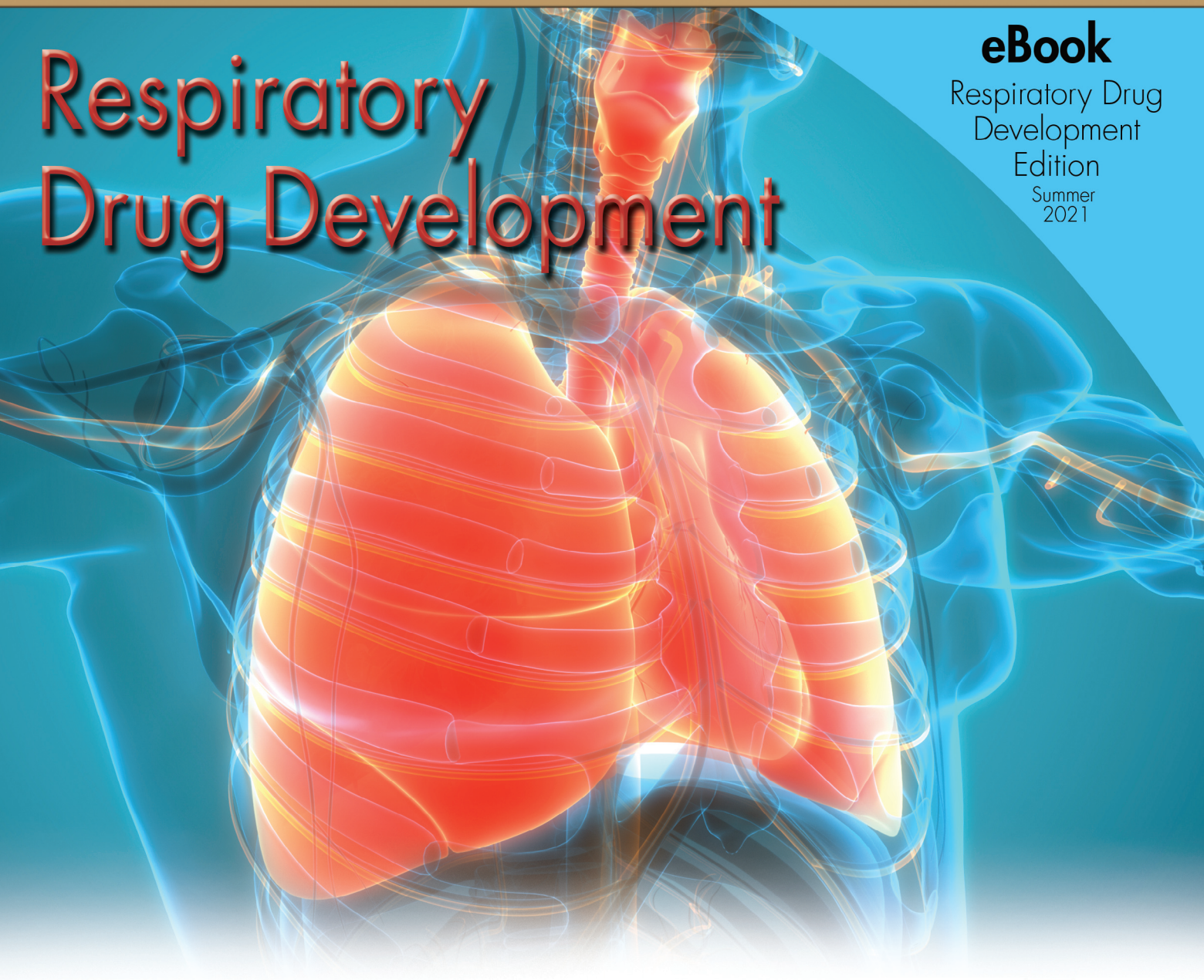
Drug Development & Delivery



Respiratory Drug Development

eBook
Respiratory Drug Development Edition
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Drug Development & Delivery
Respiratory Drug Development eBook

The Three Cs Driving Respiratory Drug Delivery

The global pulmonary drug delivery systems market was valued at $28.7 million in 2019, is expected to account for $30 million in 2020, and could reach $41 million by the end of 2027.[1] Much of this growth can be attributed to the advantages of respiratory drug delivery, including ease of administration, low drug dosing, relatively few or no side effects, rapid onset of action, prevention of drug degradation by the liver, targeted drug delivery, and a wider absorption area for the lungs. Digging deeper, experts point to three "C" factors driving the market landscape: chronic obstructive pulmonary disease, COVID-19, and carbon footprint.

