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ONdrugDelivery Issue N° 154, November 13th, 2023

PULMONARY & NASAL DRUG DELIVERY

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

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DEVELOPING AN INHALABLE FORMULATION OF THE FIRST GENERATIVE AI DRUG

In this article, Brita Belli, Head of Public Relations at Insilico Medicine, introduces the company's inhalable formulation of its AI-designed therapy for the treatment of idiopathic pulmonary fibrosis, its progression through clinical trials and the company's approach to generative AI in the pharmaceutical space more broadly.

On the heels of announcing Phase II trials for the first generative artificial intelligence (AI) drug, targeted for idiopathic pulmonary fibrosis (IPF), Insilico Medicine announced another breakthrough – an inhalable solution for its anti-fibrotic small molecule inhibitor, designed to give patients another treatment option. The new formulation has been announced as a preclinical candidate, and the company is proceeding with an IND filing. Insilico is now the first AI drug discovery company to venture into nebulised formulations.

"At Insilico, innovation never stops, and that means multidimensional validation of our AI platform capabilities, for various disease areas, indications and formulations," said Dr Feng Ren, Co-Chief Executive Officer and Chief Scientific Officer of Insilico Medicine. "We hope to advance the inhalation formulation of ISM001-055 to clinic as soon as possible to address unmet clinical needs."

ADDRESSING THE LIMITATIONS OF CURRENT IPF TREATMENTS

IPF is a chronic progressive scarring disease of the lungs, in which a combination of excessive extracellular matrix deposition and alveolar tissue results in a build-up of scar tissue that leads to an irreversible decline in lung function, followed by lung failure and death. This rare disease affects approximately five million people worldwide, with a median survival time of just three years.

The only two US FDA-approved therapies for IPF are the oral treatments pirfenidone and nintedanib, which may provide some relief or slow the progression of the disease but do not reverse the damage or stop it entirely. These medications also need to be taken in high doses and can cause unpleasant side effects. For example, the required daily dose of pirfenidone is nine pills, and studies show that patients on this regimen often experience adverse side effects, including nausea, abdominal pain and photosensitive rash. Meanwhile, more than 60% of patients in a nintedanib treatment group experienced diarrhoea.[1]

In addition to exploring new mechanisms for treating IPF, companies like Insilico are also looking at new formulations – specifically inhalable treatments – that could deliver therapies directly to the lungs to treat the disease with minimal off-target effects.

Initial studies have indicated that the inhaled formulation of Insilico's potentially first-in-class small molecule inhibitor, INS018_055, has the potential to address some of the limitations of current therapies (Figure 1). "Through inhalation, we can achieve high efficacy, high bioavailability and limit side effects, especially gastrointestinal-related side effects," explained Dr Ren.

WHY AN INHALABLE FORMULATION?

While Insilico is continuing to advance its lead oral drug INS018_055, which has demonstrated promising results in multiple

> "The only two FDA-approved therapies for IPF are the oral treatments pirfenidone and nintedanib, which may provide some relief or slow the progression of the disease but do not reverse the damage or stop it entirely."

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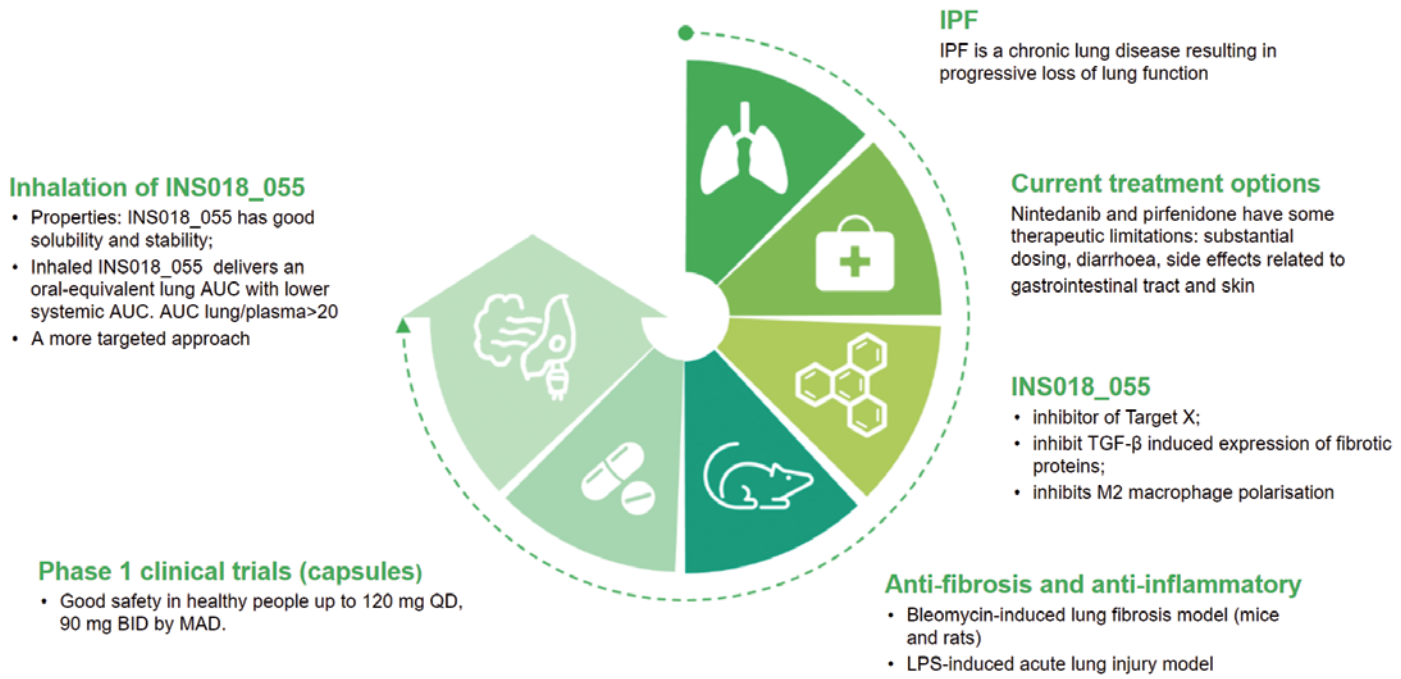

Figure 1: Infographic detailing INS018_055.

preclinical studies and was shown to have potential relevance in a broad range of fibrotic indications, the company hopes to expand the potential treatment options with its inhalation formulation. Inhalation of INS018_055 could provide a more targeted means to deliver the drug to the lung with an oral-equivalent area under the curve (AUC) but lower systemic AUC, as well as rapid onset of action, high bioavailability and lower required dose.

> "With the potential benefits offered by inhalable formulations, a number of companies are exploring the space for their own IPF treatments."

With the potential benefits offered by inhalable formulations, a number of companies are exploring the space for their own IPF treatments (Figure 2). While Insilico's is the first AI-designed inhalable IPF drug formulation in development, it joins a number of others in the field. For example, there is an inhalable version of pirfenidone by Avalyn Pharma (WA, US) that has shown favourable tolerability and is in Phase Ib studies.[2] Meanwhile, GSK is advancing the IPF drug GSK3008348, which is administered by a nebulised spray and is also presently in Phase I trials to determine safety and efficacy in healthy volunteers.[3]

THE PATH TO INSILICO'S INHALABLE IPF DRUG

Insilico's inhalable IPF drug formulation began its journey in 2021, when the company announced it had selected a preclinical candidate. The company used its AI target identification engine, PandaOmics,

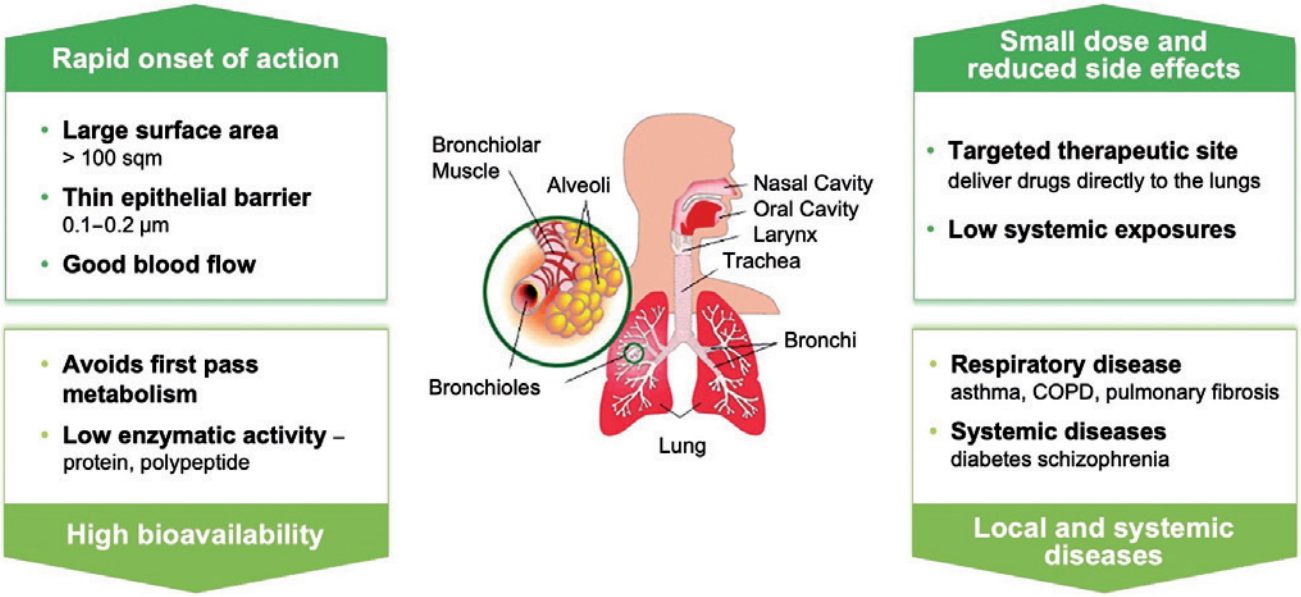

Figure 2: Infographic detailing the advantages of drug delivery to the lung for respiratory conditions.

to identify a novel pan-fibrotic target, dubbed "Target X". Insilico's generative AI small-molecule engine, Chemistry42, was then applied to Target X to design an entirely new molecule from scratch that could be explored as a new IPF treatment option. The entire process was accomplished in record time – under 30 months from target discovery to Phase I trials.

In January 2023, the Phase I trials had produced positive topline results and, in February 2023, Insilico's oral IPF drug received ODD from the FDA. This lead drug has now begun Phase II trials with patients, the first AI-discovered and AI-designed drug to reach this milestone.

"Initiating Phase II trials with this novel inhibitor for IPF represents a major milestone for deep generative reinforcement learning in drug discovery," said Insilico founder and Co-Chief Executive Officer Alex Zhavoronkov. "We will explore the efficacy for patients of AI-discovered and designed treatments in clinical trials, which is a true validation of our generative AI platform. We are eager to continue to advance this potentially first-in-class therapy forwards to help patients in need and show the value of generative AI in drug discovery and development."

THE AI TRANSFORMATION OF PHARMA

The AI transformation of the pharmaceutical industry is well underway. Insilico is one of the lead players in this effort, having developed an end-to-end pharma AI platform that has been used to develop a pipeline of over 30 drugs in development across cancer, immunity, fibrosis and central nervous system diseases. Four of these AI-designed drugs are currently in clinical stages.

> "The AI transformation of the pharmaceutical industry is well underway. Insilico is one of the lead players in this effort."

Pharma companies license both Insilico's AI-designed and developed therapeutic assets and its software to advance their internal drug development programmes. The company recently signed a strategic agreement with Exelixis (CA, US), giving the oncology-focused biotech the right to develop and commercialise ISM3091, a potentially best-in-class small-molecule inhibitor of USP1, which has emerged as a synthetic lethal target in BRCA-mutated tumours. The agreement included a US$80 million (£66 million) upfront fee, in addition to milestone payments and royalties on net sales.

Additionally, in November 2022, Insilico announced a multi-target collaboration with Sanofi to use its AI platform to advance drug development candidates for up to six new targets with upfront and target nomination fees of up to $21.5 million and other development- and commercial-based milestones that could total up to $1.2 billion, in addition to royalties.

The latest research reveals that bringing a single drug to market now costs over $6.1 billion for a big pharma company.[4] In a more nimble biotech setting, driven by the speed and efficiency of AI, faster and less expensive high-quality early drug development is possible. Strategic partnerships between big pharma companies and biotech start-ups can take these AI-designed drugs over the finish line. What began as the first fully generative AI drug to reach Phase II trials, and expanded to become the first inhalable formulation of a generative AI drug, could ultimately come to represent one of the first steps in a major industry shift.

ABOUT THE COMPANY

Insilico Medicine is a global clinical stage biotechnology company powered by generative AI, connecting biology, chemistry and clinical trials analysis using next-generation AI systems. The company has developed AI platforms that use deep generative models, reinforcement learning, transformers and other modern machine learning techniques for novel target discovery and the generation of novel molecular structures with desired properties. Insilico Medicine is developing breakthrough solutions to discover and develop innovative drugs for cancer, fibrosis, immunity, central nervous system diseases, infectious diseases, autoimmune diseases and ageing-related diseases.

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Brita Belli is Head of Public Relations for Insilico Medicine. Her writing has appeared in the New York Times, National Geographic, Yale Medicine Magazine, Union of Concerned Scientists, OR Manager Magazine and European Biopharmaceutical Review. Ms Belli is the author of "The Autism Puzzle: Connecting the Dots Between Environmental Toxins and Rising Autism Rates" (Seven Stories Press) and the digital playbook "Elevating Women in Entrepreneurship" (JP Morgan Chase and InBIA).

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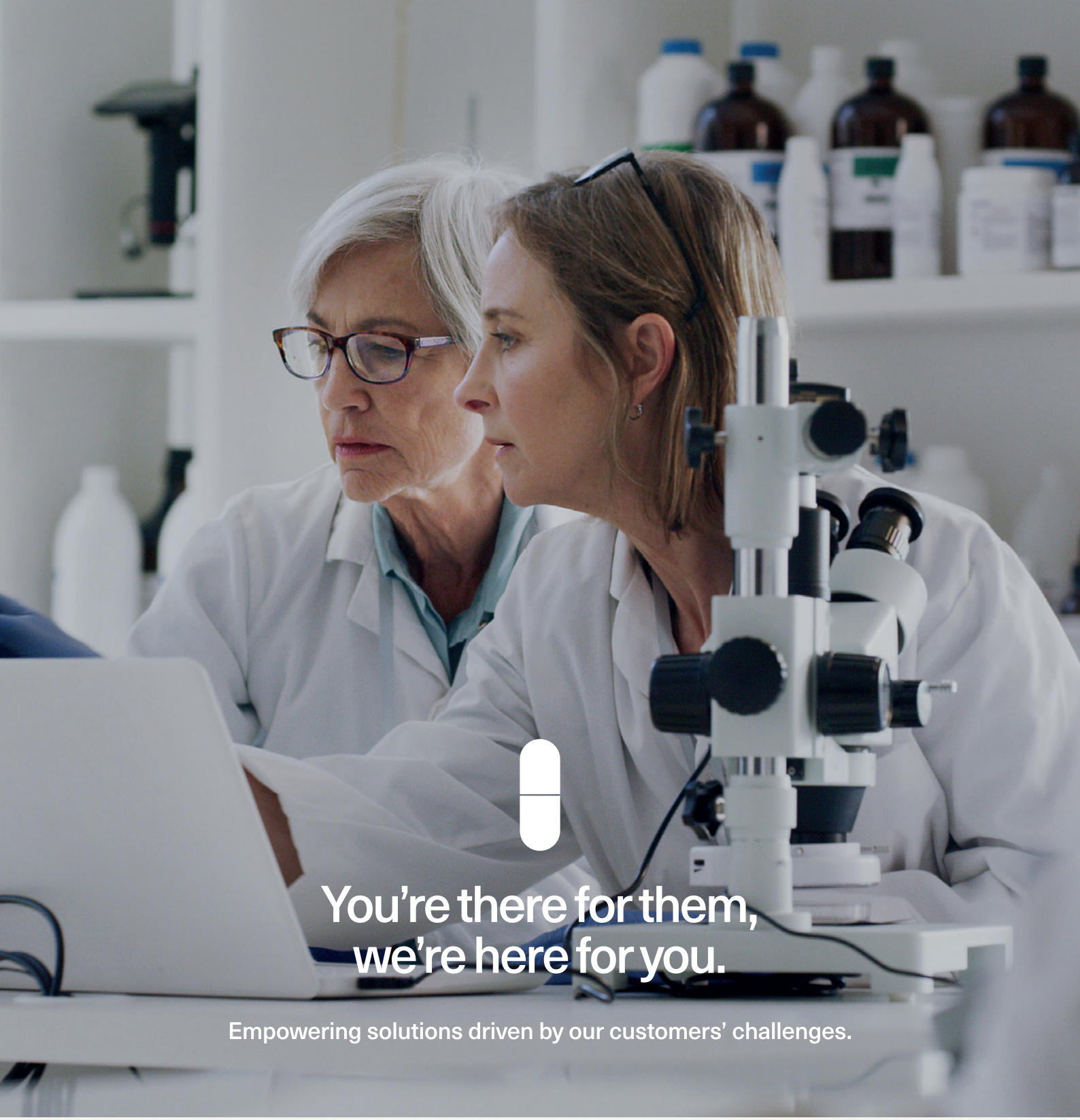

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December	Connecting Drug Delivery	Nov 7, 2024

hcmed
Nebulize High Value Therapeutic Drugs

THE VALUE OF CUSTOMISABLE MESH NEBULISER PLATFORMS IN COMBINATION PRODUCT DEVELOPMENT

In this article, Edgar Hernan Cuevas Brun, Business Development Manager & Scientist, Aerosol Drug Delivery, and Yuan-Ming Hsu, PhD, Research and Development Director, both at HCmed Innovations, look at the advantages of customisable nebuliser platforms for new combination products.

Advancements in inhalation therapy during the last decade have enabled the pharmaceutical industry to overcome some of the challenges commonly associated with the delivery of drugs to the respiratory airways and the lungs. In the past, dosing limitations resulting from inconsistent delivery of APIs, as well as the variability of patients' physiological and anatomical conditions across different population groups, were frequently reported as shortcomings of the inhalation administration route. Thanks to innovative technological approaches and research, there is a growing understanding of the importance and benefits of the inhalation route, along with the significant influence of formulation-device interaction.[1,2] Likewise, the establishment of standardised aerosol characterisation and drug delivery studies has also supported the evolvement of this field.[3]

During this period, the implementation of new regulatory pathways and guidelines for market approval filing has further increased confidence in the direct delivery of drugs to the lungs, especially for the treatment of respiratory diseases and conditions that could benefit from the faster absorption of APIs into the bloodstream via the thin alveolar-capillary barrier in the lungs. The result of these findings is shaping a more solid route for the development of inhaled drug-device combination products, with pharmaceutical companies and device manufacturers working on innovative treatment options that focus on optimising drug delivery efficiency and repeatability.

As new formulations are developed with consideration given to drug-device interactions, device manufacturers are transitioning into becoming contract development and manufacturing organisations (CDMOs) that offer customisation platforms for the delivery of inhalable formulations. Nowadays, these platforms can fulfil requirements ranging from aerosol properties and delivery efficiency to intuitive usability functions that satisfy human factors needs for the patient population target. Consequently, in the drug-nebuliser combination product space, CDMOs are developing mesh nebuliser platforms to add value to the development process. These customisable platforms are being developed to support innovative inhalable treatments, which range from the delivery of small molecules to biologics.

> "Consequently, in the drug-nebuliser combination product space, CDMOs are developing mesh nebuliser platforms to add value to the development process."

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DRUG-NEBULISER IMPLICATIONS AND DEVELOPMENT

For the development of drug-nebuliser combination products, identifying the unmet needs for the target population is one of the key initial steps for development, both for the formulation of the drug substance and the selection of the device. Dry powder inhalers may be more suitable for populations that do not exhibit significant difficulties reaching a specific inhalation flow rate, whereas nebulisers are preferable for patients who are not able to reach the necessary flow peak for actuation.

While small molecules are thought to be easier to deliver than large molecules, suspensions and highly viscous formulations, each formulation interacts with a delivery system in a unique way. Biologics and liposomal formulations are often classified as the most susceptible groups to drug-device interaction. Biologics have been reported to aggregate or lose activity, particularly when exposed to detrimental forces during delivery, while liposomes can burst prematurely, releasing the API.

As mitigating mechanisms, formulating solutions or suspensions with suitable excipients and solvents is essential, as is selecting a suitable delivery platform that can fulfil the delivery requirements. For this reason, drug-nebuliser development is paving a new path in which both formulation and device can be tailored from an early stage to achieve more positive delivery outcomes and increase the likelihood of a successful development.

Establishing the efficacy and therapeutic effect of a combination product constitutes the central point of the development. In many cases, this is primarily related to the efficacy of the API and the aerosol performance; however, usability and human factors studies have shown another increasingly valuable aspect for the success of new therapies – compliance. From here, the possibility to tailor a device extends beyond aerosol delivery and characterisation, via a customised user interface and functionality that can accommodate the needs of diverse population groups, such as children, young adults and the elderly, each one presenting a different set of needs when it comes to the device's ergonomics, indicators and feedback mechanisms.

Forged on these principles, and due to the existing demand and development spectrum, a CDMO offering customisable platforms should be capable of offering flexible, yet mature, customisation options as the basis of its combination product development, thereby supporting pharmaceutical companies from an early stage.

MESH NEBULISER BENEFITS AND SELECTION SCOPE

Active mesh nebulisers are devices that rely on the oscillation of a mesh membrane to transform a liquid medication into aerosol. This process has been shown to generate less heat than ultrasonic nebulisers and lower stress and shear forces than jet nebulisers. As such, mesh nebulisers are often described as a more suitable option for delivering molecules that are susceptible to detrimental forces, while also delivering them in a shorter time and with lower residual mass. However, the performance and specifications of devices from different manufacturers have shown that there is a wide range of outcomes that can occur even with the same mesh technology base. Therefore, selecting the appropriate mesh nebuliser for a new formulation or even group of candidate formulations can be challenging.

Exploration of device selection is often initiated with a feasibility study to gain an understanding of aerosol characterisation performance and the stability and activity of the API post-nebulisation, especially with biologics. During this step, the interaction of the device and formulation should be studied and development further reinforced. Meanwhile, the formulation's physicochemical properties, such as viscosity, surface tension and osmolality, among others, may be some of the driving factors of its aerosolisation characteristics. Equally, from the device perspective, the mesh membrane specification, power consumption and other electrical and mechanical components form the aspects that contribute to the drug-device interactions.

Considering these aspects, the requirements from the pharmaceutical company and the device CDMO are heavily intertwined, but can be simplified with a customisable platform product – a product with an essential foundation in aerosol performance but that is only considered completed after adding other factors, such as usability, connectivity and activation options.

ADDED VALUE OF A CUSTOMISABLE PLATFORM

A customisable platform can effectively facilitate and shorten the development process of a drug-nebuliser combination product, as well as support the initial feasibility assessments. During the feasibility assessment, pharmaceutical companies looking for a mesh nebuliser to deliver candidate formulations can avoid investigating a series of over-the-counter products by using a nebuliser platform that can be tailored to a range of specifications. This can result in a device that is a better match for the candidate formulation in the early stages of development before getting into more specific customisation options later on, adding significant value to the development process.

Feasibility Study

At HCmed Innovations – a CDMO focused on mesh nebuliser platforms and devices operating under continuous (Pulmogine®) and breath-actuated (AdheResp®) modes (Figure 1) – identifying the ideal

Figure 1: HCmed's AdheResp smart breath-actuated nebuliser and Pulmogine vibrating mesh nebuliser.

Pulmogine Development Kit

Group 1: Small Pore Size Meshes x 3
Group 2: Medium Pore Size Meshes x 3
Group 3: Large Pore Size Meshes x 3

AdheResp Development Kit

Group 1: Small Pore Size Meshes x 3
Group 2: Medium Pore Size Meshes x 3
Group 3: Large Pore Size Meshes x 3

Figure 2: AdheResp and Pulmogine nebuliser development kits for early feasibility assessment.

device mode at an early stage is essential for future development and can reduce the burden that would otherwise result from testing both nebuliser platforms.

For each nebuliser platform, the feasibility study process starts with the development kits, which are presented as a standard set of nine nebulisers divided into three groups based on their mesh pore size specification (Figure 2). By grouping three devices of each specification in the same group, repeatability can be investigated, providing an insight into the initial aerosol delivery performance parameters, including volume median diameter or mass median aerodynamic diameter, as well as fine particle fraction, geometric standard deviation, output rate, delivered dose, delivery rate and overall treatment time. Furthermore, the same kit can be used to confirm the stability of the molecule and compare the therapeutic activity of the API both pre- and post-nebulisation as part of a preliminary assessment. Additionally, by performing the assessment within the same platform, it is possible to generate a comprehensive set of data that could later add more value to the development process.

Design Customisation and Development

Once the aerosol delivery has been assessed and positive results have been obtained for the most optimal formulation-device combination, further customisation planning, including aspects other than aerosol characterisation, can commence. In the case of HCmed's platforms, there are several modifications and features that can be implemented, depending on the degree of customisation required.

As part of the development plan, input requirements are defined for customisation of the features associated with specific development timelines. The degree of customisation then becomes the primary element driving the timelines for development and deliverables, as agreed upon with the pharmaceutical company.

The customisation options cover aspects at both the firmware and hardware levels. The most common customisation features include:

- **Aerosol Performance and Delivery:** Mesh membrane specification is one of the key components that directly influences aerosol characterisation. Although an initial selection is done in the feasibility study as part of the exploratory work, additional testing is required to identify the most suitable specification range and pore size. Available in both Pulmogine and AdheResp platforms.
- **Power Consumption:** The power that drives the oscillation of the mesh membrane can be tuned within an upper and lower limit, altering the output rate of the device, thereby adjusting the treatment time and delivery rate. Available in both Pulmogine and AdheResp platforms.
- **Container Fill Volume:** The maximum capacity of the container's fill volume can be customised to suit the dose to be delivered. Simultaneously, container modification can also address changes to the residue. Available in both Pulmogine and AdheResp platforms.
- **User feedback:** Both nebuliser platforms use LED indicators to provide feedback on the device operation. Additional LED indicators, as well as audible, tactile and visual feedback, are also possible. The AdheResp platform includes an embedded vibration feedback mechanism that indicates when the device is activated, aerosol generation is triggered and treatment is completed.
- **Activation:** By bonding a specific drug to the device, delivery can only be accomplished after activation with a specific tag via near field communication technology. The key purpose of this function is to avoid misuse of the device to deliver formulations other than the intended one. This function can be enabled or disabled as needed. Only available in the AdheResp platform.
- **Connectivity:** Bluetooth connectivity enables the transmission of data between the nebuliser and a mobile device. Data such as time sets, battery status and pressure during breathing can be readily transmitted during treatment. With the support of a third-party cloud, this information could be shared with physicians, healthcare professionals, patients and medical facilities. Currently, only available in the AdheResp platform.

The customisation scope of HCmed's nebuliser platforms has evolved to fulfil several input requirements that can satisfy the needs of different patient populations, taking into account the indication and age group. This enables the customised device to cover all the aspects that are related to the user characteristics of the group being treated.

As some of the modifications may lead to changes that significantly depart from the standard Pulmogine and AdheResp platforms, additional design validation and verification may also be required. During this process, the customised device's functionality, reliability and performance are checked in order to generate the corresponding technical documentation package for submission.

When considering clinical implications, the use of the platforms' standard devices can be readily applied in early stages, enabling

"When considering clinical implications, the use of the platforms' standard devices can be readily applied in early stages, enabling easier bridging in later clinical phases."

Figure 3: Nebuliser customisation scope for combination product development from early feasibility assessment to commercialisation.

easier bridging in later clinical phases. Once the technical documentation for the customised device has been fully generated, it can be incorporated into the combination product development – most commonly prior to a Phase II study – to complete the subsequent steps in verifying the treatment's safety and efficacy.

Regulatory, Supply and Post-Market Surveillance

Although customised devices that have been tailored for the delivery of a specific formulation require their own exclusive documentation packaging, part of the technical documentation can be adapted from the platform's standard version. HCmed's nebuliser platforms, Pulmogine and AdheResp, come with complete technical documents that have been used in submissions for the standard devices. These documents can be referenced or leveraged for the customised device to a certain degree, which provides two key advantages:

1. Assurance that a device operating with the same technology has been approved and is fit for its intended purpose, leading to higher confidence in the success of a customised version.
2. Speeding up the timelines for producing the development and technical documentation.

While there are specific regulatory pathways for each country or region, the fundamental design history file is adequate for reference. In the US, the submission of a combination product of a drug with a specifically customised device is highly encouraged by the US FDA. To facilitate the submission, the filing is driven by the drug formulation without requiring separate approval for the device. The CDMO plays an essential role in the market access filing process for the final product.

The next key milestone is the scaling up of the product ready for commercialisation. The existence of standard products within a customisable platform results in a faster and more reliable ramp up for mass production. This stage fundamentally relies on the experience and technology, which is developed through a reliable supply chain and ensures quality assurance for the release of the final product. A CDMO, such as HCmed, can secure the production numbers of the customised nebuliser to co-package with the drug or adapt to other commercialisation strategies, depending on the territory.

