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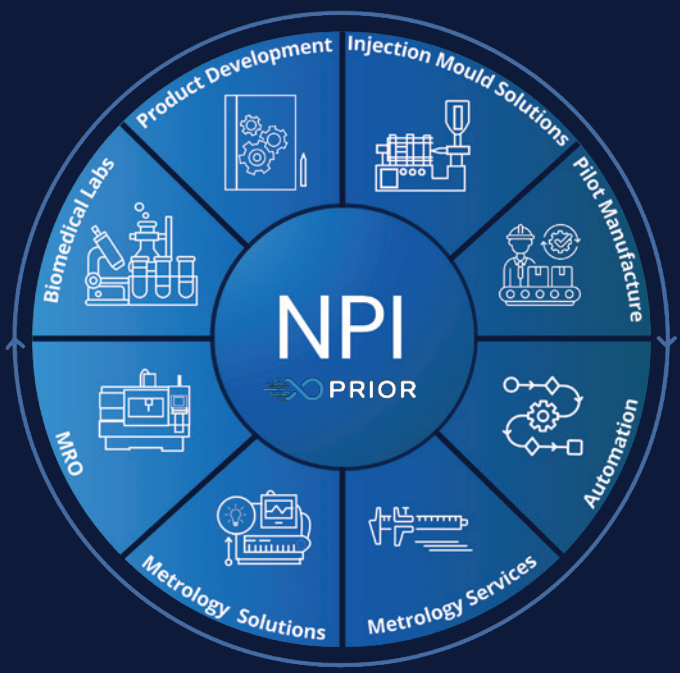

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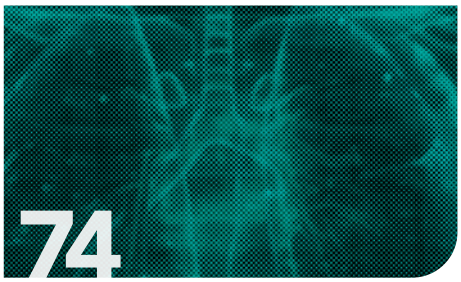

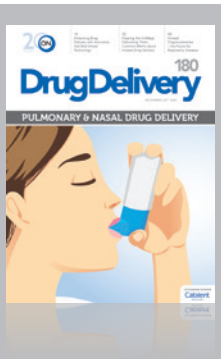

PULMONARY & NASAL DRUG DELIVERY

ONdrugDelivery Issue N° 180, November 24th, 2025

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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Possibilities in Pulmonary Delivery:
What's Next for the Respiratory Sector?

In this issue, we put the spotlight on respiratory drug delivery, with a particular focus on advancements in the pulmonary sector, including computational modelling techniques, systemic delivery of biologics and improved sustainability. While asthma, chronic obstructive pulmonary disease and pMDIs have been mainstays of pulmonary delivery for decades, there has long been an ambition within the sector to push the boundaries of what can be achieved via the inhalation route. Here, we hear from a range of contributors on what pulmonary delivery could be capable of and where the sector might be going in the years to come.

Opening the issue, **Catalent**, our Outstanding Sponsor, digs into the challenges faced by early-stage pulmonary drug development projects (Page 10). Developing therapeutics for the inhalation route is notoriously difficult, especially for smaller biopharma start-ups, so the insights of an expert CDMO such as Catalent can make the difference between a challenging development cycle fraught with pitfalls and a smooth, efficient path to market.

Naturally, tackling the inhalation route requires an inhalation device, and this issue features three promising advanced delivery devices. First, **Resyca** introduces its Pre-Filled Syringe Inhaler (Page 16), followed by **HCMed**'s discussion of how its AdheResp smart nebuliser fits into regulatory pathways (Page 20) and **Aptar Pharma**'s exploration of how its Orbital DPI meets the challenges presented by delivering high payloads of agglomeration-prone dry powders (Page 26). Broadening the subject, **Parker** considers the elastomer seals required for pMDIs (Page 38) and **Contexo** provides insights into the success achieved by a recent simultaneous engineering project (Page 46).

However, there is significantly more to pulmonary product development than just selecting a device. On this topic, **Crux Product Design** discusses how advanced *in silico* approaches can help de-risk development projects (Page 62) and **Copley Scientific** digs into some specifics on dissolution testing (Page 79). Expanding on this, **Solvias** considers the need to stress-test orally inhaled and nasal drug products (Page 84). Furthermore, **Bespak** (Page 34), **Phillips Medisize** (Page 42) and **Aptar Pharma** (Page 90) all present advances that they've made in the services they are able to offer to pharma partners in the development of respiratory products. Finally, moving the focus towards formulation, **Nanoform** discusses its Nanoforming process and the potential of nanoparticles in inhalation (Page 74).

With the need to pivot away from current pMDI propellants due to environmental concerns, there has been increased interest in the potential of DPIs. Here, **Roquette** challenges some common myths that percolate around the inhalation space (Page 52) and **Sanner Group** presents an in-depth overview of some of the challenges and solutions within DPI development (Page 58).

Rounding out the issue, we have a pair of articles looking at the potential of pulmonary delivery. **Intertek** shines a light on the significant potential inhalation has in the vaccination space and what devices and methods might be needed to realise it (Page 86) and **Merxin** elucidates the potential therapeutic benefits of oligonucleotides and makes the case for their delivery via inhalation (Page 68). On the subject of oligonucleotides, look forward to next month's issue, which will be the first ever issue of ONdrugDelivery focused fully on Delivering Gene & Cell Therapeutics – be sure not to miss it!

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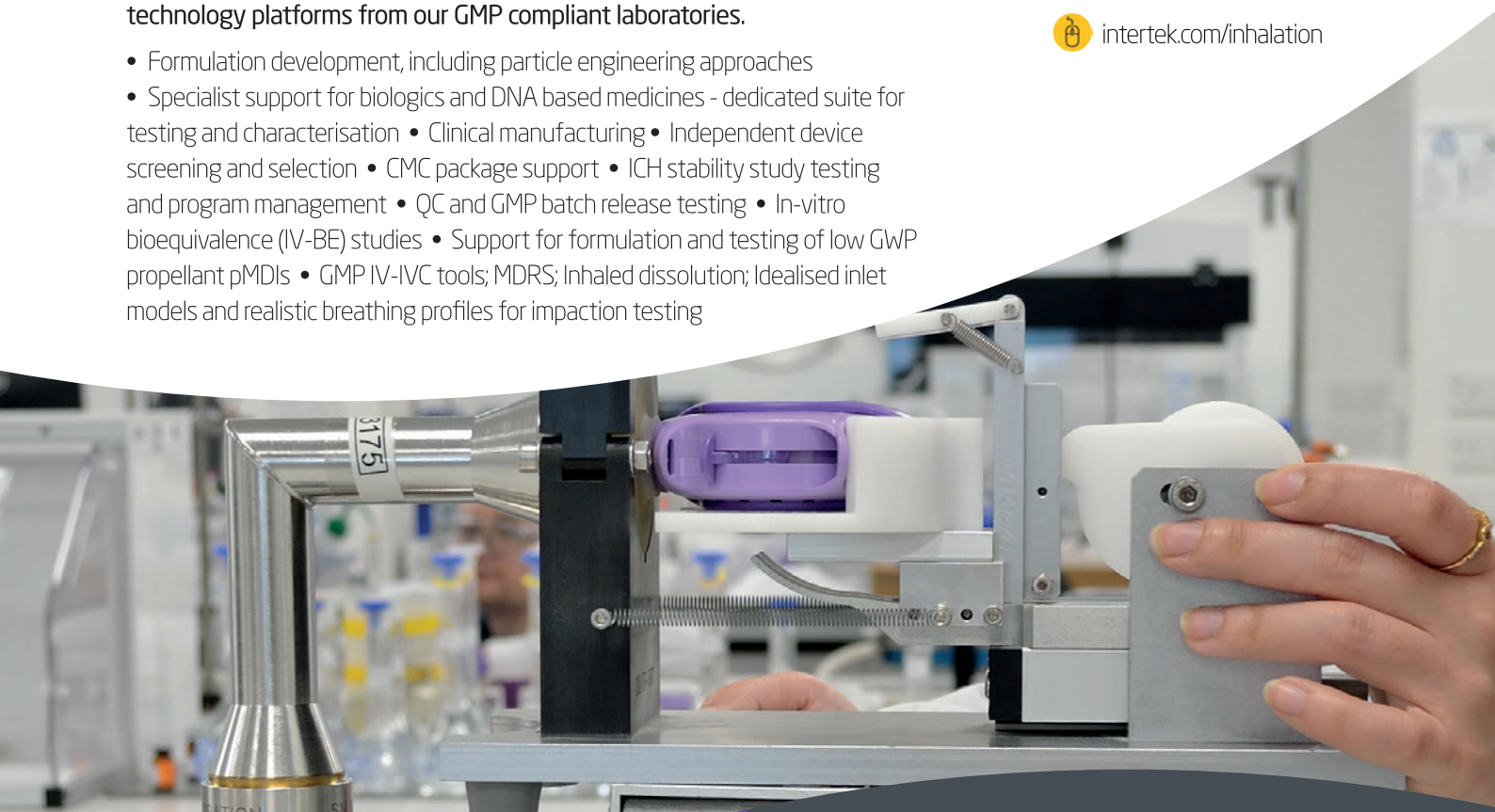

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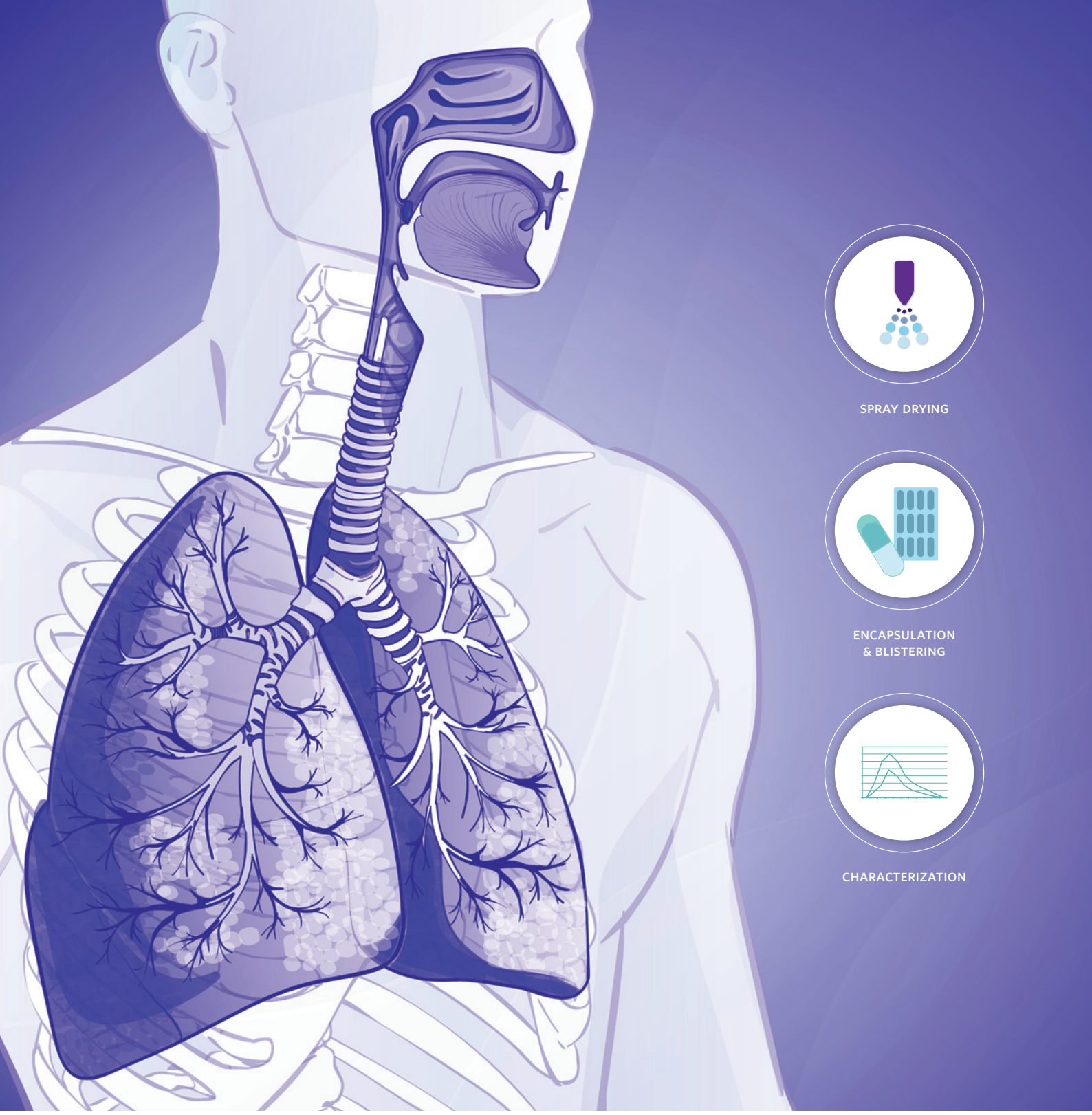
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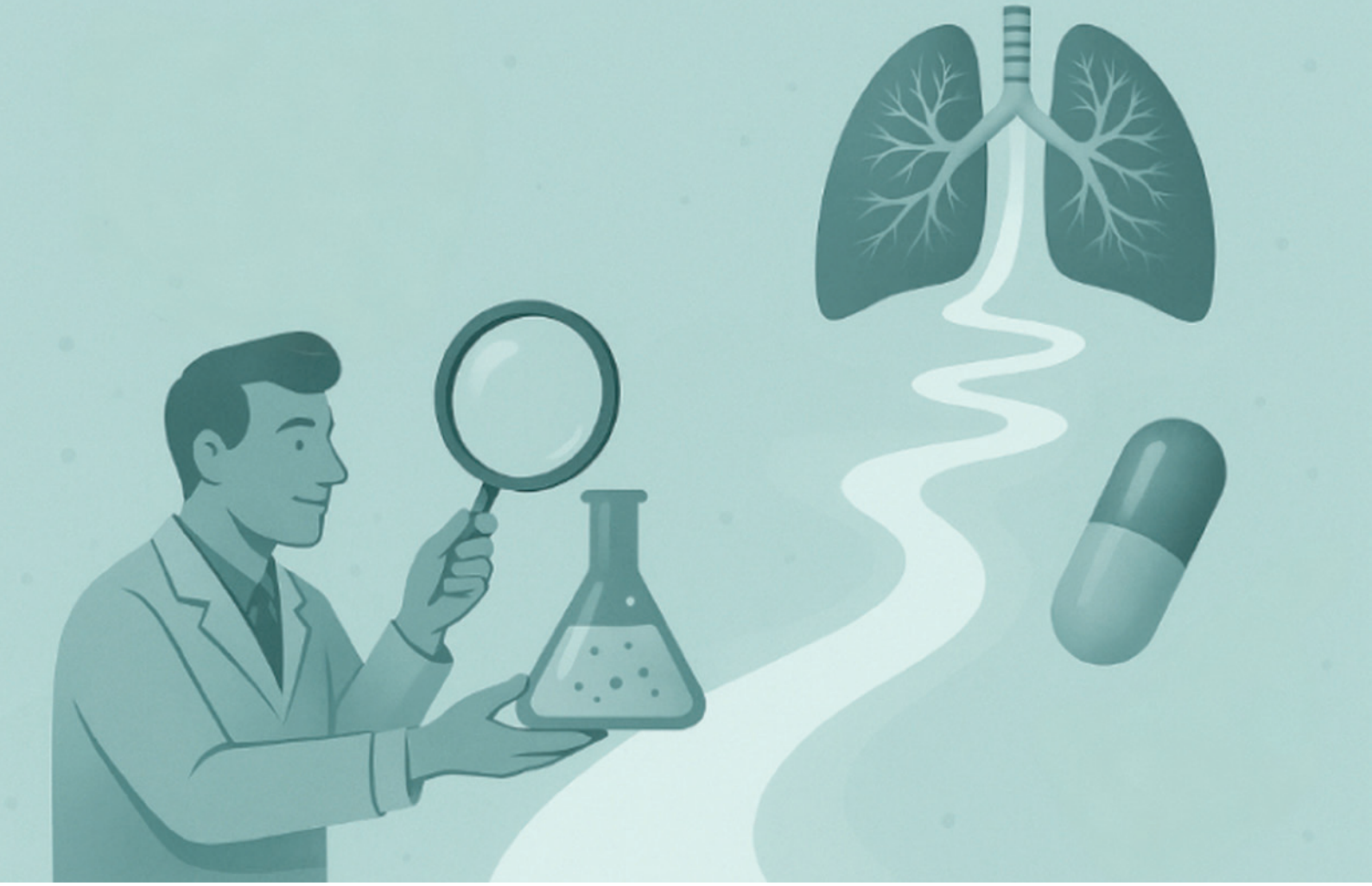

CHARTING THE COURSE FOR PULMONARY DRUG DEVELOPMENT

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Carolyn Berg and **Dr Alan Watts** of **Catalent** examine strategy considerations that can help emerging biotech companies navigate early-stage pulmonary drug development, providing practical guidance for addressing challenges of respiratory delivery and avoiding common pitfalls that can derail development programmes.

The pulmonary drug delivery landscape has evolved over the past quarter century. Once a specialised field focused almost solely on asthma and chronic obstructive pulmonary disease therapeutics, the sector has now expanded to encompass 440 active development programmes worldwide, 60% of which are in preclinical or Phase I stages (according to data from Pharmaprojects). This growth reflects both technological advancement and a reconsideration of the respiratory tract as a delivery route for a diverse range of therapeutic applications.

Notably, over 70% of pulmonary development programmes now come from emerging biotech companies. However, these organisations are often inexperienced in the development of inhalation products and face challenges navigating the complexities and regulatory requirements specific to this delivery route. The pipeline has also shifted from traditional respiratory indications to novel therapeutic areas, with large molecules now making up 40% of development candidates, introducing additional formulation and delivery challenges.

For emerging companies entering this specialised field, the development pathway presents critical decision points with far-reaching implications. Unlike oral solid-dose products, pulmonary delivery requires early commitment to both formulation platform and device technology. These decisions, made with limited clinical data, establish constraints that impact manufacturing scalability, regulatory strategy and commercial viability.

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CHALLENGES OF EARLY-STAGE PULMONARY DRUG DEVELOPMENT

Early-stage pulmonary drug development presents distinct technical and strategic challenges that differentiate this field from other administration routes. Unlike conventional oral formulations, inhalation products require consideration of multiple interdependent variables:

- The API's physicochemical properties
- Formulation approach
- Aerosol delivery system
- Human factors.

These elements must function synergistically to achieve consistent, reproducible delivery to the targeted respiratory tract region.

For emerging biotech companies, development is further complicated by resource constraints and the need to make critical platform decisions with limited data. The traditional pharmaceutical development paradigm, where formulation decisions can often be deferred until Phase II, is not applicable to pulmonary delivery. Early choices regarding particle engineering approach, excipient composition and device platform create cascading effects throughout the development timeline. As development programmes advance, resistance to change rapidly increases with both time and invested capital, making formulation or device pivots progressively more difficult and costly to implement.

The target product profile (TPP) is an essential strategic framework for managing this complexity. Rather than allowing available technical capabilities to drive product design decisions, successful development programmes begin with the end in mind, visualising the final product in the patient's hands and working backwards to define development requirements. This approach enables teams to balance patient needs against molecular constraints while maintaining focus on commercial viability and manufacturability.

The material requirements for early development introduce another dimension of complexity. While many emerging companies possess the capabilities and budget for producing small-scale API batches (≈50 g), which is sufficient for initial feasibility studies, progression to good laboratory practice inhalation toxicology studies demands 0.5–2.0 kg of material. This represents not merely a scale-up challenge but a major financial inflection point that many companies underestimate. Development teams are often surprised when they first realise the magnitude of material required for regulatory-enabling studies, which typically exceeds their combined Phase I and II trial requirements.

> "WHILE FINANCIAL PRESSURES OFTEN DRIVE COMPANIES TO DEFER CMC INVESTMENTS UNTIL CLINICAL PROOF-OF-CONCEPT IS ESTABLISHED, EARLY CMC INVESTMENT CAN LEAD TO A MORE STRAIGHTFORWARD APPROACH IN LATER DEVELOPMENT STAGES."

Investment in chemistry, manufacturing and controls (CMC) development warrants particular emphasis in early-stage planning. While financial pressures often drive companies to defer CMC investments until clinical proof-of-concept is established, early CMC investment can lead to a more straightforward approach in later development stages. Establishing robust analytical methods, identifying critical quality attributes, justifying and optimising excipient levels, and understanding manufacturing constraints early can help to prevent costly delays and reformulation further down the line.

CRITICAL DECISION POINTS IN PULMONARY DRUG DEVELOPMENT

The progression through early-stage pulmonary drug development is characterised by several critical decision points that can fundamentally alter the trajectory of a development programme. Understanding when these inflection points occur – and their downstream implications – can enable development teams to allocate resources effectively and mitigate development risks.

The initial feasibility assessment represents the first major decision point, where developers must evaluate whether their molecule's intrinsic properties align with pulmonary delivery requirements. This evaluation extends beyond basic solubility and stability parameters to encompass the broader question of dose quantity and their compatibility with inhalation constraints. With patient comfort and device capabilities generally limiting single inhalation doses to approximately 50 mg of powder or 10 mL of liquid, high-dose compounds may face insurmountable delivery challenges regardless of formulation sophistication or device performance.

Device platform selection constitutes perhaps the most consequential early decision, as it influences virtually every subsequent development activity from formulation approach to clinical trial design. The selection between device types, such as dry powder inhalers, nebulisers or metered dose inhalers, must balance multiple factors:

- Anticipated dose range
- Target patient population characteristics
- Stability requirements
- Manufacturing complexity.

Each device platform presents distinct advantages and limitations that must be carefully evaluated against the specific requirements of the development programme and TPP.

Formulation strategy decisions carry particular significance in pulmonary development due to the limited list of excipients in approved products and the stringent safety requirements for respiratory delivery. Formulation should be kept as simple as possible while achieving the desired performance and stability. Any changes become progressively more difficult to implement as development programmes advance through clinical phases.

The timing of technology transfer and scale-up activities is also important. While maintaining internal control over

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early development offers maximum flexibility, the specialised equipment and expertise required for inhalation product manufacturing often necessitates external partnerships. Determining when to engage a CDMO, and which capabilities to transfer to them, requires careful consideration of both immediate development needs and long-term strategic objectives.

Analytical methods used during clinical development should be phase-appropriate – they should be qualified for early clinical work and will require full ICH validation in later stages. The unique performance requirements for inhalation products demand resource-intensive methods to determine aerodynamic particle size distribution and delivered dose uniformity – and should follow compendial requirements. These methods are used to characterise the ability of the API to target the lungs effectively and are used not only to support formulation development but also to allow for meaningful comparisons across batches and manufacturing scales.

Unlike clinical trials for oral products, where dose escalation can be achieved by simply administering additional tablets or capsules, inhalation products may require reformulation or device modifications to accommodate different dose levels. This reality necessitates careful planning of Phase I studies to generate sufficient dose-ranging data while minimising the need for subsequent formulation changes.

The commitment to specific manufacturing processes and equipment represents a particularly important inflection point with long-term implications. While laboratory-scale processes may use equipment and techniques that do not scale efficiently, early commitment to scalable technologies can obviate the need for costly process redesigns later in development. This consideration becomes especially critical for the specialised manufacturing approaches common in pulmonary product development, such as spray drying, jet milling and coarse lactose blending.

THE DOSE DILEMMA: MANAGING UNCERTAINTY IN PULMONARY DRUG DEVELOPMENT

The challenge of dose determination in pulmonary drug delivery represents one of the most significant paradoxes in pharmaceutical development. This fundamental uncertainty – dose ranges can span a 10–100-fold range in early development – creates cascading complications throughout the development process that require strategic management.

Unlike systemic delivery routes, where pharmacokinetic modelling can provide reasonable dose predictions, pulmonary delivery introduces multiple variables that confound traditional approaches. The site of action – whether topical within the lung, systemic via pulmonary absorption or targeted to specific lung regions – dramatically influences dose requirements. Local delivery for respiratory conditions may achieve therapeutic effects with microgram quantities, while systemic delivery through the lung might require doses approaching tens of milligrams or more, pushing the boundaries of what can be practically delivered via inhalation.

The relationship between nominal dose, lung deposition and therapeutic effect adds layers of complexity unique to inhalation products. Device efficiency, patient inspiratory patterns and formulation properties collectively determine what fraction of the nominal dose actually reaches the target site. A formulation delivering 20% of the nominal dose to the lung might be acceptable by historical industry standards; however, such a five-fold difference between nominal and delivered dose must be accounted for in all development activities from analytical method development to manufacturing scale considerations. On the other hand, particle engineering approaches or advanced breath-synchronised devices are capable of delivering upwards of 60% of the nominal dose to the lungs.

Early-stage companies face particular challenges in generating the data necessary for informed dose selection. Traditional pharmacology studies in animal models are often poor predictors of human pulmonary delivery due to significant anatomical and physiological differences in respiratory tract architecture and breathing patterns. The expense and complexity of conducting early in-human studies with inhalation products, which require specialised clinical facilities and equipment, may delay acquisition of critical dose-ranging data until significant investment has already been committed to specific formulation and device approaches.

The manufacturing implications of dose uncertainty extend beyond simple batch size calculations to impact fundamental process design decisions. Analytical method sensitivity, content uniformity requirements and process control strategies all depend on the target dose. A product delivering 10 µg per actuation demands different analytical sensitivity and extraction approaches than one delivering 10 mg. Early investment in analytical methods spanning the potential dose range can help to avoid delays when clinical data clarify actual requirements.

The interplay between dose and formulation strategy creates additional complexity that must be addressed early in development. Low-dose products often require carrier particles or other bulking agents to ensure consistent delivery and handling properties. High-dose products, on the other hand, may push the limits of what patients can comfortably inhale, necessitating careful optimisation of powder properties to minimise the inhaled volume while maximising delivery efficiency. The practical limit of approximately 50 mg for a single inhalation creates hard constraints that must be considered even in early feasibility assessments.

"WHILE LABORATORY-SCALE PROCESSES MAY USE EQUIPMENT AND TECHNIQUES THAT DO NOT SCALE EFFICIENTLY, EARLY COMMITMENT TO SCALABLE TECHNOLOGIES CAN OBVIATE THE NEED FOR COSTLY PROCESS REDESIGNS LATER IN DEVELOPMENT."

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Regulatory expectations for dose justification in pulmonary products adds another dimension to the challenge. While systemic products might support dose selection through pharmacokinetic and pharmacodynamic modelling, inhalation products often require direct clinical evidence of dose-response relationships. This expectation creates pressure to explore multiple doses in early clinical studies, multiplying formulation development requirements and extending timelines.

PRACTICAL GUIDANCE FOR EMERGING BIOTECH COMPANIES

For emerging biotechnology firms entering the field of pulmonary drug development, achieving success necessitates not only technical proficiency but also strategic decision-making and prudent resource management. Based on Catalent's experience supporting numerous development programmes from concept through commercialisation, it can offer the following practical guidance for navigating this challenging but rewarding field.

Build Strategic Partnerships

Recognise that pulmonary product development requires specialised expertise and infrastructure that few emerging companies can efficiently maintain internally. Therefore, it is important to identify partners with proven track records in inhalation product development and manufacturing. Look for organisations that understand the unique challenges of respiratory delivery and can provide guidance beyond simple contract services. Structure agreements to maintain flexibility as clinical data emerge, allowing for technology changes if findings demand adjustments to the development approach.

Understand Regulatory Expectations

Pulmonary products face unique regulatory requirements that differ from other delivery routes. Early engagement with regulatory authorities and experts in inhalation product development can help to clarify expectations and avoid costly missteps. Consider that demonstration of local delivery may require different approaches than for systemic delivery, and plan studies accordingly. Regulatory agencies typically expect direct clinical evidence of dose-response relationships for inhalation products, creating pressure to explore multiple dose sizes in early clinical studies.

Manage Investor Expectations

Educate investors about the unique challenges and timelines associated with pulmonary development. The need for early device selection and formulation commitment differs from oral product development patterns. Help stakeholders understand that apparent delays for technology development actually reduce overall programme risk and development time. Be transparent about the material requirements for toxicology studies and the financial implications of scale-up activities required before clinical proof of concept.

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Learn from Others' Mistakes

There are numerous examples of development programmes within the pulmonary field that failed due to preventable errors. Study these cases to understand common pitfalls. Development programmes typically struggle when they underestimate material requirements, overcommit to narrow technology choices or assume that pulmonary delivery follows oral development paradigms. The combination of a new molecule, new device and new manufacturing process can add unnecessarily high levels of risk. Developers should look to incorporate novel approaches only when it is necessary to enable the product.

CONCLUSION

The pulmonary route provides unique benefits for emerging biotech companies, allowing for targeted delivery of therapeutics or a means to rapidly deliver drugs systemically avoiding first-pass metabolism without the use of needles. Successful development requires careful navigation of technical challenges, strategic resource allocation and thoughtful partnership decisions. By understanding the unique requirements of respiratory delivery and avoiding common pitfalls, emerging companies can efficiently advance promising therapies that address significant unmet medical needs.

Carolyn Berg

Carolyn Berg, Vice-President of Business Development for Catalent's inhaled drug delivery solutions, has more than 25 years of experience in pharmaceutical sales, marketing and business development. Since 2021, she has been responsible for all commercial, strategic and sales efforts to develop and grow Catalent's inhalation business globally. Throughout her career, Ms Berg has produced a solid record of meeting sales and business targets through individual and team efforts.

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Dr Alan Watts

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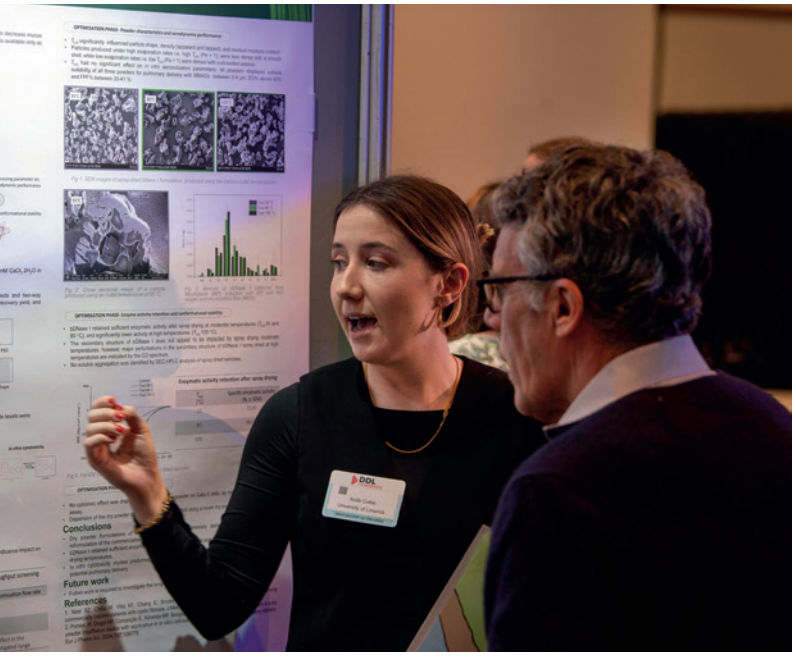

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ENHANCING DRUG DELIVERY WITH INNOVATIVE SOFT MIST INHALER TECHNOLOGY

Dr Nicolas Buchmann and **Bernhard Müllinger**, both of **Resyca**, discuss the capabilities of soft mist inhalers in terms of usability for patients, sustainability, compatibility with biologics and cost-effective delivery, showcasing these advantages in Resyca's Pre-Filled Syringe Inhaler (PFSI).

Inhaled drug delivery has long been central to the treatment of respiratory diseases. However, traditional inhaler types come with inherent design limitations that can contribute to higher rates of patient use errors, resulting in inefficient delivery, wasted drug product and suboptimal therapeutic outcomes.[1] Often, these inhalers are not designed for next-generation therapeutics, which require more accurate and sensitive delivery technologies, limiting their use in novel life-changing treatments.[2]

Soft mist inhaler (SMI) technology was developed to address these challenges. SMIs generate a slow-moving aerosol cloud, enabling inhalation over several seconds of spray duration. This reduces the risk of co-ordination errors, enhances pulmonary drug deposition and improves usability across diverse patient populations. The potential of SMI technology is particularly exciting for inhaled

"THE POTENTIAL OF SMI TECHNOLOGY IS PARTICULARLY EXCITING FOR INHALED BIOLOGICS, SUCH AS VACCINATIONS AND GENE THERAPIES, WHERE EFFICIENCY, PATIENT USABILITY AND GENTLE AEROSOLISATION ARE CRUCIAL."