Coping With COPD

COPD is the third-leading cause of death worldwide, causing 3.23 million deaths in 2019, according to the World Health Organization. While there are more than 60 therapies currently in different stages of development, there are 9 approved drug categories for COPD maintenance medication. And the majority of these available treatment options are primarily iterations of bronchodilators.[2]

The COPD and asthma devices market size was estimated at $36.45 billion in 2019, and is anticipated to hit $51.62 billion by 2027.[3] Patent expiration for blockbuster drugs and smart inhalers are anticipated to create lucrative opportunities for the key players in the industry. One such company is Aptar, which offers a broad range of pMDI technology platforms, including metering valves, dose counters, Breath Activated Inhalers (BAIs) and Dry Powder Inhalers (DPIs), for the treatment and management of asthma and COPD.

COVID-19 Puts Focus on Nasal Vaccinations

Love it or hate it, FluMist established a framework for intranasal vaccines. Small biotechs are pushing forward to develop intranasal vaccines for patients who are needle averse. Nasal vaccines offer ease of administration for a variety of respiratory pathogens, including COVID-19. AstraZeneca is currently testing the safety of an intranasal version of its COVID-19 vaccine that is authorized for use as an injection in Europe and India. And throughout this past year, preclinical studies of intranasal vaccines have proven that musical immunity is significant.

Proveris Laboratories works with drug developers to evaluate nasal spray performance by screening key parameters to determine how the product will perform in use. Catalent, too, is seeing an increased focus on the orally inhaled and nasal drug product (OINDP) pipeline due to lower dosing, higher efficacy, and increased patient compliance. Vital to the development of OINDPs is testing, and Copely Scientific offers a range of automated test solutions.

Greener – and Smarter – Inhalers

Solving one problem can often incur a new one. So, while pressurized Metered Dose Inhalers (pMDIs) deliver life-saving medications, they also emit CO_2. MDIs contain hydrofluorocarbons (HFCs), which are known to contribute to global warming. According to the Asthma + Respiratory Foundation of New Zealand, the carbon footprint of a standard (200-puff or 100-dose) salbutamol inhaler amounts to approximately 28kg of CO_2 per inhaler. Thus, companies like Recipharm and Aptar are seeking propellant alternatives.

While pMDIs aren't going anywhere – the metered dosage inhaler segment is expected to exceed 2.5 billion by 2025[4] – propellant-free DPIs are gaining preference as a greener option than MDIs. One expert estimates that switching from an MDI to a propellant-free DPI could save the equivalent emissions of 33mph of driving per patient per month based on once daily dosing.

DPIs make up part of the digital dose inhaler sector. Digital dose inhalers contain sensors that record when medication is being administered and can be paired wirelessly with a smartphone or computer to automatically transfer data. And Vectura is exploring smart nebulizer technology whereby controlling 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 gets to central or peripheral parts of the lungs.

In this third annual *Drug Development & Delivery* Respiratory eBook, several companies discuss what they are currently working on to propel the respiratory sector.

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Moving Toward a More Sustainable Future With pMDIs

By: Chris Baron, Director of Business Development, Pulmonary Category, Aptar Pharma

It is now more than half a century since patients were introduced to the pressurized metered dose inhaler (pMDI) as a convenient, effective vehicle for the symptomatic relief and sustained management of conditions such as Asthma and Chronic Obstructive Pulmonary Disease (COPD). This innovation has since become a dominant drug-delivery device for Asthma and COPD patients, helping millions of people around the world. Recent history has also seen us better understand how human activities can negatively impact our planet, which includes growing evidence of the causal link between increasing levels of atmospheric carbon dioxide and rising global temperatures.

These important revelations in environmental science have had significant consequences for pharmaceutical companies and their supply chain partners, particularly in relation to pMDIs. In 1987, for example, the Montreal Protocol set out a pathway for eliminating the use of compounds proven to be harmful to the ozone layer, which included chlorofluorocarbons (CFCs), which were also used as propellants in pMDIs. Although the industry was given an exemption to the 10-year CFC phase-down deadline to maintain continuous provision to patients with respiratory conditions, the industry urgently looked for replacement propellants with the necessary attributes of low toxicity and flammability, but also with reduced global warming potential (GWP).

