PULMONARY & NASAL DRUG DELIVERY

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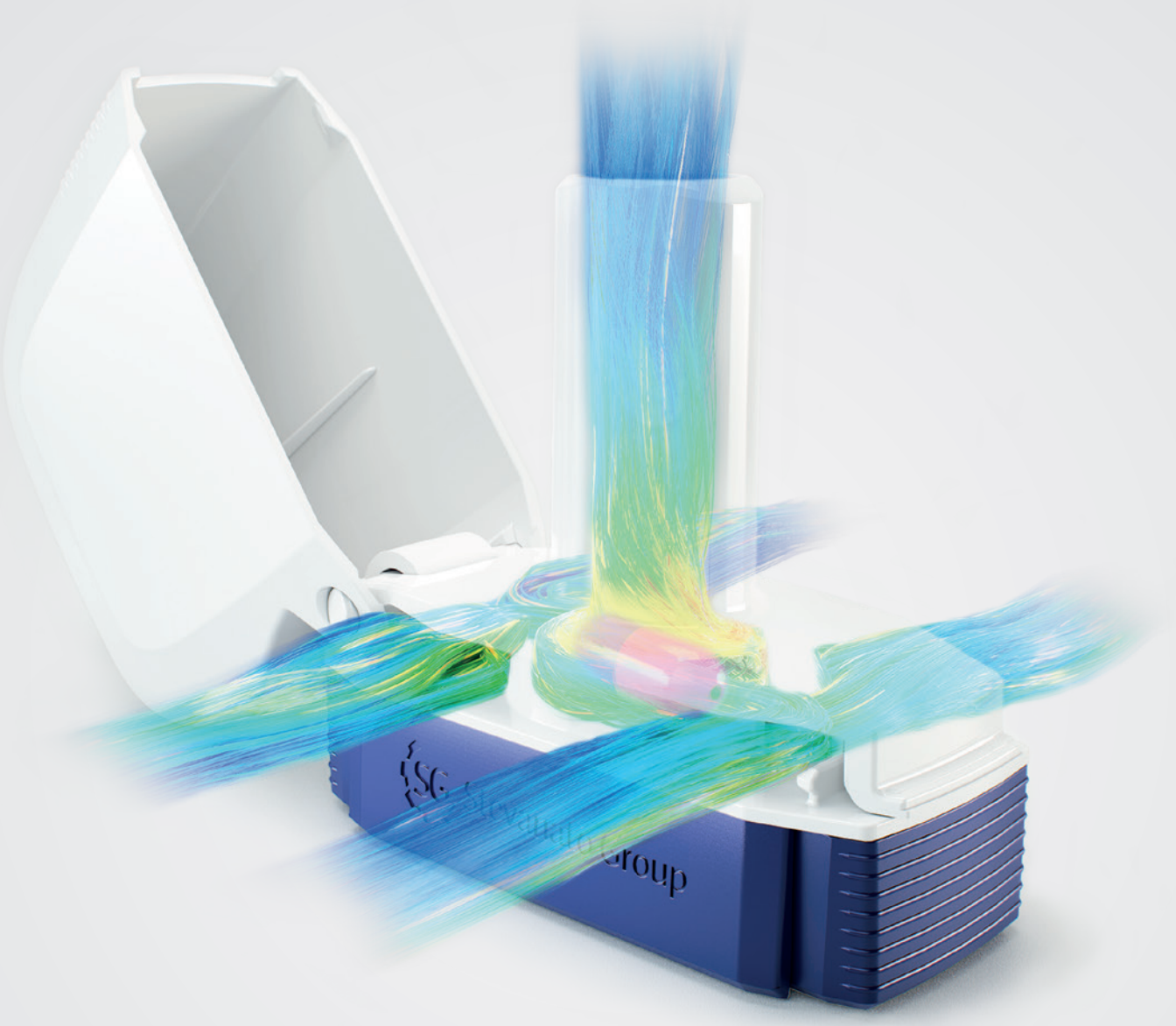

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WAITING FOR THE OUTBREATH – WHAT MIGHT COVID-19 BIOAEROSOL RESEARCH HAVE TO TELL US ABOUT INHALABLE DRUG DELIVERY?

Here, Deborah Norris, Senior Consultant – Healthcare Devices Engineer, Mark Allen, PhD, Associate Mechanical Engineer, Karl Hewson, Senior Consultant – Design and Usability Engineer, and Karla Sanchez, PhD, Senior Consultant – Biomedical Engineer, all at Cambridge Design Partnership, discuss how the covid-19 pandemic has spurred research in the pulmonary space, which suggests that a patient-tailored approach based on their individual lung characteristics, facilitated by advanced technology, could improve patient health outcomes and quality of life.

Over the past year-and-a-half living through the covid-19 pandemic, research into the generation and emission of bioaerosols has increased significantly. Studies have looked into the mechanics of how viruses are communicated through respirable droplet production, not just for droplets generated during coughing and sneezing but also during normal breathing and talking.[1] Examining these mechanisms has reinforced the existence of "super emitters" – people who produce aerosol particles at an order of magnitude greater than the baseline.[2] This research has led to compelling findings.

> "There is particular interest in the generation of the small aerosol particles that are believed to be generated primarily in the deep lung, at the level of the bronchioles leading to the alveolar sacs – a phenomenon known as 'bronchiolar fluid film burst'."

There is particular interest in the generation of the small aerosol particles that are believed to be generated primarily in the deep lung, at the level of the bronchioles leading to the alveolar sacs – a phenomenon known as "bronchiolar fluid film burst".[3] These tiny passages close at the end of a forceful exhalation and re-open as the person inhales, but are covered over by a thin mucosal film – similar to a bubble-wand. This film bursts as inhalation completes, generating microscopic droplets of fluid in the alveolus. Then, during the ensuing exhalation, these tiny particles are ejected from the lung and expelled as an extremely fine bioaerosol.

This is instructive in terms of disease transmission and therefore a hot topic for understanding the communication of bioaerosol-borne viruses. However, it also provokes an interesting discussion around inhaled drug delivery mechanisms. Typically, patients are told to breathe out

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"The strong exhalation cycle may, in fact, be *inhibiting* optimal deposition of drug product by encouraging the closure of areas of the lung for targeted medication."

strongly immediately before administering an inhaler dose. This encourages the patient to achieve the "empty lung" residual volume point and allows for deep inhalation by pulling inhaled medication deeper into the lung. Or does it? Does it, at least, achieve this most effectively? The strong exhalation cycle may, in fact, be *inhibiting* optimal deposition of drug product by encouraging the closure of areas of the lung for targeted medication. Should we perhaps be looking more closely at understanding and characterising the mechanics of the outbreath to help us improve the efficacy of drug delivery and treatment outcomes?

Studies show that whilst bronchiole closure happens mainly during the deep exhalation stage, age, disease or excess weight can cause this closure point to come at an earlier stage of exhalation, thereby altering bioaerosol emission.[4] Could there be room for a patient-specific protocol based on an individual's lung performance during typical and conscious breathing? This could help healthcare practitioners prescribe patients with inhalers best suited to their physiology – for example, a dry powder, soft mist or pressurised metered dose inhaler, or even a nebuliser – and, in so doing, improve treatment efficacy and possibly adherence too, if the patient feels that they are receiving an enhanced medicinal benefit by using an inhaler that has optimal performance for their breathing patterns.

Devices exist that monitor and analyse patient behaviour in real time during clinical studies and training, such as Cambridge Design Partnership's Quantii.[5] By combining traditional diagnostic technologies with cutting-edge techniques to monitor the condition of the lung during the breath cycle, it is possible to open up further potentially exciting developments. An example is Wheezo (Respiri, Melbourne, Australia), a monitoring tool aimed at helping asthmatics better measure and manage their condition using a connected acoustic device that characterises wheezing episodes.

"By combining traditional diagnostic technologies with cutting-edge techniques to monitor the condition of the lung during the breath cycle, it is possible to open up further potentially exciting developments."

This highlights the fact that artificial intelligence-based diagnosis devices are no longer the sole preserve of science fiction but a tangible reality. Therefore, the question is how best to use these new insights into outbreath mechanics to develop diagnostics as technology advances. The possibilities include a smart spirometer that can identify the early warning signs of lung conditions; a handheld device that can identify the current health risk for those with lung conditions posed by the environment they are in; and smart-inhaler technology that gathers long-term patterns of a patient's respiratory profile that, over time, could enable healthcare providers to fine-tune prescriptions and treatment regimens, or even produce on-the-fly adjustments to the applied dose, depending on real-time diagnostic readings at point of care.

Building a picture of an individual's "lung characteristics" could improve the quality of life and health outcomes for patients with respiratory conditions. Combining advances in artificial intelligence with a deeper understanding of lung mechanics could lead to earlier diagnoses for diseases

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that are not currently identified before significant structural damage has already occurred. Such a diagnosis could enable healthcare practitioners to offer earlier intervention strategies and a tailored inhaler profile to best match an individual patient's needs.

Some of these ideas still belong in the field of sci-fi – but there are clearly exciting developments for the respiratory field to pursue, courtesy of research catalysed by the covid-19 pandemic.

ABOUT THE COMPANY

Cambridge Design Partnership is an end-to-end innovation partner, propelling global brands and ambitious start-ups to success. The company builds breakthrough products and services – from insight to ideas, prototypes to production – bringing innovation to life. Its teams are multi-disciplinary, uniting scientific rigour, design ingenuity and engineering excellence for consumer, healthcare and industrial clients.

People-centred, deeply collaborative and, above all, expert, Cambridge Design Partnership is uniquely positioned to shape the future for consumers, patients and industry. Even the company's ownership model is innovative – the company is 100% owned by employees, ensuring an open culture and a total commitment to each project's success.

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Mark Allen, PhD, is an Associate Mechanical Engineer at Cambridge Design Partnership. He has a PhD and MEng in Mechanical Engineering from Loughborough University (UK) where he specialised in the prediction and measurement of liquid and gas flows and sprays, working on internal flow imaging and analysis of internal combustion engine technologies to reduce harmful emissions and improve performance. After leaving academia, Dr Allen moved to the medical device sector, working on the design and development of a range of devices from early-to-late stage, including the design and development of multiple autoinjectors for highly viscous formulations and a novel nasal spray device. His specialisms include simulation, mathematical modelling and data analysis.

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Karla Sanchez, PhD, is Senior Consultant – Biomedical Engineer at Cambridge Design Partnership, working as a mathematical modeller, researcher and bioengineer with several years of experience in product development. She obtained her PhD from Imperial College London (UK) at the Physiological Fluids Group, where she focused on blood flow of the cerebral vasculature and distribution of cerebrospinal fluid. She has also worked alongside clinicians and academics to study blood flow in the kidney and complications of chronic kidney disease. Dr Sanchez has managed several successful commercial projects, launching a large range of infusion sets, orthopaedic and surgical devices. She is an enthusiastic STEM ambassador and holds an honorary visiting researcher position at Imperial College London.

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DELIVERING ON THE PROMISES OF INTRANASAL VACCINATION

Here, Julie Suman, PhD, President of Next Breath and Manager of Scientific Affairs, and Nektaria Karavas, Director Business Development, Prescription Division, both of Aptar Pharma, review intranasal delivery as a method of vaccine administration and consider the challenges and benefits of intranasal delivery.

As dawn broke on January 1, 2021, people around the world awoke with the hope that the new year would bring a greater level of protection against SARS-CoV-2, the virus behind the covid-19 pandemic.

At that point in time, the proportion of the globe's population to have received any dose of a covid-19 vaccine stood at an almost negligible 0.07%, but, within months, the picture had changed dramatically. Following the intensive roll-out of national vaccination programmes, more than 5.5 billion vaccine doses have now been administered, and this figure is increasing by more than 30 million doses every day as the covid-19 immunisation programme continues worldwide.[1]

These staggering numbers show just how quickly the pandemic moved vaccines from the background of everyday life to the forefront of public consciousness, underlining their critical importance to the health and wellbeing of people the world over.

One of the knock-on effects has been a dramatic disruption to the value of the global vaccines market. Worth an estimated US$33 billion (£24.3 billion) prior to the pandemic, growth projections multiplied within months of covid-19 surfacing on the world stage.[2] Today, the WHO reports that pharma revenues from covid-19 vaccines alone could have the potential to reach $150 billion over the 2021–2022 period.[3]

> "The respiratory nature of SARS-CoV-2 has led to greater interest in nasal drug delivery as a method for tackling the virus."

Within this highly active space, more than 3,300 vaccines, involving 415 different indications, are currently in development, including both therapeutic and prophylactic varieties (Figure 1). While injection remains the dominant delivery in the vaccine space, the respiratory nature of SARS-CoV-2 has led to greater interest in nasal drug delivery as a method for tackling the virus.

There are many factors driving this interest, but the predominant reason is that nasal vaccines can directly instigate mucosal immunity at the site of infection. In the case of SARS-CoV-2, after binding with ACE2 receptors in the nasal cavity, the virus starts to replicate before it transfers to the lungs, where the infection takes hold. Mucosal immunity would provide the first line of defence at the mucous membranes, adding another layer of protection to the systemic immunity offered by existing covid-19 vaccines. Further analysis in this emerging area is required, but it is believed that inducing mucosal immunity in this way may yield benefits not seen with conventional parenteral routes of vaccine administration.[4]

INTRANASAL VACCINE DELIVERY

Intranasal delivery of vaccines remains relatively uncharted territory. To date, only three intranasal products have been

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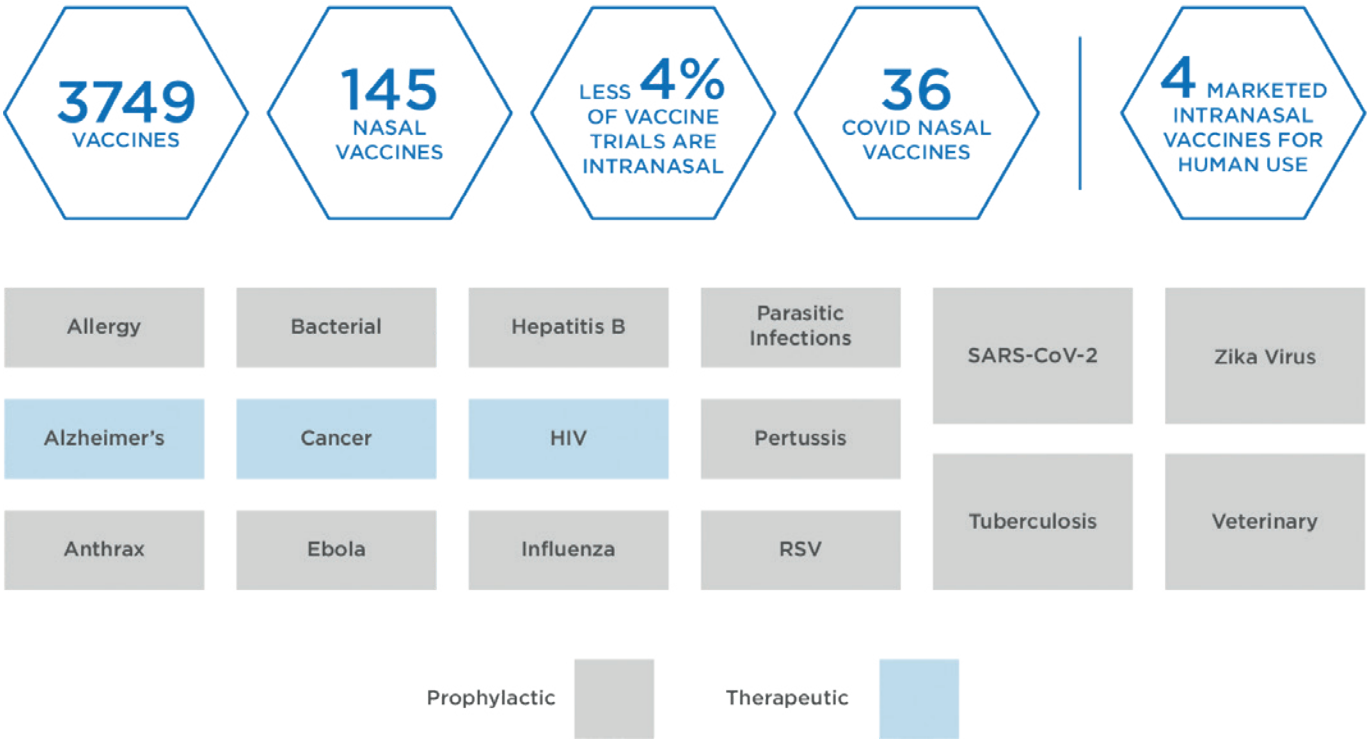

Figure 1: Global vaccines in development.

granted market licences for human use, including a seasonal influenza vaccine FluMist® (AstraZeneca, Cambridge, UK). Currently, exploratory work continues on 146 nasal vaccines, accounting for less than 4.4% of all active vaccine trials – of these, 40 are targeted at covid-19.

Despite this activity around intranasal delivery, patients are most familiar with vaccines being delivered by injection or oral administration. Given the breadth of vaccine treatments that employ these methods, there is a much greater depth of knowledge regarding formulation development and the associated pathways for regulatory approval. However, these methods also suffer from several challenges.

The invasive nature of injections, whether intramuscular, subcutaneous or intravenous, is an obstacle for some patients. Some will simply find the experience unpleasant, while others will find it distressing – and may actively avoid vaccination altogether where injections are required as a result. Indeed, needle phobia is believed to affect as much as 10% of the UK population[5] and research has shown that it may be responsible for 10% of covid-vaccine hesitancy in the country.[6]

It is not only patients who are affected; healthcare professionals may also be uncomfortable due to the potential for needlestick injuries.

These risks are eliminated with orally delivered vaccines, which can present in various forms – such as drops in the case of oral poliovirus vaccines or capsules in the case of the Typhoid fever vaccine Vivotif (Typhoid Vaccine Live Oral Ty21a) (Janssen Vaccines, formerly Crucell, Leiden, Netherlands). Oral delivery forms can also induce a mucosal, as well as systemic, immune response. However, the harsh environment of the gastro-intestinal (GI) tract, with its high acidity and presence of molecule-degrading enzymes, is known to compromise the local bioavailability of vaccines. This introduces the requirement for higher doses which, in turn, brings challenges relating to formulation development.[7]

Intranasal delivery similarly induces a mucosal and systemic response, but eradicates the complications associated with enzymatic metabolism in the GI tract. Using this method, drug molecules are aerosolised for deposition in the nasal cavity. For vaccines specifically, the target area is the nasopharynx-associated lymphoid tissue, an area rich in various cell types, including the immunocompetent antigen-presenting cells, such as T cells, B cells, M cells and dendritic cells, which are critical in generating local and systemic immune responses.

In terms of its anatomical and physiological structure, the highly vascularised lateral wall of the nasal cavity provides a welcome environment for drug molecule absorption. It contains immunocompetent cells, such as dendritic cells, that facilitate antigen interaction. Slightly acidic and isotonic, it has a total surface area of approximately 150 cm^2, around 85% of which is covered by the respiratory region.[8]

"Needle phobia is believed to affect as much as 10% of the UK population, and research has shown that it may be responsible for 10% of covid-vaccine hesitancy in the country."

"In terms of its anatomical and physiological structure, the highly vascularised lateral wall of the nasal cavity provides a welcome environment for drug molecule absorption."

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THE CHALLENGES AND SOLUTIONS FOR NASAL VACCINE DELIVERY

The intranasal delivery route is not free from its own challenges, however. Many of these challenges can be attributed to the natural defence mechanisms designed to keep invasive particles, allergens, viruses and bacteria from entering the body through the nose. This includes the enzymatic processes present within the nasal cavity, which increases the likelihood of degradation and destabilisation of particulate drug compounds. Although the impact of enzymes such as cytochrome P450 is felt to a much lesser extent in the nasal cavity compared with the GI tract.

Mucociliary clearance is another important consideration when it comes to intranasal drug delivery. Although it is an incredibly helpful defence mechanism, clearance of the mucous layer lining and the nasal epithelium also obstructs the uptake of vaccines – the level of immunity achievable is directly related to the level of exposure that antigens can achieve prior to clearance taking place. Studies have determined that the normal range for nasal mucociliary clearance is up to 20 minutes, providing a clear indication of the time limitations involved.[9] The residence time needed for a vaccine is currently unknown.

Mucociliary clearance can be addressed, however, by the inclusion of a series of excipients within the formulation to assist with the muco-adhesion of antigens. This underlines the importance of vaccine formulations being optimised for nasal delivery through the accommodation of the antigen itself – whether whole virus, viral vector, protein subunit or nucleic acid (RNA or DNA). In addition, adjuvants increase the potentiation and longevity of the immune response, and stabilisers maintain the integrity of the formulation and its active ingredients over time. FluMist, for example, is a suspension of live attenuated virus that incorporates gelatine, sucrose and amino acids as stabilisers, as well as excipients that control for viscosity and acidity.

"In bringing an intranasal vaccine to market, challenges such as those discussed in this article underline the importance of understanding nasal physiology and vaccine formulation to elicit the desired immune response. This has been amplified in the context of covid-19, where there remains a clear urgency around developing treatments."

In some cases, the vaccine is more stable in a non-aqueous environment. Further stabilisation can be introduced through the lyophilisation of the formulation. Here, a bulking agent may be required to help with aerosolisation of the resulting vaccine powder, which can be delivered in a higher payload, as well as avoid the need for cold-chain storage as it demonstrates greater stability at room temperature. Indeed, studies of a recombinant protective antigen intranasal vaccine for anthrax indicated that effectiveness was retained at room temperature after two years.[10]

Particulate systems for intranasally delivered vaccines include liposomal formulations and polymeric nanoparticle formulations. Because respiratory viruses are in the range of 10–200 nm, this should also be reflected in the size of formulation particles, with a particle size of >10 µm deemed necessary to minimise deposition in the lung and a particle size of 200–300 nm deemed optimal for uptake by dendritic cells.[11]

As well as size, other particle characteristics can influence the level of immune response. This includes addressing the risk of particle agglomeration through the inclusion of stabilisers, and exploiting the benefit of positively charged particles, which are found to enhance interaction at the cell membrane. Indeed, cationic carrier particles, such as chitosan, a biodegradable, biocompatible polymer with mucoadhesive properties, have been found to help with vaccine uptake into the cell and the slowing of mucociliary clearance.[12]

Chitosan is one of several adjuvants explored for use in nasal vaccines with the purpose of stimulating and enhancing the immune response, potentially reducing the level of antigen required. In injectable vaccines, adjuvants such as aluminium salts commonly fulfil this role, but they are not suitable for nasal vaccine formulations. An example of an approved nasal vaccine adjuvant is E. coli heat-labile toxin, although it was subsequently withdrawn following concerns over adverse effects and the possibility of transportation to the brain via the olfactory neurons. As such, there are currently no widely approved adjuvants for nasal vaccines, and the avoidance of olfactory deposition continues to be a key focus in product development.

In bringing an intranasal vaccine to market, challenges such as those discussed in this article underline the importance of understanding nasal physiology and vaccine formulation to elicit the desired immune response. This has been amplified

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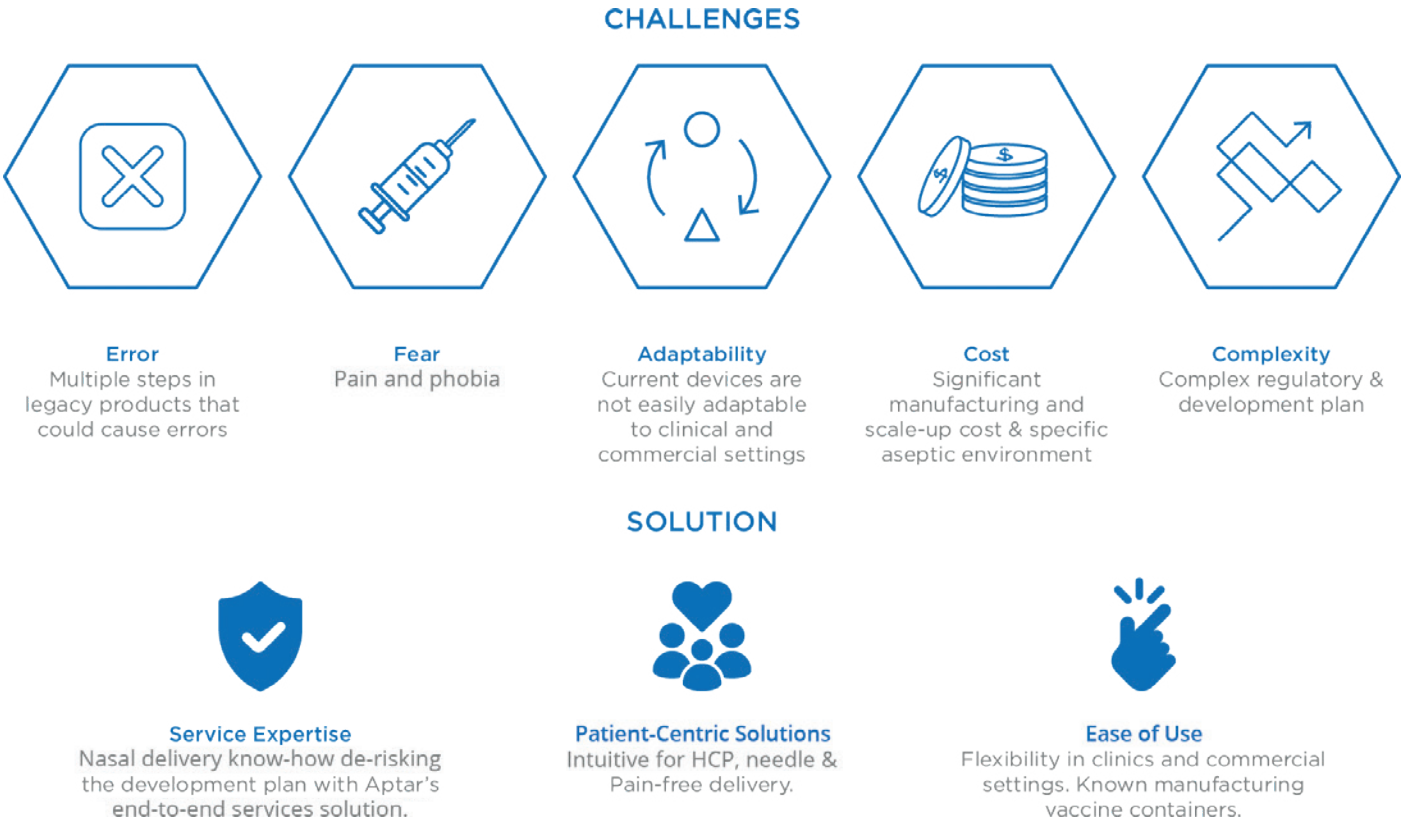

Figure 2: The challenges and solutions associated with nasal vaccine delivery.

in the context of covid-19, where there remains a clear urgency around developing treatments. The US FDA's Emergency Use Authorization provides an accelerated pathway to answer this, although regulators must be satisfied with the available data on the "chemistry, manufacturing, and controls" for vaccine candidates.[13]

Aptar Pharma supports pharmaceutical partners with an end-to-end service that encompasses all aspects of development and delivery for nasal vaccines, as well as providing a framework for regulatory compliance. This begins at the preclinical phase, with *in vitro* modelling to support target deposition studies to assess stabilisation, extending to scale-up support for GMP market-ready production.