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biologics, such as vaccinations and gene therapies, where efficiency, patient usability and gentle aerosolisation are crucial.[3]

The Pre-Filled Syringe Inhaler (PFSI™) by Resyca® is a step forward in SMI technology. By integrating a prefilled sterile syringe, precision spray nozzle engineering and a patient-centric design, the PFSI sets new standards for usability, scalability and drug delivery efficiency.[4]

EXPLORING THE POTENTIAL OF SMI TECHNOLOGY

The effectiveness of certain inhaled therapies depends largely on the proportion of drug that reaches the lungs. This requires not only the right technology but also patient ease-of-use. Instead of relying on propellants or patient-generated force, SMIs deliver a therapeutic aerosol cloud through a mechanically activated system, dispersing the drug over approximately 3 seconds. This longer inhalation window reduces dependency on co-ordination, supporting successful use by certain patient groups, such as children, the elderly and those with disabilities. As the mechanism requires less effort and precision from the patient, SMIs can support improved outcomes through consistent dosing and increased lung deposition.

In addition to facilitating ease-of-use for patients and efficient drug delivery into the lung, SMI technology is creating opportunities for inhaled biologics. These biologics could expand treatment far beyond those for respiratory disease, enabling systemic therapies such as inhaled insulin or messenger RNA (mRNA) vaccines, as well as novel routes to target the central nervous system.

OVERCOMING THE CHALLENGES OF BIOLOGIC DELIVERY

While inhaled biologics offer significant therapeutic potential, their delivery presents unique challenges due to the large, fragile and often costly nature of these molecules. Effective pulmonary administration requires a container closure system (CCS) capable of maintaining the stringent requirements for biologics, as well as gentle aerosolisation to preserve molecular integrity and to ensure efficient lung deposition.

> "THE PFSI CAN BE CUSTOMISED TO ACCOMMODATE DIVERSE TARGET PRODUCT PROFILES, ENABLING TAILORED DOSING AND TARGETED LUNG DEPOSITION TO ADDRESS THE NEEDS OF VARIOUS PATIENT POPULATIONS."

A primary challenge for inhaled biologics is the packaging within the CCS. While biologics require a sterile environment throughout their use, they cannot tolerate preservatives or additives used in more traditional inhaler types. The PFSI uses a prefilled, sterilised glass syringe to maintain stability. This CCS has a valve that opens and then closes immediately as the patient inhales to prevent bacterial entry and maintain sterility for multidose use.

Highly sensitive biologics, such as mRNA and protein therapeutics, are often encapsulated in lipid nanoparticles (LNPs) to protect them from degradation during aerosolisation and to facilitate their delivery to the appropriate region of the lung. After deposition in the lung, these lipid carriers are typically taken up by cells, where they are degraded and can release the biologic payload that exerts its therapeutic effect. However, many conventional aerosolisation methods generate high shear forces that can disrupt or damage LNPs, leading to aggregation or loss of the encapsulated drug, or reduced biological activity.

The Resyca PFSI is uniquely suited to this challenge. Its spray nozzle employs the Rayleigh spray principle to create fine, uniform droplets under low shear forces, preserving the integrity of LNPs and other delicate carriers. A recent study evaluated aerosolisation techniques for preserving the integrity of mRNA-LNPs and optimising pulmonary deposition. The PFSI was shown to maintain mRNA-LNP physicochemical properties with minimal aggregation and superior encapsulation efficiency, while other devices induced particle alterations and mRNA degradation.[5] This gentle aerosolisation makes inhaled biologics clinically viable where other platforms fall short.

> "THROUGH GUIDED INHALATION, THE PFSI CAN ACHIEVE HIGH LUNG DEPOSITION OF UP TO 60%."

ENHANCING PATIENT CENTRICITY

Due to the cost of these next-generation therapeutics, inefficient delivery directly translates to reduced affordability and accessibility for patients.[6] Patient centricity is therefore an important consideration when designing any drug delivery device, as it can only be effective if patients are compliant and can use the device without errors.

Novel SMIs, such as the PFSI, offer flexibility to enhance patient centricity.[7] The PFSI can be customised to accommodate diverse target product profiles, enabling tailored dosing and targeted lung deposition to address the needs of various patient populations. Delivery characteristics such as particle size distribution, metered dose and fill dose can be customised to provide the best possible drug-device combination, for both efficiency and patient usability.

Even with optimised spray technology, inhalation performance varies between patients.[8] To address this, the PFSI incorporates guided inhalation through built-in flow resistance. This feature passively guides patients to perform slow and deep inhalations, a technique that encourages high lung deposition. Importantly, it requires no training and reduces both patient-to-patient and dose-to-dose variability. Through guided inhalation, the PFSI can achieve high lung deposition of up to 60%.[9]

As well as providing flow resistance for improved inhalation, the PFSI has a pocket-sized design for patient convenience, along with a reloadable cartridge, further enhancing the sustainability and affordability of the product. Patients can retain the device body while only replacing the cartridge, significantly reducing plastic waste compared with single-use inhalers.

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The device also leaves a low residual volume of around 100 µL, maximising product yield and reducing waste of costly biologics. Together, these features lower both the environmental footprint and the overall cost of therapy.

DESIGNING FOR SEAMLESS MANUFACTURING

For successful adoption, device technologies must demonstrate clinical efficacy and integrate seamlessly with established pharmaceutical manufacturing processes. The PFSI achieves this by using prefilled glass syringes as its primary packaging. Glass syringes are already widely used, well-characterised and supported by global filling capacity. This reduces regulatory risk and development timelines, while also eliminating the need for dedicated facilities.

The PFSI can be used from early clinical studies through to commercial launch, avoiding the need to switch delivery platforms mid-development. This continuity reduces device development risks and regulatory complexity. Furthermore, in an era of evolving environmental regulations and demands, sustainability is also central to the design. Reloadable cartridges and minimal residual volumes reduce waste and environmental impact.

By combining existing, proven technologies with novel engineering, the PFSI enhances drug delivery performance, reduces waste and prioritises patient centricity. On top of this, by combining Resyca's SMI technology with the contract development and manufacturing capabilities of Bespak (Holmes Chapel, UK), developers can take advantage of comprehensive support to bring their SMI concept to life.

UNLOCKING IP PROTECTION AND DEVELOPMENT EXPERTISE

As a novel platform, the PFSI offers compelling opportunities for intellectual property (IP) protection. Unlike many inhalers that imitate existing designs, the PFSI introduces functional differentiation that can result in new patents. This can extend exclusivity for drug-device combinations and enhance the commercial lifetime of therapies.

"THROUGH PROVEN PREFILLED SYRINGE PACKAGING, PRECISION SPRAY NOZZLE ENGINEERING, GUIDED INHALATION AND A RELOADABLE CARTRIDGE SYSTEM, THE PFSI ADDRESSES THE KEY CHALLENGES OF DEVELOPING INHALED THERAPIES."

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The device is well suited to the US FDA's 505(b)(2) pathway and NDA projects, providing flexibility for developers balancing innovation with speed-to-market. Resyca's expert team can further support such development projects, helping developers navigate device strategy, regulatory needs and delivery science to simplify and de-risk the path to commercialisation.

SHAPING THE FUTURE OF SOFT MIST INHALATION

The Resyca PFSI marks a significant advancement in SMI technology. Through proven prefilled syringe packaging, precision spray nozzle engineering, guided inhalation and a reloadable cartridge system, the PFSI addresses the key challenges of developing inhaled therapies.

For patients, the PFSI simplifies use, reduces errors and improves outcomes. For developers, it offers a scalable, customisable and IP-protected platform compatible with existing infrastructure. For healthcare systems, it reduces waste, enhances sustainability and improves the cost-effectiveness of biologic delivery.

With the increasing demand for new inhalation therapies, the need for efficient, patient-centric and sustainable delivery platforms is paramount. The Resyca PFSI is uniquely positioned to meet these needs, enabling precise and reliable delivery of even the most fragile molecules. In this way, it is shaping the future of soft mist inhalation, advancing innovation while keeping patients at the centre.

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DEEP DIVE INTO TOMORROW'S DRUG DELIVERY INNOVATIONS

NAVIGATING THE REGULATORY PATHWAY FOR NEXT-GENERATION NEBULISERS IN COMBINATION WITH BIOLOGICS

Edgar Hernan Cuevas Brun of **HCmed Innovations** discusses the role of nebulisers in delivering larger doses of fragile biologics, delving into the global regulatory landscape that must be understood in order to deliver these drugs on the market.

The development of new biologic formulations for delivery via inhalation has continued to advance in recent years with several novel therapeutics reaching clinical stages.[1] When it comes to liquid formulations, identifying a suitable device to effectively deliver the API is essential. Nebulisers are often the preferred delivery system for therapies that require aerosolisation of larger doses.

One of the major challenges for the delivery of biologics using nebulisers is the stability and activity of the API post-nebulisation.[2,3] Amongst the various established nebuliser technologies, mesh nebulisers are often considered to be the most suitable option for avoiding high shear forces and heat generation, which is critical

"DUE TO THE HIGH VALUE OF BIOLOGICS, EFFICIENT, OPTIMISED DELIVERY IS PRIORITISED ALONGSIDE THE NEED FOR CONSISTENT AND RELIABLE DOSING, RESULTING IN A PREFERENCE FOR NEXT-GENERATION NEBULISERS WHEN DELIVERING BIOLOGIC MEDICATIONS."

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as these factors may lead to aggregation, thermal denaturation or other undesirable effects. Due to the high value of biologics, efficient, optimised delivery is prioritised alongside the need for consistent and reliable dosing, resulting in a preference for next-generation nebulisers when delivering biologic medications.

The availability of next-generation nebulisers is still limited compared with more traditional devices. This can be attributed to several factors, including the complexity of development, a lack of clear guidelines for new features and reimbursement obstacles in some markets. The regulatory pathway plays an essential role in market access for next-generation nebulisers. Therefore, gaining a suitable understanding of these pathways can lead to a more effective development strategy for their use in combination with biologics.

BASIC APPROVAL PATHWAYS

The approval pathway for medical devices varies from one market to another. When considering two of the major global markets, the US and the EU, nebulisers are classified as Class II devices based on their intended used and risk level (moderate risk). Further subclassification is found in the EU, where they are divided into Class IIa and IIb.[4]

The regulatory pathway for general-purpose nebulisers can be summarised as follows:

- **US Market, 510(k) Premarket Notification**: This pathway focuses on substantial equivalence to a predicate device in terms of intended use, technology and safety.

- **EU Market, Medical Device Regulation (MDR EU 2017/745)**: This regulation defines the requirements to obtain CE marking focusing on safety, performance and clinical benefit. The approval process involves a notified body and requires clinical evaluation.

In the drug-nebuliser combination space, the main difference is that the US FDA does not require the nebuliser to be 510(k) cleared. The device is approved as part of the combination product package, with the key institution being either the Center for Drug Evaluation and Research or the Center for Biologics Evaluation and Research.[5] For the EU market, drug-nebuliser combination products that comply with MDR Article 117 can be submitted with the nebuliser as part of the drug marketing authorisation application.[6]

Clarifying basic regulatory requirements is the first step towards comprehending the challenges of next-generation nebuliser development in terms of market access.

UNDERSTANDING THE IMPLEMENTATION OF EXISTING GUIDELINES

Existing guidelines cover different aspects of the device to ensure that a nebuliser is safe and efficacious. In the US, the FDA grants approvals, whereas, in Europe, marketing authorisations are granted by the EMA. When it comes to performance assessment, there are three major guidelines: ISO 27427:2023 – Nebulising Systems and Components, United States Pharmacopeia (USP) Chapter <1601> and European Pharmacopeia (EP) Chapter 2.9.44 (Table 1).[7–9] ISO 27427:2023 is an international standard for nebulising systems and components, and it serves as the basis for testing guidelines. It is commonly used as the standard for nebuliser manufacturers of general-purpose devices.

The test substance is often saline with albuterol, which is used for obtaining CE marking and, in some cases, to support 510(k) packages. The USP and EP guidelines apply to device and drug manufacturers and are drug specific. In the case of biologics, testing aerosol performance is not sufficient, since stability and activity post-nebulisation need to be confirmed, resulting in additional test requirements.

Other aspects that need to be satisfied according to the guidelines are also dependent on the territory, with the MDR requiring a risk management assessment as per ISO 14971:2019, biological safety as per ISO 10993 and ISO 18562, software validation as per IEC 62304 and usability as per IEC 62366, amongst other requirements. Similarly, a 510(k) premarket notification submission package comes with requirements for analogous aspects, including quality system upgrades as per QMSR/ISO 13485:2016.

Due to the complexity of the guidelines and documentation landscape, it is indispensable to have an experienced group of experts to generate comprehensive packages for submission. The degree of

	ISO 27427:2023	USP <1601>	EP Chapter 2.9.44
Region	International (especially EU via MDR harmonisation)	US	Most of Europe
Type	Device performance standard	Pharmacopeial chapter	Pharmacopeial chapter
Scope	General-purpose nebulisers (device-centric)	Nebulised drug products (drug-centric)	Nebulised drug products (drug-centric)
Applies to	Medical device manufacturers	Drug and device manufacturers	Drug and device manufacturers
Test Substance	Uses standard solutions (e.g. 0.1% albuterol in 0.9% NaCl)	Uses actual drug product	Uses actual drug product
Main Use	Device benchmarking, CE marking (EU), support 510(k) (US)	Drug registration – NDA/ANDA (US)	Marketing authorisation (EU and Canada)

Table 1: Main guidelines for the assessment of nebulisers' aerosol performance.

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complexity increases significantly when developing next-generation nebulisers, and even more so for drug-nebuliser combination products.

APPROVAL CHALLENGES FOR NEXT-GENERATION NEBULISERS

Next-generation nebulisers are equipped with features that can support the effective delivery of biologics; however, only a few of these devices have been approved in major markets. Moreover, the regulatory pathway for a general-purpose device and a customised nebuliser for a specific drug-device combination vary significantly. Therefore, mapping a clear regulatory pathway from the start of development is a crucial step for a successful market launch and is a core factor for nebuliser developers and manufacturers.

When it comes to the approval of innovative products, challenges related to generating documentation packages for submission may arise not only from the complexity added by the new technologies but also from the lack of clear guidelines, or even from commercial obstacles such as reimbursement issues.

A successful example of the submission of an innovative nebuliser, which had to overcome the aforementioned obstacles, is the approval of the AdheResp Smart Breath-Actuated Mesh Nebuliser, designed and manufactured by HCmed Innovations (Figure 1). This connected, breath-actuated device was cleared in June 2025 under the traditional 510(k) pathway. The submission strategy was initiated by defining suitable predicate and reference devices in order to cover the key aspects of the package (Figure 2). AdheResp was specifically developed to deliver high value drugs with three innovative features that can significantly enhance the delivery of biologics:

- **Breath Actuation:** This mechanism allows aerosol delivery only during a fraction of the inhalation phase. The breath-actuated mode in AdheResp is adaptive, which means that it can predict the length of the next inhalation by computing the average of previous ones. Moreover, the amount of aerosol that is delivered during each inhalation can be adjusted to allow for chase air to pass through the device and enhance delivery to the lungs. Only a few breath-actuated nebulisers have received 510(k) clearance in the past two decades. Amongst them, the I-Neb AAD system (Philips, Amsterdam, Netherlands) was the first breath-actuated mesh nebuliser and then, most recently, the AdheResp nebuliser was also cleared with this function.[7,8]
- **Connectivity:** Aiming to support patient adherence monitoring, this feature allows for data transmission from the nebuliser to a mobile device. The first connected nebuliser was cleared in 2020, and the AdheResp nebuliser is the first breath actuated mesh nebuliser to be cleared with this function as part of its submitted package.[9]

Figure 1: AdheResp® Smart Breath-Actuated Nebuliser.

"THE FIRST CONNECTED NEBULISER WAS CLEARED IN 2020, AND THE ADHERESP NEBULISER IS THE FIRST BREATH-ACTUATED MESH NEBULISER TO BE CLEARED WITH THIS FUNCTION AS PART OF ITS SUBMITTED PACKAGE."

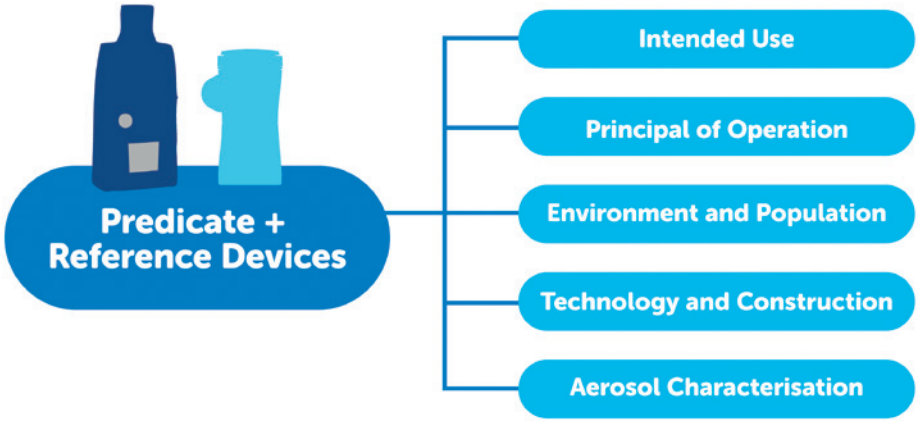

Figure 2: Substantial equivalence aspects for predicate and reference devices required in 510(k) premarket notification submission package.

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- **Activation:** Designed for drug-specific nebulisers, the activation feature binds the use of the nebuliser with the specific drug in order to ensure safety. RFID technology is commonly used for this function, and only a few devices have incorporated it to date.

The features listed above bring substantial value to AdheResp, however, the challenges involved in incorporating them extend from the lack of specific testing and apparatus guidelines to the limited number of breath-actuated nebuliser (BAN) predicates and the additional considerations required by strict software and cybersecurity regulations (Figure 3). The clearance of the AdheResp nebuliser is, without a doubt, a positive case, but the points mentioned here may be the main factors discouraging adoption of these technologies, thus reducing their market availability.

The development of inhaled biologics in liquid form can be directly influenced by these factors. This has generated the demand for real solutions that can guarantee the use of approved nebulisers during early clinical phases with customisation capabilities for further optimisation of the commercial product.

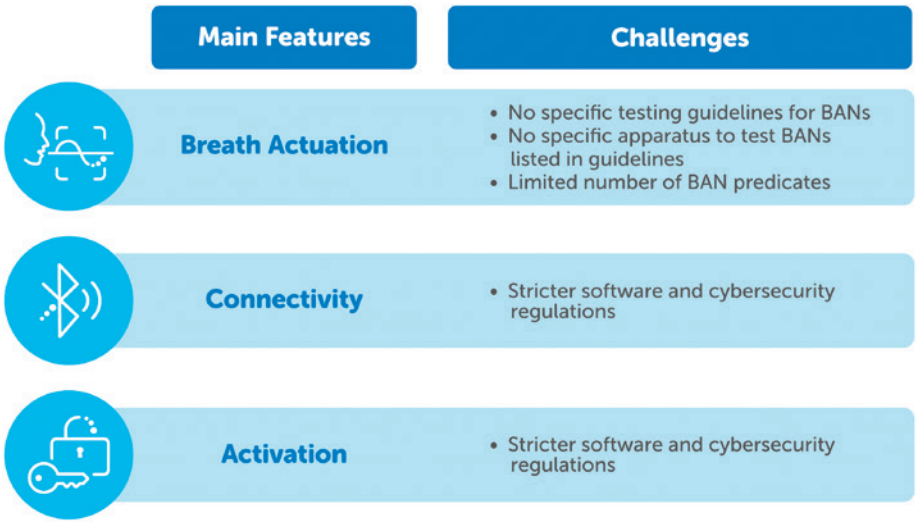

Figure 3: Challenges for the incorporation of new technologies in nebulisers.

FINDING THE RIGHT SUPPORT FOR DEVELOPMENT

CDMOs like HCmed Innovations provide support for drug-nebuliser combination products. HCmed's strategy focuses on having its standard devices for each platform primed for clinical use. This approach facilitates readiness for clinical trials, including ensuring that a sufficient volume of devices are available.

HCmed's platforms can be customised based on performance and usability requirements for drug-nebuliser combination products. In most cases, tailoring nebulisers for drug-specific delivery can trigger the initiation of a new design along with the respective design validation and verification processes of the customised device. One of the main benefits of counting on nebuliser platforms is that some of the documents from approved standard devices can be reused for customised versions, thus de-risking development and shortening overall development timelines.

For large pharmaceutical companies or small- and medium-size biotech companies, having the right support for nebuliser development processes is crucial to these projects. An important part of this is the regulatory expertise that elaborates the strategy for submission and compiles the documentation to demonstrate the safety and efficiency of the delivery system.

Considering the high value of biologic formulations, finding the right support from early development is essential to arrange an appropriate strategy and ensure compliance from the nebuliser perspective of the combination product. This is certainly more critical when working with next-generation nebulisers, where an experienced partner in the field can make navigation through the complex regulatory pathway to market access significantly easier.

> "AN IMPORTANT PART OF THIS IS THE REGULATORY EXPERTISE THAT ELABORATES THE STRATEGY FOR SUBMISSION AND COMPILES THE DOCUMENTATION TO DEMONSTRATE THE SAFETY AND EFFICIENCY OF THE DELIVERY SYSTEM."

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ORBITAL: A NOVEL HIGH-PAYLOAD, MULTI-BREATH DPI POISED FOR CLINICAL ADVANCEMENT

David Farrow, **Jonathan Mulpas** and **Solange Le Nuz**, all of **Aptar Pharma**, discuss the patient-centric and data-driven development of the company's Orbital dry powder inhaler platform, tracing its evolution from an initial concept to a clinically-ready device.

The therapeutic landscape for pulmonary drug delivery is increasingly defined by an urgent clinical need for high-dose therapies.[1] Conditions such as cystic fibrosis (CF), non-CF bronchiectasis and severe pulmonary infections often require the administration of hundreds of milligrams of API directly to the lungs in order to achieve therapeutic efficacy.[2] However, many conventional dry powder inhaler (DPI) technologies face fundamental limitations in this regard, often needing the device to be reloaded with multiple dose subunits to deliver the total required dose.

The particles required for deep lung deposition (typically 1–5 µm) are inherently cohesive due to their high surface-area-to-volume ratio and possess strong interparticle forces, leading to poor powder flow, agglomeration and inefficient aerosolisation. Consequently, existing devices often struggle to deliver large payloads consistently, which can lead to high oropharyngeal deposition and frequently require patients – many of whom have compromised lung function – to generate high inspiratory flow rates for effective drug aerosolisation.[3,4]

In response to this significant unmet need, Aptar Pharma has developed Orbital a novel, high-payload, reloadable DPI platform (Figure 1). The strategic impetus behind the Orbital programme was to directly address the challenges of the high-dose market segment. Aptar has undertaken detailed engineering of Orbital's aerosolisation engine, demonstrated its versatility with diverse

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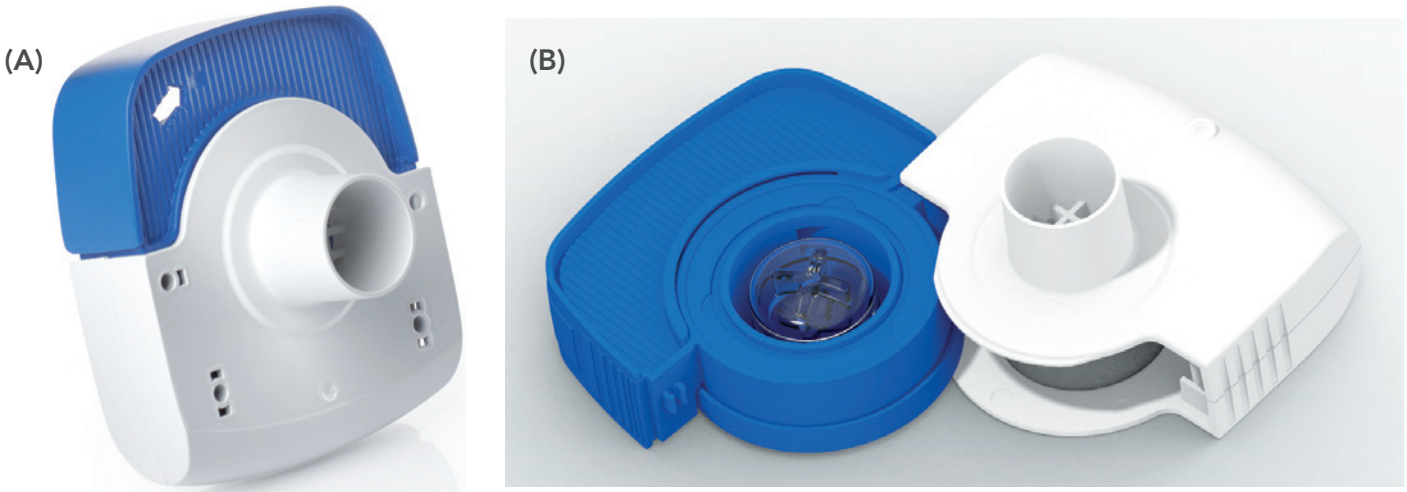

Figure 1: The Aptar Pharma Orbital device (a) in its closed state for storage or use and the (b) open configuration for loading.

"THE STRATEGIC IMPETUS BEHIND THE ORBITAL PROGRAMME WAS TO DIRECTLY ADDRESS THE CHALLENGES OF THE HIGH-DOSE MARKET SEGMENT."

and challenging formulations and assembled a robust preclinical data package that supports its advancement into clinical studies.

THE ORBITAL ENGINE: ENGINEERING A POWERFUL AND DIFFERENTIAL DE-AGGLOMERATION MECHANISM

At the heart of the Orbital device platform is a unique and powerful aerosolisation engine designed to overcome the strong attractive interparticle energies of cohesive dry powders. The mechanism is fundamentally different from other DPIs, relying on a high-energy, multistage de-agglomeration processes, driven by the patient's own inspiratory breath (Figure 2).

The de-agglomeration process begins when the patient inhales. Air is drawn through strategically placed peripheral inlets in the chamber, creating tangential jets of air. This airflow propels the powder-containing reservoir, known as the "container", into a high-speed orbital and elliptical motion around the chamber's circumference. As the container orbits, its contact with the chamber wall induces a simultaneous spin on its own axis. This combined orbital and spinning movement creates a high-energy epicyclical motion, which is the primary driver of powder fluidisation and de-agglomeration. This dynamic motion facilitates a multistage de-agglomeration process that ensures the efficient dispersion of agglomerated powder into respirable primary particles:

- **In-Container Fluidisation:** The epicyclical motion imparts significant energy into the bulk powder within the container, initiating the break-up of loose agglomerates
- **Controlled Emission:** Centrifugal force progressively expels the fluidised powder through precisely engineered, rate-controlling orifices in the container wall
- **In-Chamber Dispersion:** The emitted particles enter the turbulent airflow of the de-agglomeration chamber, where further dispersion occurs through high-energy particle-particle and particle-wall collisions
- **Final Sizing:** The aerosolised powder cloud then passes through a grid in the mouthpiece, which serves as a final de-agglomeration stage before moving from the device into the patient.

This mechanism is engineered to address the fundamental physics of fine, cohesive powders. Particles in the respirable range are dominated by interparticle forces, such as van der Waals forces, that cause them to agglomerate and resist aerosolisation. The Orbital engine is specifically designed to impart sufficient and

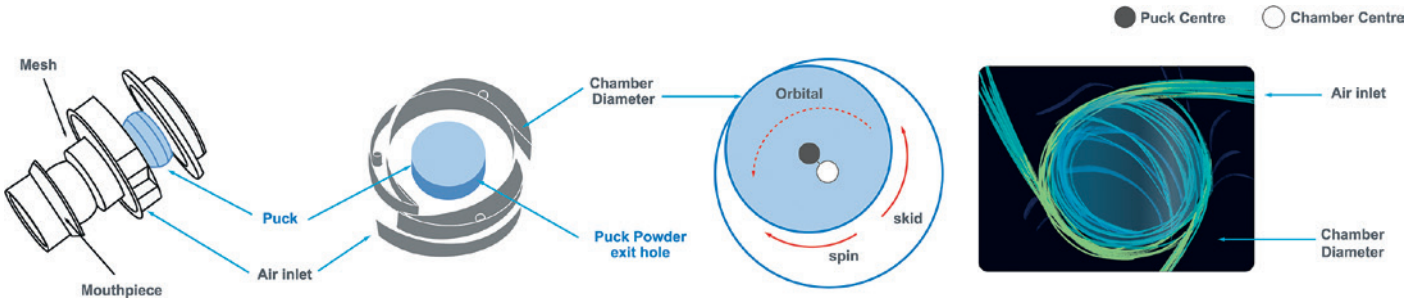

Figure 2: The core mechanism of the Orbital device.

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sustained shear and impact forces to overcome these cohesive bonds, ensuring high emitted dose levels and a fine particle fraction (FPF) capable of reaching the deep lung.

MULTI-BREATH DOSING WITH CONSISTENT PERFORMANCE – A KEY PATIENT BENEFIT

A critical innovation of the Orbital platform is its ability to deliver a large powder payload (e.g. 100–400 mg) over multiple, more gentle inspiratory breaths, unlike many traditional DPIs. By tuning the aperture size and number of the container's exit orifices, the rate of drug emission can be precisely controlled. This allows the patient to inhale the full dose in several consecutive breaths rather than in a single, large inhalation, which often results in an uncomfortable bolus of powder.

Crucially, this design decouples the two primary functions of a DPI: dose emission and particle de-agglomeration. In many conventional devices, the energy from a single patient inhalation drives both processes simultaneously; a weaker breath results in both a lower emitted dose and poorer aerosolisation (i.e. a larger, less effective particle size).

The Orbital engine, however, separates these functions. The epicyclical motion, which requires only minimal airflow to initiate, is the primary de-agglomeration driver, ensuring that the quality of the aerosol remains high and consistent. The dose emission rate, meanwhile, is governed by the container's orifices under centrifugal force. As a result, the aerodynamic particle size distribution remains remarkably consistent with each consecutive breath. This ensures that whether a patient with compromised lung function takes five gentle breaths or three stronger ones, the particles delivered to the lung are of a consistently optimal size for therapeutic efficacy, representing a significant advance in device reliability and patient-centric design.

A PATIENT-CENTRIC DEVELOPMENT PATHWAY FROM CONCEPT TO CLINICAL READINESS

The journey of the Orbital device from a nascent concept to a clinically-ready platform was guided by a rigorous, iterative and patient-centric development philosophy. This process began with the strategic acquisition of the intellectual property for a single-use mannitol device in 2022. Recognising a broader market opportunity,

> "RECOGNISING A BROADER MARKET OPPORTUNITY, THE APTAR PHARMA TEAM INITIATED A PROGRAMME TO TRANSFORM THE DEVICE FROM A DISPOSABLE, SINGLE-PRODUCT FORMAT INTO A VERSATILE, RELOADABLE PLATFORM CAPABLE OF ADDRESSING THE HIGH-DOSE MARKET."

> "THE ORBITAL ENGINE IS SPECIFICALLY DESIGNED TO IMPART SUFFICIENT AND SUSTAINED SHEAR AND IMPACT FORCES TO OVERCOME THESE COHESIVE BONDS, ENSURING HIGH EMITTED DOSE LEVELS AND AN FPF CAPABLE OF REACHING THE DEEP LUNG."

