co-prescription criteria are present:

1) A patient receives a prescription for an opioid medication that has a 90 mL morphine equivalent
2) The prescriber suspects a potential for abuse of the opioid medication or the patient has a history of substance abuse
3) The opioid medication is also prescribed with a benzodiazepine.

In September 2018, California passed a co-prescription law mandating prescribers to co-prescribe naloxone with opioid medications. Other states are following the same pathway to co-prescription of naloxone with opioids.

To increase speed of access and wider availability of naloxone, the CounterAct Cap was designed (Figure 1). It places a single-unit-dose of Naloxone on top of the container holding an opioid patient's prescription pills. In a suspected overdose emergency, a patient's family members, friends or associates can instantly administer the naloxone spray after calling 911, thus saving precious time.

The safety cap twists off to reveal a folded nozzle that is easily extended. Once the nozzle is fully extended, it can be placed into the overdose victim's nose and the spring-loaded trigger can be pressed to instantly release a 4 mg dose of naloxone to the victim (Figure 2). The idea behind the CounterAct Cap was also that having the two medications paired together would act as a reminder of the necessity of prescriber compliance – and that mismanagement and abuse of opioid medication can lead to death.

The specific features of the CounterAct Cap include an integrated system of opioid medication housed in a pill container and a 4 mg dose of naloxone located on top inside the CounterAct Cap. The bright-red colour of the cap is designed to help with visually locating the cap. CounterAct has also developed a Smart Cap that has a connectivity component to increase the likelihood of locating the naloxone formulation when an opioid overdose has occurred.

CounterAct is at the beginning of its FDA 505(B)(2) regulatory path as a drug-device combination product. The company has been collaborating with major drug and device manufacturers and investors to bring the CounterAct Cap to market.

Figure 2: The spring-loaded trigger can be pressed to instantly release a 4 mg dose of Naloxone to the victim.

ABOUT THE COMPANY

CounterAct is comprised of Co-Founders Todd Pizitz and Donald Mealing. The company has completed its pre-IND meeting with the FDA and has a developmental regulatory pathway mapped out – a 505(B)(2) regulatory path as a drug-device combination product. Counteract has filed both national and international non-provisional patents.

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ABOUT THE AUTHORS

Todd Pizitz, PhD, is a licensed clinical and forensic psychologist in private practice. As a forensic psychologist, Dr Pizitz works with those afflicted with various types of addiction. For the past 17 years, he has worked closely with private and public defence attorneys, family court services, the US District Attorney's Office, County Adult and Juvenile Probation, and Federal Probation.

Don Mealing is an entrepreneur with more than 25 years' experience as a Chief Executive Officer in a variety of successful businesses. He was Founder and Chief Executive Officer of American Corrective Counseling Services, one of the largest private counseling diversion companies servicing courts and prosecutors across the US criminal justice system. Mr Mealing has served on numerous boards, including 14 years on the board of Regents, Harris Manchester College, Oxford University (UK), Mr Mealing has lost three close relatives to opioid overdose.

hcmed
Nebulize High Value Therapeutic Drugs

ENHANCING INHALATION THERAPY BY REINTRODUCING ANTIBIOTICS USING MESH TECHNOLOGY

In this article, Edgar Hernan Cuevas Brun, Marketing Manager at HCmed Innovations, looks at how the administration of some old antibiotics could be a valuable response to fight infections.

The last three decades have seen a slow movement when it comes to the development of new antibiotics. Different reasons can be attributed, mostly involving regulations governing drug approval, market forces and scientific bottlenecks.[1] As a result, a new antibiotic resistance era was confirmed in 2015, and it has not been brought under control so far. There is no doubt that there is a need for new antibiotics. However, in the meantime, clinicians around the world have started to reappraise the use of antibiotics that have not been used for a long time – colistin being one of them.[2]

> "Clinicians around the world have started to reppraise the use of antibiotics that have not been used for a long time – colistin being one of them."

REINTRODUCING COLISTIN

Colistin, also known as polymyxin E, is an antibiotic that belongs to the polymyxin class and is mostly effective against Gram-negative bacilli.[3] It was discovered in 1949 and initially used in Japan, Europe and the US in the 1950s.[4] Its usage was eventually reported to cause nephrotoxicity. Consequently, its application was largely reduced only 20 years after its discovery.

In recent years, colistin has regained the interest of clinicians and scientists alike, leading to the need for a deeper understanding of the pharmacodynamics, pharmacokinetics and toxicodynamics of this old antibiotic to properly set the right administration regimens.[5,6]

For patients suffering from cystic fibrosis, colistin has become an important tool to fight infections. At the same time, the critical practice guidelines from the Infectious Diseases Society of America and the American Thoracic Society have also cited the administration of inhaled colistin to treat ventilator-associated pneumonia.[7] Nowadays, finding the most efficient and effective pathways to deliver colistin is undoubtedly a top priority for the reintroduction of this drug.

INHALATION THERAPY: MESH NEBULISERS

Inhalation therapy has mainly been associated with the treatment of respiratory diseases. Metered dose inhalers, dry powder inhalers and nebulisers are among the most commonly used devices to treat diseases that affect the respiratory system. Invented in the early 1990s, mesh nebulisers have gradually attracted pharmaceutical companies to evaluate the delivery of inhalation drugs. They are a type of nebuliser that has been praised for providing a better performance while improving conditions of usage.[8,9]

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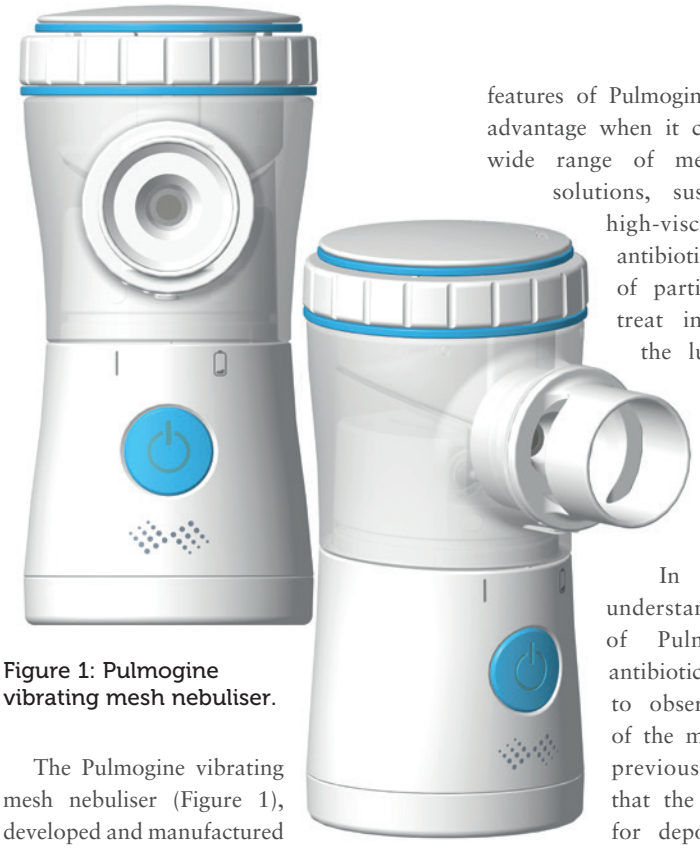

Figure 1: Pulmogine vibrating mesh nebuliser.

The Pulmogine vibrating mesh nebuliser (Figure 1), developed and manufactured by HCmed Innovations, aims to improve the efficiency of drug delivery. Pulmogine has been designed based on a customisable platform intended to improve diverse parameters. The tailoring features of Pulmogine provide it with an advantage when it comes to delivering a wide range of medications, including solutions, suspensions, biologics, high-viscosity drugs and antibiotics – the last one being of particular importance to treat infectious diseases in the lungs and under the scope of the study in this article.

> "The tailoring features of Pulmogine provide it with an advantage when it comes to delivering a wide range of medications."

DELIVERING ANTIBIOTICS

In order to further understand the capabilities of Pulmogine to deliver antibiotics, colistin was used to observe the performance of the mesh nebuliser. It had previously been reported that the optimal particle size for deposition in the lungs is between 1 and 5 µm.[10] Different concentrations of colistin were aerosolised during the study to identify any meaningful variabilities. Nonetheless, it is relevant to point out that appropriate prescriptions are indispensable to effective treatment and also to avoid major side effects.

Throughout the series of tests, standard indicators were measured to examine aerosol characteristics. The conducted tests demonstrated that mass median diameter (MMD) remained between 3.578 and 3.996 µm even after quadrupling the initial concentration, while the fine particle fraction (FPF) remained above 58% at all times.

Moreover, the output rate was also seen to stay high, although there was a more considerable decrease when the concentration of colistin was increased. The summary of the mean values obtained from the tests performed with three devices is displayed in Table 1.

Colistin Conc. (mg/mL)	MMD (µm)	FPF (%)	Output Rate (mg/min)
16.7	3.578	63.85	0.493
33.4	3.647	63.39	0.407
50.1	3.755	61.39	0.347
66.8	3.996	58.82	0.280

Table 1: Mean Pulmogine performance values when aerosolising different colistin concentrations.

CONCLUSION

Given recent concerns caused by antibiotic resistance, the administration of some old antibiotics has become a valuable response to fight infections. When it comes to respiratory infections, inhalation therapy can be used as a primary pathway of treatment by using new technologies that are able to increase the efficiency of drug delivery. The platform offered by Pulmogine is a clear example of advancements.

ABOUT THE COMPANY

HCmed Innovations was founded in 2014 and completed the development of its first-generation portable mesh nebulisers in less than five years. Since 2017, its medical device has successfully received regulatory approvals in Europe, Taiwan, Brazil and Indonesia. Currently, HCmed also collaborates with one of the world's top pharma companies in Brazil. In the future, HCmed plans to build up its manufacturing facility in Wuxi, China, to co-operatively expand into China's large healthcare market.

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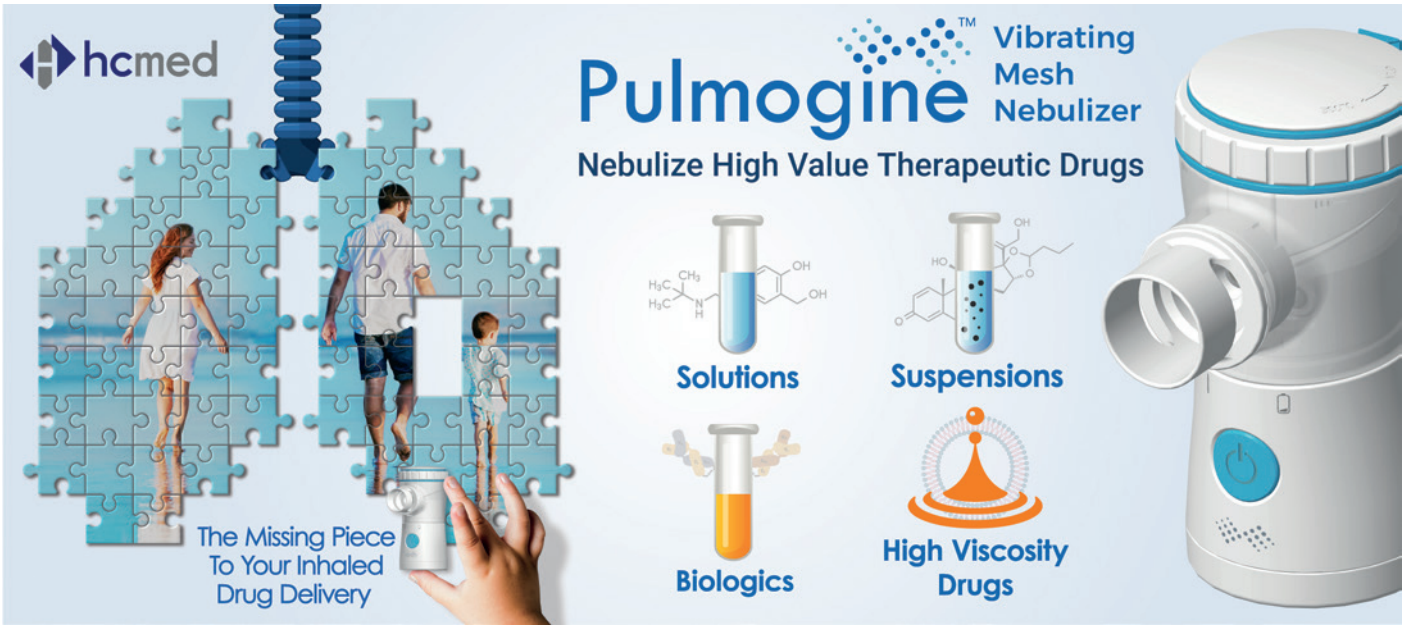

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REDUCING VASCULAR MORTALITY IN PATIENTS WITH SUSPECTED ACUTE MI

In this article, Mark Stansfield, Senior Project Manager, and Kambiz Yadidi, Founder and Chief Executive Officer, both of Otitopic, discuss initial results of their pilot Phase I clinical study of dry powder inhalation of aspirin for the treatment of acute myocardial infarction.