A crucial aspect of Aptar Pharma's multi-faceted development process is ensuring that vaccine formulations are complemented by the device to support intranasal administration. Given the prevalence of standard-adjacent containers, including blow-fill-seal, syringes and vials, flexibility and adaptability are key factors to facilitate delivery, whether for liquid or powder formulations on either single- or multiple-dose vaccines.

Aptar Pharma's BiVaX, for example, is a bi-dose device containing an adapter that allows the syringe to be filled from a vial. The nozzle is then refixed to the device and the plunger is depressed to deliver the first dose. Turning the plunger, which acts as an integrated dose divider, allows the second dose to be delivered.

Another example is Aptar Pharma's CPS Multidose, which enables a CPS pump to be fitted directly to the top of a standard glass container. After priming and fitting with a mass vaccination cap, the device can be used to spray the required dose into the patient's nose. After removing the cap and disinfecting the actuator nozzle tip, a new cap can be applied to facilitate administration to another recipient, without priming.

In each case, delivery of the vaccine via the nasal cavity presents a preferable option for patients when compared with legacy injectable systems for all the reasons previously discussed. These devices and techniques are also intuitive for healthcare providers, providing a simple delivery method in both clinical and commercial settings that complements the existing landscape for vaccine containers.

Successfully arriving at this point and realising the promise of intranasal immunisation via such innovative delivery solutions relies on robust relationships between pharmaceutical companies and their trusted device development and delivery partners. These foundations are fundamental to derisk and accelerate the market readiness of nasal vaccine solutions, addressing the known hurdles (Figure 2) and responding to the ongoing demand for much-needed mucosal and systemic immunity in the face of the ongoing threat presented by SARS-CoV-2.

ABOUT THE COMPANY

For pharma customers worldwide, Aptar Pharma is the go-to drug delivery expert, providing innovative drug delivery solutions across a wide range of delivery routes, including nasal, pulmonary, ophthalmic, dermal and injectables. Aptar Pharma Services provides early stage to commercialisation support to accelerate and de-risk the development journey. With a strong focus on innovation, Aptar Pharma is leading the way in developing connected devices to deliver digital medicines. With a global manufacturing footprint of 14 GMP sites, Aptar Pharma provides security-of-supply and local support to customers. Aptar Pharma is part of AptarGroup, Inc. (NYSE:ATR), a global leader in the design and manufacturing of a broad range of drug delivery, consumer product dispensing and active material science solutions.

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ADDRESSING THE CHALLENGES OF NASAL BIOTHERAPEUTIC DRUG DELIVERY

In this article, Robert Lee, PhD, President of the CDMO Division at Lubrizol Life Science Health, discusses the benefits of administering drugs to the nasal cavity, as well as the main challenges in formulation for this route and the strategies that can be applied to overcome them.

Over the last decade, biotherapeutics have rapidly proliferated. Highly potent, patient-centric and offering a desirable safety profile, these drug products have fast become a staple of the development pipeline.

Most biological drugs are peptide- or protein-based therapeutics and have poor oral bioavailability, making parenteral injection the default route of administration. But, as with any innovation in pharma and biotech, there are unmet clinical needs that require novel delivery mechanisms. In meeting these needs, liquid-based and dry powder nasal drugs have emerged as a class of medications with significant benefits.

Nasal delivery is an attractive alternative for local and systemic delivery of biologics, being a non-invasive route of administration with the potential to treat various diseases, including cystic fibrosis, respiratory viral infections and asthma. Driven by this potential, the market was valued at US$7.8 billion (£5.7 billion) in 2018 and is predicted to reach close to $12 billion by the end of 2025.[1] Nasal products, however, are complex and require significant formulation expertise for successful development.

BENEFITS OF NASAL DELIVERY

The diversity of nasal delivery formulations is central to their appeal – they can be water based, hydroalcoholic, nonaqueous, suspensions or emulsions. Moreover, they can include diverse excipients, including solvents, mucoadhesive agents, buffers, antioxidants, preservatives and penetration enhancers, all of which address some of the fundamental challenges to drug development – solubility, bioavailability and patient acceptance being the big-ticket items.

Formulations for systemic delivery are absorbed directly into the bloodstream, bypassing the liver and first-pass metabolism, which can be an important consideration for drugs that are degraded in the gastrointestinal tract. Rapid absorption also leads to fast-acting systemic effects, even when a patient is unconscious, which can be important for emergencies. Delivery to the olfactory region of the nasal cavity also allows direct access to the central nervous system for some neurological therapies. Nasal delivery is also non-invasive and easy to use compared with injectables, leading to improved patient acceptance and compliance. In addition, it offers a method to administer diverse APIs for both local and systemic applications.

Where solution and suspension dosage forms cannot be developed, dry powders may offer an alternative method and offer additional benefits, including enhanced chemical stability, the absence of preservatives, lower risk of microbial spoilage (which means fewer or no preservatives) and the ability to administer larger amounts of API in each dose. The suitability of a powder formulation is dependent on the solubility, particle size, aerodynamic properties and nasal irritancy of the active drug and/or excipients.

> "The diversity of nasal delivery formulations is central to their appeal – they can be water based, hydroalcoholic, nonaqueous, suspensions or emulsions."

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CHALLENGES TO FORMULATION DEVELOPMENT FOR NASAL DELIVERY

Biological Barriers

Despite relatively easy access, the complex geometry of the nose makes reliable and efficient delivery to the mucosal surfaces deep in the nose a challenge. The narrowest segment of the respiratory tract is the nasal valve, which accounts for around 80% of nasal resistance and a significant portion of total respiratory resistance. If the area is irritated or the patient has symptoms that lead to sniffing, this causes additional narrowing of the valve.

Bioavailability

The bioavailability of nasally administered drugs can be restricted by low drug solubility, enzymatic degradation in the nasal cavity, poor membrane penetration and rapid clearance. Particularly large molecular weight peptides and proteins also exhibit notably limited permeability in nasal mucosa.

While formulations can address these problems using a variety of strategies, they must be fully understood to ensure a tailored approach.

Clearance

The epithelium of the nasal passage is covered by a mucus layer that entraps particles. The mucus layer is cleared from the nasal cavity by cilia and is renewed every 10–15 minutes, with mucus moving through the nose at an approximate rate of 5–6 mm/min, resulting in particle clearance every 15-20 minutes. Drugs with poor solubility would be particularly challenging in this scenario, as they must guarantee sufficient bioavailability to achieve the desired therapeutic effect.

Mucoadhesives and bioadhesives are often used to reduce nasal clearance and may be formulated with permeation enhancers, certain co-solvents and, in order to avoid or minimise degradation, enzymatic inhibitors. In all instances, the potential for irritation has to be considered as it could lead to sniffing, which would counteract any reduction in clearance rate.

> "Ergonomic aspects of the delivery device systems are also a factor as orientation, patient handling and actuation forces can affect use and patient compliance."

COMPATIBILITY WITH THE DELIVERY DEVICE

There is a relatively small selection of dry powder nasal devices, considering the attractiveness of this route of administration. Nasal devices use numerous methods to deliver the drug, including actuation by pressure (manual actuation), patients blowing into the device, pressurised systems or propellants. When it comes to powders, there can be variability of efficacy when using devices where patients have to blow into the device to eject the powder to the nose. Pressurised systems or the use of propellants can result in more reproducible results, dependent upon the device, but they can create discomfort for patients during application.

Patient acceptance

Ergonomic aspects of the delivery device systems are also a factor as orientation, patient handling (dexterity) and actuation forces can affect use and patient compliance. The use of preservatives can also have an impact. Preservative-free systems are gaining popularity with patients who have experienced discomfort with preserved formulations and the local side effects attributed to them.

FORMULATION STRATEGIES

API solubility

The API needs to be formulated with excipients that enhance adhesion and, therefore, absorption in the nasal mucosa. The excipients selected depend on

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the solubility of the API as well as the concentration needed to provide the necessary dose in each spray. The formulation needs to be made so it maximises contact with the nasal mucosa, holds off clearance for as long as possible and is rapidly absorbed.

Minimising clearance with mucoadhesives

With nasal delivery, versatile polymers can be leveraged as mucoadhesive and bioadhesive excipients in complex topical mucosal formulations to slow down clearance in the nasal cavity, increasing residence time to up to 30 minutes. The key benefit is in maximising drug absorption by prolonging contact time, which can increase bioavailability, reduce dosing frequency and subsequently improve patient compliance.

ADDRESSING BIOAVAILABILITY CHALLENGES

Bioavailability is always an essential consideration during the development of a new nasal drug. Absorption via the nasal mucosa directly into the bloodstream bypasses the liver and first-pass metabolism – a key consideration for drugs that have poor oral bioavailability. The bioavailability of large-molecule drugs delivered nasally can be improved with permeation enhancers.

> "By aligning development with the selection of the device, factors such as the method of powder ejection and deposition mechanism in the nasal cavity can be factored into the formulation."

Nanomilling and lipidic-based systems have proven to be a highly effective means of addressing bioavailability challenges in the case of small molecules.

The smaller API particles generated by nanomilling can dissolve more readily, with the rate of dissolution being inversely proportional to the diameter of the particle. This creates a high concentration gradient that facilitates the transfer of the API across biological barriers, including membranes.

Lipid-based systems, including nanoemulsions, liposomes and cubosomes, as well as mixed systems, such as lipid nanoparticles with a solid matrix or nanostructured lipid carriers (NLCs), have also been successfully employed in nasal formulations. While there are numerous articles describing these dosage forms and *in vitro* data, there is a scarcity of marketed products using these technologies. For example, in the case of solid lipid nanoparticles and NLCs, Montoto[2] counted 12 out of 211 reviewed publications (with pharmacodynamic and/or pharmacokinetic data) concerned a nasally administered formulation. They go on to state that, in general, very few nasal dosage forms reach the clinical trial stage.

CO-DEVELOPING FORMULATION AND DEVICE

Co-operation between teams that are involved in formulation and device development is often essential to successful commercialisation. Effective, targeted nasal drug delivery requires reaching the high and deep part of the nasal passages. This means the drug must be delivered beyond the nasal valve and above the inferior turbinate bone to reach the broad surfaces that are lined by the respiratory epithelium that surround sinus openings and where the nerves from the brain can be accessed. Selecting the nasal powder device in the early stages of formulation development is critical, due to the impact it can potentially have on the final product performance.

By aligning development with the selection of the device, factors such as the method of powder ejection and deposition mechanism in the nasal cavity can be factored into the formulation. The intended deposition location in the nasal cavity is important for efficacy and will depend on both the formulation and the device. The delivery device, whether a spray pump or a metered dose inhaler, must be effective for delivering a precise dose to this target area. The device should also be easy to use by the intended patient population.

CONCLUSION

Driven by the inherent benefits of nasal delivery, the number of new drug applications for nasal drugs will continue to increase in the coming years as pharmaceutical companies continue to explore more patient-friendly routes of administering biologics. Bioavailability, solubility and compliance remain the core challenges for formulations. However, a variety of strategies can be adopted and tailored to each drug. To successfully bring such products to market, extensive experience with a full range of formulation, analytic and manufacturing services in complex nasal drug products is required.

ABOUT THE COMPANY

The Lubrizol Corporation, a Berkshire Hathaway Company, leverages its unmatched science to unlock immense possibilities at the molecular level, driving sustainable and measurable results to help the world Move Cleaner, Create Smarter and Live Better. Founded in 1928, Lubrizol owns and operates more than 100 manufacturing facilities, sales and technical offices around the world and has approximately 8,800 employees.

ABOUT THE AUTHOR

Robert Lee, PhD, President, Lubrizol Life Science Health, CDMO Division, is responsible for product and business development, along with providing strategic direction. He holds BSc degrees in Biology and Chemistry from the University of Washington (Seattle, WA, US) and a PhD in Physical Bioorganic Chemistry from the University of California (Santa Barbara, CA, US). Dr Lee has published more than three dozen articles and five book chapters, as well as holding 11 issued patents and 15 provisional or PCT patent applications. He has over 30 years of experience in pharmaceutical research and development of both therapeutic drugs and diagnostic imaging agents.

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COPLEY

IMPROVING *IN VITRO* TEST METHODS FOR NASAL DRUG PRODUCTS

In this article, Mark Copley, Chief Executive Officer, and Anna Sipitanou, Business Development Manager, both of Copley Scientific, look at how *in vitro* testing is being refined for greater repeatability and to maximise its value as a low-cost tool for product development, including an assessment of the role of automation in improving the sensitivity of *in vitro* testing.

There are sound reasons why *in vitro* test methods for nasal drug products are currently subject to scrutiny with a view towards their improvement, such as by shaping them to provide more precise information for targeted delivery. The nasal route is of growing interest for systemic drug delivery, in no small part due to the access it provides to the central nervous system and the associated potential to bypass the blood-brain barrier.[1] Nasal drug products for migraine already demonstrate this potential, which holds promise for the treatment of neurological conditions such as Alzheimer's disease, depression and schizophrenia. For therapies such as these, drug delivery to specific areas of the nasal cavity can be important. Nasal vaccine delivery is also now increasingly well-established, offering recognisable advantages for the delivery of vaccines for influenza, HIV and hepatitis.[2] Furthermore, trials for covid-19 nasal vaccines are already underway.[3]

On the other hand, nasal sprays for local action, such as those for the treatment of allergic rhinitis and hay fever, still dominate the market, making them an important target for generic manufacturers. Pharmacokinetic studies have limited relevance when it comes to demonstrating bioequivalence for locally acting products,[4,5] intensifying the need to optimise the application of *in vitro* techniques. Sensitive techniques with proven clinical relevance have a vital role to play in supporting abbreviated new drug applications.

NASAL DRUG DELIVERY – FROM GENERATION TO DEPOSITION

Many commercial nasal drug products are mechanical metered dose sprays, packaged either as a multi- or unit-dose format. Nasal aerosols that employ a propellant for drug delivery are an alternative for liquid formulations, along with nasal drops, which are a popular choice for locally acting therapeutics. Nasal powders have also been commercialised, as exemplified by Baqsimi (glucagon) (Eli Lilly), for the treatment of severe hypoglycemia.[6] Closer examination of the mechanisms of drug delivery via nasal spray can help to elucidate the challenges associated with product development, many of which are common to all nasal drug products.

> "Pharmacokinetic studies have limited relevance when it comes to demonstrating bioequivalence for locally acting products, intensifying the need to optimise the application of *in vitro* techniques."

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Drug delivery via a nasal spray is driven by a manually actuated metering pump, the performance of which is manipulated via design parameters such as precompression ratio and the length, geometry and orifice size of the actuator. Nasal spray formulations are solutions or suspensions of one or more APIs, often in an aqueous-based system, with precisely controlled physical properties, notably their rheology. The properties of such formulations are optimised for stability and for dispersion by the shear force applied via actuation of the chosen device.

The patient is the final variable in the drug delivery process. Factors such as insertion depth into the nostril, orientation angle and the force/time profile applied during actuation all influence the characteristics of the delivered dose. Furthermore, there is the unique physiology of the patient's nasal cavity to contend with. The vasculature-rich turbinates are the typical target for drug delivery, however, there is the potential for very fine (<10 µm) droplets to penetrate through the nasal cavity and deposit in the lung, compromising drug safety, while larger droplets may deposit at the front of the nose, undermining efficacy. Droplet collection in the anterior cavity and subsequent dripping from the nostril or, conversely, an unpleasant taste after product use due to droplets reaching the nasopharynx, are both unwanted side effects of suboptimal drug deposition.

This brief examination of the factors influencing nasal drug delivery highlights the multifactorial space that must be robustly explored to develop a nasal drug product with consistent, reproducible and well-defined deposition characteristics. *In vitro* test methods generate vital information and are lower cost, less variable, easier to control and more reliably differentiating than clinical trials. However, they may lack clinical relevance. Scrutiny as to whether the precision, relevance and application of current techniques is optimal is therefore a natural consequence of the desire for faster, more cost-efficient development.

> "*In vitro* test methods generate vital information and are lower cost, less variable, easier to control and more reliably differentiating than clinical trials."

ASSESSING THE PERFORMANCE OF NASAL DRUG PRODUCTS

In vitro tests recommended in US FDA guidance for nasal drug products include:[5]

- Single actuation content (alternatively referred to as dose uniformity) through the life of the container
- Droplet size distribution by laser diffraction
- Drug in small particles/droplets (for nasal sprays) or particle/droplet size distribution by cascade impaction (for nasal aerosols)
- Drug particle size distribution by microscopy (for suspension formulations)
- Spray pattern
- Plume geometry
- Priming and repriming.

These well-established tests provide a wealth of information to guide product development and/or demonstrate bioequivalence. Dose uniformity testing, for example, confirms the consistency with which the label dose is delivered across the lifetime of the product. Droplet size distribution has a defining influence on *in vivo* behaviour; droplet sizes in the range of 20–30 µm, in combination with low injection velocities, are associated with high levels of drug deposition in the turbinates,[7] and the amount of drug in small particles is relevant to the potential hazard of pulmonary deposition. Priming and repriming tests assess how reliably and consistently the product works if used according to the instructions for use with respect to, for example, storage and shaking.

However, the standard methods and equipment have their limitations, especially when set against efforts to extend the application of nasal drug delivery, in particular with respect to the study of regional deposition. Supplementary techniques deployed for the study of regional deposition behaviour include testing with nasal casts or replicas and gamma scintigraphy, though neither is readily deployed in routine workflows. Important issues relating to the use of realistic nasal replicas include the manufacture of such replicas and the time-consuming, manually intensive nature of drug recovery, due to the complex geometry involved.

Gamma scintigraphy is a non-invasive imaging technique that involves incorporating radioactive tracers into a formulation and subsequently detecting their location, *in vivo*, following product use. With this technique, it is possible to generate confirmatory data that test and reference product deposits analogously, to support bioequivalence claims and to compare formulations and/or devices with respect to drug delivery to a specific target. However, again, gamma scintigraphy is far from a routine benchtop tool.

When it comes to shaping analytical tools to better support nasal drug product development, it is important to consider both the information being sought and the practicalities of routine measurement.

AUTOMATION AND ITS ROLE IN REDUCING CONFOUNDING VARIABILITY

Automation is a well-recognised route to easing the manual burden associated with routine analysis while simultaneously improving data quality. Just as patient technique is a source of variability in nasal drug delivery, manual spray actuation can erode the sensitivity of *in vitro* testing. Automating device actuation can therefore play a useful role in reducing variability and improving data integrity, as evidenced by the US Pharmacopeia (USP) specification that "a mechanical means of actuating the pump assembly be employed to deliver doses for collection" when testing nasal sprays.[8]

Reducing method variability enables better investigation of the variability that is actually of interest to drug developers – the variability that arises from differences relating to the device, formulation or patient. In the same way, reducing method variability improves the sensitivity of comparative studies in generic product development, making it easier to robustly detect differences between a test and reference product, or conversely to confirm equivalence more reliably.

Table 1 shows data from a single-actuation content study carried out using Vertus II, Copley Scientific's automated system for nasal spray actuation, in combination with Copley's Nasal Spray Dose Collector (NSDC), an innovative accessory for dose sampling. Crucial to any testing method is the complete and demonstrable capture of the delivered dose. However, sample loss due to dripping and leakage is commonplace, due to the need to

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fire nasal sprays upwards to simulate actual product use coupled with the widespread use of glass flasks or vials for dose collection.

Copley's NSDC has a curved impaction surface that minimises dripping onto the spray nozzle tip and an internal geometry that guides the collected sample to a small collection sump. The Vertus II interfaces directly with the NSDC, fully automating actuation and test flow control. The speed, angle and duration of shaking ahead of actuation; firing force, including the speed of application and release of that force; and time delay between shaking and firing can all be defined and closely controlled, in accordance with test requirements.

In the single actuation content study, testing was carried out using a commercial beclomethasone dipropionate formulation filled into a standard commercial nasal spray pump/bottle (Aptar Pharma). The delivered dose was determined by opening the NSDC and recovering the drug via a process of rinsing and sonication. Drug was also recovered from the nasal spray nozzle via rinsing and dissolution. The total metered dose was determined by summing the drug recovered via both routes and then compared with the label claim. The results showed extremely high repeatability across a series of ten tests, far higher than the 75–125% acceptability limits specified in the European Pharmacopoeia.[9] As discussed, such precision translates into high sensitivity, enabling studies to differentiate between products more accurately.

Figure 1 shows an alternative test set-up for automated dose delivery measurement using a standard metered dose inhaler (MDI) dose uniformity sampling apparatus (DUSA). Recent revisions to the European Pharmacopoeia and USP <601> updated guidance on delivered dose uniformity for nasal sprays, aligning it with guidance for pressurised MDIs.[8,9] Direct interfacing of the DUSA with the Vertus II provides a simple, easy-to-use and high integrity set-up for automated testing.

A BENCHTOP TOOL FOR ASSESSING REGIONAL DEPOSITION

Recognition of the potential benefit of a better benchtop tool for investigating regional deposition for nasal drug products has led to the development of the Alberta Idealised Nasal Inlet (AINI),[10] using analogous methodologies to those deployed in the development of the Alberta Idealised Throats. Both products were originally developed by researchers working with Professor Warren Finlay at the University of Alberta (Edmonton, Canada) and subsequently commercialised by Copley Scientific. Rather than realistic replicas of the nasal cavity or throat, these "idealised" accessories are easy-to-use tools that accurately mimic deposition behaviour for a wide range of patient physiologies.

Development work for the AINI began with computational fluid dynamic simulations of drug deposition behaviour in realistic nasal airway geometries derived from computer tomography (CT) scans of seven adult subjects.[7] Close to 250,000 data sets were produced to rigorously assess the impact of various parameters, including droplet size and injection velocity, for sprays injected separately in both left and right nostrils. An idealised geometry was developed from these data,[6,9] striking a balance between an accurate representation of the deposition behaviour observed in the replicas and a simple, easy-to-use solution (Figure 2).

NSDC ID	DD NSDC (µg)	Nozzle (µg)	MD (µg)	Recovery (MD % of label claim)
NSDC 1	49.909	0.224	50.13	100
NSDC 2	48.567	0.494	49.06	98
NSDC 3	49.944	0.330	50.27	101
NSDC 4	49.125	0.431	49.56	99
NSDC 5	47.781	0.453	48.23	96
NSDC 6	49.679	0.458	50.14	100
NSDC 7	49.726	1.168	50.89	102
NSDC 8	43.359	0.312	43.67	87
NSDC 9	49.320	2.597	51.92	104
NSDC 10	49.044	0.535	49.58	99
Mean (±SD)	48.65 (± 2)	0.7 (± 0.7)	49.35 (± 2.2)	99 (± 4)

Table 1: Dose uniformity testing for a beclomethasone dipropionate nasal spray with automated actuation (Vertus II) and NSDC for dose collection.

Figure 1: A test set-up for dose uniformity testing with automated actuation (Vertus II) and MDI DUSA.