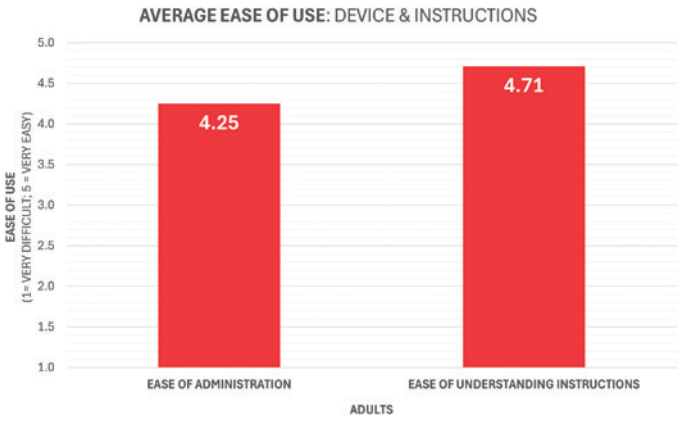

Figure 3: Findings from the human factors study.

the Aptar Pharma team initiated a programme to transform the device from a disposable, single-product format into a versatile, reloadable platform capable of addressing the high-dose market.

Human factors engineering was integrated at the earliest stages of development through Aptar Pharma's Noble subsidiary. Initial concepts and early prototypes were evaluated to gather direct feedback on usability and ergonomics. This research was critical in identifying key areas for improvement, such as a flimsy drawer mechanism that participants felt lacked a proper seal, confusing container loading orientation and suboptimal ergonomics that made the device difficult to grip securely. This direct user feedback became the catalyst for targeted engineering enhancements. The development team initiated an iterative design process, leading to more advanced prototypes that systematically addressed these usability challenges. The initial drawer was replaced with a robust integrated sliding mechanism, and the device's external housing was reshaped to improve grip and handling.

Subsequent usability validation confirmed the success of this patient-centric approach. The refined Orbital device was found to be intuitive, with participants reporting a high level of confidence and rating the device as "easy to use" (Figure 3). This research also provided more nuanced feedback that informed final design considerations. For instance, observations highlighted the potential need for a dose-completion feedback mechanism to help users to track the multi-breath dosing sequence. User feedback also indicated a five-to-three preference for a digital inhalation counter over a visualisation window, providing a clear directive for future smart

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device integration, which is currently well underway at Aptar. This continuous loop of design, testing and refinement has ensured that the final Orbital device is not only technically proficient but also demonstrably usable and tailored to the needs of its intended patient populations.

UNLOCKING NEW THERAPEUTIC POSSIBILITIES – FORMULATION VERSATILITY FOR SMALL MOLECULES AND BIOLOGICS

A defining feature of the Orbital platform is its ability to effectively aerosolise a wide spectrum of powder formulations, from conventional blended powders to highly challenging engineered particles, which are often required for biologic modalities. The device's robust performance has been extensively demonstrated with standard carrier-based formulations, which typically consist of a micronised API blended with a larger excipient carrier, such as lactose monohydrate. The development programme has included comprehensive testing of itraconazole (ITZ) formulations blended with both lactose and mannitol, confirming the platform's capability to efficiently de-agglomerate and deliver these common powder classes.

The delivery of biologic modalities, such as proteins, peptides and nucleic acids, via the pulmonary route represents one of the most significant challenges in drug delivery today.[5] These molecules are notoriously "fragile" and highly susceptible to the physical and chemical stresses encountered during formulation and aerosolisation. Shear stress, heat and moisture exposure can lead to denaturation and aggregation, resulting in a loss of therapeutic activity and the potential for immunogenic responses.[6]

To overcome these stability issues, biologics are typically formulated into inhalable particles using advanced engineering techniques such as spray-drying or freeze-drying, often with stabilising excipients, such as polyols or polymeric additives. While these processes create stable particles, the resulting powders are often amorphous, porous and highly cohesive, making them extremely difficult to disperse using conventional, low-energy DPIs.[5]

> "THE ORBITAL PLATFORM IS UNIQUELY POSITIONED TO SOLVE THIS CRITICAL "FORMULATION-DEVICE PARADIGM". ITS HIGH-ENERGY DE-AGGLOMERATION ENGINE PROVIDES THE FORCE NECESSARY TO OVERCOME THE STRONG COHESIVE BONDS OF THESE ENGINEERED PARTICLES, ENSURING THAT THEY ARE DISPERSED INTO PRIMARY PARTICLES SUITABLE FOR DEEP LUNG DEPOSITION."

The Orbital platform is uniquely positioned to solve this critical formulation-device paradigm. Its high-energy de-agglomeration engine provides the force necessary to overcome the strong cohesive bonds of these engineered particles, ensuring that they are dispersed into primary particles suitable for deep lung deposition. At the same time, the brief residence time within the engine and the nature of the dispersion forces minimise exposure to destructive shear stresses that could damage the fragile biologic modalities. Furthermore, the formulation is protected from ambient moisture ingress with a sealed container, sealed in a blister or pouch (with desiccant if required) until the moment of use – a key advantage for hygroscopic amorphous biologic powders.

This capability transforms Orbital from a simple delivery device into an enabling platform technology that can significantly de-risk the development of inhaled biologics. These biological modalities are often extremely expensive compared with traditional small-molecule therapeutics, so achieving efficient, consistent dosing while ensuring long shelf lives is more important than ever for developers and payers. By providing a pre-validated, high-performance delivery solution for such challenging powders, the Orbital platform enables developers to focus on optimising their formulation with the confidence that a compatible and effective delivery system already exists. This has the potential to unlock a new generation of inhaled biologic therapies that were previously considered undeliverable.

FUTURE-PROOFING INHALATION THERAPY – DESIGNING FOR DIGITAL INTEGRATION

The future of respiratory medicine is increasingly intertwined with digital health technologies. "Smart inhalers" are emerging as powerful tools to address two of the most persistent problems in inhalation therapy: poor patient adherence and incorrect inhaler technique.[4] Published data indicate that up to 90% of patients make at least one critical error in their inhaler technique, which can lead to suboptimal disease management and an increased burden on healthcare systems.[7,8]

From its inception, the Orbital platform has been designed with this digital future in mind. The findings from the human factors studies provided clear clinical justification for this approach; the observed use error where participants failed to complete the required number of inhalations is precisely the type of issue that can be mitigated by a connected device. The strong user preference for a digital counter further validates this development trajectory.

The device's design readily accommodates the integration of sensors and communication modules. A "Smart Orbital" device has already been developed in collaboration with the Aptar Digital Health group and an initial proof-of-concept version is already active in testing. Future versions are likely to incorporate a range of functionalities with the potential to enhance patient outcomes and provide valuable data for clinicians:

- **Adherence and Dose Completion:** On-board sensors could track each inhalation, providing patients with real-time feedback and reminders to ensure that the full multi-breath dose is administered correctly

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- **Technique Monitoring:** Integrated airflow sensors could measure inspiratory flow rate and duration, offering patients feedback to optimise their inhalation technique for optimal drug delivery
- **Data for Clinicians:** Data on adherence patterns and inhalation technique could be transmitted via Bluetooth to a secure application and clinician portal, providing objective insights to guide personalised treatment adjustments.

The reloadable nature of the Orbital device, where the core hardware is reused, aligns perfectly with the environmental sustainability and long-term use model of a connected health device, requiring only the replacement of the disposable container. This forward-thinking design ensures that the platform is not only ready for today's clinical challenges but is also prepared for the next wave of innovation in digital respiratory care.

CLINICAL APPLICATION – A CASE STUDY IN INHALED ITZ FOR PULMONARY ASPERGILLOSIS

To validate the Orbital platform, Aptar Pharma has undertaken a comprehensive development programme using ITZ as a model compound for treating pulmonary aspergillosis. This programme serves as a powerful case study, demonstrating the device's capabilities with a challenging molecule in an area of significant unmet medical need.

The management of chronic and allergic pulmonary aspergillosis presents a significant clinical challenge, necessitating therapies that can achieve high local drug concentrations within the airways while minimising systemic toxicity. ITZ, a broad-spectrum triazole, is a therapeutic cornerstone for pulmonary aspergillosis, but its use in oral formulations is frequently complicated by a narrow therapeutic window, variable bioavailability, extensive drug-drug interactions and dose-limiting toxicities, including hepatotoxicity and cardiotoxicity.[9,10] Consequently, the development of an inhaled formulation to deliver ITZ directly to the site of infection has been a long-standing goal in respiratory medicine.

The primary objective for an inhaled antifungal is to deliver a sufficient mass of drug to the lungs to exceed the minimum inhibitory concentration (MIC) for target pathogens, such as *Aspergillus fumigatus*, which typically ranges from 0.125 to 2.0 µg/mL.[11–13] Achieving this requires overcoming the substantial formulation challenges posed by ITZ's physicochemical properties, namely its high cohesiveness and poor aerosolisation efficiency.

Developmental efforts for DPI formulations of challenging compounds such as ITZ have historically yielded modest fine particle doses (FPDs) – the critical measure representing the mass of drug particles likely to reach the therapeutic target within the lungs. Early-stage clinical investigations confirmed the feasibility of the inhaled route but were often constrained by the payload limitations of existing DPI technologies.

While specific, peer-reviewed FPD data for ITZ using this technology is limited, its delivery efficiency potential can be illustrated using the TOBI Podhaler® (tobramycin – Viatris, Canonsburg, PA, US), a marketed product using Pulmosphere™ (Novartis, Basel, Switzerland) particles. Clinical scintigraphy studies in healthy volunteers demonstrated that TOBI Podhaler® achieved a mean whole-lung deposition of 34% of the nominal dose, significantly higher than nebulised tobramycin,[14] with an FPD per capsule of ~9.5 mg. Although tobramycin has different physicochemical properties than ITZ, this demonstrates the high efficiency achievable with this engineered particle approach.

Techniques such as advanced spray drying are employed to create particles with desirable aerodynamic properties, often targeting high FPFs. Research on inhaled voriconazole, another azole antifungal with similar delivery challenges, formulated via spray drying with leucine as an excipient, reported achieving FPFs up to approximately 60.8% using specific devices.[15] Extrapolating this FPF to a hypothetical high-performance ITZ formulation using a similar technique highlights the FPD constraints. For example, delivering a 10 mg nominal dose with 90% device emission and 60% FPF would yield an FPD of roughly 5.4 mg, which is still within the low-to-mid single-digit milligram range.

These examples, while using advanced formulation techniques, underscore a persistent limitation in delivering a sufficiently high FPD (i.e. tens of milligrams) of drugs such as ITZ in a single, convenient administration. This often necessitates multiple daily actuations to achieve a cumulative therapeutic dose, which can compromise patient adherence and limit overall efficacy.

The Orbital platform represents a paradigm shift in this context. By using both high-concentration blends and particle-engineered

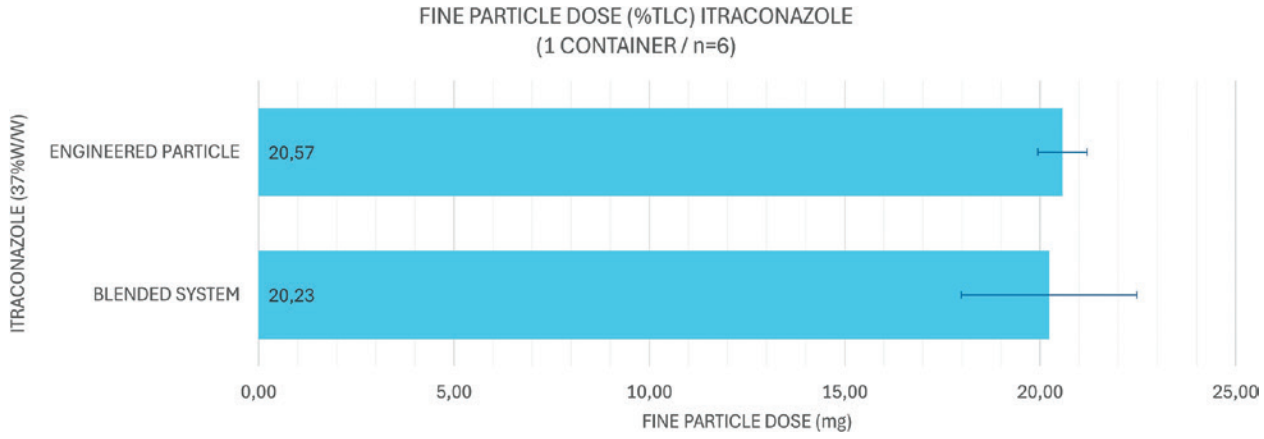

Figure 4: Current state of ITZ formulations for Orbital.

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formulations, alongside the high-efficiency, high-payload device, Aptar has developed a DPI system capable of delivering an FPD of ITZ exceeding 20 mg in a single dose. This was determined from a formulation exhibiting an emitted fraction of ~74% and an FPF of the emitted dose of ~74%, from a 37% w/w formulation containing ITZ, loaded with a formulation mass of 100 mg into a container. This result constitutes a 5- to 10-fold increase in the deliverable FPD compared with previously reported systems in clinical development (Figure 4).

The therapeutic implications of achieving such a high lung dose are profound. A single dose delivering over 20 mg of ITZ is predicted to generate local concentrations in the airway mucosal lining that are orders of magnitude above the MIC_{90} for *A. fumigatus*. This has the potential to enable more effective treatment regimens, improve fungal clearance, overcome emerging antifungal resistance and reduce the treatment burden for patients. Furthermore, by maximising local delivery, this high-payload system maintains the critical safety advantage of the inhaled route, minimising systemic exposure, thereby circumventing the toxicities associated with high-dose oral ITZ therapy. The ability to deliver such a high dose with a gentler inspiratory breath is also highly advantageous, as those suffering with the disease may find deep breaths more challenging.

CONCLUSION

This exhaustive development work – from its strategic inception to address the high-dose market, through patient-centric design evolution, to its validation with a challenging clinical candidate – demonstrates its maturity and readiness. Aptar Pharma's Orbital is now poised to enter clinical studies, offering a compelling and powerful new solution for partners seeking to overcome the most significant challenges in pulmonary drug delivery.

David Farrow

Dave Farrow is Director – Scientific Affairs at Aptar Pharma. He began his career as an inhalation scientist at Sanofi Aventis, working on exploratory development products through to commercial marketed products. He held a similar role at Novartis, where he further developed his inhalation knowledge. Following this, Mr Farrow moved to Vectura as Particle Engineering Specialist, going on to become Principal Scientist, then manager of the Bioformulation and Particle Engineering group. At Charles River, he led and developed the team conducting safety assessment/toxicology studies with aerosols. Mr Farrow then moved to Albany Molecular Research (now Curia) leading the R&D groups and conducting business development activities before joining Nanopharm, starting as Director of Operations, then became Chief Operations Officer. Mr Farrow moved to Nanopharm's parent company, Aptar, and was appointed to Director of Science and Technology for Aptar Pharma's prescription division in February 2024 and Director of Scientific Affairs for Aptar Pharma in 2025.

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GWP, global warming potential; **HFA**, hydrofluoroalkane; **HFO**, hydrofluoroolefin; **pMDI**, pressurized metered dose inhaler.

FACILITY SPOTLIGHT: UK-BASED CAPABILITIES IN INHALED AND NASAL DRUG-DEVICE PRODUCT DEVELOPMENT

Ross Errington of **Bespak** introduces the company's Holmes Chapel (UK) site, which is equipped to support device development programmes from early-stage formulation to large-scale manufacture.

The inhaled and nasal drug-device industry is undergoing rapid transformation, from the urgent shift to low-global-warming-potential (GWP) propellants in pressurised metered dose inhalers (pMDIs) to the development of next-generation novel therapies. Navigating this landscape means overcoming regulatory, environmental and supply chain challenges while still striving for innovative solutions that can enhance patient therapeutic outcomes.

To succeed, pharmaceutical developers need support across the development process, from analytical and formulation services to regulatory guidance and commercial supply. On top of that, these services and capabilities are needed across a wider range of platforms and drug types than ever before.

Bespak, a specialist inhalation CDMO, has established itself as a complete partner for developers navigating this changing industry. Following the consolidation of operations in North Carolina (US), the company's Holmes Chapel (UK) site is now equipped to support programmes from early-stage formulation to large-scale

> "THE FACILITY BRINGS TOGETHER MULTIPLE FUNCTIONS UNDER ONE ROOF, ENABLING A SEAMLESS TRANSITION TO COMMERCIALISATION."

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manufacture and sits proudly alongside Bespak's established device development and manufacturing site at King's Lynn (UK). With state-of-the-art laboratories, GMP manufacturing suites and access to advanced analytical capabilities, the facility plays a central role in Bespak's mission to drive innovation and lead the industry's transition to a more sustainable future.

A WALK THROUGH THE HOLMES CHAPEL SITE

Bespak's Holmes Chapel site is the company's headquarters, and supports customers from pilot- to large-scale supply of inhaled and nasal drug-device products. The facility brings together multiple functions under one roof, enabling a seamless transition to commercialisation. The site is dominated by its GMP manufacturing facilities, where finished pharmaceutical products are produced. This area is currently being expanded to encompass new manufacturing lines for pMDIs with next-generation low-GWP propellants.

Across the site, a product development area includes seven GMP suites, allowing Bespak to set up dedicated equipment to manufacture different types of inhaled or nasal products at clinical or commercial scale, depending on customer needs. In a third area, analytical laboratories enable the testing of raw materials, components and finished products. By consolidating capabilities previously spread across multiple sites, Holmes Chapel has increased efficiency and broadened the scope of services available to customers.

SUPPORTING MORE THAN pMDIs

Bespak is a leader in the green transition to low-GWP propellants, and its Holmes Chapel site is central to that work. The facility has seen significant investment in the form of new filling lines capable of manufacturing low-carbon pMDIs using HFO-1234ze and HFA-152a, the next-generation propellants currently at the forefront of the green transition. These lines have been, and continue to be, vital to the redevelopment of existing inhaler products, and the facility also has space for further planned expansion.

However, the Holmes Chapel site is not solely focused on pMDIs. The site also has proven expertise in dry powder and aqueous nasal formulations, supporting both existing therapies as well as next-generation therapeutic applications, including APIs capable of treatment via the central nervous system.

The Holmes Chapel team has recently collaborated on new molecules and novel APIs, helping customers to develop products that are ready for regulatory filing and commercial manufacturing. Since these new therapies often come with limited safety data, Bespak has established robust systems to handle them and ensure safe, compliant operations.

Furthermore, the Holmes Chapel site supports customers looking to reformulate existing therapies to take advantage of novel devices and administration routes that may improve ease of use or speed of onset. The facility can also provide technology transfer services for those looking for additional capacity. No matter the requirement, Holmes Chapel can provide bespoke solutions to meet each customer's unique needs, with Bespak's regulatory team on hand to support CMC filings and provide expert guidance to streamline the process from development through to market readiness.

EXPERTS IN ANALYTICS

Within the walls of the Holmes Chapel site, Bespak's formulation and analytical specialists have experience that spans suspensions, solutions and dry powders. The site's capabilities range from API characterisation and dosage form selection through to comprehensive aerosol and device performance testing. The facility also offers extractables and leachables studies, helping developers to understand how formulations interact with their container closure systems over time.

Stability testing is another service that Bespak offers to its customers. Products can be stored under controlled conditions, with GMP-compliant testing carried out to evaluate degradation, compatibility and performance across a product's lifespan. These services are particularly valuable for developers adapting to the transition to low-GWP propellants, where understanding the compatibility with their new formulations is essential. The Holmes Chapel site has already supported customers facing challenges when changing propellants, helping them to adjust device and componentry parameters to restore or optimise performance.

"NO MATTER THE REQUIREMENT, HOLMES CHAPEL CAN PROVIDE BESPOKE SOLUTIONS TO MEET EACH CUSTOMER'S UNIQUE NEEDS, WITH BESPAK'S REGULATORY TEAM ON HAND TO SUPPORT CMC FILINGS AND PROVIDE EXPERT GUIDANCE TO STREAMLINE THE PROCESS FROM DEVELOPMENT THROUGH TO MARKET READINESS."

The Holmes Chapel site also has access to world-leading modelling capabilities offered as part of Bespak's overall development service offering. By simulating design and formulation changes virtually, developers can test hypotheses without needing to run large numbers of physical experiments. This allows them to identify critical parameters and predict large-scale performance with ease. This approach streamlines early development, cutting both time and cost, while reducing reliance on manual testing and minimising experimental waste. It also enables more intelligent design of experiments, improving efficiency and consistent quality to deliver faster, smarter outcomes for customers.

A LOCAL PARTNERSHIP NETWORK

Collaboration is crucial in an industry undergoing rapid transformation, and the Holmes Chapel site does not operate in isolation. Not only does the team work

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"COMPONENT MANUFACTURERS, PROPELLANT SUPPLIERS, CLINICAL TRIAL CENTRES AND FORMULATION EXPERTS ALL WORK IN CLOSE CO-ORDINATION TO ACCELERATE PRODUCT DEVELOPMENT WHILE MINIMISING ENVIRONMENTAL IMPACT."

in lockstep with Bespak's device and componentry experts at the King's Lynn site, the facility is also part of a broader network across the north west of England that creates a collaborative hub for inhaled and nasal innovation. Component manufacturers, propellant suppliers, clinical trial centres and formulation experts all work in close co-ordination to accelerate product development while minimising environmental impact.

As the industry transitions to low-GWP propellants, limited manufacturing capacity poses a significant bottleneck. Bespak's partnerships address this gap, creating an end-to-end service that encompasses formulation development through to commercialisation of low-GWP pMDIs. Strategic relationships with H&T Presspart (Blackburn, UK) and Orbia Fluor & Energy Materials (Runcorn, UK), as well as Solstice Advanced Materials (Morris Plains, NJ, US), formerly Honeywell Advanced Materials, help to ensure access to GMP-grade materials and propellants. Early-stage formulation development is also supported through collaboration with OzUK (Chippenham, UK), using the latest developments in metering valve technology from Bespak's King's Lynn site.

Clinical trials are another essential component of taking a product to market. Bespak collaborates with experts at the Medicines Evaluation Unit (Manchester, UK) in designing and managing clinical trials for inhalation therapies to help streamline this process for customers.

As well as offering reassurance around confidentiality and intellectual property, these partnerships provide immediate access to critical capabilities. With many partners based locally, and its team of device and componentry experts at King's Lynn on call, Holmes Chapel can bring expert advisors on site within hours – speeding up decision-making, keeping development timelines on track and decarbonising the supply chain to support Bespak's wider environmental commitments.

SUSTAINABILITY IN ACTION

Sustainability is central to Bespak's operations in Holmes Chapel. The site integrates renewable energy, waste reduction and efficient operations to minimise its environmental impact. The facility is also thoughtfully integrated into its natural surroundings through on-site biodiversity assessments and action plans. A supply chain biodiversity footprint assessment was conducted to evaluate the environmental impact of every stage of operations, from raw material sourcing to transportation and logistics.[1]

The adoption of low-GWP propellants is a huge step forward in improving the carbon footprint of the industry, and the Holmes Chapel site has played a significant part in this shift. Even so, propellants can be lost to the atmosphere unnecessarily during manufacturing. As such, Bespak has put waste and capture systems in place that allow for the appropriate disposal or recycling of these propellants.

Packaging design is another area where sustainability has been considered.

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By optimising commercial packaging processes, Bespak can reduce both material loss and environmental impact. For instance, careful design ensures that only a minimal number of units are discarded during unexpected line stops, conserving aluminium and propellant, along with the associated costs. Automated filling and testing processes reduce the need for on-site staff, further decreasing the facility's carbon footprint.

These factors all support Bespak's ambitious net-zero and emission reduction targets, which are validated by the Science Based Targets initiative (London, UK), a corporate climate action organisation. This includes a long-term target of reducing greenhouse gas emission intensity by 97% by 2050. This validation marks a significant step in Bespak's climate journey and reinforces its commitment to taking science-aligned climate action to reduce its carbon footprint.[2]

THE FUTURE OF HOLMES CHAPEL

Bespak is actively investing in expanding its Holmes Chapel facility. Following the installation of the first manufacturing line to produce pMDIs with a low-GWP propellant in 2025, additional construction is already underway, with additional filling lines in both the design and build phases to support the growing demand for production. Capacity is projected to grow exponentially as Bespak continues to lead the transition to next-generation low-carbon inhalers. These investments are not limited to manufacturing equipment, as they also include new operational space and infrastructure to support staff and warehousing.

The industry-wide shift towards low-GWP propellants remains a dominant trend and, as such, Bespak is continuing to invest in equipment capable of handling both HFO-1234ze and HFA-152a at its Holmes Chapel site. Manufacturing with these next-generation propellants requires capacity that meets evolving safety requirements, such as flammability risks, as well as regulatory and performance needs. Rising costs and legislative pressures around existing propellants further underscore the urgency for the industry to transition, and Bespak's expanding capacity and integrated network allows developers to move rapidly from development through to regulatory approval and large-scale production.

Alongside the transition to low-GWP propellants, the future of inhaled and nasal drug delivery is being shaped by next-generation therapies and device innovations, and the Holmes Chapel facility is ready to support customers with bespoke, end-to-end solutions.

A TRUSTED PARTNER

Bespak represents a new era in inhaled and nasal drug-device development. By integrating analytical, formulation, manufacturing and regulatory capabilities at one site, supported by device and componentry expertise at a second site, the company provides end-to-end support for developers navigating this evolving landscape. Its leadership in low-GWP propellant adoption, expertise in novel therapies and commitment to sustainability position Bespak as a trusted partner in the delivery of life-changing treatments.

Through strategic partnerships and ongoing investment in capacity and technology, Bespak continues to strengthen its position as a leader in innovation, collaboration and environmental stewardship. The company brings together advanced manufacturing and formulation expertise in Holmes Chapel with device and component design and modelling capabilities in King's Lynn, creating an integrated offering. For developers, this means access to an efficient and sustainable path from early-stage formulation through to commercial-scale production, ensuring that patients continue to receive the therapies they need in a rapidly changing world.

"FOLLOWING THE INSTALLATION OF THE FIRST MANUFACTURING LINE TO PRODUCE pMDIs WITH A LOW-GWP PROPELLANT IN 2025, ADDITIONAL CONSTRUCTION IS ALREADY UNDERWAY, WITH ADDITIONAL FILLING LINES IN BOTH THE DESIGN AND BUILD PHASES TO SUPPORT GROWING DEMAND FOR PRODUCTION."

Ross Errington

Ross Errington is Head of Drug Product Development at Bespak. He is a chemist by training with over 30 years' experience in pharmaceutical product development and manufacture, specialising in inhaled delivery systems. He has deep experience of pMDI product development and commercialisation, having supported numerous customers to successfully design, develop, register and commercialise products across global markets. Mr Errington is also an IPAC-RS Board Member.

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ADVANCING ELASTOMER SEAL SOLUTIONS FOR THE PRESSURISED METERED DOSE INHALER MARKET

Nathan Sowder of **Parker O-Ring & Engineered Seals Division** discusses the company's role and history in providing advanced elastomer seals and components to the drug delivery industry, with a particular emphasis on pressurised metered dose inhalers.

The pressurised metered dose inhaler (pMDI) market remains a vital segment of respiratory drug delivery, providing critical treatment to millions of patients worldwide with asthma, chronic obstructive pulmonary disease and other respiratory conditions. Parker has manufactured seals to support the pMDI market since 1956 (Figure 1), delivering reliable, high-performance solutions tailored to the stringent demands of pMDI applications, and has established a long-standing tradition of quality, innovation and customer commitment that continues to drive its leadership in the industry today.

Figure 1: Precision-cut seal and O-rings for use with pMDIs.

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"PARKER HAS MANUFACTURED SEALS TO SUPPORT THE pMDI MARKET SINCE 1956, ESTABLISHING A LONG-STANDING TRADITION OF QUALITY, INNOVATION AND CUSTOMER COMMITMENT THAT CONTINUES TO DRIVE ITS LEADERSHIP IN THE INDUSTRY TODAY."

THE CRITICAL ROLE OF ELASTOMER SEALS IN pMDIs

Elastomer seals are fundamental to the performance and safety of pMDIs. Their key functions include:

- **Consistent Dose Delivery:** Elastomer seals prevent leakage of both medication and propellant, ensuring that each inhaled dose is accurate and effective
- **Device Integrity:** These seals withstand harsh chemical exposure from propellants and resist environmental stresses, such as temperature fluctuations and mechanical wear
- **Patient Safety:** The elastomers used in pMDIs must meet rigorous biocompatibility standards and comply with stringent regulatory requirements, safeguarding patient health.

KEY CHALLENGES IN ELASTOMER APPLICATIONS FOR pMDIs

The evolving landscape of pMDI propellants and device designs presents several technical challenges for elastomer seals:

- **Chemical Compatibility:** Seals must be able to resist aggressive propellants such as hydrofluorocarbons (HFAs) and adapt to emerging low global-warming-potential (GWP) propellants, such as HFA-152a and HFO-1234ze. This requires advanced material formulations that maintain integrity without degradation or swelling over time.

- **Gas Permeability:** Minimising permeation of propellant gases through elastomer seals is crucial to preserving drug potency, ensuring dose accuracy and meeting environmental regulations aimed at reducing greenhouse gas emissions.

- **Compression Set Resistance Over Time:** Elastomers must maintain elasticity and sealing force over their entire product shelf life, resisting permanent deformation (compression set) that could compromise seal integrity during storage and use, leading to leakage or device failure.

PARKER'S PROPRIETARY COMPOUNDS AND GLOBAL MANUFACTURING EXCELLENCE

Parker's leadership in pMDI sealing solutions stems from its deep expertise in material science and its ability to innovate, develop and mix proprietary elastomer compounds. The company's advantages enable it to offer:

- **Tailored Material Formulations:** Parker's in-house compound development capabilities enable it to customise elastomer properties for optimal chemical resistance, permeability and durability, meeting mechanical and regulatory requirements. Additionally, its materials are optimised for multiple manufacturing processes, enabling personalised designs that provide optimal component sealing solutions, including extrusion, splicing, injection or compression moulding.

"PARKER'S IN-HOUSE COMPOUND DEVELOPMENT CAPABILITIES ENABLE IT TO CUSTOMISE ELASTOMER PROPERTIES FOR OPTIMAL CHEMICAL RESISTANCE, PERMEABILITY AND DURABILITY, MEETING MECHANICAL AND REGULATORY REQUIREMENTS."

- **Consistent Quality Control:** By manufacturing proprietary compounds in its own facilities, Parker can ensure stringent quality controls and batch-to-batch consistency.

- **Innovation for Emerging Propellants:** Parker is actively developing next-generation compounds specifically designed for compatibility with new low-GWP propellants, such as HFA-152a and HFO-1234ze. These materials promise best-in-class performance in permeability, chemical resistance and compression set resistance, providing future-proof sealing solutions.

- **Global Manufacturing Footprint:** With strategically located production sites spanning North America, Europe and Asia, Parker provides supply chain resilience, rapid response to market demands and regional regulatory compliance.

THE FUTURE OF pMDI SEALING TECHNOLOGY

As drug formulations and propellants evolve for pMDI delivery, sealing materials often require tailored modifications to maintain their compatibility and performance. By drawing on its sealing application engineering expertise, Parker can compress development timelines and deliver designs optimised for efficient manufacturing.

Furthermore, as the pharmaceutical industry accelerates its transition to environmentally sustainable pMDI propellants, the demand for advanced sealing materials that can meet evolving regulatory and performance requirements will only grow. Parker is committed to leading this innovation curve by delivering

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elastomer seals that not only meet today's rigorous standards but also anticipate the challenges of tomorrow's drug delivery technologies.[1]

PARKER'S 70-YEAR LEGACY OF EXCELLENCE

With a legacy spanning over 70 years, Parker combines material science expertise with manufacturing excellence to deliver elastomer seals that meet the highest standards of the pMDI market. The company's commitment to innovation and sustainability positions Parker as a trusted partner in advancing respiratory drug delivery solutions worldwide, delivering reliable and high-performance solutions tailored to the stringent demands of pMDI applications.

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1. *Ewing D, "Next-Generation Propellants for pMDIs: Seal Material Challenges and Sustainable Alternatives to P-134a". Web page, Parker, accessed Oct 2025.*

"FURTHERMORE, AS THE PHARMACEUTICAL INDUSTRY ACCELERATES ITS TRANSITION TO ENVIRONMENTALLY SUSTAINABLE pMDI PROPELLANTS, THE DEMAND FOR ADVANCED SEALING MATERIALS THAT CAN MEET EVOLVING REGULATORY AND PERFORMANCE REQUIREMENTS WILL ONLY GROW."