The answer was found in the form of two hydrofluoroalkanes (HFAs): 1,1,1,2-tetrafluoroethane (HFC 134a) and 1,1,1,2,3,3,3-heptafluoropropane (HFC 227a). The first to be introduced was HFA 134a, approved by the US Food and Drug Administration (FDA) in 1996 in an MDI for albuterol sulfate.

In the 25 years since, the number of products incorporating HFA-based propellants has continued to rise, with the FDA having banned the manufacture and sale of CFC-based products entirely in 2012. While there has been notable innovation around non-propellant-based technologies such as dry powder inhalers (DPIs) and, more recently, soft mist inhalers (SMIs), HFA-based products now dominate, with at least 13 companies producing branded or generic HFA-based inhalers for the US market.[1]

Over time, as climate-related concerns have intensified, the focus on limiting the use of products with GWP has brought a sharper focus on the wider group of fluorocarbons known as F-gases, which encompass HFC 134a and HFC 227a. F-gases account for around 2% of total greenhouse gas emissions and are predominantly used in the refrigeration and air-conditioning industry. While they may not be responsible for ozone depletion, they are known to contribute to global warming, and the Kigali Amendment to the Montreal Protocol aims to have reduced use by over 80% by 2047.

Although pMDIs, which contribute a comparatively low 2.4% of total F-gas emissions, are subject to varying exemption protocols across different regulatory jurisdictions, pharmaceutical stakeholders are again working to secure the use of lower carbon propellants. This effort is given even greater urgency as reduced volumes of industrial-grade gases are expected to negatively impact the manufacturing cost of medical-grade gases.[2,3]

Aptar Pharma – Working Collaboratively With Our Pharmaceutical Partners

At Aptar Pharma, we are committed to supporting our pharmaceutical partners on the next phase of the sustainability journey. As it stands, the two leading candidates to replace HFAs are HFC 152a and HFO1234ze, both of which present significantly lower GWP compared with existing HFA propellants. Of course, this is not the only attribute such gases must demonstrate, and key factors such as critical thresholds for levels of toxicology and flammability must also be considered in addition to the economic aspects of these respective alternative propellants compared with the future costs of current propellants, and also the costs of alternative delivery platforms.

Our company's work in this area is dedicated to evaluating the compatibility of Aptar Pharma metering valves with both HFC 152a and HO1234ze. Drawing on the expertise within our R&D team, we are exploring multiple model formulations and valve configurations, working collaboratively with our pharmaceutical partners and other key stakeholders.

It is only through this level of active collaboration and partnership that we will ensure the safe development of new forms of lower GWP-propellant pMDI devices, answering a fundamental environmental need, and maintaining the convenience and familiarity of a proven drug delivery device that has satisfied patient need for the past 75 years.

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Working daily to improve the health of our patients and our planet

As the market leader in pMDI valve technology for asthma and COPD, Aptar Pharma is committed to improving the environmental impact of our products and ensuring our devices are safe and effective.

That's why we are actively engaged in defining the next generation of pMDIs, finding more sustainable solutions with alternative propellants that align with our sustainability commitments as well as those of our partners and their patients.

To find out more about how Aptar Pharma is advancing pMDI technologies, please visit **www.aptar.com/pharmaceutical /delivery-routes/pulmonary/**

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Orally Inhaled & Nasal Drug Delivery – An Evolving Pipeline Creating New Opportunities

By: Carla Vozone, Vice President of Inhalation Strategy, Innovation & Partnerships, Catalent

Recent years have seen a rapid expansion of the orally inhaled and nasal drug product (OINDP) pipeline, with an intent to explore targeted delivery to the lung or nasal cavities and achieve higher efficacy with lower doses, limited exposure to secondary organs, reduced systemic adverse effects, and increased patient compliance and convenience. This resurgence is underpinned by scientific, technological, manufacturing, and regulatory advances across drug products and devices, which are allowing both established companies and new entrants to the respiratory field to advance drug-device combination programs using new molecular entities to target therapeutic classes that have not traditionally been addressed.

Whereas biologic molecules represent less than 2% of approved marketed drugs in pulmonary delivery today, about 30% of the current clinical development pipeline for lung administration is made up of a diverse range of biologic entities, such as recombinant proteins, monoclonal antibodies, and vaccines.[1] Furthermore, the race to develop and produce effective treatments against COVID-19 has advanced the study of DNA and RNA therapeutics delivered through the lungs. A similar trend can be observed in nasal delivery, in which small molecules constitute 75% of currently marketed products, but only around 60% of clinical-stage programs. In the preclinical phase, the trend is even more pronounced, with the percentage of small-molecule projects currently in development falling to only 45%. The impact of COVID-19 is particularly noticeable in nasal administration, with research focusing on virus-like particles looking to stimulate an immune response.