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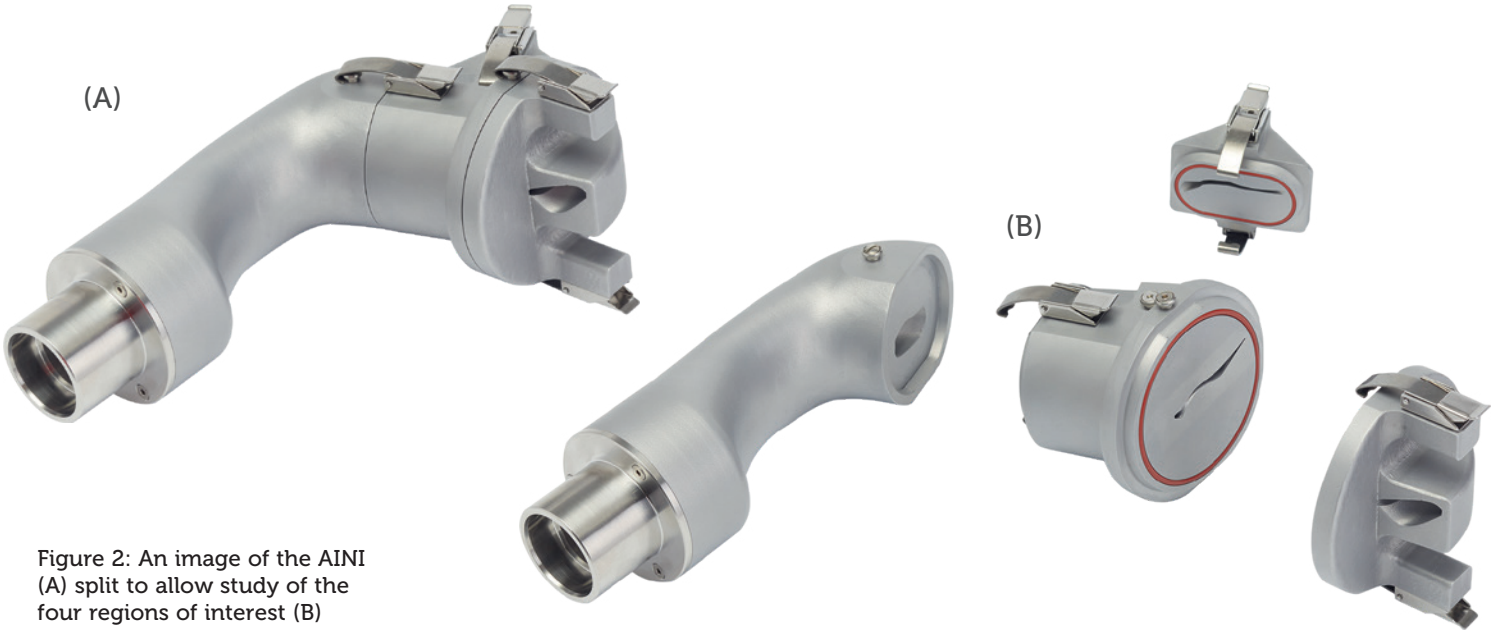

Figure 2: An image of the AINI (A) split to allow study of the four regions of interest (B)

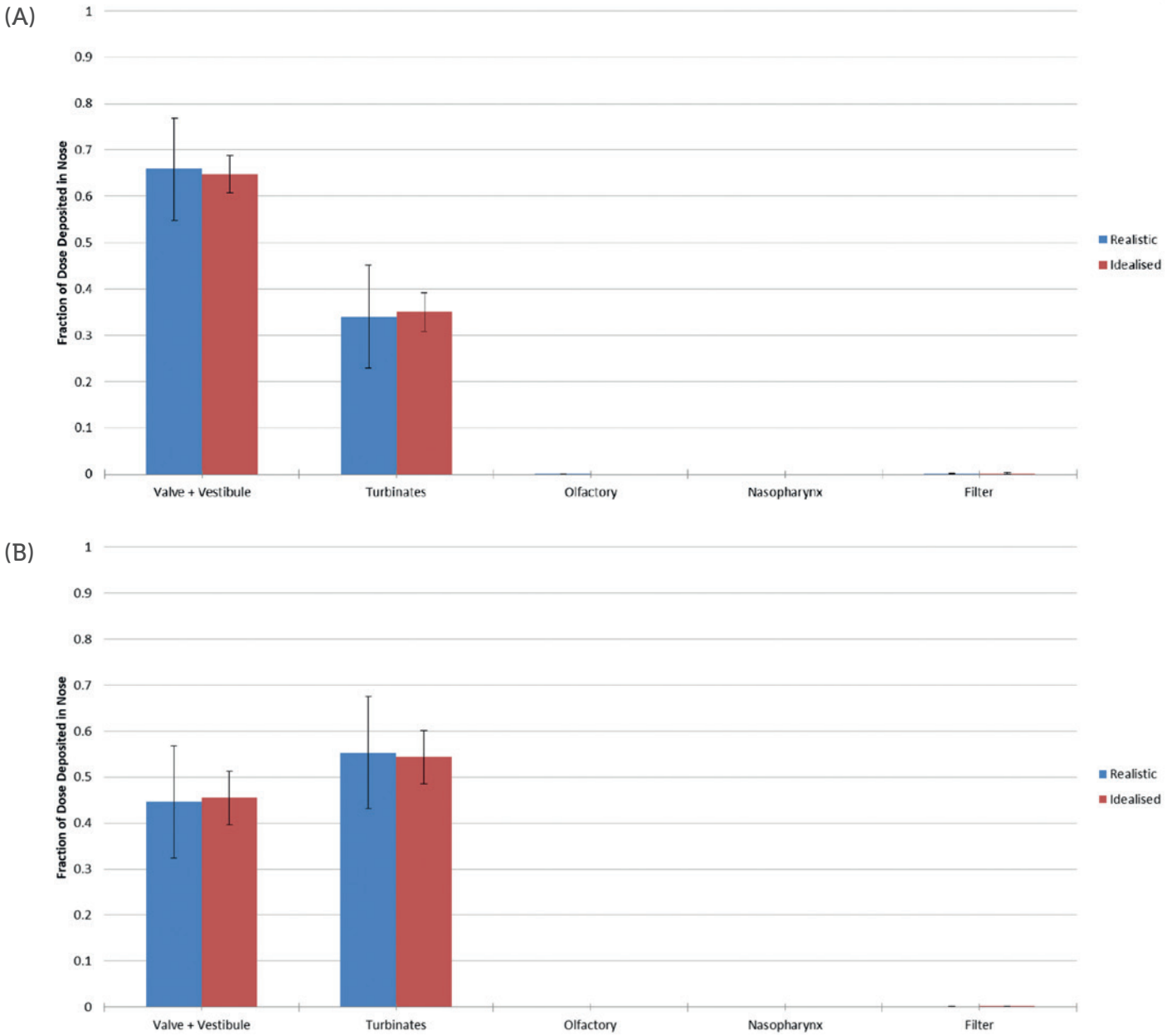

Figure 3: Deposition data for a commercial nasal spray, at an orientation angle of 60° (A) and 45° (B), highlight the ability of the idealised geometry to accurately reflect behaviour in realistic nasal geometries and reduce variability.

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Figure 3 shows data from an experimental study of the performance of the idealised geometry relative to realistic nasal replicas.[11,12] In this work, five polymeric nasal replicas were manufactured from CT data gathered from adult subjects, using a rapid prototyping technique. These were then used to assess drug deposition from a commercial nasal spray pump (specifically a 5.2 mg cromolyn sodium spray). Testing was carried out at an inspiratory flow rate of 7.5 L/min at two different orientations: 60° and 45° from horizontal. Comparative testing was also carried out with a rendering of the idealised geometry produced using the same prototyping technique. Note that, in this study, the element of the idealised geometry referred to as "vestibule" in the AINI is referred to as "vestibule + valve" for comparison with the nasal replicas.

The results showed close agreement between the data generated using the idealised geometry and the realistic nasal replicas. However, the results generated with the idealised geometry exhibited far less variability, enhancing their value for scientific studies. Interestingly, the data gathered at different orientations showed a significant difference in deposition behaviour, underlining the importance of this patient technique-related variable in the drug delivery process.

For this nasal spray there are also published gamma scintigraphy data quantifying *in vivo* deposition in five male subjects.[4] In this work, average deposition in the anterior region, which translates approximately to the valve + vestibule, was found to be 0.56 ± 0.3 µg, while posterior deposition, which can be equated with deposition in the turbinates, was 0.44 ± 0.1 µg. The administration angle was not reported in this work, but this compares with 0.45–0.65 µg and 0.35–0.55 µg respectively, depending on orientation (Figure 4). In both studies deposition in the nasopharynx was found to be negligible.

These results confirm the relevance and utility of the AINI which, in practice, has two key applications. Firstly, it can be attached directly to an external filter to directly investigate regional deposition, as exemplified by this study, as well as to representatively measure respirable mass – the mass of dose that may reach the lung. Such studies are valuable for targeting drug delivery in new drug development and for the demonstration of bioequivalence in generic product development. The second application is to interface the AINI with

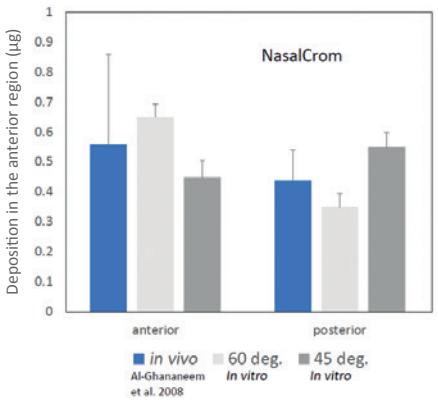

Figure 4: Deposition data for a commercial nasal spray measured with the idealised geometry show good agreement with *in vivo* gamma scintigraphy data.

a cascade impactor to representatively determine the amount of drug in small particles/droplets with a higher degree of clinical realism. An inlet that fails to simulate drug capture in the nasal cavity prevents representative assessment of the respirable dose.

GOING FORWARD

Better solutions for *in vitro* testing have an important role to play in accelerating the development of nasal drug products, whether the goal is new vaccines for covid-19, more clinically efficacious therapies for neurological diseases or cost-effective products for everyday ailments that negatively impact quality of life. Automation can reduce the variability associated with testing, sharpening sensitivity while also boosting analytical productivity. On the other hand, benchtop tools for the study of regional deposition are a cost-effective option for researchers investigating how to target specific areas of the nasal cavity to enhance drug delivery, as well as for those looking to support claims of bioequivalence. For new and generic nasal product developers alike, these tools are an important step forwards in efforts to exploit the full potential of the nasal route for drug delivery, and realise the exciting possibilities it promises.

ABOUT THE COMPANY

Copley Scientific is recognised as a leading manufacturer of inhaled drug test equipment. Products include delivered dose-sampling apparatus, Andersen and Next Generation impactors, critical flow controllers, pumps, flow meters and inhaler-testing data analysis software. Copley Scientific also supplies novel systems for improving productivity and *in vitro/in vivo* correlations, including semi-automation ancillaries, abbreviated impactors, breath simulators and the Alberta Idealised Throats. Training, calibration, maintenance and impactor stage mensuration services are also available. Founded in 1946 in Nottingham, UK, Copley Scientific remains family owned and managed. The company continues to work closely with industry groups and leading experts to bring relevant new products to market, with all equipment backed by expert training and lifetime support.

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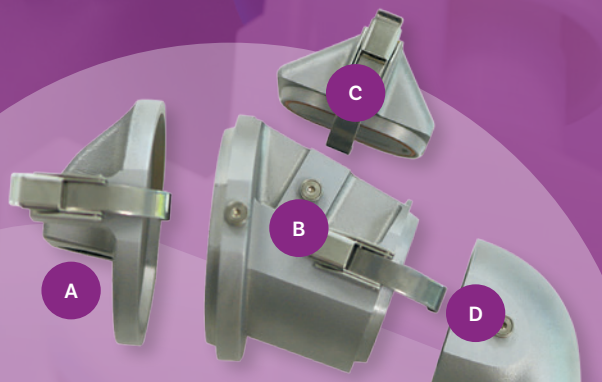

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TOWARDS A MORE SUSTAINABLE FUTURE WITH pMDI SOLUTIONS

In this article, Howard Burnett, Vice-President and Head of Global Pulmonary Category; Chris Baron, Director of Business Development; and Jay Bhogaita, Business Development Director, Pulmonary Category, all of Aptar Pharma, summarise the findings of a recent forum that looked at the development of more sustainable pressurised metered dose inhalers.

Those working in pulmonary drug and device development recognise the complexities associated with developing a combination product. For over 60 years, the challenges faced in delivering a pressurised metered dose inhaler (pMDI) to market have been largely consistent. These include ensuring valve compatibility with the drug formulation, safeguarding the integrity of the container closure system and adding in more measures to encourage greater levels of adherence – all while protecting both the efficacy of the drug product and the safety of the patient.

Perhaps one of the greatest challenges to date came in 1987 with the signing of the Montreal Protocol, and the initiation of phasing out chlorofluorocarbon (CFC) propellants. In 2016, the Kigali Amendment to the Montreal Protocol recognised that the hydrofluorocarbons (HFCs) that replaced CFCs are also powerful greenhouse gases with high global warming potential (GWP).[1] Ratified by over 120 countries, this amendment brought in measures to phase down (rather than phase out) the production and consumption of 18 designated HFCs by more than 80% over the next 30 years.

And so, today, we are faced with a similar challenge to the phasing out of CFCs – how to move away from HFA propellants, such as 134a and 227, to an even more sustainable approach that further reduces the sector's carbon impact.

As a market leader in respiratory devices, Aptar Pharma, together with Pharmaserve NW, recently convened a forum of experts to discuss "where next?" with the end-to-end development of more sustainable pMDI solutions. Recognising that only an integrated, collaborative approach involving experts throughout the product lifecycle can address the challenges ahead, Aptar Pharma and Pharmaserve NW invited a broad range of representatives to the forum, who collectively provided a high-level blend of scientific, pharmaceutical, clinical and engineering expertise. This article summarises the key findings.

A MORE SUSTAINABLE FUTURE FOR pMDIS IS CRITICAL FOR WORLD HEALTH

Respiratory diseases, including asthma and chronic obstructive pulmonary disease (COPD), are amongst the leading causes of death and disability worldwide. In the UK alone, the number of people to have received an asthma diagnosis is estimated to stand at 5.4 million[2] – and COPD affects approximately three million people.[3] Inhaled treatments, using devices such as pMDIs, dry powder inhalers (DPIs), soft mist inhalers (SMIs) and nebulisers, are used across the world as the mainstay of treatment for patients with respiratory conditions.

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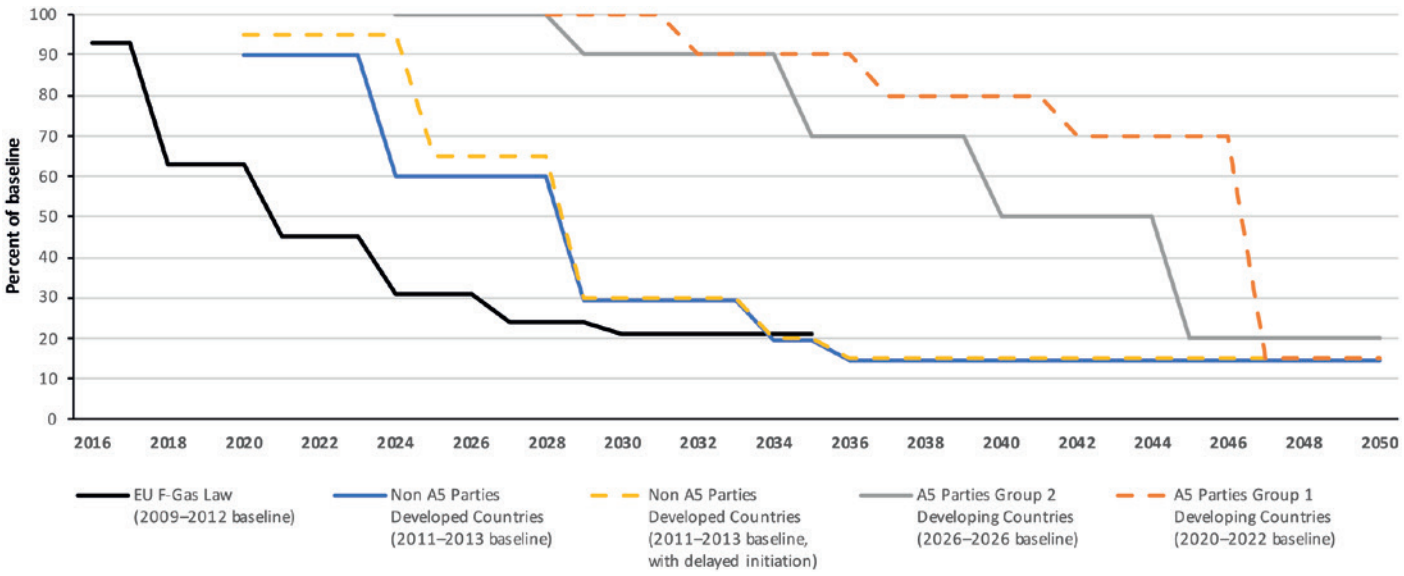

Figure 1: HFC phase-down schedules.[6]

However, the healthcare market's total contribution to worldwide net emissions (4.4% in 2014)[4] continues to be a key focus for global and regional legislation, national healthcare guidelines, policies and recommendations. In this context, the use of HFCs in pMDIs forms a relatively small part of the greater whole. In the UK, for example, where pMDI use is proportionately higher than other European nations, it accounts for 3% of the UK NHS's carbon footprint and 0.1% of the total national carbon footprint.[5] Nevertheless, it remains imperative to reduce this figure further as part of a more sustainable future for pMDIs and other inhalation devices. It is also worth stating that, with the use of lower-GWP propellants, the contribution to carbon footprint may be lower or at least equivalent to other formats such as DPIs (Figure 1).

FINDING THE RIGHT DRUG FOR THE RIGHT PATIENT AT THE RIGHT COST

From the forum's clinician contributor, the message was clear: the climate crisis presents a considerable threat to human health and urgent, concerted action is required. Although the contribution of propellant-based pMDIs is relatively low in terms of their overall global carbon footprint, the transition to propellants with an even lower GWP will play an important part in improving the overall environmental burden associated with pMDI devices.

"For patients who currently prefer the familiarity and convenience of aerosolised inhalers, device choices in the future will increasingly be influenced by questions around sustainability."

For patients who currently prefer the familiarity and convenience of aerosolised inhalers, device choices in the future will increasingly be influenced by questions around sustainability. As personalised medication becomes more prevalent, devices must therefore become much more fit for purpose, addressing financial burden, environmental cost, patient compliance and efficacy of treatment in equal measure.

"Given that there is mounting pressure from prescribers to find other, more sustainable alternatives, the future for pMDIs could be deemed to be up in the air."

IS THE FUTURE OF pMDIS UP IN THE AIR?

Given that there is mounting pressure from prescribers to find other, more sustainable alternatives, the future for pMDIs could be deemed to be up in the air. Taking the UK as an example, the NHS has set a target of a 50% reduction in the carbon footprint of inhalers by 2028. However, most DPIs and SMIs feature a large amount of plastic and/or metal components that will contribute to their GWP potential.

That said, a key consideration for the industry is the need to balance the cost of such devices, in terms of their impact on the environment, with the financial burden for payers. Delivering affordable reliever medication in a pMDI format will likely become more of a challenge than meeting emission targets, given that the decreasing use of current HFC propellants (p134a and p227) in other applications could lead to increased cost pressure on pMDI manufacturing. The year 2025 could see the tipping point, when there are no exceptions to reduction under the Montreal Protocol. It is possible that this could result in an increase in the price of medical-grade propellants, leading to a rise in overall manufacturing costs.

One of the benefits of the forum was the richness and diversity of viewpoints and data sources. While some experts maintain the world cannot afford not to switch as soon as possible, others express a more cautious tone. The forum was presented with a survey of 452 asthma and COPD patients who ranked "environmentally friendly" as the ninth most important characteristic of an inhaler.[7] A further combined study of 150 asthma and COPD patients, 90 healthcare professionals and 10 NHS managers ranked "environmental impact" as an important factor in treatment decisions in 60%, 40% and 25% of respondents, respectively. Above all, cost was ranked as more important than any other consideration.

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LEARNING FROM THE PAST TO DELIVER FOR THE FUTURE

One manufacturer of HFA medical propellants was clear that regulation will happen as the societal requirement for low-carbon inhalers (or low-GWP products) accelerates. Pharma and drug delivery supply chains need to react to find better products for partners and patients while learning the lessons from the CFC transition in the 1990s.

One of the challenges associated with the CFC to HFA transition was that the Montreal Protocol was implemented before 134a was fully proven for pMDI use. Indeed, 134a was, in part, selected because it was what chemical manufacturers had already identified as "their CFC-12 replacement". The industry was not ready, so urgent technical, stability, formulation, materials and facility investment work was needed to meet the regulation within the timescales. This time we know it is coming and we need to be better prepared.

While low GWP is a key component, it should not be the only consideration in the development of a new propellant, it was argued at the forum. Stakeholder satisfaction is another key criterion. For pharma partners, the formulation must be optimal in both suspension and solution forms. It must be a similar cost to current propellants and the supply chain must be stable, with multiple options for supply. And, of course, the formulation must be safe for patients and meet the anticipated regulatory demand. From a lifecycle perspective, the propellant must display stable characteristics and not decompose when exposed to persistent environmental factors. And, in today's world, recover, reclaim and re-use are core imperatives.

This transition should also be viewed as a generational opportunity to make improvements. The baseline is that the new propellant must be at least as good as 134a or 227 on pMDI performance measures. However, further investment, both financial and intellectual, is required to deliver the aspirational 90–99% environmental impact reduction and enable a more comprehensive coverage of available technologies – particularly in low-income economies.

SUSTAINABILITY IS PROPELLING IMPROVEMENTS IN CANISTER MANUFACTURE AND FILLING

While much of the focus is on discovering low-GWP propellants, there are notable advances coming from the wider supply chain, including canister manufacturers and filling lines. One expert at the forum presented the business case for the use of fluorocarbon polymerisation plasma, which produces a low surface energy (hydrophobic) fluorocarbon nanolayer on the internal surface of the cannister. Covalently bonded to the internal surface of the canister, this approach presents many benefits over the traditional solvent-based fluoropolymer-coated canisters, and notably less CO_2 emissions, in fact 143 kg per million plasma-coated cans compared with 1,445 kg per million for anodised cans. Of course, formulations that only require uncoated canisters would not be subject to such a process and, as such, would further lower the GWP burden.

In terms of filling, there are clear opportunities to reduce CO_2 emissions during the filling process, making it an important consideration for the development of low-carbon inhalers. Purging the can of air prior to crimping using propellant is a well-recognised process designed to remove any impurities, negate pressure rise within the can and eradicate the opportunity for reactions with the drug substance. Both traditional methods of purging result in propellant loss which, when filling large batches, constitutes a great deal of wastage. To prevent such wastage, an alternative purging technique, vacuum crimping, is being advocated, as the process has zero propellant emissions.

The change in propellant will, of course, have implications for existing filling lines designed and approved for use with incumbent propellants. Consideration must be given to the specific properties of 1234ze and 152a in areas such as flammability, meaning some investment will need to be made in new equipment infrastructure for filling.

WITHOUT BIOEQUIVALENCE, THERE WILL BE NO FUTURE

Of course, without regulatory approval, there is no future. And, for an issue that affects the planet, it is essential to address the requirements of regulatory bodies across the globe. To secure approval in the US, for example, the US FDA states that it will need to see "supporting data relating to the proposed variation(s)" in terms of input material specifications, device specifications, manufacturing process changes and product performance. To achieve bioequivalence (BE), the following performance criteria must be met: single actuation content, aerodynamic size distribution, spray pattern, plume geometry, priming and repriming.[8]

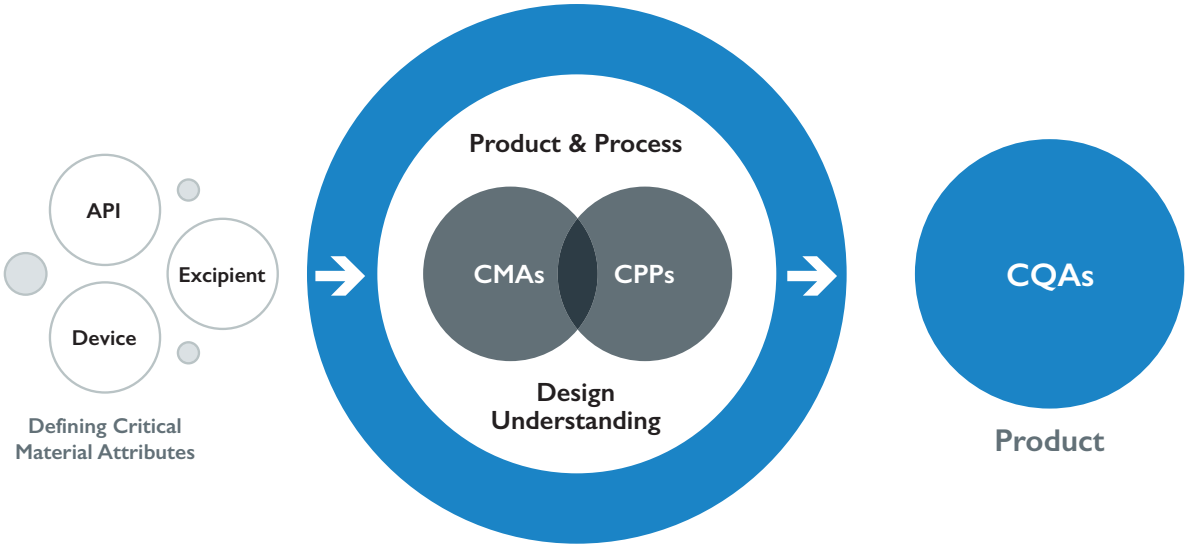

Figure 2: SmartTrack™ – the unique, integrated solution to fast track local BE.

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"It is estimated that more than half a million tonnes of CO_2 equivalent would be saved if every inhaler user in the UK returned all their inhalers for one year."

A major barrier to the development and proof of these criteria is the cost and requirements for clinical endpoint BE studies. Patient numbers can be significant, sometimes larger than the originator's efficacy study, and considering the high variability, the low sensitivity and the inability to detect formulation differences, these studies are only confirmatory of local equivalence. One alternative is the SmartTrack™ integrated solution from Nanopharm, an Aptar Pharma company. This solution combines integrated device and formulation approaches, realistic performance testing tools and *in silico* modelling and simulation to streamline the project, reducing the time, cost and risk in demonstrating local BE (Figure 2).

THE GRASS MAY NOT BE GREENER WHEN IT COMES TO REGULATORY APPROVAL

For a new chemical entity (NCE), the regulatory pathway for the development of pMDI products using newer propellants with lower GWP is clear – i.e. marketing authorisation application/new drug application (NDA). Clinical safety of new propellants would be evaluated in parallel to the NCE.

The replacement/repurposing of HFA 134a/HFA 227 in already approved pMDI products with lower GWP propellants could therefore be conceivably considered as hybrid generic development. However, the propellant makes up a significant proportion of the formulation composition, and there is poor availability and acceptability of human safety data on new propellants. As a locally acting medication, it will be more challenging to demonstrate BE.

Regulators may therefore consider switching the regulatory burden for low-GWP propellants to one like new product/NDA development, even though the active ingredient already has an established safety/clinical profile. This approach will increase the regulatory agency expectations for preclinical assessments, clinical safety and efficacy assessment, the weight of the stability data package at time of submission and the demonstration of BE. All of which could result in a significant impact on cost and timelines without implementing solutions such as SmartTrack™.