Finally, once the product is marketed, the job of a mesh nebuliser CDMO partner is to provide further appropriate post-market surveillance for the device components. The CDMO's ultimate goal is to consolidate its commitment to the combination product developed with a pharmaceutical partner to provide the best possible treatment to patients.

CONCLUSION

The advantages provided by the adoption of a customisable nebuliser platform in new combination products extend from as early as the feasibility phase, continue throughout the development phase and reach all the way to final commercialisation (Figure 3). The platform approach facilitates the overall process for combination product development, shortening timelines and increasing the probability of success, with CDMOs able to create value from their existing platforms.

At HCmed, the company's commitment to and flexibility in customising its Pulmogine and AdheResp platforms constitutes its main contribution for pharmaceutical companies looking for mesh nebuliser platforms to deliver inhalable drugs, from small molecules

to biologics. As new treatments are developed with the aim of being directly delivered to the lungs, it is expected that the partnership between pharmaceutical companies and CDMOs will remain part of the foundation for drug-nebuliser combination product development.

ABOUT THE COMPANY

Founded in 2014, HCmed Innovations is a contract development and manufacturing organisation that provides high-quality and cost-effective vibrating mesh nebuliser technology and services to support global pharmaceutical partners in the development of drug-nebuliser combination products for inhalation therapies. HCmed offers mature customisable mesh nebuliser platforms to enhance drug delivery. The company's technology enables efficient and reliable nebulisation of different types of medication, ranging from small-molecule synthetics to large molecule biologics, as either solutions, suspensions or even difficult-to-deliver high viscosity drugs. Its latest platform includes the incorporation of breath actuation and connectivity features to enhance drug delivery and monitor patient adherence.

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Edgar Hernan Cuevas Brun is Business Development Manager at HCmed Innovations. He has over nine years of experience in the drug delivery field and holds a BS in Biomedical Engineering from National Tsing Hua University (Taiwan) and a Master's in Business Administration. He is responsible for expanding and co-ordinating the establishment of new partnerships with global pharmaceutical companies, while also supporting the development of drug-nebuliser combination products. Furthermore, he is involved in the development of connected devices, assisting in the company's programmes and establishing alliances with new partners to expand into digital health.

Yuan-Ming Hsu, PhD, is R&D Director at HCmed Innovations, leading the R&D department. He is responsible for new product development and product customisation for drug-nebuliser combination products. He holds a PhD in Biomedical Engineering from National Yang-Ming University (Taiwan). Additionally, he has worked as a researcher at a medical centre in the field of regenerative medicine and controlled-release drug delivery systems. Dr Hsu also gained experience in animal and clinical studies while he was the R&D supervisor in a pharmaceutical company. In the medical device field, he has more than eight years of experience in developing Class II and III products and clinical trials, including for drug-device combination products.

THE IMPORTANCE OF THE BREATHING MANOEUVRE IN NEBULISED THERAPIES

Here, Carolina Dantas, MD, Manager of Medical and Scientific Affairs, and Ulf Krueger, Chief Executive Officer and Founder, both at Pulmotree Medical, highlight the importance of the breathing manoeuvre in nebulised therapies – and describe a small study designed to test the effectiveness of patient feedback technology when it comes to guiding the inhalation manoeuvre.

Nebulised therapies, by delivering medication directly into the lungs, have been essential in the treatment of respiratory diseases such as asthma, chronic obstructive pulmonary disease and infections. The breathing manoeuvre plays a pivotal role in drug deposition within the respiratory system, particularly when aiming for deep lung penetration and minimal upper airway impaction.

THE BREATHING MANOEUVRE AND PULMONARY DRUG DEPOSITION

Several studies have investigated the main influencing parameters in pulmonary drug deposition: the airway structure, the aerosol characteristics and the breathing manoeuvre.[1,2] Targeted lung deposition is an important concept in nebulised therapies, and it is defined by the intentional manipulation of one or more of these parameters to promote aerosol deposition in certain locations in the respiratory system.

When using a nebuliser, spontaneous breathing patients naturally perform different breathing manoeuvres, with a wide variability of flow rate, respiratory rate or inhaled volume. Therefore, the aerosol deposition – and consequently the dose – varies considerably among patients.

> "When using a nebuliser, spontaneous breathing patients naturally perform different breathing manoeuvres, with a wide variability of flow rate, respiratory rate or inhaled volume."

So, how can this variability be reduced? According to Brand et al, by controlling the breathing manoeuvre. With slow inhalations, at low flow rates, a drug can be targeted to the lung periphery with high efficacy and low variability. Additionally, to achieve a higher alveolar deposition, it is also important to consider the need for higher inhaled volumes.

Overall, the inhalation manoeuvre of the patient has a major relevance for the amount of drug that will deposit deep into the lungs.[2] When considering the strong influence of the particle size and the breathing manoeuvre, there seems to be an "opportunity window" when lung deposition is maximised. This, in particular for nebulised therapies, allows the development of devices that provide some control over targeted lung deposition.[3]

NEBULISATION – CONTINUOUS OR BREATH TRIGGERED?

There are several types of nebulisers in the market, and these are frequently categorised according to their mechanism of action into three main types: jet nebulisers, ultrasonic nebulisers and vibrating mesh nebulisers. Considering the importance of the breathing manoeuvre, nebulisers can also be differentiated by their nebulisation mode. Some devices deliver aerosol continuously during the entire breathing cycle (inspiration and expiration). Aerosol waste can be reduced by storing the aerosol generated during exhalation in a reservoir, and subsequently releasing it during inhalation, allowing optimisation of the nebuliser performance. On the other hand, breath-triggered/activated/actuated devices deliver aerosol only during the inspiratory phase using a breath actuation mechanism triggered by the patient.

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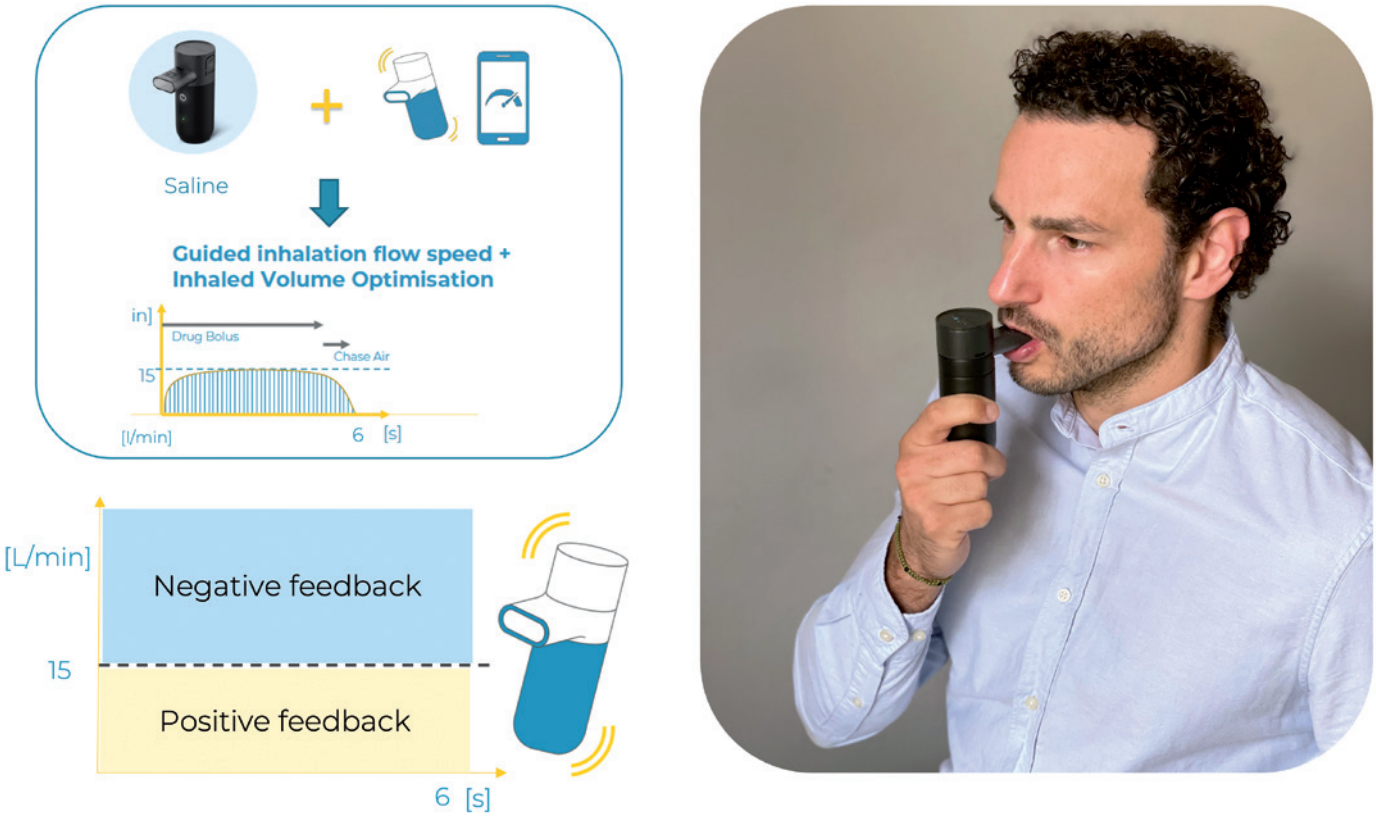

Figure 1: Study protocol, feedback settings and picture from participant (authorised).

"Patient feedback technology enables nebulisers to provide guidance for patients to perform an ideal breathing manoeuvre according to the targeted lung deposition area."

Besides the nebulisation mode, devices can have different technologies to control or guide the breathing manoeuvre of the patient, which were developed to increase the aerosol delivery efficiency. These include, for example:

- Software that predicts patient inhalation based on the previous breathing cycles
- Delivery of aerosol bolus at a precise point in the inspiration phase
- A resistance mechanism to regulate the inhalation flow
- Feedback systems to support and guide the patient.

Ultimately, these different nebulisation modes and technologies represent specific features of each existing device. Understanding the impact on respiratory drug delivery is critical for minimising medication waste, enhancing patient adherence and experience, and achieving better therapeutic outcomes.

A STUDY ON FEEDBACK TECHNOLOGY TO GUIDE INHALATION

Patient feedback technology enables nebulisers to provide guidance for patients to perform an ideal breathing manoeuvre according to the targeted lung deposition area. Haptic feedback, for example, provides tactile sensations or vibrations to the user for improved interaction or guidance. The same applies to other forms of feedback – for example, digital, visual, auditory or thermal.

This article describes a small study aimed at validating the feedback system of the Kolibri mesh nebuliser in guiding inhalation during the nebulisation of 1 mL of saline. The inhalation flow rate threshold was defined as 15 L/min. Therefore, below that threshold a positive and pleasant vibration instructed the user to maintain the inhalation flow rate, and above the 15 L/min threshold, a negative and unpleasant vibration occurred. Eight healthy subjects were included in the study and data on inhalation flow rate (in L/min) and duration (in seconds) were collected and analysed (see Figure 1).

In the individual analysis, each inhalation curve was registered, as well as the number of inhalations needed to nebulise 1 mL of saline (see Figure 2). Such detailed tracking allowed the determination of the inhalation variability of each participant. Better inhalation manoeuvres reduced the amount of time necessary for nebulisation, resulting in higher efficiency.

The group analysis showed that all the participants could easily follow the feedback and maintain the inhalations below the threshold of 15 L/min, as illustrated in Figure 3. As a group, there was little variability in the inhalation manoeuvres, with an average of 16%. Additionally, two participants illustrated

"This small study demonstrated the ability of feedback technology to effectively guide the inhalation manoeuvre during nebulisation."

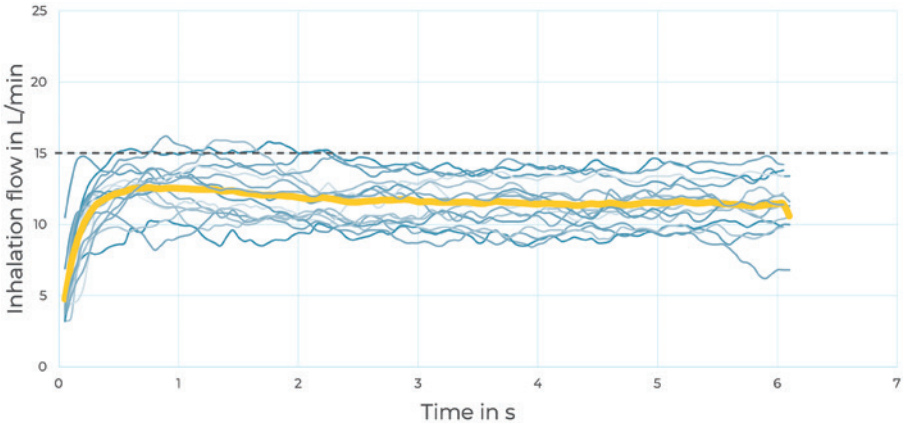

Figure 2: Example of subject 6 guided inhalation flow rate curves. Each inhalation is registered in blue and the average in yellow.

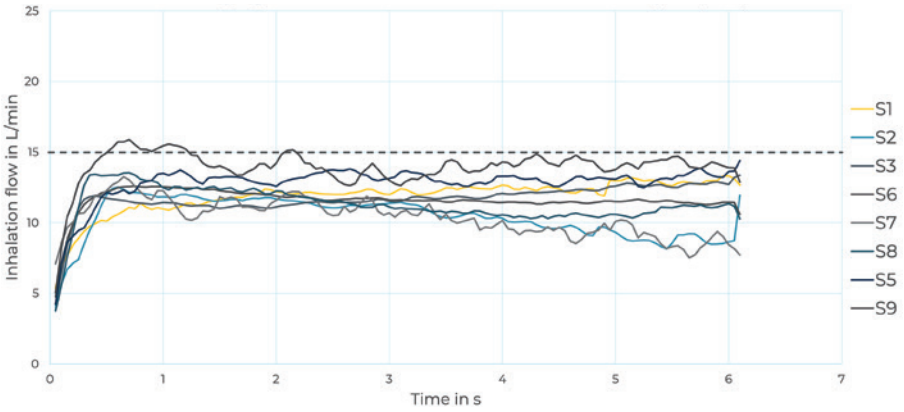

Figure 3: Group analysis, in which each curve represents the average inhalation flow rate of the eight participants. Overall, the majority of the participants could maintain the inhalation flow below the 15 L/min defined threshold.

a learning curve process – revealing their ability to recognise the different types of haptic feedback and progressively learn to follow the desired inhalation flow rate.

This small study demonstrated the capacity of feedback technology to effectively guide the inhalation manoeuvre during nebulisation. Using haptic feedback, it was possible to reduce the variability typically associated with spontaneous breathing nebuliser users. Future larger studies assessing the effect of feedback-guided inhalation on targeted lung deposition will provide further valuable data.

In nebulised therapies, the breathing manoeuvre plays a major role in achieving a targeted drug deposition and consequently the best treatment outcomes. Understanding and tackling the challenge to reduce the breathing manoeuvre's variability is key. Current technologies, in particular breath-triggered nebulisers with guided inhalation systems, provide opportunities to further enhance aerosol lung deposition. Comprehensive studies in the future will shed light on the impact of feedback-guided inhalation on targeted lung deposition, ultimately advancing the field of respiratory therapies towards more personalised and effective treatments.

ABOUT THE COMPANY

Pulmotree Medical specialises in the development of drug delivery systems with targeted deposition of drugs into specific areas of the lung. It supports pharma partners with comprehensive services around the product lifecycle of drug and device combinations.

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Ulf Krueger has extensive experience in life sciences, which is the basis of Pulmotree Medical's business – particularly managing projects, programmes and portfolios in the field of inhaled drug delivery. Throughout his career, Mr Krueger has been particularly engaged in the development of pulmonary drug delivery devices and the targeted delivery of drugs to the lungs. In his former position as Director of Fox Nebuliser Programs at Vectura, he held responsibility for the entire sector of vibrating mesh nebulisers. Before that, he held various positions in the research and development department of PARI. He is a graduate biomedical engineer and a certified senior project manager (IPMA® Level B) and member of The Aerosol Society, the European Respiratory Society and the International Society for Aerosols in Medicine.

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THE END OF THE ROAD FOR pMDIs?

In this article, Finn Heraghty, Consultant Mechanical Engineer, and Heather Jameson, PhD, Senior Engineer, both at Springboard, explore the extent to which the healthcare needs of a population could be covered by the combined use of soft mist inhalers and dry powder inhalers, and discuss the factors that will impact the continued importance of pressurised metered dose inhalers going forward.

For decades, the portable inhaler market has been dominated by two categories of inhaler – pressurised metered dose inhalers (pMDIs) and dry powder inhalers (DPIs). In recent years, other categories have emerged, such as soft mist inhalers (SMIs).

At the moment, pMDIs still make up the majority of inhalers purchased by the UK NHS. However, considering the impending transition away from high global warming potential (GWP) propellants, such as hydrofluoroalkanes (HFAs), that pMDIs currently use, how long will this remain the case? The Swedish market, where pMDIs make up only 10% of inhalers, provides evidence that heavy reliance on pMDIs is not essential to meet the healthcare needs of a population. Might we be approaching the end of the road for pMDIs?

pDMIs AND THEIR EVOLUTION

Since their introduction in the 1950s, pMDIs have been a mainstay in respiratory therapy.[1] A key advantage of pMDIs has always been their low cost. The drug is stored at high pressure in a canister in solution or suspension with the propellant(s), and aerosolisation is achieved by releasing the high-pressure propellant through a nozzle.

This method has proven effective in managing respiratory conditions, but is not without its drawbacks. For example, some patients may find it difficult to co-ordinate their inhalation with the release of the medication, potentially leading to suboptimal dosing. Some breath-activated pMDIs have been introduced to help resolve this issue, but these come with increased complexity, and therefore increased cost. Furthermore, the relatively fast spray velocity tends to result in a higher than ideal deposition of aerosol particles onto the back of the throat rather than into the deep lung. Use of a spacer (as shown in Figure 1) improves these issues, but they are bulky and so are often neglected, particularly when not at home or in hospital.

> "The main challenge to the ongoing dominance of pMDIs is the GWP of their current propellants."

Figure 1: A pMDI used with a spacer can improve ease of use.

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The main challenge to the ongoing dominance of pMDIs is the GWP of their current propellants.[2] Originally, chlorofluorocarbons (CFCs) were used in pMDIs, which are not only potent greenhouse gases, but also found to be ozone depleting.[3] After the introduction of the Montreal Protocol in 1987, which was designed to regulate the use of ozone-depleting chemicals, a transition was made to using hydrofluoroalkanes (HFAs) instead. However, although these are not known to harm the ozone layer, they are still potent greenhouse gases – the use of which vastly outweighs any environmental impact due to the materials used in the manufacture of the device itself.[2] The Kigali Amendment to the Montreal Protocol aims to reduce global HFA consumption by 80% by 2047,[4] with the even stricter requirement to do so in the EU by 2030.[5]

It is clear that we are approaching a turning point for pMDIs. The question is – will HFA-powered pMDIs be replaced by lower-GWP propellants or by different devices?

NEXT-GENERATION PROPELLANTS

Researchers and pharmaceutical companies are already actively searching for alternative propellants to replace the current options. Table 1 summarises some of the main lower-GWP candidates currently being considered, compared with some of those that are currently in use.[6]

Concerns remain around the new propellants proposed; there are flammability concerns for HFA-152a, particularly during manufacture and processing of the drug product,[5] and there is a risk that HFO-1234ze(E) could be banned under European REACH PFAS regulations[7] – the status of which should be clarified in 2024. The design of pMDI nozzles will also need to be optimised to work effectively with the new propellant(s) to compensate for the different physical properties.

> "Researchers and pharmaceutical companies are already actively searching for alternative propellants to replace the current options."

Propellant	Current or new	GWP (CO_2 = 1)	Comments
1,1,1,2,3,3,3-Heptafluoropropane (HFC-227ea)	Current	3220	High GWP
1,1,1,2-Tetrafluoroethane (HFC-134a)	Current (majority)	1430	High GWP
1,1-Difluoroethane (HFA-152a)	New	124	Flammability concerns Moderate GWP
1,3,3,3-Tetrafluoropropene (HFO-1234ze(E))	New	<1	Low GWP Could be banned in EU under REACH PFAS regulations, status should be clarified in 2024

Table 1: Summary of pMDI propellants.

Challenging timelines face pDMIs to meet the HFA restriction deadlines. New formulations will need to be brought to market in the next few years in optimised actuators with low-GWP propellants, and these propellants will need to be available at commercially viable prices with the quality and security of supply required for drug delivery devices. While pMDIs powered by low-GWP propellants may prove to be technically viable, market pressures may lead to a shift towards a greater market share of alternative devices.

DPIs: A PROVEN ALTERNATIVE?

DPIs have gained popularity as an alternative to pMDIs, first being introduced slightly later than pMDIs in 1967.[8] Unlike pMDIs, DPIs deliver medication in a fine powder form that does not require a propellant, therefore eliminating the concerns regarding greenhouse gas emissions from use. DPIs can effectively treat a similar range of respiratory conditions to pMDIs, provided the medication can be formulated as a dry powder. The powder is often stored in sealed capsules (Figure 2) to prevent contact with moisture, which could interfere with the ability of the powder to disperse effectively.

The Swedish healthcare model is often quoted as an example success story for the DPI – in 2011 approximately 90% of inhaler devices sold and used in Sweden were DPIs whereas, in the UK, approximately 80% were pMDIs.[9] This demonstrates that it should be theoretically possible to provide

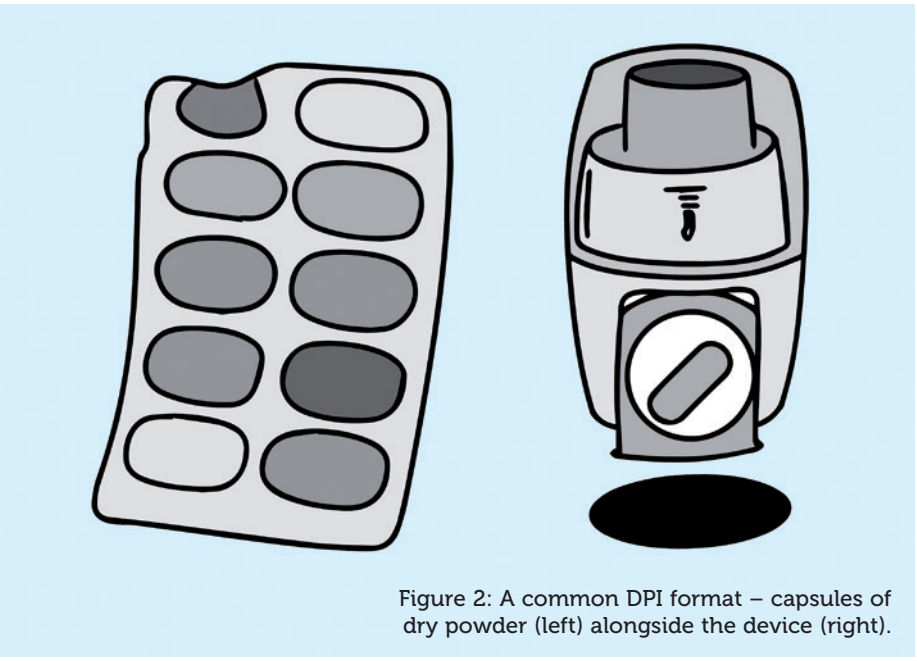

Figure 2: A common DPI format – capsules of dry powder (left) alongside the device (right).

for the healthcare needs of a population with a lower reliance on pMDIs. However, there are practical reasons why healthcare services in countries such as the UK and the US have a preference for pMDIs over DPIs.

Economic Pressures

A key reason for the widespread use of pMDIs is their low cost per unit. Analysis presented in 2019 assessed the potential cost to the NHS of a wholesale switch from using pMDIs (currently pMDIs account for approximately 80% of inhaler devices) to DPIs.[10] The study concluded that there would be a £127 million rise in prescribing costs per annum, representing around an additional 10% cost of respiratory therapy. The estimate was dependant on the ratio of branded products to generics employed, and it was suggested that a cost saving could be made if only generic DPIs were used.

However, given the investment that will be needed to transition pMDIs to new propellants, it is to be expected that their unit cost may increase, reducing the perceived benefit of pMDIs over DPIs.

Usability Concerns

DPIs work by relying on the patient's own inhalation to disperse and deliver the powdered medication into the lungs, which ensures that the medication is released only when the patient inhales correctly. This eases the need for careful co-ordination compared with pMDIs but, conversely, the sharp intake of breath required may not be possible for some patients, particularly those with the types of chronic lung conditions often treated with inhaled medications. Hence, there may be a subset of a population for which DPIs are simply not suitable – such as children, the elderly and those with severe respiratory conditions. This could mean there is an ongoing need for pMDIs for some users, even if diminished – unless alternative options could cover this gap?

SMIs: A GENTLE APPROACH

SMIs have been a recent and successful addition to the suite of available inhaler options, with the Boehringer Ingelheim Respimat being the first SMI, marketed in 2004.[8] As Spiriva (Boehringer Ingelheim, CT, US), a successful drug for the treatment of chronic obstructive pulmonary disease (COPD), is also beginning to come off-patent across the globe, several companies have designs for generic alternatives in the pipeline, from Merxin (King's Lynn, UK) to invoX Pharma, previously Softhale (Diepenbeek, Belgium),[11] and we should expect other novel soft mist device platforms to follow.

Figure 3: The fine mist produced by the Respimat SMI.

SMIs generally work by forcing liquid through one or more small nozzles to generate a fine aerosol mist, although different mechanisms have been explored, including impinging jets (Respimat – Figure 3) and Rayleigh break-up (Medspray, Enschede, the Netherlands). A spring or other mechanical system is used to generate the required pressure instead of a propellant, thereby also removing the issue of emissions from use.

The aerosolised drug solutions are expelled in a slow-moving jet, which reduces undesired oropharyngeal deposition and makes it much easier to successfully perform the sequence between actuation and inhalation[11] compared with a pMDI. The aerosol fine-droplet fraction from the Respimat is reported to be approximately double that of a pMDI,[12] meaning half the dose with a Respimat is able to achieve the same therapeutic outcome as the full dose administered by pMDI. The soft mist delivery format is also well suited for patients who struggle with generating the required inspiratory force for DPIs.

However, SMIs are not suitable in all applications. As the medication is typically forced through a very small nozzle (sometimes less than 5 µm), current technologies cannot be used with drugs in suspension, as the particles could either block the nozzle or be filtered out in the filter typically employed upstream of the nozzle. SMIs are also currently significantly more complex and expensive than pMDIs, but there is active interest in the market to identify new, simpler soft-mist mechanisms, with the goal of bringing the cost per unit closer to that of pMDIs. If this could be realised, the usability benefits of the SMI will provide strong competition to the pMDI.

FUTURE PHARMACEUTICAL TRENDS – BIOLOGIC DELIVERY

There has been growing interest in recent years about the potential advantages of delivering biologic drugs via inhalation.[13] The inhalation route is non-invasive and suitable for both local and systemic delivery, and inhalers have advantages for unassisted use in non-clinical environments.

> "When considering the delivery of biologics via oral inhalation, discussion of devices generally focuses on the varying merits and demerits of DPIs, nebulisers and SMIs – neglecting pMDIs."

Device Type	Reasons to Expect Continued or Growing Use	Barriers to Growth
pMDI	• Low unit cost • Minimal inhalation force required • Consistency bias	• High GWP of propellant • Uncertainty of new propellants • Potential rise in unit costs • Unsuitability for biologic delivery
DPI	• No greenhouse gas propellant used • Already the main inhaler used in some countries	• Not suitable for all users due to high inhalation force required • Unit cost generally higher than pMDIs
SMI	• No greenhouse gas propellant used • Good usability and high fine droplet fraction achievable • Generics and new, simpler mechanisms may bring unit cost down	• High unit cost and complexity • Not suitable for suspensions

Table 2: Summary of advantages and disadvantages for different inhaler options.

When considering the delivery of biologics via oral inhalation, discussion of devices generally focuses on the varying merits and demerits of DPIs, nebulisers and SMIs – neglecting pMDIs. The inherent temperatures and pressures involved in delivery and the risk of denaturing on aerosolisation[14] means pMDIs are not easily compatible with biologic drugs. There is concern over the interaction between the propellant used in pMDIs and the biologics, which can lead to the denaturing of proteins and peptides.[15] Poor solubility of biologics in the propellants also limits the dose range that can be delivered per actuation.[16] This is a growing market sector where pMDIs appear to be being left behind – a further indicator that their days may be numbered (Table 2).

CONCLUSION

So, are the next few years the end of the road for pMDIs? They will have a future if new formulations can be brought to market in the next few years in optimised actuators with low-GWP propellants that:

- Have acceptable flammability (a concern for HFA–152a)
- Meet PFAS regulations (a concern for HFO–1234ze)
- Are available at commercially viable prices with the quality and security of supply required for drug delivery devices.

However, if those criteria are not met, then we should expect DPIs and SMIs to take an increasing market share in all markets in the years to come.

ABOUT THE COMPANY

Springboard is a privately owned technology and design consultancy. The company creates and develops new products and technology, including products in the field of medtech and drug delivery devices, assisting companies in resolving technical challenges and decreasing time to market.