Dry powder aspirin inhalation company Otitopic is currently conducting its pilot Phase I clinical study – "*A Phase I, Single-dose, Open-label, Pilot Study to Compare the Pharmacodynamics and Pharmacokinetics of Acetylsalicylic Acid Inhalation Powder with Non-Enteric-Coated Chewable Aspirin in Healthy Adults*".

The level of activity and data observed with the dry powder inhalation of aspirin has been encouraging. At the first on-treatment assessment, all subjects demonstrated 100% inhibition on platelet aggregation in two minutes. All subjects reached a complete 100% arachidonic acid (AA) response in two minutes. In addition, the dry powder inhalation of aspirin continued to demonstrate a satisfying therapeutic and safety profile.

Aspirin is an anti-platelet medicine, which means it prevents blood clotting as easily due to inhibition of platelet function. Platelet aggregation was measured with AA as the platelet aggregating agent (platelet agonist) using light transmittance aggregometry (LTA). When an agonist is added, the platelets aggregate and absorb less light; an increase in transmission occurs and this reaction is detected by the photocell.

Within two minutes of inhalation (37 mg emitted dose), the percentage of platelet aggregation fell below 5% for all subjects. Up to 20 minutes after ingestion, percentage aggregation remained high for some subjects.

Asprihale is a proprietary dry powder inhalation of aspirin formulation delivered via a portable dry powder inhaler. It is designed to be carried by high-risk patients, like an EpiPen. Once the US FDA grants approval, the rapid onset of action indicates a promising role for Asprihale in the treatment of acute thrombotic conditions such as stroke and heart attack.

> "This new method of delivery will allow those at risk to receive the benefits of aspirin without the side effects."

A study conducted by researchers at Harvard University (Cambridge, MA, US), and published this year in JAMA Neurology, found that taking "baby aspirin" is linked to an increased risk of bleeding within the skull for people without heart disease. This prompted the American College of Cardiology and American Heart Association to change their guidelines. The Harvard study presents how at least 29 million people taking daily aspirin should review the guidelines.

Although people without a history of heart problems shouldn't take daily aspirin, it's still recommended for heart attack survivors. Otitopic will seek to persuade the FDA to recommend Asprihale as a pocket-sized rescue drug device delivery system that is easy to use at the time of myocardial infarction (MI) symptoms. High-risk individuals can rapidly inhale Asprihale, and benefit from having rapid onset of action and therapeutic effect.

"TIME IS MUSCLE" DURING MI

The longer the infarct time, the greater the ischaemia and subsequent necrosis of the myocardium. This new method of delivery will allow those at risk to receive the benefits of aspirin without the side effects.

Otitopic believes that the clinical benefits the Asprihale trial has yielded thus far, and the data linking this antiplatelet activity through dry powder inhalation responses, support and confirm

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the mechanism of action and our approach. Otitopic will continue working to advance the clinical study to improve the lives of high-risk patients and individuals who need better treatment options at the time of MI.

The team is excited and looking forward to starting its Phase III clinical trial.

ASPRIHALE CLINICAL RESULTS HIGHLIGHTS

Efficacy data from the evaluable subjects based on AA results:

- All subjects achieved complete AA-induced platelet aggregation inhibition within two minutes (first blood sample timepoint), demonstrating consistent, never-seen-before performance
- These subjects have shown superior AA-induced platelet aggregation response compared with chewable (therapeutic effect 10 times faster than chewable aspirin)
- Platelet aggregation inhibition achieved with 37 mg emitted dose of proprietary aspirin formulation.

ABOUT THE ASPRIHALE CLINICAL STUDY

The Asprihale clinical study, conducted in the US, is an open-label, pilot Phase I trial to assess the PK/PD of aspirin inhalation powder in healthy volunteers, 18-55 years of age.

Platelet aggregation with AA as the platelet agonist using LTA was measured at 10 timepoints.

Pharmacokinetic (ASA and salicylic acid) and PD (adenosine diphosphate- and collagen-induced platelet aggregation inhibition, thromboxane B2 and 6-keto-PGI1α) results are yet to be announced.

ABOUT THE COMPANY

Otitopic is a clinical-stage dry powder inhalation of aspirin company with a track record of success in pharmaceutical product drug delivery and drug device development. Asprihale is a proprietary dry powder inhalation of aspirin formulation delivered via portable dry powder inhaler that is expected to enter the bloodstream faster than oral tablets at the time of MI.

Otitopic is on track with Asprihale to file a US NDA for a novel drug-device combination product in rescue management of suspected acute MI. Otitopic is committed to providing high-risk MI patients with a faster alternative for management of suspected MI. The company is currently assessing non-small-cell lung cancer as an additional indication to the MI indication therapy.

ABOUT THE AUTHORS

Mark Stansfield is Senior Project Manager at Otitopic, with more than 11 years' experience in the development of respiratory medicine and oral drug formulations. He has extensive product development and manufacturing experience, including products for the treatment of asthma, chronic obstructive pulmonary disease, cancer and acute thrombotic conditions such as heart attack and stroke.

Kambiz Yadidi, Founder and Chief Executive Office of Otitopic, is an accomplished entrepreneur in the healthcare industry, is the inventor of the underlying technology for the Asprihale product. With over 28 years of experience, he has created and helped small to medium sized businesses evolve into valuable and enduring companies that have made a difference in the healthcare market. Prior to OtiTopic, he was the founder and Chief Executive Officer of several successful healthcare businesses including Pharmalink Pharmaceutical Inc, Medquip Inc (recently sold to Drive Medical), Respitouch Inc, and General Home Pharmacy, where he created the trademarked brand Sinus Dynamics.

MANUFACTURING DPIS: CASE STUDY OF IMA ADAPTA® WITH BOEHRINGER INGELHEIM SPIRIVA®

In this article, Pietro Piera, Product Manager for Capsule Fillers, IMA Active division, and Rainer Bauer, Automation Engineer, Boehringer Ingelheim, investigate the optimal process parameters for low-dose dry powder inhalers achieved by dosator technology, presenting a case study in which IMA's capsule filler, Adapta®, is used to fill Boehringer Ingelheim's Spiriva® (tiotropium) dry powder inhaler.

In 1948, the first commercial dry powder inhaler (DPI) device was launched on the market. This first technology seems archaic by today's standards: a deep inward breath would cause a ball to strike a cartridge containing powder and shake the powder into the airstream. Since then, changes in the drug delivery market and regulatory pressures have driven innovation of DPIs forward.

> "The key to achieving optimal filling and control of low-dose dry powder for inhalers is combining the dosator technology and the direct gravimetric net weight control."

It is estimated by the WHO that, worldwide, some 300 million people suffer from asthma and 240 million people suffer from chronic obstructive pulmonary disease (COPD). DPIs represent 50% of the total asthma/COPD market by value worldwide. The latest patient-focused studies using DPIs indicate that the expectations regarding this technology have evolved. Patients and pneumologists are now increasingly focusing on convenience and ease of use, favouring a compact design. Indeed, DPIs have shown great promise in their ability to deliver drugs reliably and effectively, and novel designs can ensure that future cost, compliance and safety challenges are overcome.

> "Patients and pneumologists are now increasingly focusing on convenience and ease of use, favouring a compact design."

Some of the performance characteristics essential to DPIs are related to dose delivery, fine particle fraction content and performance levels at varying airflows. These characteristics can differ from one powder formulation to another, and some fine tuning of either device or formulation – or a combination of both – may be necessary to achieve optimal performance. Micro-dosing DPIs takes this challenge to extremes.

When producing pharmaceutical products for DPIs, industrial manufacturing aspects must be considered together with optimisation of the process to achieve a reliable control method. Achieving precise micro-dosing, gravimetric weight control, containment measures and ease of device assembly are typical challenges which could be faced.

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IMA draws on its expertise to provide advanced solutions for DPI processing and capsule filling. For example:

- Direct weight control is performed in-line on each single capsule, both before and after filling.
- Absence of mechanical powder compression for improved airway intake.
- Accurate micro-dosing and automatic feedback and adjustment.

In this article, we investigate optimal process parameters for low-dose DPIs achieved by dosator technology. We show that a major advantage of using dosators for processing DPIs is that they can be accurately adjusted without any need to compress or aspirate the powder.

CASE STUDY: SPIRIVA® PRODUCTION

The aim of the study was to explore the best process parameters to achieve a 5.5 mg dose of a powder mix including a lactose carrier, and long-acting brochodilator tiotropium bromide, which Boehringer Ingelheim markets as Spiriva®.

Boehringer Ingelheim initially carried out the process on various different capsule filler types and then optimised it thanks to IMA capsule filling machine model Adapta® 100 (Figure 1) with 100% gravimetric net weight control.

Figure 1: Adapta® 100, IMA's dosator capsule filling machine with 100% gravimetric net weight control.

Materials

Components of the case study are:

- Blend of lactose-based carrier and tiotropium bromide (Spiriva®)
- Adapta® 100 – an industrial-scale production capsule filler implementing dosator needle technology together with gravimetric 100% net fill weight checking system with scales resolution < 0.01mg.

Methods

The first steps of the study were conducted by Boehringer Ingelheim alone. Several capsule filling machines were tested, with a range of processing technologies (continuous, intermittent motion), dosing systems (dosator needle, vacuumed drum filler), and systems for mass control (capacitive sensors, elastomers for gravimetric weighing).

The processing technology did not have a direct impact on performance, unless needed for other features such as gravimetric weighing. The dosator needle was preferred when compared with drum filler for the following reasons:

1. Dosator fills the dosing chamber effectively. The drum filler relies on the force of gravity to fill the chamber (ineffective and difficult to control) and vacuum (irregular since air follows preferential routes inside the powder, creating a "rat hole", and the membrane soon clogs).
2. Dosator holds micronised powders in the chamber thanks to their cohesivity and very small dosator diameter. In addition, IMA applies a patented syringe effect. Vacuumed drum filler relies on the vacuum to hold the powder in the chamber, thin particles are aspirated and this generates high losses of product and frequent stops.
3. Average weight centred on the target weight. The chamber height of each dosator can be accurately set and individually adjusted.

Figure 2 shows the weighing statistics for the total batch (T) and for each dosator individually.

Analysis of the process

The second step of the study was conducted by IMA and Boehringer Ingelheim. After the pre-runs, the process was analysed and studied in deep detail. IMA and Boehringer Ingelheim put in place people specialised in mechanical design, statistics, and mathematics analysis and software development. Several tests were performed at the IMA factory on Adapta® with 100% gravimetric net weight control. The process analysis loop was followed as described in Figure 3.

The pre-runs showed that Adapta® was fully capable of handling Spiriva® capsules and that the dosing by dosators was perfectly achieving the requirements for the product. Boheringer Ingelheim worked together with IMA to find the right dynamic parameters and optimise the closed-loop control.