Clearly switching from HFA 134a/HFA 227 to lower-GWP propellants presents a series of different, less familiar challenges compared with "generic" inhalation development, with impacts on both pharmaceutical and therapeutic performance. The guidance from the forum's regulatory panellist was conclusive: engage early with appropriate regulatory authorities to better understand the requirements for product-specific preclinical studies; be clear about the expectations for the demonstration of pharmaceutical and therapeutic equivalence, and establish the requirements for product-specific clinical efficacy and safety studies. Only then can device companies refine their development strategy and realistically assign costs and timelines based on clear regulatory expectations.

EVERY COMPONENT SHOULD BE EVALUATED AND IMPROVED

Many industries are transitioning away from the traditional, linear model of "take-make-consume-throw away" and adopting the values of the circular economy, where waste and pollution are designed out of product lifecycles. Drug delivery is no different, and the effective recycling of pMDIs will come under closer scrutiny. But this does require effort from all stakeholders, not least patients. While a large proportion of inhalers are consigned to landfill every year, it is estimated that more than 0.5 million tonnes of CO_2 equivalent would be saved if every inhaler user in the UK returned all their inhalers for one year.[9]

WITH EVERY NEW CHALLENGE COMES NEW OPPORTUNITY

It is overstating this situation to call it a crisis but it is certainly a time of uncertainty, promise and opportunity. In isolation, the transition from propellants such as hydrofluoroalkanes HFA 227 and HFA P134a towards newer, lower-impact approaches is a sizeable task. However, this is a once-in-a-generation opportunity – one that cannot be missed – to ensure a more sustainable future for pMDI solutions for those millions of patients who need or prefer it.

Truly grasping this opportunity means learning the lessons from the CFC to HFA transition, including the need for effective collaboration, to ensure all the various complex and interconnected elements are managed in unison through the prism of a robust multi-stakeholder partnership. At the same time, priority must continue to be given to patient care while also encouraging innovation and allowing sufficient time for research and development activities. By adopting these measures, the industry can again demonstrate its collective ability to rise to the urgent global challenge presented by climate change.

ABOUT THE COMPANY

For pharma customers worldwide, Aptar Pharma is the go-to drug delivery expert, providing innovative drug delivery solutions across a wide range of delivery routes, including nasal, pulmonary, ophthalmic, dermal and injectables. Aptar Pharma Services provides early stage to commercialisation support to accelerate and derisk the development journey. With a strong focus on innovation, Aptar Pharma is leading the way in developing connected devices to deliver digital medicines. With a global manufacturing footprint of 14 GMP sites, Aptar Pharma provides security-of-supply and local support to customers. Aptar Pharma is part of AptarGroup, Inc. (NYSE:ATR), a global leader in the design and manufacturing of a broad range of drug delivery, consumer product dispensing and active material science solutions.

To learn more about Pharmaserve NW, visit: *www.pharmaservenorthwest.co.uk/technologies*

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Jay Bhogaita is Business Development Director within Aptar Pharma's Pulmonary Category team, where he is responsible for developing pulmonary delivery strategies, especially relating to sustainability, which includes transition to newer, lower-GWP propellants and exploring alternative innovative technologies. In addition, he contributes to the service provision strategy for Nanopharm, an Aptar Pharma company, enabling faster route-to-market, particularly for generic medicines. With over 30 years' experience in the medical devices industry, Mr Bhogaita has primarily focused on the inhalation sector.

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MAKING THE CONNECTION BETWEEN EFFICACY AND ENVIRONMENTAL SUSTAINABILITY

Andreas Meliniotis, Director of Device Development at Vectura, looks at the factors that should be considered when designing devices with a view to sustainable connectivity.

For any developer of an inhaled drug delivery device, the key design focus is on the user and the intended use to ensure that patient needs are met. There are, however, other needs that should be considered, particularly those of wider stakeholders across the supply chain, including the manufacturer, prescriber and payer. Considering these wider needs may alter the attractiveness of different design concepts by modifying the importance of certain attributes.

> "By carefully selecting design concepts, materials and manufacturing processes, environmental impact can be minimised whilst improving adherence."

Evaluating all these stakeholder needs can also result in conflicting or contradicting requirements. Understanding these, and taking steps to reduce their impact, allows innovators to choose design concepts that meet the demands of the market as a whole.

When designing products, giving consideration to user and environmental needs at a conceptual level can increase the effectiveness of the medication by attaining a high level of confidence in the measured data, while achieving a minimised level of environmental burden. This will ultimately lead to a more attractive product proposition prior to progression into full development – and, potentially, products with more longevity and lower risk throughout the development, commercialisation and market lifecycle.

The effectiveness of any treatment is a combination of many factors, most notably patient adherence to the dosage regimen and, in the case of complex products, the correct use of drug delivery devices by the patient. The lack of adherence and/or patient-use error can seriously compromise treatment outcomes.[1] Ineffective treatment is widely understood to be a key contributor to increased levels of disease exacerbations and/or poor clinical outcomes, which clearly have a large environmental impact due to the burden on health systems dealing with hospitalisations. By carefully selecting design concepts, materials and manufacturing processes, environmental impact can be minimised whilst improving adherence, which potentially improves clinical outcomes[2] and allows products to be cost effective at point of manufacture and supply.

CONNECTED DRUG DELIVERY

As their sophistication increases, delivery devices are likely to be increasingly designed with connectivity in mind, which could open up possibilities for integrated connectivity or high-functionality add-on devices. Currently, connected drug delivery is achieved predominantly through the use of add-ons to existing approved devices with a low level of functionality – or as integrated connected systems with higher

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Option	Device type	Plastic (g)	Devices per annum	Plastic per annum (kg)	Hydraulic	Hybrid	All-Electric
1	Integrated connectivity disposable DPI device	89	12	1.07	20.60	14.49	13.77
2	Disposable, combination product device	62	12	0.74			
	Connectivity module with non-rechargeable battery	27	4	0.11			
	Total			0.85	16.44	11.56	10.98
3	Base, disposable, combination product device	62	12	0.74			
	Connectivity module with changeable or rechargeable battery	27	0.5	0.01			
	Total			0.76	14.61	10.28	9.76
4	Integrated connectivity, re-useable, medical device with changeable or rechargeable battery	70	0.5	0.04			
	Replacement mouthpiece and nebuliser head	55	12	0.66			
	Total			0.70	13.41	9.43	8.96

Table 1: Levels of energy consumption during the manufacture of plastic components for different types of connected devices.

levels of functionality. Current examples of this are pressurised metered dose inhaler (pMDI) add-on devices, which sense the user pushing the pressurised canister to release the medication.

Although effective, the functionality of such devices is limited, as the base device has not been designed with connectivity in mind, so the options for communication between devices are restricted. Additional features such as orientation, shaking regimen or breathing duration sensing can now be easily included, often as standard with the integrated logic controller, and can offer useful insights that help to interrogate correct inhaler usage and give feedback to the patient.

Connected devices can have a positive impact on adherence and can identify user errors. However, these systems are costly, both financially and environmentally, and therefore should be applied only where needed most. For example, whereas insulin injections for diabetes generally have a high level of adherence because of immediate severe medical outcomes, an asthma maintenance therapy may exhibit poor adherence as there is no immediate, obvious decline in health. Using a connected device for the latter can provide a high level of monitoring, giving an early trigger for intervention to prevent uncontrolled disease and potential hospitalisation.

Some therapies can be affected significantly by user technique – and identifying this can have a dramatic effect on the efficacy of a treatment, particularly if it prevents a patient being prescribed a medication at a higher dose or additional medication to compensate for poor technique. Connected devices can provide both feedback and metrics to encourage patients to comply, while measuring physiological effects and reporting to the patient and the clinician can also help monitor the effectiveness of the medication, which can provide financial benefits in terms of reimbursement.

It is also important to consider the requirements of other parties or institutions that are involved throughout the supply chain. For example, attributes that may be highly important to the manufacturer include cost of goods, time to market and manufacturability. Whereas those relating to the clinician include effectiveness of treatment, effective disease management and market availability. These wider design requirements are unlikely to completely align with the user needs in all cases but clearly require consideration early in the design process.

> "Environmental requirements are likely to be in direct competition with those requirements related to user needs or the supply chain."

Environmental requirements are likely to be in direct competition with those requirements related to user needs or the supply chain. For example, changing a propellant in a pMDI could require significant investment by the manufacturer; and including connectivity functionality could increase the cost of goods (both plastic and electronics) leading to higher levels of energy used during manufacture, and greater quantities of waste materials being discarded at the end of use.

GOOD DESIGN PRINCIPLES

By employing good design principles, it is possible to meet the requirements of both the end user and the wider stakeholders. For example, a device with a simple and easy-to-use interface and a low component count and volume can minimise both the cost of goods and the impact on the environment. The same can be achieved by using efficient manufacturing equipment, such as hydraulic rather than electric plastic injection moulding machines, and siting manufacturing facilities close to raw material suppliers to reduce transport costs.[3]

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An analysis of the energy consumption related purely to plastic component manufacture shows how different ways of splitting the functionality in a device and the use of efficient injection moulding machines can alter the energy requirements for an annual therapy. Table 1 illustrates a monthly dry powder inhaler (DPI) combination product with either an integrated (option 1) or a clip-on connectivity unit (options 2 and 3), with different types of battery arrangements. These options lead to different lengths of a device's lifespan – and hence different levels of energy required to manufacture the plastic components for an annual treatment. A re-usable handheld nebuliser-type device (option 4) is also considered, where it is sensible to replace the minimum level of plastic required for hygiene or performance considerations. The levels of energy are the average without considering raw material production.

By splitting the device functionality such that the re-usable functional elements are retained for as long as possible, and by using efficient manufacturing methods, the energy required can be minimised. Table 1 shows that a device manufactured by option 1 on a hydraulic press would use more than twice the amount of energy as option 3 that is manufactured on an all-electric press, for instance.

The ultimate goal is to describe an ideal product by taking all these requirements into consideration, then to address those conflicting and contradicting requirements at a conceptual level, thereby arriving at a theoretical direction that can inform decisions in the top-level product design stages.

Connectivity and sustainability have contradictory requirements. But techniques such as TRIZ (the theory of inventive problem solving) can be used to explore available options at the concept level and to define the desired conceptual direction (Figure 1). The TRIZ analysis highlights the need to include systems or materials only in the components or units for which they are needed – and recover parts of the system that can be re-used.

An "ideal" product would maintain a high level of functionality in a package that minimises the environmental impact, both through accurate analysis and recording of the correct use and by the minimised level of additional material and waste. To achieve this, the base DPI would need to be designed with the connectivity unit in mind to ensure the necessary level of sensing can occur – but packaged in such a way that the addition of a connectivity unit does not reduce the ease of use of the device.

Focusing on minimising the environmental impact at a conceptual design level and recognising that increasing functionality can increase levels of adherence and reduce use errors, which in turn will improve therapy and hence reduce levels of medical intervention, can potentially have a net positive impact on the environment.

VECTURA: INTEGRATED PRODUCT DEVELOPMENT SERVICES

Vectura integrates formulation, device and development capabilities to offer a broad range of services to help customers bring inhaled medicines to market. The company has development expertise across a range of platforms, including capsule- and blister-based DPIs, pMDIs and smart nebulisers. This allows a "device agnostic" approach to be taken to meet the needs of the customer, the development programme and, ultimately, the patient.

In early development, a unit-dose capsule or blister device or a nebuliser may offer benefits in terms of speed and cost, whilst a multidose DPI, pMDI or nebuliser may be required as a commercial-ready platform to support a later-phase programme.

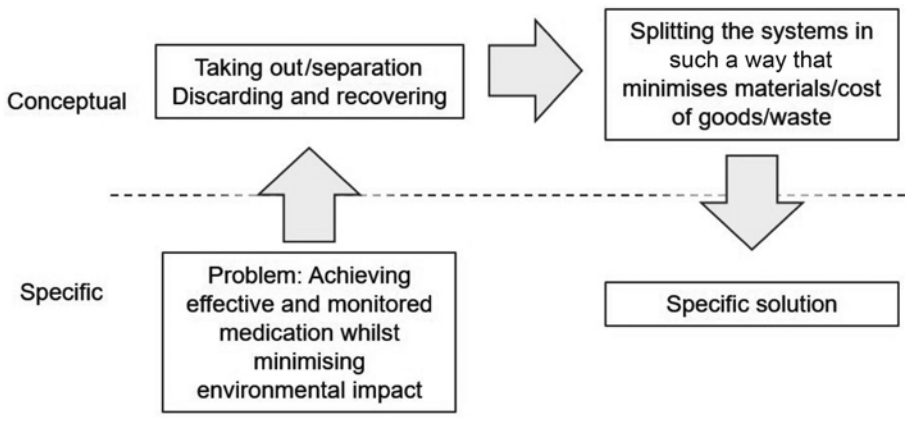

Figure 1: TRIZ methodology applied to connectivity and sustainability.

> "Vectura's state-of-the-art, breath-actuated nebulisers with guided inhalation have been developed to improve lung delivery for inhaled small molecules and biologics."

DPI Technology

Unit-dose capsule inhaler technology offers flexible dosing and a fast-to-clinic option in early development. Vectura can support capsule-based DPI programmes from preclinical development to small-scale commercialisation.

Vectura's blister-based DPI platforms offer customers a range of options with simple design, intuitive user interfaces, low component count and access to devices used in products that are globally approved for multidose applications.

pMDI Technology

pMDIs remain an important device option for many patients. With extensive expertise in pMDI development and lifecycle management, including flutiform® and breath-actuated flutiform® K-haler®, Vectura can assist in the development of new pMDI products or optimise liquid formulation and device performance, based on either standard or novel propellants.

Nebuliser Technology

Vectura's state-of-the-art, breath-actuated nebulisers with guided inhalation have been developed to improve lung delivery for inhaled small molecules and biologics, with the aim of achieving better clinical outcomes and/or shortened treatment times.

A patient's breathing pattern can impact the efficiency of drug delivery to different regions of the lung. Control of the inspiratory flow rate, the inspiratory volume of the inhalation and the timing of aerosol delivery during the inspiration can materially affect how much drug accesses the central or peripheral parts of the lungs. This is the basis of Vectura's proprietary, smart nebulisation technology.

Vectura has developed the FOX® nebuliser, which is a handheld, breath-actuated, smart mesh device, combining small droplet size, controlled flow rate and guided inhalation to offer high-performance

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drug delivery to the lungs. Small aerosol droplets are delivered consistently via silent, vibrating mesh technology. During inhalation, the FOX device guides the patient to inhale slowly and deeply, whilst the airflow resistance is varied to ensure a constant flow rate during inhalation, and an illuminating mouthpiece provides patients with a visual cue to ensure they inhale at the correct rate.

Vectura also offers the AKITA® JET device, which is a desktop, breath-actuated inhalation system that uses proprietary positive pressure technology to assist drug delivery to the lungs. The AKITA JET also guides the inhalation manoeuvre, providing real-time feedback and inhalation performance information to the patient or caregiver.

ABOUT THE COMPANY

Vectura is a leading specialist inhalation CDMO that provides innovative inhaled drug delivery solutions that enable customers to bring their medicines to patients. With differentiated proprietary technology and pharmaceutical development expertise, Vectura is one of the few companies globally with the device, formulation and development capabilities to deliver a broad range of complex inhaled therapies. Vectura has 13 key inhaled and 11 non-inhaled products marketed by partners with global royalty streams, and a diverse partnered portfolio of drugs in clinical development.

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May	Delivering Injectables: Devices & Formulations
June	Connecting Drug Delivery
July	Novel Oral Delivery Systems
August	Industrialising Drug Delivery
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October	Prefilled Syringes & Injection Devices
October /November	Drug Delivery & Environmental Sustainability
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DELIVERING SUSPENSIONS WITH MESH TECHNOLOGY

Here, Edgar Hernan Cuevas Brun, Business Development Manager & Scientist, Aerosol Drug Delivery, and Yuan-Ming Hsu, PhD, Research and Development Director, both at HCmed Innovations, discuss the performance of mesh nebulisers for the delivery of suspensions in inhalation therapy.

TREND OF MESH NEBULISERS IN INHALATION THERAPY

Inhalation as a route of administration has been proven to offer a wide range of advantages over other administration routes when it comes to the treatment of diseases that affect the respiratory airways. By locally delivering drugs into the lungs, it is possible to overcome several issues related to systemic side effects as well as to reduce the dose required to achieve a therapeutic effect.[1]

From the three most commonly used devices in inhalation therapy – dry powder inhalers (DPIs), metered dose inhalers (MDIs) and nebulisers – nebulisers are preferable to treat children and older adults who may struggle to co-ordinate the actuation of inhalers or reach a high peak inspiratory flow to guarantee proper lung deposition. With the introduction of mesh technology, extra value was brought to nebulisers thanks to a new mechanism that converts liquid medication into aerosol by the oscillation of a mesh membrane with thousands of tiny pores. Over the past two decades, several companies have worked on mesh nebuliser development – improving these devices and driving them to a mature state that has translated into their major benefits, which include appropriate particle size distribution with aerosol droplets below 5 µm in diameter, silent operation, portability, shorter treatment time and low residue.[2]

It is important to mention that the combination of biologic formulations and mesh nebulisers is further creating a shift in the route of administration of these formulations. The intravenous route is gradually being replaced by inhaled biologics as a new treatment offering for respiratory diseases. This is possible due to the characteristics of nebulisers equipped with mesh technology, which produce low shear forces and heat generation during aerosolisation, especially when compared with jet and ultrasonic nebulisers.[3]

> "The combination of biologic formulations and mesh nebulisers is further creating a shift in the route of administration of these formulations."

SUSPENSIONS AND MESH TECHNOLOGY

Most formulations developed for nebulisation are in a liquid state, with a few presented as powders that require reconstitution into liquid form before administration. The vast majority of these formulations are solutions with APIs and excipients homogeneously distributed; however, suspension formulations are also available for inhalation as inhaled corticosteroids (ICSs). These suspensions are heterogeneous mixtures in which the APIs are not fully dissolved in the liquid buffer, clearly differentiating them from the solutions.

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"Customisable mesh nebuliser platforms allow device manufacturers to tailor the mesh components... to make delivery of suspensions more efficient."

When it comes to the use of mesh nebulisers to deliver suspensions, the existence of the suspended fine particles has been associated with a phenomenon called mesh clogging. Mesh clogging is the result of a blockage of the mesh membrane pores, which can adversely affect the aerosolisation of medication, potentially leading to low drug delivery efficiency and extended treatment time.[4] Two commonly used suspension formulations of ICSs for asthma and chronic obstructive pulmonary disease treatment are budesonide and fluticasone propionate. Budesonide's particle size in the formulation medium has been reported to be 2–3 µm in diameter, close to the pore size of the mesh membrane in several mesh nebulisers.[5] Although budesonide and fluticasone propionate have been approved for several years, and are administered via jet nebulisers in many countries, their delivery using mesh nebulisers has been brought into question, leading device manufacturers to specify that their mesh nebulisers should not be used with suspensions.

Besides the classification of formulations into solutions and suspensions, a wide range of physicochemical properties also influence drug delivery efficiency in mesh nebulisers. Viscosity, surface tension and osmolality can greatly affect several aerosol performance parameters and delivery conditions, such as mass median aerodynamic diameter, fine particle fraction (FPF, the percentage of particles with diameter lower than 5 µm), geometric standard deviations (GSDs) and output rate.[6] Other properties, such as pH and temperature, should also be carefully considered as abrupt changes could result in chemical modifications and aggregation of the APIs.[7] Therefore, understanding the properties of formulations is essential for the optimisation of delivery efficiency.

Fortunately, to overcome these issues, customisable mesh nebuliser platforms allow device manufacturers to tailor the mesh components, which may include the membrane's material composition, pore size, thickness and pitch to control aerosol characterisation, as well as the oscillation module and firmware, to operate under different frequencies and amplitudes to make delivery of suspensions more efficient.

DELIVERING FLUTICASONE SUSPENSION WITH MESH NEBULISERS

To examine the delivery performance of two mesh nebulisers with a suspension formulation, the ICS fluticasone propionate 2 mg/2 mL (Flixotide®, GlaxoSmithKline (GSK)) was selected. In 1999, the respiratory division of today's GSK introduced Flixotide Nebules as a nebulised formulation for use with jet nebulisers, specifically targeting adults and children suffering from chronic, severe asthma at a time when fluticasone was only available in DPIs and MDIs.[8] HCmed Innovations explored delivery efficiency of fluticasone by using two of the company's mesh nebuliser platforms. The purpose of the experiment was not just to demonstrate the delivery of fluticasone suspension with mesh nebulisers but also to compare the delivery efficiency between a device operating under continuous output and a breath-actuated device.

Figure 1: Pulmogine vibrating mesh nebuliser.

DEVICES: MESH NEBULISERS

- **Pulmogine® vibrating mesh nebuliser:** Pulmogine (Figure 1) is a mesh nebuliser that operates under continuous output mode and is able to deliver a wide range of medications. A selected mesh was used in the testing with fluticasone.
- **AdheResp® smart breath-actuated mesh nebuliser:** AdheResp (Figure 2) is a smart mesh nebuliser that counts with Bluetooth connectivity to transfer nebulisation treatment data. This device operates under breath-actuated mode, meaning that aerosol is generated during a fraction of the inhalation phase only. Breath actuation has become an important feature for new high-cost formulations as higher drug delivery efficiency is desirable. The AdheResp platform counts with different levels of customisation to enhance aerosol performance, as well as firmware tailoring to adjust the fraction of time in which aerosol is generated. For comparison purposes in the study, a mesh with the same specifications as the one selected for the Pulmogine device was used in the AdheResp device.

Figure 2: AdheResp smart breath-actuated mesh nebuliser.

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Device	DV10 (µm)	DV50 (µm)	DV90 (µm)	FPF (%)	GSD
Pulmogine	1.969 ± 0.072	4.568 ± 0.167	9.775 ± 0.154	54.68 ± 3.61	1.80 ± 0.03
AdheResp	1.630 ± 0.133	3.470 ± 0.363	8.720 ± 0.708	69.13 ± 4.06	2.21 ± 0.46

Table 1: Aerosol particle size distribution measured with Spraytec (mean ± SD).

Testing Procedure and Results

To assess the particle size distribution of the aerosol generated with both devices, a laser diffraction particle size analyser (Spraytec, Malvern Panalytical, (Worcestershire, UK)) was used. A 1 mL fill volume of fluticasone was loaded into the reservoirs to conduct testing in triplicate with each device. The volume median diameter (DV50) for the devices was below 5 µm, which is understood as a parameter to achieve higher lung deposition and which, in time, was supported by FPF values higher than 50% for both devices. Although Pulmogine and AdheResp share the same mesh technology, the mesh orientation – vertical for Pulmogine and horizontal for AdheResp – along with the existence of a chamber in the AdheResp device, were presumed to cause the difference in performance, stressing the sensitivity of aerosol performance towards factors such as airflow. The particle size distribution values are summarised in Table 1.

Delivered dose was assessed using a breathing simulator (BRS2100, Copley Scientific (Nottingham, UK)), which was operated according to the guidelines in the US Pharmacopeia, USP <1601>, to simulate adult breathing pattern (tidal volume: 500 mL; frequency: 15 cycles/min; waveform: sinusoidal; inhalation:exhalation = 1:1). A filter was used to capture the aerosol generated by the devices in the apparatus and a mixture of methanol and water (7:3 in volume) was used to wash the filters and extract the API. Quantification of API was conducted with an ultraviolet–visible spectrophotometer (Lambda 365, Perkin Elmer (MA, US)) at the wavelength 237 nm for which a calibration curve was generated prior to testing.[9] Triplicate assessment with each device was conducted.

The mean delivered dose with the Pulmogine device stood slightly above 37%, demonstrating a good delivery efficiency with the continuous output device. On the other hand, the breath-actuated device, AdheResp, presented a more superior mean delivery efficiency of 72%, close to twice the amount reached with the Pulmogine device. Moreover, by multiplying the delivered dose and FPF, the inhalable fraction – which constitutes the percentage of delivered dose involving droplets with size lower than 5 µm in diameter – of the breath-actuated device was close to 50%, while the continuous output device only reached 20% of the loaded API. Gravimetric measurements of residual mass after nebulisation were negligible for both devices, with barely 3% of the loaded mass remaining in the reservoirs at the end of each treatment.

> "It was demonstrated that breath actuation highly enhanced the delivery efficiency of the formulation, successfully delivering a larger percentage of inhalable fraction, while also reducing the emission of fugitive aerosols."

As aerosol generation only took place during a fraction of the inhalation phase with the AdheResp device, the treatment time was doubled when compared with Pulmogine. Nevertheless, a treatment time of 12 minutes can be considered within a reasonable range for nebulisation treatment. Table 2 summarises the data obtained from the breathing simulation testing.

CONCLUSION

Delivery of suspensions with mesh nebulisers has been questioned for an extended period of time, especially due to the potential blockage that suspensions could cause to the mesh membrane. The two mesh nebulisers assessed in the study showed no significant variations in performance after six runs, maintaining high performance levels. Furthermore, it was demonstrated that breath actuation highly enhanced the delivery efficiency of the formulation, successfully delivering a larger percentage of inhalable fraction, while also reducing the emission of fugitive aerosols. This technology is significantly relevant to the development of drug-nebuliser combination products that involve costly APIs.

Moreover, as the number of biological formulations for inhalation delivery continues to expand, assessing the delivery of suspensions can provide better prospects of what could, in the future, comprise delivery of biological suspensions. This is undoubtedly an important implication, considering that proteins, peptides and nucleic acids may be encapsulated by hydrophobic materials and distributed in the liquid formulations, resulting in the development of new suspension formulations.

Although the devices were tested with a single medication, it would be useful to extend testing to examine delivery performance with other suspensions presenting various properties. Generating sufficient data on the combination of nebulisers and suspensions is an endeavour that HCmed continues to pursue to improve its mesh delivery platforms, as it constitutes the main vehicle to understand the device and drug implications and how they affect one another to achieve higher drug efficiency in the development of new inhalation treatments for respiratory diseases.

Device	Delivered API (%)	Residue (g, gravimetric)	Time (m:s)
Pulmogine	37.30 ± 1.98	0.061 ± 0.050	05:40 ± 0:20
AdheResp	72.01 ± 0.75	0.029 ± 0.004	11:54 ± 0:16

Table 2: Breathing simulation testing and delivered dose quantification (mean ± SD).