ABOUT THE AUTHORS

Finn Heraghty is a Consultant Mechanical Engineer at Springboard with a keen interest in materials, manufacturing and innovative products. He completed his master's degree in Engineering at the University of Cambridge (UK), during which he carried out a research project on a novel solid-state powder welding process. He has since had a wide breadth of experience in the medical device sector, working on projects ranging from complex delivery systems and implantables to medical robotics and surgical tools. His strong background in practical work has led him to enjoy designing parts for manufacture while working alongside clients to refine their ideas.

Heather Jameson, PhD, is a Senior Engineer at Springboard, taking a leading role in planning and executing both design and test projects and has worked on the design and development of several drug delivery devices. She read Engineering at the University of Cambridge (UK) before completing a PhD in Fluid Mechanics at the distinguished Whittle Laboratory. She continues to play an active part in university relations in addition to her public speaking engagements on STEM and outreach.

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In this article, Carolyn Berg, Vice-President, Business Development, William Chin, PhD, Manager, Global Scientific Affairs, and Patrick Goncalves, Account Executive, Business Development, all at Catalent, discuss the considerations for filling capsules for dry powder inhalers across the various stages of clinical trials and commercialisation, and how to tackle the challenges of scaling up filling processes.

Over the past two decades, the field of respiratory medicine has undergone significant growth and evolution. What was once a focus on developing drugs to treat asthma and chronic obstructive pulmonary disease (COPD) has expanded to include a range of therapy areas, including the respiratory, anti-infective, neurological and cardiovascular sectors, among others (Figure 1). According to industry clinical trial databases, nearly 100 molecules for respiratory delivery are currently in the clinical development pipeline, spanning from preclinical to Phase III stages, for both pulmonary and non-pulmonary indications.[1]

The growing interest in targeting the lungs as a viable drug delivery route reflects the potential of this approach to improve the treatment of a wide range of diseases.

By targeting the lungs directly, the pulmonary route of administration can minimise the systemic side effects often associated with other delivery methods. Traditionally, large doses of inhaled drugs have been administered by nebulisers. However, these devices are inconvenient for patients, as they are bulky, noisy, require a power source and have a longer administration time than other inhalation devices.[2] On the other hand, dry powder

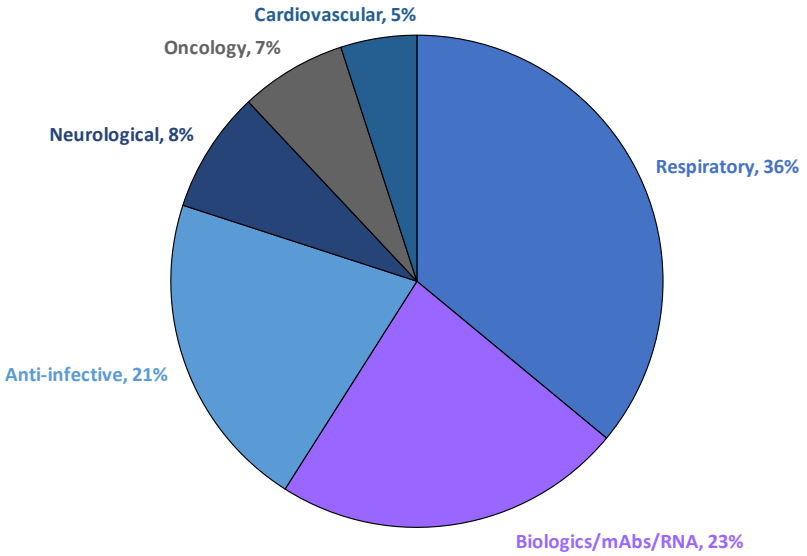

Figure 1: Pulmonary drug delivery sector by therapy area. Pulmonary delivery is a growing field with the potential to revolutionise the treatment of a wide range of diseases. (Source: Catalent's internal research on PharmaProjects database, 2022.)

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"DPIs are easy to use and their propellant-free design makes them a safe and convenient choice for individuals across age groups."

inhalers (DPIs) are easy to use and their propellant-free design makes them a safe and convenient choice for individuals across age groups. DPIs are based on the concept of a dose metering system that delivers a determined dose to the patient.

Various dose metering systems, such as single-dose capsule-based DPIs (sDPIs), blister-based devices and reservoir-based devices, each offer unique advantages and challenges.[3] Furthermore, they provide a good delivery method by offering targeted lung delivery with reduced side effects.[4] While blister- and reservoir-based systems offer advantages for specific applications and patient needs, sDPIs are generally considered to be the most versatile and user-friendly type of DPI due to two important factors:

1. Different-sized capsules, ranging from Size 00 to Size 3, can be used.
2. Different fill weights per capsule can be achieved, depending on the manufacturing technique of the powder and the variability of the fill weight per capsule.

Typically, sDPIs devices use a capsule containing the drug product, which is punctured to release the drug upon inhalation. Most inhalable drugs in development use hydroxypropyl methylcellulose (HPMC) capsules due to their high moisture barrier and lower risk of breakage upon puncture, thereby ensuring effective drug release.

However, manufacturing sDPIs presents its own set of challenges, including meticulous control over capsule materials and dimensions, as well as powder characteristics. The capsule's design must facilitate puncturing with a specific force and ensure uniform powder release. The performance also depends on the capsule's material, the inhaler design and the powder formulation contained within. This last point is the most crucial, as the flow characteristics of the powder can vary depending on the type of powder formulation. Each type of powder, whether it be a blended, carrier-based product with micronised drug or an engineered particle obtained through spray drying, has a unique set of rheological properties that can have a significant impact on the downstream manufacturing processes involved in capsule filling.[5]

Feature	Drum Filling	Dosator-based Filling
Principle	• A rotating drum with dosing cavities is filled with powder and then rotated to transfer the powder into the capsules • A vacuum can be used to draw powder into the dosing cavities	• A dosator, which is a precision metering device, is used to dispense powder into the capsules
Dosing range	• 1–50 mg	• 10–600 mg
Accuracy	• Very high with low variability; usual RSD < 3%	• Not as high as drum filling, influenced by high concentration of fines
Flexibility	• Can fill low doses; depends on dosing bore and vacuum • Fill weight can be slightly adjusted by vacuum setting to overcome batch-to-batch variations	• Can compact and retain powder in the pin for transfer • Fill weight can be adjusted by compaction force and pre-positioning of compaction pin
Powder characteristics	• Better for flowable powders • Arching in hopper can occur • Suitable for extremely cohesive powders • Particle size from 1 µm upwards with Carr's Index of 30% and higher	• Can handle hydrophilic powders with increased cohesiveness • Challenging when filling large particles with excellent flow behaviour • Plug formation issues • For powders with a Carr's index between 15 and 25% • Particle size ideally in the range of 50–150 µm
Equipment complexity	• Requires vacuum and specific dosing bore; typically higher equipment cost	• Requires plug formation and compaction in the pin; medium equipment cost
Residual volume	• Less, approximately 50 mL	• Higher than drum filling, approximately 200 mL

Table 1: Comparison of drum filling and dosator-based filling for sDPIs.

FACTORS TO CONSIDER WHEN SELECTING CAPSULE-FILLING TECHNOLOGY FOR DPIs

When it comes to filling capsules for DPIs, there are two primary methods to choose from – drum filling and dosator-based filling. It is important to determine which dosing system is most suitable for the given powder formulation as early as possible during product development so as to reduce the risk of needing to change the manufacturing process during clinical trials and commercialisation.

Drum filling is a method that uses a rotating drum to transfer powder into the capsules, with a vacuum capability to draw in the powder. On the other hand, dosator-based capsule filling uses a precise metering device called a dosator to dispense the powder into the capsules. Both filling methods are highly accurate, but drum filling has an edge over dosator-based filling due to its superior accuracy. Drum filling has also proved to be very robust across a range of powder properties,[6] making it a reliable option for precise dosing, especially for high-dose formulations. Additionally, drum filling is suitable for low-potency, high-dose drugs.[7] Both methods can fill a wide range of capsule sizes and formulations, but dosator-based filling has some limitations compared with drum filling (Table 1).

Molecule	Product	Company	Technology		
			Manufacturing	Filling	Device
Insulin	Exubera®*[2]	Nektar	Spray dried	Drum	Unit dose blisters Proprietary inhaler
Insulin	Afrezza®	Mannkind	Freeze-dried Technosphere®	Drum	Cartridge Dreamboat®
Treprostinil	Tyvaso DPI®	United Therapeutics & Mannkind	Spray dried	Drum***	Single-dose cartridge Dreamboat®
Levodopa	Inbrija®***[9]	Acorda	Spray dried	Drum (inferred)	Capsule Proprietary inhaler (pen device)
Tobramycin	Tobi®[10]	Novartis	Spray dried	Drum	Capsules Podhaler®

Withdrawn in 2007 for commercial reasons
**Original patents suggest dosator technology, but manufacturing facility supports drum technology*
****Uses same device and technology as Afrezza*

Table 2: Commercialised spray-dried inhalable powders.

Choosing between a dosator or a drum system for filling capsule-based DPIs with spray-dried powder depends on specific project needs and requirements. One key factor to consider is the flowability of the powder, as it determines which filling system is most suitable. Powders with a flow function coefficient (FFC) of less than four can be filled using a dosator system, while those with an FFC greater than four are more compatible with a drum system.[8] Another important consideration is the strength of the vacuum in the drum system, which has a significant effect on the fill weight. If there is a need to fill many capsules quickly and efficiently, vacuum-based drum filling is a good option. According to the data presented in Table 2, it can be observed that, in the case of most approved spray-dried products available in the market, drum-based filling is the prevalent technology used for capsule filling.

ADVANCED DOSING SYSTEMS FOR CAPSULE-BASED DPIs

Catalent's state-of-the-art facility is equipped with two advanced compact benchtop dosing devices – the Drum TT and Drum Lab – both of which are capsule-filling machines leveraging the latest drum dosing technology from Harro Höfliger (Allmersbach im Tal, Germany). The Drum TT, a compact manual filling machine, can be conveniently placed on any tabletop. It can precisely measure and fill as little as 0.5 mg of material into capsules within a short period of time. Additionally, it features a sophisticated pneumatic control system to regulate vacuum and compressed air. In the initial stages of clinical development, the Drum TT can be used to prepare galenic formulations for capsule-based DPIs. It is particularly useful for testing different powder formulations and optimising them for batch manufacturing.

The Drum Lab system is designed to semi-automatically dose small quantities of powder into capsules. This equipment is suitable for small-batch production, making it an ideal option for scaling up to a pilot scale. Additionally, this system also has an integrated check weighing system that ensures that the filled capsules meet the required weight criteria, resulting in more accurate dosing. Dose accuracy and weight checks are crucial from both a quality and operator standpoint.

From a quality perspective, it is vital to ensure that each capsule contains the correct amount of medication. Even a small variation in dose can significantly impact the medication's efficacy and safety. From an operator's perspective, dose accuracy and weight checks can help to reduce the time spent in manufacturing. By ensuring that each capsule meets the required weight criteria, operators can avoid having to rework or reject capsules.

Historically, contract development and manufacturing organisations (CDMOs) have had to send powders and capsules to external labs for testing, which could be a time-consuming process, taking several days or even weeks to receive results. However, with Drum Lab, CDMOs can perform dose accuracy and weight checks in-house, significantly reducing the time required to develop and launch new products.

The Drum TT and Drum Lab are highly versatile systems that can fill capsules, as well as other customised containers or cartridges, for use in proprietary devices that may be in development. Both systems are capable of dosing blended and spray-dried powders with ease. The Drum TT and Drum Lab systems can be used in various scenarios, such as preparing small batches of a blended powder formulation for clinical trials or dosing spray-dried powder formulations for commercial production.

The Catalent facility also includes a Harro Höfliger Omnidose powder-filling machine, a versatile semi-automatic machine that can fill capsules with high precision. It is ideal for pharmaceutical companies working on DPI formulations, whether for new developments or scaling existing products. The Omnidose can be easily adjusted to handle different types of powders, making it an excellent tool for prototyping and developing new DPIs, while ensuring accurate powder filling in each capsule, which is crucial for the safety and efficacy of DPIs.

Furthermore, the design of the machine is scalable to meet the production-level demands of pharmaceutical companies. For larger quantities of powders, the Harro Höfliger Modu-C MS high-speed filling machine is capable of manufacturing up to

"One of the significant challenges in the process is scaling up capsule filling for clinical trials, which requires comprehensive planning and execution."

100,000 capsules per hour. This advanced equipment can encapsulate a wide range of powders at kilogram scale, is capable of filling doses as low as 0.5 mg and is particularly useful for highly cohesive products, such as spray-dried formulations. The Modu-C MS also includes the inline capsule de-duster, 100% net weighing via a capacitive advanced mass measurement sensor for minimal quantities dosing and containment systems. The high-speed and high-volume capabilities of Modu-C MS can provide an efficient pathway to commercial production.

INTEGRATED SCALE-UP PATH

Developing sDPIs is a complex process that demands careful consideration and execution. One of the significant challenges in the process is scaling up capsule filling for clinical trials, which requires comprehensive planning and execution. During different phases of clinical trials, the number of capsules needed may vary significantly. It has been proven that scaling up drum filling is feasible, and the sDPI development process can be easily scaled up from Drum TT, Drum Lab and Omnidose to Modu-C MS. The Modu-C MS is designed to be compatible with the same dosing and filling systems used on the Omnidose, ensuring that the scale-up process is as seamless as possible. This makes it quick and simple to transfer the existing process parameters. This integrated scale-up path can help pharmaceutical companies accelerate the development and launch of new sDPI products while maintaining the highest quality and consistency at all production scales (Figure 2).

CONCLUSION

The development and manufacture of sDPIs present a multifaceted challenge that spans material selection, device design, powder formulation and filling technologies. Drum filling emerges as a superior method for capsule filling, offering high accuracy and speed, particularly beneficial for high-dose formulations. Catalent's advanced dosing systems, including the Drum TT, Drum Lab, Omnidose and Modu-C MS, provide an integrated and scalable solution for sDPI development, from early-stage clinical trials to commercial production. To overcome the challenges associated with scaling up capsule filling, pharmaceutical companies can partner with a CDMO, such as Catalent, that has the necessary equipment and expertise to manage complexities, ensure quality and navigate regulatory requirements. By gaining access to this specialised knowledge and experience, pharmaceutical companies can de-risk the scale-up process and maximise the chances of commercial success. Partnering with a CDMO can mitigate the risks associated with scaling up and expedite time to market, ensuring both quality and commercial viability.

ABOUT THE COMPANY

Catalent (NYSE: CTLT) is a global leader in enabling pharma, biotech and consumer health partners to optimise product development, launch and full lifecycle supply for patients around the world. With broad and deep scale and expertise in development sciences, delivery technologies and multi-modality manufacturing, Catalent is a preferred industry partner for personalised medicines, consumer health brand extensions and blockbuster drugs. Catalent helps accelerate over 1,500 partner programmes and launch over 150 new products every year. Its flexible manufacturing platforms at over 50 global sites supply approximately 70 billion doses of nearly 8,000 products annually. Catalent's expert workforce of nearly 18,000 includes more than 3,000 scientists and techncians. Headquartered in Somerset, New Jersey, the company generated nearly US$4.3 billion (£3.5 billion) in revenue in its 2023 fiscal year.

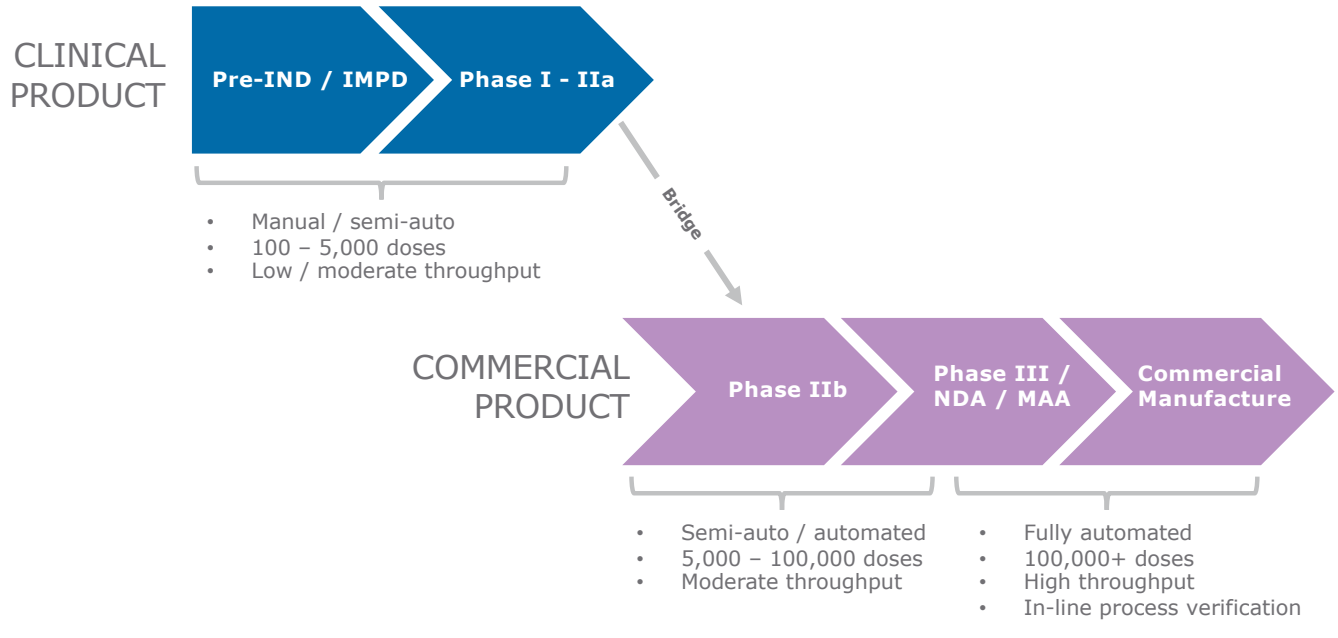

Figure 2: A seamless scale-up path for the development and manufacturing of an sDPI.

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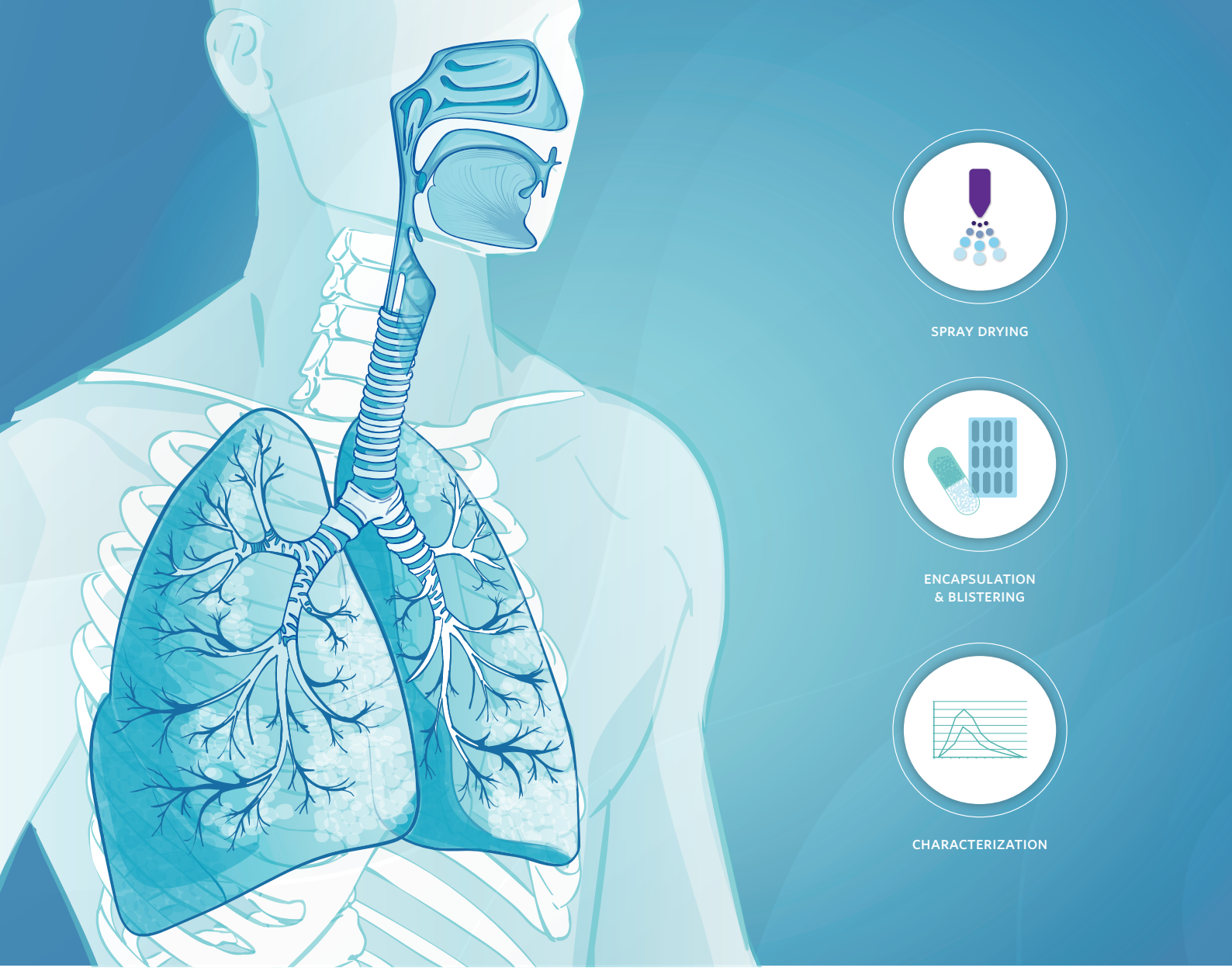

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FUTURE-PROOFING pMDI DESIGN TO FIT A CHANGING MARKET

In this article, Ross Errington, Head of Drug Product Development at Recipharm, explores how pharmaceutical companies can evolve their pMDI drug products to make them fit for the future considering the several recent regulatory changes that are transforming the landscape of inhalation drugs.

The pulmonary drug delivery market is growing rapidly and forecast to be worth US$76.9 billion (£63.4 billion) by 2027 — up from $57.4 billion in 2022.[1] A significant contributor to this increase is the pressurised metered dose inhaler (pMDI) segment — which was valued at $16 billion in 2022 and is on track to reach $22 billion by 2031.[2]

One of the biggest factors in the rapid rise of the pulmonary market is the global increase in the number of diagnoses of asthma and chronic obstructive pulmonary disease (COPD), as well as other chronic respiratory conditions. A total of 262 million people worldwide were reported to be living with asthma in 2019, with 455,000 deaths attributed to the disease.[3] COPD, meanwhile, was responsible for 3.22 million deaths in 2019.[4] Between 2007 and 2017, the number of people dying from COPD increased by 17.5%,[5] making it one of the three most common causes of death globally.[6]

Thankfully, pMDIs possess key features that make them ideal for use in combination products to transform the lives of the growing number of patients living with these serious conditions:

- **Manufacturing efficiency:** pMDIs are cost-effective to provide to a large number of patients living with chronic conditions.
- **Ease of use:** pMDIs offer breath-independent actuation, reducing the inspiratory flow rates required to achieve adequate drug deposition in the lung.[7] As a result, they can be used to treat both elderly patients and children, delivering a uniform drug dose every time.

A RAPIDLY CHANGING REGULATORY LANDSCAPE

Taking these benefits into account, it is clear why there is a correlation between the global prevalence of chronic pulmonary diseases and the increase in demand for pMDIs. However, the market landscape is changing fast, particularly when it comes to the regulatory environment governing medical devices and the propellants used in pMDIs. Pharmaceutical companies need to understand the most important of these changes and carefully consider both the design of their pMDI devices and their manufacturing processes to ensure that they continue to be compliant.

Introduction of the EU MDR

The EU Medical Device Regulation (MDR) replaces the existing Medical Device Directive (MDD) and the Active Implantable Medical Device Directive (AIMDD). These two directives previously governed the design of all devices used for medical purposes, including inhalation device technology. Under the MDR, all new and existing devices used with medicinal products, including combination products such as pMDIs, must show conformity to the general safety and performance requirements (GSPRs) in Annex I of the MDR. In March 2023, the EU extended the MDR transition periods from May 26, 2024, to May 26, 2026, for Class III implantable custom-made devices, and to December 31, 2027, for Class III and implantable Class IIb devices.[8]

> "The market landscape is changing fast, particularly when it comes to the regulatory environment governing medical devices and the propellants used in pMDIs."

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Post-Kigali Amendment Changes to Propellant Regulations

The Kigali Amendment to the United Nations Montreal Protocol was signed in 2016 to phase down global consumption of hydrofluorocarbons (HFAs) by 80–85% by 2047.[9] Widely used across many industries, HFAs have been the principal pMDI propellants for decades. However, the most common of these gases have a high global warming potential (GWP) and a long atmospheric life.

Following the signing of the Kigali Amendment, key pMDI markets, such as the EU, the UK and the US, have either enacted or begun to consider new legislation requiring existing high-GWP HFAs to be phased out in all applications. It remains uncertain what the timeline will be for this move away from traditional HFA propellants in pMDIs in key global markets, but companies must prepare for the transition to low-GWP alternatives now to minimise disruption of critical medicine supplies to patients.

A Potential EU REACH Ban on PFASs Could Impact the HFA Transition

Germany, the Netherlands, Norway, Sweden and Denmark submitted a joint restriction proposal under the European REACH regulations for polyfluoroalkyl substances (PFASs) in January 2023. This recommends further restrictions or even bans on HFCs and hydrofluoroolefins (HFOs)[10] potentially including gases that are being explored as low-GWP alternatives for current pMDI propellants, such as 1,3,3,3-tetrafluoropropene (HFO-1234ze(E)). Any restrictions on the manufacture and use of these propellants would have negative implications for the industry's efforts to reduce reliance on HFAs in inhalation drug products.

At the time of writing, it is unclear whether the total ban proposed will come into effect — news in recent months suggests it may be subject to revision before it comes before the EU Parliament.[11] Nevertheless, if it does pass, and the ban comes into force in 2025, the industry would have just 18 months from that date to remove any pMDIs containing these gases from the EU market.

DEVELOPING FUTURE-PROOFED pMDIs

Pharmaceutical companies need to take action now to prepare for these changes to the market and ensure the ongoing compliance of their pMDIs. The Kigali Amendment has particularly significant ramifications for the design of the container closure system of pMDI devices and the formulations they administer, due to the need to explore more sustainable alternative propellants. Potential alternatives to current pMDI propellants include both HFO-1234ze(E) and 1,1-difluoroethane (HFA-152a). However, the selection process for new propellants is complex, with many key issues needing to be considered.

> "Compatibility of potential new propellants and container closure systems can be ensured by maintaining seal integrity and valve delivery performance throughout the product's shelf life."

Propellant Compatibility with Formulation and Container Closure System

Compatibility of potential new propellants and container closure systems can be ensured by maintaining seal integrity and valve delivery performance throughout the product's shelf life. Maintaining acceptable levels of extractables and leachables is also key, making comprehensive testing essential. Propellant vapour pressure and molecular weight also need to be considered when determining the propellant leak rate – exposing filled canisters to extreme temperatures and pressures during testing can establish this.

Propellant Physicochemical Properties

These have implications for the formulation to be filled in the pMDI. Two of the leading propellants being explored have similar properties to currently used HFAs in terms of vapour pressure, density and compatibility with surfactants and solvents such as ethanol. This suggests that radical changes to formulation platforms may not be required, but appropriate studies will be needed to confirm this.

Environmental Impact and Safety

The propellant's toxicity must be considered – it is vital that any propellant is safe for human ingestion and that there is no detrimental interaction with the formulation. Flammability is also a concern – ATEX certification of the production line machinery will need to be addressed if there is any explosive risk.

Scalability Concerns

Failure to consider how the manufacture of the new propellant, along with the formulation and device design, can be scaled up could lead to costly delays in commercialisation. These considerations should start at the beginning of the development project to minimise risk. This is true for both new treatments and reformulation of existing pMDI treatments.

COMPLIANCE CONSIDERATIONS

These Kigali Amendment-related issues aren't the only factors to take into consideration when future-proofing pMDI therapies. It is also important to take into account changes to managing regulatory approvals and quality control processes to ensure compliance with the new MDR in the EU. Furthermore, the regulatory landscape continues to evolve – the recent (Oct 11th, 2023) IPAC-RS workshop on "The Transition to Low Global Warming Potential Propellants for Metered Dose Inhalers" showed how that discussion is progressing.

Updates to Quality Management Systems

Design control and GMP protocols need to be updated to meet MDR requirements. New clinical evaluation procedures will be needed to enhance the collection of clinical data, along with a post-market surveillance system to track the performance of the pMDI in the real world after commercialisation.

Changes to Requirements for Supervision of Notified Bodies

Companies must find a notified body to review information regarding the GSPRs under Annex 1 of the MDR to issue an opinion that the product conforms with requirements. Failure to consider this early in development could result in delays in regulatory filing.

PARTNERS ARE KEY TO FUTURE SUCCESS

The regulatory landscape for pMDIs is transforming, and if pharmaceutical companies want to continue to benefit from the convenience and manufacturability

"There are contract development and manufacturing organisations that can offer expert support throughout the process to ensure that companies continue to comply with new legislation."

advantages of these devices, they need to act now. Updating both the design and formulation of pMDI devices, as well as regulatory and commercialisation processes, will be a major undertaking for any pharmaceutical company.