The OINDP route is also being used for new therapeutic classes and indications as an alternative to the traditional intravenous route, which displays limited distribution from the blood into the lungs, and difficult systemic access to certain organs such as the brain. Today, around 80% of the marketed products are for local respiratory diseases (e.g., asthma, COPD), while nearly 50% of clinical programs target new indications, most notably, in the areas of anti-infectives, CNS, and cardiovascular conditions.[2] The market trend away from traditional targets is even more pronounced in the nasal clinical pipeline, which has now shifted to anti-infectives (with a prominence in antivirals for systemic use and vaccines) and CNS-targeted drugs, together making up more than 60% of nasal clinical programs. This is highlighted by the fact that there are 70 programs in clinical or pre-clinical development for the delivery of antivirals or vaccines through the nose.

In general, CDMOs have not developed strong capabilities to serve OINDP programs because the space was dominated by large pharma with its knowledge of drug-product device combinations, and integrated, multi-disciplinary, and highly skilled teams with competence across all disciplines, including device design, formulation development, regulatory compliance, and in-house manufacturing.

Catalent's recently acquired 90,000-sq.-ft. FDA-inspected facility in Chelsea, MA.

The changing pipeline landscape, which now features an increase in small biotech entrants, larger molecules, and systemic indications, is creating opportunities for specialized CDMOs to provide solutions through focusing on the emerging needs of inhalation innovators and programs. Some CDMOs have followed horizontal integration models by acquiring specialized medical device companies with a portfolio of respiratory platforms. While this approach may add value for a small number of programs, it could also restrict choice of the best device for each specific therapeutic modality, clinical application, and patient profile. There is also a tendency for companies to offer generalized inhalation development and manufacturing through 'universal' services. However, this may underestimate the diversity in knowledge, capabilities, and manufacturing assets required to deliver successful products across the multitude of possible approaches, which includes nebulization, pressurized-inhalers, soft-mist inhalers, unit-dose or multidose dry-powder inhalers, unit-dose liquid nasals, and nasal powders, as well as customized approaches. Formulation development for each device platform requires specialized, in-depth scientific knowledge, and a combination of small- and large-scale industrial manufacturing assets that can precisely deliver particles or formulations for inhalation through processes such as micronization or spray drying, carrier-free or carrier-based formulations, potent and biosafety containment, liquid and powder filling, and primary packaging. End-to-end solutions that bring clinical-stage development and commercial manufacturing solutions together through integrated, multi-disciplinary, and highly collaborative teams are critical to create value, accelerate development, and advance these highly innovative and much-needed programs for patients.

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Semi-Automating Inhaler Testing – A Good Idea, But Where to Start?

By: Anna Sipitanou, MSc, Business Development Manager, Copley Scientific

Cascade impaction is a vital technique in the development and manufacture of orally inhaled and nasal drug products (OINDPs), used to measure aerodynamic particle size distribution (APSD), a critical quality attribute. However, it is a complex analysis that remains predominantly manual in most laboratories. This has significant implications for variability and productivity. Copley Scientific, the global leader in inhaler testing equipment, offers a range of automated solutions that can be deployed to help.

Where Should I Start When Considering Automation?

A primary point to recognize is that full automation is not realistic for most labs. The complexity and product-specificity of OINDP testing makes it too expensive, too complicated, and too labor-intensive. Semi-automation is the pragmatic alternative and can be achieved using commercial, off-the-shelf, easily validated solutions.

Much has been written about sources of variability in OIP testing because it is such as critical issue. In 2005, the International Pharmaceutical Aerosol Consortium on Regulation and Science (IPAC-RS) constructed an Ishikawa diagram that classifies all the sources of error that can affect cascade impactor testing.[1] This is a great place to start investigating variability and may bring problem areas quickly into focus. Alternatively, invest in an inexpensive tool that helps with just one task and see how much difference it makes.

A great example would be something like Copley's Sample Preparation Unit (SPU 200i), which automates drug recovery from induction ports (NGI, ACI, and FP/Salmeterol) and the NGI pre-separator. Simply add solvent to the component and then attach it to the SPU to apply consistent agitation, controlled via an easy-to-use touchscreen. More reproducible drug recovery, more time for your analysts, and a lowered risk of repetitive strain injury (RSI).