Nathan Sowder

Nathan Sowder is a Life Science Business Development Engineer at Parker O-Ring & Engineered Seals Division. He works with pharmaceutical and medical device original equipment manufacturers and distributors to deliver compliant sealing solutions for regulated drug delivery applications, including pMDIs. Mr Sowder focuses on material selection, qualification testing and scale up, translating technical requirements into certified, low extractable seals that meet production and supply chain needs.

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Interview: Integrating Phillips Medisize and Vectura's Operations

In this interview, **Phillips Medisize**'s **Charlie Schumacher** and **Sandy Munro** discuss the company's progress on its integration of **Vectura**, covering aspects such as cultural alignment, technical innovation and the evolving role of CDMOs in the inhalation landscape.

Q To begin with, could you provide an overview of the combined offering Phillips Medisize presents to the industry in the inhalation space following its acquisition of Vectura?

CS The integration of Vectura has enabled us to deliver a truly comprehensive service in the inhalation space. We can now support customers from early formulation and combination product development through to commercial launch, all within a single organisation. This structure helps us to reduce risk and complexity for our customers. Since the acquisition, we've seen strong engagement from the market – including from organisations that had never worked with either company before. This enthusiastic response underscores the value and relevance of our combined capabilities.

Additionally, as we integrate Vectura into the Phillips Medisize R&D organisation, we are discovering that the Vectura acquisition not only complements our parenteral drug delivery expertise but also may, over time, provide unique advantages to our customers in the *in vitro* diagnostic and medtech industries. Plus, Phillips Medisize's platform technologies and capabilities are already adding value that can ultimately benefit patients. For example, our R&D team's software engineering capability is already enhancing technology roadmaps for future inhalation devices.

SM Bringing together all the necessary expertise required to develop an inhalation product means that we can understand the whole system. This facilitates rapid product development, including the resolution of issues when they sometimes inevitably arise. Our focus is on helping our customers bring new therapies to market so that patients can benefit from innovative treatments sooner. With more than 25 years' experience in inhaled product development, and 13 inhaled medicines launched by our partners and licensees, we offer practical, proven solutions across a wide range of molecules, devices and delivery routes.

Q Where are you in the process of integrating Phillips Medisize's commercial manufacturing capabilities with Vectura?

CS We've made rapid progress in developing our manufacturing capabilities. Construction is underway on a new multidose dry powder product manufacturing line capable of commercial scale mixing, filling, assembly and packaging. With these capabilities built internally, we can now support customers through every stage of development and manufacturing, without the need to hand off to external organisations, meaning that we can meet the needs of both early-phase and commercial programmes.

Q How important is culture when bringing two companies together, and how well are the cultures of both organisations coming together during the integration process?

CS Cultural alignment is absolutely fundamental when bringing two companies together. In this case, both organisations were mission-driven and shared a focus on solving technical problems to help patients live healthier, more productive lives. Even though we expressed our missions differently, the underlying values and sense of purpose were remarkably compatible from the outset, which was reinforced by our commitment to Principle Based Management, which emphasises value-driven decision-making and long-term value creation.

SM What's been rewarding is how both teams have worked hard to learn from each other and adopt the best of both organisations' ways of working. We've made a conscious effort to cross-pollinate ideas and take new approaches on board. Rather than simply assimilating, we're building something stronger by combining the strengths of both sides. This willingness to adapt and collaborate is making the new organisation even better than either company was on its own.

"WITH MORE THAN 25 YEARS' EXPERIENCE IN INHALED PRODUCT DEVELOPMENT, AND 13 INHALED MEDICINES LAUNCHED BY OUR PARTNERS AND LICENSEES, WE OFFER PRACTICAL, PROVEN SOLUTIONS ACROSS A WIDE RANGE OF MOLECULES, DEVICES AND DELIVERY ROUTES."

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Q How has the role of CDMOs changed over recent years, and how is Phillips Medisize positioned within the inhalation landscape post-integration?

SM The inhalation landscape has changed dramatically over the past decade. Where it was once dominated by a handful of large companies focused on major diseases – primarily asthma and chronic obstructive pulmonary disease – there's been a shift toward addressing unmet needs in rarer diseases and developing high-value, lower-volume products, including biologics. CDMOs are now expected to offer more sophisticated capabilities, particularly for biologics and complex formulations, and the sector is seeing significant consolidation.

CS We're responding to these trends by expanding our skill set and global resources. Whether supporting biotech companies in moving quickly to the proof-of-concept stage or enabling large pharmaceutical companies to overcome technical challenges, our team has the experience and flexibility to help customers address the needs of patients in new and meaningful ways.

Q What are some of the innovations and efficiencies that have emerged from combining Phillips Medisize's commercial manufacturing capabilities with Vectura's formulation expertise?

SM Vectura has a long history of innovation in both device and formulation development. Our platforms include our open-inhale-close dry powder inhaler with only three simple user steps, and the FOX™ Vibrating Mesh Nebuliser, which offers precise lung deposition, minimised waste and digital connectivity for monitoring adherence. By combining this expertise with Phillips Medisize's commercial manufacturing capabilities, we can reduce the need for tech transfers and can minimise the risk of inefficiencies when transferring knowledge and processes across organisations. This helps our customers bring therapies to market more efficiently so that patients can benefit from innovative treatments sooner.

Q What sets your scientific approach apart and how does that differentiation help your customers bring therapies to market more effectively?

SM Our R&D approach is distinguished by being device- and platform-agnostic. We're not limited to a single technology or delivery route, which means that we can advise customers on the most suitable path for their molecules and target patient populations. This flexibility is underpinned by deep analytical expertise and a focus on practical, patient-centric solutions. Customers can bring us their molecule and their target patient group, and we'll help them develop, manufacture and launch the right combination product.

Q In your opinion, what are the most significant trends currently shaping the future of inhalation drug delivery?

SM The next frontier of drug delivery is enabling the delivery of biologics and other advanced

Charlie Schumacher

Vice-President, Global Innovation and Development UK

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Charlie Schumacher, Vice-President, Global Innovation and Development UK, at Phillips Medisize, is responsible for the day-to-day leadership of the Phillips Medisize inhalation team, formerly Vectura, which was acquired in early 2025 to expand the capabilities of the company's global R&D organisation. He joined the company in 2022 to lead research and development for the North America region. Prior to Phillips Medisize, Mr Schumacher spent nearly 30 years in leadership roles within the medical device, high-tech and durable consumer product industries, successfully advancing product development, commercialisation, operations and mergers & acquisitions in global organisations including Medtronic and Honeywell.

Dr Sandy Munro

Chief Inhalation Scientist

E: pmcinfo@molex.com

Sandy Munro, PhD, Chief Inhalation Scientist at Phillips Medisize, became part of the company through its acquisition of Vectura in early 2025. He had been at Vectura since 2008 in a variety of pharmaceutical development leadership roles that focused on dry powder inhaler and smart nebuliser product development, as well as leading novel inhaled technology development programmes and defining the company's technology strategy. Prior to Vectura, Dr Munro spent 20 years at GSK, joining as an analytical scientist in 1987 and progressing through a number of roles to become GSK's Global Director of Inhaled Science and Technology. He holds a chemistry degree from the University of Edinburgh (UK) and a PhD in synthetic organic chemistry from the University of East Anglia (UK). He is an honorary life member of The Aerosol Society of Great Britain.

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"LEVERAGING PHILLIPS MEDISIZE'S DEEP EXPERTISE IN DEVICE DESIGN AND MANUFACTURING ALONGSIDE VECTURA'S ADVANCED FORMULATION AND INHALATION SCIENCE CAPABILITIES, WE CAN NOW OFFER COMPREHENSIVE R&D SUPPORT ACROSS THE FULL SPECTRUM OF INHALED DRUG DELIVERY."

therapies via inhalation. This is a significant step beyond traditional approaches, as it requires not only getting the medicine into the lungs, but also ensuring that it crosses biological barriers, reaches the right cells and is delivered into the cell and released at the right time.

Another major trend is the rise of nasal delivery. Around a third of new respiratory products are now being developed for administration via the nasal route, which opens up possibilities for systemic delivery and even direct-to-brain therapies for conditions like Alzheimer's disease and other neurological disorders.

We're also seeing a growing trend towards the use of inhaled routes for non-respiratory diseases, such as central nervous system conditions. Our goal is to help customers bring the next generation of inhaled therapies to patients more effectively, whether that means supporting complex biologics, enabling new delivery routes or providing the technical expertise needed to navigate the challenges of modern inhaled drug development.

Q How does the acquisition of Vectura reflect the broader vision for Phillips Medisize, and how does that vision serve your customers?

CS The integration of Vectura reflects our commitment to expanding the breadth and depth of our offering across the healthcare landscape. Leveraging Phillips Medisize's deep expertise in device design and manufacturing alongside Vectura's advanced formulation and inhalation science capabilities, we can now offer comprehensive R&D support across the full spectrum of inhaled drug delivery. Our vision is to be the resource customers turn to when they want to find the right solution and delivery strategy for their API, regardless of modality.

Q How do you balance speed, scale and scientific rigour, especially in a space as specialised as inhalation?

CS Our comprehensive capabilities allow us to help reduce risk, time and cost by keeping expertise and processes within our organisation. By harnessing our existing advanced device platforms and manufacturing infrastructure to support our customers, we can leverage proven solutions as a starting point, meaning that we're not starting from scratch with every project. This helps accelerate timelines while still allowing us to tailor our approach to each customer's needs.

SM Flexibility is essential. We work with organisations of all sizes and at all stages of development, adapting our support to their specific requirements, budgets and timelines. Our team brings together decades of experience with formulation and device technology, so we're able to provide strong, practical advice. Ultimately, our goal is to help customers move efficiently from concept to commercialisation.

Q If you had to define the role of Phillips Medisize in shaping the future of inhalation therapies, what would it be, and how will customers benefit?

SM We help bring innovative solutions to problems the market hasn't yet solved, whether that's enabling delivery across the blood-brain barrier, formulating complex biologics or supporting new therapeutic modalities.

CS We see ourselves as a resource and contributor to the entire scientific community. We actively collaborate with universities and industry forums, sharing knowledge and helping to shape the broader inhalation landscape. In so doing, we can help to maximise the probability of success for our customers and, ultimately, for the patients who rely on the new therapies being developed.

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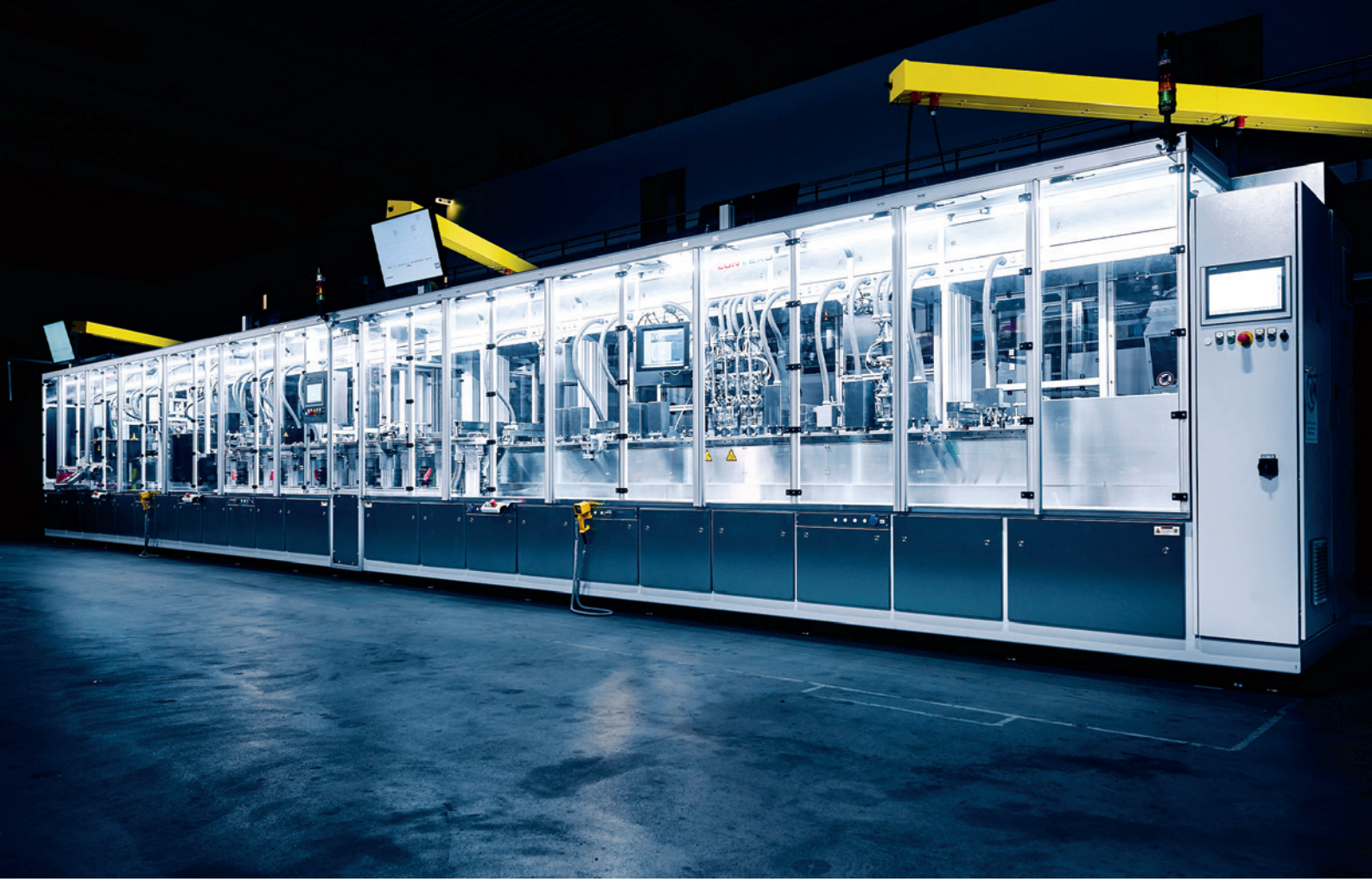

FAST-TO-MARKET DEVELOPMENT OF A NOVEL NASAL SPRAY WITH SIMULTANEOUS ENGINEERING

CONTEXO automation

Matthias Müller of **Contexo** details how a close collaboration between Contexo and a pharmaceutical manufacturer led to the rapid development of a novel nasal spray product, taking the project from prototyping to market within 14 months, shaving 10 months off the anticipated launch date.

OVERVIEW

During the development of a novel nasal spray, the device went from a prototype to industrial series production in just 14 months, thanks to the close and early co-operation between a pharmaceutical manufacturer and Contexo, the machine manufacturer. Simultaneous engineering was a key component of this process that enabled the market launch to be brought forward by 10 months and increased the standard market output by 20%.

The project began with the question: "How can we bring a new product to market as quickly as possible?" At the initial meeting, the pharmaceutical manufacturer presented the first samples and set a tight timeframe for the launch. Although the first prototypes and drawings were available, the design freeze was not yet in sight. This stage was the perfect time to start planning production and, consequently, the assembly plant. At this point, changes could still be made to optimise the new product, with the ultimate aim of ensuring efficient series production. Product finalisation and machine development could therefore be carried out in parallel.

Specifically, Contexo, the machine manufacturer, was given the opportunity to co-develop the nasal spray for automation and safe, cost-effective mass production. This approach forms the basis of a cost-effective machine concept that minimises process complexity while guaranteeing safe and stable production. It enables

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rapid project implementation and a swift product launch while guaranteeing profitable long-term production. Growth factors and the further development of the plant can also be considered.

THE ASSEMBLY SYSTEM IN DETAIL

45 Integrated Processes

The basic layout of the system is based on a modular machine platform. The on-site conditions are then taken into account, considering factors such as:

- How can the machine be positioned to ensure that it is always accessible to the operator?
- Where are the obstacles?
- How can accessibility for maintenance and servicing be optimised?

In this case, the machine was intended for use in a Class 7 cleanroom, so the highest GMP design requirements also had to be met. A linear-indexing machine with a toothed belt drive was chosen. Experience has shown that this abrasion-free system can be operated hygienically and efficiently for several years. The project involved assembling seven components and integrating 45 processes, including laser welding and hot crimping (Figure 1).

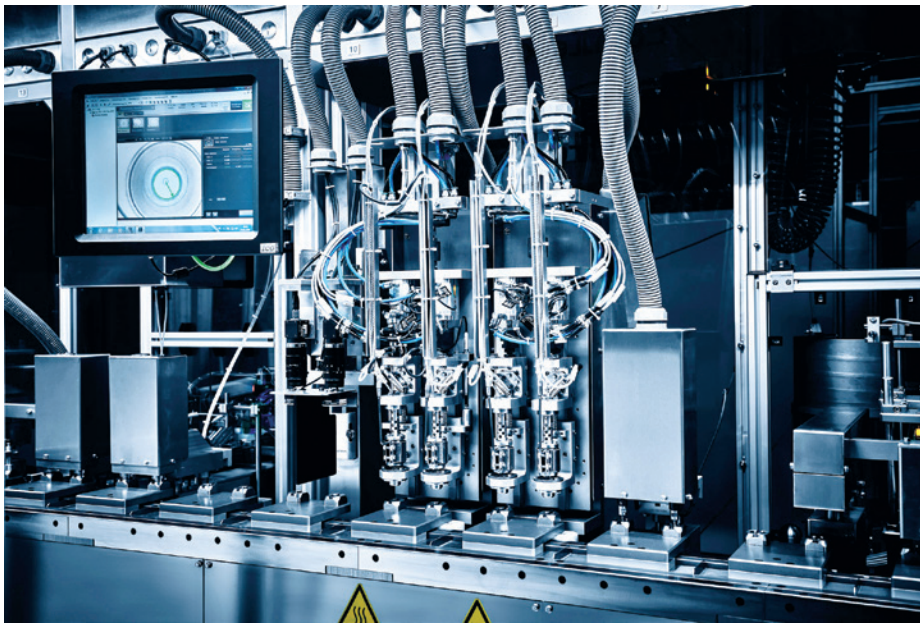

Figure 1: Hot crimping and checking.

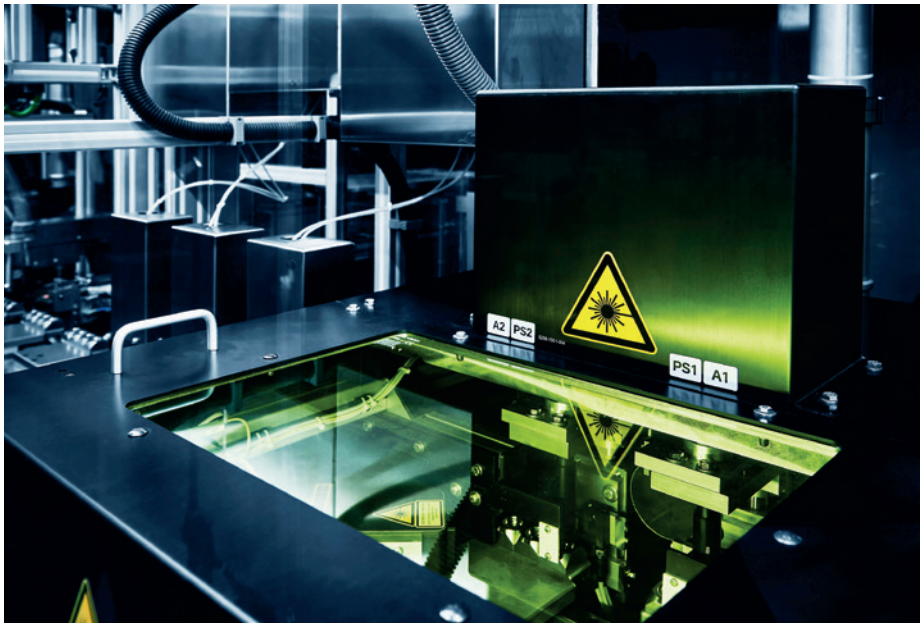

Figure 2: Full laser integration.

Rotary Quasi-Simultaneous Laser Welding With 3° Precision

First, Contexo developed prototypes of the stations and processes. An initial test series could then be quickly started in a test station, which enabled Contexo to gain a rapid understanding of the processes and offer recommendations for product optimisation. The laser processes were a significant challenge to establish, as they involved weld seams in the micrometre range. Intensive testing and consistent further development were essential. Contexo fully parameterised the process by providing detailed specifications, including the number of lasers to be used the number of revolutions required, the welding angle, the wattage and many more.

"AN INITIAL TEST SERIES COULD THEN BE QUICKLY STARTED IN A TEST STATION, WHICH ENABLED CONTEXO TO GAIN A RAPID UNDERSTANDING OF THE PROCESSES AND OFFER RECOMMENDATIONS FOR PRODUCT OPTIMISATION."

These delicate welding processes use fully integrated laser technology to guarantee high process stability and precision, ensuring stable production over the long term (Figure 2). Careful use of laser processes can significantly reduce the financial investment required for laser technology, resulting in considerable cost savings.

A quasi-simultaneous laser process was chosen, whereby the product can be welded in two places at once through rotation.

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Four laser sources were installed and distributed across six fixed optics. Fully integrated servo spindles rotate the product, which is fixed in place by a vacuum during the laser process. The laser is positioned with an accuracy of 3° on the axis of rotation.

Laboratory System

The construction of the prototype stations and laser processes took place in Contexo's laboratory system. Once these processes were running smoothly, the test system was delivered to the pharmaceutical manufacturer for thorough on-site testing and inspection of their products.

Meanwhile, Contexo continued to assemble the linear-indexing machine, implementing optimisations based on feedback from the pharmaceutical manufacturer during the process. This approach saved an immense amount of time and significantly reduced costs. After the testing phase, the laser system was essentially recycled by being installed in the final machine. It is also crucial at this stage to conduct further evaluations to ensure that the machine is safe and that the lasers comply with Laser Class 1 regulations and are therefore harmless.

Component Feeding

Special attention was also paid to how device components were fed into the machine, as they are extremely small and lightweight (Figure 3). They are also particularly susceptible to damage due to the materials used in their construction. The springs, for example, needed a solution to untangle them, as they easily become entangled with each other. Therefore, special attention had to be paid to the technique used to untangle them and to feed the other components correctly. Contexo was able to solve this challenge as it has its own sorting bowl construction facility. By drawing on lessons from its decades of experience, Contexo was able to implement precise and reliable sorting and feeding.

Product Safety – Testing Processes

Product safety is also a key focus, as the quality of medical devices must be perfect. Numerous testing processes were therefore integrated into the system, including testing for pressure, tightness and flow (Figure 4). Testing processes ranging from

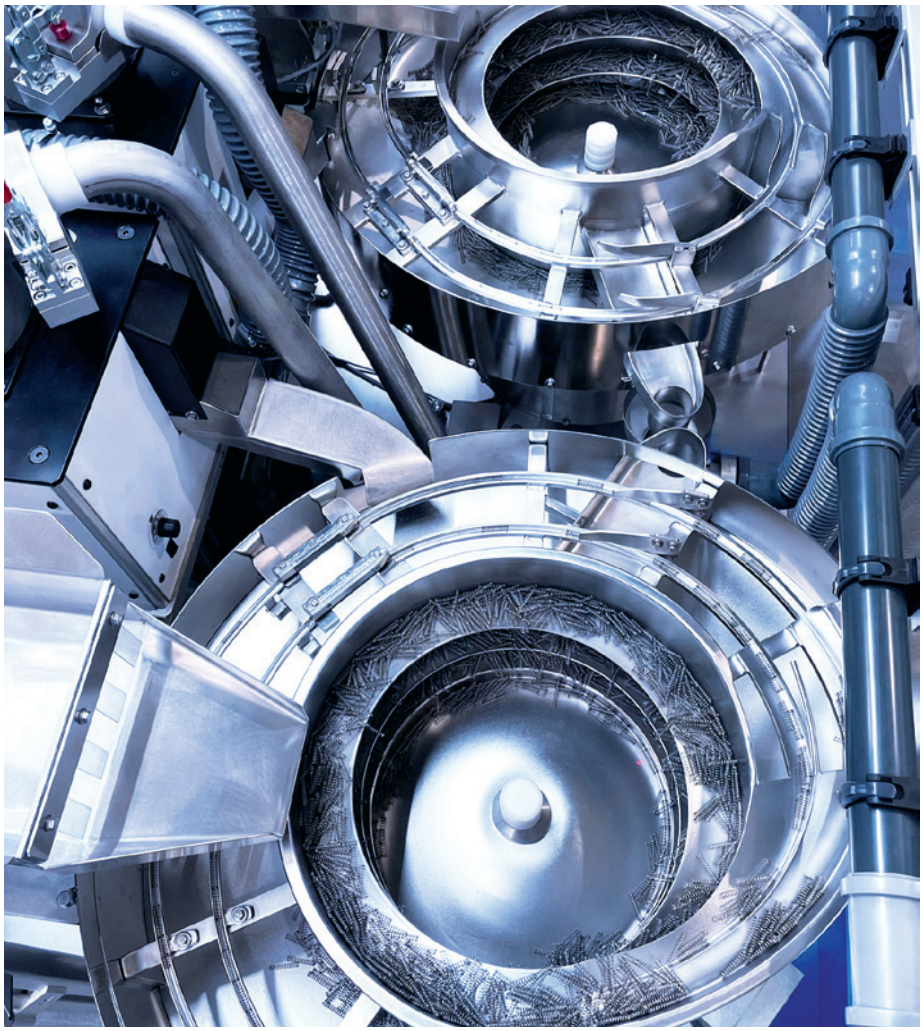

Figure 3: Smooth component feeding.

Figure 4: Testing pressure, tightness and flow.

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"THANKS TO THIS COLLABORATION, THE NASAL SPRAY AND THE PRODUCTION MACHINE WERE ABLE TO BE DEVELOPED IN PARALLEL, ENABLING THE DEVICE TO BE PERFECTLY TAILORED TO THE AUTOMATION PROCESS."

0.3 bar at ±4 Pa to burst testing have been developed. To ensure cleanliness during assembly, all stations were encapsulated and kept free of corners, edges and dead space. The final design's minimal footprint and individualised layout were also taken into account with the aim of minimising cleanroom production costs.

Simultaneous Engineering

The system was ready for operation immediately upon completion, enabling the first batches of the nasal spray to be produced right away. It was no coincidence that the market launch was brought forward by 10 months. Close collaboration between the two project teams was a key factor in this success. Thanks to this collaboration, the nasal spray and the production machine were able to be developed in parallel, enabling the device to be perfectly tailored to the automation process. Contexo provided complete validation support for all process parameters, ensuring validation-compliant recording and backup in the machine control system (Figure 5). This success has its roots in many years of experience in the fields of automation in medical technology, encompassing technical expertise, GMP know-how and Contexo's development partnership.

Figure 5: GMP full service.

Matthias Müller

Matthias Müller is the Chief Commercial Officer of Contexo, which he runs together with his two brothers. His father founded the company in 1975 and the brothers took over the management together in 2011.

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Aseptic Processing Summit 2026
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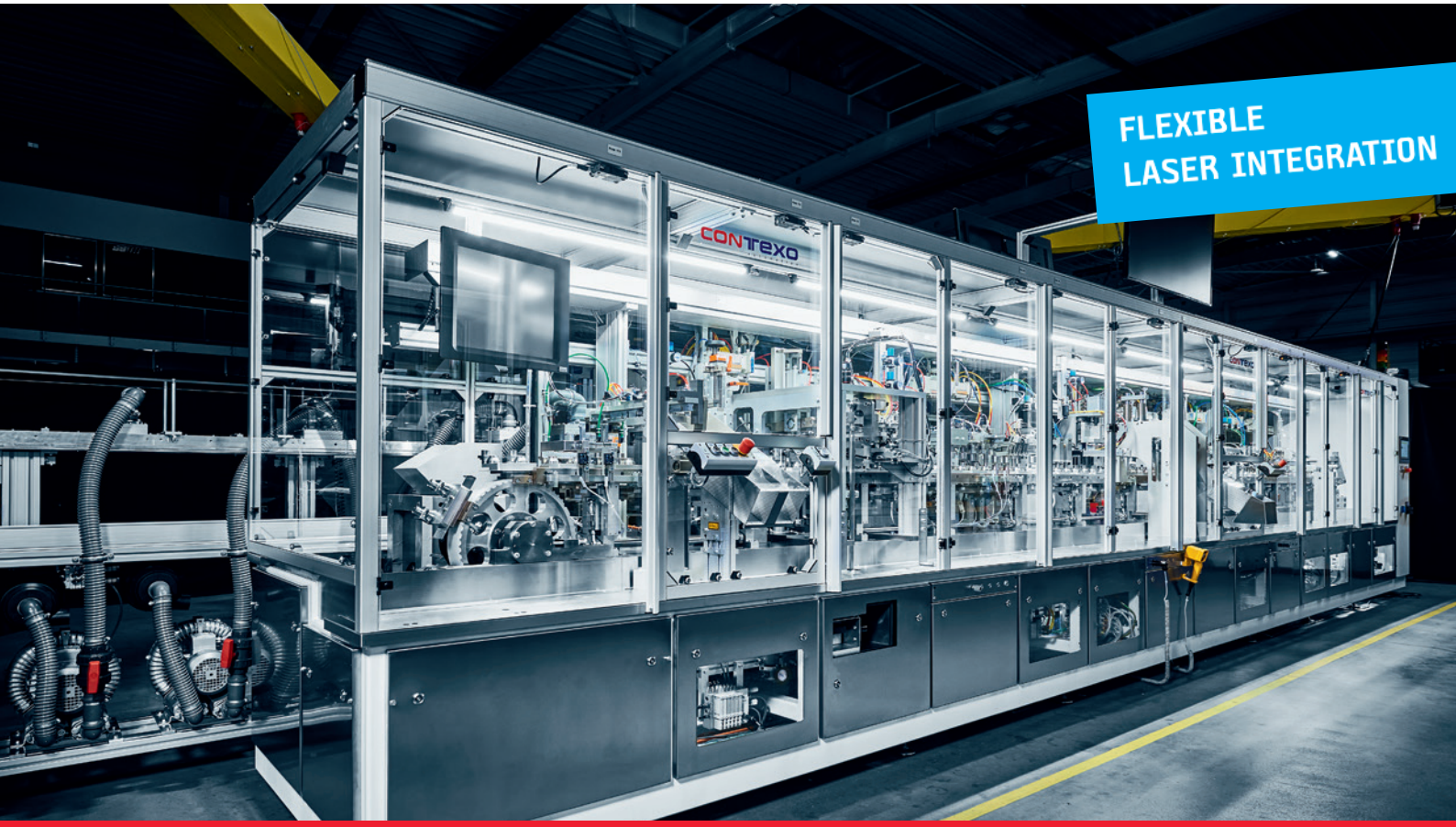

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CLEARING THE AIR(WAY): DEBUNKING THREE COMMON MYTHS ABOUT INHALED DRUG DELIVERY

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Dr Keat Theng Chow and **Susana Ecenarro** of **Roquette** explore three myths surrounding inhalation as a route of administration, clearing the way for a deeper understanding of one of pharma's most exciting areas for innovation.

The economic potential of inhaled therapies is truly breathtaking – and yet somehow misunderstood. Increasing urbanisation, worsening pollution in some regions and a growing global population mean rates of asthma, chronic obstructive pulmonary disease (COPD) and cystic fibrosis are on the rise.[1–4] As a result, the pulmonary and respiratory drug delivery market is expected to grow at a CAGR of 6.5% over the next four years to reach a value of US$87.7 billion (£65.3 billion) by 2029.[5]

At the same time, an advancing understanding of both pharmaceutical science and the patient experience are ushering in a new era of drug development where there are options beyond the traditional pill or capsule format. Inhalation as a route for drug delivery offers promising potential for broad drug development, both in and outside the treatment of respiratory diseases, yet inhalation remains a lesser-known route of administration compared with oral dosage or parenteral delivery.

WHAT IS INCLUDED IN "INHALATION"?