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ABOUT THE COMPANY

HCmed Innovations is focused on the development of drug-device combination products for inhalation therapy. It develops and manufactures portable vibrating mesh nebulisers that offer a mature customisation platform. This technology enables efficient and reliable nebulisation of different types of medication, including small molecule synthetics and large molecule biologics, as either solutions, suspensions or even difficult-to-deliver high viscosity drugs. The newest products include the incorporation of breath-actuation and connectivity features to enhance drug delivery and reinforce patience adherence.

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ABOUT THE AUTHORS

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

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

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Nemera
we put patients first

LEVERAGING HUMAN FACTORS TO DEVELOP PATIENT-CENTRIC INHALERS

Here, Raphaële Audibert, Global Category Manager, Inhalation & Dermal, Mark Tunkel, Global Category Director, Services, and Manuela Basso, Communications Manager, all at Nemera, look at the role patient-centricity has to play in the development of inhalers to treat chronic respiratory diseases.

THE CHALLENGE OF DEVELOPING PATIENT-CENTRIC INHALATION DEVICES

Living with a chronic respiratory disease, such as asthma and chronic obstructive pulmonary disease (COPD), is more than a challenge, not only because these pathologies affect the airways, causing breathing difficulties, but also because correct use of the device to administer the treatment is not always easy. Almost 800 million people worldwide suffered from a chronic respiratory disease in 2018, primarily asthma and COPD.[1]

Asthma makes breathing difficult by causing the air passages to become narrow or blocked, especially during exacerbations. This, in turn, leads to wheezing, coughing, shortness of breath and chest tightness. At the other end of the scale, COPD is characterised by long-term breathing problems and poor airflow. Although neither disease is curable, they can be treated to help dilate airways and reduce inflammation or provide relief from coughing.

Global recommendations for the management of asthma[2] and COPD[3] highlight the importance of ensuring patients are adherent to their prescribed

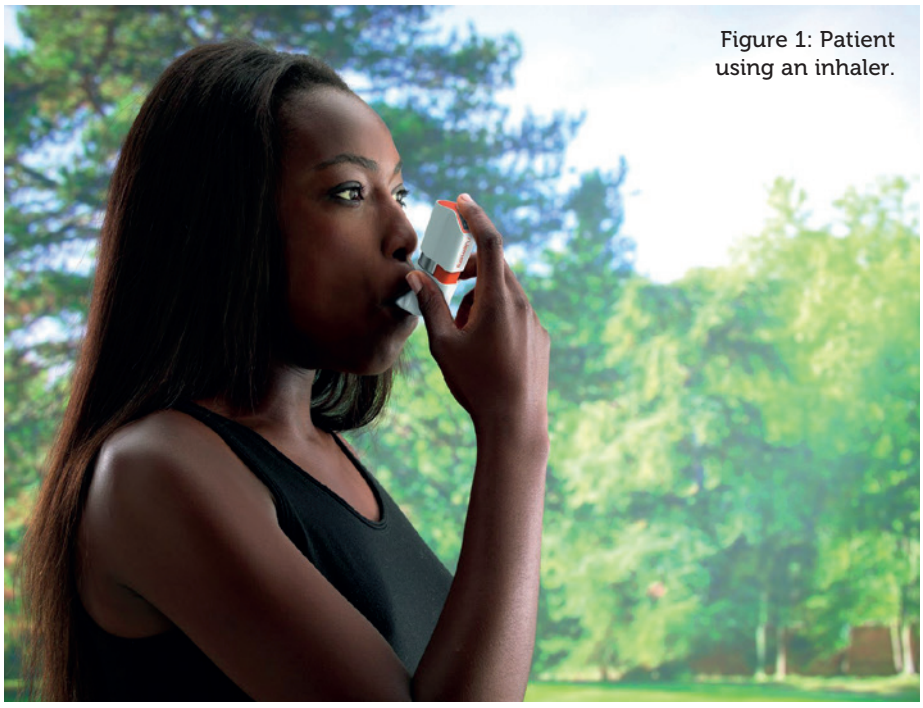

Figure 1: Patient using an inhaler.

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"Traditionally, the inhalation route is used for drug administration to the respiratory system – inhalers being an effective way to administer the drug into the lungs through breathing."

long-term dosing regimen. However, adherence remains a big challenge, in large part due to improper use of inhalation devices and a lack of patient comprehension and training.

Traditionally, the inhalation route is used for drug administration to the respiratory system – inhalers being an effective way to administer the drug into the lungs through breathing (Figure 1). This allows medicines to be delivered directly to the site of action, ensuring rapid absorption and rapid action, as well as a reduction in the side effects associated with oral medications. There is a comprehensive choice of inhalers in the market, the two main types being dry powder inhalers (DPIs) and pressurised metered dose inhalers (pMDIs).

DPIs deliver powder medications that can either be preloaded in the device or contained in capsules and loaded by the patient before use. The drug is released only when the patient takes a deep, fast breath in through the inhaler. With DPIs, the patient's breathing capacity is critical in generating the desired therapeutic outcome as the dispersed powder needs to be broken into particles of the right size and deposited appropriately into the lungs.

pMDIs deliver pressurised drug contained in an aluminium canister that is fitted into a plastic body with a mouthpiece. In most instances, the medication dose is released into the lungs by pushing the canister into the mouthpiece. Co-ordination between inhalation and activation of the device is crucial to ensure a proper delivery of the drug to the lung.

Several studies have shown that patients commonly make errors in their inhaler technique, with both pMDIs and DPIs, despite advances in inhaler device technology. Analysis reveals that 31% of patients have a correct inhalation technique, 41% have an acceptable technique and 31% have a poor technique.[4]

Training patients in the correct use of their inhaler can reduce the number of technique errors, but it may not be sufficient to solve the problem. Better management of chronic respiratory therapies could be achieved by working on the ease-of-use of inhalers or by providing real-time feedback to the user on its technique to ensure more successful drug delivery.[5] However, developing the best inhalation device to administer the most suitable treatment is technically challenging for various, equally important, reasons.

First of all, it is essential to ensure compatibility between drug and device to avoid chemical or physical (electrostatic) interactions. Good delivery performance can be achieved through working on fluid path optimisation, for instance. Specific functions may also be needed, such as a dose counter or automatic actuation. Also fundamental for the final result is to ensure the manufacturability of the device.

However, it is impossible to develop a drug delivery device without taking into account the high requirements set by regulatory guidance and standards, including new rules, recommendations and device specifications. All these elements form the basis for developing an effective inhaler, but what about user-friendliness and patient adherence?

PATIENT-CENTRICITY: NOT ONLY A GROWING TREND, BUT A REAL NEED

Nemera understands the challenges encountered by patients living with chronic respiratory diseases and the difficulties of using existing inhalers correctly every day. To design and develop a user-friendly and high-performing device that answers patients' and technical needs, the only viable solution is to develop the device with the patients, from the early-stage phase to the final steps of validation. Patients' opinions and feedback are crucial to ensure the best results for usability, as they can offer ideas and inspiration based on their experience.

"To design and develop a user-friendly and high-performing device that answers patients' and technical needs, the only viable solution is to develop the device with the patients, from the early-stage phase to the final steps of validation."

PATIENT JOURNEY AND CLINICIAN EXPERIENCE AS FOUNDATION FOR NEW DEVICE DEVELOPMENT

At the onset of establishing the functional requirements and user needs for a new device application, it is critical to fully understand the patient journey, as well any related clinical processes, to ensure that every decision made takes the patient's needs into account. Such needs focus on adherence and the integration of new technologies into a variety of inhalation therapeutic areas. This foundation, acquired through an understanding of this journey, the patient's interactions with the healthcare system and the healthcare provider experience, enables Nemera to capture the complete process patients go through when managing their disease – both from a self-administration standpoint and from a longitudinal perspective – as they progress with their condition and treatment through the healthcare system and their life stages (Figure 2).

To achieve this, Nemera's team of design research experts use a technique called applied ethnography. This method relies on a combination of interviews and in-context observations of practices, processes and experiences within the patient's home or actual use environment. At this stage, potential use cases are looked at broadly, that is beyond the administration event or solely complying with instructions for use as you might see in a human factors study. This can potentially start from when a patient is first diagnosed, to receiving their device, and through the entire process of preparation, administration and disposal as well as the times in between treatment, so that Nemera can understand how that process changes over time and how the frequency of administration, and other factors, may impact the patient experience.

This gives the most natural view of the patient experience in relation to their environment, social/emotional context and all the other factors that influence use. It is equally important to gain an understanding of the experience of healthcare professionals (HCPs), as well as to consider this in relevant settings in clinical environments, because the diagnosis and prescription pathways for

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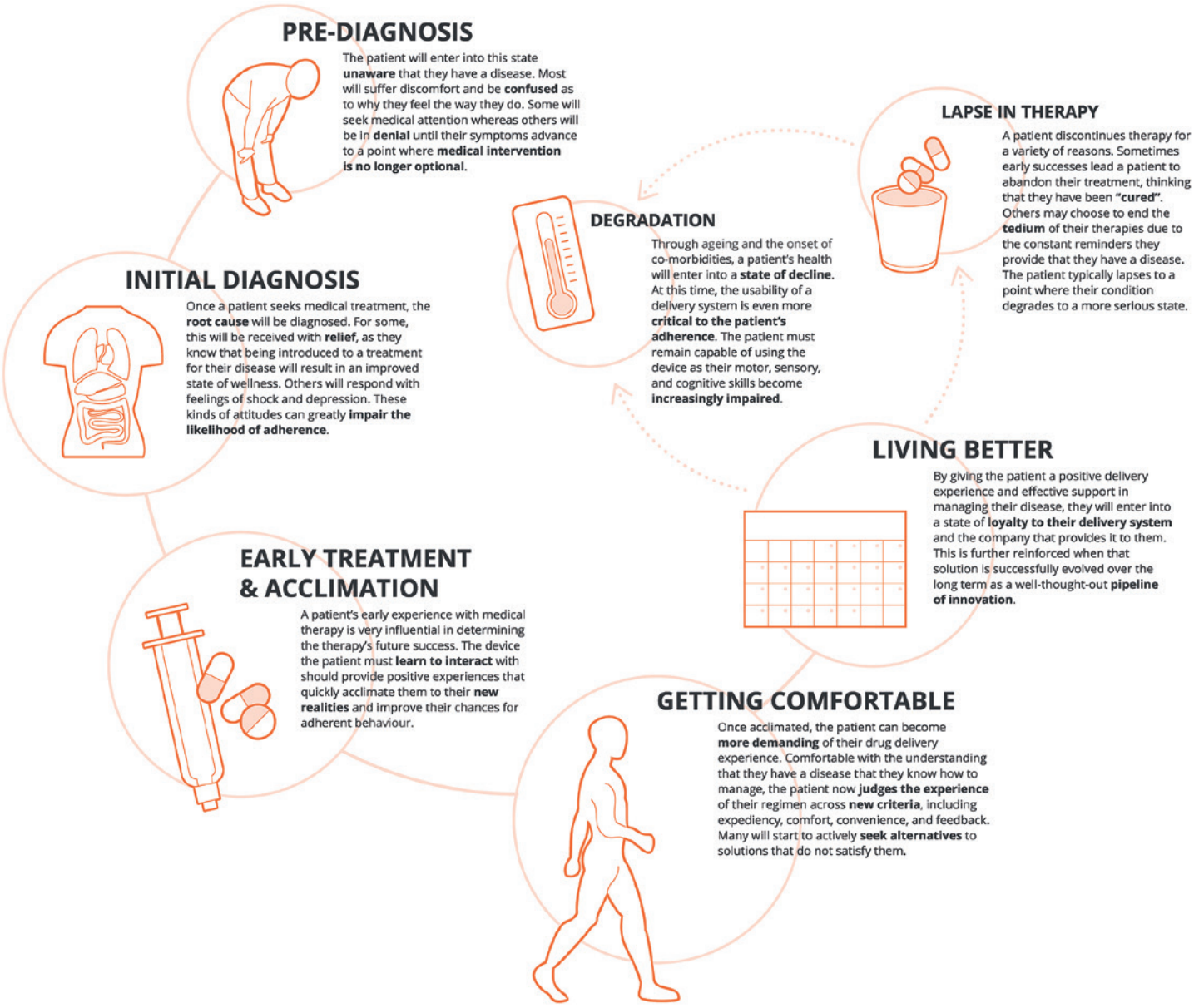

Figure 2: Key milestones along the patient journey and implications for delivery device design.

applications addressing asthma and COPD can be complex and involve many strategies for diagnosing and recommending treatment. This holistic foundation is of particular importance in inhalation applications where there are many drivers and aspects of disease-state management related to environmental factors, such as air quality and pollen levels, or co-morbidities that can impact a patient's day-to-day use of their device. Nemera is also increasingly seeing customers consider using the inhalation modality for new therapeutic applications, such as biologics. It is therefore critical to consider the feasibility of integrating this means of delivery into a patient or clinical experience to project future state user experiences and care models.

The outputs from this work include patient journey maps, clinical process maps and a robust understanding of prioritised user needs and values, identification of pain points that can be harnessed into possibilities for improving the patient and provider experience across all aspects of the journey to make a significant impact on their lives beyond medication delivery. This can often include opportunities for integrating connectivity and electronics, both "add-on" and mobile applications, into devices to better support patients with managing their wellbeing and increasing their engagement with HCPs through information transfer and support.

> "It is very important that human factors and patient experience activities are integrated for a successful drug-device combination product development process."

This enables Nemera to consider how best to satisfy those needs as holistically as possible while making decisions around establishing user needs and functional requirements for the intended device and related drug product attributes. This includes decisions around modality, such as DPI versus MDI versus nebuliser, as well as variations within that modality, if considering existing intellectual property (IP) platforms. Nemera continually develops this foundation throughout the entire combination

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product journey, regardless of the device selection decisions made by its customers, through its development expertise.

It is very important that human factors and patient experience activities are integrated for a successful drug-device combination product development process. It is essential to ensure that the selected device, in combination with the drug, is appropriate, safe and effective for the target population. This also extends to optimising the patient experience to create competitive differentiation, and to ensure adherence and engagement with patients and clinical stakeholders by any means at Nemera's disposal.

A good example of this approach might be the consideration of generic applications in a wide variety of device types (DPI, pMDI or breath-actuated MDI) where competitors are targeting the same reference drug and devices. This is compounded by the US FDA's ANDA regulatory pathway, which requires that a generic version of a reference device must be indisguishable to a trained user from an intended use/use case standpoint as outlined in the device's instructions for use. However, many on market devices have significant IP portfolios that must be navigated by generic players. This presents a unique challenge in which the requirements for an identical device conflict with considerations to circumvent IP and Trade Dress/Markings. A partner with broad development capabilities, such as Nemera, can apply a variety of development methods and frameworks to help customers manage these often competing requirements. Nemera can also provide consulting services for the unique human factors requirements for generic development projects, such as threshold analysis and, potentially, comparative usability studies. Balancing these requirements within the context of the development approach is critical for success.

Alternately, for NDAs and new device development programmes, the company needs to project what a future use case might look like and anticipate areas of risk to ensure that development is tailored to mitigate them. In both instances, the company needs to be sure that it is addressing the defined user groups populations and early use-related risk analysis activities to define the human factors and usability programme necessary for the intended regulatory/filing strategy. Furthermore, clinical risks must be identified through conducting formative and summative usability testing for all aspects of the device and supporting assets in alignment with the human factors programme definition, including the production of human factors engineering report documentation for use in regulatory submissions. Human factors processes must satisfy not only regulatory requirements but also lead to the development of safe, effective and differentiated combination products.

This also includes "surrounding the device" with custom support materials, such as training programmes, optimised instructions for use and other means of engagement that are critical in most inhalation applications. Nemera can use the foundation of the patient journey to anticipate key areas of clinical risk or areas in which the development of connected accessories might have value.

Nemera can offer customers consulting and development services to meet these needs. The company works closely with its customers to develop a custom human factors and user experience strategy for their combination product. In this, user adherence is taken into account to support the identified regulatory pathway with longitudinal engagement to ensure competitive differentiation. Moving forward, Nemera believes this will include developing personalised digital experiences in order to engage with patients and HCPs beyond the inhalation event, to more fully address external factors that may influence their disease-state management. When linked to the company's capabilities in commercial manufacturing, Nemera can be a partner over the lifecycle of an application and any of its extensions.

NEMERA: FACE THE CHALLENGES AND FIND THE BEST SOLUTIONS FOR YOUR NEED

Nemera combines both technology advancement and human factors to find the most adapted solutions, allowing the improvement of both usability and performances, for improved adherence and clinical outcomes.

Best in class in inhalation drug-device combination products, Nemera is recognised for its leadership position in the DPI market, and for its development and manufacturing know-how, based on strong customer references. The company has a longstanding and proven expertise in precise metering systems, design for high-speed manufacturing and dose counters co-development, as well as programme management, product development, tooling and automation. From the concept idea to large scale manufacturing, Nemera is the utmost holistic partner to develop customers' inhalers, helping them succeed in the sprint to market.

ABOUT THE COMPANY

As a world-leading device combination solutions specialist, Nemera's ethos of putting patients first enables the company to design and manufacture devices that maximise treatment efficacy. Nemera is a holistic partner and helps its customers succeed in the sprint to market.

From early device strategy to state-of-the-art manufacturing, Nemera is committed to the highest quality standards. Agile and open-minded, the company works with its customers as colleagues. Together, they go the extra mile to fulfil their mission.

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Raphaële Audibert, Global Category Manager, Inhalation & Dermal at Nemera, holds a biomedical engineering degree from ISIFC (Besançon, France). Ms Audibert has worked in the medical device industry as a project manager for five years, where she led the development of a surgical instrument set for neurosurgery. Ms Audibert joined Nemera in 2016 as Category Manager for Inhalation and Dermal. Since then, she has helped identify the needs of tomorrow and in building franchise strategies.

Mark Tunkel, Nemera's Global Category Director, Services, was previously a partner at Insight Product Development, which was acquired by Nemera in 2019 and became the Insight Innovation Center. With more than 20 years of global business development experience and a deep understanding of the marketplace challenges and trends impacting the pharmaceutical industry, Mr Tunkel has advised many of the world's leading companies on their product development and innovation strategies, with an emphasis on driving realisation and the most favourable business outcomes.

Manuela Basso is an experienced communications professional, with a journalism and marketing background. Ms Basso holds a European Master's in Management and specialised in International Marketing. With more than 10 years of marketing and communication experience in different fields, Ms Basso has been working at Nemera for six years, developing effective communications to support Nemera's overall vision and mission: to put patients first.

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Nemera
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From design to manufacturing, we partner in your device strategy

NEMERA: YOUR COMBINATION PRODUCT PARTNER

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Always.

Partnering in drug delivery devices.
Holistically.

Going the extra-mile.
Together.

ROUNDTABLE: CAPSULE-BASED DRY POWDER INHALERS

In this roundtable discussion, Frédérique Bordes-Picard, Business Development Manager for Innovative Products at Lonza's Capsules and Health Ingredients segment, Marco Franza, Sales and Business Development Director – Global Inhalation and Medical Devices at Berry, Mirjam Kobler, PhD, Head of R&D, BG Excipients and Technology at Meggle, and Marco Laackmann, Sales Director, Inhalation Technology at Harro Höfliger, discuss the accelerating development potential of capsule-based dry powder inhalers (DPIs) and the potential of these effective and efficient drug delivery devices in the modern drug delivery market.

FRÉDÉRIQUE BORDES-PICARD

Lonza
Capsules & Health Ingredients

Frédérique Bordes-Picard is Business Development Manager for Innovative Products at Lonza Capsules and Health Ingredients. A biochemical engineer by training (Bordeaux Polytechnic Institute, France), Ms Bordes-Picard holds a master's in business administration from KEDGE Business School (France). She has been working in the pharmaceutical industry for more than 20 years, first at AstraZeneca, working on analytical development of therapeutic proteins and antibodies, then within Bertin Pharma (now Eurofins), mainly on generic product development and licensing out. She then joined Capsugel in 2010 as Pharmaceutical Business Development Manager, providing technical and regulatory support for new capsule-based product developments. Ms Bordes-Picard has developed specific expertise around capsule-based DPI product development and filing, supporting multiple companies in the EMEA and US working on both innovative and generic DPI projects.

MARCO FRANZA

Berry | healthcare

Marco Franza is Sales and Business Development Director – Global Inhalation and Medical Devices at Berry and has worked in various different roles in the commercial area but has always remained part of sales, business development and marketing. As inhalation devices have constantly been identified as the key growth factor for Berry, Mr Franza has always had a particular focus on them, driven by both business reasons and personal interest.

MARCO LAACKMANN

Harro Höfliger

Marco Laackmaan is Sales Director, Inhalation Technology at Harro Höfliger. He has a degree in chemical engineering with applied biotechnology from the University of Applied Sciences Emden (Germany) and an MBA from the Bradford School of Management (UK), as well as 15 years' experience working in the DPI industry, including device development, manufacturing, device quality control, powder dosing technology and process development. Mr Laackmann joined Harro Höfliger in 2011 and in his current role he handles global business development, sales and product management for specialist production machinery for the DPI industry.

DR MIRJAM KOBLER

MEGGLE

Dr Mirjam Kobler, PhD, is Head Of R&D, Excipients and Technology at Meggle. She started working in the R&D Department of Meggle in 2013 as a Project Manager for Analytical Development, focusing on DPIs. In 2016 she became Senior Project Manager, with growing responsibilities in product development for lactose for inhalation, DPI technical support and characterisation techniques. Since February 2018, she has headed the R&D Department of Meggle's Excipients and Technology business group. Dr Kobler's background includes seven years of experience in various areas of lactose excipients, especially for DPIs.

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Q Ms Bordes-Picard, can you give us an overview of the factors currently driving the increased therapeutic interest in pulmonary administration via DPIs?

FBP DPIs enable the delivery of an API for either local effect to treat respiratory diseases or for systemic indications, acting as a needle-free delivery system suitable for APIs ranging from small molecules to peptides and proteins. The lungs offer an enormous absorptive surface area, the highly permeable membrane in the alveolar region being of particular interest for systemic delivery. Slow clearance in the lung also results in the prolonged residency of APIs, and its low-enzyme environment is devoid of the problematic hepatic first-pass metabolism that reduces bioavailability for orally administered medications.

For local action, the pulmonary route allows for high concentrations of API to be delivered directly to the disease site, which can provide a rapid clinical response. Pulmonary delivery bypasses several barriers to therapeutic efficacy and can achieve a similar or superior therapeutic effect compared with oral delivery at a fraction of the systemic dose, thereby helping to minimise the risk of systemic side effects.

That being said, pulmonary pathologies remain a key target for the inhalation delivery route. Respiratory diseases account for five of the 30 most common causes of death – clearly there are still unmet needs. An estimated 65 million people suffer from moderate to severe chronic obstructive pulmonary disease (COPD), which makes it the third leading cause of death worldwide. Furthermore, asthma is similarly entrenched, especially when looking at children – more than 15% of children are affected, making it the most common chronic disease among this group.

According to Pharmacircle 2020, from preclinical through to Phase III development, 21% of DPI programmes are capsule based and 70% are developed by small or virtual companies. We now have studies being conducted for indications in infectious disease, the central nervous system and cardiology areas. About 44% of APIs are new molecular entities (NMEs), but there are even more promising compounds using 505(b)(2) development routes, with developers looking at either repositioning existing generic molecules or associating known molecules with DPIs to improve the treatment of existing pathologies. Asprihale (Otitopic, Los Angeles, CA, US) is one promising ongoing development, leveraging the faster bioavailability of compounds in the lungs to deliver a formulation of aspirin using a DPI to treat sudden myocardial infarction symptoms.

> "DPIs are the preferred choice for high-tech biological inhalation formulations, have a low carbon footprint and are likely the most sustainable choice on the market today – they are re-usable, require less packaging and fewer components, and use no pressurised propellants to dispose of."

Figure 1: Capsule-based DPIs offer four key advantages: the capsule acts as both primary container and delivery device, integration of the capsule into the user experience, simplicity of design and cost efficiency.

Q Mr Franza, can you further expand on the advantages of DPIs compared with other drug delivery devices?

MF As Frédérique mentioned, there is an increasing interest in the inhalation route across pharma development – the industry has been consistently identifying new indications for DPI formulations and DPIs across the therapeutic spectrum.

Simple, patient-friendly DPI devices cost less and perform better than other device formats. DPIs are the preferred choice for high-tech biological inhalation formulations, have a low carbon footprint and are likely the most sustainable choice on the market today – they are re-usable, require less packaging and fewer components, and use no pressurised propellants to dispose of. A lightweight and well-designed DPI device can have less impact on the environment than other popular drug delivery solutions. These features support affordability and payer value – the keys to better patient access.

However, that's not to say that DPI formulation development is simple. There are a number of complex factors to consider, including aerodynamics, compatibility between specific chemistries and the interactions of varying particle morphologies relative to the container and device activation. There are a number of parameters to consider when it comes to DPI technology selection relative to the other primary device types, and it's important to make sure that patient compliance and user friendliness come first.

Regarding capsule-based designs, there are four key advantages to consider. Firstly, with current state-of-the-art DPI technology, the capsule acts as both primary package and delivery device. Secondly, capsules are thoroughly integrated into the user experience with designers leveraging both audio and visual cues to support confident dose delivery and better patient compliance. Thirdly, the simple design of DPIs requires fewer manufacturing resources. Lastly, from a cost-of-goods perspective, DPIs are less expensive to make overall, especially when combined with cost efficiencies associated with high-volume capsule manufacture (Figure 1).

Single-dose re-usable DPIs now account for a growing portion of the global DPI market. According to Berry's research, most of these are capsule based. Generally speaking, all these devices employ some sort of system to make the dose contained in the capsule accessible to the airflow generated by the device when the patient inspires.

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This occurs one of three ways: opening the capsule by separating the body and cap, cutting the capsule with blades or piercing the capsule with needles.