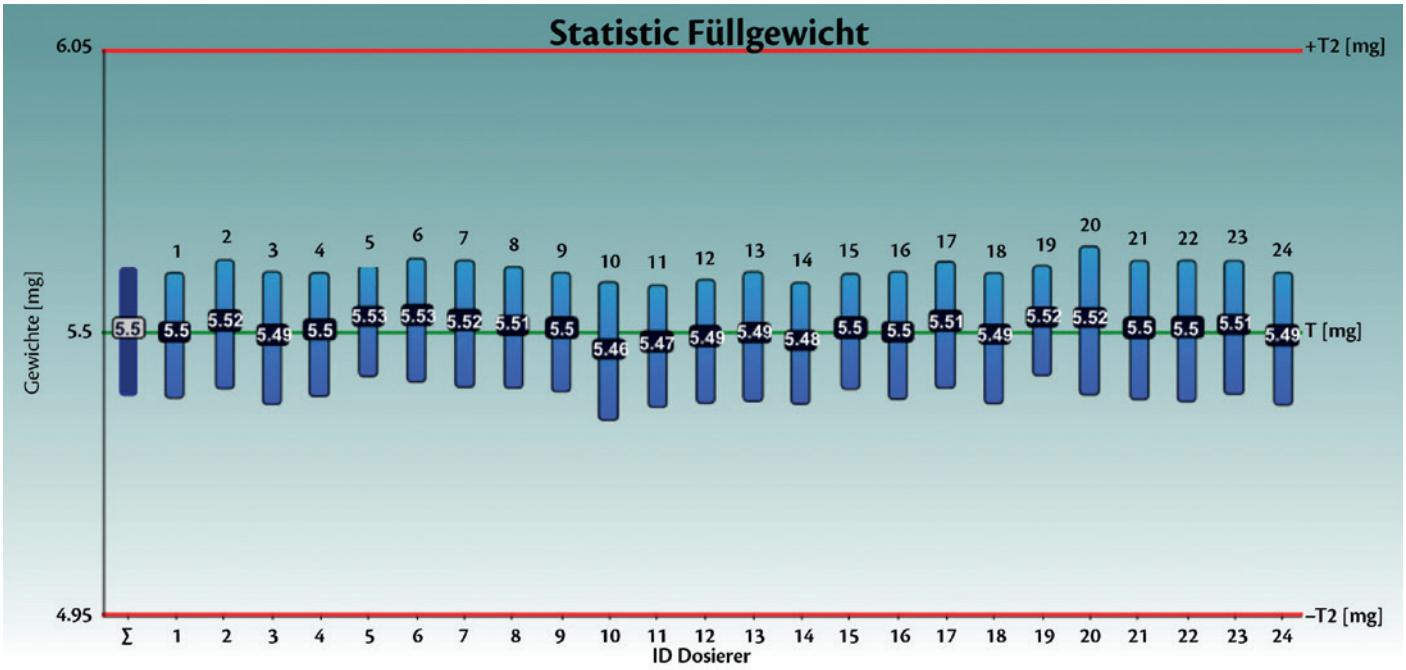

Figure 2: Weighing statistics for the total batch (T) and for each dosator individually.

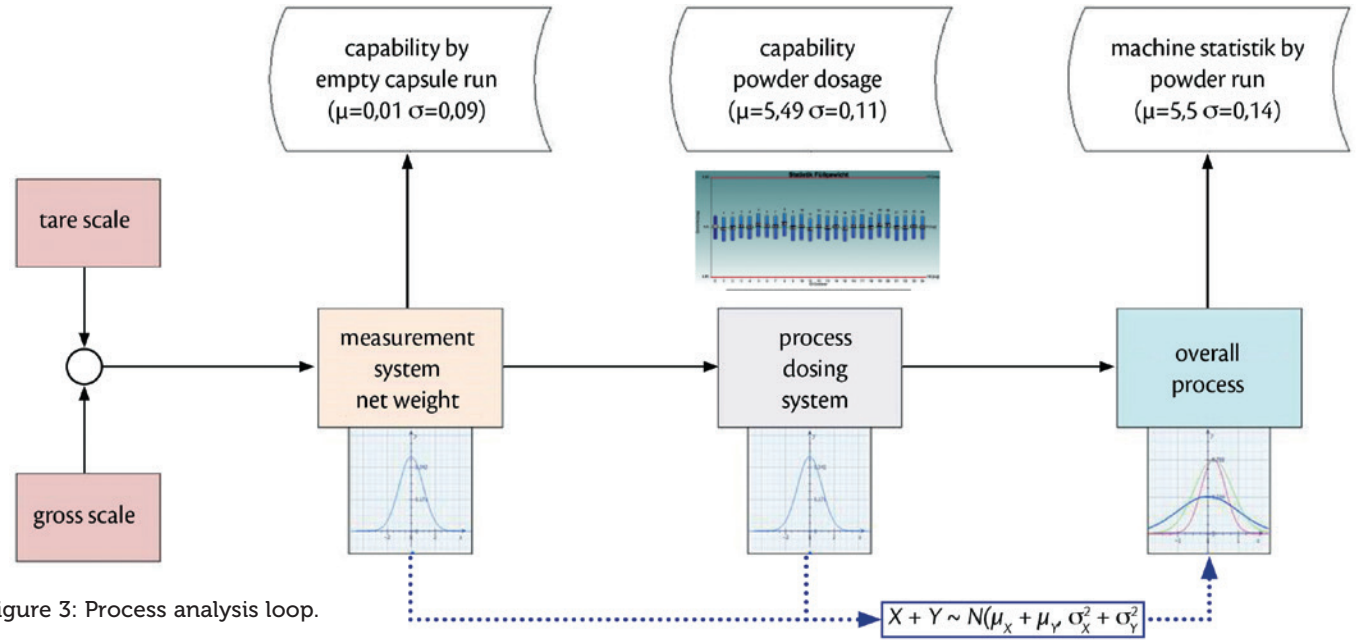

Figure 3: Process analysis loop.

The weighing system was optimised. Several tests were performed when no powder was dosed (Figure 4). The "ideal" system should result in a net weight equal to zero, since the capsule is empty. The standard deviation represents possible errors in scale accuracy and air flows, for example, due to the vacuum opening, vibration, etc.

The timing for the weight sampling was changed and the calibration weight was set to 100 mg (tolerance class E2). Figure 5 shows the results achieved. This provides feedback and an evaluation method for the weighing method itself.

"A major advantage of using dosator technology for processing low-dose DPIs is that the system can dose very small amounts of powders into capsule."

The joint work demonstrated that a perfect dosing system needs to be controlled by a perfect weighing system (Figures 4 and 5).

Process requirements

- Capsule size 3
- Powder for inhalation
- Net fill weight 5.5 mg +-10% ➔ LSL = 4.95 mg, USL= 6.05 mg
- 100% control for filling
- Smooth capsule run
- Easy to use – fast setting up, cleaning and operation
- Production data accessible.

Technical criteria

- Machine speed
- Machine size
- Machine kind (intermitted pulsed / continuous run)
- Filling technology (dosator needle, sliding chamber, vacuumed drum)
- Capsule handling: opening / move (body, cap) / close
- Machine complexity (easy to run)
- Set up and disassemble speed
- GMP design (surfaces / materials / easy to clean / no dead room)
- Measurement system (principle / stability / influences)
- Sold machines in the market (support, developed to use)
- Costs (invest, maintenance, media).

Results

Figures 4-7 show the achieved fill weight for the total batch ("T") and for each dosator individually – perfectly centered and on target (μ= 5.5 mg and bias= 0.00 mg).

After several sessions of trials, machine parts optimisation, deep analysis of the measuring system and its synchronisation with the capsule filling process, Adapta® with 100% gravimetric net weight control was able to perfectly match process capability requirements with very low target dosage. And in particular Adapta® is able to incorporate:

1) a very accurate and reliable system for auto-diagnosis when handling with empty capsules, able to achieve:
   – Standard deviation σ <0.1mg
   – Bias -0.03 to +0.03

2) a very stable and reproducible system for dosing DPI, able to achieve:
   – Standard deviation σ= 0.13 to -0.16 mg
   – Totally centered on average, with Bias 5.5 mg +/-0.05mg

Conclusion

As shown by this study, a major advantage of using dosator technology for processing low-dose DPIs is that the system can dose very small amounts of powders into capsules. This powder-dosing technology does not require powder compaction to transfer the powder to the capsule, ensuring that the powder within the capsule is less likely to form aggregates and is maintained as a free-flowing powder. Maintaining the free-flowing properties of the dispended powder within the capsule better ensures the release of powder from the capsule into the inhaler when the capsule is pierced – thereby better controlling both the emitted dose and the fine particle fraction of the dose discharged from the DPI.

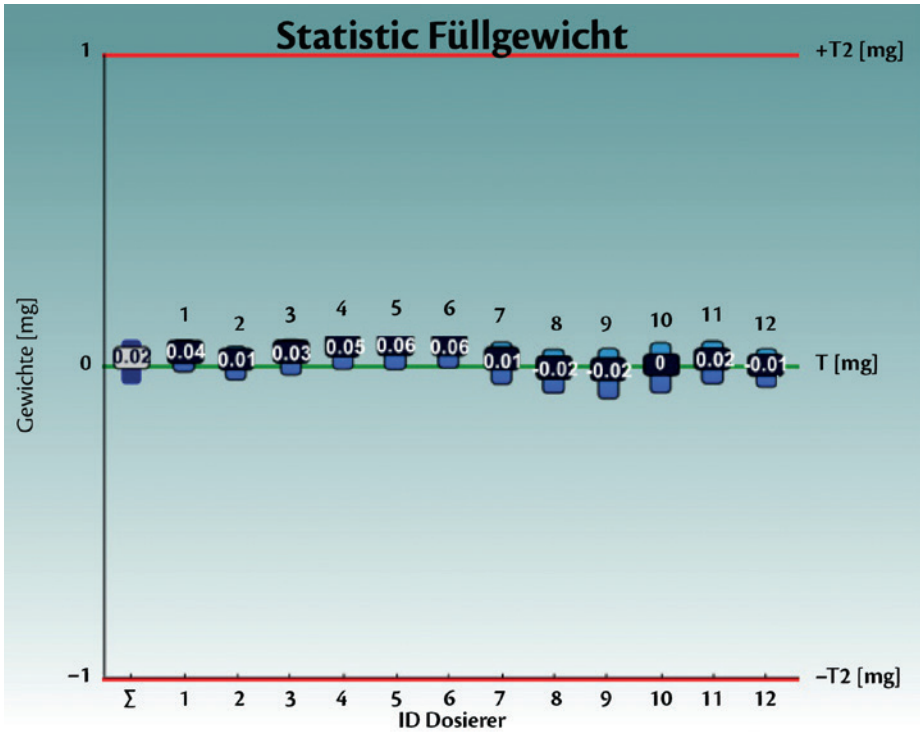

Figure 4: Test with empty capsules on Adapta® 100 with 100% gravimetric net weight control.

Boehringer Ingelheim	Maschine	Equipment Nr.	Seriennumer der Maschine
	Kapselfüller ADAPTA 2	21283511	PM1078
Chargenreport			
–	Materialnummer/Produktname	Chargenstart	Chargenende
–	Leerkapseln	01.03.2019 - 13:24:49	01.03.2019 - 14:06:30

ID	Average [mg]	σ [mg]	σ%	Min [mg]	Max [mg]	Samples
T	0.018	0.071	385.314	-0.29	0.7	12360
1	0.037	0.05	133.789	-0.09	0.2	1030
2	0.014	0.053	370.586	-0.14	0.17	1030
3	0.033	0.056	169.74	-0.13	0.21	1030
4	0.053	0.06	113.826	-0.12	0.24	1030
5	0.057	0.069	120.932	-0.14	0.7	1030
6	0.055	0.061	112.423	-0.13	0.26	1030
7	0.01	0.067	702.778	-0.21	0.19	1030
8	-0.018	0.07	-396.541	-0.23	0.19	1030
9	-0.024	0.08	-341.083	-0.28	0.2	1030
10	-0.005	0.08	-1.473.197	-0.29	0.23	1030
11	0.015	0.07	451.951	-0.21	0.24	1030
12	-0.007	0.061	-864.106	-0.2	0.18	1030

Figure 5: Test with empty capsules on Adapta® 100 with 100% gravimetric net weight control.

The key to achieving optimal filling and control of low-dose dry powder for inhalers is combining the dosator technology and the direct gravimetric net weight control. This is available on an industrial production scale capsule filler, Adapta®.