What Activities are Particularly Amenable to Automation?

The drug recovery process associated with cascade impaction is a prime target for automation. With cascade impaction, the generation of robust APSD data relies not only on correct sample collection but also on the effective recovery of samples and assay of the resulting solutions; drug product must also be rigorously recovered from other ancillaries in the test set-up. When operated manually, these recovery processes are lengthy, tedious, and prone to error, resulting in mass balance failures and/or flawed APSD results. Such errors call for test repetition, incurring additional cost and delaying development.

This is an area where solutions range from the simple (as already mentioned) to the relatively complex. For example, the NGI Assistant is a turn-key solution that automates drug recovery from the point of solvent delivery through to the presentation of sample solutions for HPLC analysis. Offering 'load-and-go' operation and relatively short cycle times, it can significantly boost analytical productivity. But you can step up to solutions like this gradually as your product hits its development milestones. Modular automation solutions are readily validated back to the manual method so switching back is easy, if needed.

If you're working on MDIs or nasal sprays, consider the benefits of automated shake and fire systems. Automated shake and fire systems, such as Copley's Vertus II and Plus, allow you to control shaking speed, angle, duration prior to actuation (or firing), the actuation profile, and other relevant parameters to improve the consistency of drug delivery. Automating this aspect of testing simultaneously reduces the risk of RSI, particularly when firing to waste; delivered dose uniformity over entire contents testing can necessitate the reproducible wasting of thousands of shots for just one batch.

Top Tips for Success

Adopt a modular, low-risk approach, focusing first on areas with high variability, high risk of operational error, and high labor-intensiveness. Start with simple tools, validating each step, and opting for more complex solutions as your confidence grows. While the biggest pay-off comes down the line in QC and stability testing, consider semi-automated methods early in the development cycle so that they can transition along with the product. Off-the-shelf solutions can be deployed elsewhere should a project fail and duplication is straightforward should you need to increase capacity. Finally, consider the long-term. Look for equipment with a track record of reliable operation from a trusted supplier that can support you effectively. Done right, the semi-automation of OINDP testing can be a win-win: better quality data, analyst time freed up for more important tasks, and a good return on investment.

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Helping Manage the Risks of Implementing & Validating a Total Solution for COVID-19 Intranasal Vaccines & Preventatives

By: Ian Flaherty, Senior Product Manager, Proveris Scientific

The Appeal of Nasal Sprays as a Delivery Method for a Vaccine or Similar Preventative

Vaccines administered through the nasal route have the potential to bring a wide range of unique benefits to protect the public and address unmet needs. Primarily, the nasal route has excellent potential for vaccination delivery due to the organized immune response of the mucosal membranes of the respiratory system. Recent research has shown, for example, that natural SARS-CoV2 infections trigger both systemic and mucosal immunity.[1] However, the top available vaccinations currently only offer systemic protection. The additional mucosal protection could stop infections at their source before they have the ability to infect systemically. The analogy of the "guard at the gate" is often used to underscore this point.

In addition, vaccines administered intranasally are far less invasive and promote patient compliance. The fact that current COVID-19 vaccinations are only administered via an injection turns away many people who are averse to needles. Also, given the simplicity of a nasal delivery, vaccinations in this form could be administered by the patients themselves. Finally, there is ongoing research and development into formulating a COVID-19 vaccine to be delivered via nasal spray that would not require ultra-low-temperature (ULT) refrigeration for storage and transport. Imagine walking to your local pharmacy and picking one up over the counter or even having one delivered to your home!

How Proveris Laboratories Manages Risks for Nasal Spray Drug Developers

The performance of a drug-device combination product is influenced by a multitude of factors usually falling under the umbrella of patient usage, formulation, and device performance. Proveris Laboratories works with drug developers to evaluate the actual spray performance on all the formulation and device combination candidates to determine the best device-formulation combination by evaluating all critical quality attributes (CQAs).

Using the unique, patented Proveris by Design™ approach, our team incorporates Quality by Design (QbD) at all stages to identify the key drivers for product success and efficacy. As an end-result, we can deliver to your team powerful data-driven insights that can help pave the path to product approval. Following the QbD guidelines as a basis, we focus on the following major areas.