Capsules deliver multifunctional characteristics to DPIs and have become integral to their performance. The mechanically actuated DPIs available to developers today can spin capsules at relatively high rates to deliver a high degree of controlled and repeatable turbulence. The aerodynamics of the spinning capsule help aerosolise the powder prior to it being propelled out of the device. As such, the capsule plays an essential role in a complex dynamic system, greatly influencing the pharmaceutical performance of the drug substance and offering a simple but highly functional synergy in combination that other drug delivery methods have a hard time matching (Figure 2).

Figure 2: Modern DPI capsules form an integral part of their delivery device's functionality.

"Most successful DPI formulations depend on lactose as a carrier material for the API; lactose is proven and the *de facto* excipient for inhaled APIs."

DPIs are truly among the higher-performing devices available in terms of emitted dose and respirable delivery ratio on the market today. Access to a platform using capsules, proven to be compatible and functional with most DPI formulation chemistries, is key to further application and effective development.

Q **Dr Kobler, Mr Franz touched upon the complexities of formulating APIs for use in a DPI, can you shed some more light on common themes in DPI formulation?**

ML Most successful DPI formulations depend on lactose as a carrier material for the API; lactose is proven and the *de facto* excipient for inhaled APIs. Of course, developers need to carefully consider all aspects of the project as early as possible, including the formulation of the finished drug substance, the device, the dose's primary packaging – in this case the capsule, magazine or reservoir – and ultimately the filling and finishing of the product for commercial dispensing. When considering DPI formulations in combination with device and packaging, there are many synergistic aspects that developers need to be aware of. Ideally, all functional and formulation interactivity is evaluated at the beginning of development.

"For DPIs, the overall compatibility and functionality of the "triangle" of critical parameters – device, formulation and capsule – is of the utmost importance for developers to get right."

Let's briefly talk about why a carrier material is such a pivotal excipient for a DPI formulation. Particles that are capable of being delivered to the lungs are typically in the range of 1–5 µL in size and often come with a common major disadvantage – they can be very, very cohesive. This leads to poor flow, processability and variation. Dispersing the API formulation in the lung requires a carrier material to support the function of airborne delivery and improve dispensing and metering. For most current formulations, that functionality is why lactose is the carrier of choice for many of today's top-selling DPI formulations.

Q **Ms Bordes-Picard could you elaborate on the key principles that need to be considered during the design of a DPI?**

FBP A DPI's success rests on four key pillars: formulation and flow, capsule compatibility, filling flexibility and device form and function. Additionally, for DPIs, the overall compatibility and functionality of the "triangle" of critical parameters – device, formulation and capsule – is of the utmost importance for developers to get right. For each of these components, there are a number of critical attributes to identify and key issues to mitigate.

Optimal DPI formulation composition and dose are generally primarily defined by particle mass, with particle size distribution (PSD) and the shape or morphology as significant characteristics. Formulation chemistries need to offer several other functional attributes to the mix as well, including chemical stability, hygroscopicity and the ability to deagglomerate. Generally speaking, optimal performance of an inhalable dry powder formulation depends on the aerodynamic PSD and the emitted dose's fine particle mass.

Q **Let's discuss commercial manufacturability. Mr Laackmann, could you shed some light on this topic?**

ML Of all the things to consider regarding DPI formulations in the context of effective downstream commercial scale manufacturing, compatibility with feeding and filling operations is absolutely critical. Within the DPI world, there are three semi-standard inhaler technologies to choose from: reservoir-based, blister-based and capsule-based. So far, we've been focusing on capsule-based DPIs, however, with reference to the filling and finishing of any of the three packaging types, it's important to understand the critical role of the powder-feeding process.

Powder feeding for DPI formulations can be challenging, especially with the micronised powders and engineered particles associated with some currently popular formulations. The top challenges DPI

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"The top challenges DPI formulators face when filling-finishing capsules are segregation of the powder components, agglomeration of powder particles, adhesion of powder with the equipment and powder flow, which is especially problematic with low-density, soft spray-dried particles."

formulators face when filling-finishing capsules are segregation of the powder components, agglomeration of powder particles, adhesion of powder with the equipment and powder flow, which is especially problematic with low-density, soft spray-dried particles.

Powder segregation is often caused by incorrect mixing, poor powder storage, which creates an uneven distribution of the API, and errors in powder feeding, which leads to segregation within the powder blend. Segregation can also occur during the sieving process and during sliding, because of different friction coefficients, or can result from other kinetic forces.

Segregation is not optimal for flow. If not mitigated, it leads to poor content uniformity and an increased risk that fine particles of the powder will get lost. Segregation may also lead to an undesired drop in assay – the loss of active on machine surfaces. Fortunately, at this point in processing there are a few potential options for mitigation, including modifying the powder formulation, such as by adding magnesium stearate, and modifying the powder-feeding system.

Another formulation-induced issue between machine and chemistry is agglomeration. Generally caused by cohesion among particles, it occurs relative to the ambient conditions of the environment, including temperature, humidity and the moisture content of the formulation. These can all lead to unpredictable changes in the flowability of the powder and may require several additional powder preparation steps, such as sieving, conditioning or ionisation, for mitigation at commercial volumes.

Dealing with cohesion and adhesion, as well as other similar undesired properties limiting flow, can be challenging. If not addressed, these issues can compound causing increased variation and other quality and process control issues. Fortunately, powder-feeding technology suppliers have introduced innovations to mitigate formulation and environmental issues and support the optimal feeding of powdered formulations. These systems include features such as beam feeding, auger feeding, pneumatic assist feeding, vibration feeding, fluidisation and bag systems.

Manufacturing a highly feed- and flow-oriented formulation is a good place to start for any DPI developer to ensure the therapeutic and commercial success of their product. Although it may be the last component to think of in this scenario, in some ways the filling and finishing of the capsules should be considered first. It's very important to understand how the formulation can affect manufacturing as early as possible in development.

Q **Ms Bordes-Picard, can you offer some closing thoughts?**

FBP DPI combination products are providing the flexibility developers need to optimise the delivery of their increasingly complex DPI formulations. Because capsule-based DPIs offer an affordable delivery route for treating chronic conditions like COPD and asthma, they will always have a place in drug development. Furthermore, because capsule-based delivery can offer a more economical and sustainable DPI development path to developers, it will continue to feature prominently in advanced pulmonary drug development and delivery innovation. Compatible, affordable and patient-centric capsule-based DPIs are here to stay.

ABOUT THE COMPANY

Lonza's Capsules and Health Ingredients segment is a global capsule and equipment developer and manufacturer, which designs and produces products for a range of oral dosage forms. The company provides customised solutions that optimise formulations to more than 4,000 customers in 100 countries.

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CHARACTERISING THE WALL THICKNESS OF QUALI-V®-I CAPSULES AND ITS EFFECT ON CAPSULE PUNCTURE BY A DPI PIN

Here, Siamac Parker, PhD Student, Sion Coulman, PhD, Senior Lecturer, and Prof James Birchall, PhD, Professor of Pharmaceutical Sciences, of Cardiff University, alongside Susana Ecenarro, Vice-President R&D/Regulatory Affairs, and Mahmoud Farag, Scientific Business Development Manager, at Qualicaps Europe, present a study that uses optical coherence tomography to characterise the wall thickness of capsules at the dome position and investigates the importance of controlling the dome thickness of hard-shell capsules to be used in a dry powder inhaler.

Hard shell capsules are commonly used in dry powder inhalers (DPIs) as reservoirs for the API formulation prior to inhalation. Powder inhalation occurs in two principal stages: actuation of the DPI to facilitate a physical insult to the capsule wall and inspiration to aerosolise the capsule contents. One of the most common mechanisms used to perforate the capsule prior to inspiration is by having two stainless steel pins simultaneously puncture the dome regions of the cap and body of the capsule. A robust methodology has been developed to help characterise capsule puncture[1] and subsequently used to understand how temperature, humidity and capsule formulation influence the capsule puncturing event.[2]

Qualicaps' Quali-V®-I capsule, a hydroxypropyl methylcellulose (HPMC) formulation with a moisture content of 4.5–6.5% w/w, has been designed and optimised for use in DPIs, with puncture tests demonstrating a robust and reproducible puncture performance following storage at a range of relative humidities. Furthermore, the development of this capsule stimulated development of an extra low moisture content capsule formulation, Quali-V®-I Extra Dry (moisture content 2.0–3.5% w/w). However, whilst capsule moisture content is an established determinant of capsule puncture performance, the impact of capsule wall thickness on puncture has not been characterised.

> "Whilst capsule moisture content is an established determinant of capsule puncture performance, the impact of capsule wall thickness on puncture has not been characterised."

Deviations in the capsule drying process or film thickness during manufacture can impact the thickness and uniformity of the capsule wall, which poses a risk of creating physical defects during handling and transport or a change in capsule puncture performance within a DPI. As such, it is prudent to isolate a sample of capsules from each batch and determine the wall thickness (at the dome position) of each to ensure that they meet a minimum specification of 100 µm – a process that requires the use of a laborious manual measurement technique. However, the relative importance of this arbitrary value on the puncture performance of a DPI capsule is unknown.

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To gain insight into this subject, a study was conducted to understand more about the relationship between capsule wall thickness and puncture performance in a DPI. The study also investigated whether optical coherence tomography (OCT) can viably be used as part of a rapid high-throughput in-line quality control method to characterise capsule wall thickness.

EXPERIMENTAL METHODS

Empty Quali-V®-I Size 3 hard-shell capsule caps were manufactured and supplied by Qualicaps Europe and categorised into three groups by their capsule wall thickness at the dome position, measured using a Mitutoyo (Kawasaki, Japan) Absolute Digimatic Indicator ID-C125XB micrometer:

- <100 µm
- 100–110 µm
- >110 µm.

These measurements are an established element of capsule quality control. Following categorisation, capsules were stored in resealable plastic bags at ambient conditions (relative humidity 54–60%) for one week.

To perform a puncture test,[1] 10 caps were removed from the bags and manually combined with 10 Quali-V®-I capsule bodies, ensuring that the cap and body were in the locked position. The complete capsules were then placed immediately in a weigh boat and allowed to equilibrate at ambient conditions for 15 minutes before starting the puncture test. The ambient room temperature and relative humidity were recorded immediately prior to the 15-minute ambient conditioning period and immediately after the puncture testing was completed.

The puncture test used a bespoke materials testing machine from ZwickRoell (Ulm, Germany) with an XForce P 500 N load cell. A collet chuck containing an angular metal pin from an RS01 2-pin inhaler (Plastiape, Osnago, Italy, part of Berry Healthcare) was mounted on the load cell, and a stainless-steel bush (Qualicaps) from a capsule filling machine was used to secure the Size 3 capsules in a fixed position, below the angular metal pin. The materials testing machine was then programmed, using testXpert II software (ZwickRoell), to conduct a compression test at a speed of 10 mm/min, with the test programmed to end upon 3.5 mm of displacement into the capsule dome. Force-displacement profiles were captured following contact (0.1 N registered force) between the angular pin and the capsule.

Following the puncture tests, the punctured capsules were removed from the bush for visual inspection. Each of the three capsule categories were puncture tested (N=10 for each capsule type) within a 15-minute testing period. Following puncture tests, the capsules were removed from the temperature-controlled room and imaged within 2 hours using a Carl Zeiss (Oberkochen, Germany) stereo microscope. Differences between the maximum recorded force (the puncture force) for each of the capsule types were statistically compared using GraphPad Prism 9 (GraphPad Software, San Diego, CA, US).

Capsules were also imaged using OCT, which provided a rapid inspection method to confirm the correct categorisation of the capsules and to check the capsule wall integrity prior to puncture testing. OCT is a non-destructive high-resolution imaging technique that has been conventionally used to characterise anatomical features of the eye and skin,[3] but which has been proposed as a potentially valuable tool to characterise sub-surface capsule features and their dimensions in the x, y and z planes.[4,5]

For OCT analysis, the caps were removed from the capsule body and positioned in a pre-determined location on an imaging stage. A Michelson Diagnostics (Maidstone, UK) VivoSight OCT instrument with associated probe was then used to perform a 4 mm scan of the capsule surface at 120 frames per scan using VivoSight Software Version 4.8. Each OCT scan produced a series of cross sections of the scanned capsule collected into a single data set, each of which was then imported into Fiji imaging software (based on ImageJ)

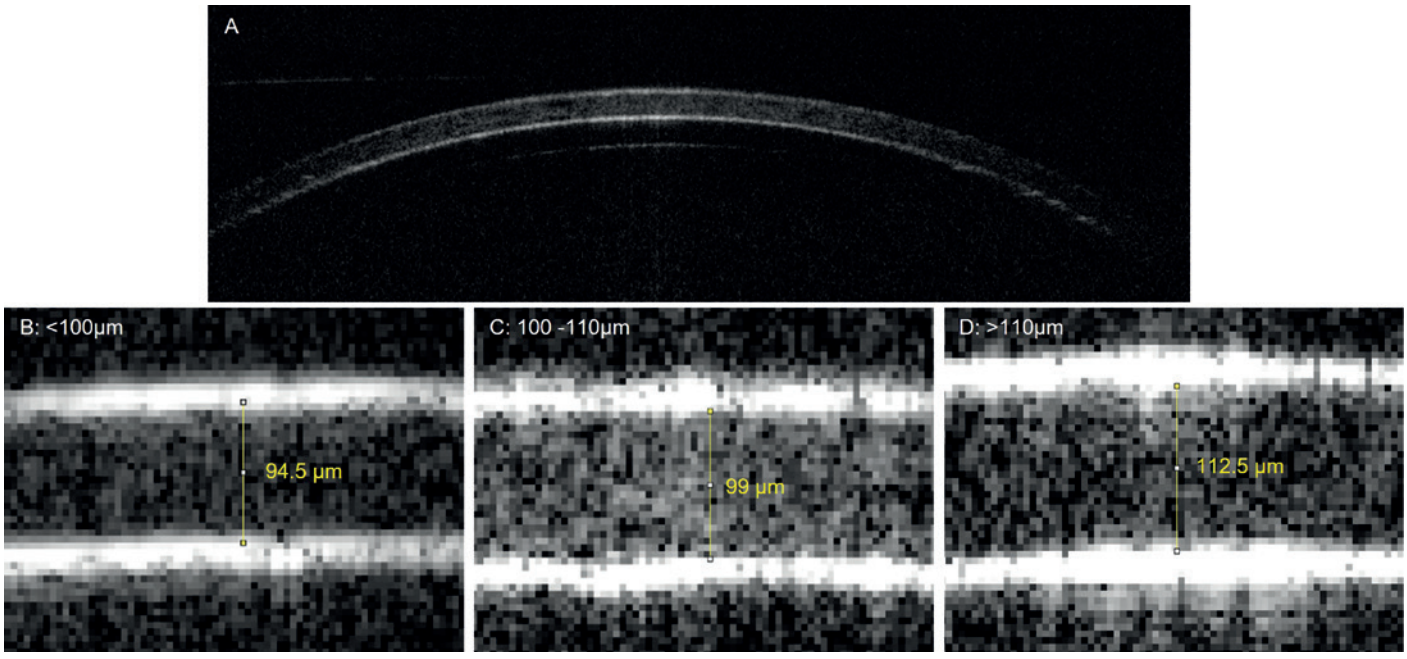

Figure 1: A representative transverse OCT image (section) of a Quali-V®-I capsule, taken at the apex of the dome at low magnification (A). High magnification images of the capsule walls of the three categories of Quali-V®-I capsule provide quantitative evidence of the three categories of capsule thickness used in this study, measured as (B) <100 µm, (C) 100–110 µm and (D) >110 µm using a micrometer. Images B–D are at the same magnification, and measurement of the dome thickness is exemplified by the yellow line.

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and analysed to isolate the image that corresponded to the transverse cross section taken at the apex of the capsule dome.

For measurement, the pixel dimensions (4.5 µm by 4.5 µm) were calculated based on the known dimensions of the transverse image captured by the calibrated OCT system. The interior and exterior surfaces of the capsule wall at the apex of the capsule dome were then identified on the OCT image as discernible white lines, typically 3–5 pixels wide (Figure 1). The thickness of the capsule wall was then measured by drawing a perpendicular line from the base of the white pixelated line on the exterior surface to the top of the white pixelated line on the interior surface. Ten capsules from each of the three capsule categories under investigation were imaged under the same conditions, with the data subsequently analysed using GraphPad Prism 9.

RESULTS

Capsules were conditioned and tested at an ambient temperature of 19°C and a relative humidity of 54–56%. Using OCT imaging it was possible to demonstrate a quantitative, and statistically significant, difference in capsule wall thicknesses that roughly corresponded to the categories assigned by the manual micrometer measurements (Figure 2):

- **<100 µm:** 87 µm (± 4.8)
- **100–110 µm:** 99 µm (± 8.8)
- **>110 µm:** 113 µm (± 11.4).

The mean force required to puncture capsules was 1.57 N (± 0.11), 1.68 N (± 0.12) and 1.99 N (± 0.15) for capsules with dome thicknesses of <100 µm, 100–110 µm and >110 µm respectively (Figure 3). Whilst there was a statistically significant difference ($P < 0.0001$) in the force required to puncture capsules with a dome end thickness >110µm, the shape of the force displacement curves was comparable for the three categories of capsules (Figure 4). There was also no significant cracking or fragmentation during or after the puncturing event, and the shape of the puncture was highly reproducible both within and between the capsules tested, with the "flap" remaining attached in all cases (Figure 5).

> "Whilst there was a statistically significant difference ($P < 0.0001$) in the force required to puncture capsules with a dome end thickness >110 µm, the shape of the force displacement curves was comparable for the three categories of capsules."

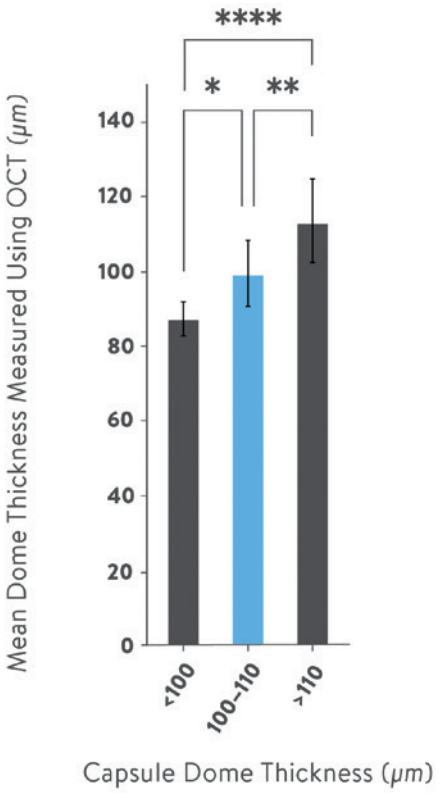

Figure 2: OCT measurements of the mean thickness of the wall at the apex of Quali-V®-I capsule domes for capsules previously categorised as <100 µm, 100–110 µm and >110 µm using a micrometre. Statistics used one-way ANOVA with Tukey's multiple comparisons between means. Error bars illustrate the standard deviations. * denotes p = 0.014, ** denotes p = 0.0034 and **** denotes p < 0.0001.

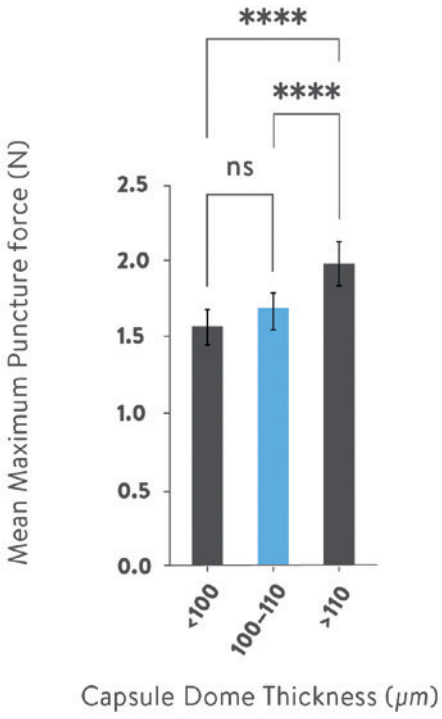

Figure 3: The mean force required to puncture <100 µm, 100–110 µm and >110 µm Quali-V®-I capsules with an angular DPI pin from a Plastiape RS01 2-pin inhaler. Statistics used one-way ANOVA with Tukey's multiple comparisons between means. Error bars illustrate the standard deviations. ns denotes p > 0.05, **** denotes p < 0.0001.

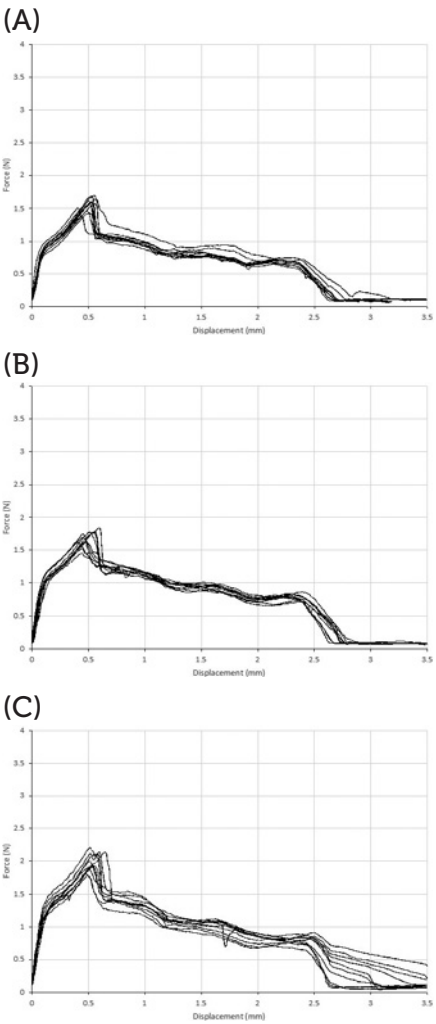

Figure 4: The force displacement curves produced for <100 µm (A), 100–110 µm (B), and >110 µm (C) capsules.

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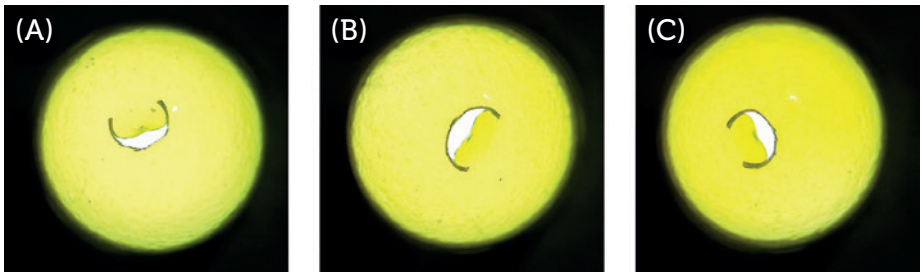

Figure 5: Representative images of <100 µm (A), 100 -110 µm (B), and >110 µm (C) caps following puncture with an angular DPI pin from a Plastiape RS01 2-pin inhaler.

DISCUSSION

Three different HPMC (Quali-V®-I) capsule products were manufactured, with intentional differences in the thicknesses of the capsule wall at the dome position. These capsules were categorised, by an established quality control method, as possessing a dome wall thickness of <100 µm, 100–110 µm and >110 µm. OCT imaging was used to confirm these categorisations and was evaluated as a potential rapid, non-destructive and high throughput means to measure capsule wall thickness, with the added benefit of providing additional information on capsule morphology and integrity. The measurements made by the micrometer and OCT were generally in agreement.

The minor deviation in the second category, 100–110 µm by micrometer measurement compared with 99 µm (± 8.8) by OCT, is to be expected, as the two methods of measurement use different fundamental principles of operation and OCT image analysis has not yet been optimised or automated for this task – the measurement was drawn by eye from the white pixels at the internal edges of the interior and exterior surfaces of the capsule wall. Measuring the distance between the midpoint of the two pixelated bands may rectify the minor difference in the two measurement methods. Therefore, whilst this study exemplifies the potential of OCT as a useful quality control tool in the capsule manufacturing industry, future studies are needed to provide validation, calibration against a recognised standard and optimisation for capsule analysis.

It is also important to acknowledge that the OCT imaging method, which is governed by the refractive index of an object, may not be ubiquitously applied to all capsule formulations. Intense backscattering from a more opaque material, such as a capsule formulation containing titanium dioxide, would likely prevent OCT image capture. However, for transparent capsule formulations, an automated non-destructive OCT imaging system for in-line quality assurance of capsule morphology is a real possibility.

OCT corroboration of the successful manufacture of Quali-V®-I capsules with three different capsule wall thicknesses facilitated investigation into how capsule wall thickness impacts on the force required to puncture capsules. As might be predicted, there was a direct relationship between these two variables, with a greater force needed to puncture the thickest capsule walls (>110 µm). However, the difference in force required to puncture those capsules categorised as <100 µm and those >110 µm were less than 0.5 N. This is unlikely to be practically or clinically significant – it would not affect the ability of a patient to manually actuate a DPI and puncture the capsule.

The different capsule thicknesses also had no effect on the dimensions of the puncture orifice or the physical integrity of the capsule following puncture, meaning that capsule thickness is unlikely to impact on the inhaled dose. Transport and handling would also likely be unaffected by a reduced capsule wall thickness, as exemplified by oral HPMC capsule products, which already have a lower capsule wall thickness specification than their DPI counterparts. The data therefore indicate that the mechanical properties of HPMC capsules allow for the specification of wall thickness to be adjusted to suit the needs of the specific manufacturer or product. Capsule specifications could also potentially be modified to include a wider range of dome thickness values, potentially reducing the waste associated with out-of-specification samples, although further work would be required to determine the upper and lower limits of the dome thickness and to demonstrate that changes in capsule thickness do not affect the inhaled dose.

ABOUT THE ORGANISATIONS

Cardiff University is a member of the Russell Group of research-intensive universities (ranked fifth overall by the Research Excellence Framework 2014) and has been recognised as a leader in translational science (second overall in impact by the Research Excellence Framework 2014). The School of Pharmacy and Pharmaceutical Sciences was ranked the joint top School of Pharmacy in the UK on the basis of its publications, research environment and impact and twelfth in the world by the Shanghai World Rankings. The department's research is highly interdisciplinary, spanning the full translational pathway associated with pharmaceutical medicine.