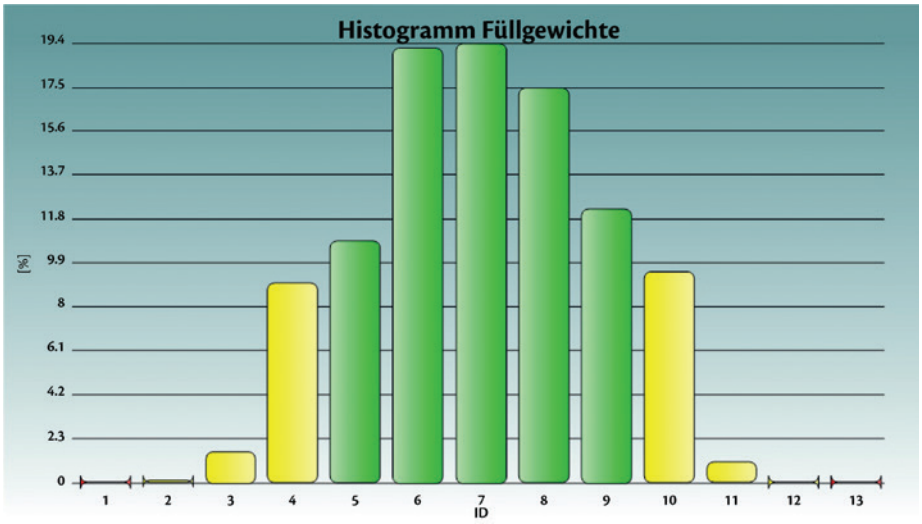

Figure 6: Spiriva® achieved fill weight on Adapta® with 100% gravimetric net weight control.

Boehringer Ingelheim	Maschine	Equipment Nr.	Seriennumer der Maschine
	Kapselfüller ADAPTA 1	21255995	PM1073
Chargenreport			
–	Materialnummer/Produktname	Chargenstart	Chargenende
–	Tiotropium	12.08.2019 - 02:51:0119	16.08.2019 - 16:51:00

Statistik Füllgewicht							
ID	Mittel [mg]	σ [mg]	σ%	Minimum [mg]	Maximum [mg]	Stückzahl gut	Ausschuss%
T	5.501	0.125	2.278	–0.29	10.86	5706793	0
1	5.496	0.123	2.23	0.11	6.83	237720	0.1
2	5.518	0.126	2.263	0.03	6.56	237847	0
3	5.49	0.13	2.376	0.06	6.47	237721	0.1
4	5.496	0.12	2.187	–0.01	7.67	237826	0
5	5.526	0.108	1.946	–0.01	7.94	237824	0
6	5.526	0.12	2.166	0	7.21	237842	0
7	5.516	0.123	2.231	–0.18	8.26	237770	0.1
8	5.509	0.118	2.146	–0.01	7.32	237837	0
9	5.501	0.117	2.135	3.75	6.11	237857	0
10	5.463	0.134	2.448	0.08	6.15	237806	0
11	5.474	0.12	2.188	4.19	6.27	237853	0
12	5.485	0.12	2.189	–0.03	6.6	237833	0
13	5.493	0.127	2.305	–0.17	6.62	237723	0.1
14	5.478	0.118	216	–0.05	6.08	237855	0
15	5.504	0.112	2.042	–0.06	6.63	237858	0
16	5.495	0.125	2.284	1.56	7.7	237819	0
17	5.514	0.123	2.224	–0.21	10.86	237184	0.3
18	5.491	0.127	2.309	0.08	6.69	237760	0.1
19	5.523	0.108	1.946	–0.29	8.37	237742	0.1
20	5.522	0.144	2.614	1.84	6.22	237772	0.1
21	5.504	0.136	2.446	–0.04	6.15	237834	0
22	5.502	0.137	2.484	4.23	6.24	237840	0
23	5.511	0.131	2.386	4.25	6.22	237843	0
24	5.489	0.13	2.374	–0.03	6.18	237828	0

Figure 7: Spiriva® achieved fill weight on Adapta® with 100% gravimetric net weight control.

ABOUT THE COMPANY

IMA Group is a world leader in the design and manufacture of automatic machines for the processing and packaging of pharmaceuticals, cosmetics, tea, coffee and food. IMA Active, one of the three pharmaceutical divisions of IMA Group, partners with pharma for each solid dose processing phase: granulation, tableting, capsule filling and banding, weight checking, coating, handling and washing.

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ABOUT THE AUTHORS

Pietro Pirera is Product Manager for capsule filling at IMA Active. He graduated with a degree in Mechanical Engineering from the University of Bologna (Italy), and has been working in the field of solid dose processing and manufacturing for more than 20 years. He is an expert in pharmaceutical engineering and the processing of micro-dosing DPIs.

Rainer Bauer is an Automation Engineer at Boehringer Ingelheim. He has 15 years of engineering experience in the pharmaceutical industry in several positions. With a keen interest in gravimetric 100% control for micro-dosed dry powder inhalers, calibration robots, vision and control systems (VCSs) for programmable logic controllers (PLCs), and wireless temperature monitoring, Mr Bauer's experience spans instrumentation, measurement analysis, process analysis, software development, IT in automation, agile dev tools, networks and automation business systems. He is trained as an electrical engineer.

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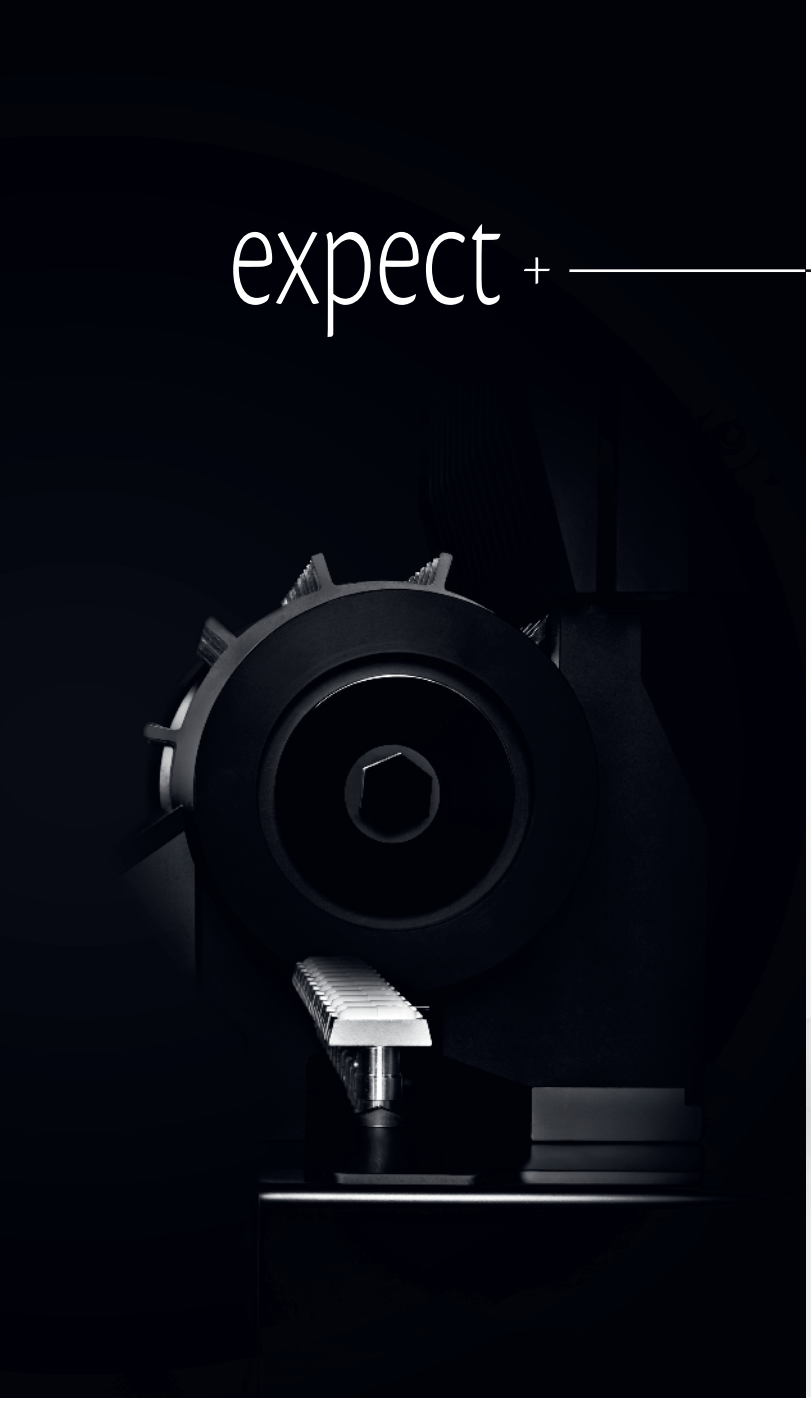

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IN VITRO BIOEQUIVALENCE – WHERE ARE WE NOW?

With a focus on bioequivalence testing in the development of generic inhalables, Mark Parry, Technical Director, Intertek Melbourn, highlights some of the shortcomings of aerodynamic particle size distribution and delivered dose testing, and introduces newer testing techniques that Intertek offers to allow its clients to de-risk clinical studies or even to support *in vitro* data submissions so robustly as to avoid clinical work.

In vitro bioequivalence for the development of generic inhaled pharmaceutical products continues to present industry with significant and evolving challenges. Developing and performing suitable analytical strategies to satisfy evolving regulatory requirements – whilst establishing a robust development process which ensures that the developed generic product is successful – continues to highlight the limits of the traditional approaches to *in vitro* characterisation.

Regulators are advancing the expectations for the content of *in vitro* testing programmes through continued development of general and product-specific guidance. These expectations include newer techniques such as spray pattern plume geometry testing for metred dose inhalers – and a clearer focus on identifying and controlling critical quality attributes (CQAs) as an integral part of the overall development.

The traditional inhaled product performance tests of aerodynamic particle size distribution (APSD) and delivered dose have proven themselves to be vital tools in the development and testing of inhaled products and form the backbone of any inhaled product specification. We must, however, understand the shortcomings of these tests. While they can tell us information about how much drug is released and its size, they do not provide information on other factors such as the nature of the deposition (e.g. individual particles, agglomerates or co-deposited with a carrier or a second API particle) or the morphology of the particles themselves. Both are factors that will influence actual bioavailability and delivery of the drug locally and systemically.

Many companies have been in the position where *in vitro* work has delivered a strong and comprehensive data package showing good equivalence between the reference and generic products, only to see pharmacokinetics or pharmacodynamics *in vivo* data show unacceptable differences between the products. Clearly, we need more physiologically relevant data for our *in vitro* analysis and, while standard APSD and delivered dose tests themselves are not accurate physiological models, they do provide a platform we can build on.

NEW TECHNIQUES

Several advanced techniques are now available which can provide useful input to improve the ruggedness of the development programme to de-risk clinical studies or to bridge *in vivo-in vitro* correlation (IV-IVC), thus strengthening *in vitro* data submissions with a view to potentially avoiding clinical work.

Flow Profiles

Standard APSD and delivered dose testing make use of simplified flow profiles for testing, effectively a square wave where the flow is on or off, at a physiologically relevant flow rate. For dry powder inhalers (DPIs), the air flow is critical as it provides the energy for delivering the drug from the device itself. However, a square wave is not an accurate reflection of a normal human inhalation flow profile.