Before diving fully into the misconceptions surrounding inhaled drug delivery, it is first important to lay out the facts. Inhaled drug administration, at its core, refers to the delivery of drugs to the respiratory tract via inhalation through the use of various devices, such as metered dose inhalers (MDIs), dry powder inhalers (DPIs) and nebulisers.[6] Their value as highly effective

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therapies stems from their capacity for rapid systemic absorption and targeted delivery to specific regions of the lung, leading to rapid onset of action with a lower risk of side effects.[7]

While they all share the same end goal, the various technologies that sit under the umbrella of inhaled therapies vary significantly in their approaches, advantages and applicability. MDIs, for instance use an aerosol and propellant system, providing a convenient and portable option, though their effectiveness relies on a patient's individual self-administration technique.[8] Soft mist inhalers (SMIs) generate a fine, slow-moving mist, which can improve drug deposition and reduce the need for precise timing – a notable improvement over MDIs for patients with dexterity or co-ordination difficulties.[9] DPIs, meanwhile, are a range of breath-actuated devices that enable a wide array of drug types to be dispersed solely by the patient's inspiratory effort.[8] DPIs and SMIs only provide a simpler method of administration, but also eliminate the need for propellants.[10,11]

MYTH 1: INHALED ROUTES OF ADMINISTRATION ARE INHERENTLY UNSUSTAINABLE

As with many misconceptions, the perception of inhaled drug delivery as less than sustainable is based on a kernel of truth. Beginning in the late 1980s, efforts to reduce damage to the Earth's ozone layer eventually culminated in the banning of chlorofluorocarbons (CFCs); a class of chemicals that were widely used in refrigeration, air conditioning, and – most importantly for a pharmaceutical discussion – as aerosol propellants in MDIs.[12]

After CFCs were phased out, hydrofluorocarbons (HFCs), which do not contribute to ozone degradation, were introduced as an effective alternative for MDIs, but this switch unfortunately raised a fresh set of concerns.[12] While less harmful to the ozone layer specifically, HFCs are nevertheless potent greenhouse gases with a warming effect of up to 3,800 times that of carbon dioxide. Looking only at these more traditional delivery methods, the assertion that inhaled therapies are inherently harmful to the environment seems reasonable. However, when widening the view to other forms of inhalers, the myth begins to break down.

> "SIMPLY BY MERIT OF THE FACT THAT THEY DO NOT REQUIRE THE USE OF PROPELLANTS, THE AVERAGE DPI IS ESTIMATED TO HAVE A CARBON FOOTPRINT 18 TIMES LOWER THAN THAT OF AN EQUIVALENT MDI."

Since their introduction in the 1990s, DPIs have proven themselves to be an effective, and far more sustainable alternative to aerosol-propelled MDIs.[13,14] In fact, simply by merit of the fact that they do not require the use of propellants, the average DPI is estimated to have a carbon footprint 18 times lower than that of an equivalent MDI.[12]

The power of these propellant-free devices lies in their simplicity and flexibility. Under the wider category of DPIs are several subtypes, each with a unique dose metering and delivery action. Whether designed for single- or multi-unit dosages, pre-metered DPIs feature capsules, blister disks or blister strips that are punctured during use. This allows for the inhalation of pre-measured doses of an API accompanied by a carrier excipient. In contrast, doses delivered by reservoir-based DPIs are metered by the device itself, removing the need for capsules and blisters but also necessitating more complex inhaler designs with less opportunity for reuse.

> "AS A NON-REDUCING SUGAR ALCOHOL, MANNITOL OFFERS SUPERIOR CHEMICAL STABILITY COMPARED WITH REDUCING SUGARS SUCH AS LACTOSE, MAKING IT PARTICULARLY SUITABLE FOR CO-FORMULATING WITH SENSITIVE APIs."

From an environmental perspective – particularly regarding plastic waste – DPIs do not offer a marked improvement over MDIs beyond the elimination of potentially damaging aerosol propellants. The vital point, as is often the case in pharmaceuticals, is balance. Because DPIs require adequate inspiratory effort for effective drug delivery, they may not be suitable for patients with severely reduced lung function. In such cases, MDIs – especially when used with a spacer – or SMIs can offer a more reliable alternative. The task for pharmaceutical producers is therefore to optimise the manufacture of each form of inhaler to allow clinicians to make the right choice for their patients and the planet.[15]

MYTH 2: LACTOSE IS THE ONLY VIABLE EXCIPIENT FOR DPI FORMULATION

Put simply, this misconception is patently untrue. While it can still be argued that lactose is the most dominant excipient in the inhalation market,[16] it is far from being the only carrier that has proven effective in the delivery of APIs to the lungs, nor is it universally suitable. Not only is lactose known to be an allergen, but its dairy origins make it unattractive or even dangerous as an inhalation excipient for some patients.

Considering these drawbacks, pharmaceutical producers have begun to turn to alternatives such as mannitol. Widely used across various pharmaceutical dosage forms, mannitol is universally prized as a safe and effective excipient with broad patient appeal, and this is no different for DPI formulations. As a non-reducing sugar alcohol, mannitol offers superior chemical stability compared with reducing sugars such as lactose, making it particularly suitable for co-formulating with sensitive APIs, including proteins, peptides and drugs with primary amine groups, which are susceptible to Maillard reactions.[17,18]

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Mannitol's crystalline and non-hygroscopic nature also ensures better physical stability and lower moisture uptake than lactose, making it the superior choice for maintaining powder flowability, preventing aggregation during storage and achieving consistent dose delivery.[17,19] Furthermore, mannitol's ability to be engineered into various particle sizes and morphologies allows for optimisation of aerodynamic performance, contributing to improved fine particle fraction (FPF) and deep lung deposition of the co-formulated drug.[20,21]

Directly comparing the performance of the two excipients in an exemplary formulation makes mannitol's advantages over lactose clear. In a recent product study, researchers at Roquette assessed the maximum FPF achievable with either a lactose or a mannitol carrier, mixed to form an interactive mixture with the APIs salbutamol sulfate and budesonide. The results showed that the mannitol-based formulations produced a significantly higher FPF than lactose carriers, with the best performance achieved with PEARLITOL® 200 INH mannitol, a specialised grade optimised for use in DPIs.

Whether opting for a lactose or mannitol carrier, in the case of devices such as GSK's Rotadisk or Diskus, the choice of capsule material is equally crucial. As in the world of oral drug delivery, gelatin is the traditional material of choice for encapsulating drugs for inhalation, but here again the tide is turning. A growing body of research points to the unsuitability of gelatin capsules for encapsulating hygroscopic APIs such as salbutamol sulphate, which can draw moisture from surrounding materials, thereby becoming unstable.

"A GROWING BODY OF RESEARCH POINTS TO THE UNSUITABILITY OF GELATIN CAPSULES FOR ENCAPSULATING HYGROSCOPIC APIs SUCH AS SALBUTAMOL SULPHATE, WHICH CAN DRAW MOISTURE FROM SURROUNDING MATERIALS, THEREBY BECOMING UNSTABLE."

Just as mannitol provides an effective alternative to lactose, hydroxypropyl methylcellulose (HPMC) offers a plant-based solution to the drawbacks of gelatin capsules, displaying excellent chemical stability and a low moisture content of between 4.5% and 6.5%, which is ideal for hygroscopic APIs. As found by Roquette's researchers, combining the improved powder flow and aerodynamic performance of high-quality mannitol with the optimal stability and delivery characteristics of HPMC-based capsules results in an inhalation formulation that delivers more lifesaving drug to the lungs. This shows that lactose is far from being the only option for impactful inhaled therapies.[12]

MYTH 3: INHALATION IS ONLY SUITABLE FOR THE TREATMENT OF PULMONARY CONDITIONS

While it is true that inhaled therapies are predominantly employed in the treatment of pulmonary diseases, reflecting their primary clinical application, this does not define the full extent of their therapeutic potential. DPIs in particular are emerging as a promising platform for systemic drug delivery, extending their utility beyond the localised treatment of lung diseases to encompass applications such as vaccine administration and therapies for central nervous system (CNS) disorders.[17,22,23]

For vaccine delivery, DPIs have been shown to trigger local mucosal immunity – which is critical for protection against respiratory pathogens – and systemic immune responses, all without the use of off-putting needles.[24] This approach offers obvious benefits in terms of patient compliance and can also contribute to improved vaccine stability at ambient temperatures, simplifying logistics to give more people access to vital vaccines.[17,24]

In the context of CNS disorders, while direct nose-to-brain pathways are more often associated with nasal delivery, systemic absorption via the lungs can still contribute to drug concentrations in the brain by bypassing peripheral metabolism.[25] Recent research highlights the potential for inhaled delivery to achieve improved pharmacokinetics and rapid onset of action for various neurological drugs, exhibiting once again that the opportunities offered by DPIs extend far beyond respiratory conditions.[25]

Harnessing all this potential relies heavily on the development of advanced excipients.[17] Safe, effective and widely applicable carriers such as mannitol will play a critical role in addressing emerging formulation challenges, such as safeguarding the stability of moisture-sensitive APIs or effectively masking unpleasant flavours or odours to ensure that these exciting new forms of drug delivery do not leave a bad taste in patients' mouths.[17]

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A BREATH OF FRESH AIR

The common adage is that progress moves slowly in pharma, but that belies the substantial volume of cutting-edge research and discovery that takes place in labs around the world every day. The evolution of inhaled routes of administration from their aerosol propellant beginnings to DPIs capable of replacing parenteral vaccinations offers a perfect example of this dichotomy – both rapid and decade-spanning, both gradual and seismic. With millions more people each year requiring safe, effective and convenient treatments, no avenue for innovation should be closed to pharmaceutical formulators, particularly not one with as much multifaceted potential as inhaled therapies. So, with some of the more common myths debunked and the air beginning to clear, inhaled therapies could be poised for a whole new era of innovation.

"THE EVOLUTION OF INHALED ROUTES OF ADMINISTRATION FROM THEIR AEROSOL PROPELLANT BEGINNINGS TO DPIs CAPABLE OF REPLACING PARENTERAL VACCINATIONS OFFERS A PERFECT EXAMPLE OF THIS DICHOTOMY – BOTH RAPID AND DECADE-SPANNING, BOTH GRADUAL AND SEISMIC."

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Expert View

DELIVERING AND MAINTAINING OPTIMAL DPI PERFORMANCE

Chris Gilmor of Sanner Group considers the issues affecting dry powder inhalers and explains how formulators use a range of techniques to ensure dose dispersion and API detachment. He goes on to explain the importance of controlling the moisture level in these devices and how it can affect the drug delivery performance of the formulation.

Demand for inhaled therapeutics continues to grow steadily with estimates suggesting that the market for respiratory inhalers will reach a value of US$41.4 billion (£30.8 billion) by 2030.[1] Rising rates of respiratory illnesses, such as asthma and chronic obstructive pulmonary disease, are the primary driver of growth. Pressurised metered dose inhalers (pMDIs) and dry powder inhalers (DPIs) are the delivery devices of choice for these conditions. Hence, systemic drug delivery via the pulmonary route continues to attract considerable attention.

The high carbon footprint of pMDIs underlines an advantage of DPIs: drug delivery is patient- rather than propellant-driven, which has the additional benefit of co-ordinating dose delivery with patient inhalation.[2] Therapeutics for the treatment of respiratory illness dominate the DPI market with notable successes, including Breztri® Aerosphere (budesonide/glycopyrrolate/formoterol fumarate) (AstraZeneca), Respimat® (Boehringer Ingelheim) and Orbital™ (Aptar Pharma). However, achieving success with a DPI formulation, for either localised or systemic action, is far from straightforward. Advanced powder engineering techniques are routinely deployed to ensure necessary dose dispersion (Figure 1).

Figure 1: An individual using an inhaler.

DPI DEVELOPMENT AND SPECIFIC CHALLENGES

To reach the lower respiratory tract successfully, active drug particles must be less than 5 µm in size; 1–5 µm tends to be the target range. Unfortunately, within this target range, particles tend to be both cohesive and adhesive, with a marked tendency towards agglomeration. Developing an effective DPI that delivers particles of the required size, in the absence of any active device delivery mechanism, is therefore a substantial formulation and engineering challenge.

While carrier-free formulations are an option, a common strategy is to attach the fine API particles to larger carrier particles tens of microns in size. Lactose is a popular choice of carrier because it is well-tolerated by the lungs.[3] The API particles detach from the carrier during inhalation, which goes on to deposit predominantly in the oropharynx due to particle size.[4] With this approach, the carrier accounts for the bulk of the resulting formulation, making it easier to handle and to accurately dose the very small amounts of API required.

Formulators deploy a range of techniques to ensure dose dispersion and/or API detachment, manipulating both the composition of the formulation and particle properties – such as shape, surface morphology and charge – to achieve success. The particle engineering techniques deployed range from jet milling through spray drying and spray freeze drying to supercritical fluid technology, each associated with distinctly different physicochemical property development.[5]

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"TESTING EARLY FORMULATIONS IN A PROTOTYPE DEVICE IS ESSENTIAL, AS PRODUCT DEVELOPERS HAVE THE FREEDOM TO ADAPT BOTH DEVICE AND FORMULATION CHARACTERISTICS TO MEET DRUG DELIVERY GOALS."

Testing early formulations in a prototype device is essential, as product developers have the freedom to adapt both device and formulation characteristics to meet drug delivery goals. DPIs use complex internal geometries to translate the pressure drop induced by the inhaling patient into the energy needed for dose aerosolisation, pressure drop across the device being a key differentiator for device design. Iterative development ultimately leads to a formulation device optimised for drug delivery to the lungs for a given API. Yet this is a complex, fine-tuning exercise.[6]

As a result, DPI products are relatively sensitive. They require protection from the external environment, notably from the ingress of moisture but also potentially from oxygen. The requirement is to ensure optimum shelf life and reliable performance, regardless of location. This requirement is also reflected in US FDA guidance relating to stability, which indicates that testing should include both long-term storage at 25°C/60% relative humidity (RH) and at 30°C/65% RH for one-half of the proposed expiration dating period.[7] Understanding the impact of moisture on DPI effectiveness and taking steps to mitigate any potential deterioration are critical for successful product development and use.

EXPLORING THE IMPACT OF MOISTURE ON DPI PERFORMANCE

The moisture level is widely recognised as playing an important role in powder behaviour and can have a significant impact on how a DPI formulation behaves, thereby compromising drug delivery. The low density, high porosity and small size of many DPI particles result in a relatively large specific surface area, making them susceptible to moisture adsorption and a corresponding change in physicochemical properties. Generally, higher moisture levels reduce the amount of drug that reaches the lungs by promoting agglomeration and compromising dose dispersion. However, there are a range of factors that influence the response to moisture of any given formulation, notably the preparation method and the potential for electrostatic effects.[5,6]

In terms of preparation technique, jet milling is a ubiquitous process across the pharmaceutical industry. It uses a highly compressed gas to force energetic high-speed collisions both between particles and with the vessel walls. These comminution processes tend to produce particles prone to having high surface energy and electrostatic charge, with a relatively high concentration of amorphous content. On storage at high humidity, this content can crystalise, thereby promoting agglomeration.[5,8] Similarly, spray drying may produce relatively hygroscopic, somewhat amorphous particles, particularly with lactose-based formulations.[4] Thus, the optimal particle properties achieved through precise process control may be compromised by suboptimal moisture control.

Such inherent process-related tendencies can be reduced by, for example, relaxing particles under controlled temperature and humidity immediately after jet milling, by coating the resulting particles and, in the case of spray drying, by co-spraying with a suitable excipient.[4,5] An alternative option is to select a preparation method, such as supercritical fluid technology, that tends to produce particles with greater crystallinity and fewer amorphous sites.

Preventing moisture ingress to the product is a primary focus. However, excessively dry conditions can also be problematic due to exacerbated electrostatic effects. DPI formulations can pick up electrostatic charge by triboelectrification during formulation preparation, product manufacture and the aerosolisation processes associated with product use, as particles undergo collisions between themselves and interact with the surfaces of processing equipment or the device. Highly charged particles may flow poorly, adhere to device surfaces and/or fail to maintain content uniformity, making electrostatic charge control essential for effective drug delivery.[9]

Water is a highly effective conductor of electrical charge, which is why electrostatic charge is much less likely to accumulate under conditions of higher humidity. A RH of 40% is routinely quoted as the cut-off figure above which sufficient moisture is present to effectively earth a product and minimise electrostatic effects. However, this is a generalised figure. Individual formulations, manufactured in different ways, differ with respect to the electrostatic charge they pick up (typically via triboelectrification), their ability to

"THE MOISTURE LEVEL IS WIDELY RECOGNISED AS PLAYING AN IMPORTANT ROLE IN POWDER BEHAVIOUR AND CAN HAVE A SIGNIFICANT IMPACT ON HOW A DPI FORMULATION BEHAVES, THEREBY COMPROMISING DRUG DELIVERY."

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discharge it and the extent to which moisture levels can be elevated to tackle the issue, given other sensitivities to moisture.

In summary, the optimal environment for any given DPI with respect to moisture content depends on an array of physicochemical properties and may vary considerably from product to product. It is not always possible to prevent exposure to high or variable humidity, particularly during product use. Yet moisture control that is well matched to the product requirements can safeguard and optimise DPI performance during routine storage and use.

ENSURING EFFECTIVE MOISTURE CONTROL

The best strategy for protecting any given DPI is dependent on the device involved. There are essentially three types of DPI: single dose, multi-unit dose and multidose reservoir. With a single-dose device, the patient inserts a capsule containing the formulation immediately prior to use. Multi-unit dose devices, in contrast, come preloaded with multiple doses held individually within compartments of a blister pack or cartridge, while in a multidose reservoir, formulation is metered from a single reservoir at the time of use.[3] Each type of product offers different opportunities for moisture control.

Figure 2: Desiccant sachet used to manage moisture.

"THE OPTIMAL ENVIRONMENT FOR ANY GIVEN DPI WITH RESPECT TO MOISTURE CONTENT IS DEPENDENT ON AN ARRAY OF PHYSICOCHEMICAL PROPERTIES AND MAY VARY CONSIDERABLY FROM PRODUCT TO PRODUCT."

For example, capsules for single-dose devices are commonly made of gelatine or hydroxypropyl methylcellulose (HPMC), which protect the formulation from moisture ingress. HPMC capsules, which have a moisture content of between 4.5% and 6.5 % at 35–55% RH, are particularly effective, offering excellent protection against moisture ingress and robust puncturing performance across a range of relative humidities. As such, they may be the preference for hygroscopic products.[10,11] Gelatine capsules, in contrast, pick up water more easily, reaching a moisture content of between 10% and 16% at 35–55% RH.

Primary packaging offers a clear opportunity for moisture control within inhaler packaging to control moisture levels and, in some cases, to additionally address the secondary issue of oxygen ingress.[12] Placing drop-in desiccants, such as desiccant sachets, into the aluminium packaging pouch in which the DPI is supplied is also common practice to safeguard inhaler performance prior to initial use by the patient.

The preceding strategies are analogous to those used for oral solid dosage products using drop-in desiccants (Figure 2). DPIs, however, present the additional opportunity to fit desiccant into the device itself. The range of suitable, commercially available desiccants for DPIs includes silica gel, molecular sieves, activated clay, calcium oxide, calcium sulphate and zeolites. More rarely, a humectant may be used, such as a modified desiccant that can both absorb or release moisture, thereby enabling the maintenance of specified RH, which is a highly desirable characteristic for DPIs. In either case, the desiccant or humectant must, of course, be arranged within the device to prevent any possible contact with the drug.

By deploying the right desiccant technology, in one or more of these ways, DPI manufacturers can safeguard product stability and prolong shelf life while, at the same time, help to ensure consistent performance over the lifetime of the product.

SUPPORTING DPI DEVELOPMENT

Controlling the moisture level in a DPI is crucial, as it can significantly affect the drug delivery performance of the formulation. This article makes a clear case for determining a target level for moisture control on a product-by-product basis for DPIs and underlines the value of considering moisture control strategies at an early stage when the detailed design of the device is still in play. Effective moisture management requires technical know-how of desiccants and related packaging solutions that can be applied from the very beginning of the device development process.

ABOUT THE COMPANY

Sanner is a global German CDMO that develops and produces primary packaging and drug delivery systems for pharmaceutical and healthcare customers. Sanner has specialist knowledge in desiccants and effervescent packaging for the healthcare industry.

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Expert View

HOW CUTTING EDGE *IN SILICO* APPROACHES CAN REDUCE TIME AND RISK IN DEVELOPMENT OF INHALATION DEVICES

Dr Peter Harley, **Mariam Al-Amari** and **Matt Jones** of Crux Product Design explore how *in silico* approaches can transform pulmonary and nasal drug delivery device development, illustrating through case studies – spanning low-global-warming potential propellants, assembly robustness, device-user interaction, variability and capsule piercing dynamics – how simulation-led *in silico* approaches can improve understanding of device performance and identify risks early, reducing development costs and accelerating the path to more reliable, innovative and patient-friendly drug-device systems.

Pulmonary and nasal drug delivery are among the most complex routes of administration to engineer for successfully, as device performance is highly influenced by the nuances of both the drug formulation and user behaviour. Pressurised metered dose inhalers (pMDIs), dry powder inhalers (DPIs), soft mist inhalers (SMIs) and nasal delivery devices must operate reliably under a wide range of use scenarios, manufacturing variabilities and environmental conditions. Typically, development programmes rely heavily on limited sets of highly controlled physical tests on prototype devices that represent a small range of possible manufacturing variation. While these tests are necessary, they frequently fail to capture the complete variability of real-world use. This creates a significant gap in knowledge and understanding that can lead to expensive late-stage or on-market manufacturing and performance issues.

Conventional development programmes are usually constrained by the risks that engineers can anticipate. If there is limited understanding of the way that drug-device combinations will behave with real-world use, the breadth of risks that can be anticipated and mitigated with good design or manufacturing controls will also be limited.

Tolerance analyses and physical tests tend to be the workhorses of most design and development programmes. In practice, however, it is the unanticipated and poorly understood conditions – or combinations of conditions – such as component misalignments or deflections at tolerance extremes, storage outside expected ranges or non-ideal user technique, that most often drive late-stage device failure. These difficult-to-quantify extreme conditions and hidden variables can compromise device robustness, manufacturing reliability and therapeutic efficacy.

The use of *in silico* approaches to design and evaluate inhalation devices provides a deeper understanding of the modes and limits of performance. This understanding generates opportunities to create more successful designs, minimise development timelines and provide enhanced insights that can unlock next-generation engineering concepts. By applying computational modelling and simulation methods during device development, engineers can explore and understand vast arrays of virtual scenarios and configurations featuring varying geometry, materials, environments and user interactions, enabling them to predict device performance across the entire design space. *In silico* approaches can now be adopted from pre-design and development activities all the way through to supporting regulatory submissions, as outlined by the American Society of Mechanical Engineers (ASME) V&V40 standard.

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COMPUTATIONAL MODELLING AND SIMULATION IN THE DESIGN OF INNOVATIVE PULMONARY AND NASAL DRUG DELIVERY DEVICES

Next-generation development approaches are being enabled by rapidly evolving technologies. Device engineers can deploy *in silico* approaches to deepen their understanding of why a device behaves as it does and identify unknown and unexpected risks so that they can be mitigated before a device reaches critical development phases, dramatically reducing the risk of a development programme's failure. As computing power and the sophistication of software increases, *in silico* approaches are beginning to unlock previously unknown insights into device performance, as well as the robustness of the device-user interface. These approaches can be applied to a broad range of device types, including pMDIs, DPIs, SMIs and nasal sprays with delivery intended either to the lung (via the nose and mouth) or to the nasal cavity (and potentially onward to the brain).

Modern computational modelling and simulation (CM&S) techniques can cover a wide range of performance areas, as summarised in Table 1. Design and performance in these areas can be optimised to ensure that inhalation devices are robust, patient-friendly and have predictable performance in real-world conditions.

"AS COMPUTING POWER AND THE SOPHISTICATION OF SOFTWARE INCREASES, *IN SILICO* APPROACHES ARE BEGINNING TO UNLOCK PREVIOUSLY UNKNOWN INSIGHTS INTO DEVICE PERFORMANCE, AS WELL AS THE ROBUSTNESS OF THE DEVICE-USER INTERFACE."

Performance Area Examples	What Simulation Can Help Designers Understand
Thermal effects	Impact of temperature on device performance
Material variability	Impact of material strength variation on device performance
Capsule or blister evacuation	Efficiency and completeness of drug release
Deagglomeration	Powder break up
Drug deposition (upper airway versus deep lung)	Distribution profile and therapeutic targeting
Aerodynamic particle size distribution (APSD)	Particle size exiting the device and its effect on deposition
Resistance tuning	Optimisation for user inhalation profiles
Capsule robustness	Sensitivity to humidity, bevel geometry and robustness
Mouthpiece/nosepiece geometry	Seal with lips or nose, ergonomics and user comfort
Robustness under external effects	Gravity, blocked inlets, tolerance extremes, device orientation and freefall drop
Nasal delivery positioning	Effect of position in the nose on deposition
Breath profile robustness	Impact of pressure drop and user-to-user variability

Table 1: Performance areas addressable by *in silico* approaches.

USING *IN-SILICO* APPROACHES TO DE-RISK DEVICE DEVELOPMENT

Identifying Risks Associated with Low-GWP Propellants in pMDIs

With existing propellants such as HFC-134a and HFC-227ea accounting for a significant proportion of the carbon footprint of the pharmaceutical industry, the drive to move to low carbon alternatives is strong. However, the switch to low global warming potential (GWP) propellants such as HFO-1234ze and HFA-152a has introduced new challenges for device developers – challenges that can be de-risked and understood using *in silico* approaches.

One relevant unknown may be related to a system's resuspension dynamics as the device is shaken. Understanding these dynamics through simulations can enable instructions for use, suitability assessments and predictions of dosing profiles and spray plume dynamics. These and similar risks can be better understood either before the first devices are built or following physical tests on a limited number of devices. The fidelity and accuracy of the simulation's predictions can be enhanced by using real-world data from users, captured using sensor-enabled devices, as inputs.

Decoding an Assembly Issue

Simulating components in their nominal geometry and positioning is incredibly valuable for understanding the detailed modes and mechanisms by which a device functions. However, certain failure modes only become apparent when components are considered at the extremes of their design tolerance. *In silico* approaches can be coupled with a design of experiments (DoE) approach to decode challenges such as failed assembly steps.

In such studies, virtual device populations are generated, simulated and examined to unveil multifactor drivers on key assembly steps across the full range of relevant tolerances (Figure 1). This can involve developing simulations to assess in excess of 1,000 virtual assemblies. Importantly, creating physical prototypes that represent even a very small number of these tolerance combinations can be

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challenging, time consuming and expensive. By using a simulation-DoE approach, statistically significant variables can be extracted, enabling existing tolerance definitions to be challenged, part costs to be reduced and the assembly process to be improved to maximise yields with minimised downtime.

Understanding Device-User Robustness

It is widely reported that pMDIs suffer from significant deposition in the mouth and throat of a patient. When a patient uses any type of inhaler, the angle at which they hold the device in their mouth or nose will have a noteworthy impact on the final drug lung deposition. Without recruiting a single participant, *in silico* approaches can be used to determine the sensitivity of the device to non-ideal user actuation, such as a patient accidentally pointing the nozzle towards their tongue; simulating this exact scenario has shown that lung deposition could swing from 6–8% of the metered dose, to <1% for a worst-case mouth/throat impaction (Figure 2).

Deep lung localised deposition can be modelled using next-generation numerical lung modelling, further enabling the ability to estimate the best- and worst-case deposition profiles for a range of patients, which in turn can inform predictions of drug efficacy variability that may be seen during clinical trials. Then, flipping the requirement to targeted deposition, the same *in silico* techniques can be deployed to understand the robustness of nasal dosing to targeted zones to support the next generation of devices capitalising on the nose-to-brain delivery pathway.

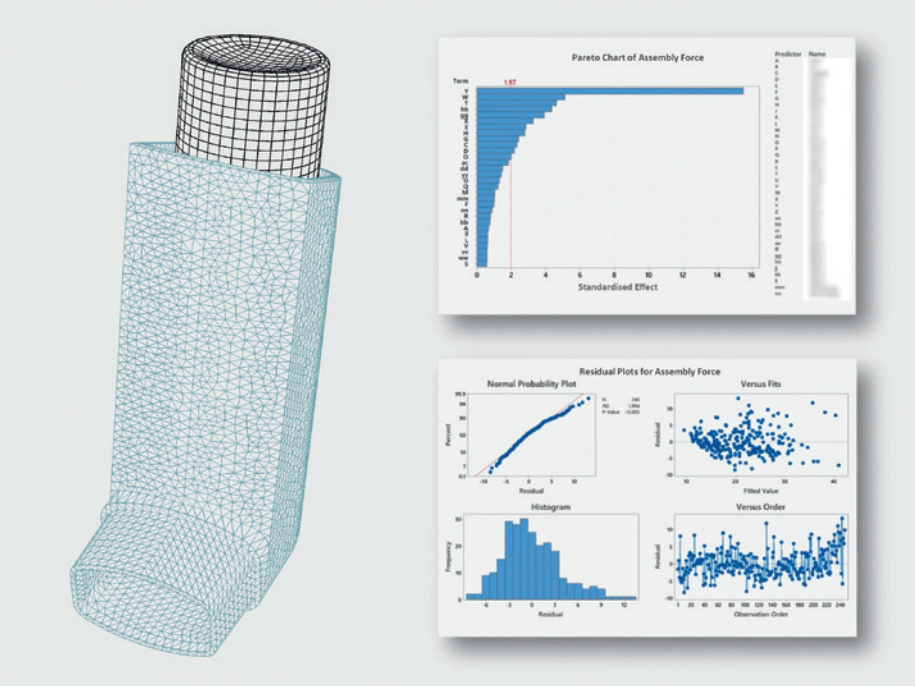
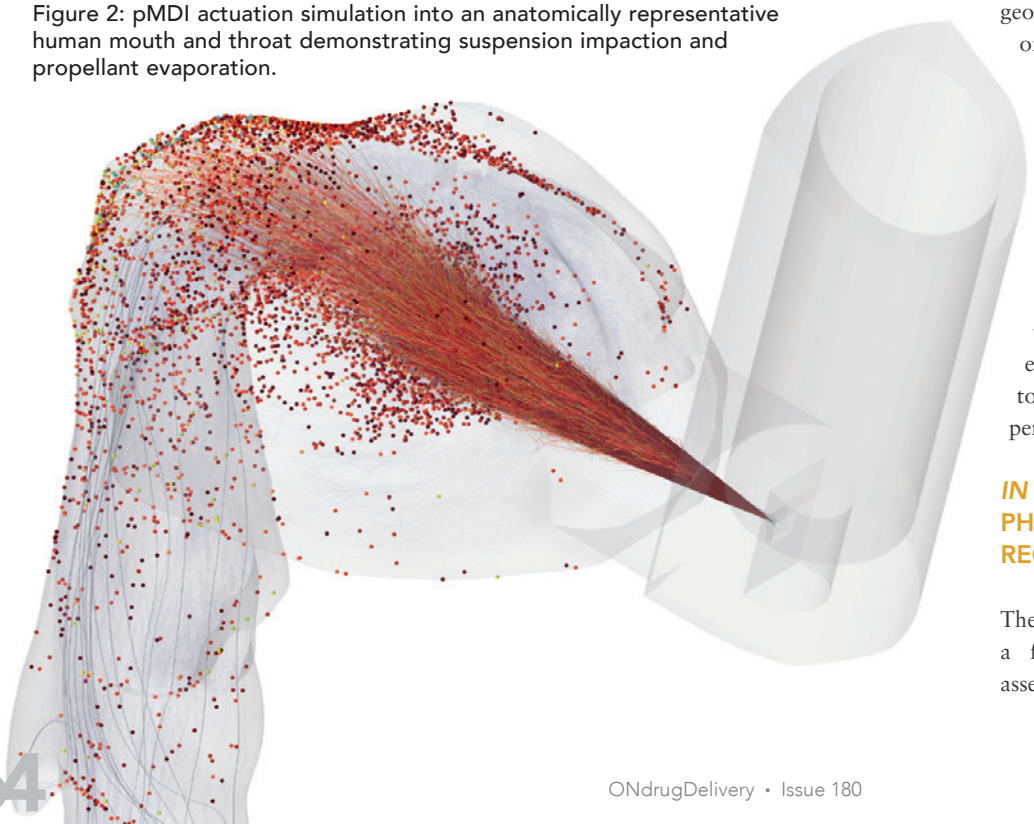


Figure 1: Assembly steps can be simulated to understand the effect of component tolerance variation, allowing prediction of the impact of new tooling being introduced, for example.

Figure 2: pMDI actuation simulation into an anatomically representative human mouth and throat demonstrating suspension impaction and propellant evaporation.