Qualicaps has a proven record of pioneering in new forms of drug administration, having over 120 years of experience developing products and features that have since become industry standards, such as the first hypromellose capsule for DPIs, with superior functional properties tailored to inhalation. Qualicaps offers a broad portfolio of capsules in gelatin and HPMC specifically designed for inhaled drug delivery, with superior aerosolisation and puncturing properties, even for very hygroscopic and moisture-sensitive inhalation formulations.

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Professor James Birchall is Professor of Pharmaceutical Sciences at Cardiff University. He graduated from Bath University (UK) in 1993 and completed his PhD researching drug and DNA delivery systems in 1998 at Cardiff University. Professor Birchall's current research is focused on pulmonary drug delivery and microneedle drug and vaccine delivery to the skin. Professor Birchall has acted as Associate Editor of Critical Reviews in Therapeutic Drug Carrier Systems, as a temporary advisor to the WHO and as an expert panel member to the British Pharmacopoeia. He has conducted research funded by the EU, UK Department for International Development, Bill and Melinda Gates Foundation, US National Institutes of Health, Wellcome Trust, Engineering and Physical Sciences Research Council, Medical Research Council, Welsh Government, Royal Society and Innovate UK, as well as various other charities and pharmaceutical companies.

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POWDER CHARACTERISATION: A CRITICAL TOOL FOR THE EVOLUTION OF INHALED DRUG DELIVERY

In this article, Jamie Clayton, Operations Director at Freeman Technology, and Joana Pinto, PhD, Senior Scientist, and Sarah Zellnitz, PhD, Senior Scientist, both of Research Center Pharmaceutical Engineering's Area II – Advanced Products & Delivery section, discuss the benefits of multi-faceted powder characterisation in dry powder inhalation formulations and how it can support efforts to achieve net zero emissions.

Inhaled drug delivery technology has matured considerably in recent decades but there are now new issues to address. Efforts being made towards net zero emissions have highlighted the environmental impact of inhalers, notably metered dose inhalers (MDIs), while the covid-19 pandemic has triggered the evaluation of inhaled therapies for both prevention and treatment. Addressing these new challenges calls for further evolution of inhaled drug delivery, which will simultaneously help with longer-standing goals, such as with the development of efficacious therapies for rarer infectious lung diseases and the better exploitation of the pulmonary route for systemic drug delivery.

> "Switching to DPIs is an attractive strategy for companies working towards net zero."

With respect to environmental impact, there is much to recommend dry powder inhalers (DPIs). The hydrofluoroalkanes (HFAs) used as propellants in MDIs have a global warming potential 1430–3200 times that of CO_2,[1] which results in commercial MDIs having an estimated carbon footprint per actuation around ten times that of DPIs (based on full product lifecycle analysis).[2] Switching to DPIs is an attractive strategy for companies working towards net zero. However, relying on a complex device to achieve acceptable drug delivery makes device recycling difficult. As such, developing simpler devices in combination with formulations engineered for optimal aerosolisation is a more sustainable option.

Covid-19 proceeds by rapid viral replication following infection via the respiratory tract, making the targeted, inhaled delivery of antiviral drugs potentially beneficial. While remdesivir has been successfully delivered intravenously, in hospitals, trials are underway to explore delivery by DPI or nebuliser,[4] with DPIs being the easier option for routine, community-based use. Comparable trials are also in place for hydroxychloroquine (HCQ), as consensus grows that the lung airway concentration reached is too low to be effective when administered under a safe oral dosing regime. In place of twice-daily oral doses of 400 mg, the intended DPI dose is just 20 mg.[4] Targeted delivery is expected to result in an efficacious concentration with this much lower dose, but 20 mg is still relatively high in inhaled drug terms.[5]

The HCQ trials are being conducted using the Cyclops™ inhaler (Pure IMS, Roden, the Netherlands), a device with the efficiency to deliver high drug loads with

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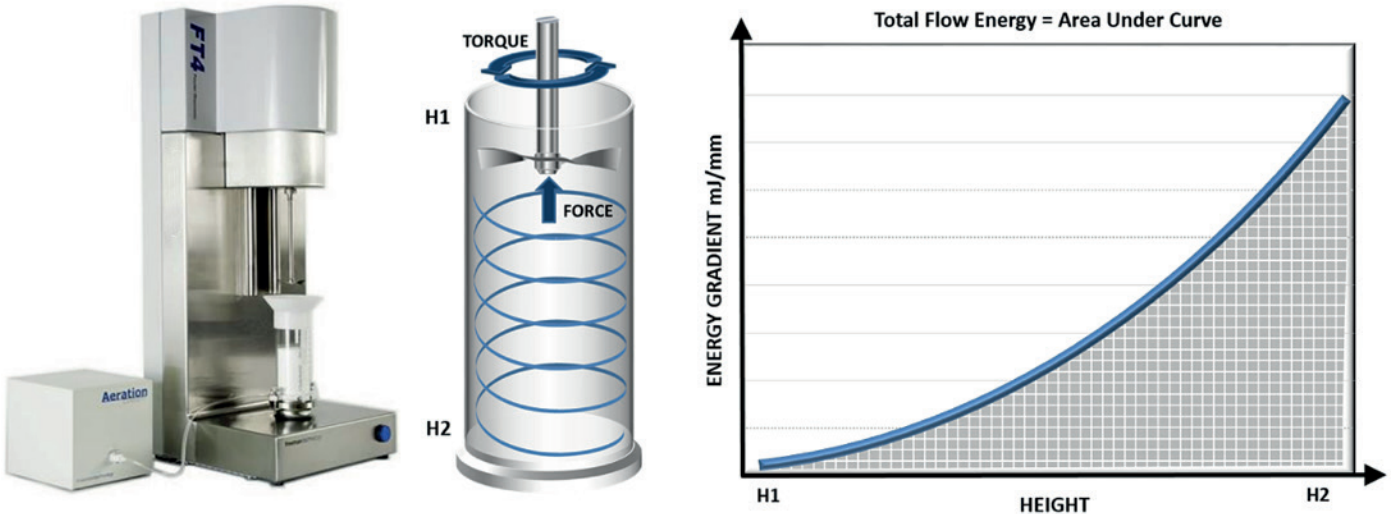

Figure 1: Measuring the torque and force acting on the blade of a powder rheometer as it traverses down or up through the sample generates values of BFE and SE, respectively.

minimal throat irritation. New devices, in combination with particle engineering, have extended the dosage range accessible with DPIs to >100 mg.[5] This is an important trend, as increasing numbers of large molecules enter the respiratory drug pipeline, including proteins, oligonucleotides, antibodies and nanobodies, and for the treatment of infectious diseases, as exemplified by the use of high doses of tobramycin for the treatment of *Pseudomonas aeruginosa* infection in cystic fibrosis.[5] Going forward, there is an expectation that formulators will need to deliver ever higher drug loads with powder formulations that are low density and exhibit poor flowability.[3,6]

In this article, we show how multi-faceted powder characterisation can support effective DPI formulation within this changing landscape. Referencing studies led by researchers from the Research Center Pharmaceutical Engineering GmbH (Graz, Austria),[7,8] we illustrate how measuring dynamic, shear and bulk powder properties delivers understanding that is inaccessible with traditional techniques to aid formulation optimisation.

WHAT CAN BE MEASURED: QUANTIFYING FORMULATION PROPERTIES

The central challenge of DPI formulation is to deliver fine active particles, 1–5 µm in size, within the constraint of minimal energy input. The passive nature of most DPIs means that drug dispersion is driven solely by the inhalation manoeuvre of the patient, but inhalable actives tend to have a large specific surface area and correspondingly high cohesivity. Carriers are routinely used to create formulations with improved flowability and dispersibility, but this introduces the complications of attachment and detachment of the active, during manufacture and dose delivery respectively.

> "Parameters that provide insight into aerosolisation behaviour, including particle-particle interactions, such as those between active and carrier, help formulators to build the understanding needed to engineer superior performance."

Parameters that provide insight into aerosolisation behaviour, including particle-particle interactions, such as those between active and carrier, help formulators to build the understanding needed to engineer superior performance. Particle properties – such as size, shape, specific surface area and surface morphology – are highly relevant, but so too are bulk powder properties, such as flowability. Unfortunately, traditional techniques for powder flow testing, such as tapped density methods, often exhibit poor repeatability and sensitivity, limiting their value for DPI applications. In contrast, dynamic powder testing with a powder rheometer delivers high sensitivity flowability measurement under a range of test conditions.

Figure 1 illustrates how values of basic flowability energy (BFE) and specific energy (SE) are generated by dynamic testing. BFE values are highly reproducible and can be used to securely differentiate formulations classified as identical by traditional techniques.[9] Dynamic testing is also uniquely valuable with respect to quantifying a powder's response to air – a critical characteristic for DPI formulations. Measuring flow energy as air flows up through the sample at a defined velocity, through to the point of fluidisation, generates values of aerated energy (AE), which have been correlated with fine particle dose (FPD)/fine particle fraction (FPF) – the dose or fraction likely to deposit in the lung due to its size, typically <5 µm.[9,10]

Alongside dynamic testing, powder rheometers, as exemplified by the FT4 Powder Rheometer®, offer shear cell analysis and bulk property measurement – density, compressibility and permeability – substantially enhancing their value for DPI formulation characterisation. Permeability values are especially relevant since these also elucidate response to air, quantifying resistance to airflow and the ease with which a powder releases air, both of which can be pertinent to DPI behaviour.

In summary, using a sophisticated powder rheometer not only produces more sensitive and reliable data than traditional techniques, but also generates multiple properties, helping formulators to build a stronger knowledge base to support faster, more efficient DPI development, as the following studies demonstrate.

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BUILDING BETTER MODELS: HARNESSING THE POWER OF *IN SILICO* EXPERIMENTS

A cost-effective way to accelerate DPI development is to increase the use of *in silico* models. Maximising the relevance and utility of both *in vitro* techniques and *in silico* models reduces reliance on *in vivo* testing, which is slower, more complex and more costly. Research reported by Pinto *et al* (2021)[7] demonstrates the potential value of a combined *in vitro-in silico* approach. In this study, four lactose carriers were characterised in terms of specific surface area and porosity (gas adsorption, Tristar II 3020 (Micromeritics, GA, US)), density (helium pycnometry, AccuPyc II 1340 (Micromeritics)) and surface morphology/shape (scanning electron microscopy, Zeiss Ultra 55 (Zeiss, Oberkochen, Germany)).

Samples of each carrier were blended with 2% w/w salbutamol sulphate (SS) and all carriers and blends were characterised in terms of particle size (laser diffraction by pressure titration, HELOS/KR (Sympatec, Clausthal-Zellerfeld, Germany)), tensile strength and hardness (PTB 311E (PharmaTest, Hainburg, Germany)). Permeability, compressibility and shear properties were also measured (FT4 Powder Rheometer®, Freeman Technology). The aerodynamic performance of the blends was assessed as a function of airflow rate using both capsule and multi-dose/reservoir DPI devices.

A physiologically based pharmacokinetic model (PBPK) model of *in vivo* SS uptake was developed, predominantly from published data, although measured values of drug solubility and density were also used. Such models consider the clinical impact of patient physiology, an important factor in drug delivery by DPI, and are becoming an increasingly popular tool in drug development. Once validated, the model was used with the aerodynamic performance data for each of the four blends to predict *in vivo* performance. By identifying correlations between *in vivo* performance and carrier/blend properties via statistical analysis, it was then possible to determine the most relevant powder properties for carrier characterisation and selection.

Aerosolisation and drug delivery parameters, including the extent of drug deposition in the lung relative to the extra-thoracic region and FPF, were found to correlate with shear properties. In addition, for the capsule device only, correlations were observed between key pharmacokinetic properties such as maximum drug concentration level in the plasma and the bulk powder properties of permeability and compressibility. Possible rationalisations for these observed correlations are provided in reference nine.

This discussion affords only the briefest of insights into this detailed piece of work, but it highlights certain key points. Firstly, there is scope to use *in silico* models as learning tools in combination with relevant powder property measurement to support the selection and engineering of carriers to deliver enhanced *in vivo* performance. Secondly, access to multiple test capabilities was vital for this work since shear, permeability and compressibility data were all recommended for ranking carriers for different DPI devices. Shear testing alone would not have been able to perform the same role with respect to supporting carrier selection.

IMPROVING AEROSOLISATION: ENGINEERING HIGH-PERFORMANCE CARRIERS

A further study illustrates the use of advanced powder characterisation techniques in the development of novel carriers with superior drug delivery performance.[8] Engineering carrier particles to which active particles will readily attach and then detach during aerosolisation calls for a precise control of carrier morphology that, in turn, relies on having information on which to base particle engineering decisions. In this study, three distinct types of spherically agglomerated lactose were prepared using the quasi-emulsion solvent diffusion method of spherical crystallisation. These carriers were characterised in terms of particle size, surface morphology, specific surface area and porosity (techniques and instrumentation as described for the preceding study). Bulk and tapped density were determined (PT-TD200 (Pharmatest)) to produce Hausner ratio values, and dynamic properties (including BFE and AE), shear properties, permeability and compressibility were all measured (FT4 Powder Rheometer, Freeman Technology). Characterisation was also carried out with a commercially available lactose grade Lactohale 100 (DFE Pharma (Goch, Germany)) for comparative purposes.

Blends of each carrier with 2% w/w and 5% w/w SS were then produced, and aerosolisation performance was assessed via *in vitro* testing (cascade impaction) using a capsule-based DPI device. A principal components analysis was carried out to determine which carrier properties correlated most strongly with aerosolisation performance. The results showed that, with this system, carriers with higher specific surface area, higher fines, lower permeability and higher cohesion resulted in higher FPFs. Higher BFE values were associated with lower FPFs. It is worth noting that Hausner ratio values were not observed to correlate with aerosolisation performance. In contrast, permeability was singled out for the strength of correlation with FPF and for its ability to effectively account for the combined impact of specific surface area, particle size and shape,surface roughness and morphology.

> "Our understanding of formulation behaviour needs to improve to effectively shape DPI technology to deliver the performance required."

LOOKING AHEAD

DPI technology is attractive from an environmental perspective and has the potential for the delivery of high dosages – an increasingly important clinical requirement. However, the particle engineering involved in DPI formulation is complex and challenging. Our understanding of formulation behaviour needs to improve to effectively shape DPI technology to deliver the performance required.

Reliable, multi-faceted powder characterisation has an important role to play in extending the knowledge base for DPI formulation. Multiple studies suggest that dynamic, shear and bulk powder property measurements can help to elucidate DPI formulation behaviour, notably in response to air and aerosolisation behaviour. The recent studies reported here demonstrate the value of powder testing when it comes to optimising the use of *in silico* models – a vital tool for cost-efficient progress – and for the development of new carriers. Modern, advanced powder-testing

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techniques offer the sensitivity, flexibility and relevance required to deliver unique insight into DPI formulation behaviour and can directly support the development of this vital technology.

ABOUT THE COMPANIES

Freeman Technology specialises in systems for measuring the flow properties of powders and has over 15 years' experience in powder flow and powder characterisation. Expert teams provide comprehensive support alongside the company's range of products. Freeman Technology's systems are installed around the world across a diverse range of industries, delivering data that maximise process and product understanding, accelerating R&D and formulation towards successful commercialisation, and supporting the long-term optimisation of powder processes. Freeman Technology, a Micromeritics company, is headquartered in Tewkesbury, UK, with operations and distribution partners in key global territories.

Founded in 2008, **Research Center Pharmaceutical Engineering** (RCPE) is an independent research centre comprising a multidisciplinary team of about 150 people, from over 20 different countries.

Area II – Advanced Products & Delivery develops physicochemical and predictive bases for addressing drug formulation and delivery challenges (poor solubility and stability) for oral, buccal, inhalation and implant products of small and large drug molecules.

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Jamie Clayton is Operations Director at Freeman Technology, based at the company's headquarters in Tewkesbury, UK. He graduated from University of Sheffield with a degree in control engineering, and is responsible for overall management of company activities, including the R&D, production, sales and customer support teams. During his time with the company, Mr Clayton has worked as a mentor with several academic groups and is an active member of ASTM F42. He is also a regular contributor to conferences and workshops on the topic of powder rheology and works closely with clients on the application of the company's technology.

Joana Pinto, PhD, holds a Masters in Pharmaceutical Sciences from the University of Lisbon (Portugal) and has a PhD from the University of Graz (Austria). During her PhD in pharmaceutical technology, she focused on particle engineering for dry powder inhalation. Since then, Dr Pinto has worked as a senior researcher at the Research Center for Pharmaceutical Engineering where her research has been focused on combining particle engineering principles to the development of advanced formulations. Under this topic, she has led, and is leading, projects with the pharmaceutical industry and has published several research papers.

Sarah Zellnitz, PhD, is a pharmacist by training. During her PhD at the Graz University of Technology (Austria), she explored glass beads as new model carries in DPIs and gained expertise in particle engineering via surface modification and detailed material characterisation. Dr Zellnitz currently holds the position of Senior Scientist at Area II – Advanced Products & Delivery at the Research Center Pharmaceutical Engineering in Graz. Her research focus is on tailoring DPI formulations via mechanistic understanding of the interplay of material properties, formulation properties, adhesive-cohesive force balance and drug detachment.

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TRANSFORMING DRUG DELIVERY WITH SYNERGISTIC WORKING

Here, Bas van Driel, Chief Executive Officer of DFE Pharma, discusses how expert collaborations can help develop a knowledge base to transform drug delivery and manufacturing. He shares how recent collaborative research projects involving lactose-based dry powder inhalation formulations, with and without magnesium stearate and lactose as an excipient in 3D tablet printing, have done just that.

The covid-19 pandemic has seen an unprecedented rate of innovation in the pharmaceutical industry. However, to continue this pace, the industry must harness the potential of collaborative working. It must recognise the value that committed stakeholders from industry, government, academia and patient advocacy groups can create by working together closely.

Successful partnerships can provide access to new technologies, provide valuable data-driven insights, help unlock new funding and contribute to delivering treatments for patients' unmet needs. Cross-sector working has already helped accomplish a great deal – proactive players in the market are keen to engage further in order to maintain and deepen their dialogues, as well as push the boundaries of what they can achieve (Figure 1).

Here are some recent examples of DFE Pharma's collaborations that are helping to transform the knowledge base for drug delivery and manufacturing.

Figure 1: A DFE Pharma manufacturing site in Germany.

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IMPROVING DPI FORMULATION STABILITY WITH MAGNESIUM STEARATE

Lactose-based dry powder inhaler (DPI) formulations are well established in the market for the treatment of asthma and chronic obstructive pulmonary disease (COPD). Recently, they have also been used in the treatment of covid-19. There is now a growing trend towards developing DPI formulations that are ternary mixtures that include magnesium stearate as well as lactose and the API. However, the successful delivery of the API into the lungs depends on numerous interconnected factors during the production process – the smallest formulation changes can have a major effect on the end result.

> "It is essential for partners across the processing industry to work together to grow the evidence base and provide data-driven insights that could accelerate progress."

Drug developers need to know how different qualities and combinations of excipients affect their final formulation, and what kind of equipment and technologies are best suited to their project. They need very specific details, such as which grade of lactose to use, and how magnesium stearate will affect their end product, however, that information is often simply not available. As such, development work is often a matter of trial and error, leading to lengthy and costly delays in the process. Therefore it is essential for partners across the processing industry to work together to grow the evidence base and provide data-driven insights that could accelerate progress.

CROSS-INDUSTRY WORKING

Putting these principles into practice, DFE Pharma has worked collaboratively with fellow processing companies Hosokawa Micron (Runcorn, UK), a powder processing technology manufacturer, and Harro Höfliger (Allmersbach im Tal, Germany), a machine and technology expert, to examine the industry's understanding of lactose-based DPI formulations with and without magnesium stearate. With three leading companies joining forces in this way it became possible to conduct a unique multidisciplinary study that resulted in valuable practical insights.

By testing various formulations of magnesium stearate-coated lactose in the blending and filling process, valuable data-driven insights were gained, enabling DFE Pharma and its collaborators to offer even better advice and support to their pharmaceutical customers. The collaboration has not stopped there – phase two of the study will present information on the magnesium stearate coating used to coat the lactose formulation and analysis of the flow properties and filling. In phase three, the results of adding the API and analysis of the stability of the formulation will be shared.

By sharing knowledge and expertise, this cross-industry, multidisciplinary team has generated insights that could give generic players a head start in the development process, enabling them to reduce their costs and shorten their time to market.

3D POWDER BED PRINTED TABLETS

Currently, a key area of innovation in medicine production to reduce development time and cut costs is 3D printing. As such, it is one of the main innovation areas within DFE Pharma. This technology offers great opportunities around dose flexibility, taste masking, solubility enhancement, shape modifications and producing pills with multiple APIs. 3D-printed tablets can also be created on demand in local healthcare settings, opening up a new era of personalised medicines.

What's more, the 3D printing of medications can potentially accelerate the scaling up of manufacturing and offer global security of supply (Figure 2) – a need highlighted during covid-19. However, to make the most of these opportunities, experts must pool resources and knowledge between industry, innovators and academia.

There is limited literature available on excipient selection for 3D printing, and the only marketed 3D-printed drug is prepared with powder bed printing. It is key to understand powder blend characteristics in relation to tablet features when using pharmaceutical 3D printing in order to obtain tablets that comply with pharmaceutical specifications.

The whole sector would benefit from the creation of a centralised database on 3D-printed tablet research. This database should bring together all key players, from pharmaceutical companies to researchers and academia. Bridging the data gap as to how different excipients impact the powder parameters central to the success of the 3D printing process is vital. This will help us learn which materials or techniques are appropriate for each case.

DFE Pharma envisages a repository including data on excipient usability and applicability and their impact on powder and tablet parameters. This would provide investigators with an invaluable tool and bring the industry together in the common aim of providing patient-centred care.

COLLABORATING IN 3D

It was with this goal in mind that DFE Pharma research teams recently carried out a project on the use of lactose as an excipient for 3D tablet printing in collaboration with The Netherlands Organisation for Applied Scientific Research (TNO). The primary objective was to develop a lactose-based blend with sufficient flowability, wettability and binding to be used effectively in powder bed 3D tablet printing.

Figure 2: Security of supply is a critical issue for formulators.

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The research resulted in 3D-printed products with properties that, while not yet equal to traditional tablets, were approaching the industry standard for hardness and friability. Ultimately, lactose works. This joint project is the first step towards creating a centralised dataset that could accelerate progress throughout the industry and encourage future collaborative input.

INTERNATIONAL, MULTIDISCIPLINARY NETWORKS

To truly embrace collaborative working, it is key to have an international outlook. The Drug Delivery Innovation Center (DDIC), recently joined by DFE Pharma, is an international centre of excellence based on partnership and close collaboration between academia, industry and public stakeholders. By fostering international, multidisciplinary networks in the research area of drug delivery and manufacturing, DDIC is helping to promote pharmaceutical science along the value chain.

Another valuable knowledge sharing partnership looking to maximise technology opportunities within the medicines supply chain is the UK-based Medicines Manufacturing Innovation Centre. This centre, now also joined by DFE Pharma, is a collaboration between CPI, the University of Strathclyde and founding industry partners GSK and AstraZeneca, with funding provided by Scottish Enterprise and UK Research and Innovation. It aims to advance emergent and disruptive technologies through a series of flagship "Grand Challenge" projects to increase productivity in the pharmaceutical industry and improve patient outcomes. DFE Pharma's new partnership will focus on Grand Challenge 1, which aims to develop a novel digitally twinned continuous direct compression (CDC) platform to reduce waste and cut costs during the manufacture of oral dosage medicines.

As a leading global excipient manufacturer, DFE Pharma will help accelerate phase one of Grand Challenge 1, as well as minimise associated costs and risks. The partnership builds on the company's existing contributions to Grand Challenge 1, including the supply of direct compression excipients that have been particle engineered for the CDC platform. These unique data insights could significantly reduce the number of trials needed to develop the CDC platform.

ACADEMIA – A KEY PLAYER FOR INNOVATION

Knowledge from academia plays a key role in innovation – collaborating with these institutions can boost progress in the drug delivery and manufacturing industry. To further expand these collaborations, DFE Pharma supports a four-year PhD at the University of Groningen in the Netherlands, focusing on increasing the understanding of how biologic APIs and DFE Pharma's excipients can be combined into stable formulations. This research contributes towards a global push to create new, functional, stable and safe biologic formulations for patients.

> "Expert collaborations and synergistic work are helping to develop knowledge bases which will drive the next innovations in drug delivery and manufacturing."

NOW IS THE TIME FOR PARTNERSHIPS

Expert collaborations and synergistic work are helping to develop knowledge bases which will drive the next innovations in drug delivery and manufacturing. Those who strike early and establish partnerships will be able to take advantage of post-covid-19 growth.

DFE Pharma is committed to using innovation to further medical research and providing premium excipients and services. The company believes that partnering and collaborating with top science organisations is the best way to achieve this. Sharing knowledge and expertise can allow pharmaceutical players to gain new data insights, embrace new technologies, lower costs and improve patient outcomes.

ABOUT THE COMPANY

DFE Pharma is a global leader in pharmaceutical excipient solutions. The company strives to develop, produce and supply the highest quality functional excipients for use in the pharmaceutical, biopharmaceutical and nutraceutical industries for respiratory, oral solid dose (OSD), ophthalmic and parenteral formulations. DFE Pharma's excipients play an essential role as fillers, binders and disintegrants, as well as in stabilising active ingredients for release in a predictable and effective manner into the patient's system. With over a century of experience and more than 400 people worldwide in over 100 countries serving more than 5,000 customers, DFE Pharma is committed to supporting (bio)pharmaceutical and nutraceutical companies in their journey to improve patients' lives.

ABOUT THE AUTHOR

Bas van Driel is Chief Executive Officer at DFE Pharma. He joined the company from Royal FrieslandCampina (Amersfoort, the Netherlands), where he held a number of commercial management positions. Mr van Driel brings vast experience in the field of marketing, sales and key account management and also a wealth of knowledge in general management. He holds a master's degree in Business Administration, Strategic and Financial Management.