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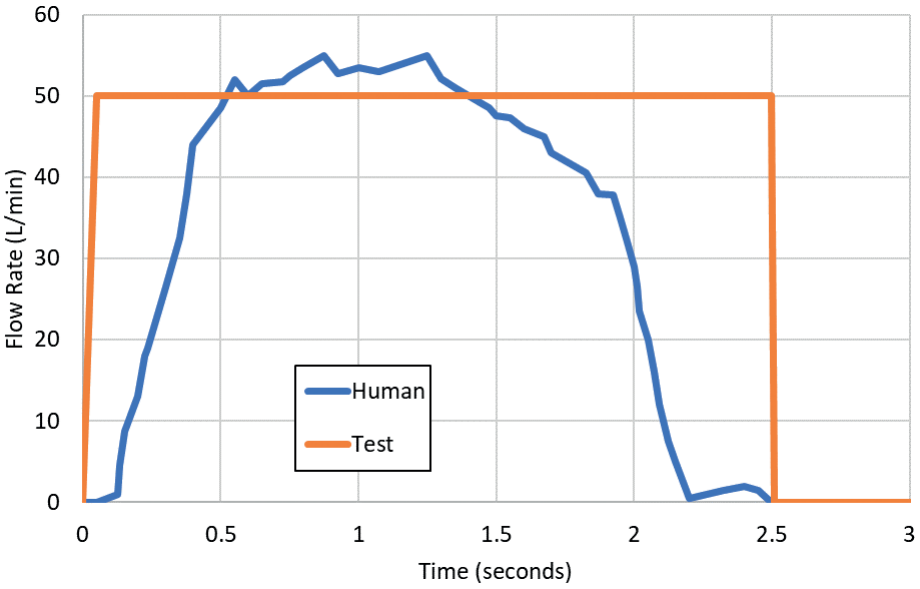

Figure 1: Differences between human and test flow profiles.

Current DPI regulatory guidance does acknowledge the need to look at a range of flow rates for the reference and generic product to explore the robustness of the product to the varying maximum flow rates likely to be seen in any typical population. Nevertheless, normal conditions do not provide an effective simulation of the actual likely behaviour observed in both healthy and inhalation-compromised users, where a range of flow profiles will be seen.

Particular attention to the impact of the patient's condition on the typical inhalation manoeuvre observed can provide for a more biorelevant test that can be incorporated into the APSD and delivered dose testing – and provide data likely to be more clinically relevant. An example of a normal human profile versus the test profile is given in Figure 1.

Lung Dissolution

While impaction testing provides good information on the aerodynamic size of the inhaled product, it does not provide information on the likely behaviour of the drug observed at the various particle sizes when deposited in the lung. The dissolution and absorption of the API can be affected by factors beyond just its size, with the particle morphology, salt and crystal form all likely to have an impact.

In the same way that traditional dissolution tries to mimic the dissolution of tablets and capsules in the stomach, lung dissolution testing aims to do the same thing for inhaled products. There are, however, several factors to address.

First, we need to identify a method of preparing the sample. Modified impactor stages and similar techniques present a way of isolating the relevant size particles as we only want to test particles that can deliver to the lung. We then need to identify a suitable medium, with simulated lung fluids requiring a complex mix of salts and other components to mimic expected behaviour, and then a suitable equipment approach is needed. This can involve the use of traditional dissolution vessels with suitable holders for the collected particles. However, other options are being explored as well.

Work continues across the industry to develop and optimise lung dissolution models to allow for the dissolution behaviour of the delivered API to be assessed. While there may not yet be a harmonised method available, these techniques provide a better way to model a drug's bioavailability and are proving to be an increasingly important part of generic product development.

Morphologically Directed Ramen Spectroscopy

Recent work looking at morphologically directed ramen spectroscopy (MDRS) provides evidence for a useful orthogonal technique to complement impaction. This technique combines optical microscopy, computerised particle measurement and per-particle ramen spectroscopy to deliver information on the size, shape and identity of individual particles.

Using modified NGI stages we can examine individual size fractions and information regarding particle morphology to be generated and compared. Further development of the technique also allows for assessment of the product's deposition behaviour, allowing information regarding the deposition and distribution of API only, API/carrier, API1/API2 and API1/API2/carrier particles to be directly measured – which was not previously practical. See Figure 2 for an example of the differences in API particle deposition for two products at the same size fraction.

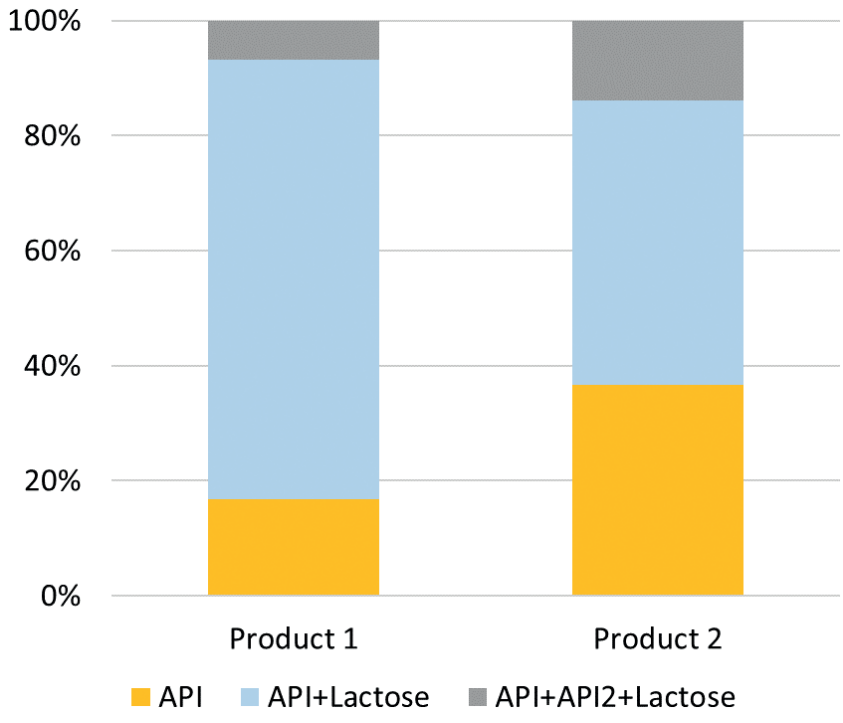

Figure 2: The different deposition behaviour of API particles in two products at one size fraction.

Having this data provides vital information on both the morphology and deposition behaviour of the product and allows for further differentiation in performance of products – even when traditional drug mass data may suggest they are equivalent.

INTERTEK'S SOLUTIONS

Given the challenges in delivering successful clinical bioequivalence studies – even with acceptable *in vitro* data – recent expansion at Intertek's Centre of Excellence for Inhaled and Nasal Drug Development in Melbourn, UK, has focused on new, powerful *in vitro* analytical strategies. The expansion of our laboratory footprint also enables us to help our clients' key decision-making activities throughout the product development lifecycle.

We understand the need to invest time to establish rugged methodology with a focus on identifying and controlling CQAs as an integral part of product development. Intertek's experienced scientists deliver *in vitro* analytical programmes to support all stages of development for both innovator and generic products as well as maintaining involvement in development of new and improved techniques and technologies. Looking ahead, these new analytical strategies should allow for the development of stronger *in vivo* data packages supporting both greater clinical success and the possibility of successful *in vitro* only generic approvals.

ABOUT THE COMPANY

With more than 25 years of experience in supporting clients' orally inhaled and nasal drug product development, Intertek Melbourn provides product performance testing, method development/validation, stability, chemistry, manufacturing and control support, formulation development and clinical manufacturing capabilities. The company's services are designed to provide the right information at the right time, ensuring total quality assurance for products and processes. Intertek's network of more than 1,000 laboratories and offices and over 44,000 people in more than 100 countries, delivers innovative and bespoke assurance, testing, inspection and certification solutions for its customers' operations and supply chains across a range of industries worldwide.

ABOUT THE AUTHOR

Mark Parry has more than 16 years' experience working within the pharmaceutical analysis and formulation development industry, with a particular focus on orally inhaled and nasal drug products. Mostly working in the pre-approval stages, his background includes extensive experience with product and formulation development for novel and generic products, as well as method development and validation, stability studies, pharmaceutical development activities, and clinical trial manufacturing for a wide range of clients.

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HOW TO GAIN A FULL UNDERSTANDING OF POWDER FLOW PROPERTIES, AND THE BENEFITS OF DOING SO

In this article, Geoffroy Lumay, PhD, Professor of Physics, University of Liège, and Naveen Mani Tripathi, PhD, Particle Scientist, and Filip Francqui, Managing Director, both of Granutools, show how the association of three recently developed flow measurement techniques – improved angle of repose measurement with GranuHeap; cohesiveness measurement with GranuDrum; and improved tapped density measurement with GranuPack – can be used to gain valuable insights into powder characteristics and properties.

INTRODUCTION

Granular materials, fine powders and nanostructured powders have wide applications in pharma[1-4] including in oral tablets and capsules, and in inhalation. A robust manufacturing process involving powder requires reliable powder-flow properties. Unfortunately, pharmaceutical powders are usually cohesive and so a deep understanding of the forces acting between the grains is necessary.

Moreover, post-processing methods are commonly used to reduce cohesiveness.[5,6]

Powder behaviour is influenced by:

- steric repulsions
- friction forces
- cohesive forces, and
- interaction with the surrounding gas.[7,8]

Steric repulsion is related to the grain geometry. Friction forces are influenced by both surface state (rough or smooth surface) and the chemical nature of the grains.

> "Spray-dried powders can be characterised before and after granulation with recently developed measurement devices to predict the processability."

Cohesive forces may be induced by the presence of liquid bridges,[9,10] by electrostatic charges,[11-14] by van der Waals interactions[15] or, more rarely, by magnetic dipole-dipole interactions.[16] The predominance of one of these forces depends on both environmental conditions and the physicochemical properties of the grains.

Here, we show how spray-dried powders can be characterised before and after granulation with recently developed measurement devices to predict the processability. According to the spray-

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"The repose angle refers to the angle of the isosceles triangle with the same projected surface as the powder heap. The lower the repose angle is, the better the powder flowability."

drying method, in particular according to the nozzle characteristics, the obtained powder is processable or not. We discuss how the granulation step modifies powder flow behaviour. In particular, we focus on two granulation methods: high shear granulation (HSG) and fluid-bed top-spray granulation (FBG).

EXPERIMENTAL METHOD

Spray-Drying

Amorphous solid dispersion (ASD) was obtained by spray-drying a 10% (w/w) ethanol solution containing 20% indomethacin (as model drug) and 80% polyvinylpyrrolidone (PVP)-K30. Spray-drying was performed using a ProCepT (Zelzate, Belgium) spray-dryer, using two different nozzles, bi-fluid and ultrasonic, in order to obtain different particle sizes.

Granulation

Wet granulation was performed by FBG and HSG (both ProCept machines). In order to obtain a good granulation process, 50% microcrystalline cellulose was added to the spray-dried powder. As granulation liquid 5% (w/w) PVP-K30 in ethanol was used. Fluid bed the temperature was kept low (product temperature 30°C) to avoid an additional negative effect on the ASD. HSG was more efficient compared with FBG as only 0.5% of PVP-K30 was needed to obtain a strong granule whereas with FBG 3.8% PVP-K30 was needed to obtain a granule with similar characteristics. In order to obtain a product with a similar ethanol content, the granules obtained by FBG were additionally dried for 1 hour in the fluid bed.

As the amount of granulation liquid needed is lower during HSG, it should be the preferred wet granulation technology to granulate ASDs. However, in all cases the ASD was maintained with a Tg of 110°C. So the addition of the ethanol (and increased temperature) had no influence on the ASD.

"This method gives the opportunity to study complex rheological properties of powders (shear thinning, shear thickening and thixotropic behaviour) by varying the rotation rate."

Angle of Repose (GranuHeap)

The GranuHeap instrument carries out an automated repose angle measurement technique based on image processing.[6] A powder heap is created on a cylindrical support to be analysed by image processing. In order to obtain reproducible results, an initialisation tube with an internal diameter equal to the circular support is installed on the support. After filling the initialisation tube by hand with a fixed volume of powder (100 mL in the case of the present study), the initialisation tube moves up at a constant speed of 5 mm/s. Thereby, the powder is flowing from the tube to form a heap on the cylindrical support, which is then evaluated by image analysis.

In the present study, 16 images separated by a rotation of 11.25° were recorded. A custom image recognition algorithm determines the position of the powder/air interface. The repose angle refers to the angle of the isosceles triangle with the same projected surface as the powder heap. The lower the repose angle is, the better the powder flowability.