Exploring DPI Capsule Piercing Risks

Capsule piercing success is typically experimentally assessed via powder evacuation measurements. However, the mechanism of piercing and subsequent design variables of interest are difficult to understand experimentally. CM&S can be used to determine ideal piercing geometry, as well as to uncover the risk of powder migration immediately post puncture. CM&S can also enable rapid exploration of system variables on overall system performance, with example variables being capsule material strength, piercing geometry and component tolerances (Figure 3). Again, these techniques can be used both to optimise design before tooling investments, to provisionally explore device performance, and to understand why a prototype is not performing as expected after production.

IN SILICO PLUS ADVANCED PHYSICAL TESTING FOR REGULATORY SUBMISSIONS

The ASME V&V40 standard provides a framework to support the credibility assessment of models generated using *in silico*

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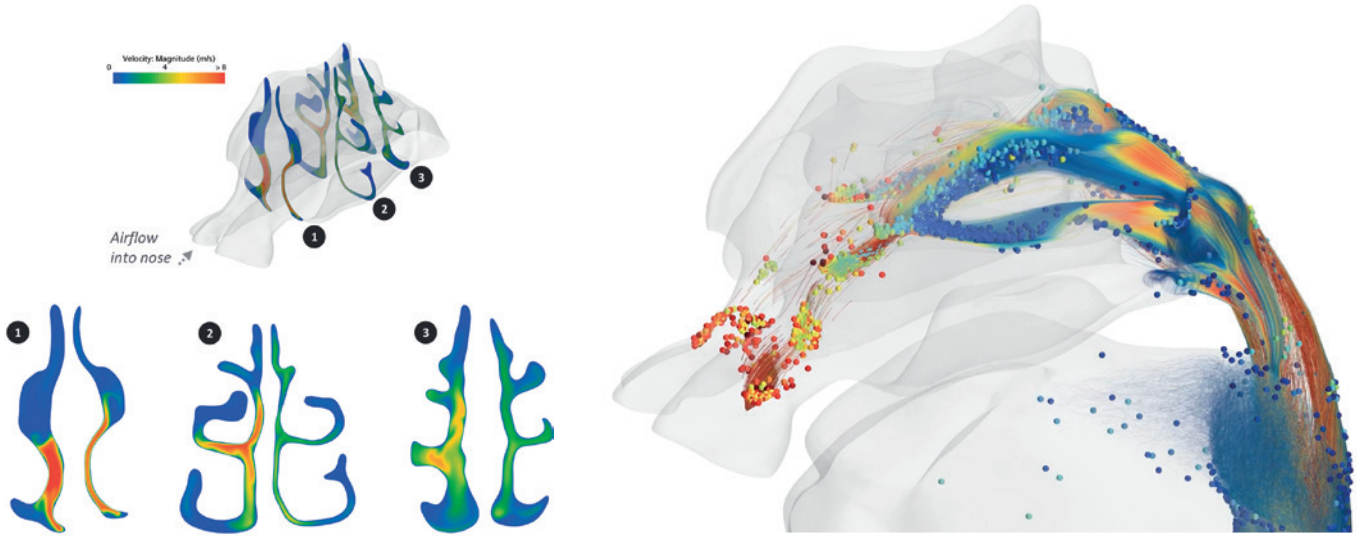

Figure 3: DPI inhalation simulation into an anatomically representative human nasal passage demonstrating flow paths and powder deposition patterns.

approaches, with an aim of integrating the modelled outputs as regulatory evidence. Interpretation of V&V40 for any given scenario requires subject matter experts to review the context of use (COU) with respect to the Question of Interest. Establishing credibility goals and designing a relevant V&V40 plan requires an in-depth understanding of not only the simulated physics, but also the risk associated with the COU. Modelling experts routinely develop a range of simulations that replicate standard testing, an example being the robustness of the actuation counter to ensure target functionality is achieved, as described in ISO 20072.

Alongside pushing boundaries in simulation, it is important to step beyond the standard physical test methods to develop devices that are reliable and robust in the full variety of real-world manufacturing and use scenarios. For example, the next-generation impactor (NGI) test was designed and introduced in the late 1990s and adopted widely in the early 2000s – now, more than 20 years later, it is often as far as developers go in understanding the delivery performance of their drug-device system. By embracing the latest testing technologies and method developments, it is possible to further enhance analysis and understanding of device performance and robustness, while also providing further credibility for *in silico* simulations (Figure 4).

As an example, laser diffraction testing is regularly used in specialist test laboratories to characterise aerosol performance (Figure 5). Coupling this with *in silico* approaches can enable a rapid assessment

Figure 4: Anatomically representative human nasal passage airflow ducting used to quantify deposition patterns in experimental characterisation campaigns.

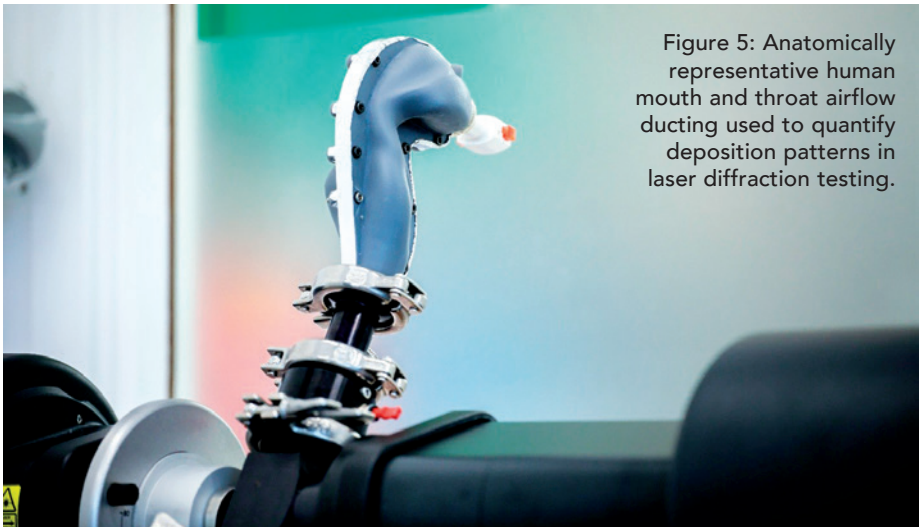

Figure 5: Anatomically representative human mouth and throat airflow ducting used to quantify deposition patterns in laser diffraction testing.

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of a device's ability to aerosolise its formulation and provide a direct link to the predicted anatomical deposition patterns. Furthermore, anatomically representative geometries can be introduced into the test method such that the characteristics of the aerosol after impaction in the mouth and throat can be captured and used for higher fidelity deep-lung simulations. This capability to front-load development programmes with sophisticated de-risking activities ensures that when the time comes for final design verification (DV) and clinical testing, the performance is well understood and the risk of encountering costly issues is dramatically reduced.

Once an *in silico* model's credibility has been established, virtual populations unlock the ability to complement DV testing with qualified virtual results. Depending on the COU and risks associated with the model-based decision making, these simulated virtual populations can enable test quantities to be reduced, saving significant effort in the production of real-world devices.

CONCLUSION

Embracing the latest technologies across *in silico* techniques alongside advanced experimental methods can provide an avenue to revolutionise existing device development methodologies, with the ultimate objectives of:

- Developing a deeper understanding of how drug-device-patient systems behave and why, unlocking enhanced insights to enable better designs
- More rapidly optimising designs and minimising prototyping tooling loops, resulting in reduced time to market
- Reducing late-stage and on-market challenges caused by a lack of insight and understanding, de-risking the development programme.

The examples and case studies summarised here indicate the range of opportunities available in the pulmonary and nasal delivery device space, where physics-based modelling and simulation and advanced physical testing can not only help identify risks and potential

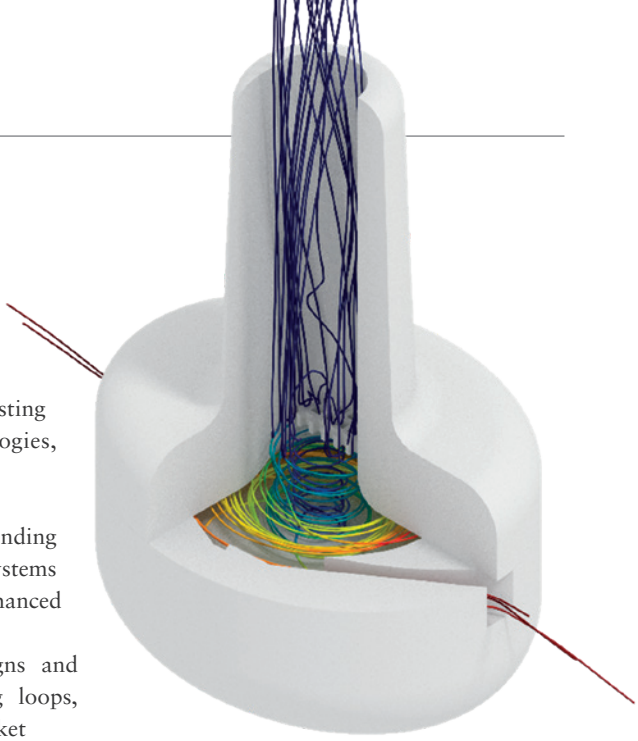

Figure 6: Example of a DPI airflow simulation used to tune device resistance and understand powder transport.

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mitigations but also deepen understanding of drug-device-patient systems to unlock novel thinking for the next generation of device technologies (Figure 6). Introducing *in silico* approaches can also automate evidence generation, reducing costs and accelerating development.

ABOUT THE COMPANY

Crux Product Design is a technology-driven consultancy specialising in drug delivery and healthcare innovation. The company partners with leading pharmaceutical companies to develop inhalers, injection devices, wearables and novel delivery systems. Its multidisciplinary team combines engineering, sciences, human factors and design expertise to turn complex challenges into successful products, certified to ISO 13485, ISO 9001 and ISO 14001 standards, as well as an Ecovadis Gold rating.

Dr Peter Harley

Peter Harley, PhD, is Head of Technology at Crux Product Design, leading a multidisciplinary team of experts in applied sciences, simulation, data analytics, machine learning and life sciences that operates across the drug delivery sector and is the sitting Chair of the NAFEMS Medical Device & Life Sciences simulation working group. Dr Harley has a background in the automotive and consumer electronics industries, where simulation is key to rapid development and de-risking, and therefore reduced time to market. He now translates technologies into robust investment opportunities in the medical device and pharmaceutical spaces, aiming to deliver accurate digital twins via *in silico* approaches, develop forensic post-processing techniques and drive sustainable artificial intelligence modelling techniques.

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Matt Jones, Engineering Director at Crux Product Design, sits on the board of Crux and has responsibility for the Mechanical, Electronics and Software Engineering departments and the Applied and Life Sciences departments. A mechanical engineer by training, he has over 20 years' experience in leading multi-disciplinary teams and supporting clients through all stages of the development process, from devising product strategies and roadmaps, through design and evaluation, to detailed support of manufacturing scale-up and beyond. A named inventor on 47 patents, Mr Jones has device development experience covering a wide range of technologies and routes of administration and has worked on a number of multi-award winning and successfully marketed devices.

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INHALED OLIGONUCLEOTIDES – THE FUTURE FOR RESPIRATORY DISEASES

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Dr Philippe Rogueda of **Merxin Ltd** discusses the therapeutic potential promised by oligonucleotides and presents the case for prioritising the inhalation route as the ideal delivery mechanism for these drugs, highlighting how direct delivery to the lungs via devices such as dry power inhalers or soft mist inhalers can maximise the therapeutic efficacy and minimise the side effects of these exciting drugs.

In the vast universe of the human genome, a small fraction – only about 1.5% – is dedicated to coding for proteins, the building blocks and machinery of our cells. Of these proteins, only a minority have active sites that can be targeted by traditional medications, leaving a vast number of diseases beyond the reach of conventional therapies.[1] This limitation has ushered in the era of oligonucleotides, a revolutionary class of therapeutics that promises to unlock new treatments by targeting previously inaccessible proteins within our genetic material.

Oligonucleotides, short sequences of synthetic DNA or RNA, are designed to interact with our genetic machinery, allowing for the precise modulation of gene expression. By either blocking harmful proteins from being made or correcting genetic messages, these molecules offer a new pathway to treat a myriad of conditions. With the potential to target over 10,000 proteins, oligonucleotides represent a leap forward in medicine, providing hope for diseases once deemed untreatable.

The journey of oligonucleotides from concept to therapeutic reality has not been without challenges, especially in delivering these fragile molecules to the right part of the human body. This article focuses on one of the most promising avenues for oligonucleotide delivery – inhalation into the lungs. Direct lung delivery offers a non-invasive route to treat respiratory conditions, maximising therapeutic effects while minimising systemic side effects.

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OLIGONUCLEOTIDES FOR RESPIRATORY CONDITIONS

Oligonucleotide therapies have shown remarkable efficacy against respiratory conditions through their mechanism of modulating intracellular gene expression. There are currently 71 oligonucleotide molecules in the development pipeline for respiratory conditions, and the diseases they target can be grouped into three distinct categories:

- Genetic disorders, such as cystic fibrosis (CF)
- Inflammatory diseases, such as asthma and COPD
- Lung infections, such as coronavirus infections.

To date, the majority of oligonucleotides for respiratory conditions in development are delivered parenterally or through inhalation (Figure 1).[2] An important aspect of maximising the therapeutic effect of the oligonucleotide – with or without the appropriate delivery cargo – is the identification of an efficient route of administration. Parenteral administration presents numerous challenges to naked oligonucleotide delivery,[3] including:

- Short half-life due to rapid nuclease degradation[4]
- Rapid clearance from the kidney due to small size[4]
- The need to cross cellular barriers
- Unwanted side effects
- Risk of needlestick injuries and blood-borne diseases
- The requirement of trained personnel for administration
- Sterile formulations.

Another interesting challenge is that oligonucleotides can accumulate in off-target tissues following parenteral administration, but local delivery mitigates this problem. Many side effects can be minimised with a lower dose of oligonucleotides, and local delivery allows for lower doses. In the case of respiratory infections and lung diseases, pulmonary delivery would allow the optimal dose to be delivered directly to the target tissue, minimising side effects and accumulation in off-target tissues.

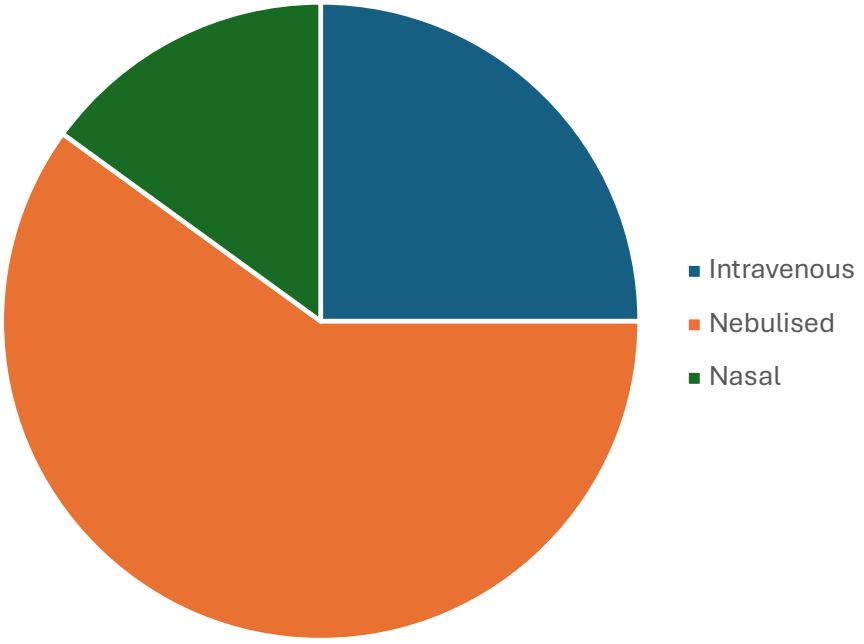

Figure 1: Routes of administration for oligonucleotides intended for respiratory conditions.

DELIVERING OLIGONUCLEOTIDES DIRECTLY TO THE LUNGS

While it has clear and powerful benefits, direct delivery of oligonucleotides to the lungs is not without its challenges. Mucociliary clearance, for example, is a protective mechanism by which inhaled particles are removed from the lungs. This is a rapid process, meaning that the overall time available to inhaled RNA for absorption is restricted, and has been shown to trap and promote the removal of RNA delivery vectors to great effect, therefore presenting a formidable barrier to inhaled oligonucleotide delivery.[5]

Moreover, when dealing with lung diseases, the mucosal barrier is often more difficult to bypass when compared with a healthy state. For example, in CF and COPD, the viscosity and elasticity of the mucus is greater, making RNA penetration harder.[6] Furthermore, inflammation of the airway can cause mucin hypersecretion, leading to a greater number of mucins available to potentially bind RNA delivery vectors and impede their delivery.[7]

Delivery vectors can be used to traverse the lung mucus barrier, such as placing the RNA in chitosan nanoparticles, which have mucoadhesive properties – prolonging the contact time between the nanoparticle and mucosal surface, thereby enhancing the absorption of its drug cargo.[8] Another delivery strategy is to densely graft polyethylene glycol (PEG) onto the surface of the nanoparticles – a process termed PEGylation. This strategy has been widely investigated to overcome the mucus barrier for several routes of delivery including vaginal, oral, ocular and nasal. Via PEGylation, a hydrophilic and neutrally charged polymer has been shown to effectively enable nanoparticles that would have otherwise been immobilised to diffuse rapidly through lung mucus,[9] and its success is well-documented in the literature over the past decade or so.[3,6]

Another barrier that must be overcome for effective pulmonary delivery of RNA is the presence of alveolar macrophages. These cells operate as part of the immune system to protect the body by engulfing and degrading inhaled foreign macromolecules

"WHILE IT HAS CLEAR AND POWERFUL BENEFITS, DIRECT DELIVERY OF OLIGONUCLEOTIDES TO THE LUNGS IS NOT WITHOUT ITS CHALLENGES."

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through phagocytosis.[3] The primary method employed for macrophage evasion so far has been particle engineering. The aim has been to produce large, porous particles with a physical diameter of less than 10 µm, making them too big for phagocytosis but leaving them with a small aerodynamic diameter due to their lower density. Hitting this sweet spot represents one option to evade macrophages in the deep alveolar regions.

It is uncommon to deliver "naked" oligonucleotide molecules, as they are unlikely to overcome the challenges associated with each route of administration. Therefore, another consideration is ensuring that the inhalation delivery method can properly aerosolise the carrier vector as well. Potential carrier vectors include:

- Bioconjugation – covalent binding of oligonucleotide to:
  - Lipids (e.g. cholesterol)
  - Peptides
  - Aptamers
  - Antibodies
  - Sugars (e.g. N-acetyl galactosamine)
- Nanocarriers:
  - Liposomes
  - Exosomes
  - Spherical nucleic acids
  - DNA nanostructures.

SELECTING THE RIGHT INHALATION DELIVERY DEVICE

Beyond engineering the oligonucleotide structure and delivery vector, an important consideration is selecting the right delivery device for inhaled oligonucleotide therapies. To date, there are several platforms for effectively delivering oligonucleotide therapies to the lungs, and each platform has its own advantages and disadvantages.

Dry Powder Inhalers

Dry power inhalers (DPIs) are propellant-free, portable and easy-to-use inhalation devices. They store drug formulation as a dry powder, typically in capsules, blisters or a reservoir, and rely on the patient's inspiratory effort to aerosolise the powder and deliver it into the upper respiratory tract. However, one of the concerns in the powder formation of nucleic acids is their stability – individual powder-forming techniques involve several physical treatments, such as heating, agitation, atomisation, freezing and drying, some or all of which may reduce the structural and functional integrity of nucleic acids under physical stresses, such as shear force and extreme temperatures.

To mitigate the destabilisation of nucleic acids during powder formation, non-viral vectors, such as cationic lipids and polycations, have commonly been included as powder components for their stabilising effects, as well as their high transfection efficiency through electrostatic complexing.[10] However, from the viewpoint of safety, it is also desirable to produce the powders of naked nucleic acids without using vectors.[10–12] Merxin Ltd's capsule-based DPI, MRX003, and multidose DPI, MRX006, are ideally suited for the delivery of oligonucleotide formulations. MRX003 is already available on the European market, trusted by prescribers and patients alike for its reliability and ease

"SMIs ALLOW FOR A SLOWER RELEASE OF AEROSOL COMPARED WITH TRADITIONAL INHALERS, RESULTING IN A WEAKER DESTRUCTIVE EFFECT ON DRUGS. THIS GENTLER APPROACH IS IDEAL FOR DELIVERING OLIGONUCLEOTIDES."

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of use. MRX006, designed for advanced therapeutic applications, supports triple combination therapies and enables the separation of two or more incompatible formulations through its dual blister strip mechanism.

Soft Mist Inhalers

A soft mist inhaler (SMI) is a convenient, portable inhalation device that delivers the drug as a fine, slow-moving mist. To achieve this, a spring provides mechanical energy that forces a solution containing the API through a fine nozzle, producing a particle cloud or soft mist, which allows relatively easy inhalation deep into the lung. SMIs allow for a slower release of aerosol compared with traditional inhalers, resulting in a weaker destructive effect on drugs.[13] This gentler approach is ideal for delivering oligonucleotides.

For example, in one study by Wang *et al*, a small interfering RNA (siRNA) loaded in a polymer lipid nanoparticle intended for lung cancer treatment was aerosolised using a commercially available SMI. The authors measured changes in particle size and polydispersity index (PDI) to determine the physical stability of the siRNA molecules after aerosolisation via the SMI. The particle size had a slight increase (approximately 10 nm) and the PDI also increased – although it remained under 0.26, indicating that the particle sizes were still uniform. Importantly, the nanoparticles loaded with siRNA showed good physical stability when aerosolised via the SMI.[14]

In a direct comparison of SMIs with nebulisers, Miao *et al* compared the delivery of lipid nanoparticles (LNPs) containing mRNA using different atomisation methods:

- Two fluid nozzle
- Jet nebuliser
- Ultrasonic nozzle
- SMI
- Vibrating mesh nebuliser.

The authors found that the SMI was a softer atomisation method than the vibrating mesh nebuliser. According to transmission electron microscopy, the morphologies of the LNPs were maintained after the SMI aerosolisation; however, the LNPs tended to be destroyed and reassembled to form the LNPs with larger size distribution after vibrating mesh nebulisation. Additionally, the entrapment and transfection efficiencies of the LNPs were superior after the SMI atomisation compared with after using vibrating mesh nebulisers, as demonstrated by *in vivo* and *ex vivo* fluorescence imaging of the RNA after administration of doses. There was approximately a four-fold increase in concentration following SMI administration, compared with the vibrating mesh nebulisers.[15] MRX004, Merxin Ltd's SMI illustrates this perfectly. While delivering three to five times the dose of a traditional nebuliser,its mild aerosolisation process simultaneously protects delicate molecules, such as oligonucleotides, preserving their integrity and optimising therapeutic outcomes.

CONCLUSION

As oligonucleotide therapies continue to redefine the boundaries of respiratory medicine, the importance of effective pulmonary delivery cannot be overstated. From overcoming biological barriers to selecting the right inhalation device, every step in the development process plays a critical role in ensuring therapeutic success. Merxin Ltd's inhaler devices, MRX003, MRX004 and MRX006 are purpose-built to meet the unique demands of oligonucleotide delivery, offering both protection and precision in administration. For companies developing oligonucleotide molecules, it is critical to consider their choice of delivery route and how delivery of their drug candidates could be enhanced by tailored device technology, such as those offered by Merxin Ltd.

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"FROM OVERCOMING BIOLOGICAL BARRIERS TO SELECTING THE RIGHT INHALATION DEVICE, EVERY STEP IN THE DEVELOPMENT PROCESS PLAYS A CRITICAL ROLE IN ENSURING THERAPEUTIC SUCCESS."

Dr Philippe Rogueda

Philippe Rogueda, PhD, co-founded Merxin Ltd in 2015 and currently serves as Chief Business Officer. His expertise spans across multiple facets of the inhalation field, particularly with dry powder and soft mist inhalers. Dr Rogueda's passion lies in the development of soft mist inhaler technology, particularly for biologics, which he believes holds immense potential to revolutionise the delivery of inhaled therapies. With over a decade of experience in the inhalation sector, Dr Rogueda's deep knowledge and innovative approach to inhalation technologies make him a key figure in advancing medical device development for improved drug delivery systems.

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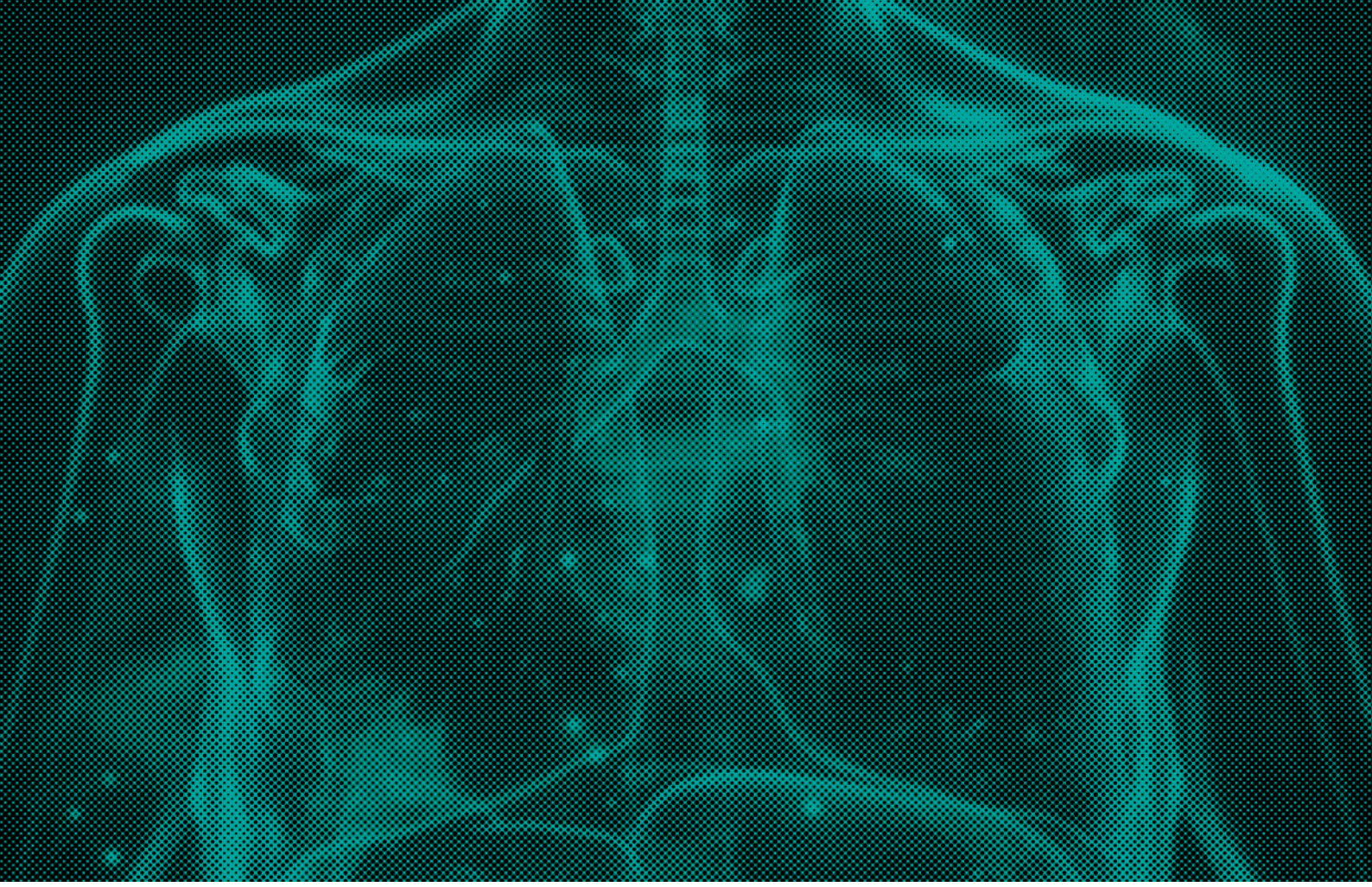

EXPANDING OPPORTUNITIES FOR INHALED DRUG DELIVERY

nanoform
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Dr Gunilla Petersson of **Nanoform** considers the challenges associated with efficiently delivering drugs to the lungs and the potential of nanoparticle-based formulations to achieve high lung deposition of small molecules and biologics, using gentle particle processing techniques that enable the delivery of sensitive drugs.

Whether to treat localised respiratory disease or because the lung provides a fast, non-invasive and efficient route of delivery for systemic effect, the administration of pharmaceuticals to the lung is gaining increased attention; even beyond treatments for globally prevalent diseases such as asthma and chronic obstructive pulmonary disease (COPD). Although well established and accepted, oral and parenteral administration of drugs can require much higher doses than topical administration to the lung, which can lead to significant unwanted systemic exposure and the resulting side effects. However, the lung also presents unique challenges due to the complex structure of the airways, the presence of various protective barriers and the need to generate a suitable aerosol using an inhaler.

Respiratory diseases represent one of the world's biggest health concerns and are a leading cause of death worldwide.[1] They include conditions such as COPD (which the World Health Organisation lists as the world's third leading cause of death),[2] pneumonia, asthma and lung cancers. Several rare lung diseases, such as pulmonary arterial hypertension and cystic fibrosis, are life -shortening and have a severe impact on quality of life. Idiopathic pulmonary fibrosis is deadly, and patients are given only a short life expectancy following a diagnosis.

Systemic delivery via the lung is often applied to obtain a fast onset of action. This is advantageous in treating the symptoms of neurological disorders such as Parkinson's disease; can reduce feelings of agitation

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in bipolar disease and schizophrenia; and can help alleviate acute and breakthrough pain, for example, in cancer patients. For diabetics, inhaled insulin provides a less invasive alternative to frequent needle use.

The main advantage of delivering by inhalation directly to the lung to treat respiratory disease is that the actual site of action is targeted, allowing for localised treatment that minimises the required dose and any systemic side effects, with a tenfold higher lung dose reported for several drugs reformulated for lung delivery.[3] A reduction in dose is particularly advantageous for delivering novel or very expensive biologics or gene therapy vehicles, which have dramatically changed the development landscape for research organisations focused on respiratory diseases.

LUNG DRUG DELIVERY SYSTEMS: A CHALLENGE FOR PULMONOLOGISTS & FORMULATORS

For an inhaled particle or droplet that contains a drug to reach a disease target in the lung, it must first negotiate the relatively narrow and bending regions of the mouth, throat and perhaps the upper airways to avoid unintended deposition there, before reaching the specific disease targets or receptor locations. The anatomical structure of the airway system is complex and is characterised by 23 generations of branching airways ending with the alveoli. Diseased airways may be constricted, collapsed, partially blocked by mucus or bacteria biofilms, or scarred and stiffened. All these abnormalities may inhibit efficient breathing and oxygen uptake by the patient.

Particles are mostly deposited in the lung by inertial impaction, sedimentation or diffusion. Inertial impaction tends to occur in the upper airways when particles' velocity and mass cause them to collide into the airway walls. Sedimentation occurs more often in more peripheral airways, and is driven by gravity, so it can be influenced by breath-holding to allow gravity to have an effect. Diffusion occurs through Brownian motion and is relevant to particles of less than 1 µm in diameter.[4,5] Thus, regional deposition in the throat or lungs is controlled mainly by the patient's breathing patterns and particle size.

"MACROPHAGES INGEST AND DESTROY INVADING PATHOGENS, AS WELL AS DRUG PARTICLES IN THE 0.5–6 µm RANGE. CONSEQUENTLY, PARTICLES OF LESS THAN 500 nm ARE AN ADVANTAGE IN AVOIDING THIS FORM OF CLEARANCE."

To avoid losses and irritation in the throat and to maximise peripheral lung deposition, small particles combined with a low inhalation flow rate is recommended. Particles may, if deposited in the upper airways, provoke coughing during inhalation treatment,[6] thus limiting drug penetration and causing the patient discomfort. Conversely, efficient powder dispersion from a dry powder inhaler (DPI) often requires a strong inhalation effort and an increased risk that particles will not pass further than the back of the mouth and the throat.