1. Design Space - How does the product perform in actual patient use?
   Human Actuation Studies are performed using the Proveris Ergo™ technology to quantify how people in the targeted age and gender group (trained testers) actuate the product in a way that is transferrable to statistical analysis. This information can be translated into parameters for Vereo® automated actuators to reproduce the actuation profile and then perform all subsequent *in vitro* testing using a repeatable and reliable automated instrument.

2. Control Space - Which factors have the most impact on product performance?
   The unique, patented Proveris by Design approach involves executing screening experiments that are relevant for the product. These experiments are intended to "screen" the parameters generated for their influence on the required test metrics – e.g., which parameter(s) influence shot weight, droplet size distribution, and/or spray pattern, and to what extent.

3. Operating Space - Which variables need to be controlled most closely in production?
   The result of the control space experiments produces a set of multivariate sensitivity/performance curves for the product for each test metric (e.g., plume geometry, spray pattern, shot weight, etc.). These curves indicate regions of high and/or low sensitivity of the test metric to its corresponding input variables, providing valuable insights into which input parameter(s) drive product performance and which outputs need to be controlled and which do not.

Conclusion

The issues with COVID-19 vaccine distribution as well as patient aversion to injections make it a logical decision to pursue vaccines and therapies based on a nasal delivery method. In addition, empirical data on the effectiveness and ease of administration of intranasal vaccines show a clear advantage to that delivery route. Proveris Laboratories offers a wide range of customizable services for all OINDP products, including syringe-based devices with intranasal mucosal atomizers popular for vaccine delivery. We are proud to partner with companies working on the front lines to develop therapies and vaccines to combat this disease and hopefully more in the future!

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Propelling the Pharmaceutical Industry to a Greener Future

By: Peter Hirst, Vice President, Commercial, Bespak by Recipharm, and Lei Mao, Director of Inhalation Science & Product Development, Recipharm

Hydrofluoroalkanes (HFAs) or F-gases have been used as propellants in inhalation products for many years as an alternative to the ozone-depleting chlorofluorocarbons (CFCs). However, HFAs produce greenhouse gases with high Global Warming Potential (GWP) and long atmospheric life (AL) and, as a result, are being phased out of use in other industries.[1] For example, the United Nations (UN) countries have committed to phase-down global HFA consumption by 80-85% by 2047.[2] This decision will have a knock-on impact for the respiratory healthcare sector as HFAs become more difficult to procure.

Life-Saving pMDIs

Pressurised metered dose inhalers (pMDIs) are one of the most prominent delivery methods for inhalation treatments with the need for pMDIs expected to grow by 6.5% annually between 2017-2023.[3]

The role of propellants in a pMDI system is to atomize the drug formulation into micron-scaled droplets that can be inhaled by patients. While the amount of HFAs used in pMDIs is only a very small portion (1Mt or 0.2% of annual CO_2 emissions), they are fundamental to the delivery of life-saving medicines.[4] The pharmaceutical industry should start to consider alternatives as soon as possible in order to overcome the potential challenges associated with the handling requirements of these new propellants, and to develop alternative formulations and manufacturing processes. By actively looking at propellant alternatives, companies will be able to maintain supply of critical medicines for patients with respiratory diseases.

It is also important to ensure that pMDI components are compatible with the new lower GWP propellants.

Recipharm & Environmentally Friendly Propellants

Over the years, the prominence placed on creating a 'greener' future has increased dramatically. As a result, companies globally are facing growing pressure to adopt sustainable processes and reduce their carbon footprint.

While there is currently no legal requirement to change propellants in pMDIs, this will likely become the case in the coming years. HFAs will also become more difficult to procure as suppliers reduce their production. Therefore, it is vital to have viable alternatives to ensure continued supply of critical medicines delivered in pMDIs.

At Recipharm, we work with the most common HFA propellants (HFA227 and HFA134a), as well as the new lower GWP propellants, such as 1,1-difluoroethane (HFA-152a) and 1,3,3,3-tetrafluoropropene (HFO-1234ze(E) (ID, assay, related substances, water, acidity, non-volatile matter, and non-condensable gases).

Changing the propellant in an existing pMDI product is a large scope of work that takes several years to perform, including generating the necessary stability data and clinical results. We are taking a proactive approach to the situation. For example, by evaluating and identifying new valve components that are compatible with the new propellants, and engineering control design for handling these new propellants, we can ensure we are well equipped to handle this transition and be ready to adapt to any future changes of legislations, as well as overcome supply challenges.