Dynamic Cohesive Index (GranuDrum)

GranuDrum is an automated powder flowability measurement instrument that uses the rotating drum principle.[6,7] A horizontal cylinder with vertical glass sidewalls, the drum, is half filled with sample powder. For the present study, the drum rotates around its axis at an angular velocity from 2-10 rpm. A charge coupled device camera takes snapshots (50 images separated by 0.5 s) at each angular velocity. The air/powder interface is detected on each snapshot with an edge detection algorithm. Afterwards, the average interface position and the fluctuations around this average position are computed. Then, for each rotation rate, the flow angle is computed from the average interface position and the dynamic cohesive index is measured from the interface fluctuations.

Interface fluctuations are induced by the cohesive forces between the grains. The dynamic cohesive index is close to zero for non-cohesive powders and increases when the cohesive forces intensify. In addition, this method gives the opportunity to study complex rheological properties of powders (shear thinning, shear thickening and thixotropic behaviour) by varying the rotation rate.

Tapped Density (GranuPack)

GranuPack conducts automated and improved tapped density measurement.[6] The Hausner ratio Hr (or the Carr index), the initial density ρ0 and the final density ρ500 are measured precisely. Moreover, dynamic information and an extrapolation of the optimum density (ρ∞) can be extracted from compaction curves. The compaction curve is a plot of the bulk density as a function of the tap number. At the beginning of the measurement, the powder is placed in a metallic tube with a rigorous initialisation process. Afterwards, a light hollow cylinder is placed on the top of the pile to keep it flat during compaction. A single tap consists of moving up the tube containing the powder sample to a height (ΔZ) of 1 mm and then performing a free fall. The free-fall height ΔZ can be adjusted. The height h of the powder bed is measured automatically after each tap.

From the height (h), the volume (V) of the bed is computed. As the powder mass (m) is known, the bulk density ρ is evaluated automatically and plotted after each tap. The measurements are performed with 35 mL of powder subjected to 500 taps.

Size Distribution

The particle size distribution of the spray-dried powders was obtained by dry powder laser diffraction. Powders were dispersed with compressed air at 1.5 bar through a RODOS dry disperser before sizing with a HELOS laser diffraction sensor (measurement range R1: 0.18 – 35 µm and R3: 0.5-175 µm) (all from Sympatec, Etten-Leur, The Netherlands). The particle size distribution of the granules was evaluated by dynamic image analysis with QicPic granulo-morphometer (Sympatec). The granules were gravimetric dosed via the GRADIS disperser.

MATERIALS

Four powders with different granulometries were created by spray-drying. The powders and the associated production process are listed in Table 1. For all powders, a complete amorphous system was created. Powder P1 was spray-dried with a small cyclone, 0.2 mm nozzle and an air flow-rate of 5.5 L/min at 2.75 bar. Powder P2 was spray-dried with a large cyclone, 0.6 mm nozzle and an air flow rate of 8 L/min at 0.41 bar. Powder P3 was spray-dried with large cyclone, 0.6 mm nozzle and an air flow rate of 4.1 L/min at 0.41 bar. Finally, powder P4 was spray-dried with an ultrasonic nozzle at a frequency of 25 kHz at 35%.

The granules were created starting from powders P2 and P4. The reasons of this selection will be discussed hereafter. G1 granules were produced with HSG starting from powder P2. G2 and G3 granules were produced starting with powder P4 using HSG and FBG, respectively.

Name	Short name	Process	Information
Powder1	P1	Spray-drying	Bi-Fluid nozzle
Powder2	P2	Spray-drying	Bi-Fluid nozzle
Powder3	P3	Spray-drying	Bi-Fluid nozzle
Powder4	P4	Spray-drying	Ultrasonic nozzle (25 KHz)
Granules1	G1	High shear granulation (HSG)	with Powder2
Granules2	G2	High shear granulation (HSG)	with Powder4
Granules3	G3	Fluid bed top spray granulation (FBG)	with Powder4

Table 1: Powders and granules used in the study and corresponding production processes.

RESULTS & DISCUSSION

Particle Sizes

The main parameters extracted from grain size distributions are summarised in Table 2. Both powders and granules cover a wide range of grain sizes. Compared with the spray-dried powder, the particle size increased for all granules combined with a decrease of the span, indicating a narrower particle size distribution. Powder P4, which is directly processable, has the highest grain size among the spray-dried powders. The granules obtained by HSG (G2) or FBG (G3) of powder P4 resulted in a similar particle size distribution.

Short name	D10 (µ)	D50 (µ)	D90 (µ)	Span
P1	0.63	3.33	8.11	2.25
P2	1.87	9.25	24.73	2.47
P3	3.81	18.48	46.08	2.29
P4	16.09	48.05	116.20	2.08
G1	41.73	97.99	209.32	1.71
G2	87.12	252.79	475.29	1.54
G3	154.63	291.39	516.46	1.24

Table 2: Summary of grain size distribution parameters of powders and granules studied.

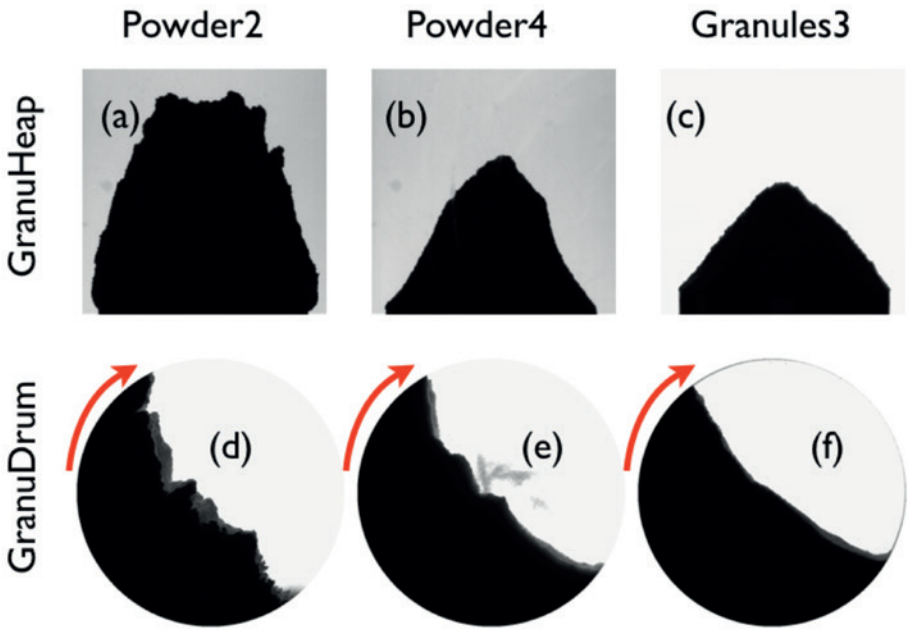

Figure 1: Typical pictures of heaps and of the flow inside the rotating drum with two powders (P2 and P4) and with G3 granules.

Repose Angle

Figure 1 shows typical pictures obtained with GranuHeap. One can see that the different powders have qualitatively very different behaviours and that the flowability of granules is better. The quantitative results obtained with GranuHeap are shown in Figure 2. Globally, the repose angle decreases when the grain diameter increases. The powder P1 is found to be an exception to this general rule because this fine powder has the tendency to form agglomerates. The repose angle decreases significantly after granulation, showing the better flowability of granules. Among the spray-dried powders, powder P4 has the lower repose angle.

Error bars corresponding to the standard deviation over three repose angle measurements are relatively small compared with the differences between the samples. This good reproducibility is obtained thanks to GranuHeap being automated and its use of a camera.

Based on the repose angle results obtained with the powders, the choice was made to granulate two of them having respectively bad and good flow behaviour.

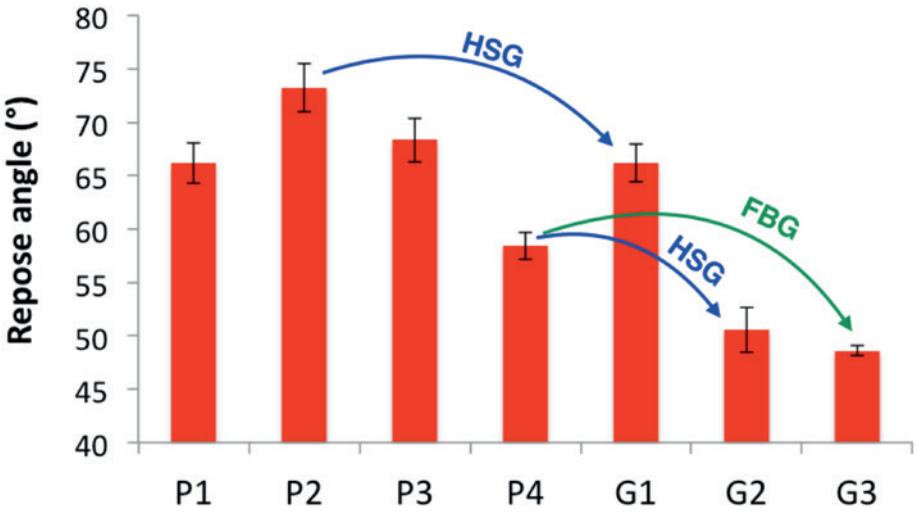

Figure 2: Repose angle measured with GranuHeap. The measurement is repeated three times to perform an average and the error bars correspond to the standard deviation.

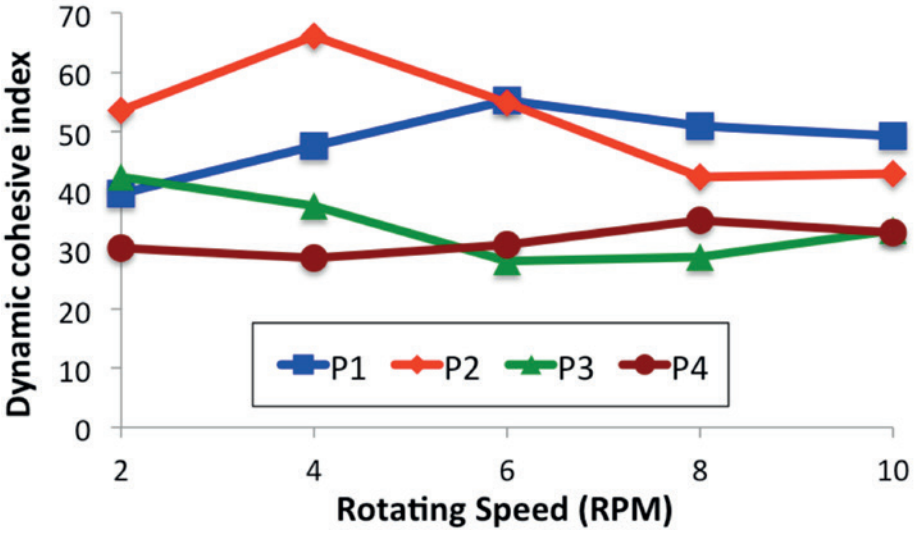

Figure 3: Dynamic cohesive index of the powders measured from the fluctuations of the flow in GranuDrum.

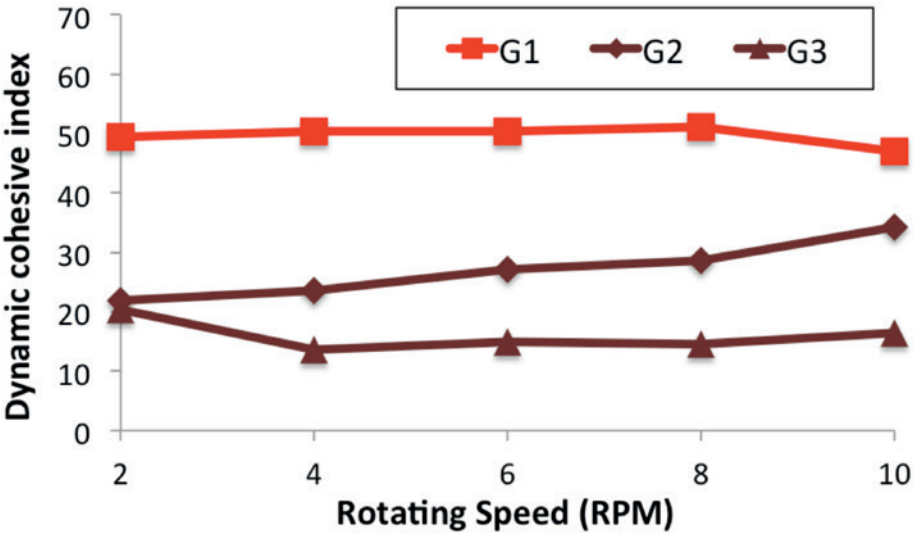

Figure 4: Dynamic cohesive index of the granules measured from the fluctuations of the flow in GranuDrum.