Interstitial lung diseases that lead to severe breathing difficulties and consistent coughing, such as pulmonary fibrosis, are located mainly in the distal alveolar region, which is reached via the smallest airways in the lung. Consequently, to access this region meaningfully, ultrafine particles are required in combination with a device that permits a slow breathing technique.[7] This requires both highly dispersible powders in DPIs or a type of active liquid inhaler, usually a nebuliser. To minimise patient effort needed and treatment time, high drug load formulations are preferred, as these reduce the powder amount to inhale and the risk for coughing.

The physiological barriers of the lung are mainly mucociliary clearance, whereby cilia remove excess mucus, including any adhered drug particles not yet dissolved for absorption, and macrophageal clearance. Macrophages ingest and destroy invading pathogens, as well as drug particles in the 0.5–6.0 µm range. Consequently, particles of less than 500 nm are an advantage in avoiding this form of clearance.[8] Three-dimensional biofilms generated by invading bacteria limit the access of antibiotics or other drugs that need contact with the lung epithelium. Bacteria may hide in the biofilm network with poor drug (antibiotic) access and, consequently, the infection becomes chronic through repeated flare-ups. This may also lead to antibiotic-resistant bacteria.

Many drugs will be quickly absorbed and cleared unless they are designed for extended residence time in the lung, which permits once or twice per day inhalations. One design strategy is to use poorly soluble drugs like the well-established inhaled glucocorticosteroids. However, it is a delicate balance to design drugs that have an optimal dissolution rate and lung retention, which is why formulators often need help balancing the *in vivo* drug concentration versus time profile (Figure 1).

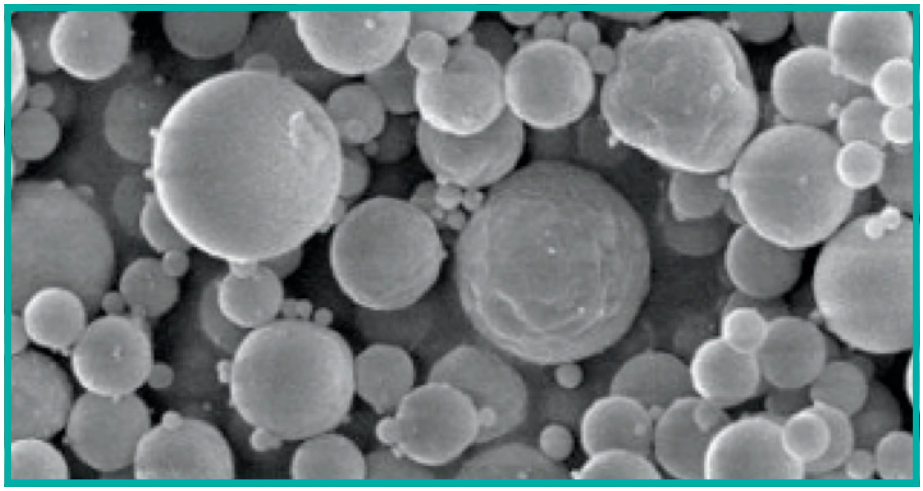

Figure 1: Direct manufacturing of particles suitable for inhalation.

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Device and formulation interactions is another area of consideration for lung delivery. Any powder formulation will have to be of the relevant particle size for lung access, i.e. less than approximately 5 µm (Figure 2), which often makes powder "sticky" and prone to agglomerate and/or adhere to surfaces within the inhalation device. The patient's inhalation force is used to disperse the powder during a short breath (1–3 seconds), which means that a certain minimum inhalation capacity is required to achieve efficient powder delivery. This is a concern for patients with severely diseased lungs, and sometimes liquid formulations delivered via nebulisers must be used instead.

Liquid inhalers do not offer a fast treatment time and, when poorly soluble drug particles held in a suspension are administered, a significant fraction of the drug will be retained in the device. The main reason for this retention is due to the small holes in the nozzle filtering out the particles. There is also a risk of clogging in the micron-sized nozzle holes. For some nebulisers, these phenomena lead to an even slower delivery rate using traditional micro-suspensions.

NANOFORMED API FORMULATIONS

The potential advantages of nanoformulations for effective delivery to the lung of small molecules and biologics are numerous and have been reflected in the literature. Firstly, nanoformulated drugs improve dissolution, solubility and bioavailability due to their smaller size and higher surface area:

- Poorly soluble drugs milled to nanoparticles avoid accumulation in the lung due to faster and complete dissolution[9]
- A nebulised glucocorticosteroid nanosuspension has a faster dissolution and absorption rate in the lung versus a microsuspension of the same drug[10]
- Mucociliary clearance of drug particles reduces the dissolved and bioactive fraction of poorly soluble drugs less for smaller particle sizes.[11]

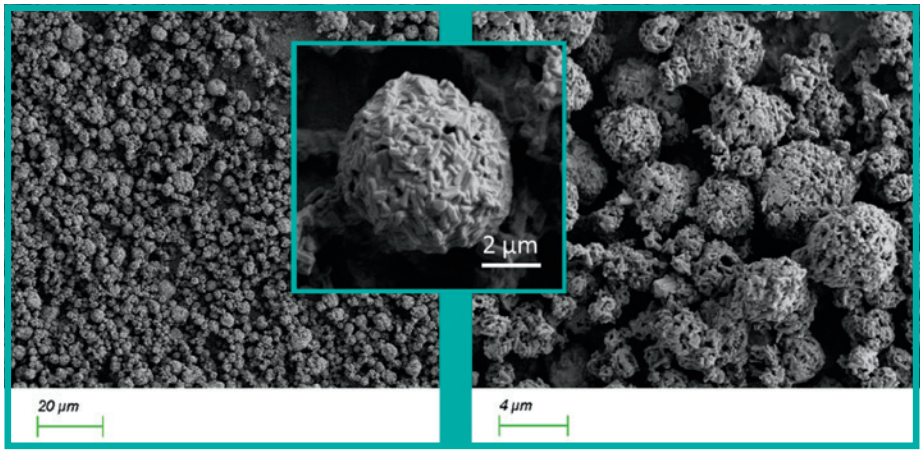

Figure 2: Nanoclusters of inhalable size.

Ensuring the dispersion of sticky, ultrafine (nano and sub-micron) particles enables inhalation of drugs, particularly for severely diseased lung patients:

- Efficient delivery of dry nanoparticles has been accomplished by spray-drying of nano-embedded microparticles (NEMs)[12,13]
- Nanoclustering of crystalline nanoparticles to porous particles of inhalable size reduces particle cohesion and increases the powder dispersibility for inhalation[14,15]
- Nanoclusters of submicron size may also be encapsulated in spray-dried matrices such as NEMs.

Nanoformulations allow for improvement of drug adhesion and penetration related to biofilms and mucus in infected lungs:

- Nanoparticles have been widely studied to overcome biofilms; however, their surface charge needs to be controlled to be positively charged[15,16]
- Nanoparticles have been found to have more efficient mucus penetration in the lung.[17]

Higher drug load in dry powders minimises the patient inhalation burden of repeated inhalations of high powder amounts, e.g. inhaling from five to ten capsules in sequence.

- Formation of nanoclusters for inhalation are highly dispersible with low amounts of excipients, even with just the pure drug.[12]

Reduced throat deposition and a higher lung dose by combining highly dispersible powders with low flow rates:

- A study comparing differently sized, inhaled particles indicates that cough reflexes could be avoided using smaller particles to reduce throat and upper airway deposition[6]
- *In silico* modelling and *in vitro* patient-simulated testing show a clear effect of particle size and inhalation flow rate on both throat and lung deposition.[18]

Finally, there is an increase of delivered dose output using liquid nebulisers:

- Delivery of budesonide as nanoparticles over microparticles increases the average dose (≤5 µm) two-fold[19]
- Control of drug particle shape – avoiding needle-shaped particles – is very important when using nebuliser delivery.[20]

NANOFORM'S CAPABILITIES

Nanoform's proprietary Nanoforming technology enables the production of small-molecule API nanoparticles without excipients and solvents. The manufacturing process is based on the precipitation of the API from a supercritical carbon dioxide ($scCO_2$) solution, where precise process parameter control can lead to tight particle-size distribution and the desired crystalline or amorphous form. It is the only technology capable of manufacturing nanoparticles at the lower end of the

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Nanomilling (wet bead milling)	Nanoforming
Multiple process steps; bead milling, separation of beads and nanoparticles, potential need for recrystallisation of surfaces post milling.	One step, semi-continuous process forming dry, crystralline or amorphous nanopartices.
Higher energy, top-down process to break microsized crystals into nanosized with poor control of particle characteristics, potential amorphous surface material, risk of crystal defects. For very small particles, long milling times and cooling may be needed. Particles are re-circulated many times in the milling system.	Gentle, bottom-up process to improve control of particle size distrubution, shape and crystallinity/polymorph. Drug to be soluble in CO_2 (predictive tool availability). No recirculation of particles during processing.
A complex process with many process parameters to adjust for each new API; bead material and size, rotation speed, time, drug media content, stabilisers (steric and/or electrostatic stabiliser), stabiliser content, mill movement pattern, temperature control, particle harvesting.	CO_2 removed after formation of particles. No organic solvent used and potential to recycle CO_2.
Liquid medium selected for bead milling should not dissolve the drug, to control and maintain particle size distribution during milling and storage.	Low amounts of surfactant needed to facilitate re-dispersion.
Significant amounts of polymers and/or surfactants (often two) to stabilise suspension during milling and storage.	Nanoforming process step as part of an aseptic process line.
For use in suspension formulations (injectable, inhalable, ophthalmological), need to sterilise the suspended particles.	For use in suspension formulations (injectable, inhalable, ophthalmological), need to sterilise the dry particles. An aspirational objective is sterilisation using $scCO_2$.
Liquid intermediate (nanosuspension), chemical/physical stability may be challenging, risk for mircobial growth.	Dry intermediate (nanoparticles or nanoaggregates in bulk), chemical/physical stability likely less challenging, no microbial growth.

Table 1: The Nanoforming process versus conventional nanomilling.

"IT IS THE ONLY TECHNOLOGY CAPABLE OF MANUFACTURING NANOPARTICLES AT THE LOWER END OF THE NANO RANGE WITHOUT SOLVENTS, EXCIPIENTS AND COMPLEX PRODUCTION PROCESSES."

nano range without solvents, excipients and complex production processes. Nanoparticles may be used in liquid suspensions or encapsulated into a spray-dried matrix for inhalation, either as individual nanoparticles or as submicron nanoclusters, e.g. to facilitate blending of different drugs in drug combinations or to tune drug dissolution rate.[21]

The Nanoforming process used for inhaled nanoparticles is compared to the use of conventional nanomilling in Table 1. The Nanoform Biologics platform addresses water soluble, sensitive drugs such as peptides, proteins and oligonucleotides. Traditionally, spray drying is attempted as the first formulation route for DPIs, but due to the demanding process – which involves heat to evaporate the solvent (water) immediately after droplet formation – as well as during secondary drying in the cyclone where particles are collected, some drugs do not tolerate spray drying. The platform uses nebulisation to form the droplets and dry gas at room temperature to remove the water phase, which is less stressful for sensitive drugs.

The platform process used for inhaled particles of standard excipients (including peptides and proteins) delivers material with similar characteristics as spray-dried material. These include a tight particle size distribution around a target of 2–3 µm, high dispersibility with fine particle fractions of up to 80% of the delivered dose and high drug loads in the range of 50–80% of the protein with a particle density suitable for efficient filling of standard capsules or blisters. Formation of protein aggregates was confirmed to be low using size exclusion chromatography, both post-processing and during storage.

Nanoform has experience in nanoforming and formulating APIs for lung delivery. Studies have seen the generation of particles for incorporation into clients' formulations and include:

- Crystallisation of poorly soluble, difficult-to-crystallise drugs for inhaled delivery
- Nanosuspension, including nanoclusters, for nebulisation using a vibrating mesh inhaler
- Direct manufacturing of particles of peptides/proteins in the appropriate size range with optimal aerosolisation performance using the Nanoform Biologics platform.

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Dr Gunilla Petersson

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Expert View

DISSOLUTION TESTING FOR ORALLY INHALED PRODUCTS: CONFRONTING THE CHALLENGES, REALISING THE POTENTIAL

As dissolution testing rises up the agenda for orally inhaled product developers, **Jamie Clayton** at Copley Scientific explores drivers behind its adoption and key considerations for developing a robust and relevant method.

Dissolution testing has long been a topic of interest for the inhaled drug product community. This is logical given that, following deposition in the lung, dissolution is the first step towards absorption and therapeutic effect for both locally and systemically acting drugs.

Over the last couple of decades there have been ongoing efforts to define appropriate methods for orally inhaled product (OIP) dissolution testing, but there are currently no compendial specifications. However, in recent years, the US FDA has released several Product-Specific Guidances (PSGs) that highlight dissolution testing as part of an enhanced suite of *in vitro* methods that can be deployed to eliminate the requirement for a clinical endpoint study – an important development. As a result, today's OIP developers find themselves with a growing body of background information and regulatory incentive to pursue dissolution testing. A clear understanding of the challenges and opportunities is essential to navigating this evolving landscape.

"TODAY'S OIP DEVELOPERS FIND THEMSELVES WITH A GROWING BODY OF BACKGROUND INFORMATION AND REGULATORY INCENTIVE TO PURSUE DISSOLUTION TESTING."

MOTIVATIONS FOR OIP DISSOLUTION TESTING

While much attention is often given to the potential of pulmonary drug delivery as a route for systemic drug delivery, the reality is that OIPs for the localised treatment of respiratory illness dominate the commercial marketplace. At least a quarter of a billion people worldwide are estimated to be living with asthma alone, and it is still under-diagnosed and under-treated, notably in low- to middle-income countries.[1] More effective and inexpensive OIPs for the treatment of respiratory illness are a high priority for healthcare providers the world over.

Against this backdrop, three motivations for dissolution testing can be identified:

- To accelerate the development of generic products
- To improve the efficiency and efficacy of OIPs for localised action
- To optimally employ the pulmonary route for systemic drug delivery.

Demonstrating Bioequivalence

The FDA's strategy of releasing PSGs "to facilitate generic drug availability"[2] is progressively establishing clearer pathways for the demonstration of bioequivalence (BE) for a growing number of OIPs. Most of these products are locally acting, a complicating factor in clinical endpoint studies that can lead to unreliable and/or unpredictable data. Given that such studies are also time-consuming, recent PSGs outlining a streamlined pathway almost exclusively reliant on *in vitro* methods are welcome.

This alternative pathway calls for seven *in vitro* studies to demonstrate BE, expanding on the traditional battery, by incorporating realistic aerodynamic particle size distribution (APSD) and dissolution testing. As reliance on *in vitro* data increases, so too does the need for rigour with respect to capturing any potential for clinically significant difference. Given the time and cost benefits of eliminating a clinical endpoint trial, these PSGs provide a strong incentive for the implementation of dissolution testing within OIP development.

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"AS RELIANCE ON *IN VITRO* DATA INCREASES, SO TOO DOES THE NEED FOR RIGOUR WITH RESPECT TO CAPTURING ANY POTENTIAL FOR CLINICALLY SIGNIFICANT DIFFERENCE."

Developing a Better Understanding of *In Vivo* Behaviour

Beyond its regulatory value, dissolution testing is becoming increasingly important as a tool to better understand what happens to inhaled drug particles post-deposition, and how to control this behaviour in ways that enhance local efficacy and/or systemic drug delivery.

The overarching goal for pulmonary drug delivery is to disperse the dose to a respirable particle size, with 5 µm typically stated as the upper limit for pulmonary deposition. This explains the critical role of APSD measurement. Digging deeper, it is known that the APSD of the <5 µm fraction influences regional deposition within the lung and that the targeted deposition needs to be matched with the mechanism of action of the drug to maximise therapeutic effect.

For example, studies with three monodisperse salbutamol aerosols (mass median aerodynamic diameter (MMAD) -1.5, 2.8 and 5 µm) have demonstrated that, for patients with mild to moderate asthma, an MMAD of 2.8 µm is optimal with respect to bronchodilation. This is consistent with the understanding that finer particles (<5 µm) can penetrate the small airways where receptors for salbutamol are concentrated.[3]

Knowledge of where to deposit different drugs optimally, and how to do so, although incomplete, far exceeds understanding of the next steps towards therapeutic action. There are three possible fates for particles deposited in the lung:

- Dissolution and absorption, ultimately into systemic circulation
- Degradation via drug metabolism
- Removal via mucociliary clearance.

The relative rates of these processes are critical considerations for those seeking to:

- Extend the residence time of locally acting drugs at the site of action
- Accelerate and maximise systemic uptake, or, conversely, to minimise it
- Maximise the fraction of the delivered dose that has a clinical impact, relative to that lost/wasted.

Such goals align with efforts towards greater efficacy, improved cost-efficiency and effective systemic delivery. A growing push to deliver higher drug loads (especially for systemic drug delivery), increasing numbers of poorly soluble drug candidates and intense activity to realise inhaled biologics further augment the value of dissolution test data.

OSD DISSOLUTION: LESSONS FOR OIPS

Of course, the pharmaceutical industry is not new to dissolution testing. Therefore it is reasonable to see what can be learned from experiences of testing oral solid dosage (OSD) forms. The United States Pharmacopoeia (USP) Dissolution Methods Database[4] highlights the key parameters defined for methods for dissolution testing for OSDs and other pharmaceutical product forms. These include:

- Apparatus design
- Dissolution medium (e.g. composition, quantity, temperature aeration state)
- Apparatus-specific parameters (e.g. flow rate, agitator speed)
- Timeframes for testing (i.e. sampling times and total test time)
- Assay method (for quantifying dissolved drug).

In combination these factors define:

- How the sample and dissolution medium contact with one another
- The extent to which the dissolution medium mimics the clinically relevant chemical characteristics of the *in vivo* environment
- Whether testing is carried out under sink conditions or not
- The hydrodynamic regime applied during testing
- The sensitivity with which the concentration of dissolved drug can be detected
- The ability to robustly track the dissolution process (i.e. fast or slow).

All these issues are equally pertinent to OIP dissolution testing and can provide a valuable starting point as methods continue to evolve.

REPRODUCIBILITY VERSUS CLINICAL REALISM

The overarching context in any *in vitro* method development is the balance between reproducibility and clinical realism. Generally, improving clinical realism increases the complexity of a technique, which can reduce reproducibility and, by extension, differentiating capabilities. Given that OIP performance is further impacted by a range of patient-specific factors, there is also the risk that improving clinical realism for one patient population reduces it for another.

Debates around whether to apply sink conditions during OIP testing illustrate this point. Typically, OSD dissolution testing is carried out using a volume of dissolution medium at least three times greater than that required to form a saturated solution of the drug substance.

"A GROWING PUSH TO DELIVER HIGHER DRUG LOADS (ESPECIALLY FOR SYSTEMIC DRUG DELIVERY), INCREASING NUMBERS OF POORLY SOLUBLE DRUG CANDIDATES AND INTENSE ACTIVITY TO REALISE INHALED BIOLOGICS FURTHER AUGMENT THE VALUE OF DISSOLUTION TEST DATA."

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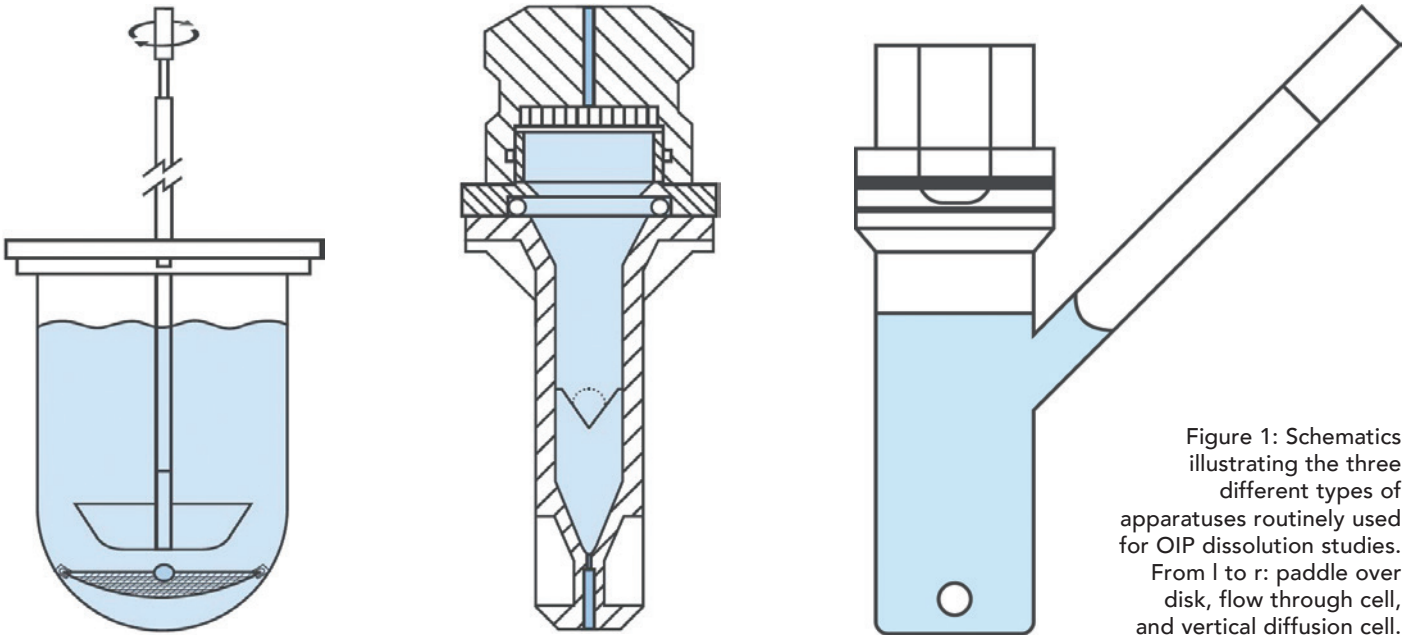

Figure 1: Schematics illustrating the three different types of apparatuses routinely used for OIP dissolution studies. From l to r: paddle over disk, flow through cell, and vertical diffusion cell.

Under these "sink" conditions, the bulk concentration of drug in the dissolution medium is too low to affect dissolution rate, eliminating a potentially confounding factor. For most OSD drugs, sink conditions are clinically relevant.

By contrast, the pleural fluid film that covers the surface of the lung amounts to a total volume of just 10–20 mL in a healthy patient.[5] The likelihood of sink conditions being clinically relevant is therefore questionable. While the volume of fluid into which the drug dissolves is small, the subsequent rate of drug absorption is also relevant. Theoretically, with sufficiently high permeability or absorption, sink conditions could prevail, despite the low fluid volume.

What can be asserted is that testing under sink conditions will deliver test data unaffected by bulk concentration, increasing the chances of good reproducibility. Testing with far lower volumes of dissolution medium may increase clinical relevance – or not. True clinical relevance would call for testing under conditions that accurately simulate the amount of fluid present, taking into account any change associated with disease state and, at the same time, allowing for permeability differences of the drug. The result: a more complex test set-up, greater scope for variability and, ultimately, lower reproducibility.

In a similar vein, there may be difficult choices to make over the composition of the dissolution medium. Options range from simple phosphate buffered saline to simulated lung fluid, which is usually a solution of minerals and salts with or without added surfactant. *In vivo*, the composition of lung fluid varies across lung regions and may also be impacted by disease state,[6,7] adding further complexity to the method design.

SURVEYING THE OPTIONS FOR OIP DISSOLUTION TESTING

A first point to note when considering options for OIP dissolution is that there are few commercially available solutions for those looking to establish in-house testing. Many of the experimental set-ups reported in the literature are custom made for specific studies. Nevertheless, the majority can be classified as follows (Figure 1):

- **Paddle Over Disk**: Modified versions of USP Apparatus 5
- **Flow Through Cell**: Modified versions of USP Apparatus 4
- **Diffusion-Controlled Cell**: Vertical Diffusion Cell or Transwell.

Regardless of apparatus choice, dose collection is an important first step. Here, consensus has converged on use of the fine particle dose (FPD), typically the sub-5 µm dose as determined by cascade impaction.[6–8] FPD is a well-established metric for OIP characterisation, so this approach is a good starting point with respect to both clinical relevance and alignment with existing practices.

Use of the FPD requires careful consideration of sample transfer from the dose collection device to the dissolution testing apparatus. Various solutions have been developed, but it is important to:

- Recognise the potential to disturb the precise aerodynamic regime in an impaction device
- Ensure effective transfer and consistent positioning within the dissolution apparatus.

"FPD IS A WELL-ESTABLISHED METRIC FOR OIP CHARACTERISATION, SO THIS APPROACH IS A GOOD STARTING POINT WITH RESPECT TO BOTH CLINICAL RELEVANCE AND ALIGNMENT WITH EXISTING PRACTICES."

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Returning to dissolution testing apparatus choice, diffusion-controlled cells hold the sample in a far smaller volume of fluid than alternative apparatuses, a favourable point with respect to replicating conditions within the lung. However, results can be difficult to interpret, notably the relative rate of diffusion and dissolution, and highly dependent on the properties of the selected membrane, as diffusion is the controlling mechanism.[6,7]

Paddle over disk and flow through cells enable the application of sink conditions. With paddle over disk, it is also possible to reduce the dissolution medium volume deliberately to simulate the impact of drug concentration build-up. Possible issues associated with the use of paddle over disk apparatuses include the potential for dead space beneath the sample holder and inconsistencies in sample positioning within the dissolution vessel. The need to ensure wetting of the sample can be met through appropriate membrane selection and choice of dissolution medium. Wetting can likewise be an issue with flow through cell designs, which can also suffer from air build-up around the sample holder, flow gradients and other flow rate-related dissolution effects.[6,7]

MEETING CURRENT OIP TESTING REQUIREMENTS

A key question in OIP dissolution testing is the extent to which any proposed method satisfies the requirements set out in PSGs, to "demonstrate discriminatory ability (e.g. ability to detect meaningful differences in formulation or manufacturing process, such as a difference in deposited drug particle size) in measuring the dissolution kinetics of the product".[9]

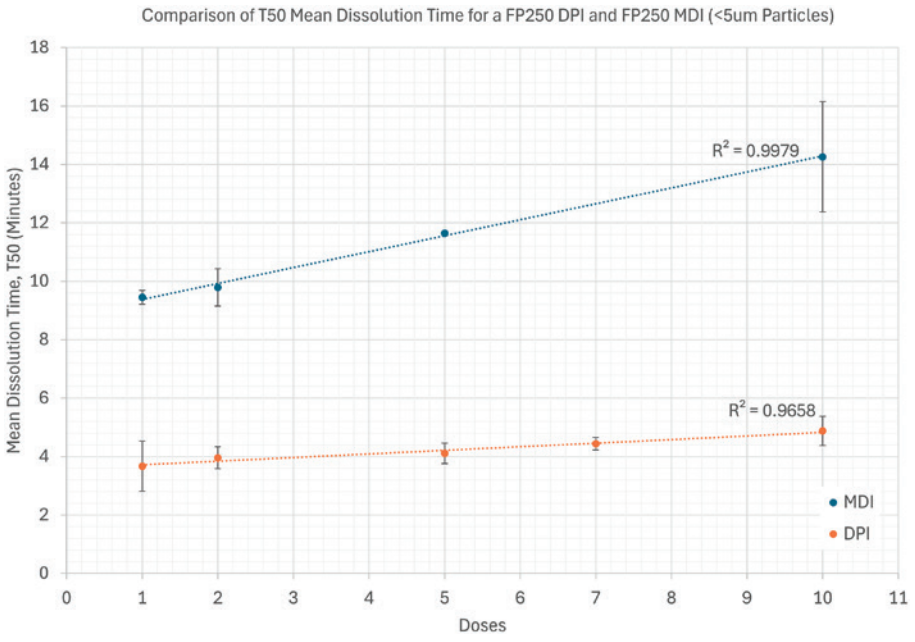

Figure 2: Example data contrasting the dissolution behaviour of FP delivered by MDI (Evohaler, GSK) and DPI (Accuhaler, GSK) measured using a paddle over disk apparatus for OIP dissolution testing (Inhaled Dissolution Apparatus, Copley Scientific).

Within this context, there is good reference data comparing the dissolution behaviour of fluticasone propionate (FP) delivered by metered dose inhaler (MDI) and by dry powder inhaler (DPI). Here, we have datasets made with different apparatus types and test methods.[10–12] All identify DPI-delivered particles as dissolving faster than those delivered by MDI, despite published APSD data indicating that MDI analogues deliver finer particles.[12] There is also evidence that this difference in dissolution rate correlates with observed differences in *in vivo* absorption rate,[10] highlighting the value of dissolution testing for OIPs.

Figure 2 shows data exemplifying the device-dependent dissolution behaviour of FP and illustrating a further factor in OIP dissolution testing – the effect of drug product loading. The high surface area of the lung, relative to that used for dose collection, make loading effects relatively unlikely *in vivo*. Conversely, the tendency for a sample to distribute non-uniformly on the collection surface of impaction devices, notably beneath nozzles, compounds the likelihood of drug-loading issues during FPD collection.

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In the dataset shown, there is some dependency on dose number, notably with the MDI, which has a higher FP recovery per dose; ten actuations of the MDI equate to a deposited dose of 800 µg of drug; the equivalent figure for the DPI is 500 µg. However, such effects are far outweighed by the degree of differentiation between the devices. Minimising the number of actuations within the constraint of assay viability – a standard approach for other forms of OIP testing – is a sensible strategy for mitigating such effects and maximising the method's capability for robust differentiation.

LOOKING AHEAD

Given the growing number of PSGs, OIP dissolution testing is likely to become more common, and there are already signs of its application for nasal drug products too. Developers looking for appropriately differentiating methods have commercially available equipment to use and valuable data to reference, as discussed here.

Beyond that, pioneers in OIP dissolution continue to advance test set-ups incorporating, for example, mucous gel layers and/or cell-based monocultures to better bridge *in vitro* to *in vivo*.[8] While not yet practical for routine testing, such solutions have the potential to elucidate our understanding of the *in vivo* processes to optimally deploy pulmonary drug delivery for the widest possible array of applications. Lessons already learned with OIPs will help to accelerate uptake in the nasal drug product arena, where opportunities for systemic delivery demand equally rigorous and insightful approaches.

ABOUT THE COMPANY

Copley Scientific is a manufacturer and supplier of inhaled product testing equipment and a major provider of testing systems for other pharmaceutical dosage forms. The company also supplies equipment for detergent testing. Copley's pharmaceutical product range includes testing equipment for all types of orally inhaled and nasal drug products – metered dose inhalers, dry powder inhalers, nebulisers and nasal products – with a focus on solutions for delivered dose uniformity and aerodynamic particle size distribution measurement. It also includes testers for tablets (dissolution, disintegration, friability and hardness), capsules, powders, suppositories, semisolids and transdermals. Used from R&D through to quality control, this extensive range of equipment is supported by a full validation and aftersales service. Copley works in partnership with specialist distributors, extending localised support across the world and providing expert help and training to every customer.

Jamie Clayton

Jamie Clayton is Chief Executive Officer at Copley Scientific, a leader in inhaler testing equipment, where he is responsible for driving innovation, strengthening customer relationships and guiding the company's continued growth. With many years of experience in material characterisation and life sciences, combined with a background in engineering, he brings a clear understanding of the challenges manufacturers face in developing reliable, high-quality products. Mr Clayton is committed to delivering practical, user-focused solutions and fostering collaborations that help scientists deliver safer and more effective treatments worldwide.

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Expert View

STRESS-TESTING INHALED MEDICINE SO PATIENTS CAN BREATHE EASIER

Dr Yannick Baschung discusses the benefits and challenges of orally inhaled and nasal drug products and examines how drug developers can stress test their products to improve regulatory success and patient safety, as well as how partnering with an expert CRO can provide an efficient way of performing critical characterisation testing.

Orally inhaled and nasal drug products (OINDPs) have long been a familiar sight on pharmacy shelves. From asthma inhalers to allergy relief nasal sprays, these devices provide patients with a comfortable option for fast-acting drug administration. Over the last decade, drug developers have become increasingly innovative in their use of the respiratory route, designing nasal flu vaccines for at-home administration and inhaled insulin to reduce reliance on needles when managing diabetes.[1,2] However, despite their apparent ease of use, OINDPs are challenging to manufacture behind the scenes. Ensuring consistent dosage and proper airway distribution of aerosolised compounds can pose a significant challenge.