However, there are contract development and manufacturing organisations that can offer expert support throughout the process to ensure that companies continue to comply with new legislation. Such partnerships can help ensure that patients living with chronic pulmonary diseases continue to receive inhalation treatments that are not just effective, but convenient.

ABOUT THE COMPANY

Recipharm is a leading CDMO in the pharmaceutical industry, with almost 9,000 employees. The company offers manufacturing services of pharmaceuticals in various dosage forms, production of clinical trial material and APIs, pharmaceutical product development and development and manufacturing of medical devices. Recipharm manufactures several hundred different products for customers, ranging from big pharma to smaller research and development companies. The company operates development and manufacturing facilities in France, Germany, India, Israel, Italy, Portugal, Spain, Sweden, the UK and the US, and is headquartered in Stockholm, Sweden.

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Ross Errington is Head of Drug Product Development for the Advanced Delivery Systems business at Recipharm. Mr Errington is a chemist by training and has 30 years of experience in pharmaceutical product development and manufacture, specialising in inhaled delivery systems.

EXPLORING THE PERFORMANCE OF LOW-GWP PROPELLANTS

In this article, Grant Thurston, Applications Scientist, and Lynn Jordan, Senior Applications Manager, both at Proveris Laboratories, discusses the performance of pressurised metered dose inhaler propellants with a low global warming potential.

In 1987, the landmark multilateral Montreal Protocol was finalised, initiating the phasing out of chlorofluorocarbon (CFC) refrigerants and propellants to limit environmental damage. The Kigali Amendment to the Montreal Protocol was ratified by the US in 2022 and signals additional efforts to reduce the environmental damage caused by fluorinated refrigerant, including hydrofluorocarbon (HFC) propellants.[1]

To reduce the impact of climate change, the HFC propellants used in pressurised metered dose inhalers (pMDIs) are being phased out and devices are being reformulated with new low global warming potential (GWP) propellants. The race to reformulate existing pMDIs to use low-GWP propellants is underway. To achieve these reformulations by the time Kigali comes into force in 2033, the industry needs new tools to accelerate development.[2]

A pMDI is a combination drug product that has a complex relationship between the device, formulation and human actuation. The propellant is a major component of any pMDI formulation and any change to it could significantly influence overall performance. Current laboratory testing tools, such as aerodynamic particle size distribution (APSD), require considerable time investments and, because of the time requirements, do not facilitate accelerated development. New technologies are needed to rapidly screen the drug/device formulations to select high-potential candidates for advancement. Regional deposition under human-realistic conditions can provide a rapid assessment of equivalence between test and reference products.

> "The propellant is a major component of any pMDI formulation and any change to it could significantly influence overall performance."

A NEW PARADIGM FOR DEPOSITION

In vitro inhaled drug analysis (INVIDA) services provide a complete rapid screening and bioequivalence tool, using human-realistic breathing profiles and respiratory tract models to determine regional deposition. INVIDA provides the speed to determine the knowledge needed to support traditional testing methods. The INVIDA services illustrated in Figure 1 show that INVIDA is a realistic model of human anatomy. The standard induction port for cascade impaction has a 90° turn, whereas the INVIDA mouth-throat model is human-idealised, more closely resembling human anatomy.

Table 1 summarises the factors associated with APSD and INVIDA services. INVIDA services enable fully customisable patient-specific breathing profiles that can represent normal breathing profiles for paediatric

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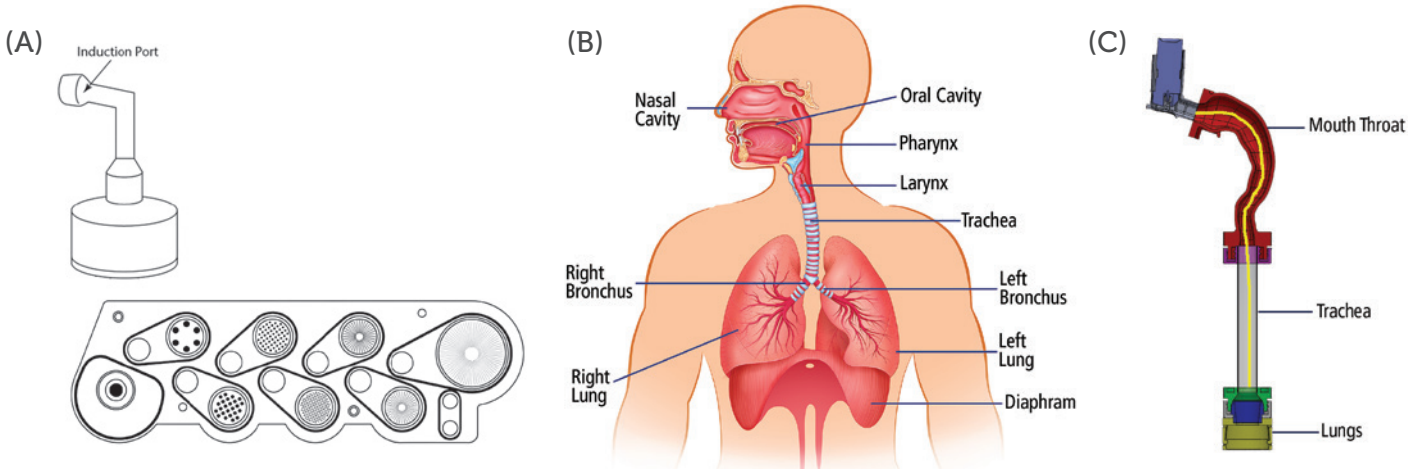


Figure 1: Visual comparison of (A) cascade impaction, (B) human anatomy and (C) INVIDA Services.

Experimental Factor	APSD	INVIDA
Flow Rate	Constant	Human-Realistic (Breathing Simulator)
Geometry	NGI with 90° Throat Model	Human-Idealised
Analyst Time per Sample	2 Hours	25 Minutes
Prep / Cleaning	10 Components	4 Components
Data Output	Size Distribution and Fine Particle Mass (>5 µm)	Mouth-Throat, Trachea, and Lung Deposition (mcg)

Table 1: Comparison of experimental factors associated with APSD and INVIDA services.

and adult patients, as well as mild, moderate and severe disease states of breathing. Traditional methods for APSD use a fixed flow rate for testing, whereas INVIDA can simulate realistic inhalation, hold and exhalation. Analysis by INVIDA requires approximately 25 minutes per sample for sample preparation and collection, whereas APSD will require a minimum of two hours for sample preparation and collection. Depending on the equipment, APSD can require extraction of drug from 10 components per sample run, whereas INVIDA only requires extraction from four components.

Traditional deposition studies do not measure deposition directly, but rather study particle size, which is thought to be indicative of human deposition. The INVIDA system consists of three extractable regions: idealised mouth-throat models (Virginia Commonwealth University, VA, US), trachea and lungs, yielding direct recovery of API (mcg).

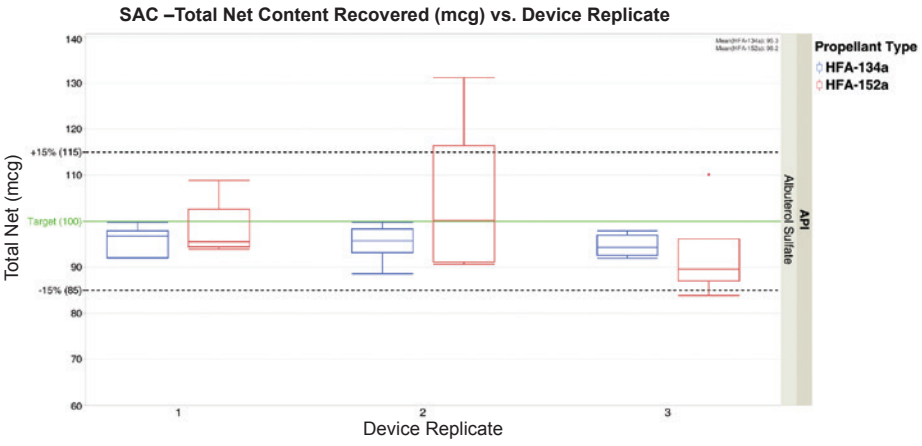


Figure 2: SAC – total net content recovery of albuterol sulfate (mcg) of formulations containing 134a and 152a propellants.

The speed of analysis makes INVIDA services an ideal development tool and can be used early and often to reduce dependence on costly and time-consuming APSD testing.

CASE STUDY

Proveris Laboratories evaluated a combined human-realistic deposition/APSD workflow that reduces development times while maintaining performance insights and regulatory compliance. To demonstrate the use of human-realistic deposition as a tool for development, an evaluation of the performance characteristics of HFA 134a and low-GWP propellant 152a was performed using APSD and INVIDA services.

Canisters containing API formulated with HFA 134a and HFA 152a were provided by Koura Global (Cheshire, UK) and had target doses of 100 mcg of albuterol sulfate. Testing used three devices and six replicates per device of each formulation. The tests performed included:

- Single actuation content (SAC)
- APSD using a next-generation impactor (NGI)
- Human-realistic regional deposition and delivered dose with INVIDA services.

Manual shaking and actuation conditions were performed for all samples.

SAC – Total Net Content Recovery

SAC samples were collected for both formulations using the same standard albuterol sulfate collection, extraction and high-performance liquid chromatography (HPLC) protocol. The target API dose for each formulation was 100 mcg.

Figure 2 shows similar results for both propellant formulations, with most data

points falling within the acceptance range of ±15%. However, low-GWP propellant 152a showed a higher degree of variation and some outliers. Average recovery values were well within the acceptance range, with 95.3 mcg for 134a and 98.2 mcg for 152a. Similar results from this test consistently showed that both formulations delivered the same amount of API. This established a baseline for delivered dose and allowed for comparison of APSD and INVIDA.

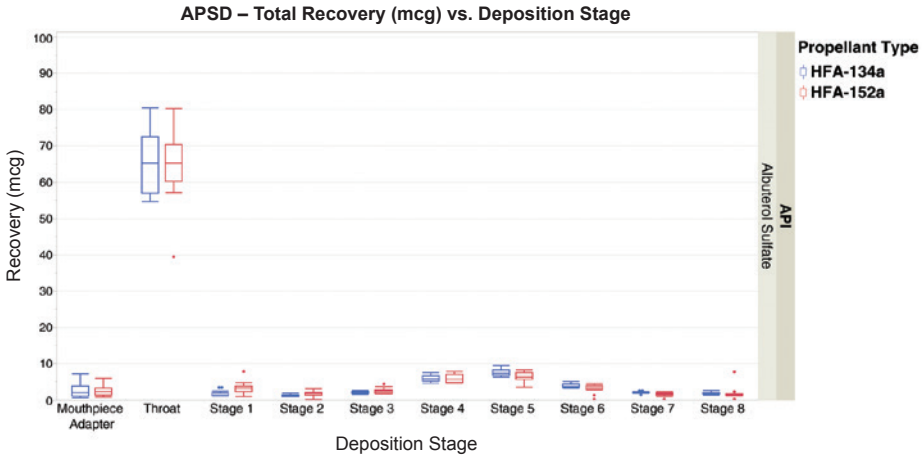


Figure 3: APSD – total albuterol sulfate recovery from NGI stages for formulations containing 134a and 152a propellants.

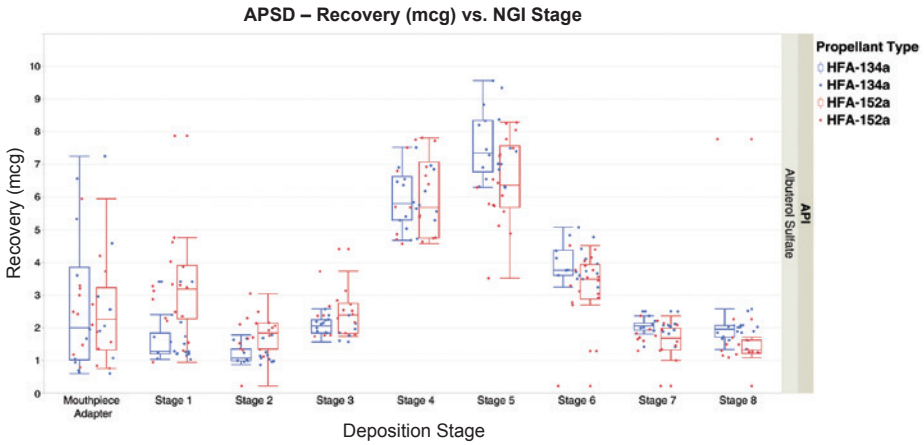
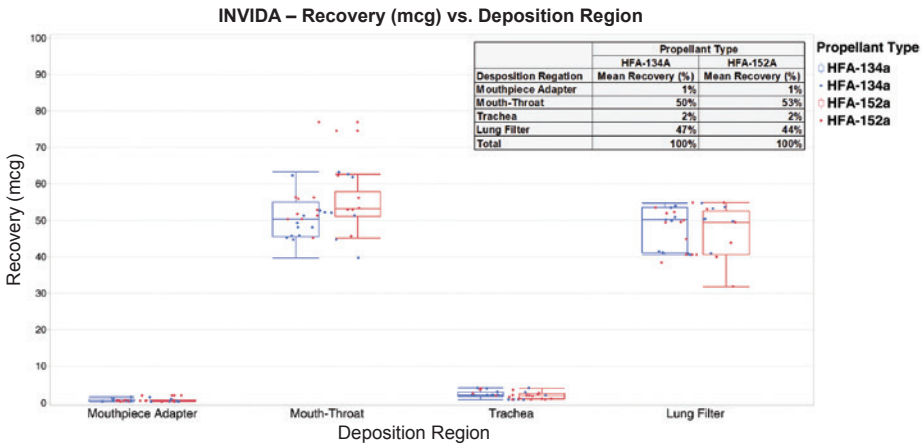


Figure 4: APSD – total albuterol sulfate recovery from NGI stages for formulations containing 134a and 152a propellants, excluding induction port.



	Propellant Type	
	HFA-134A	HFA-152A
Desposition Regation	Mean Recovery (%)	Mean Recovery (%)
Mouthpiece Adapter	1%	1%
Mouth-Throat	50%	53%
Trachea	2%	2%
Lung Filter	47%	44%
Total	100%	100%

Figure 5: INVIDA regional recovery and relative delivered dose for formulations containing 134a and 152a propellants.

APSD – Total API Recovery from NGI

APSD was performed using an NGI and US Pharmacopoeia induction port at a constant flow rate of 30.0 L/min. Each data point consisted of one actuation and a standard eight-stage extraction, with standard HPLC used for quantification.

Figure 3 shows that both formulations have similar performance across all stages. The vast majority of API was deposited in the induction port.

Figure 4 excludes the induction port, allowing for a more focused look at the mouthpieces and stages 1–8. Again, similar performance is seen across all stages for both propellant formulations. While variation is seen for both propellant formulations, 152a showed more variation overall.

INVIDA – Regional API Recovery

Regional deposition with INVIDA services used a breathing profile that represented a normal healthy adult male, obtained from published data.[3] API recovery was performed for the mouthpiece adaptor and the three regions: mouth-throat, trachea and lungs.

Figure 5 shows similar performance for both propellant formulations in all the regions. Most of the API was deposited in the mouth-throat and lungs, with little deposition seen in the mouthpiece adaptor and trachea. Variation was observed in both propellant formulations, with 152a showing more outliers.

SUMMARY OF FINDINGS

- Results from SAC, APSD and INVIDA show similar performance for 134a and 152a propellants
  - HFA152a resulted in slightly more variable output compared with HFA134a across all tests
- Minor differences in regional deposition when comparing APSD with INVIDA can be expected, given the following differences:
  - Constant flow rate for APSD and human-realistic breathing profile of INVIDA
  - 90° angle versus human-idealised mouth-throat model
  - The regional breakdowns are not one-to-one between the APSD and INVIDA
- INVIDA technology showed comparable performance between the propellants in a fraction of the time compared with APSD.

"When compared with traditional APSD, INVIDA services highlighted the same performance differences in a fraction of the time."

CONCLUSION

APSD is an essential test for pMDI development and approval that provides an indication of overall product performance. However, its considerable time requirements limit the speed of development and increase costs. To accelerate development, pMDI development and reformulation, the industry needs a tool for rapid evaluation of product performance that provides the same insights as traditional methods. In this study, Proveris Laboratories has illustrated the use of human-realistic regional deposition to support traditional development processes.

Similar results from SAC, shown in Figure 2, established a delivered dose baseline that allowed for comparison of APSD and INVIDA results. Both APSD and INVIDA identified the same performance for unoptimised formulations containing 134a propellant and a 152a low-GWP propellant. These techniques showed that both formulations performed similarly and that the 152a formulation had more variable results. One of the differences between these two techniques is the time required – when compared with traditional APSD, INVIDA services highlighted the same performance differences in a fraction of the time. Comparing time requirements for sample collection in Figure 6 shows a fivefold increase in throughput for INVIDA when compared with APSD. This represents a considerable time saving that would be even greater in a large-scale study.

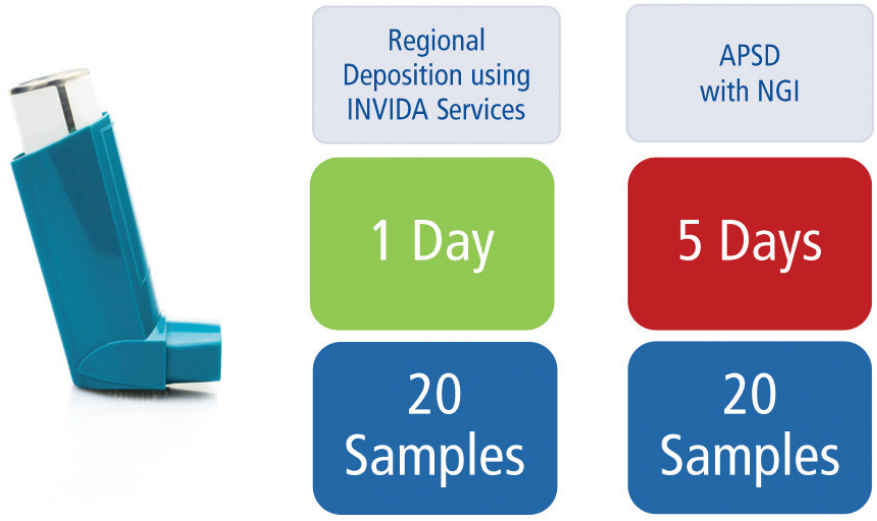


Figure 6: Time required for pMDI sample collection using INVIDA and APSD for 20 actuations.

Given similar findings and time savings provided by INVIDA services, a workflow that minimises dependence on APSD would be advantageous. Using INVIDA services for extensive early-development testing, such as product viability, device formulation screening and initial indications of equivalent performance, can provide the speed to knowledge needed to make informed decisions quickly. After development using INVIDA, pharmaceutical developers can be confident that APSD data for submission will resemble INVIDA data. Rapid performance indications provided by INVIDA services allow developers only to use APSD when necessary, reducing development time and cost.

This work would not have been possible without the expertise of Naveen Madamsetti, Senior Application Chemist, and Ellen Krett, Application Chemist, both at Proveris Laboratories, in generating the study data, and Koura Global, which provided inhaler propellant formulations for testing.

ABOUT THE COMPANY

Proveris Scientific and Proveris Laboratories are leaders in spray and aerosol product testing technology and laboratory test services for orally inhaled and nasal drug products (OINDPs). The company's instrumentation and over 25 years of expertise set the industry standard, driving healthcare advancements and enhancing patient well-being.

Proveris Scientific provides advanced spray characterisation instrumentation and product automation solutions, ensuring OINDPs meet the highest standards of safety, efficacy and quality. Proveris Laboratories excels in providing comprehensive testing services for OINDP development that uphold strict quality and regulatory criteria.

Both organisations share a common commitment to innovation and environmental responsibility, including the transition to low-GWP propellants, contributing to a more sustainable pharmaceutical future. Proveris aims to provide cutting-edge solutions, industry expertise and a dedication to improving patient outcomes.

"Given similar findings and time savings provided by INVIDA services, a workflow that minimises dependence on APSD would be advantageous."

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PERFECT TIMING FOR THE AUTOMATION OF OINDP TESTING

In this article, Adam Smith, Automation Product Manager, and Clair Brooks, PhD, Applications Specialist, both from Copley Scientific, take a look at the benefits of automation, focusing on the actuation of metered dose inhalers and multidose nasal sprays/aerosols.

Key factors shaping the orally inhaled and nasal drug product (OINDP) testing landscape make the benefits of automation increasingly attractive. The reformulation of metered dose inhalers (MDIs) triggered by the Kigali Amendment to the Montreal Protocol and an increase in the application of nasal drug delivery are already adding substantially to the OINDP test burden and will continue to do so over the coming decade.

Automation reduces variability, increases productivity and simplifies training in both delivered dose uniformity (DDU) testing and aerodynamic particle size distribution (APSD) measurement.[1] For a growing, increasingly geographically diverse industry facing exciting but challenging times, these are all major gains.

The shaking and firing that actuation of MDIs and multidose nasal sprays/aerosols requires is repetitive, arduous and a recognised source of variability that can be eliminated by automation. The newly launched Vertus® III+ from Copley fully automates shake, fire and shot weight measurement in a single benchtop system, while its partner DecaVertus® III, which employs the same shake and fire conditions, enables efficient firing to waste. Together, they mitigate variability and deliver a much sought-after productivity boost.

"The shaking and firing that actuation of MDIs and multidose nasal sprays/aerosols requires is repetitive, arduous and a recognised source of variability that can be eliminated by automation."

THE CASE FOR AUTOMATION

Inhaled drug delivery was first commercially realised by experts working in just a few large pharmaceutical companies, primarily in the US and Europe. Fast forward almost seven decades and the OINDP community has diversified enormously. Today, newer generic companies, innovators, and specialised contract development and manufacturing organisations flourish alongside the original pioneers in countries across the globe. An ever-growing number of people are involved in routine OINDP testing.

Such proliferation is not without its challenges. The test methods applied in the development of OINDPs and for quality control (QC) are complicated by the "combination product" classification, with both device and formulation contributing to drug delivery performance. Patient practice and physiology are also influential. Automation is an obvious strategy for minimising the substantial scope for variability – from operator to operator and site to site – that this complexity brings while, at the same time, simplifying the training needed for the analyst workforce. Easier method transfer and greater productivity are also vital gains.

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"Increased interest in intranasal delivery for vaccines, systemic drug delivery and nose-to-brain access is also responsible for a shift in testing patterns."

These benefits are especially appealing as the industry steps up to some distinct challenges. The reformulation of MDIs with propellants of lower global warming potential than the ubiquitously used HFA 134a and HFA 227a is a pressing task. Both innovators and generic companies are reliant on test data to learn how to achieve, and demonstrate, bioequivalence (BE) with new formulation chemistry. Favoured candidates for replacement are already in place – HFA 152a and HFO1234ze – but timescales are short.

Increased interest in intranasal delivery for vaccines, systemic drug delivery and nose-to-brain access is also responsible for a shift in testing patterns. These trends are encouraging more players into the OINDP market, for both new product development and, notably, drug repurposing. Taking an already approved drug and repurposing it for intranasal delivery can produce an enhanced therapeutic effect, improve ease of use/patient adherence and, at the same time, reinvigorate revenue streams via an abbreviated approval pathway. US FDA approvals for the first nalmefene hydrochloride nasal spray (May 2023) and the first over-the-counter naloxone nasal spray (March 2023) exemplify recent activity in this area.[2]

Against this backdrop, the case for automation is strengthening – to boost analytical productivity but also to enhance the precision of test methods by improving repeatability relative to manual methods. More repeatable and reliable data make it easier to identify and quantify differences in performance, enabling users to rigorously demonstrate BE, for example, or to learn how to robustly target nasal sprays within the nasal cavity for optimal drug delivery.

"The case for automation is strengthening – to boost analytical productivity but also to enhance the precision of test methods by improving repeatability relative to manual methods."

FOCUSING ON ACTUATION

USP <601> recommends "the use of a mechanical means of actuating the metering system or pump assembly to deliver doses for collection" when testing nasal sprays and aerosols, drawing attention to the potential for variability arising from device actuation[3] and, while there is no such specification for MDIs, there is considerable advice to consider. For example, Bonam et al highlight storage conditions and orientation, firing rate and inhaler handling as potential sources of variability for cascade impactor testing.[4]

The European Pharmacopoeia (Ph Eur) highlights the need to wait for five seconds between actuations of an MDI, nasal aerosol or pressurised metered dose nasal spray to "prevent excessive cooling".[5] USP <601> similarly specifies to "wait for 5s" between actuations when a dose consists of more than one actuation and to "not cause canister cooling" when firing to waste.

An understanding of device operation is helpful when examining the impact of actuation parameters. With a nasal spray, the patient applies mechanical force to operate a metering pump, thereby squeezing formulation though an orifice within the device to release a finely dispersed dose. In contrast, with nasal aerosols and MDIs, pressing down on a cannister compresses the metering valve stem, releasing the pre-metered dose via the rapid expansion and vaporisation of a propellant. Device handling and actuation parameters are important for the following reasons:

- Shaking technique – the speed, angle and duration of shaking – determines the homogeneity of the formulation, the extent to which settled solids are re-suspended, for example, and the scale of intimate contact between the propellant and other formulation ingredients.
- Time delays between shaking and firing define the opportunity for dose separation via creaming (emulsions) or settling (suspensions), both of which can occur rapidly with some formulations.
- Applied actuation force-time profiles can impact device operation and, by extension, dose release and dispersion.
- The length of time between repeat firings can affect refilling of the metering valve chamber – priming – an essential precursor to effective delivery, as well as the degree of chilling with propellant-driven devices.
- Storage conditions, notably temperature and orientation, have been securely associated with variability in dose delivery and propensity to loss of prime, the drainage of formulation from a previously filled metering chamber.[6,7]

Automated shake and fire systems eliminate this potential for variability but must be specified to handle two distinct tasks: firing to dose collection and firing to waste. The first involves actuation into a suitable dose uniformity sampling apparatus (DUSA) or cascade impactor under representative flow control, following an initial priming step. The second is shaped by specific test requirements. For example, the Ph Eur specification for dose uniformity testing of MDIs involves device priming, followed by the measurement of 10 samples in total, from the start, middle and end of label claim, with the regulatory expectation that intervening doses are fired to waste under comparable conditions. Both applications can be readily handled with a single-station shake, fire and shot weight system.

However, with some tests, the fire to waste requirement is far more substantial, notably the USP specification for dose uniformity over the entire unit life, for MDIs and nasal sprays, which involves sampling at least 10 units at the beginning and end of label claim.[3] This means just 20 determinations but close to 1,000 shots to waste for a 100-dose device. These figures draw attention to the enormous burden of manual testing and demonstrate the requirement for multi-station systems.

INTRODUCING THE VERTUS® FAMILY

The Vertus range answers directly to these requirements for single- and multi-station automated shake, fire, flow control and shot weight measurement platforms. Designed to complement one another, each system

Figure 1: Vertus III+ is a single-station automated shake, fire and flow control platform with integrated shot weight measurement for MDI and nasal drug product testing.

applies the same rotational shaking motion to appropriately represent patient/analyst practice and, at the same time, enable straightforward method transfer. Each benefits from electronic records/electronic signatures (ERES) functionality, providing a basis for obtaining ERES regulatory approval compliant with 21 CFR Part 11 requirements.

Vertus III is Copley's new single-station automated shake, fire and flow control platform. Vertus III+ (Figure 1) additionally offers integral shot weight measurement, making it the flagship single-station solution. For multidose nasal solution sprays, compendial methods allow delivered mass uniformity measurement, as an alternative to delivered dose uniformity, on the assumption of formulation uniformity, making integrated shot weight measurement a valuable feature for accelerated testing.[3,5] In a study with a multidose nasal spray, shot weight measurement for each of 200 doses was measured in just over 100 minutes, with no manual attention. This is an appealing approach that simultaneously produces highly repeatable data with estimates suggesting a reduction in relative standard deviation of around 50% compared with manual testing.[8]

These newly launched systems allow users to control all the actuation and test parameters highlighted above as potential sources of variability, and include the following key features:

- An extensive range of interchangeable interface plates, including options for the full range of Copley test method configurations for MDIs and nasal sprays, including spray force tester (SFT), thin layer chromatography (TLC) plate for spray pattern assessment, Alberta Idealised Throat (AIT) (see Box 1) and the Alberta Idealised Nasal Inlet (AINI).
- A new priming and waste module that integrates firing to waste into automated test methods, enabling compendial entire contents testing with minimal manual input.

"The Vertus range comprehensively and efficiently meets requirements for automated shake, fire and flow control for MDIs and nasal sprays."

- Intuitive user interface with large adjustable touchscreen for efficient operation for every user, with minimal training.
- Broader shaking angle and firing force range for representative testing of an even more comprehensive array of device types.
- Dedicated exhaust system to enable active extraction, if required, when working with high-potency drug substances and more flammable propellants, such as HFA 152a.