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NUMERICAL SIMULATIONS FOR INHALATION PRODUCT DEVELOPMENT: ACHIEVEMENTS AND CURRENT LIMITATIONS

Here, Andrea Benassi, PhD, New Technology & Innovation Scientist, and Ciro Cottini, PhD, Drug Product Manufacturing & Innovation Head, both of Chiesi, discuss the current state of CFD and DEM computational modelling, how it is used to improve inhaler design and manufacturing, and what the current limitations of this technology are, as well as how those limitations may be overcome.

The role played by physical and engineering simulation techniques in the design of pharmaceutical products, and related manufacturing processes, has, undoubtedly, grown rapidly in recent years. The increasing number of technical publications in scientific literature (Figure 1), the appearance of modelling and simulation services in the portfolio of many contract research and manufacturing organisations working with pharma companies, and the opening of new funding opportunities from regulatory agencies to explore the reliability of such simulations for pharma and medical applications[1] are all testament to this growth. Many application areas can be identified in the context of inhalation products, amongst which the most notable are:

- Manufacturing process development
- Inhaler design
- Modelling of drug delivery to the lungs.

A trait common to most of these applications is the presence of pharmaceutical powders interacting with fluids (liquids or gasses). This occurs both during the powder manufacturing process and the use of the device by the patient, some specific examples being:

- A drug substance powder crystalising and precipitating in a liquid solvent in a synthesis reactor
- A drug product powder dose entrained and aerosolised by a swirling air flow in a dry powder inhaler
- Airborne drug substance particles travelling down the patient's tracheo-bronchial tree.

Powder-fluid interaction is an intrinsically complex and non-linear phenomenon that is still both difficult to accurately model and poorly understood at the fundamental level. Predictions based on simple rules of thumb or empirical formulae are impossible, especially in complex geometries such as industrial

> "Powder-fluid interaction is an intrinsically complex and non-linear phenomenon that is still both difficult to accurately model and poorly understood at the fundamental level."

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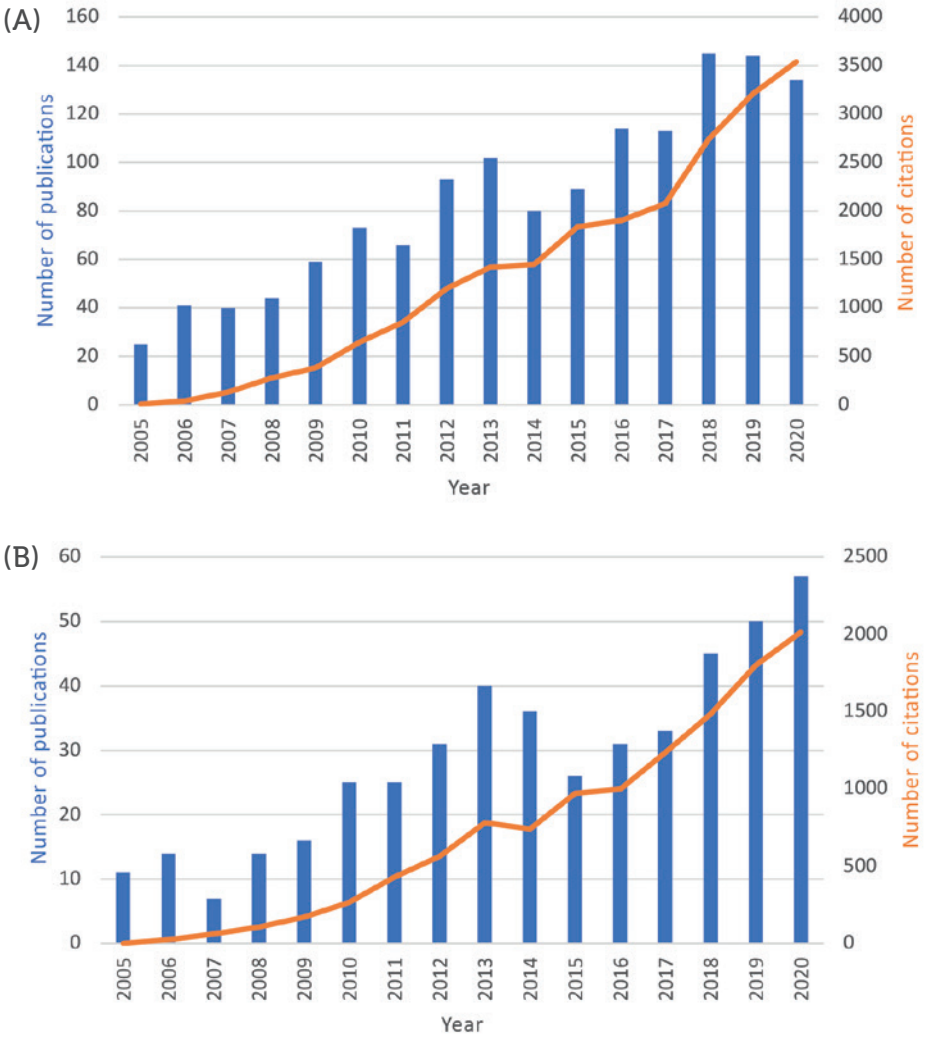

Figure 1: Number of published papers per year, and their citations, with topics related to CFD/DEM simulation of pharmaceutical processes (A) and CFD/DEM applied to inhaler design and drug deposition in the lungs (B).

machinery, inhalers or human airways. In most cases, a direct measure of powder and fluid behaviour is difficult or impossible due to:

- Harsh environments, such as hot corrosive solvents in reactors or abrasive conditions in powder mills
- Limitations imposed by quality and safety protocols in manufacturing for human-use productions
- Difficulty in measuring fast phenomena occurring in extremely limited volumes, such as drug dose aerosolisation inside an inhaler camber
- Absence of easy access to the product, such as in sealed bins during mixing
- Lack of suitable devices for taking measurements.

The success of simulation-based design stems precisely from these limitations – being able to reproduce the behaviour of products during manufacturing and administration *in silico* (i.e. using computer simulations) allows for a better understanding of the underlying mechanisms governing these interations and a more conscious approach to product design and optimisation, eventually leading to performance and quality enhancements.

Simulations can also be fed with data measured directly from patients, such as inhalation profiles recorded via spirometry or 3D lung morphologies acquired with CT or MRI scanners, becoming a formidable tool in a patient-centric drug product design approach. To take the principle further, study and optimisation of inhaler performance could be conducted for specific populations of patients with peculiar lung morphologies and/or inspiratory profiles as a consequence of different degrees of disease severity or comorbidities.

SIMULATION TECHNIQUES AND THEIR VALIDATION

Despite the great variety of possible applications, the simulation methods employed are always the same. Computational fluid dynamics (CFD) is used to simulate the fluid behaviour, based on the solutions of Navier-Stokes equations, while discrete element methods (DEM) are used to reproduce a powder flow by solving the Newton's equation of motion for each individual particle composing it.

When describing a powder entrained and interacting with a fluid, these two simulation techniques must be coupled together (Figure 2), with different coupling conditions used depending on the level of dispersion of the powder particles.[3] In the case of very diluted powder suspensions, a one-way coupling is typically adopted. In this

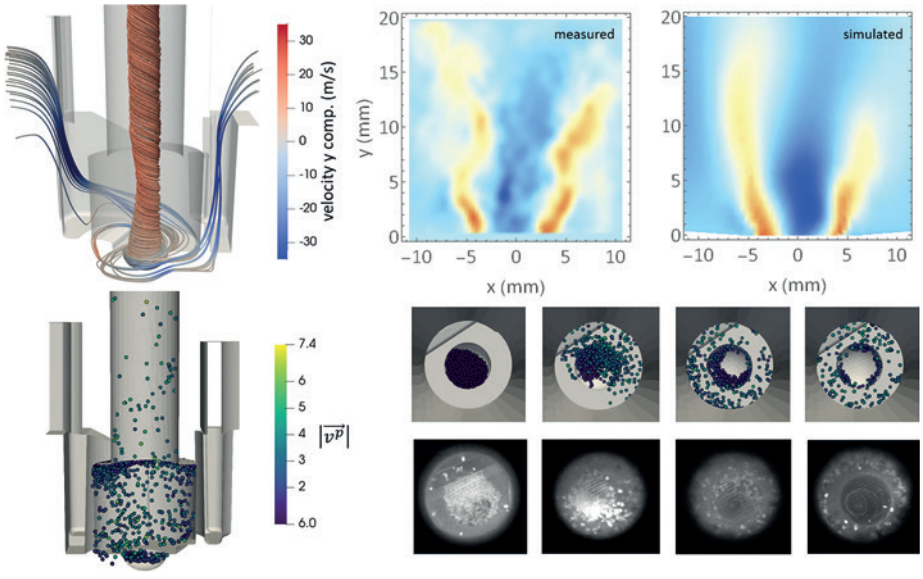

Figure 2: Coupled CFD-DEM has been used to model the emission of particles from a dry powder inhaler during inspiration.[2]

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approximation, the fluid drags along the particles, but the energy lost in the process is considered negligible – thus the fluid is not perturbed at all by the powder's presence. When the powder concentration is high, the energy and momentum exchanged with the fluid are no longer negligible and therefore a two-way coupling is necessary. In this case, the fluid accelerates the powder mass and, in so doing, decelerates. In one-way coupling conditions the particles are so diluted that they do not feel each other, however, as the particle density increases they perceive other particles by the perturbations they leave in the fluid (wakes) – an effect typically referred to as three-way coupling. Finally, when the powder density is significantly high, particle-particle collisions and inter-particle interactions start to become relevant. Including them means running a fully coupled, or four-way coupling, simulation.

Both the simulation methods make use of different approximations and assumptions, and can also depend on certain model parameters not known *a priori*. The level of realism and the reliability of simulations must therefore be evaluated by comparing their outcomes with experimental data – a procedure known as simulation validation. On the other hand, a model calibration is necessary when a value must be set for a parameter that is not known *a priori* and not easily experimentally measurable. This is typically the case for certain DEM parameters determining the interparticle interaction, such as the elasticity of the collisions or the friction forces between particles. In this case many simulations are run varying that free parameter until a good match is found with experimental data. Clearly, there must be only one value (or a narrow range of values) for a given parameter where the simulation result and experimental data match. However, verifying this for increasing numbers of free parameters becomes very challenging.

As mentioned prior, acquiring experimental data is neither easy nor always possible in the regions of interest of a manufacturing facility, piece of equipment or drug delivery device, thus model validation/calibration is usually performed on simplified geometries or for small-scale laboratory prototypes. In practice, this means using simplified working conditions that are still representative of the real processes, but where data acquisition is much easier. In some other cases it is not possible to measure what is going on in a region of interest, but it is easy to measure what enters and exits from that region. Thus, some validations and calibrations are performed by matching the physical quantities and profiles measured at inlets and outlets of a system to those of a simulation.

MANUFACTURING PROCESS DEVELOPMENT

Among all application areas, manufacturing process development is the widest, encompassing particle engineering applications such as spry-drying and milling,[4-6] design of manufacturing unit operations such as dry powder mixing, tableting and spray-coating,[7] and design of equipment and facilities such as freeze dryers or bio-reactors.[8-11] Covering all these aspects is beyond the scope of this brief perspective and many details are intimately connected to each specific application. Most of the works on modelling and simulation are not even found in the pharmaceutical technology literature – they belong more generally to the chemical engineering and powder technology realm.

In cases where the scale of the problem or the total mass/volume of product involved is large, surface effects and other details are negligible, so a satisfactory description of the phenomena can be achieved by simulating only the average properties of the fluids and powders. The fluid turbulence and its interaction with single powder particles can be neglected, as well as the correct shape of the particles – usually assumed to be spherical. For such cases, standard commercial software already provides all the necessary features and the validation of the simulations is straightforward.

In other cases, where a specific feature is extremely relevant but many others can be neglected, such as the spray-coating of tablets, it is necessary to model the real tablet shape with a high degree of accuracy while the presence of air in the tumbler can be completely neglected. This means that, under such circumstances, it is possible to work with DEM simulations alone.

Finally, applications exist that challenge even state-of-the-art software. For example, in jet mills, particle size reduction is achieved through a supersonic gas accelerating a large mass of powder in order to promote particle-particle collisions and breakage. Simulating such phenomena requires specific CFD algorithms able to treat transonic and supersonic gas flows, while fully coupling them with DEM simulations of a large mass of powder (Figure 3). Such a requirement is beyond the capabilities

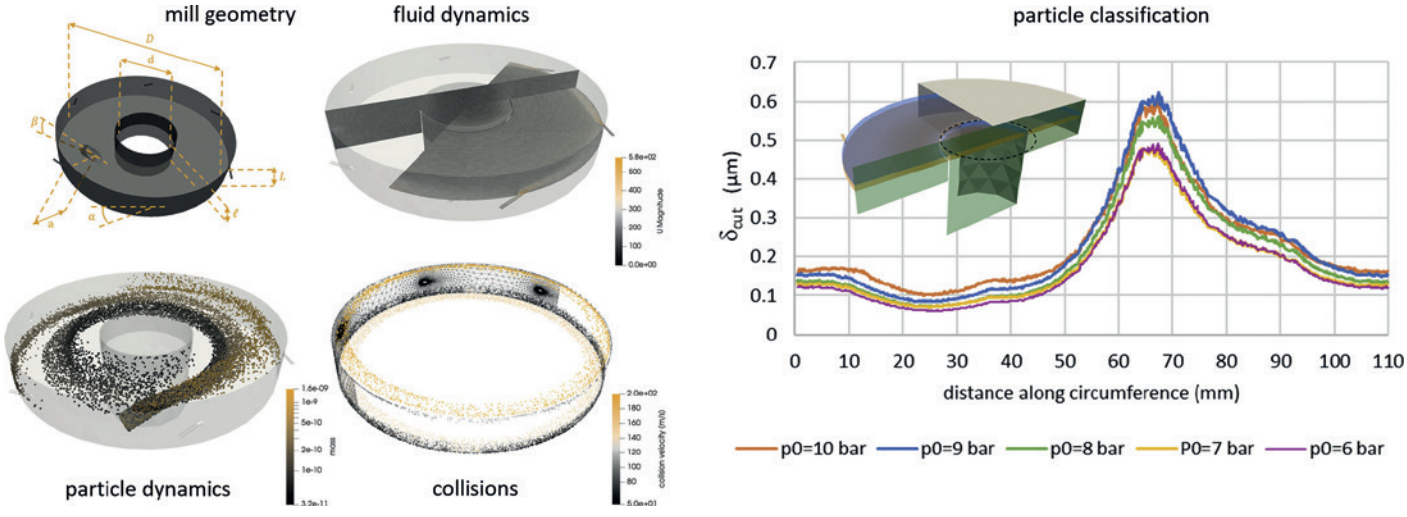

Figure 3: While CFD-DEM analysis can be used to gain insights into the mechanics of jet milling, current technology is yet to produce a satisfactory simulation the covers all elements of the process simultaneously.[12]

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"Although very useful during the design phase of processes and products, coupled CFD-DEM simulations are rarely able to give real-time information during batch manufacturing."

of most commercially available software. Furthermore, on top of that, a good description of particle fragmentation is necessary and specific models coming from fracture mechanics must be implemented in the DEM software.[13,14] To date, the combination of all these elements is still missing, and as such it is not possible to simulate the jet milling process to a satisfactory level.

To conclude, it must be noted that it is only on rare occasions that it is possible to build digital twins for pharmaceutical processes. The need to account for the properties of both fluids and powders makes the simulations complex, usually requiring dedicated computational resources and taking many hours, or even days, to obtain the numerical results and process them. Thus, although very useful during the design phase of processes and products, coupled CFD-DEM simulations are rarely able to give real-time information during batch manufacturing.

DESIGN OF INHALERS

The methods for collecting certain data from outside inhaler devices are well established:

- Air flow rate and pressure drop profile can be easily recorded at the inlets and outlets of inhalers
- Particle and droplet emission time and size distribution can be measured optically at the device outlet[15-17]
- Temperature and the shape of aerosol plumes can be imaged with fast thermo-cameras.[18,19]

Measuring what happens inside devices is definitely more complex. In most cases, X-ray-based methods are used to image fast phenomena, such as the flash boiling of a propellant in pressurised metered dose inhalers (pMDIs)[20] or the initial lift of carrier particles in a carrier-based dry powder inhaler (DPI),[21] but quantitative data are rare. In this sense, simulations can be extremely helpful – after validating/calibrating them with the data available for both fluids and aerosol particles at the outlet, they offer a complete insight into what happens inside inhalers.

In DPIs, for instance, carrier particle collisions as well as API agglomerate breakage by air turbulence are known to enhance inhalation performances, in particular the fine particle fraction. Such phenomena can be easily quantified and studied with a validated CFD-DEM model.[22-25] *In silico* geometry optimisation studies can be performed on inhalers to maximise both such phenomena and the conditions that lead to API aerosolisation and deagglomeration.[26,27] Finally, inhalation profiles of different patient populations can be used as boundary conditions for the simulations to see how an inhaler responds to weak inspiratory acts, or how ineffective it becomes in misuse conditions.

This kind of information can be used during inhaler design to improve patient compliance and to customise it for specific patient needs, achieving high performance even in the case of weak flow conditions. For DPIs, when the drug dose is initially concentrated at rest in a cup/pocket or in a capsule, fully-coupled simulations are fundamental to correctly capture an accurate model of the aerosolisation process.[22]

Improving On the State of the Art

Due to intrinsic limitations of the DEM technique, it is very difficult to simultaneously simulate both the carrier particles and the fine API particles in carrier-based DPIs. For a qualitative understanding of the API detachment and disaggregation mechanisms, simulations can be performed with the carrier surface covered with smaller particles that still have a diameter 50–100 times larger than real API particles – this means that the total number of API particles in the simulated dose will be orders of magnitude smaller than in reality. The tough part is that API-carrier adhesion forces, elasticity and frictional coefficient must be set in the DEM simulation through a complex calibration procedure.[28]

In aiming to achieve quantitative and predictive simulations of DPIs, an implicit approach has been suggested and successfully employed where only the carrier particles are simulated, while fine API particles are treated as a continuum phase diluted in air.[29] The concentration of API particles is increased close to a carrier particle depending on its relative velocity with respect to air and any time it experiences collisions. This approach requires a huge effort in the parametrisation of the API release from carrier particles, but allows for the simulation of a realistic concentration of API inside the air.

No matter how fast, and thus turbulent, the air flow is in the inhaler, close to the inner walls its velocity must drop to zero, which creates a narrow region, called the boundary layer, with strong air velocity gradients. With the typical flow rates of DPIs inhalers, the thickness of this layer is estimated to be few hundreds microns – comparable to the size of the carrier particles and much larger than that of the API particles.[30,31] This means that both carrier and fine API particles sitting at the bottom of an inhaler, as well as API particles on the surface of carrier particles, feel the presence of such a layer. Corrections of particle-air forces in the vicinity of walls, to account for the existence of this boundary layer, are not implemented in most of the available software.

Particles of lesser size (and thus reduced inertia), such as the API ones, are strongly influenced in their motion by turbulence in the air flow entraining them. Exactly as random thermal fluctuations generate a stochastic Brownian motion for nano-sized particles, random air velocity fluctuations (turbulence) generate a stochastic trajectory for those particles small enough to be entrained in the turbulent eddies. To reduce the computational cost, in most industrial CFD simulations the presence of turbulence is included without explicit simulation of the velocity fluctuations, not at least at all

"The possibility of simulating the deposition of aerosol particles in the respiratory system reliably is now concretising, thanks to the recent and substantial progresses in *in vivo* real-time 3D functional imaging."

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the scales at which these fluctuations occur. Thus, when dealing with small particle dispersion, particle-turbulence interaction must be re-introduced with an ad-hoc stochastic term.[30,32] These particle turbulence effective interaction models are not always implemented in most of the available software and, when present, their general-purpose implementation is questionable.[33,34]

Simulating the behaviour of drug products during the actuation of a pMDI is much more complex, owing to the occurrence of the propellent flash-boiling phase transition – the phase change and latent heat exchange require a complex treatment of the thermodynamics of the fluid mixture. Many models for the nucleation of gas bubbles have never been tested in this context, and in general they are not even implemented in most of the open source or commercially available software. For these reasons most of the models available to predict drug product behaviour inside a pMDI actuator are based on phenomenological zero-dimensional models – time dependent equations describing the thermodynamic properties without any spatial resolution.[35,36] It is only recently that some progress and a first implementation has been made available.[37]

DRUG DELIVERY TO THE LUNGS

The possibility of simulating the deposition of aerosol particles in the respiratory system reliably is now concretising, thanks to the recent and substantial progresses in *in vivo* real-time 3D functional imaging.[38,39] These techniques not only provide realistic models of 3D lung geometry to be used with CFD, but they also allow investigators to monitor the API concentration inside the patient lungs, thus providing data to validate the simulated deposition. In the extra-thoracic airways and nose, where air flow is dominated by turbulence, its explicit inclusion in the CFD simulations has proven to be necessary to achieve realistic results in the description of particle deposition. In other cases, simulations are validated against data collected on casts realised from realistic 3D models constructed using 3D printing or moulding.[40,41] The advantage of these experiments is that that air flow conditions are much more controllable and reproducible, as well as that, besides deposition data, air velocity maps can be recorded (using particle image velocimetry) in mouth, throat and upper airway generations.

> "Scientific software development requires great effort – one that pharma companies are not well suited to undertake – however, commercial software companies are not always keen to implement cutting-edge algorithms, still under debate in the academic literature, that are of limited interest among their broader userbase."

Aerosol particles are assumed to be already highly diluted while entering the patient mouth, thus a one-way coupling is generally used. The deposition in the intrathoracic generations is entirely dominated by inertia for particles above 10 microns, while Brownian diffusion plays a major role for particles below 0.5 microns. The intermediate range between 10 and 0.5 microns – the most interesting one from the drug delivery point of view – is the most complex one to simulate, where the effect of the weak turbulence, surviving from the upper airways, might contribute to deposition comparable to sedimentation and to inertia-driven impactions from the secondary flow. To the best of our knowledge, the contribution of the different deposition mechanisms for this intermediate range of particles in the conductive intra-thoracic airways remains unclear and requires further investigation.

However, as the diameter of the airways decreases, it drops below the resolution of the scanner around the sixth or seventh airway generations, which prevents an imaging-based reconstruction of the lung. Mathematical models are thus used to continue the lung reconstruction of the lower functional generations up to the alveolar sacs.[42-45] Whole-lung models use multi-scale CFD simulations of multiple branching paths to complete the deposition statistics in the lower airways.[46]

Alternatively, statistical approaches can be used to simulate the deposition in the lower airway. Here the laminar (simpler) nature of the air flow allows the calculation of analytical expressions for the deposition probabilities.[30,47] However, the uncertainties in the mathematical models used to generate the bifurcations and the absence of spatially resolved deposition data for the deeper airways reduce the reliability of deep airway simulation. Most of the explicit CFD-DEM simulations found in literature are thus limited to the upper airways only, which, when compared with deposition data, usually demonstrate discrepancies of less than 10%.[46,48]

There is, of course, room for improvement – small particles (5 to 0.5 microns) are known to accumulate and travel in the boundary layer, but many simulations approach this region using wall functions. In cases where turbulence is explicitly simulated, typically large eddy simulations, a cut-off is usually adopted, neglecting the small eddies that populate the region close to device walls. The implications of such approximations in the particle-fluid interaction, and thus on particle depositions, are still unclear and poorly debated in the current literature. Efforts are needed to improve the description of the lung model, for instance allowing the 3D lobes to change their volume and enabling certain anatomical features, such as the glottis, to move during the inspiratory act.[49] Finally, in pursuit of a predictive tool that is able to resolve the spatial deposition of API particles in every airway generation, attempts are ongoing to couple it with pharmacokinetic and pharmacodynamic

> "To fully exploit the potential of modelling and simulation, a cultural change must take place in the pharmaceutical manufacturing sector, a change that was started with the introduction of quality by design principles, the digital revolution and the Industry 4.0 philosophy, but that has not yet been completed."

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models to improve our understanding and predictions for bioavailability and systemic exposition.[50]

CONCLUSION

CFD and DEM simulations are proving to be valuable tools for product and process design, offering new insights into poorly understood phenomena and enabling new predictive capabilities. Best practices and reference standards have been recently proposed for specific CFD-DEM simulations of inhalers[51] and human lung deposition.[52] Indeed, there is still plenty of room for improvement, as well as new applications and challenges for the current state of the art of technologies and algorithms.

However, to fully exploit the potential of modelling and simulation, a cultural change must take place in the pharmaceutical manufacturing sector, a change that was started with the introduction of quality by design principles, the digital revolution and the Industry 4.0 philosophy, but that has not yet been completed. To master the complexity of CFD and DEM simulations, competences in physics, computational engineering and scientific high-performance computing are needed. However, physicists, engineers and information technicians are rarely found among the ranks of research professionals currently employed in drug product design.

Most of the software for CFD and DEM simulations is developed to be general purpose and lacks certain features necessary for specific pharma applications. Scientific software development requires great effort – one that pharma companies are not well suited to undertake – however, commercial software companies are not always keen to implement cutting-edge algorithms, still under debate in the academic literature, that are of limited interest among their broader userbase. A possible solution is the adoption of open-source software, for which customisation and implementation of these cutting-edge algorithms could be achieved through partnerships with academic research groups and scientific computing centres. With this in mind, the culture in the industry should evolve from a contract/consultancy driven collaboration to an open innovation approach.

ABOUT THE COMPANY

Chiesi is an international research-focused pharmaceutical and healthcare group with over 85 years' experience, operating in 30 countries with more than 6,000 employees. The group researches, develops and markets innovative drugs in its three therapeutic areas: AIR (products and services that promote respiration, from new-born to adult populations), RARE (treatment for patients with rare and ultra-rare diseases) and CARE (products and services that support special care and consumer-facing self-care). Since 2019, Chiesi has been the world's largest B Corp certified pharmaceutical group. By incorporating a double purpose for the creation of shared value, Chiesi changed its legal status to a benefit corporation in 2018, generating value for its business, for society and for the environment. The group is committed to becoming carbon neutral by the end of 2035.

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