CHALLENGES AND OPPORTUNITIES FOR OINDPs

Administration via the respiratory route offers an impressive range of advantages. The most apparent use case for OINDPs is for the treatment of respiratory conditions, where medicines can travel through the airways and coat affected tissues to treat respiratory conditions such as seasonal allergies, asthma or chronic obstructive pulmonary disease (COPD). Intranasal administration also provides an attractive route for drug delivery to brain tissues, as the unique physiology of the sinuses allows certain compounds to bypass the blood-brain barrier, which would otherwise filter them out.[3] Inhaled compounds are also rapidly absorbed, providing immediate benefits and saving lives, as seen with naloxone's ability to rapidly reverse an opioid overdose.

But that does not mean that inhaled medicines are not without their challenges. The anatomy and mucosal tissues of the respiratory tract have evolved to filter and trap dust and contaminants in the air that we breathe, and OINDP designs must account for this protective mechanism. Additionally, OINDPs are self-administered, so carefully measured spray patterns in the lab may look entirely different when a patient is using these devices at home. To ensure safety and efficacy, developers must design robust formulations and thoroughly evaluate device-formulation performance to achieve consistent dose delivery and distribution.

Creating the right formulation in which to suspend a drug product is a much more involved process than many people realise. To guide the formulation design, scientists can use solid state characterisation to develop a deep knowledge of the drug's properties. This can inform selection of the right excipients – molecules that are added to the drug formulation to stabilise the API, modulate viscosity or otherwise improve the formulation. To function as a spray, the final formulation needs to maintain a certain viscosity, but without aggregation, which can compromise dosing uniformity. The formulation must also protect the API from degradation to ensure the drug's efficacy remains unaffected.

STRESS-TESTING OINDPs

For OINDPs, formulation and device development must be approached as an integrated process. The performance of an aerosolised therapy depends on how effectively the formulation interacts with its delivery system, whether that's a pressurised metered dose inhaler (pMDI), dry powder inhaler (DPI), soft mist inhaler (SMI), nebuliser or nasal spray. Throughout development, specialised analytical studies are used to characterise critical performance attributes of the combined drug-device system.

> "OINDPs ARE SELF-ADMINISTERED, SO CAREFULLY MEASURED SPRAY PATTERNS IN THE LAB MAY LOOK ENTIRELY DIFFERENT WHEN A PATIENT IS USING THESE DEVICES AT HOME."

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For spray-based platforms such as pMDIs, SMIs and nasal sprays, parameters including spray pattern and plume geometry are evaluated to ensure consistent dose delivery. Additionally, aerodynamic particle size distribution is measured, typically using cascade impactors, to determine the fine particle dose and to assess how effectively and likely the aerosol is to reach the target regions of the respiratory tract. Together with emitted dose uniformity, these tests consider critical quality attributes, reflecting the influence of formulation properties and patient inhalation profiles on drug delivery.

To complement these tests, drug developers are increasingly employing anatomically realistic *in vitro* airway models that mimic the geometry of the human nasal passages or upper respiratory tract. These models help predict regional deposition and provide valuable insights into how a given drug-device combination product will perform under real-world conditions.

Alongside performance studies, developers assess whether impurities can migrate from the container closure system or delivery device into the drug product. OINDPs are considered to be among the highest risk dosage forms for extractables and leachables (E&L), as even trace amounts of foreign compounds can pose a major risk when inhaled directly into the lungs or nasal passages. Effectively analysing E&L requires multidisciplinary expertise in materials science, analytical chemistry and toxicology, combined with advanced instruments capable of detecting and characterising impurities at very low concentrations. This robust E&L testing is critical for both patient safety and compliance with stringent regulatory guidelines.

Many drug developers find that partnering with a CRO is the most efficient way to perform these important characterisation experiments. The right CRO partner has the appropriate facilities and equipment, along with the scientific personnel to interpret the results. Beyond these practical considerations, a high-quality CRO partner can help smooth out the drug development journey by finding creative solutions to formulation issues that are revealed during rigorous stress testing. With the right CRO partner, drug developers can feel confident in their product as they move from concept to commercialisation.

"A HIGH-QUALITY CRO PARTNER CAN HELP SMOOTH THE DRUG DEVELOPMENT JOURNEY BY FINDING CREATIVE SOLUTIONS TO FORMULATION ISSUES THAT ARE REVEALED DURING RIGOROUS STRESS TESTING."

CONFIDENCE WITH EVERY BREATH

OINDPs will continue to play an important role in the effective administration of therapies. They provide easy, effective and speedy means of delivering drugs locally to the respiratory system and hold promise for systemic delivery. However, good science rarely occurs in a silo. By partnering with CROs skilled in characterising and designing safe and reliable OINDPs, drug developers can be confident that their product will fulfil the promise of inhaled medicine.

ABOUT THE COMPANY

Solvias is a global provider of chemistry, manufacturing and control analytics to the life sciences industry. Its expert team combines decades of experience with regulatory expertise across small molecules, biologics, and cell and gene therapies. Solvias offers end-to-end solutions from raw material testing to drug product release and API development for small molecules. Headquartered near Basel, Switzerland, Solvias operates six global Centers of Excellence, all adhering to the highest ISO, GMP, GLP and FDA standards.

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Dr Yannick Baschung

Yannick Baschung, PhD, is the head of the Drug Delivery & Physical Characterisation Services team at Solvias. He has more than ten years of experience in chemistry, manufacturing and controls activities, including five years in OINDP development and analytical services. Previously, he led the OINDP analytical services team at Solvias, where he oversaw several products from early clinical trials to successful commercial launch. Dr Baschung is a member of the European Directorate for the Quality of Medicines and Healthcare inhalation working group and holds a master's degree from the University of Bordeaux (France) and Uppsala University (Sweden), as well as a PhD in Biomedical Mass Spectrometry from the University of Rostock (Germany). His interests include formulation science, aerosol science and drug-device combination products.

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Expert View

RESPIRATORY MUCOSAL VACCINATION: HOW COULD WE DELIVER ANOTHER GLOBAL VACCINATION RESPONSE WITH CURRENT DEVICE TECHNOLOGIES?

Mark Parry of Intertek discusses the potential needs and opportunities for respiratory drug delivery devices in the context of a hypothetical global vaccination strategy, considering a variety of factors and how different respiratory device approaches could perform.

Devices for delivering small-molecule therapeutics via the nasal and inhalation routes represent a well-established pillar of the drug delivery sector. These technologies represent a range of solid- and liquid-based delivery systems that can be employed for effective delivery of therapeutics.

However, the increasing importance of large-molecule and biological drug products within the respiratory space over the past several years has spurred innovation and the development of new technologies to address key challenges. This progress is closely aligned with advancements in formulation science and delivery methods.

Looking towards the future, the context of developing a global vaccination strategy presents considerations with different priorities to those that have driven device development to date.

CONSIDERATIONS FOR A GLOBAL VACCINATION EFFORT

Target Population Size and Context

For context, let us examine one of the major respiratory targets: chronic obstructive pulmonary disease (COPD), which is the fourth leading cause of death worldwide, causing 3.5 million deaths in 2021 – approximately 5% of all deaths globally.[1] Estimates of COPD's prevalence in the population are around 10.4%,[2] although less than 6% of the population have been specifically diagnosed with COPD. The availability of COPD therapeutics is inconsistent across different regions, with the World Health Organization and other researchers noting that inhaled medicines for COPD are poorly available and largely unaffordable in low- and middle-income countries (LMICs).

A new gold-standard COPD therapeutic would represent a massive new blockbuster product for the industry, which would create a need for investment in dedicated manufacturing capabilities and distribution. However, even that level of demand would be modest compared with the scale required for a global respiratory vaccination programme. Such a strategy could potentially represent a 20-fold or greater increase in target population compared with a hypothetical blockbuster COPD therapy.

Cost To Manufacture

Costs for covid-19 vaccines are somewhat difficult to define and, commercially, costs range widely across different markets; however, the cost of manufacture based on 100 million doses has been estimated to be between US$0.54 and $0.98 per dose (£0.40–£0.73).[3]

FluMist® (AstraZeneca) is one of the few respiratory vaccination products on the market and represents what is likely to be the simplest possible device option. The Centers for Disease Control and Prevention's (CDC's) wholesale costs are around $18 per dose,[4] compared with $50–80 for current covid-19 vaccines, but retail costs are not a reliable guide to the exact cost of manufacture.

For a respiratory vaccine to be a competitive option versus traditional needle-based solutions, the cost of goods

"THE CONTEXT OF DEVELOPING A GLOBAL VACCINATION STRATEGY PRESENTS CONSIDERATIONS WITH DIFFERENT PRIORITIES TO THOSE THAT HAVE DRIVEN DEVICE DEVELOPMENT TO DATE."

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"DRY POWDER-BASED DEVICES PRESENT A SIGNIFICANT OPPORTUNITY TO SIMPLIFY LOGISTICS AND REDUCE COSTS FOR THE DISTRIBUTION OF VACCINES GLOBALLY."

needs to adapt to the demands of the required scale. Every $0.10 increase in the cost per unit means an increase in manufacturing costs of over $8 million per 1% of the population treated.

Manufacturing Capacity

Manufacturing capacity for vials and prefilled syringes is well established, but the manufacture of covid-19 vaccines at a global scale still required a significant investment in increasing manufacturing capability.

Identifying a suitable device strategy requires consideration of what capabilities can be accessed both in-house and through contract services; realistically, however, most respiratory device forms would need investment in additional facilities to meet the demands of a global pandemic response. Identifying the best solution will require consideration of factors such as the scalability and the novelty of the technology used to understand its suitability for global scale-up.

Distribution and Cold Chain

Considering device technologies for respiratory vaccines based on the above points naturally leads to a consideration of solution-based formulations. A FluMist-style presentation allows for the use of existing prefilled syringe technologies and device parts that are relatively inexpensive. However, this approach will alsohave the same cold chain distribution needs as needle-based products.

Cold chain distribution costs are estimated to be 22 times higher than at ambient temperature, with cold chain distribution estimated to be a $25 billion industry in 2025.[5] In addition to this, covid-19 vaccine wastage in LMICs, where distribution is complicated by remote areas and varying cold chain equipment availability, was estimated to be as high as 30% in 2022.[6]

Dry powder-based devices present a significant opportunity to simplify logistics and reduce costs for the distribution of vaccines globally. This advantage could potentially offset the likely higher manufacturing costs for these dosage forms, making them more competitive compared with traditional needle-based presentations – even given equal efficacy of the dose.

Self-Administration

One of the many challenges of a global vaccination programme using current delivery methods is the practicality of dose administration. Trained healthcare staff are required to deliver the vaccine, which necessitates the establishment of vaccination centres to meet the demands of vaccinating most of the population.

On the other hand, while support from healthcare personnel may still be the best approach for some patient groups, healthy adults would be capable of administering a respiratory vaccine to themselves, their children and any other people that they care for, such as elderly relatives. This would also be an advantage for remote distribution, where the demands on limited trained healthcare staff can be reduced.

FluMist has seen recent growth as a self- or caregiver-administered vaccine in the US, following its approval for this use case in 2024.[7] Monitoring the feedback and success of this first self-administered flu vaccine should provide a useful source for patient feedback in due course.

"ENGINEERING DRY POWDER FORMULATIONS PRESENTS AN ADVANTAGE IN DELIVERING INCREASED PRODUCT STABILITY, AS WELL AS OPPORTUNITIES TO SHAPE PARTICLE SIZES AND OPTIMISE DEVICE OPERATION TO TARGET DIFFERENT AREAS OF THE NOSE."

REVIEWING CURRENT DEVICE TECHNOLOGIES

Nasal Liquids

Liquid-based formulations are well served by existing nasal delivery device technologies, with uni-dose devices being an increasingly important class of nasal devices. Simple syringe-type options, such as those used for FluMist, are most likely to represent the lowest cost, while other options are available that use glass vials as the primary container/closure system, which may present stability and compatibility advantages and allow more sophistication in tuning of the aerosol plume. For example, the Narcan® nasal spray (naloxone hydrochloride – Emergent BioSolutions, Gaithersburg, MD, US).

Liquid-based nasal sprays can be considered active devices, where the patient does not need to co-ordinate activation and breathing, and are likely to be accessible to most age groups, as inspiratory effort is not a limiting factor.

Nasal Powders

Nasal powder devices are a growing space, with biologics fuelling part of this growth. Engineered dry powder formulations present an advantage in terms of increased product stability, as well as the potential to optimise particle sizes and device operation to target different areas of the nose.

Active devices that blow out the powder will have the advantage of not requiring patient co-ordination, making them easier for wide populations to use. This category of nasal powder devices, such as Baqsimi® (glucagon – Amphastar Pharmaceuticals, Rancho Cucamonga, CA, US), offers important delivery capabilities, though design complexity and cost considerations may limit their practicality for large-scale vaccination programmes.

Passive devices, such as the ICOone® nasal device (Iconovo, Lund, Sweden), have the potential to be lower cost products. However, these devices often require user effort and co-ordination to deliver a dose successfully and therefore may be less suitable for some population groups.

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Inhaled Liquids – Nebulisers

Nebulisers are a common starting point for inhaled biologics as they are effective as a bridge between injectable and respiratory formulations, often providing the quickest route to clinical trials if a suitably stable formulation – or a reconstituted formulation – can be identified.

Convidecia Air™ from CanSino Biologics (Tianjin, China)[8] is a nebulised covid-19 vaccine using a similar formulation design to their needle-based vaccine, which may represent a more viable use case where a nebulised form is available for special population groups. However, nebulisers are not well-suited for mass vaccination, as the devices are expensive to distribute widely and not easily shared between users.

One potential model could be the use of nebulisers with disposable elements for each patient and dosing performed at vaccination centres or other healthcare settings. However, this would require similar logistical co-ordination to needle-based delivery with higher costs for the device aspects.

While nebulised delivery is not likely to be the most cost-effective route for large-scale vaccination, if advantages in efficacy are demonstrated and device designs are developed to support this usage model better, it is certainly achievable. However, it may be better suited as a complimentary formulation for specific patient groups.

Inhaled Liquids – Soft Mist Inhalers

Soft mist inhalers (SMIs) are a relatively new class of device are proving effective for delivering biologics in aqueous formulations with greater efficiency than nebulisers. These are similar to pressurised metered dose inhalers (pMDIs) in terms of needing user co-ordination but, with a softer and longer plume duration, it is easier for users to co-ordinate their inspiratory effort.

Unlike nebulisers, SMIs are not based on tidal breathing, which may present a greater opportunity to develop disposable parts, enabling multiple patients to use the same device. Again, individual disposable devices are unlikely to be cost effective with current technologies.

Inhaled Powders

Inhaled powders offer a broad range of device options, with devices available for both multiple- and single-use dosing. These are likely to present the most cost-effective option for individually disposable inhalers, but they do present their own challenges.

Dry powder inhalers (DPIs) are almost always passive and require inspiratory effort to administer the dose effectively, meaning that the use of DPIs is less common for children and some elderly populations. However, dose flexibility in vaccination may compensate for lower device performance in these more challenging populations.

"ANY GLOBAL VACCINATION RESPONSE WILL NEED TO CONSIDER THE SCIENCE AND EFFICACY, AS WELL AS THE LOGISTICAL PRACTICALITIES, OF ANY APPROACH."

Pressurised Metered Dose Inhalers

Propellent-based pMDIs are commonplace in respiratory medicine; however, they have not been a focus for inhaled biologics due to challenges in finding formulation designs that ensure compatibility between the API, the propellant and the device.

pMDIs are unlikely to suit individual disposable device strategies, but they may be suitable for dosing multiple patients in a controlled setting with appropriate disposable parts.

One significant challenge with pMDIs is user co-ordination of breathing and dosing, as the dose is emitted within a second – user error in pMDI dosing is a significant obstacle for managing respiratory conditions. One solution to this is the use of a spacer that allows the patient more flexibility in breath co-ordination, making device co-ordination less critical.

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Disposable pMDI spacers already exist,[9] such as the DispoZABLE® Spacer (Clement Clarke International, Mountain Ash, UK). These could provide a model for multi-patient dosing, but will add some costs and, again, would rely on dedicated vaccination centres rather than self-administration.

Manufacturing capacity for pMDIs is well established and could potentially respond to global demand if a suitable formulation strategy can be identified. For reference, in 2020, over 16 billion doses of salbutamol were sold in pMDIs in the EU, which accounts for more than half of the EU's total pMDI sales.[10]

CONCLUSION

Any global vaccination response will need to consider the science and efficacy, as well as the logistical practicalities, of any approach. The role of respiratory vaccination is still developing and, if it were the selected approach, would present challenges that the chosen device/delivery strategy would need to address.

Beyond this hypothetical discussion, respiratory vaccination is a developing area. Its potential advantages in efficacy and self-administration are likely to see significant development in formulation and device programmes in the coming years. Respiratory vaccines have the potential to become a critical component of global vaccination efforts, working alongside needle-based vaccines to strengthen pandemic preparedness and routine vaccination programmes.

ABOUT THE COMPANY

Intertek is a specialist contract orally inhaled and nasal drug product services provider, with GMP labs in Melbourn (UK), Manchester (UK) and Basel (Switzerland). The company's respiratory Centre of Excellence provides formulation development, performance testing, clinical manufacturing, impurities testing and extractables and leachables services. Intertek works with all the main inhaled and nasal delivery systems and has experience in both small- and large-molecule modalities. The Intertek team has over 35 years' experience working in the respiratory space and has served companies all over the world. As an independent product developer, holding no intellectual property, Intertek helps its clients design products using optimal device and formulation technology from across the industry.

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Mark Parry

Mark Parry has worked with Intertek for over 20 years since graduating from Cambridge University (UK) and currently works as the Senior Scientific Director, supporting the wide range of analytical, formulation, product development and research activities across the company. Mr Parry has worked in a range of pharmaceutical analysis and formulation development areas, with a particular focus on inhaled and nasal drug products. Mostly working in the pre-approval stages, Mr Parry's background includes extensive experience with product and formulation development, as well as method development and validation, IVBE studies, and pharmaceutical development activities for a wide range of clients across the pharmaceutical industry. Mr Parry is one of DDL's scientific advisers, a member or chair of several EPAG and IPAC-RS working groups, and an elected member of the RSC Inclusion and Diversity Committee. He routinely presents at conferences, as well as contributing to articles, research papers and posters on a range of respiratory topics.

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Interview: Aptar Pharma Expansion With New R&D Center

In this interview, **Christophe Pierre** of **Aptar Pharma**, introduces the company's new R&D Center in France, and outlines how the new facility will assist the development of smarter, more integrated drug delivery solutions, facilitating progression from concept to full-scale industrialisation across multiple therapeutic fields.

Q Aptar Pharma has just opened its expanded R&D Center in France – how does this facility enhance your global innovation footprint and reinforce your focus on patient-centric drug delivery?

"WITH THIS EXPANSION, WE ARE NOW BETTER POSITIONED TO SUPPORT THE DEVELOPMENT OF ADVANCED DRUG DELIVERY SYSTEMS THAT SERVE OVER 1.6 BILLION PATIENTS ANNUALLY."

A In a healthcare landscape increasingly shaped by precision, speed and sustainability, innovation in drug delivery has never been more critical. Aptar Pharma's recent expansion of its R&D Center in Le Vaudreuil and Val-de-Reuil, France, marks a strategic step in its global approach to meeting these evolving demands. As part of the company's innovation network, the upgraded facility is designed to accelerate the development of smarter, more integrated drug delivery solutions – supporting progress from concept to industrialisation across therapeutic areas.

The expanded R&D Center in Le Vaudreuil reflects Aptar Pharma's commitment to strengthening our innovation infrastructure in Europe. It complements our global network of innovation hubs and gives us additional capacity to support development programmes across multiple therapeutic areas. The facility is designed to enable faster iteration and deeper collaboration with our partners, particularly in developing solutions that improve treatment accessibility, usability and therapeutic outcomes for the patients. It allows us to localise development efforts while maintaining alignment with global standards and regulatory expectations.

The building spans more than 3,000 square metres, with dedicated areas for device development, testing and simulation, as well as collaborative workspaces. It was designed from the outset to support sustainability goals, integrating features that reduce its carbon footprint and enable more efficient operations. This physical setup directly supports our ability to accelerate innovation and deliver high-impact solutions to the market.

The facility also reflects Aptar Pharma's long-standing presence in France, where we've built deep technical expertise over several decades. With this expansion, we are now better positioned to support the development of advanced drug delivery systems that serve over 1.6 billion patients annually.

Q How does the Le Vaudreuil R&D Center integrate with Aptar Pharma's global innovation network – particularly with the hubs in North America and Asia?

A The Le Vaudreuil R&D Center operates as a fully integrated part of Aptar Pharma's global innovation network, which spans North America, Asia and Europe. This integration allows us to co-ordinate development efforts across regions, share data and insights in real time, and align on platform technologies and regulatory strategies.

For example, our teams in France collaborate closely with their counterparts in the US and Asia to ensure consistency

Christophe Pierre

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Christophe Pierre, Vice-President Global R&D – Prescription at Aptar Pharma, is an engineer and a biomedical sciences postgraduate. He joined Aptar in 2001 and has over 25 years of experience across the pharmaceutical, beauty and food & beverage industries. Throughout his career, he has led international R&D teams and global portfolios, championing innovation, digital transformation and operational excellence to deliver impactful and sustainable results.

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in device performance and quality, while also adapting to local market needs. The Le Vaudreuil R&D Center's expanded capabilities in rapid prototyping and digital simulation enable us to contribute more actively to global programmes from early feasibility studies through to industrialisation.

With engineering, testing, simulation and regulatory functions all housed in one location, the facility fosters seamless collaboration and faster decision-making. It's where deep technical expertise meets advanced development tools – making it a strategic hub for prescription drug delivery innovation. In many ways, this is the place to be for prescription R&D globally.

Figure 1: Aptar Pharma's advanced R&D Center, Vaudreuil & Val-de-Reuil, France, with a sustainable design, featuring energy-efficient architecture and optimised use of natural light.

Q How are the R&D Center's advanced capabilities transforming the way Aptar Pharma designs and develops next-generation drug delivery platforms?

A Our new capabilities are helping us move from traditional, sequential development to a more integrated and predictive model. For example, digital simulation and predictive modelling allow us to assess performance variables early in the design phase, reducing the need for physical iterations. Rapid prototyping shortens the feedback loop with customers and partners, while artificial intelligence (AI) tools are increasingly being used to optimise device geometry and material selection. These technologies not only accelerate speed-to-market but also play a critical role in de-risking development by enabling earlier validation, reducing reliance on physical iterations and improving predictability throughout the design cycle.

Q What are the regulatory or quality advantages of having an R&D Center in France, especially for EMEA-focused drug delivery programmes?

A Our location in France gives us proximity to key regulatory bodies and partners in the EMEA region. It allows for more direct engagement with the EMA and national regulatory agencies, which can be particularly beneficial during early-stage development, submission planning and regulatory alignment. The facility also supports quality compliance with European standards, which is essential for lifecycle management and post-market surveillance.

An additional advantage is that our services – spanning device design, testing and regulatory support – are physically close to one another and to many of our customers. This proximity enhances responsiveness and fosters more agile collaboration. It reinforces our ambition not just to be a supplier but a trusted and preferred partner in the development of complex drug delivery solutions.

Q How does this facility reflect Aptar's broader commitment to sustainable innovation?

A The building was designed from the ground up with sustainability in mind, incorporating infrastructure and systems specifically aimed at reducing its carbon footprint. From the outset, the facility was equipped with solar panels, heat recovery systems and rainwater harvesting – all of which contribute to lowering energy consumption and minimising its environmental impact.

Beyond the physical infrastructure, the facility supports Aptar Pharma's long-term environmental, social and governance roadmap by enabling the development of drug delivery solutions that are both effective and environmentally responsible. This includes innovations such as recyclable components and metal-free pumps, which align with our goal of reducing material waste and improving product sustainability across the lifecycle of our products (Figure 1).

Q What role do you see the new R&D Center playing in strengthening Aptar's partnerships across EMEA and attracting top regional scientific and engineering talent?

A The R&D Center is already helping us deepen relationships with academic institutions, research consortia and regional biotech companies.

"ONE OF THE KEY STRENGTHS OF THE FACILITY IS THAT IT BRINGS TOGETHER A WIDE RANGE OF CAPABILITIES UNDER ONE ROOF – INCLUDING MECHANICAL AND CHEMICAL ENGINEERING, ANALYTICAL TESTING AND REGULATORY EXPERTISE – ENABLING US TO SUPPORT THE FULL DEVELOPMENT CYCLE FROM FORMULATION THROUGH TO PATIENT USE."

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It provides a physical space for joint development and technical exchange, which is essential for building trust and accelerating innovation.

One of the key strengths of the facility is that it brings together a wide range of capabilities under one roof – including mechanical and chemical engineering, analytical testing and regulatory expertise – enabling us to support the full development cycle from formulation through to patient use. This integrated setup allows for more efficient collaboration and faster problem-solving, which is particularly valuable in co-development projects with external partners.

From a talent perspective, having a modern, well-equipped facility in France makes us more attractive to engineers and scientists who want to work on meaningful healthcare challenges with global impact. It's a place where they can contribute to high-value innovation while being part of a multidisciplinary team that's shaping the future of drug delivery (Figure 2).

Q Can you share any early-stage projects or therapeutic areas that are already being supported by the new R&D Center?

A We're currently supporting several programmes focused on nasal and pulmonary delivery, including platform enhancements for chronic respiratory conditions and emergency-use nasal sprays. The facility is also contributing to exploratory work in connected devices and digital health integration. While many of these projects are still in their early phases, the facility has already proven valuable in accelerating feasibility studies and prototype validation.

One example that illustrates our innovation approach is Aptar Pharma's contribution to the development of a glucagon nasal spray – a life-saving emergency treatment for severe hypoglycaemia. This project successfully repurposed an existing molecule into a needle-free format using our proprietary delivery system, demonstrating how device innovation can unlock new therapeutic value and improve treatment accessibility.

Another strong example is the ZEN30 Futurity™ valve platform, developed

Figure 2: FabLab at Aptar Pharma's R&D Center – a collaborative space designed to inspire creativity and hands-on innovation.

Figure 3: Testing nasal spray system for vaccine delivery at Aptar Pharma's R&D Center.

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"THE FACILITY'S EXPANDED CAPABILITIES ALLOW US TO SUPPORT MORE PROGRAMMES IN PARALLEL, TO SCALE PROMISING CONCEPTS MORE QUICKLY AND TO MOVE FASTER FROM CONCEPT TO INDUSTRIALISATION."

to support the transition to low-global warming potential propellants in pressurised metered dose inhalers. Produced entirely in our Normandy (France) facilities, ZEN30 Futurity™ is compatible with both HFA-152a and HFO-1234ze and is designed to ensure robust performance while reducing environmental impact. The valve's optimised geometry and proprietary elastomer technology help to minimise extractables and leachables, supporting regulatory compliance and reliable supply chains.

Together, these examples highlight the breadth of innovation supported by the R&D Center – from life-saving emergency treatments to sustainable respiratory platforms. The expanded infrastructure allows us to pursue these opportunities more systematically, especially in areas where ease of use, rapid onset and environmental responsibility are critical to therapeutic success (Figure 3).

Q How will this investment help to accelerate the development of next-generation drug delivery systems across a broader range of therapeutic areas?

A The facility's expanded capabilities allow us to support more programmes in parallel, to scale promising concepts more quickly and to move faster from concept to industrialisation. Pulmonary and nasal delivery are key focus areas, and the facility is equipped to handle the specific technical and regulatory demands of these platforms. It also supports our work in connected devices and digital health.

Importantly, the new facility enables us to advance combination product development – where drug and device must be optimised together – by providing the infrastructure and expertise needed to manage integrated design, testing and compliance workflows. One of the key advantages of the new R&D Center is having all core competencies under one roof. By combining the flexibility and experience of our multidisciplinary teams with advanced technologies, such as digital simulation and predictive modelling, we're able to streamline development cycles and make faster, more informed decisions. This co-location of talent and tools is a major enabler for accelerating innovation across a broader range of therapeutic areas.

Q What excites you most about this new investment and how it facilitates Aptar's role in shaping the future of drug delivery?

A What excites me most is the ability to bring together multidisciplinary teams under one roof and give them the tools they need to solve complex problems. The facility is not just about infrastructure – it's about capability. It allows us to be more responsive to market needs, more collaborative with our partners and more ambitious in our innovation goals.

Thanks to this expanded R&D Center investment, we're now positioned as a preferred partner for pharmaceutical companies seeking to co-develop advanced drug delivery solutions. Having all core competencies – device design, simulation, prototyping, testing and regulatory support – co-located in one building enables us to move faster and with greater confidence. It allows us to accelerate and de-risk development, thanks to tighter integration across disciplines and earlier visibility into potential challenges.

This setup not only improves execution but also strengthens our ability to deliver robust, scalable solutions that meet both therapeutic and operational requirements. It's a tangible step forward in Aptar Pharma's mission to shape the future of drug delivery through practical, reliable and impactful innovation.

Aptar pharma

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Aptar pharma

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Aptar Pharma offers proven drug delivery solutions and services that support pharmaceutical companies worldwide to develop safe, efficient and compliant medicines. Aptar Pharma's drug delivery systems, components and active material solutions serve the widest range of delivery routes, Aptar's digital healthcare solutions help improve patient adherence and Aptar Pharma Services helps accelerate and derisk development.

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BESPAK

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Bespak is a specialist inhalation CDMO with established capacity and ongoing expansions to enable the development and manufacture of pMDIs with low-GWP propellants. The company provides a fully integrated service encompassing early-stage feasibility, analytical and formulation development, product development and clinical supply, through to full-scale cGMP batch production.

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CONTEXO automation

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Contexo is a family-run mechanical engineering company based in Germany that specialises in building high-performance assembly machines. Most of Contexo´s machines process plastic parts with sizes of up to 500 cm^3 and can handle over 80 production processes. In the medical device sector, Contexo focuses on primary packaging and diagnostic products, as well as contract manufacturing services.

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DCA

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DCA is a product design consultancy with a wealth of experience developing leading drug delivery devices for global markets, including all types of injection, infusion, inhalation, intranasal, oral and topical devices. DCA provides comprehensive, expert support for device design and development, including strategy, usability, connectivity, engineering, electronics, medical device software and industrialisation.

See **Page 02**

HCmed

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HCmed Innovations Co. Ltd 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 with innovative features to enhance drug delivery.

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Intertek Pharmaceutical Services brings over 30 years of global expertise in formulation and inhaled or nasal drug development, supporting advanced drug delivery systems for targeted and controlled release. With specialist knowledge in large and small molecules, Intertek provides analytical development integrated with formulation and stability to drive understanding of our clients' products and processes, enabling key decision-making activities.

See **Page 07**

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Kindeva

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Kindeva Drug Delivery is a global CDMO focused on drug-device combination products. The company develops and manufactures products across a broad range of drug-delivery formats, including pulmonary and nasal, injectable and transdermal. Its service offerings span early-stage feasibility through to commercial-scale drug product fill-finish, container closure system manufacturing and drug-device product assembly.

See **Page 05**

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Nanoform is a nanoparticle medicine enabling company that works with pharma partners to reduce attrition in clinical trials and enhance formulation performance of molecules through its nanoforming™ services. Its CESS® technology produces nanoformed™ API particles as small as 10 nm.

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Parker

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Parker O Ring & Engineered Seals Division manufactures elastomer O rings and engineered seals for pharmaceutical drug delivery, including pMDIs, backed by a 70-year legacy in the pMDI market. Parker provides material development, precision moulding, custom profiles, qualification testing and certified low-extractable and chemically resistant seals at production scale.

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PRIOR

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Certified to ISO 13485, **Prior PLM Medical** collaborates with pharmaceutical companies, CDMOs and start-ups, on development of drug delivery devices. Our engagement model is tailored to accommodate different requirements, whether its end-to-end program management, or targeted, agile support at specific stages. Contact us to discuss how we can help de-risk and accelerate your device program.

See **Page 03**

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Resyca BV, a joint venture between Bespak and Medspray, is a leading innovator in soft mist inhaler and nasal spray technologies for targeted pulmonary and nose-to-brain drug delivery. Resyca provides end-to-end support from early-stage development to commercial manufacturing, accelerating therapeutic breakthroughs and efficiently bringing patient-focused drug-device combination products to market.

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