(This was the reason we choose to granulate powder P2 and powder P4 by both HSG and FBG.) However P2 seemed to be too fine to be granulated in the fluid bed.

Dynamic Cohesive Index

The angle of repose gives a static and straightforward picture of a powder's flow properties. If rheological information is needed, flow measurements at different shear rates or different speeds are needed. The cohesiveness is measured with GranuDrum at different speeds for the powders (see Figure 3) and for the granules (see Figure 4).

Globally, Powder P2 has the higher cohesiveness and powder P4 has the lowest cohesiveness. However, the cohesiveness of powder P2 decreases with the rotating speed, showing a shear thinning behaviour generally due to aeration. This kind of behaviour could be interesting for some processes and could also cause complications (dosage fluctuation for example) due to unexpected variations of the flowing properties. Typically, a low and constant cohesiveness is recommended.

The G1 granules obtained from granulation of powder P2 show a constant cohesiveness slightly lower than the cohesiveness of the powder. The decrease of cohesiveness is more important for G2 and G3 granules obtained by granulation of powder P4. The dynamic cohesive index measurements also show that powder P4 has the lowest cohesiveness compared with other spray-dried powders.

The bulk and tapped densities of the granules are lower than the density of the powders (see Figure 5). Typically, the density decreases with the cohesiveness. In the present case, the decrease of the density after granulation is attributed to the modification of the size distribution width (Span).

It is well known that a granular material having a larger span (as the spray-dried powder) has a higher density because the small grains fill the gaps between the big grains. The GranuPack results arise due to competition between cohesive forces and geometric (grain size/shape) effect.

CONCLUSION

Depending on the spray-drying process (nozzles and airflow rates), different grain sizes are produced leading to different flowing and packing behaviours. The powder P4 obtained with the ultrasonic

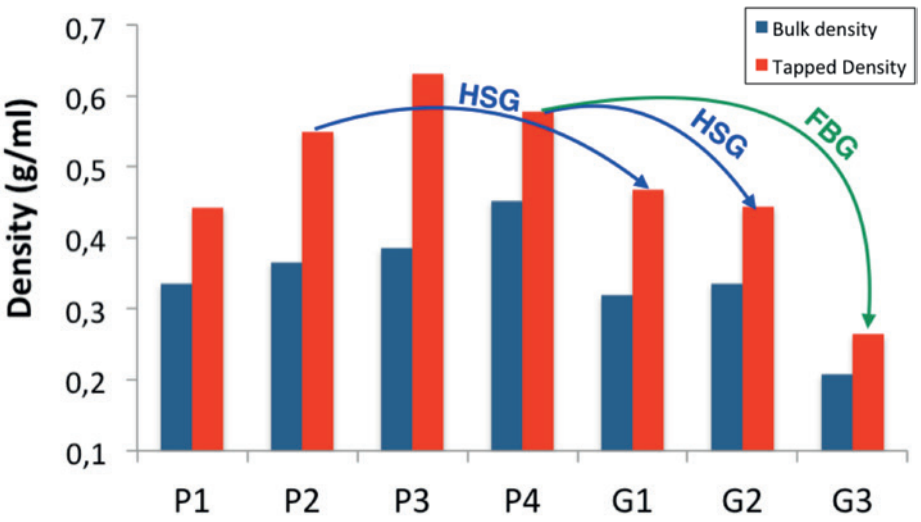

Figure 5: Bulk and tapped densities obtained with the automatic measurement instrument GranuPack.

nozzle shows good flow indexes (low angle of repose, low cohesiveness and relatively high density). The other powders have a lower average grain sizes and consequently worst flow properties.

A selection of two spray-dried powders (best and worst flowing properties) was granulated with both HSG and FBG. Globally, granulation improves the powder flow properties. The effect is particularly well evidenced by the angle of repose measured with the automated GranuHeap instrument.

Moreover, the rotating drum measurements (GranuDrum) shows that the flow properties of the granules are more stable while the powders have more complex rheological behaviour. Finally, the GranuPack instrument shows significant differences of bulk and tapped densities before and after granulation. These differences are the result of interplay between the effect of the cohesive forces and of the grain size distribution width.

ACKNOWLEDGEMENT

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ABOUT THE COMPANY

GranuTools is manufacturer of advanced laboratory and industrial instruments to characterise granular materials behaviour. The test methods are based on physical characteristics at the macroscopic scale, such as cohesion, packing and electrostatics of powders. GranuTools addresses industrial needs for precise, repeatable and operator-independent instruments with clear physical insights. This approach fits the wide gap between expensive shear cell related systems on one hand, and manual devices on the other.

All we do is powder flow characterisation.

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Geoffroy Lumay, PhD, PDF, is Professor and Head of the Experimental Soft Matter Physics Group at the University of Liege, Belgium. He has expertise in the area of powder flow characterisation and rheology of complex fluids. He has published more than 100 papers.

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Publication Month	Issue Topic	Materials Deadline
Dec 2019	Connecting Drug Delivery	PASSED
Jan 2020	Ophthalmic Drug Delivery	Dec 5, 2019
Feb 2020	Prefilled Syringes & Injection Devices	Dec 23, 2019
Mar 2020	Skin Drug Delivery: Dermal, Transdermal & Microneedles	Feb 6, 2020
Apr 2020	Pulmonary & Nasal Drug Delivery	Mar 5, 2020
May 2020	Injectable Drug Delivery: Formulations & Devices	Apr 2, 2020
June 2020	Connecting Drug Delivery	May 7, 2020
July 2020	Novel Oral Delivery Systems	Jun 4, 2020
Aug 2020	Industrialising Drug Delivery	Jul 2, 2020
Sep 2020	Wearable Injectors	Aug 6, 2020
Oct 2020	Prefilled Syringes & Injection Devices	Sep 3, 2020
Nov 2020	Pulmonary & Nasal Drug Delivery	Oct 1, 2020
Dec 2020	Connecting Drug Delivery	Nov 5, 2020

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- ISO 11608
- Glide Force
- Connectivity
- Trigger Force
- Needle Testing
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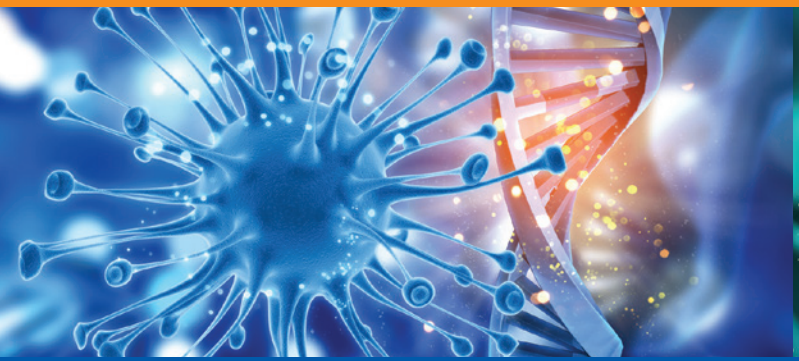
- Human Factors
- Break Loose Force
- Performance Testing
- Transit /Altitude Testing
- Design Validation Testing
- On Body Delivery Systems
- Extractables and Leachables



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REGULATORY AFFAIRS: THE UNDERESTIMATED ROLE OF PRIMARY PACKAGING

Against the background of increasingly complex, costly products and production chains, restrictive industry standards and differing regulations, regulatory affairs are becoming more important than ever. As a result, says Antje Caelers, PhD, Regulatory Affairs Manager at Sanner, manufacturers need to work with a partner who is well versed in both primary packaging production and regulatory requirements.

Primary packaging materials are either in direct contact with food, medicines or medical devices or could come into contact with them – and must therefore comply with strict regulations. The regulations are just as manifold as the packaging itself. The goal, however, is the same for everyone involved, from the drug manufacturer to regulatory authorities to the packaging manufacturer: safety, quality, function and compatibility are the focus of all efforts. Those who have specialised in the development of primary packaging materials should know for which purpose and for which final product the packaging is intended. Packaging that fits perfectly for a certain food product or dietary supplement is not automatically suitable for pharmaceutical contents.

REGULATORY AFFAIRS – AN IMPORTANT COMPETENCE

What does a manufacturer of food, pharmaceuticals or medical devices need to launch their product, including primary packaging, safely and in compliance with the directives? First, they need a partner for primary packaging production who has special expertise in all regulations for the various dosage forms and applications, and is able to develop safe solutions.

This is the task of the regulatory affairs department: it must ensure that all materials used comply with the required regulations, that the required limit values are adhered to and that this is consistently documented –

> "Primary packaging manufacturers who have established a regulatory affairs department offer their customers – manufacturers of food, pharmaceuticals and medical products – added value."

Figure 1: Primary packaging materials must not transfer any ingredients or constituents that could impair the health of consumers.

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"In addition to the active ingredient and formulation, the packaging – especially the primary packaging – also influences the quality, efficacy and safety of a drug."

from different regulations for food contact materials to pharmaceutical pharmacopoeias and Drug Master Files of the US FDA. Primary packaging manufacturers who have established a regulatory affairs department offer their customers – manufacturers of food, pharmaceuticals and medical products – added value. Not only do they receive tailor made packaging but they can also rely on the fact that all materials comply with the applicable guidelines.

Customers receive a declaration of compliance that ensures conformity with the applicable regulations and in which all regulations applicable to the raw materials used are listed. In addition, all suppliers' compliance declarations are stored and updated in a database, making them available at any time.

FOOD CONTACT MATERIALS

Primary packaging materials for food fall under the term "food contact materials" and are articles in daily use which come into contact with food, such as plastic tubes for nutritional supplements. They must not transfer any ingredients or constituents that could impair the health of consumers (Figure 1). Further, they must not result in any unacceptable modification of the food product or adversely affect its odour or taste. Accordingly, food contact materials must be manufactured in compliance with GMP, as required by Regulation (EC) No 2023/2006.

The general requirements for the safety of food contact materials are laid down in Regulation (EC) No 1935/2004. For plastic primary packaging manufacturers, Regulation (EU) No 10/2011 is decisive. It includes a list of authorised additives. To ensure that food contact materials do not pose a health risk, limit values have also been defined. Before substances are included in the register, a comprehensive health assessment is performed by the European Food Safety Authority (EFSA).

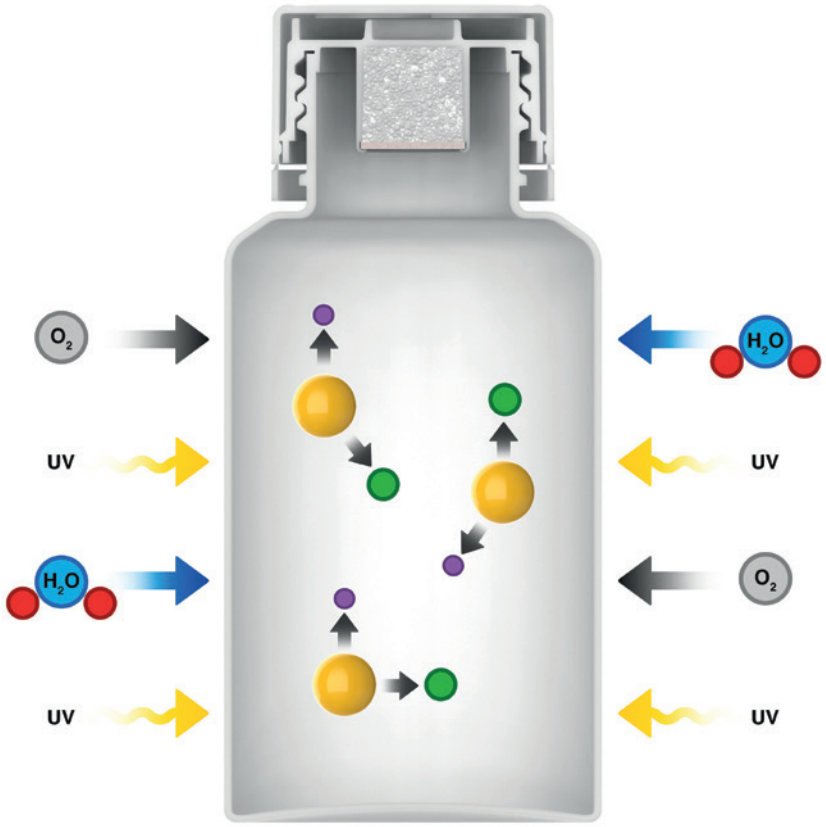

Figure 2: In addition to the active ingredient and formulation, the primary packaging also influences the quality, efficacy and safety of a drug.