DecaVertus III (Figure 2) is a multi-station fire-to-waste platform that applies firing force individually to each station and has dedicated air flow and waste channels for up to 10 MDIs or canisters. Its design ensures that each individual inhaler is subject to repeatable wasting under identical conditions, matched precisely to those applied by Vertus III/ Vertus III+ for simple and consistent method transfer. Dedicated waste channels are also associated with minimal cleaning and fewer blockages, even with high-volume products.

Figure 2: DecaVertus III is a multi-station automated shake, fire and flow control platform for MDIs with dedicated air flow and waste channels for up to 10 devices.

BOX 1: AN ARRAY OF TESTING CAPABILITIES

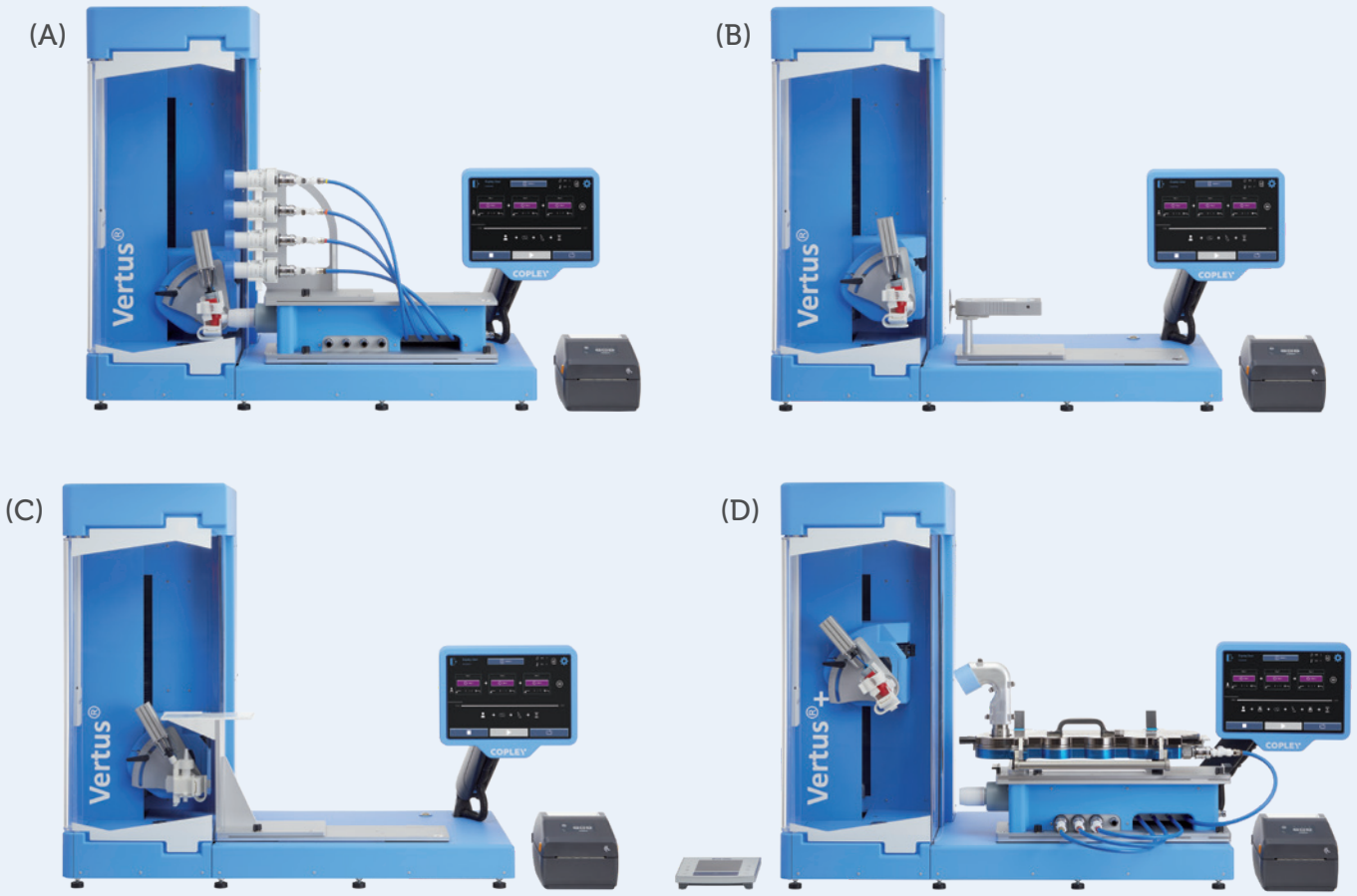

Figure 3: Interchangeable plates for Vertus III and Vertus III+ streamline all methods in the Copley testing portfolio, shown above with interface plates for (A) DUSA stack, (B) SFT, (C) TLC plate and (D) the AIT and NGI.

Vertus systems can switch automatically between priming and test levels, firing to waste or to dose collection as sequenced, with minimal manual intervention. This means automated, highly efficient routine testing, notably to meet through-life test requirements for DDU and APSD. The interchangeable plates (Figure 3) make it easy to access and automate all test methods that Copley equipment enables, including those that are especially suitable for helping establish BE as part of a reformulation exercise.

For example, the SFT allows users to investigate the force with which an MDI dose hits the back of the throat. Spray force can cause a patient to abort an inhalation manoeuvre or fail to complete it successfully – influencing the efficacy of drug delivery. It is therefore a factor in the demonstration of BE, as specifically highlighted by EMA guidance, which states that qualitative or quantitative differences in excipients should not be "likely to affect the inhalation behaviour of the patient".[9] The TLC plate holder is also a valuable tool for demonstrating BE, since it provides insight into spray pattern – allowing simple comparison of devices and/or products.

The AIT has a standardised, highly reproducible, human-like geometry that provides a more representative interface for testing than the standard USP/Ph Eur induction port. The standardised, right-angled port is known to capture less of the emitted dose than would normally deposit in the mouth-throat during routine product use, which is why the AIT is prized for testing in R&D and for the robust demonstration of BE.[10] Similarly, the Vertus is also compatible with the AINI for the respective assessment of human-like geometry for nasal delivery.

The Vertus range comprehensively and efficiently meets requirements for automated shake, fire and flow control for MDIs and nasal sprays. Studies show that automating actuation improves precision and the associated time savings can be in the region of 30% relative to purely manual analysis, notwithstanding the additional savings in training time.[1,8] These are crucial gains for anyone working with MDIs and/or multidose nasal sprays/aerosols but especially for those facing the challenge of MDI reformulation or getting to grips with nasal drug product testing. In the face of challenges such as these, the case for automation has never been stronger.

ABOUT THE COMPANY

Copley Scientific is recognised as a leading manufacturer of inhaled drug test equipment. Products include delivered dose-sampling apparatus, Andersen and Next Generation impactors, critical flow controllers, pumps, flow meters and inhaler

testing data analysis software. Copley Scientific also supplies novel systems for improving productivity and *in vitro/in vivo* correlations, including semi-automation ancillaries, abbreviated impactors, breath simulators and the Alberta Idealised Throats. Training, calibration, maintenance and impactor stage mensuration services are also available. Founded in 1946 in Nottingham, UK, Copley Scientific remains family owned and managed. The company continues to work closely with industry groups and leading experts to bring relevant new products to market, with all equipment backed by expert training and lifetime support.

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ABOUT THE AUTHORS

Adam Smith has been automating inhaler testing for analytical laboratories since 2011, first as a director at Novi Systems and now as Automation Product Manager for Copley since its acquisition of Novi in 2019. Mr Smith graduated with a master's degree in engineering from the University of Cambridge (UK) and worked in the aerospace and defence industries prior to entering the world of inhalation.

Clair Brooks, PhD, is an Applications Specialist for Copley Scientific. Providing in-depth application support to those working with OINDPs and other pharmaceutical dosage forms, including tablets and capsules, Dr Brooks helps scientists to ensure regulatory compliance during R&D and QC assessments. As an accomplished life sciences professional with extensive experience supporting the start-up and operation of heavily regulated testing labs across both industry and academia, Dr Brooks offers support on how best to apply Copley products and services to support pharmaceutical development and manufacture to help maximise return on investment. She also leads Copley's comprehensive user-training programme, run on-site and at Copley HQ.

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- **Reduces risk of costly out-of-specification results**
  Enhance test method compliance
- **Boosts testing efficiency and productivity**
  Increase testing throughput and optimise use of valuable resources
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SPRAYTEC LASER DIFFRACTION SYSTEM: ROBUST, REPRODUCIBLE DROPLET SIZE DATA

In this article, Anne Virden, PhD, Product Manager at Malvern Panalytical, discusses the benefits and applications of the company's Spraytec laser diffraction system for the measurement of spray particles and droplets.

Controlling the size of spray particles and droplets is critical for the effective delivery of medication via drug delivery devices such as nasal sprays and inhalers. As they are influenced by interactions between the formulation and the delivery device, a detailed understanding of the impact of both of these elements is essential for successful product development and commercialisation.

Nasal spray formulations, for example, usually consist of an API that is dissolved or suspended in an aqueous solution. Typically, nasal sprays destined for deposition in the nasopharyngeal region – such as common cold and influenza remedies – will be designed to deliver a droplet size of 20–120 µm. Particles below the lower limit are susceptible to inhalation into the lungs, while those that are too large tend to remain in the front of the nose or are lost through dripping. Droplet size is therefore a critical quality attribute (CQA) for nasal sprays.

The droplet size delivered by a nasal spray is a function of the physical properties of a formulation, most notably its viscosity, as well as the mechanism and geometry of the nasal spray pump. Key characteristics of a pump include the applied actuation profile, the pre-compression ratio and the length, geometry and orifice size of the actuator. Together, these determine the shear force applied to the formulation during actuation and, as a result, the size of the droplets delivered.

By manipulating device and formulation variables, product developers can tune nasal spray systems to deliver the required droplet size. Therefore, both the parameters of the pump and the physical properties of the formulation, such as viscosity, are critical material attributes (CMAs) – variables that have a direct impact on the droplet size CQA, which must be controlled to ensure the bioequivalence of a generic nasal spray.

Suspension nasal sprays bring a further level of complexity, as both the size of the droplets produced by the nasal spray and the size of the suspended API must be considered. The API particles are potentially vulnerable to changes in morphology during the actuation process, and such changes may, in turn, affect bioavailability.

The API particle size is therefore another CMA that must be considered as part of the demonstration of bioequivalence, with the US FDA's guidance suggesting measurements pre- and post-actuation. API particle size pre- and post-actuation can be measured using a combination of analytical imaging and Raman spectroscopy with Malvern Panalytical's Morphologi 4-ID.

"FDA guidance recommends the use of laser diffraction for droplet size measurement."

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Figure 1: Spraytec laser diffraction system with nasal spray support and actuator.

SPRAYTEC LASER DIFFRACTION SYSTEM

FDA guidance recommends the use of laser diffraction for droplet size measurement. This is the technique used by Malvern Panalytical's Spraytec measurement system (Figure 1), which has been specifically designed to address the unique requirements for spray characterisation and deliver robust, reproducible droplet size data.

Incorporating more than 35 years of experience in spray characterisation applications, the Spraytec laser diffraction system provides the data required to fully understand spray and atomisation processes. It can:

- Measure across a wide size range (0.1–2000 µm) using just two lenses
- Resolve rapid changes in droplet size over time, by taking up to 10,000 measurements a second
- Deliver accurate, concentration-independent results using a patented multiple scattering analysis
- Characterise wide spray plumes without risking optical contamination
- Simply reveal the dynamic changes in spray particle size through its unique size history analysis software.

"The Spraytec laser diffraction system provides the data required to fully understand spray and atomisation processes."

The Spraytec system measures the intensity of light scattered as a laser beam passes through a spray. This data is then analysed to calculate the size of the droplets that created the scattering pattern. The system is made up of the following main elements (Figure 2):

- A transmitter module that contains the collimated laser light source used to illuminate the spray during a measurement.
- A receiver module that can hold one of two lenses (300 mm or 750 mm) that focus any light scattered by the spray onto a series of detectors. These detectors accurately measure the intensity of light scattered by the spray droplets over a wide range of angles.
- An optical bench that ensures that the transmitter and receiver are aligned. The length of this can be changed to fit various applications, with the longest bench being 2.5 m long.
- The Spraytec software that controls the system during the measurement process and analyses the scattering data to calculate spray size distributions. The results are displayed as a "size history" trend plot, allowing any changes in the droplet size over time to be recognised instantly.

SPRAYTEC APPLICATIONS

The flexibility of the Spraytec system makes it suitable for a wide range of applications, from fundamental research and development through to product quality control and batch release testing. It delivers accurate, reproducible spray size analysis in an easy-to-understand format – improving product understanding and control.

For orally inhaled and nasal drug products, for example, the Spraytec system can chart the changes in spray particle size produced during single device actuations – allowing the dynamics of particle dispersion to be identified, along with the device reproducibility. As such, formulations can be rapidly screened for the correct spray properties – reducing development times and improving drug delivery efficacy.

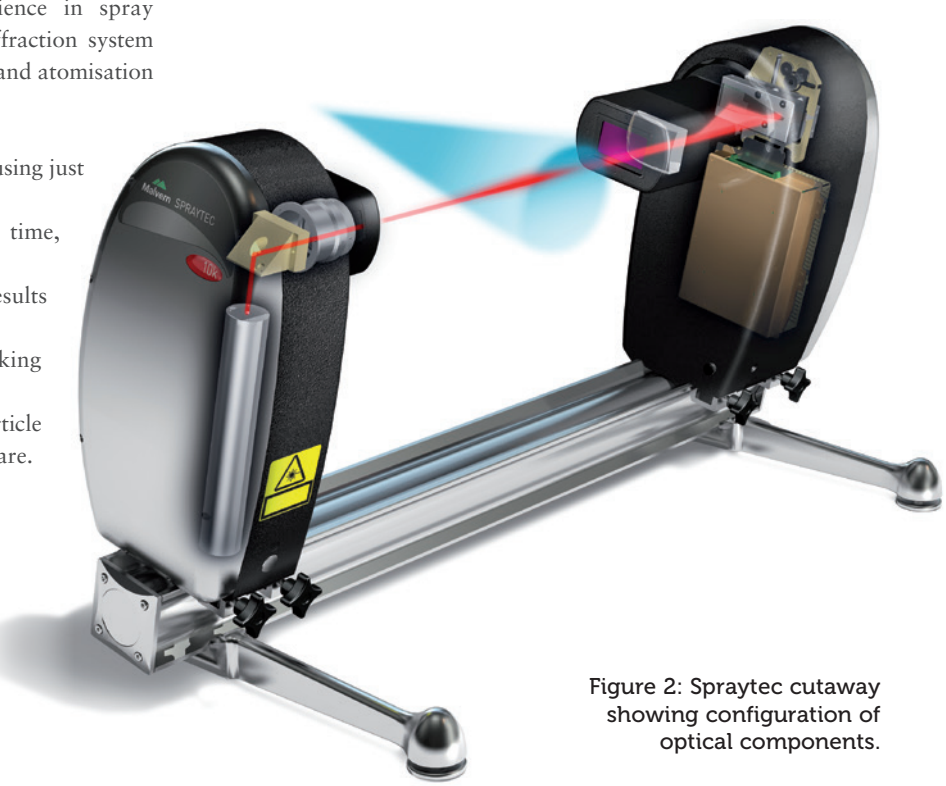

Figure 2: Spraytec cutaway showing configuration of optical components.

PULMATRIX CASE STUDY

Pulmatrix (MA, US) turned to laser diffraction when it was developing its novel iSPERSE inhaled dry powder delivery platform for use in the pulmonary delivery of drugs for local or system applications. The powders involved are characterised by small particle size, relatively high density and flow-rate-independent dispersibility, along with the ability for low or high drug loading of single or multiple drugs. The platform's properties yield drug delivery capabilities not feasible with conventional dry powder technologies, which rely on the use of lactose blending or low-density, porous particles.

iSPERSE uses proprietary formulations to create a robust and flexible platform that can accommodate low or high drug loads of a range of molecule types. The Spraytec with inhalation cell (Figure 3) is used to aid understanding of the dispersion properties of potential new formulations by measuring the dispersed particle size over a range of different flow rates. Quickly assessing the dispersibility by laser diffraction speeds up development times.

The particles are routinely prepared from aqueous or organic systems in a single-step spray-drying process. The powders can be formulated to contain as little as 5% excipients, in contrast to lactose-blend dry powders that typically consist of over 80–90% lactose and therefore only contain small amounts of drug. This fundamental formulation difference, along with the powder property of relatively high density, maps directly into the drug dose, creating feasible drug doses in a unit of up to 100 mg for iSPERSE.

Figure 3: Spraytec laser diffraction system with inhalation cell.

ABOUT THE COMPANY

Malvern Panalytical is a high-precision analytical instruments and services company that specialises in the chemical, physical and structural analysis of materials, and partners with numerous companies, universities and research organisations.

Malvern Panalytical provides its partners and clients with global training, service and support, including local and remote support, under a full and flexible range of support agreements, which continuously drives their analytical processes at the highest level. Malvern's worldwide team of specialists adds value by ensuring applications expertise, rapid response and maximum instrument uptime.

Malvern Panalytical is committed to "Net Zero" in its own operations by 2030 and in its total value chain by 2040. The company has 2,300 employees and is part of global precision measurement group Spectris plc.

ABOUT THE AUTHOR

Anne Virden, PhD, is a Product Manager in the micromaterials group at Malvern Panalytical. She joined the company in 2007 as a technical specialist for laser diffraction. This role involved supporting Mastersizer and Spraytec customers across a wide range of industries. In 2014, this role was expanded to include support for Malvern Panalytical's analytical imaging systems. Dr Virden has a PhD in Physics from the University of York (UK).

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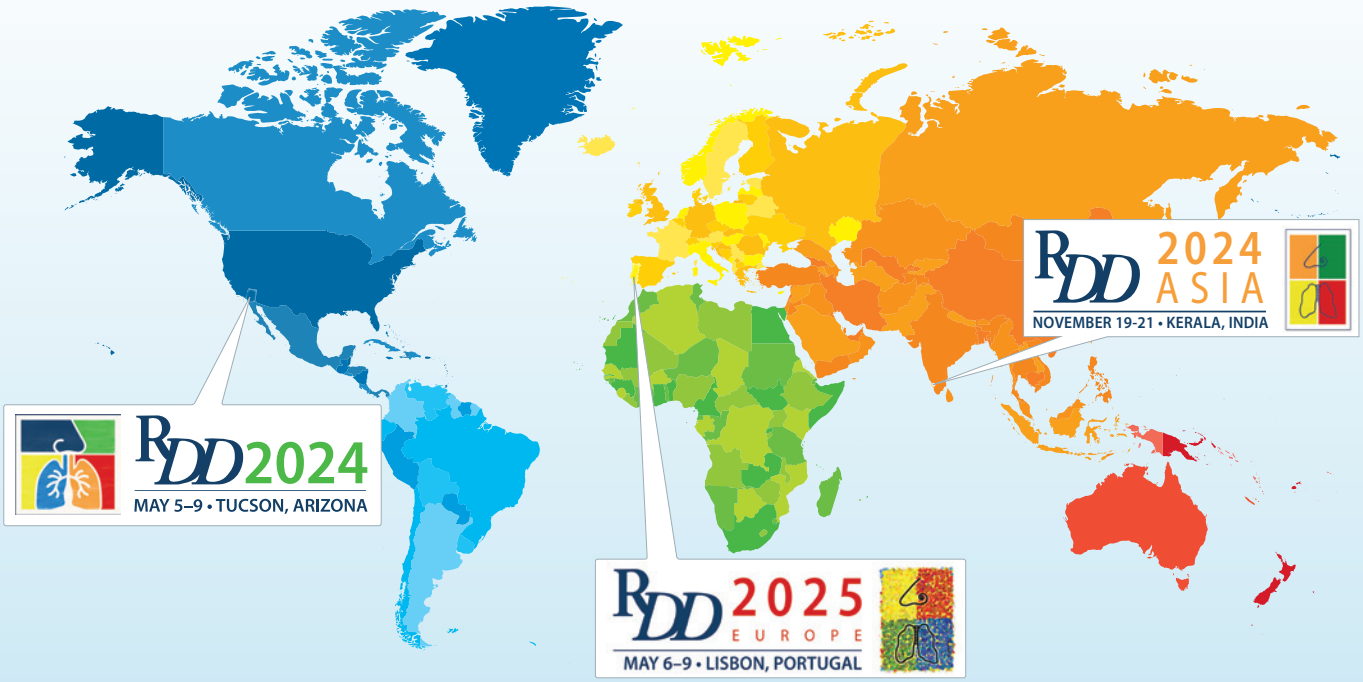

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SPRAY DELIVERY: TARGETING PATIENT NEEDS AND EXPECTATIONS WITH PRECISION

In this article, Gladys Corrons-Bouis, PharmD, Business Development Director, and Cyril Le Loc'h, R&D Director, both at EVEON, discuss the use of spray delivery for precise targeting of patient medication.

In recent years, new routes of administration have emerged and become more attractive for pharma companies. When one thinks of drug administration, one usually has in mind swallowing pills (oral administration) or getting an injection (parenteral administration). But drugs can be delivered through different routes, such as the enteral route through tubing in the gastrointestinal tract, inhalation through the mouth to reach the lungs or even a local route applied to the skin (cutaneous, transdermal) or to a mucosa (intranasal, buccal, auricular, ophthalmic).

Compared with conventional oral or parenteral methods, topical delivery brings key advantages:

- It is non-invasive and thus offers a convenient and patient-friendly delivery compared with injections – it offers a pain-free option for patients.
- It can avoid first-pass metabolism in the liver by allowing the drug to enter directly into the circulation system. This is an advantage when rapid drug absorption and onset of action are desired.
- It reduces the adverse effects induced by systemic drug delivery.

NASAL DELIVERY

Within local delivery, spray nasal delivery is particularly attractive – the rise of the nasal vaccine route is one example. Recent studies indicate that mucosal delivery of vaccines provides a better, long-lasting effect than the traditional injection route.[1] Drug repurposing is also a big trend and an opportunity to innovate for pharmaceutical companies. Some older drugs have been repackaged as unit-dose nasal sprays. This allows a broader patient population to be targeted, increasing access to different end-user groups (for example, paediatrics).

Nasal sprays are also being explored as a non-invasive way to deliver medication to treat neurological conditions, such as epilepsy and certain psychiatric disorders, as they enable drugs to bypass the blood-brain barrier.

SKIN AND MUCOSAL DELIVERY

Pharmaceutical spraying technology is a simple method of delivering a drug onto the skin or to a specific mucosa and overcomes standard galenic form issues. The use of topical sprays as an application method for innovative wound therapies has been of interest in clinical practice for the past few decades, thanks to advantages such as the ability to cover large wound/skin areas, even in cases with unfavourable topography, reduced time for application and a homogeneous distribution of the sprayed suspensions.[2]

Sublingual spray delivery has gained attention in the last few years. It combines the advantage of sublingual delivery – bypassing the first-pass metabolism and providing a quick onset of action – and spray atomisation by distributing atomised droplets that enhance bioabsorption.

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"Electromechanical spray medical devices … offer a controlled and efficient way to deliver high-value drugs."

Figure 1: The EVEON micropump.

OPTHALMIC DELIVERY

Spray delivery can also be a game changer for other administration routes. In May 2023, the US FDA approved MydCombi® – the first fixed-dose combination ophthalmic spray. Developed by Eyenovia (New York, US) and using the company's Optejet microdose delivery platform, ophthalmic spray is a new alternative to eye drops.

Nowadays, most devices delivering doses in spray form consist of multidose dispensers containing a spring pump and a spray nozzle. Doses are delivered manually, and most of the devices contain preservatives that ultimately have side effects on the tissues. In addition, manual actuation of the delivered dose depends on the pressure applied to eject the dose.

As interest grows in spray delivery, companies need to develop innovations to improve the patient experience and ensure precise delivery. Electromechanical spray medical devices provide an alternative approach that addresses these challenges, offering a controlled and efficient way to deliver high-value drugs.

GETTING FULL CONTROL OF DELIVERY PARAMETERS

Customising a unique spray for each therapeutic treatment – or even for each patient – will help to ensure the right delivery of potent drugs. Allowing for precise control over the spray pattern, volume, dose, flow rate or angle is then key. As an example, self-administration is a challenge for many patients. Conventional spray systems are manually actuated and thus the spray dose and flow rate depend on the pressure applied to eject the spray.

Giving the option of adjustable dosing may allow patients to tailor their treatment. Using an electromechanical device, with embedded software controlling the motor and therefore the micropump, in combination with fine tuning the spray nozzle physical parameters, can have a direct impact on spray performance parameters, such as the surface area for administering the drug, the droplet size or the ejection speed. Electromechanical devices may guarantee total control of dose and flow, which can be adjusted according to requirements.

TARGETING HIGH PRECISION

Many innovative formulations can be fragile, making delivery a tough challenge. Delivering the right dose of a fully preserved formulation to the right area is essential. This is particularly crucial for medications with narrow therapeutic windows. Moreover, ensuring high precision of microdoses is key. Indeed, microdoses may increase local drug bioavailability and absorption, as well as avoiding adverse effects associated with systemic absorption.

EVEON micropump (Figure 1) technologies are a valuable solution to address this challenge. Specific micropumps have been developed for such applications, with the following specifications:

- Suction of a liquid from a cartridge and unidirectional delivery to a spray nozzle
- Electromechanical operation with small-size motorisation
- Pump displacement compatible with a spray dose of 15–30 µl
- Minimum pressure resistance of 10 bar
- Very short liquid ejection time of less than 100 ms with constant ejection speed
- Industrial feasibility for mass production in plastic injection moulding using medically compatible, sterilisable materials.

This new pump technology operates in such a way as to create high pressure for spray delivery. During the first suction phase, the pump is activated by a motor driving an oscillating-rotating movement of a piston, allowing a chamber to be filled and a spring to be compressed in the micropump. During the second delivery phase, the pump is activated by the spring release, moving the piston and emptying the pump chamber to eject the fluid through the nozzle.

The way the pump has been developed, in partnership with a plastic micro-injection-moulding specialist, and in parallel with the development of a very specific nozzle, makes it possible to administer a very precise dose in spray form in the shortest possible time and deliver fine, homogeneous and highly repeatable droplet mists.

To characterise the spray dose delivered at the nozzle outlet, tests were carried out to precisely measure the volumes (Figure 2). The average dose ejected by the nozzle was 19.3 ± 0.4 µL.

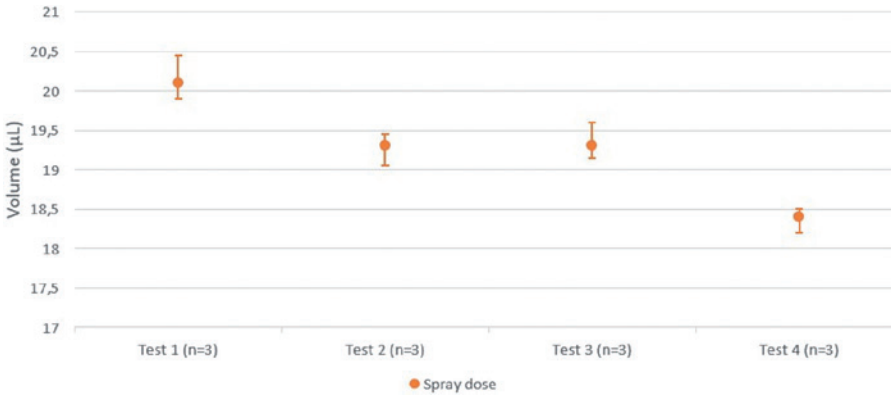

Figure 2: Test measures of spray delivery dose.

The Intuity® Spray (Figure 3) integrates EVEON micropump technologies to create a spray device that will deliver precise and accurate microdoses.

NEW USER EXPERIENCE

Today, patients want new drug delivery methods that will simplify their day-to-day life. Healthcare professionals (HCPs) want to be sure that the right dose is delivered to the right area and that patient adherence is high. Connectivity features could enable HCPs to remotely monitor patient adherence and adjust treatment plans as necessary.

With connected devices, the embedded software and the associated features on the user interface can enhance the patient experience, monitoring by HCPs and thus treatment compliance. Such devices can, for example:

- Record delivery data, such as date and time of drug administration, number of doses delivered or remaining doses
- Integrate connectivity features (with a smartphone, for example) allowing data to be sent to the HCP
- Give information to the patient regarding battery level, dose remaining, treatment reminder, etc.

In an era driven by technological advancements, the spray device landscape is still dominated by conventional mechanical systems. Today, there is a need to shift to efficient and modern topical delivery systems. As an example, electromechanical device sprayers eliminate the need for manual pumping and standardise the delivery process. Automation facilitates the drug delivery procedure for the patient.

Although automation is key to ensure patient compliance, it is also important to gather user feedback as soon as possible in any device development to guide the design. EVEON carried out a formative evaluation (in the scope of IEC 62366-1:2015) on a panel of users representative of the target population for the application defined for Intuity® Spray platform. The study was based on mock-ups and guided the patient to follow the usage scenario with visual and audio feedback.

The aim of the study was to assess the following points:

- The shape and handling of the device, the way it is used, identification of the spray outlet, etc
- Overall understanding of the device's functions and user interface, location of buttons, activation of the device and triggering of a dose
- Connection and disconnection between the consumable cassette and the reusable device
- Visual and audible signals.

Figure 3: The EVEON Intuity® Spray gives accurate airless spray or mist delivery.