PRIMARY PACKAGING IN THE PHARMACEUTICAL INDUSTRY

Primary packaging materials for pharmaceutical products are considered an integral part of the drug and therefore subject to special requirements. In addition to the active ingredient and formulation, the packaging – especially the primary packaging – also influences the quality, efficacy and safety of a drug (Figure 2). This is illustrated by the manifold requirements of the European Pharmacopoeia (EP) for medicinal products and medical devices as well as the detailed characterisation which a manufacturer has to submit when applying for market approval of a new drug.

The area of regulation is highly complex because the regulatory fundamentals for pharmaceutical packaging materials result from many laws and guidelines. In addition, each guideline on drug development, manufacture and testing also includes information on the requirements for primary packaging materials.

Primary packaging materials have a crucial protective function. They protect drugs from loss of efficacy due to oxidation, from exposure to light, and from microbial contamination. An interaction between packaging and medication that alters essential properties of the packaging or the product is not permitted. The packaging materials must not release toxicologically relevant substances such as bisphenol A, carcinogens or mutagenic substances into the formulation, which has to be proved by the pharmaceutical manufacturer when applying for marketing authorisation for a new drug. If the primary packaging performs other tasks in addition to the container function, such as dosage, these must be maintained until the end of the shelf life of the drug.

PHARMACEUTICALS, MEDICAL DEVICES AND COMBINATIONS

Determining the applicable regulations requires a distinction between medicinal products and medical devices, which is unfortunately not always obvious. Drugs (according to Regulation 2001/83/EC) act pharmacologically, immunologically or metabolically. Medical devices, in turn, (according to Regulation 2017/745) realise their intended principal use primarily by physical means.

Items such as dental products, bandages and laboratory diagnostics are considered medical devices, as well as pacemakers, implants, products for injection, transfusion and dialysis, and human medical instruments. There are also combinations of drugs and medical devices – such as inhalers for asthma or adrenaline injectors

for the treatment of anaphylaxis. Depending on their administration and effect, they are subject to different regulations from classical medicines.

PHARMACOPOEIAS – FUNDAMENTAL RULES

A pharmacopoeia is a collection of recognised pharmaceutical rules concerning the quality, testing, storage and labelling of drugs and the substances, materials and methods used for their production and testing. The EP and the US Pharmacopeia (USP) are particularly relevant. They include, for example, special test methods for plastics (USP, EP) and desiccants (USP).

EU guideline CPMP/QWP/4359/03 for the development of plastic primary packaging differentiates between solid and liquid as well as between oral, topical, ophthalmic, inhalative and parenteral dosage forms. Depending on the dosage form, certain information or tests may be required. The testing requirements of pharmacopoeias for non-solid dosage forms for parenteral or inhalative applications are much more comprehensive and stringent than for solid dosage forms for oral use. The USP also places additional requirements on the biological reactivity of polymeric primary packaging components.

DRUG MASTER FILES – NOT MANDATORY, BUT DECISIVE

The management and maintenance of the DMF is especially important in the pharmaceutical industry. The DMF is a document submitted to the FDA that documents the pharmaceutical production and quality assurance of drugs for the purpose of marketing approval. In a DMF Type III, for example, confidential information can be stored specifically for primary packaging. Once the letter of authorisation has been issued by the DMF owner, the FDA, as a third party, has the opportunity to verify its contents.

The creation of a DMF is not legally binding. However, it is of great relevance for companies operating globally, as the document is required for all drugs that are intended to receive marketing authorisation in the US. The preparation is very complex. Its main purpose is to protect intellectual property, such as the manufacturing process, for the benefit of the DMF owner. Accordingly, partners entrusted with the production of the primary packaging material should not only be familiar with the subject of DMF and be able to draw on the corresponding expertise. They should also deposit all standard products relevant for the packaging of pharmaceuticals that are to be registered in the US in DMFs Type III and update them on a regular basis.

Figure 3: From a regulatory perspective, the assessment for the MDI is carried out as part of the drug approval process.

MDI AS EXAMPLE FOR REGULATORY AFFAIRS

An example helps to illustrate the complexity of the regulations that need to be considered for primary packaging: a metered dose inhaler (MDI) is a device which delivers medicine directly into the lungs. It consists of a pressurised cartridge containing a solution or suspension of the active substance. The active ingredient is released by propellant gas. The cartridge is anchored in a plastic housing, which is connected to a mouthpiece. When the cartridge is pressed down, a valve delivers a fixed dose of the active ingredient in a fine mist, which is inhaled into the lungs via the mouthpiece.

> "Primary packaging is much more than a container for a particular formulation."

From a regulatory perspective, we must distinguish between the packaging type in which the MDI inhaler is provided pre-assembled (for single use) and the packaging type where the plastic housing is added to the packaging of the cartridge containing the drug without being assembled. The first case refers to a fixed combination of drug and medical device, which is regarded as a drug according to the requirements of the new Medical Device Regulation (MDR) 2017/745.

The term "combination product" is not legally defined in the EU. A distinction is made between:

1. a medical device containing a complementary substance which is a drug or a derivative of human blood or human plasma
2. a product intended to supply a drug, where the product and the drug form a combined product intended exclusively for use in this combination.

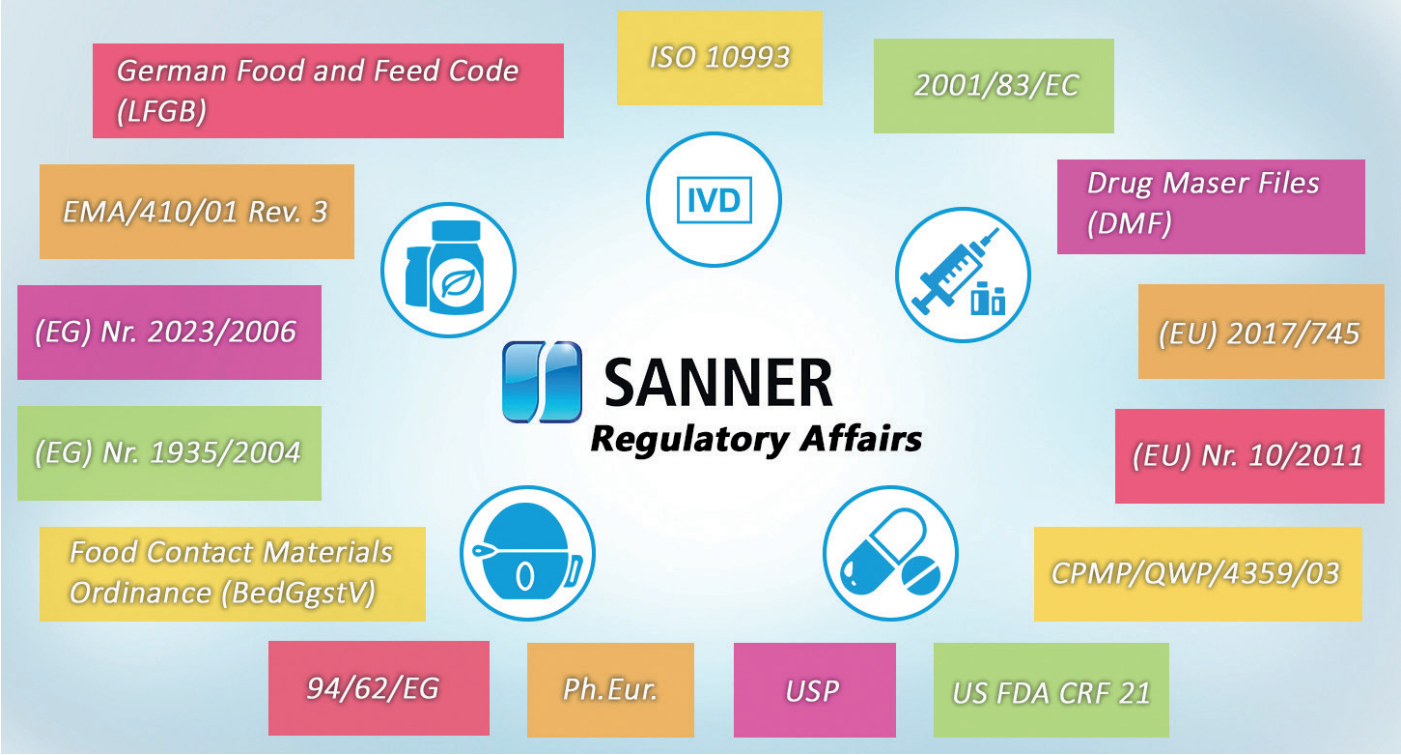

Figure 4: Primary packaging plays an increasingly important role, which requires appropriate regulatory expertise and experience.

For our example, this means that the assessment is carried out as part of the drug approval process (Figure 3). This implies that all test results according to ISO 10993 must be available in the approval documentation. This ISO standard is particularly relevant for manufacturers of medical devices and for testing laboratories – with the aim of assessing the biological compatibility of the materials with the body.

Thus, not only products, but also starting materials for the manufacture of medical devices and pharmaceuticals are examined. Accordingly, it is important to ensure that raw materials already have a statement on their use in medical devices and an ISO 10993 test report. CE marking of the medical device components is not required in this case.

Since the inhaler has to be regarded as a drug for regulatory purposes, USP and EP apply – meaning that the materials should contain a confirmation of the relevant chapters. Moreover, regarding primary packaging materials for parenteral and inhalative preparations, only materials of the USP "class VI" (strictest compatibility class) should be used.

PRIMARY PACKAGING – MUCH MORE THAN A CONTAINER

The example of the MDI shows that primary packaging is much more than a container for a particular formulation. It also shows the effort behind drug approval. It is no longer sufficient to test only the substances contained in the medicinal product. Primary packaging plays an increasingly important role, which requires appropriate expertise and experience (Figure 4). After all, primary packaging has an influence on the quality, safety, compatibility and function of the product that should not be underestimated.

The increased requirements imposed on products and primary packaging materials both enable and require constant innovation – and, above all, a partner that is familiar with the regulations. This makes the role of regulatory affairs all the more important. Fulfilling this role requires many years of experience in the development and manufacture of primary packaging for food, pharmaceuticals and medical products. At the same time, profound knowledge of and experience with the different regulations is needed. Continuous updates of the DMF should be just as self-evident as providing advice on regulatory affairs from the very beginning of packaging development. This is the only way to ensure efficient implementation and mutual satisfaction.

ABOUT THE COMPANY

Based in Bensheim, Germany, the Sanner Group was founded in 1894 and is now in its fourth generation as a family-owned enterprise. Sanner develops and produces high-quality plastic packaging and drug delivery systems for pharmaceutical, medical and healthcare customers. The group has gained international recognition for its desiccant know-how and moisture protection solutions. With more than 500 employees, Sanner is present all over the world, including Germany, China, India and the US. The company produces over two billion plastic units each year for standard and customised packaging and drug delivery solutions.

ABOUT THE AUTHOR

Antje Caelers holds a PhD in Molecular Biology from the University of Zurich (Switzerland) and has published a number of scientific articles. After positions as a postdoctoral researcher, she worked for several renowned companies in the pharmaceutical industry, both in regulatory and medical affairs, and in marketing. Since she joined Sanner in 2016, Dr Caelers has held the position of Regulatory Affairs Manager.

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