User feedback was positive overall and led to a list of recommendations for the development of such a device:

1. Immediate feedback

- The device must provide appropriate status feedback (visual or audible) in a short timeframe following the patient's actions (pressing a button or connecting a cassette)
- The absence of feedback, or a long delay between the user's actions and the feedback, can increase the risk of the user taking actions that interfere with the process.

2. Waiting times

Long processing operations are indicated by a visual or audible signal with three orders of magnitude:

- 0.1 s – not perceptible to the user, no need to indicate this to the user
- 1 s – perceptible, an indicator is needed
- 10 s – the user can do something else, in which case the waiting time and progress must be announced.

3. Indicator lights

- Indicator lights are useful for communicating device status or for capturing the user's attention
- On the other hand, several light indicators at the same time can be confusing, even in non-emergency situations
- Auditory indicators often work along with visual indicators (or replace them).

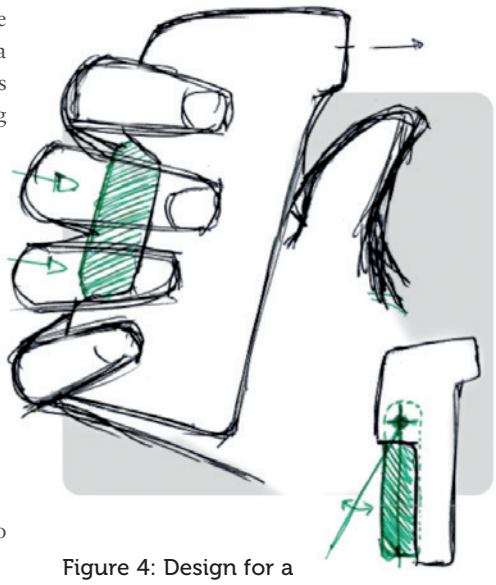

Figure 4: Design for a better user experience.

"Intuity® Spray is a proprietary drug delivery platform designed for easy, accurate and precise dosing with a modern delivery device."

4. Colour indicators
The number of colours used should be kept to a minimum. If possible, the device should be able to be used in "monochrome" mode. The following colour meanings are recommended:

- Green to indicate a normal, active state
- Red to indicate a faulty or abnormal state
- Orange to indicate a possible hazard
- White to indicate an undetermined state.

The next step involved implementing the user feedback recommendations into the design of the next generation of prototypes (Figure 4, previous page) with the goal of moving towards industrialisation and design verification and validation.

INTUITY® SPRAY

Intuity® Spray is a proprietary drug delivery platform designed for easy, accurate and precise dosing with a modern delivery device. It is a multidose and refillable device capable of delivering doses from 15–30 µL with 0.5 µL accuracy. The platform typically consists of:

- A reusable part that contains the electromechanical actuation and electronic controls
- A fluidic cassette – this interchangeable cassette holds the medication reservoir. The fluidic cassette contains:
  - The medication, ensuring sterile and efficient delivery while allowing for easy replacement
  - The micropump and the nozzle.

KEY FEATURES

- Microdose delivery: dose from 15 µL to maximum 30 µL in less than 100 ms
- Multidose delivery
- Topical administration of mist on a specific surface (Ø~10–12 mm)
- Droplet size mean of 20 µL with 90% of droplets under 100 µL and 10% under 10 µm
- Sterility preservation within the primary container/administered dose with an acceptable microbiological quality
- Portable reusable device, must fit in a pocket or handbag/must be easy to handle
- Primary container:
  - Standard 3 mL cartridge currently developed
  - Flexibility of existing containers for new developments
- Connectivity – recording of delivery hours and dates, cartridge remaining doses count
- Rechargeable battery.

The Intuity® Spray platform uses an intellectual-property-protected architecture and is compatible with standard primary containers to minimise chemistry, manufacturing and controls development impacts for pharmaceutical companies and facilitate easy adoption.

CONCLUSION

Today, there is a clear need to shift to efficient and modern topical delivery systems. By tackling patient experience and dosing precision challenges, next-generation topical delivery devices are already starting to shift the industry.

ABOUT THE COMPANY

EVEON designs and develops custom devices for the preparation and delivery of advanced therapeutic treatments, providing solutions that improve patient compliance and therapeutic performance. EVEON has built its expertise over the past decades in drug preparation, from lyophilised drug reconstitution to complex suspension preparation. EVEON is certified under ISO-13485:2016 and integrates the IEC 62304 standard for medical device software. EVEON has received several Pharmapack awards in the Best Innovation Exhibitor category for its developments in 2016, 2017 and 2021.

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ABOUT THE AUTHORS

Gladys Corrons-Bouis is Business Development Director at EVEON. She started her career in the pharmaceutical industry in regulatory affairs and market access for orphan drugs. In 2007, she joined CEA to help with the maturation and licensing-out of CEA's portfolio of drug candidates. She then participated in the creation of Avenium Consuting in 2009 and became a partner in this intellectual property strategy and business intelligence consulting firm. For 10 years, Ms Corrons-Bouis helped start-ups, small to medium enterprises, and big pharma companies to define their industrial property strategy and consolidate their technology portfolio. Ms Corrons-Bouis also contributed to the structuring of consulting activity and solution selling within Becton Dickinson's Preanalytical Systems division. Since 2019, she has been developing EVEON's commercial activity by forging key co-development partnerships with pharmaceutical companies. Ms Corrons-Bouis holds a PharmD and a degree in Regulatory Affairs and Market Access.

Cyril Le Loc'h is R&D Director at EVEON. He has 18 years of experience in product design and development, including more than 10 years in the medical industry, and has worked in project and team management at a variety of companies. Mr Le Loc'h has a master's degree in Mechanical Engineering and Industrial Design from Université de Technologie de Compiègne (Compiègne, France).

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THE FUTURE OF PREPARATION
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UNLOCKING THE POTENTIAL OF INTRANASAL DRUG DELIVERY

Here, Allan Houston, Vice-President, Healthcare Sales and Marketing, Marcel Sachs, Product Line Manager, Healthcare, and Heiko Rolland, Manager, Regulatory Affairs, all at Silgan Dispensing, discuss the healthcare potential of intranasal drug delivery systems and the necessary steps for bringing these solutions to market.

Silgan Dispensing's newest healthcare solution, the Monodose Nasal System (Figure 1), is an intranasal solution that gives healthcare professionals a simpler, faster method for administering medicine directly to the patient. The Monodose Nasal System is a primeless, ready-to-use device that can be used with one hand from any direction, due to its 360° delivery capability. The solution also is optimised for bioequivalence to help pharmaceutical partners expedite product commercialisation.

Increasingly, intranasal solutions, such as the Monodose Nasal System, have been shown to be effective at administering drugs such as naloxone, which counters the potentially lethal effects of an opioid overdose. The single-dose system allows emergency and healthcare professionals to quickly deliver these life-saving interventions.

THE POTENTIAL OF INTRANASAL DRUG DELIVERY SYSTEMS

What Are Some of the Applications?

Intranasal delivery solutions are an excellent alternative to other administration methods – namely oral and parenteral applications. Medications taken orally must first pass through the digestive system, which reduces their concentration and, subsequently, makes them slower to take effect. Intravenously administered drugs take effect much faster than orally administered ones, but can make many people anxious, plus they require medical training to use.

Intranasally administered drugs can be rapidly diffused to the brain, avoiding the digestive system and bypassing the blood-brain barrier (BBB), which can be an obstacle for larger drug molecules. Furthermore, intranasal devices can be used by people without medical training and do not carry the stigma associated with needles.

Figure 1: Silgan Dispensing's Monodose Nasal System.

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"Intranasal delivery is one of the most effective ways to treat opioid overdoses by providing a rapid and easily accessible route of administration for life-saving medications, such as naloxone."

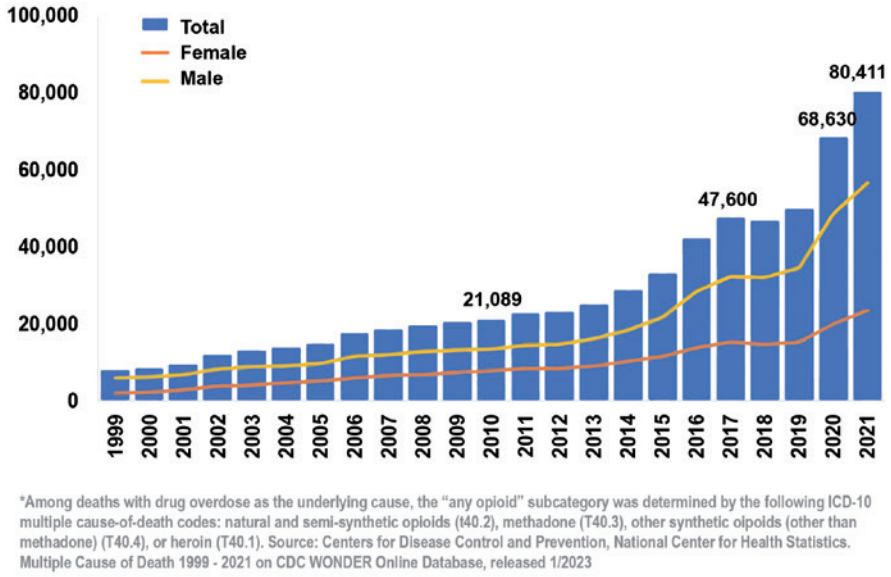
What Are Some of the Use Cases?

Intranasal delivery systems are poised to significantly impact a variety of markets, especially opioid overdoses and migraines. Intranasal delivery is one of the most effective ways to treat opioid overdoses by providing a rapid and easily accessible route of administration for life-saving medications, such as naloxone. In the US alone, there were nearly 80,000 opioid-involved overdose deaths last year – a 60% increase in just three years (Figure 2). As such, the global naloxone spray market is expected to grow accordingly. The life-saving and financial potential for a much simpler, more effective way to treat opioid overdoses cannot be overstated.

Migraines are another health concern that could benefit from a single-dose intranasal delivery device. Beyond the intense headaches, migraines can cause vomiting, sensitivity to light and sound and even temporary vision loss. More than one in 10 people worldwide experience migraines, which can be extremely debilitating.

While opioid overdose and migraine headache applications make up a significant portion of the potential market, there are many other indications that can benefit from Silgan Dispensing's Monodose Nasal System. Subject to clinical testing, these indications could potentially include treating epileptic seizures, anaphylaxis, chronic cancer pain, treatment-resistant depression and severe hypoglycaemic episodes, to name but a few.

Furthermore, intranasal delivery systems continue to be a popular method for vaccine administration, especially among children and the elderly. This is understandable, as children are frequently wary of needles, which can make critical vaccine appointments strenuous for everyone involved. With older patients, many have less stable veins, which can make successfully administering an intravenous treatment both difficult and painful. A simple nasal spray could ease these situations considerably.



*Among deaths with drug overdose as the underlying cause, the "any opioid" subcategory was determined by the following ICD-10 multiple cause-of-death codes: natural and semi-synthetic opioids (t40.2), methadone (T40.3), other synthetic opioids (other than methadone) (T40.4), or heroin (T40.1). Source: Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death 1999 - 2021 on CDC WONDER Online Database, released 1/2023

Figure 2: National overdose deaths involving any opioid – number among all ages by gender, 1999–2021.

BRINGING A NEW INTRANASAL DELIVERY DEVICE TO MARKET

Both drugs and their delivery devices share a similar market approval process, but delivery devices have a higher to-market success rate than drugs. While only roughly one in every 5,000 drugs that enter preclinical testing gets approval for therapeutic use – a process that takes 12 years, on average – delivery devices tend to be approved more frequently. However, that does not mean drug delivery devices have simple regulatory requirements. Getting caught up in regulatory missteps can lead to costly delays, revisions and resubmissions.

For a successful marketing authorisation application, a reliable drug delivery device manufacturer should be well-positioned to support a pharmaceutical manufacturer applicant. This requires being able to navigate the complex device and combination product regulations of different market requirements. Additionally, having state-of-the-art manufacturing processes for the delivery device in place will help strengthen the applicant's regulatory submissions.

The compatibility of the device with the formulation should be investigated and established before going into further clinical phases, bioequivalence testing and stability studies. The design and performance of an intranasal delivery device will directly affect the clinical efficacy of the overall combination product.

The key considerations for an intranasal delivery device should include stability with the targeted formulation components, a user-friendly design, device reliability and dosing accuracy. Furthermore, the device's material of construction should be carefully considered – critically, it must be compliant with regulatory and pharmacopoeial requirements, as well as have low extractables profile for the polymers, additives and metallic components of the device to ensure biocompatibility and patient safety.

HOW SILGAN DISPENSING AVOIDS COSTLY REGULATORY DELAYS

Providing a meaningful and approved package of supportive regulatory and technical data about the delivery device is essential for a marketing authorisation approval process. As a design and

"As a design and manufacturing partner, Silgan Dispensing offers industry-leading support for pharmaceutical partners seeking to get a new device to market in a timely fashion."

Figure 3: Silgan Dispensing conducts testing for its bioequivalence programme in its Healthcare Centre of Excellence in Hemer, Germany.

manufacturing partner, Silgan Dispensing offers industry-leading support for pharmaceutical partners seeking to get a new device to market in a timely fashion.

Unmatched Regulatory Expertise

Silgan Dispensing's commitment to regulatory compliance and its collaboration with industry stakeholders are pivotal factors in avoiding costly regulatory delays. Its bioequivalence programme, meticulously designed to align with US FDA and EMA regulatory requirements, not only expedites drug delivery device development, but also instils confidence in its customers regarding healthcare packaging compliance.

Bioequivalence Programme

Bioequivalence testing helps Silgan Dispensing's customers overcome regulatory and technical barriers that have previously slowed product commercialisation (Figure 3). Solutions like its Monodose Nasal System and Gemini™ BE Nasal Pump showcase Silgan Dispensing's ability to deliver expedited delivery device development that fits its customers' needs.

Silgan Dispensing has also used its nasal spray testing cGMP-compliant lab and equipment and developed partnerships with accredited external cGMP labs and contract manufacturing organisations (CMOs) specialising in nasal products. This collaborative approach ensures that Silgan Dispensing's customers receive full support and streamlined regulatory pathways, minimising the risk of obstacles and delays.

Extensive Drug Master Files

Silgan Dispensing also develops and submits extensive drug master files, including full biocompatibility data and reliability studies to ensure that the appropriate regulatory bodies, whether that be the FDA or EMA, are provided with the necessary information. Working closely with the different authorities and constantly being up to date is key to a quick and trouble-free qualification. This helps Silgan Dispensing's customers get their products to market timely and efficiently.

Dynamic Production Facilities

Silgan Dispensing's Healthcare Centre of Excellence in Hemer, Germany, is compliant with the highest manufacturing standards and boasts a variety of certifications (Figure 4):

- ISO Class 7 cleanroom for products
- ISO Class 8 cleanroom for warehousing
- ISO quality system certifications for cGMP ISO 15378
- Medical device quality systems for ISO 13485
- Registered as an FDA medical device establishment.

Figure 4: ISO Class 7 cleanroom production and ISO Class 8 cleanroom warehouse in Silgan Dispensing's Healthcare Centre of Excellence.

SILGAN DISPENSING

Monodose Nasal System

Confident // Reliable

Monodose makes treatment easier without the need for medical training with its quick intranasal application. It allows for rapid distribution directly to the source, reducing the potentional for side effects when compared to oral or injection alternatives. Developed with excellent ergonomics, this fine mist sprayer is intuitive and reliable for patients.

- Improved ergonomics compared to competitors' devices
- Optimized one-handed actuation
- 360° use for delivery in any position
- Ready-to-use primeless activation
- Ease of use for nonmedically trained individuals
- Microbiological integrity of the primary container

Learn More about Monodose

SilganDispensing.com/Healthcare

"Ergonomics is central to Silgan Dispensing's design philosophy – across all markets, its dispensing solutions must be comfortable and have a user-friendly design."

Figure 5: Enhanced ergonomics of Silgan Dispensing's Monodose Nasal System.

THE CONNECTION BETWEEN ERGONOMICS AND MEDICATION ADHERENCE

Why is Ergonomics Important?

Ergonomics has been found to play an integral role in medication adherence. When ergonomics is factored into the device and packaging design, it evokes a positive user experience, leading to a higher percentage of medication adherence. Medications that prove challenging or inconvenient to use are unlikely to achieve the level of adherence necessary to realise their full therapeutic effect. This is why ergonomics is central to Silgan Dispensing's design philosophy – across all markets, its dispensing solutions must be comfortable and have a user-friendly design.

The Monodose Nasal System is a notable example of this. While it is not the first intranasal delivery device on the market, the way it is designed improves upon other available options. Unlike others, the Monodose Nasal System incorporates textured concave finger pads to keep fingertips in place, optimising it for a more comfortable and secure one-handed actuation (Figure 5).

How Does the Right Design Benefit Both Healthcare Brands and Patients?

A thoughtful design for a healthcare brand not only fosters trust and credibility among healthcare providers, but also plays a crucial role in managing healthcare costs. In the short term, patients feel more confident in administering their medication, which leads to increased adherence. Over the long term, this design approach aids effective condition management and leads to a healthier life.

Silgan Dispensing's healthcare team is guided by a design philosophy centred on delivering the best user experience and enhancing adherence. This philosophy serves as the driving force behind the innovation and effectiveness of all its drug delivery devices.

ABOUT THE COMPANY

Silgan Dispensing Systems is a specialised pharmaceutical packaging and dispensing system provider with a global manufacturing presence and an extensive line of high-quality solutions that do more than simply protect medicine. The company collaborates with customers, fillers, machinery manufacturers, retailers and other partners to accelerate the commercialisation of consumer-centric packaging solutions. Silgan Dispensing is proud to serve patients' needs, from topical to ophthalmic to throat to ear to nasal; its dispensing solutions are designed to provide the best patient experience.

ABOUT THE AUTHORS

Allan Houston is Vice-President, Healthcare Sales and Marketing at Silgan Dispensing Systems and has worked in the medical device and pharmaceutical packaging industry for more than 20 years as an executive, marketer and sales leader. After an extensive career at Berry Global, Mr Houston joined Silgan Dispensing Systems in 2022 to lead the global healthcare sales and marketing team. He received a BBA from the University of Texas (TX, US) and an MBA from Wake Forest University (NC, US).

Marcel Sachs is a Product Line Manager, Healthcare at Silgan Dispensing Systems located at the Healthcare Centre of Excellence in Hemer, Germany. He started in 2016 as a technical Project Manager after finalising his Engineering degree and leading R&D, sustaining engineering and customer projects. In his current role, he is globally responsible for Silgan Dispensing's healthcare product line, including technical sales support.

Heiko Rolland is a graduate chemical engineer and Manager, Regulatory Affairs at Silgan Dispensing's Healthcare Centre of Excellence in Hemer, Germany. In this role, he ensures that the company's products meet the high and evolving regulatory requirements for pharmaceuticals and medical devices, as well as providing global regulatory support to customers. Having joined Silgan Dispensing in 2007, he draws on over 20 years of experience in cGMP-regulated industry, with a focus on medical devices.

TAKING A DRUG TO FIRST-IN-HUMAN TRIALS IN A BESPOKE DEVICE FOR TARGETED INTRANASAL DELIVERY

Here, Mark Allen, PhD, Consultant Biomedical Engineer, and Andrew Fiorini, Consultant Healthcare Devices Engineer, both at Cambridge Design Partnership, and Shai Assia, Head of Medical Device Development at Clexio Biosciences, discuss the need to develop delivery devices early when formulating nasally delivered drugs for systemic and local action, and a method by which the route to clinic can be made easier, faster and cheaper.

INTRODUCTION

Systemic delivery has long been the mainstay of drug administration, whether via the oral, injectable, inhalable, nasal or another delivery route. There are, of course, many well-documented downsides of systemic delivery, including unintended side effects in locations beyond the drug target and reduced efficacy due to dose safety requirements to reduce those side effects. Targeted drug delivery can address many of those issues,[1] with targeted intranasal delivery, in particular, having the potential to treat many debilitating conditions, from as yet underserved conditions, such as cluster headaches, through to central nervous system (CNS) conditions such as Alzheimer's disease. Indeed, there are currently many active studies on therapeutic delivery via this specialised route.[2] These targeted treatments have the potential to improve the lives of patients, their families and their carers immeasurably.

However, the key challenge lies in achieving the delivery of an accurate dose to a precise location within the nasal anatomy. A device that can enable that targeting is intrinsically linked to drug efficacy, meaning that it is necessary to consider device development earlier in the process than usual. In comparison, a drug intended for parenteral delivery has the well-trodden option of using a vial and syringe for administration by a healthcare practitioner during early development phases while proving basic safety and efficacy. A more complex drug delivery system can then be sourced or designed (if required) in parallel, ready for use in Phase III trials as part of a combination product development pathway.

This off-the-shelf-device approach, aimed at reducing the risk and cost associated with early-stage clinical studies, is not an option available to those developing highly

"The key challenge lies in achieving the delivery of an accurate dose to a precise location within the nasal anatomy. A device that can enable that targeting is intrinsically linked to drug efficacy."

targeted intranasal delivery – most of the currently available nasal devices are designed to coat as much of the nasal cavity as possible, making them unsuitable for delivery to a precise area. A nasal device with a broad spray pattern may even lead to the drug not reaching the intended target area at the required dose level.

So, how can a new, bespoke device be developed and made available for the initial Phase I and II trials? These are complex devices that need to be suitably well designed to ensure that patients or clinical professionals can use them during clinical trials to administer the drug accurately and repeatedly to the correct location, often deep in the nasal cavity.

To answer this, a minimum viable product (MVP) prototype device can be designed for the needs of the Phase I and II clinical trials. Designing for use within the controlled setting of a clinical trial and prioritising solely patient safety, spray geometry and usability (relating to holding and positioning the device) at this stage can considerably reduce the effort, cost and time required to reach the clinic. This MVP device will then allow the safety, efficacy and feasibility of the self-administered, targeted intranasal delivery method to be proven during these

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early clinical trials. The device performance and usability are critical to correctly delivering the drug, so learnings from this MVP device can be used in the further development and refinement of the device for Phase III trials, as well as the future commercial-scale device.

Carrying out risk assessments and timely iterative testing (via formative studies) on the usability of the device is crucial; misuse or an inability to use the device could stop the patient from administering the drug to the intended location within the nasal cavity, or even cause harm, ultimately preventing the drug from achieving its intended therapeutic effect. Therefore, usability and human factors engineering must be incorporated into the design and development process from the start.

DEFINING A USABLE DESIGN

The challenge for the device development team is to successfully incorporate design for usability throughout a "lean" MVP device development process, meaning that a safe, usable device must be produced with reduced cost compared with traditional development processes. This can be achieved by careful adaptations to the typical design for usability process. When applying user-centric design principles, as outlined in ISO 9241-210, four steps should be followed:

- Understand the context of use
- Define the requirements
- Build the design
- Evaluate the design against the requirements.

Although this is not the only relevant ISO standard (others, such as ISO 62366, cover the application of usability engineering to medical devices), ISO 9241-210 provides a set of recommendations and requirements for applying user-centric design principles within design and development activities. These processes help to identify "real" user needs and usability challenges, which can then be used to establish a clearer framework for user interaction and interface design.

Understand the Context of Use

Consideration of the patient, including when and why they are receiving treatment, is essential. For example, if a new targeted nasal delivery device is to replace a healthcare practitioner-administered treatment, it is likely that the patient currently visits a clinic to receive their treatment, disrupting their schedule and placing an additional burden on the healthcare system. A self-administered device will naturally put the patient in control of their treatment and improve their quality of life – as has been witnessed through the advent of self-injection devices. However, targeted nasal delivery relies on the patient not only following the treatment regimen and using the device correctly, but also positioning the device accurately to ensure that the drug is delivered to the precise location intended.

> "The best form of information gathering is to consult the patients themselves – they know their needs, and frustrations, better than anyone."

Another key factor in the design process is predicting how a patient may interpret the device and, therefore, how they would go about using it. This is where the concept of mental models is useful, as it reflects the patient's perception of how a device works and how to use it based on the patient's experiences of similar devices. Perception is what a patient sees, hears, touches or smells, which, in turn, triggers mental recall and cognition, which then drives their actions.

The best form of information gathering is to consult the patients themselves – they know their needs, and frustrations, better than anyone. Clinicians and caregivers can provide additional information about patient behaviour and trends based on their experience across a wide range of patients, but their answers should take second place.

Speaking to patients is crucial to building an understanding of the context of use; however, care must be taken with the specific questions asked – they must be suitably phrased to avoid leading patients to give similar answers, but also to gather the information required to guide the device design via user needs. Working with experienced insight researchers and human factors experts can greatly increase the value gleaned from patient interaction throughout the design and development process.

Define the Requirements

Once the context of use is understood, the findings and needs of the patient must be converted from a range of opinions and perceptions into clearly defined requirements. It is essential to align patient needs with requirements in a format that can be validated. Similarly, technical requirements need to be verifiable, while also ensuring a cost-effective and usable device design.

User requirements should drive the technical requirements for the device. Requirements are living documents, so each set of patient interviews will typically lead to updates to the requirements throughout the design process. Equally, unknown parameters in the requirements documents can be used to drive patient interviews that can, in turn, be used to refine the requirements further or provide specific values for the device design team. These documents and patient interviews can then both be iteratively tested and updated as required.

Build the Design

The design stage is the point at which activities can be prioritised to reduce development time and costs by differentiating between a prototype device suitable for first-in-human testing and a fully developed and validated device. Here, the typical process of concept generation followed by down selection (via assessment against device requirements) is used to identify a suitable device design for further development.

Once initial prototype devices are available, engineering testing against the requirements can be performed to provide confidence in the design. Full design verification testing is not required at this stage, but sufficient evidence should be generated in the key areas, including safety and dose delivery performance. Development and evaluation of the important training materials, such as the instructions for use, should be started,

> "Once initial prototype devices are available, engineering testing against the requirements can be performed to provide confidence in the design."

but with a lowered risk assessment burden, in the knowledge that there will be clinicians available during initial trials.

Focusing on the requirements of the MVP will accelerate time to clinic by concentrating on safety and usability. This MVP device is equivalent to a syringe and vial or prefilled syringe in injectable development for systemic treatments, so there will be future opportunities to refine the design for Phase III trials and commercial launch. This is an appropriate strategy, as the devices will only be used under supervision at this point. All learnings from the study can then be prioritised and incorporated into the final design as required, according to risks identified.

"Once a final prototype has been developed, it must be evaluated against the design requirements by design review, engineering testing and formative human factors studies."

Evaluate Against Requirements

Once a final prototype has been developed, it must be evaluated against the design requirements by design review, engineering testing and formative human factors studies. This should incorporate a usability assessment for self-administration and simulate as many real functionalities as possible, including tactile, visual and auditory feedback from the device. This process should prioritise evaluating areas highlighted as high risk during previous activities, but also gather information on any additional learnings relevant to future design updates.

THE FUTURE OF TARGETED INTRANASAL DEVICES

The approach discussed here aligns with developing a bespoke prototype device suitable for first-in-human trials for targeted nasal delivery. The success or failure of this strategy depends on the nature of the collaboration between the pharmaceutical partner and the device design engineers, as well as in the experience of the insight researchers and usability engineers. Experience in the process required to develop a usable device is critical to the successful outcome of such a project and will pave the way for bringing a device to market in this new and exciting area of nasal drug delivery. It will be fascinating to see just how many new, life-changing improvements will be made possible by targeted nasal delivery.

ABOUT THE COMPANIES

Cambridge Design Partnership (CDP) is an end-to-end innovation partner, propelling global brands and ambitious start-ups to success. CDP builds breakthrough products and services – from insight to ideas, prototypes to production – bringing innovation to life. By putting people and context at the centre of its thinking, and applying consumer and healthcare knowledge gathered globally by its multidisciplinary team, CDP empowers its partners to create meaningful incremental and transformational innovations that improve lives.

Clexio Biosciences is a multi-asset, CNS-focused clinical-stage pharmaceutical company with a broad and growing pipeline, dedicated to developing novel therapies for patients suffering from neurological and psychiatric conditions. One of the company's driving principles is to invent new therapeutic modalities and bring them quickly from an idea to proof of concept and then to full clinical development, identifying points of convergence between validated mechanisms of action and technology, generating new patient-centric possibilities.

ABOUT THE AUTHORS

Mark Allen, PhD, is a Consultant Biomedical Engineer at CDP. He specialised in the prediction and measurement of liquid and gas flows and sprays while in academia, including work with industry on improving engine technologies to reduce emissions. Dr Allen then moved to the medical device sector, working on the design and development of a range of combination products, from early-to-late stage, including autoinjectors and nasal spray devices. His specialisms include simulation, mathematical modelling and data analysis.

Andrew Fiorini is a Consultant Healthcare Devices Engineer at CDP. He is a versatile self-starter with a track record of quickly understanding new challenges and pursuing objectives to successful delivery. Mr Fiorini is a technical subject matter expert in parenteral technology and is experienced in leading both early-stage R&D projects and late-stage verification projects, as well as working with matrix teams both internally and externally.

Shai Assia is Head of Medical Device Development at Clexio Biosciences, a product development leader with more than 15 years of experience across a wide range of responsibilities and organisations. Mr Assia leads medical device design, development and manufacturing for novel combination products and drug delivery platforms. He holds a BSc in Bio-Medical Engineering from Tel Aviv University (Israel) as well as a MSc in Mechanical Engineering and an MBA from the Massachusetts Institute of Technology (MA, US), where he received the Leaders for Global Operations Fellowship.

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PICOCYL

BENEFITS OF INNOVATIVE COMPRESSED GAS-POWERED INTRANASAL DRUG DELIVERY DEVICES

In this article, Albie Lavin, Technical Advisory Consultant to Picocyl, discusses the exciting potential of propellant-driven systems for intranasal delivery, and how Picocyl's Pico-Cylinders provide the ideal mechanism to take advantage of this potential.

GROWING SHIFT FROM PARENTERAL TO INTRANASAL DELIVERY

Many existing molecules that are currently marketed for oral or intramuscular delivery are finding alternative applications in the intranasal space. Intranasal drug delivery has the potential to combine the non-invasive, patient friendly delivery of oral tablets or capsules with the rapid pharmacokinetic absorption profile of intramuscular injections.

Furthermore, there is potential for new drug formulations to benefit from innovations in intranasal drug delivery that enable direct nose-to-brain absorption pathways or more efficient systemic uptake. Many developing therapies in the central nervous system (CNS) and nasal vaccine spaces are harnessing these advances in delivery technology, and, as a result, the intranasal drug delivery sector is poised to experience significant growth over the next decade.

CURRENT STATE OF INTRANASAL DRUG DELIVERY TECHNOLOGY

The current landscape for intranasal drug delivery technology includes five different types of delivery device (Table 1):

- Pump-driven liquid reservoir systems for liquid formulations and suspensions
- Prefilled syringe-driven systems for liquid formulations and suspensions
- Hand-actuated piston-driven systems for liquid and dry powder formulations
- Breath-actuated systems for liquid and dry powder formulations
- Propellant-driven systems for liquid and dry powder formulations.

The use of propellants to drive nasal drug delivery can result in significant improvements in spray performance and consistency over pump-driven and hand-actuated systems, which can have variable dose delivery and spray characteristics depending on how hard or soft the user squeezes the device. However, propellant-driven systems typically require a constant trip force to release the propellant (which is what the user feels), after which the energy released by the propellant is metered by either a valve in the device or the mass of propellant filled during the manufacturing process. Therefore, variation in the actuation force applied by the user does not contribute to variation in the dose delivered.

Some currently marketed devices require breath co-ordination to achieve appropriate deposition inside the nasal cavity. Typical spray-pump devices require the user to breathe in and pump simultaneously, while some other devices are breath-actuated, requiring the user to inhale or exhale to generate propulsion. Propellant-driven systems can provide enough energy and particle velocity to overcome the pressure gradients created by the typical breath cycle, meaning patients do not need to co-ordinate breathing with dosing. This makes medication delivery easier for the user or caregiver.

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Drive System	Devices	Manufacturers	Formulation Types	Marketed Products
Pump		Aptar, Nemera	Liquid, Suspensions	Many
Prefilled Syringe		Aptar, Nipro, Teleflex	Liquid, Suspensions	Many
Hand-Actuated Piston		Aptar, Nemera, Janssen	Liquid, Suspensions, Dry Powder	Narcan, Spravato
Breath-Actuated		Optinose	Liquid, Suspensions, Dry Powder	Xhance, Xsail
Propellant		Impel	Liquid, Suspensions, Dry Powder	Trudhesa

Table 1: Current landscape of intranasal drug delivery devices.

Propellant-driven systems can also provide enough energy to deliver drug formulations into hard-to-reach areas inside the nasal cavity, specifically the olfactory region or upper nasal cavity. Intranasal delivery has also been identified as a potential nose-to-brain pathway, and an increasing number of CNS therapies are seeing success in targeting and delivering drugs to this region.[1,2] The use of propellant typically provides drug particles with sufficient momentum to overcome the airflow generated by the breathing cycle, which can help to avoid losing dose down to the lungs and throat.

Currently marketed propellant-driven intranasal drug delivery systems use multi-use metered dose inhaler (MDI) canisters filled with HFA-134a to propel drug in the nasal cavity. These canisters are robust and well-studied, and there are several options available for shot-metering valves and propellant fill capacity with different manufacturing and filling partners. However, these canisters are optimised for MDIs, which are typically used on a daily basis in a controlled environment. Consequently, their features do not always align well with single-use intranasal drug delivery applications.

> "The Pico-Cylinder was developed to provide handheld devices with a drive system that can deliver precise primary drug container force profiles for a wide variety of applications and liquid viscosities."

COMPRESSED GAS CYLINDERS ENABLE PROPELLANT-DRIVEN SINGLE-USE INTRANASAL DRUG DELIVERY

Compressed gas cylinders are a great fit for single-use spray applications. However, until recently, there have not been any compressed gas cylinders produced specifically for medical devices and combination products. Enter the Pico-Cylinder, the world's first small-volume, single-use compressed gas cylinder manufactured in a Class 8 cleanroom. The Pico-Cylinder was developed to provide handheld devices with a drive system that can deliver precise primary drug container force profiles for a wide variety of applications and liquid viscosities.

Pico-Cylinders have been used in intra-ocular lens inserters, autoinjectors, gas therapy delivery systems, subretinal injectors, ingestible small intestine drug delivery capsules and, most recently, in Impel Pharmaceuticals' (WA, US) I143 device, a single-use intranasal powder drug delivery device detailed in US patent 20200360627-A1.[3] The I143 device (Figure 1) was developed to deliver spray-dried powder formulations to the

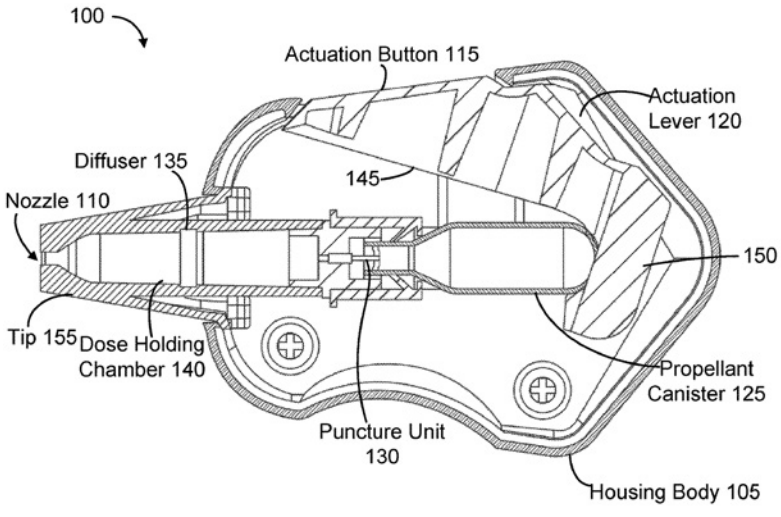

Figure 1: Impel Pharmaceuticals' single-use nasal drug delivery device, Patent US20200360627-A1, cross-section.

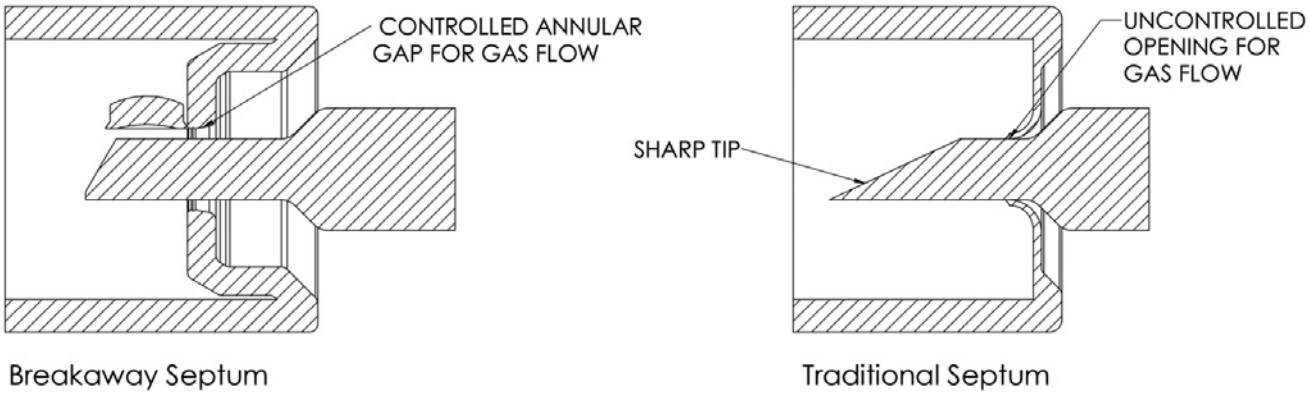

Figure 2: Proprietary breakaway septum vs traditional septum.

upper nasal cavity to facilitate precision olfactory delivery, with the spray directly powered by the gas expelled from a Pico-Cylinder.

Pico-Cylinders are deep-drawn stainless steel containers that can be filled with both vapour-phase (N_2, Ar) or dual-phase (CO_2) compressed atmospheric gases at pressures from 5 to 350 bar.[4] The cylinder is sealed with a proprietary stamped steel cap component with a breakaway septum that requires a secondary opening pin component to open – a Pico-Pin.[5] Altaviz (CA, US) , a medical device design company and affiliate company to Picocyl, designed the Pico-Pin to reliably open the breakaway septum and allow for a consistent gas flow path both through and around the pin (Figure 2).

Traditional septum-based compressed gas cylinders use a sharp puncture to cut a flat sheet metal septum, which means that the position and puncture mechanics can be unpredictable. This can lead to gas flow issues after puncture, including cases where the punctured material covers the exit hole in the puncture pin.

Because of the Pico-Cylinder's material selection, cylinder neck design and cap design, the Pico-Pin preferentially tears the perimeter of the septum to "open the hatch" in a controlled manner with a fourfold reduction in stroke length and a tenfold reduction in energy. This reduction in stroke length and force required to open the cylinder enables device embodiments that allow for user hand-actuation of the device without large spring-loaded systems – a unique offering in the compressed gas cylinder space.

> "Because compressed gas cylinders are single-use pressurised vessels, high reliability is imperative for enabling successful drug products."

Because compressed gas cylinders are single-use pressurised vessels, high reliability is imperative for enabling successful drug products. Cylinders must not leak over the shelf life of the combination product, and they must open consistently without any blockages. The Pico-Cylinder manufacturing process achieves this high reliability production using the following quality inspections.[6]

Fill Weight Verification

Each Pico-Cylinder is weighed before and after filling during the validated automated gas-filling and welding process to ensure that the correct amount of gas makes it into 100% of the cylinders.

Gross Mass and Part Identification

Each Pico-Cylinder is permanently laser-marked with its gross mass for downstream quality checks. Custom QR codes and human-readable information are possible to enable traceability throughout the manufacturing process and lifetime of the Pico-Cylinder.

Heat Conditioning

Each Pico-Cylinder undergoes a high-temperature soak to increase the internal pressure and heat stress the weld and the integrity of the components to accelerate any leaks for the subsequent leak detection process.

Leak-Free Verification Analysis

Each Pico-Cylinder is analysed for leaks using validated gas-analysis equipment. Vapour phase Ar and N_2 systems are mixed with 5% He trace gas to enable inspection with an He leak detection mass spectrometer system. This provides a conservative estimate of leak rates without compromising internal pressure or gas reactivity. Dual phase CO_2 gas is detected using gas chromatography and does not require any trace gas mixture.

Empty Canister Detection System

Each Pico-Cylinder is weighed to ensure that some gas was filled into the capsule. Without this step, it is possible that a leak detection system would not detect a fast-leaking part that had completely emptied prior to gas analysis.

Picocyl, the manufacturer of the Pico-Cylinder, has performed real-time leak testing out to 48 months using approximately 86 bar Ar gas with a 5% He trace gas using a sample size of 150. The maximum individual Pico-Cylinder mass loss at 48 months was 0.4 mg (<0.5% of gas fill mass), which is within the average measurement error of the scale used. This result demonstrates that the components do not leak over the typical shelf life of a combination product (Table 2).

Real Time Ageing (months)	Maximum Individual Mass Loss (mg)
9	0.3
12	0.5
18	0.2
24	0.5
36	0.3
48	0.4

Avg scale measurement error = 0.5 mg

Table 2: Pico-Cylinder real-time leak data at four years.

"Compressed gas cylinders are filled with a tightly controlled amount of propellant that is all released at once, so the user simply needs to overcome the opening force of the cylinder to achieve consistent spray characterisation."

COMPRESSED GAS CYLINDERS ENABLE SIGNIFICANT PERFORMANCE AND USER BENEFITS

Consistent Spray Characterisation

Typical pump-driven or hand-actuated systems are rate dependent. This can alter the velocity of the spray, which, in turn, can alter plume geometry, spray pattern or droplet size distribution from patient to patient, or even spray to spray. Compressed gas cylinders are filled with a tightly controlled amount of propellant that is all released at once, so the user simply needs to overcome the opening force of the cylinder to achieve consistent spray characterisation. This opening force is not rate-dependent, so the spray output is much more consistent across a wide range of patients.

No Priming Required

Typical pump-driven or hydrofluoroalkane (HFA) propellant-driven systems require a priming step to load liquid drug or liquid propellant into the dose chamber prior to dosing. This typically requires the device to have a drug storage chamber and a dose chamber, which makes the device larger and inevitably creates some dead volume in the flow path. This can result in wasted dose in the form of residual loss. The priming step is also typically the most common human factors error in a device's workflow, and any extra steps in the dosing process can lead to use errors.

Compressed gas cylinders do not require priming prior to actuation, which reduces the number of required user steps and enables the reduction of drug-loading procedures. This makes compressed gas cylinders an ideal drive system for rescue applications and patient populations with impaired cognitive ability or reduced fine motor function.

Consistent, Low Actuation Force

The Pico-Cylinder is designed to have an opening force low enough to enable human actuation. This enables the use of simple levers or buttons in device design rather than requiring large springs, allowing devices to be smaller and more convenient to carry and use. Table 3 lists typical puncture force data. Typical hand-actuated devices use a 3:1 or 4:1 lever to reduce user forces down to 10–20 N.

Separation of Propellant and Drug

Typical MDIs mix liquid propellant and liquid drug formulation inside the canister. Traditional HFA propellants can be volatile and pose drug stability or extractables and leachables issues in drug products. Compressed gas cylinders ensure that the propellant is kept separate from the drug inside the device, enabling all stability testing to be performed on the drug product alone. This can accelerate development time and allow the same device platform to support multiple drug products without requiring extensive stability testing.

Parameter	Lot 1 (Low Pressure)	Lot 2 (High Pressure)
Internal Pressure (Bar)	55	180
Average Puncture Force (N)	39.7	48.1
St. Dev. Puncture Force (N)	4.4	7.3
Minimum Puncture Force (N)	32.8	31.3
Maximum Puncture Force (N)	51	60.5
Cpk for 80 N Maximum Puncture Force Specification	3.08	1.46

Table 3: Pico-Cylinder puncture force data.

Range of Stable Gas Options

Pico-Cylinders can be filled with a wide range of gases and gas fill masses to suit any application. Typical community use products will benefit most from using vapour phase atmospheric gases, such as N_2 and Ar, due to their pressure consistency across temperature ranges. Across a standard community-use product temperature range of 0°C to 40°C, vapour phase gases experience a ±7% pressure shift (following the ideal gas law), while traditional dual-phase HFA-134a experiences ±77% pressure shift. Higher pressure applications can benefit from dual-phase gases, such as CO_2, in a temperature-controlled environment (15°C to 25°C).

Environmentally Friendly

Pico-Cylinders do not use the HFAs that are currently used throughout the inhaled and cosmetic industries for propellants – instead, they use inert gases such as N_2, Ar and CO_2. They provide a solution that complies with the Kigali Amendment (2019) of the Montreal Protocol on Substances that Deplete the Ozone Layer established in 1987.[7] Furthermore, gases such as N_2, Ar and CO_2 can be sustainably sourced and managed, making gas supply independent of worldwide chemical supply shocks, such as those experienced in the wake of the covid-19 pandemic.

CAPABILITIES OF PICO-CYLINDERS FOR INTRANASAL DRUG DELIVERY

Pico-Cylinders can be used to achieve a wide range of spray outputs and are suitable for a range of single-use intranasal drug delivery applications. They are suitable for delivering both liquid and dry powder drug formulations. They can be used to actuate existing primary drug container mechanisms, such as cartridges, syringes and micro-vials, or to directly propel the drug formulation out of the device.

Pico-Cylinders do not limit the spray characteristics to a specific profile – they can be used to generate a wide plume with a very diffuse spray and small particle size or to generate a narrow plume with a large particle size. Altaviz has designed and built several prototype configurations of common nasal spray actuators powered by Pico-Cylinders to demonstrate these capabilities. Images taken from high-speed video illustrate how Pico-Cylinder-powered prototypes can generate similar

spray characteristics to currently marketed intranasal drug delivery devices using 0.9% saline solution (Figure 3).

ABOUT THE COMPANY

Picocyl enables the future of drug delivery and other specialty applications through innovative device design and gas-powered solutions for the medical and pharmaceutical markets. Every product, application and solution the company delivers is built from the ground up in its state-of-the-art US-based cleanroom manufacturing facilities (ISO Class 8). A pioneer in developing unique energy sources for drug delivery, the company's flagship Pico-Cylinders have become the industry standard for single-use gas-powered devices. Picocyl is an ISO 13485-certified manufacturer.

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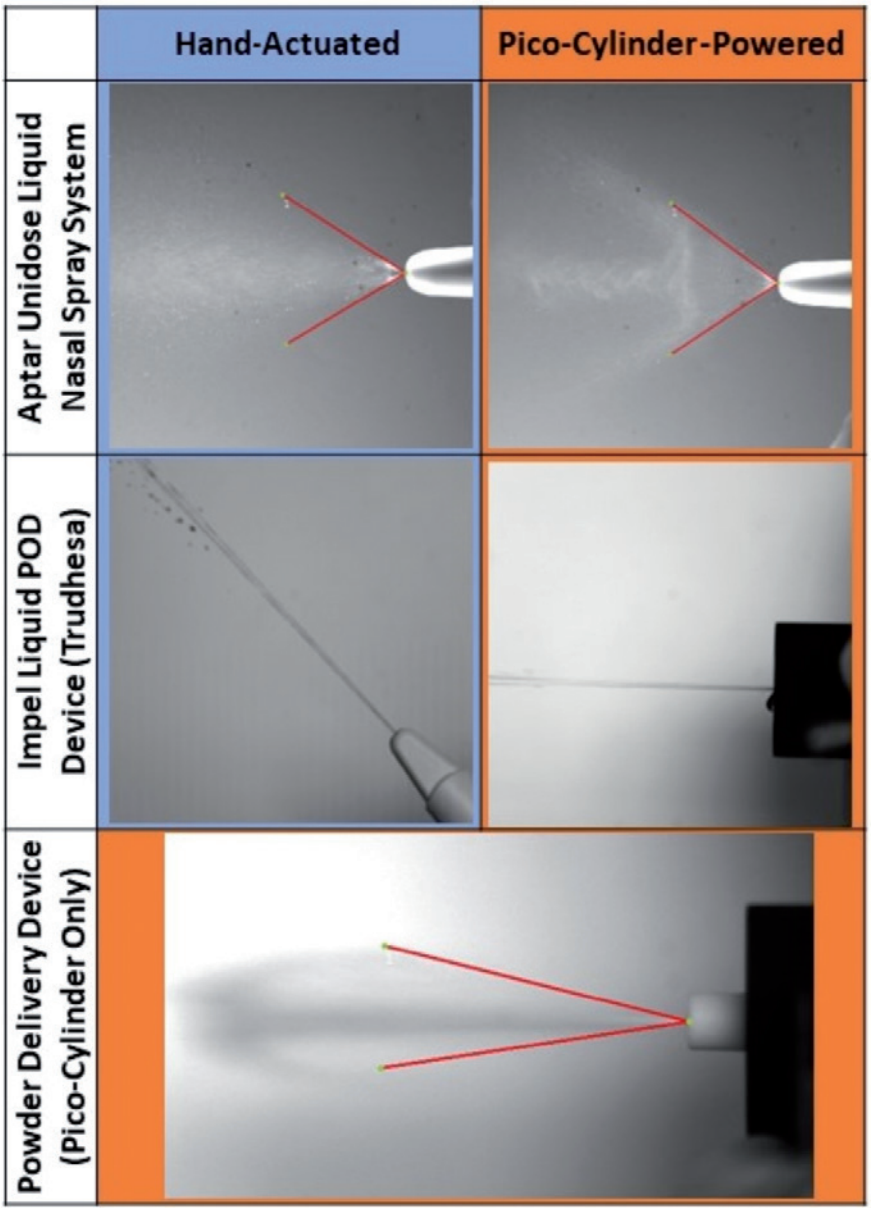

Figure 3: Plume videos from Pico-Cylinder-powered prototypes.

ABOUT THE AUTHOR

Albie Lavin is the inventor of the Impel Pharmaceuticals I143 device, the first nasal spray developed around the use of a single-use compressed gas cylinder. Mr Lavin has spent the last five years developing novel nasal spray devices designed to achieve precision olfactory delivery, including combination products indicated for acute agitation, Parkinson's disease and migraine. He currently serves as a Technical Advisory Consultant to Picocyl and remains passionate about developing novel device solutions for the drug delivery space.

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CHALLENGES BESIDES DRUG TARGETING – REGULATORY HURDLES FOR MULTIDOSE NASAL SPRAYS

In this article, Marie-Christine Klein, PhD, Head of Development & Regulatory Affairs, and Andreas Bilstein, PhD, Managing Director, both at URSATEC, and Rouven Kraus, Head of Sales at Aero Pump, discuss recent regulatory changes affecting drug-device combination products, using the example of a multidose nasal spray.

Targeted drug delivery is key to maximising the potential of state-of-the-art drug developments. In order to support targeted drug delivery, application devices combine a number of characteristics to ensure performance and patient safety: a precise dosage, the technical prerequisite to reach the target of interest and a good usability profile.

A well-known route of drug targeting is the nasal route, which is used by nasal spray devices that have been used by patients all over the world for decades. A prominent example of indications that make use of the nasal route is, of course, coughs and colds. But a lot of other indications also benefit from the nasal route because of its advantageous properties, such as high drug uptake because of good vascularisation and systemic circulation and the possibility of bypassing the liver.

> "The olfactory region can be targeted directly by adjusting multidose nasal spray devices to provide a slow-moving fine mist that has ideal properties to deposit deep within the nasal cavity."

Furthermore, the olfactory region can be targeted directly by adjusting multidose nasal spray devices to provide a slow-moving fine mist that has ideal properties to deposit deep within the nasal cavity.[1] This adds the advantage of providing access to the brain by nerval structures that connect the brain and the nose – the so-called trigeminal and olfactory pathways – and of treating brain-associated disorders of the central nervous system, such as Alzheimer's and Parkinson's disease.

REGULATORY ASPECTS OF NASAL DRUG DELIVERY

Market-ready nasalia require the development of a formulation that fits the nasal physiology and a suitable nasal spray that can transform the formulation into a spray with defined properties that lead to an effective and safe treatment. In addition, regulatory requirements pave the road to market and are key to successful development and market authorisation.

This article will elaborate on a specific aspect of regulatory provisions that has changed significantly over the last few years and which the Regulation (EU) 2017/745 on Medical Devices, better known as the MDR, brought to the field of drug-device combinations – a medicinal product administered by a multidose nasal spray.

From a regulatory point of view, the targeted administering function of a nasal

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Figure 1: Nasal pumps are an integral part of the drug-device combination product, according to MDR.

spray with its defined doses leads us to the intended purpose of the multidose nasal spray, which characterises the spray pump as a medical device. With that in mind, along with the MDR, it becomes clear that nasal sprays are very often part of drug-device combinations (DDCs). In a nutshell, DDCs contain both a medicinal product and a medical device. But, of course, different scenarios of these subsets of combinations exist and each combination requires a strong regulatory examination focusing on the definition of the principal mode of action. Depending on the latter, either the MDR or the Directive 2001/83/EC defines the regulatory landscape of the DDC. These DDCs and their intertwined regulatory provisions with the Directive 2001/83/EC are addressed in different articles of the MDR.

MDR article 1 (8 and 9) provides the definitions of incorporation and administering and outlines the concept if it is an integral device. And MDR article 117 directly amends the Directive 2001/83/EC in terms of DDCs and regulatory requirements concerning the device part in MAAs. The following sections concentrate on the respective aspects that are of interest in the example of a nasal spray used to administer a medicinal product (Figure 1).

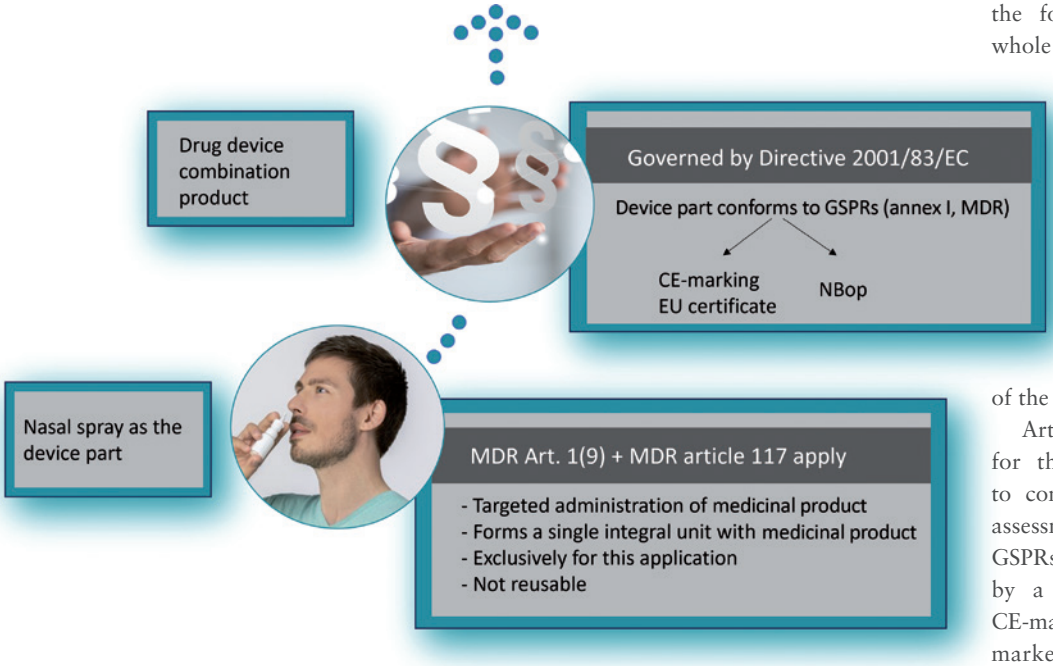

Figure 2: Regulatory route to market for DDC products, exemplarily for a medicinal product applied in a nasal spray.

> "The MDR has changed the European medical device regulatory landscape fundamentally."

Nasal Spray Pump as an Example of an Integral DDC (MDR)

Nasal spray pumps work by transforming a liquid formulation into a spray and targeting the drug to the nasal cavity. By industrial processing and aseptic filling, they are filled with the respective (sterile) formulation and, as a consequence, are fused into a single integral product that is intended exclusively for the use in the given combination. Moreover, the nasal spray pump is not reusable. All these characteristics are the subject matter of Article 1(9) of the MDR that leads the reader to the following regulatory strategy: the DDC in that case is governed by the medicinal products framework and the device part (nasal spray pump) needs to fulfil the general safety and performance requirements (GSPRs) outlined in Annex I of the MDR.

Nasal Sprays to Deliver Medicinal Products: MDR Article 117 Applies

The MDR has changed the European medical device regulatory landscape fundamentally. Within the MDR, there is more emphasis on post-market surveillance and clinical data, which substantiated the focus of interest on the product's whole lifecycle (Figure 2). In the same vein, the MDR also has influence on the MAA of medicinal products. Article 117 of the MDR alters the Directive 2001/83/EC in the case of products that combine a medical device part with a medicinal product in cases where article 1 (8, 2nd sub) or article 1 (9, 2nd sub) of the MDR apply.

Article 117 contains the requirement for the marketing authorisation dossier to contain the results of the conformity assessment of the device part with the GSPRs or the relevant certificate issued by a notified body (NB) allowing the CE-marking of the medical device. If the marketing authorisation dossier does not contain a conformity assessment although the device part itself requires the

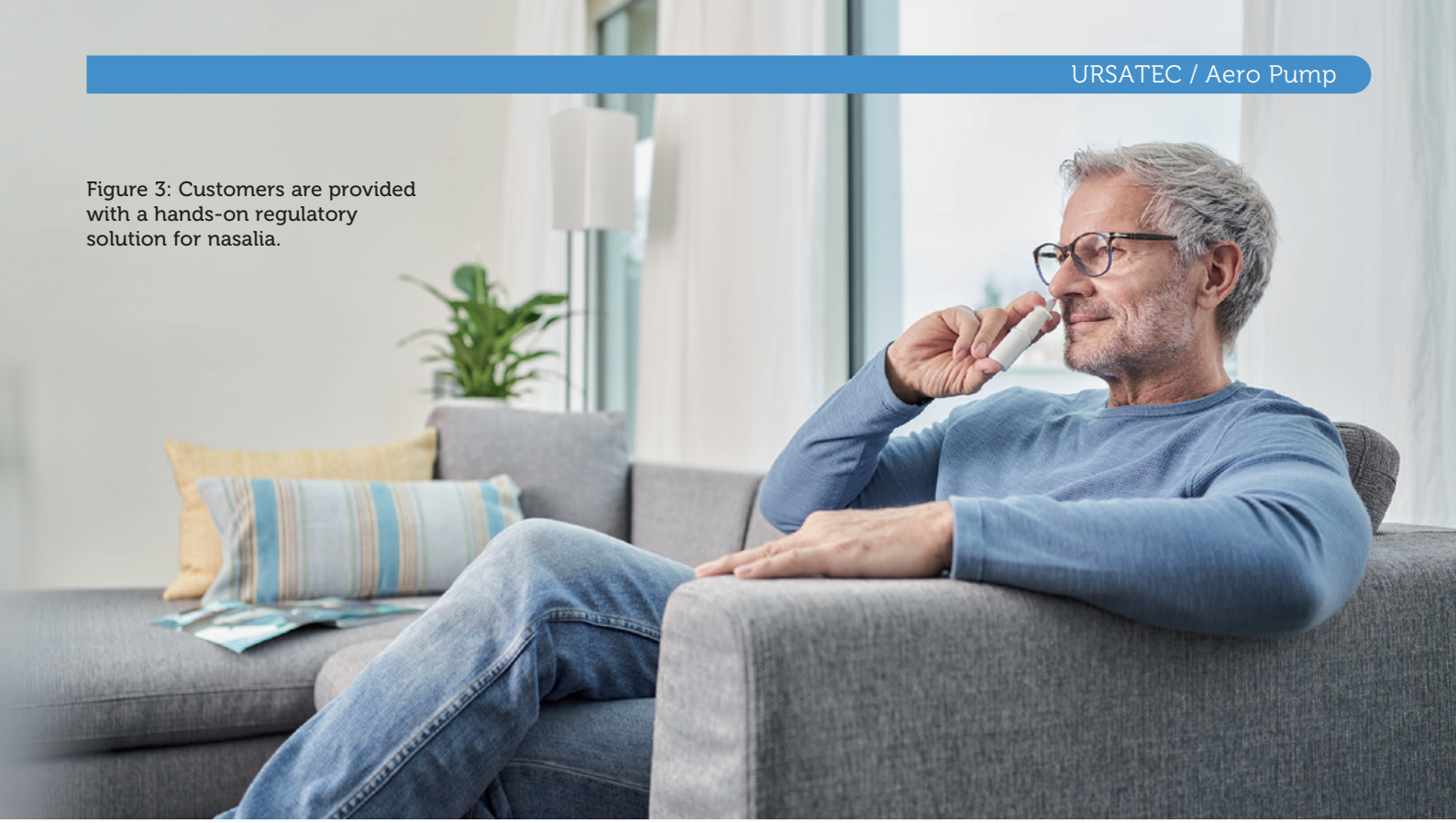

Figure 3: Customers are provided with a hands-on regulatory solution for nasalia.

involvement of an NB, the authority will require an opinion on the conformity of the device part to the above-mentioned requirements (NBop).

MDR Influences Marketing Authorisations for Medicinal Products

The good news first: for marketing authorisations that have been granted before the due date May 26, 2021 that did not undergo significant changes, this regulatory change is not effective – it is not intended to apply retrospectively. However, for marketing authorisation holders of nasal drugs that do not yet have an unlimited market authorisation, the due date applies.

Since May 26, 2021, the effective date of the MDR, new MAAs need to fulfil article 117 of the MDR. The latter is also effective for renewal applications at the end of the five-year initial marketing authorisation. Nine months before validity is due to run out, re-evaluation needs to be applied and, when granted, provides the prerequisite for an unlimited marketing authorisation. With this application, information on all variations introduced since the marketing authorisation was granted needs to be given, which may also require the conformity assessment or the NBop of the device part of the DDC. In general, significant changes to the design and intended purpose of the product may be influenced by article 117 and require action, even if an unlimited market authorisation was already granted before due date.

> "URSATEC and Aero Pump provide medical pumps CE marked with full MDR-compliant documentation that supports conformity with the GSPRs."

The EMA has issued a Questions and Answers Document[2] for applicants, marketing authorisation holders of medicinal products and notified bodies with respect to the implementation of the MDR and IVDR,[2] which outlines the above-described situation in detail. Moreover, a guideline on quality documentation for medicinal products when used with a medical device is available that helps with incorporating the regulatory requirements of the MDR into the quality part of the marketing authorisation dossier.[3]

Medical Pumps: Class I(S) Medical Devices According to MDR

With a strong focus on the evolving needs of the changing regulatory environment in the EU and what is requested by authorities, URSATEC and Aero Pump provide medical pumps CE marked with full MDR-compliant documentation that supports conformity with the GSPRs. Furthermore, in the case of medical pumps being used in medicinal products declared sterile, a class 1s EU certificate issued by an NB is available. With this added value, customers are provided with a hands-on solution when using delivery devices for nasalia in cases where article 117 applies (Figure 3). Ideally, these regulatory prerequisites coming from the MDR, and changing the provisions for medicinal products in the case of DDCs, are implemented at a very early stage of development.

ABOUT THE COMPANIES

URSATEC was founded in 1993 to accomplish one mission: the establishment of preservative-free applications, based on its proprietary packaging systems in different application areas, primarily the nasal, dermal, buccal and otological fields. Having sold almost two billion units within the last 25 years, URSATEC systems are widely established. URSATEC is consistently expanding its business and offers full development service, dosage systems, primary packaging materials and filling services for over-the-counter and prescription applications to the healthcare industry.

Aero Pump is a leading manufacturer of high-precision application systems for the pharmaceutical and healthcare industry, focused on innovation, multi-functionality and contemporary design. Its spray

pumps and dropper systems are widely established in the market and are primarily used in the nasal, ophthalmic, pulmonary and dermal fields, suitable for preserved and preservative-free over-the-counter and prescription drugs.

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ABOUT THE AUTHORS

Marie-Christine Klein, PhD, is a biochemist by training and joined URSATEC in 2019. She is Head of Development & Regulatory Affairs, leading a team that is focusing on regulatory compliance concerning URSATEC application technology, as well as drug-device combinations.

Andreas Bilstein, PhD, has been Managing Director of URSATEC since August 2020. He is a biologist with more than 15 years of experience in developing preservative-free products for various applications.

Rouven Kraus has more than 10 years of experience in the drug delivery market. He started his career in sales for a domestic iron foundry in Mainz, Germany, and joined Aero Pump in 2012 to augment the sales of its drug delivery device portfolio. In his role as Head of Sales, he manages global sales as well as the company's strategic approach to new developments and delivery technologies.

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NASAL DRUG DELIVERY: OVERCOMING CHALLENGES WITH A ROBUST PLATFORM STRATEGY

In this article, Richard Johnson, PhD, Founder and Chief Scientific Officer at Upperton Pharma Solutions, explores the changing nasal delivery landscape, highlighting challenges in nasal drug formulation and potential methods to overcome them.

Delivering drug products via the nasal cavity is not a new practice, with nasally administered treatments, such as antihistamines and cold relief medications, readily available over the counter. Now, innovation in the pharmaceutical sector is leading to a shift in exploring the use of nasal devices to deliver a wide range of therapeutics, ranging from traditional small molecule APIs to larger, more complex molecules, such as peptides and vaccines. Moreover, there is a particular interest in delivering molecules both systemically and directly to the brain.

These sensitive drugs often rely on parenteral administration to avoid the harsh conditions of the gastrointestinal (GI) tract. By delivering these drugs via the nasal route, it is possible to avoid the GI tract and first-pass metabolism, as well as making them easier to self-administer. In light of this, the global nasal delivery market is experiencing rapid growth, with its value predicted to increase from US$72.89 billion (£60.05 billion) in 2022 at a compound annual growth rate of 7.45% until 2030.

THE BENEFITS OF NASAL DELIVERY

The nasal cavity enables drug products to be absorbed quickly across the nasal mucosa and then distributed systemically. By avoiding the GI tract, this immediate absorption into the bloodstream ensures a rapid onset of therapeutic effects. Administering drugs into the bloodstream via the nose can also overcome the issues of first-pass metabolism by the liver, an issue that is difficult to overcome with oral dosage forms. Additionally, intranasal delivery offers direct access to the brain, bypassing the blood-brain barrier.

Patient-centricity is an industry priority, aiming to increase patient access, compliance and adherence. Nasal delivery devices are helping to achieve this goal, offering a delivery method that is quick, easy and non-invasive. In contrast with many parenteral delivery methods, nasal delivery devices can also be self-administered, circumventing the need for healthcare practitioner involvement and reducing the burden on healthcare systems.

> "Patient-centricity is a priority in the industry, aiming to increase patient access, compliance and adherence. The use of nasal delivery devices is helping to achieve this goal, offering a delivery method that is quick, easy and non-invasive."

However, a number of challenges can hinder the development of drug products for nasal delivery. As the industry explores administration systems for the nasal delivery of more sensitive materials, such as vaccines and peptide-based products, innovative solutions are required to successfully formulate and administer them while maintaining their stability and efficacy.

OVERCOMING NASAL FORMULATION CHALLENGES

Traditionally, nasal products are liquid-based, with the drug product solubilised in water to form droplets when sprayed from the device into the nose. When administered, the drug product is then deposited in the nasal cavity, where it can act on the nasal epithelial surface. From there, the drug product has the potential to be absorbed across the nasal

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mucosa and transported systemically through the bloodstream, and reach the target to exact a pharmacological effect. Alternatively, the drug product can be administered into the nose as a dry powder, dissolving once the powder particles impact the moist surfaces of the nasal epithelium to release the drug for either local or systemic action.

The target product profile (TPP) outlines the desired characteristics of a drug product. If created early in the development process with a thorough understanding of the properties of the API, the TPP can help to guide development, highlighting which characteristics need to be modified for the drug product to meet target standards. These present some challenges that must be overcome to successfully formulate a drug product for nasal delivery, including:

- **Solubility:** Poor solubility impacts drug distribution and bioavailability, as well as the choice of device (liquid vs dry powder).
- **Stability:** Unstable products may lose their activity, with stability often reduced when solvated, necessitating the dry powder approach for delivery.
- **Bioavailability:** Insufficient bioavailability hinders the delivery of the drug around the body and can significantly impact the therapeutic effect of the drug.

These challenges are commonly interlinked, with issues such as solubility and stability favouring a dry powder formulation that offers the best developmental approach compared with a liquid-based device. As such, some of these factors can be overcome by enhanced formulation approaches.

Excipients are added routinely to the final formulation to improve the solubility, stability and bioavailability of the API. For example, a gelling agent can be added to the formulation to increase the residence time of the API on the surface of the nasal cavity, allowing for absorption over a longer timeframe. Other excipients include agents that can enhance membrane permeation by opening up the tight junctions in the nasal epithelium.

To achieve optimal results, the addition of excipients should be coupled with other strategies to infer desired characteristics and form the final formulated product. For example, with dry powder device formulations, the engineering of particle size plays a critical role in ensuring optimal deposition of the drug in the appropriate areas of the nasal cavity while preventing the drug from entering the lungs.

DRY POWDER DELIVERY SYSTEMS OFFER AN ALTERNATIVE SOLUTION

As drug molecules become more complex, challenges such as solubility and stability are more likely to arise, and alternative solutions to overcome these limitations may be required. When the drug product is dissolved in an aqueous carrier, its stability can be reduced in comparison with a dry powder form. These stability problems can result in degradation of the drug product, significantly limiting its shelf life. Therefore, dry powder nasal formulations are increasingly being investigated as solutions for more complex drug products.

> "As drug molecules become more complex, challenges such as solubility and stability are more likely to arise, and alternative solutions to overcome these limitations may be required."

Dry powder nasal devices are designed to deliver dry powder particles directly into the nasal cavity by either actively firing the powder into the nose or the recipient inhaling the powder from the device, actively inhaling through the nostril. As the particles exit the device and make contact with the nasal mucosa, particle dissolution occurs, and the drug is absorbed onto the nasal epithelial surface for local action or transport across the membrane and distribution throughout the body. Additionally, the recent emergence of commercially available nasal devices that can deliver their drug product as a dry powder also enables temperature-sensitive products to be transported and administered without the need for cold chain storage.

Despite these advantages, challenges still arise, similar to those when developing liquid formulations. For example, particle size and distribution remain vital to dose uniformity, which ensures thatparticles are deposited and dispersed with consistency, avoiding the vestibules. Particle size and distribution are also critical to ensure delivery of the dry powder into the turbinates, olfactory and nasopharynx regions while avoiding delivery downstream into the lungs.

Device design also plays an essential role, requiring the powder to be retained in a protected environment prior to administration while ensuring that the aerodynamic properties of the delivered powder optimise deposition within the nasal cavity.

In addition to meeting the TPP, the drug product properties must also fulfil regulatory requirements to ensure safety and efficacy. In particular, aerodynamic particle size restrictions are enforced to prevent delivery of the drug product into the lung as opposed to remaining in the nasal passage.

A ROBUST PLATFORM IS KEY TO OVERCOMING CHALLENGES AND MITIGATING RISK

Employing a robust platform strategy can help to identify potential problems early when creating a drug product for nasal delivery, enabling solutions to be implemented pre-emptively to accelerate overall development and manufacture. In addition to helping to overcome challenges, an effective platform strategy can mitigate production risks. A robust platform strategy should encompass the following critical steps:

- **TPP development:** Identify the desired characteristics of the product (such as anticipated dose and frequency of dosing).
- **Pre-formulation/stability screening:** Complete stability testing studies throughout in a liquid or dry powder formulation, including excipient compatibility and accelerated stability testing.
- **Selection of dosage form:** Use the screening results to decide upon a dosage form (such as liquid vs dry powder or single shot vs multidose).
- **Formulation development:** Determine the final formulation and process following regulatory submissions and toxicology evaluation prior to clinical manufacture.

Irrespective of whether the product is to be a liquid or dry powder formulation, an effective platform strategy can help to inform key decisions, with early identification of drug product needs allowing for proactive development and manufacture. With a

> "To meet these growing demands, innovation in the nasal delivery space is essential for producing drug products that meet stability, solubility and bioavailability standards."

platform strategy helping to mitigate risk and streamline the development of the final formulation, the clinical dosage batch can then be manufactured and the device filled.

SOLIDIFYING THE FUTURE OF NASAL DELIVERY DEVICES

The pharmaceutical industry is showing an increased interest in nasal delivery as an alternative needle-free option for the self-administration and rapid delivery of drugs into systemic circulation and to the brain. To meet these growing demands, innovation in the nasal delivery space is essential for producing drug products that meet stability, solubility and bioavailability standards. Researchers are increasingly looking at the development of dry powder nasal dosage forms to overcome these challenges. Despite this growing interest in dry powder nasal drug delivery, understanding of the steps necessary for developing nasal products remains limited.

Challenges remain not only in the development of nasal dosage forms but also in the identification of analytical methods suitable to testing their performance. During the development stages and when the final prototype dosage form has been finalised, analytical test methods are essential for ensuring that the final dosage form is stable and exhibits the correct delivery performance.

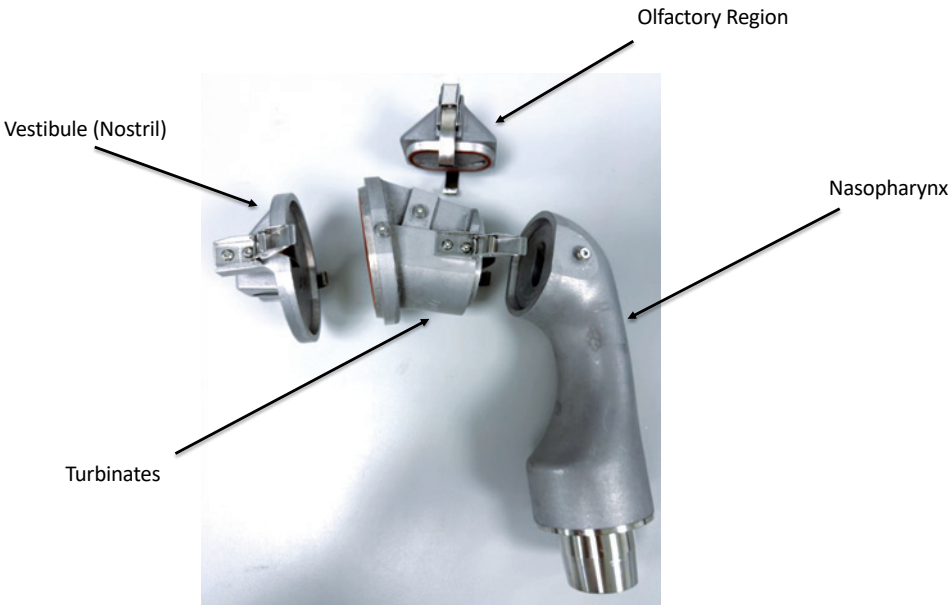

Figure 1: Parts of an AINI.

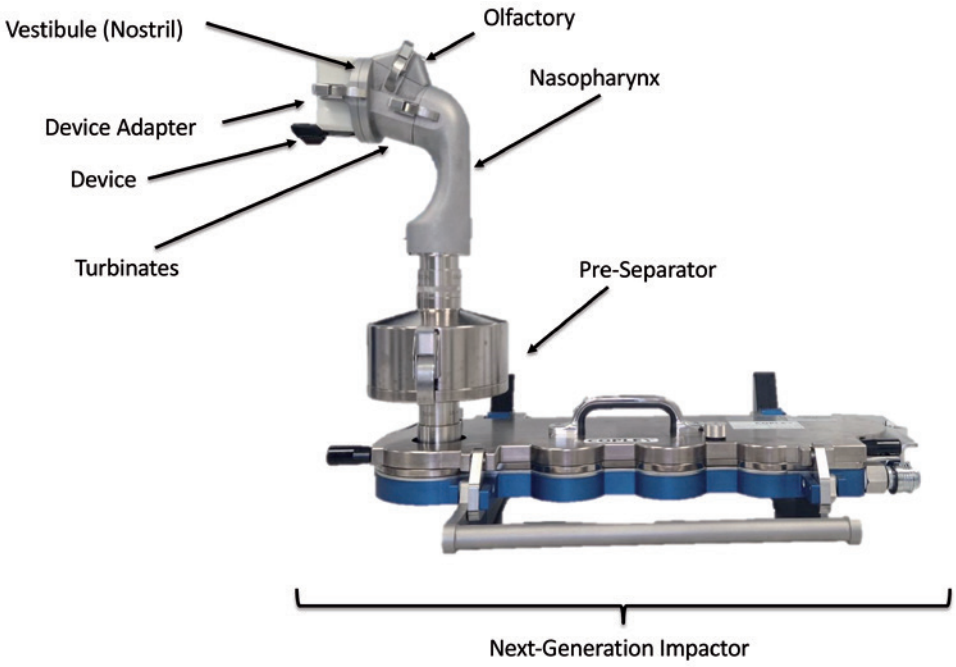

Figure 2: AINI fixed to Copley Scientific (Nottingham, UK) next-generation impactor for aerodynamic particle size distribution and lung deposition analysis.

> "One key area of research is in the development of relevant tests to determine the aerodynamic performance and nasal deposition patterns for nasally delivered drugs."

One key area of research is in the development of relevant tests to determine the aerodynamic performance and nasal deposition patterns for nasally delivered drugs. This area is attracting significant interest from developers and regulators alike, who want to know how much of the dose is delivered from the device as well as where it is deposited in the nose, and potentially in the lungs. This has led to the development of next-generation nasal deposition models, such as the Alberta idealised nasal inlet (AINI), shown in Figures 1 and 2.

A partnership with an expert in nasal manufacture and delivery can help to provide specialist technical and regulatory knowledge that can drive a nasal drug product to success. Starting a collaboration early in development allows for the TPP to be outlined and the drug product formulated and filled with the desired use in mind, accurately addressing the needs of the product and the patient.

ABOUT THE COMPANY

Upperton uses its expertise to develop a wide range of finished, non-sterile dosage formats for its clients designed for delivery via the oral, pulmonary and nasal routes. Alongside dosage form development and clinical manufacturing, the company also specialises in spray drying – a particle engineering technology that can be used to ensure targeted delivery of drugs to the lungs and nasal cavity or to provide solutions to pharma clients with poorly soluble molecules.

ABOUT THE AUTHOR

Richard Johnson, PhD, founded Upperton Pharma Solutions in August 1999 and continues to play a key role in the management and strategic development of the company. With over 30 years of experience in the pharmaceutical, biotechnology and drug delivery fields, Dr Johnson previously held senior management positions at Andaris Group (Vectura) and Delta Biotechnology (now Albumedix). Dr Johnson holds an honours degree in Biology from the University of York (UK), a PhD from the University of Warwick (UK), and has a proven track record in successfully developing innovative pharmaceutical products from early feasibility studies through to commercial products.

INTERVIEW: RDD EUROPE 2023 REVIEW & RDD 2024 PREVIEW

Respiratory Drug Delivery talks with ONdrugDelivery, summarising and reviewing highlights of the successful RDD Europe 2023 event, which took place in Antibes, France, last May, then describing what's ahead for RDD 2024, which will take place in Tuscon, AZ, US, next May, including some of the key upcoming deadlines for participants.

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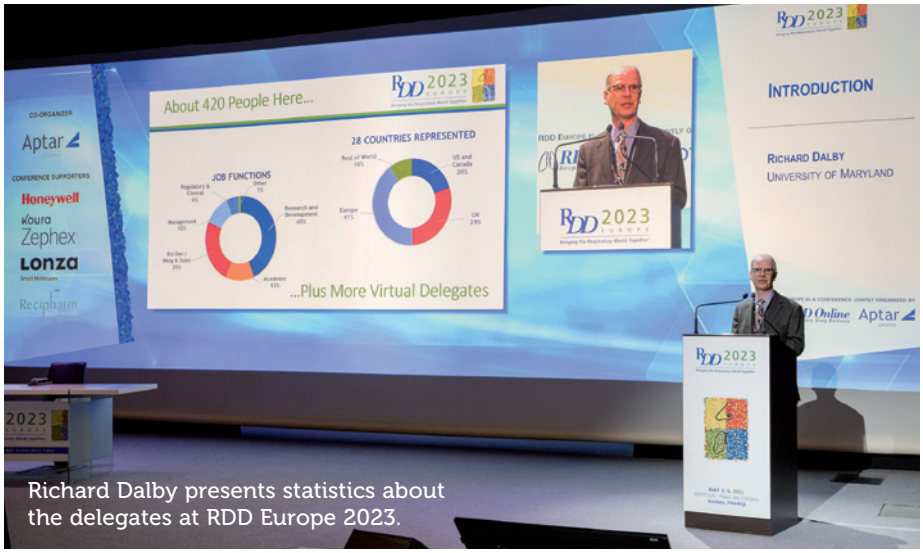
Respiratory Drug Delivery (RDD®) is a premier international conference series providing comprehensive coverage of all aspects of drug delivery to the lungs and nose. RDD has a 35-year track record of inviting key opinion leaders to present scientific, clinical, technological and regulatory insights of immediate and lasting value to individuals and organisations in an environment that stimulates introductions, networking and collaboration.

Conferences alternate annually between the US and Europe and have unique features, such as themed Knowledge Spaces, peer-reviewed publications accompanying most podium and poster presentations, and delegate-selectable workshops that allow personalisation of the conference experience during interactive, small group sessions. "Posters on the Podium" blends new and old faces during a fast-paced showcase of the most innovative, editor-selected posters. Exhibit tables are dispersed among posters and refreshment stations, ensuring that all attendees frequently meet and have a place to hatch ideas. The Charles G Thiel Award and the VCU Peter R Byron Graduate Student Award reward excellence in established and new researchers.



Richard Dalby presents statistics about the delegates at RDD Europe 2023.

Q This year saw RDD Europe 2023 held in Antibes, France. Looking back, can you give us a brief overview of the conference?

A RDD Europe 2023 was a very memorable conference, with more than 420 delegates assembling in Antibes this past May. Delegates travelled to the conference from 28 countries to learn and discuss the latest science and technology in the pulmonary and nasal space, which is vital to the development of successful inhaled and nasal drug products.

The Palais des Congrès Antipolis and the adjacent AC Ambassadeur Hotel, the primary hotel for the conference, ensured that those working in corporate R&D, business development and management roles all had opportunities to network with each other, along with academics, regulators, clinicians and consultants from across all facets of respiratory drug delivery.

Approximately 175 delegates participated for the first time, mingling with RDD regulars who have been attending for more than 30 years. Several of these first-timers expressed surprise at how vibrant and expansive RDD Europe 2023 was. Knowledge Spaces, a feature pioneered during the covid-19 pandemic and now a mainstay of RDD conferences, brought people and organisations with shared interests together, both in the conference centre and on the conference website.

Q What are some of the key highlights that made RDD Europe 2023 stand out?

A To start with, the conference's keynote speaker, Prof Martin Tobin from the University of Leicester (UK), shared up-to-the-minute analyses on how genes and pathways can influence pulmonary disease. Prof Tobin's presentation provided a great introduction to the "Bench to Bedside" Knowledge Space. Further to this, speakers in the "Aqueous Agenda: Navigating Nasal", "Inspiring Dry Powder Inhalation" and "Building a Sustainable Future" Knowledge Spaces presented insights on all the major inhalation and nasal platform technologies.

Elsewhere, low global warming potential propellants and inhaler sustainability were the focus of a lively "Explore with Experts" session. Additionally, alternative bioequivalence approaches dominated

RDD Europe 2023 was held at The Palais des Congrès Antipolis in Antibes, France.

"Each of these Knowledge Space programme themes carried over to the lively poster and exhibition space, where 62 companies showcased their innovations alongside 55 posters."

the "Advanced Inhalation: Data Driven Design" Knowledge Space, with Will Ganley of Nanopharm (Newport, UK) and Bryan Newman of the US FDA sharing their expertise.

Each of these Knowledge Space programme themes carried over to the lively poster and exhibition space, where 62 companies showcased their innovations alongside 55 posters. One of those posters was presented by Patricia Henriques, a PhD student at the University of Coimbra (Portugal), who was selected as the winner of the 2023 VCU RDD Peter R Byron Graduate Student Award for her poster and corresponding paper entitled "Benchmarking of particle engineering strategies for nasal powder delivery: Characterisation of nasal deposition using the Alberta idealised nasal inlet".

Q To what extent was online access available to RDD Europe 2023?

A Twelve workshops, "Posters on the Podium" and a meeting of the AAPS Inhalation and Nasal Community rounded out a productive and busy conference with more content than could be absorbed in three days. Fortunately, in a continuation of measures put in place during the pandemic, many presentations, posters and workshops were accompanied by on-demand online versions that could be viewed by delegates long after the in-person conference ended. In addition, delegates are able to enjoy access to more than 2,800 peer-reviewed articles in the RDD library, including those from RDD Europe 2023. In fact, during the conference, anyone – not just delegates – had access to online company profiles from exhibitors, workshop presenters and conference supporters whose financial generosity made it possible to deliver the conference programme.

"Delegates will have ample time at RDD 2024 to experience more in-depth presentations, deeper discussions of pioneering science and additional opportunities for networking in a collegial and business-friendly resort setting."

Q Looking forward, what can new and returning delegates expect to see at RDD 2024 in Tuscon, AZ, next year?

A RDD 2024 will be held at the JW Marriott Starr Pass in Tucson, from May 5 to May 9, 2024. Starting with an opening reception, the conference will have all the features expected of an RDD conference in a longer, four-day format. This means that delegates will have ample time at RDD 2024 to experience more in-depth presentations, deeper discussions of pioneering science and additional opportunities for networking in a collegial and business-friendly resort setting.

Initial programme topics include "New Targets & Treatments", "Formulation & Device Innovation", "Manufacturing & Industrialisation", "Nasal Delivery", "Regulatory Science", "Advanced Data Analytics" and "Connectivity and Sustainability". These will evolve into podium sessions as speakers are invited.

Q Lastly, can you give use some more details on RDD 2024 and highlight upcoming submission deadlines?

A Delegate registration for RDD 2024 is now open. There will be two-day integrated poster and exhibition sessions covering all aspects of inhaled and nasal pharmaceuticals. The submission deadline for poster abstracts is January 22, 2024.

Sign up for exhibit tables and online company profiles highlighting resources, solutions and connections is now open. RDD 2024 will also feature delegate-selectable workshops that will provide practical and interactive demonstrations of innovative technologies, products and services.

RDD 2024 will be held May 5–9, 2024, at the JW Marriott Starr Pass in Tucson, AZ. Delegate registration is now open.

Nominations for the RDD 2024 Charles G Thiel Award, which is given to a scientist who has pioneered significant developments in the area of respiratory drug delivery, are open until November 30, 2023. The VCU RDD Peter R Byron Graduate Student Award will also be awarded at the conference, with eligibility being automatic upon acceptance of a qualifying poster abstract.

Exhibitors, workshop presenters and conference supporters should sign up now to enjoy maximum company profile visibility on the conference website before the conference opens. We invite all members of the pulmonary and nasal pharmaceutical community to come together at this prestigious conference.

RDD 2024 will be held on May 5–9, 2024, in Tucson, AZ, US. To find out more about delegate registration and exhibiting, visit: www.rddonline.com/rdd2024.

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