Future of the Inhalation Industry & Propellants

There are at least two potential alternatives to HFAs, 1,1-difluoroethane (HFA-152a) and 1,3,3,3-tetrafluoropropene (HFO-1234ze(E)) currently being developed by Koura and Honeywell, respectively.[4] They have similar physical properties to HFA-134a and HFA-227 in terms of the vapor pressure, density, and compatibility with surfactants and co-solvents such as ethanol. However, both have a lower GWP, and shorter AL when compared to the existing propellants.

The compatibility between the propellants and container closure systems needs to be ensured by maintaining the seal integrity and valve delivery performance through the product shelf life. Acceptable levels of extractables and leachables are also key. Additionally, having an engineering control in place to handle flammable propellants such as HFA152 is another critical step towards success in manufacturing the product with this alternative propellant.

Bespak by Recipharm is one of the world's leading manufacturers of pMDI valves and is committed to ensuring their compatibility with the new, greener propellants.

It is important that developers and manufacturers now start the process of preparing their facilities for these new propellants. Those that put measures in place now will futureproof their operations, meaning they can continue bringing MDIs to patients that depend on them. For more information, visit https://www.recipharm.com/solutions/recipharm-inhalation-solutions.

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Accelerating Inhaled Drugs to Clinical Trials Using a Smart Nebulizer

By: Daniel Lock, Pharmaceutical Development Specialist, Vectura

For any new inhaled product to be successful, the device technology chosen to deliver the drug to the lungs must work well in combination with the drug. There are numerous device technology options open to developers, with pressurized metered dose inhalers (pMDIs), dry powder inhalers (DPIs), and nebulizers being the most common.

A conventional development strategy would see the commercial delivery device established at the beginning of a program, with the theory being that this will reduce the requirement to repeat certain pieces of work down the road. However, in practice, the fastest and most cost-effective route through the development process may actually involve using one delivery technology platform to confirm proof-of-concept in early development, before switching to a different, commercially representative platform in late-stage.

While a nebulizer device may cost more than a DPI or a pMDI, the overall cost of pursuing this approach in early development can be lower, especially when delivering large molecules, as the formulation is often simpler and consumes less material.

Flexibility & High Lung Deposition

A nebulizer offers greater flexibility in terms of dose range and, if a drug has good solubility in water, formulation development is more straightforward. A smart nebulizer can also provide very high levels of deep lung deposition and highly efficient delivery with minimal waste. This consistency and efficiency in deep lung delivery may help to contribute to a higher likelihood of success in early clinical development.

It is important to remember that a comprehensive review of factors is required to select the most appropriate delivery platform, and that there is no 'one-size-fits-all' solution for every project. Each individual program should be carefully considered, with all the technical characteristics and commercial constraints taken into account before the device is selected for each step on the development pathway.

Case Study: Development Using the Vectura FOX® Vibrating Mesh Nebulizer

An innovator had an inhaled small molecule development program for a rare disease, and several factors pointed to delivery via smart nebulization as the best option. The molecule was very water soluble and in the higher dose range. Very high and deep lung deposition was required to maximize the probability of success, and material consumption during development needed to be minimized. For these reasons, Vectura's FOX® nebulizer was selected.

FOX® is a small, handheld, breath-activated nebulizer that delivers liquid drugs with high performance using vibrating mesh technology. It is suitable for the delivery of small molecules and biologics, formulated as solutions or nano-suspensions, is CE-marked, and has a 510(k) premarket notification for marketing in the US.

FOX® guides the user to ensure that they inhale slowly and deeply. During inhalation, the airflow resistance is varied to ensure a constant flow rate and the mouthpiece illuminates to provide a visual cue to patients to inhale at the correct rate.

The initial dose selected was 10mg, but an advantage of FOX® is the ability to deliver six different clinical doses (1-80mg) via only two solution strengths by dispensing different volumes into the nebulizer. The dose sits on top of the mesh, meaning there is a very low dose retention, with typically >90% of the dose being delivered to the patient.

Having both inhaled formulation and device capabilities, Vectura conducted the formulation development, analytical method development and phase-appropriate validation, stability testing, and product performance characterization. This pre-clinical pharmaceutical development work was completed using only 100g of drug substance.

Lung deposition modeling using the breathing parameters when using FOX® shows clear superiority over conventional nebulizers. Breath-actuated delivery, control of the inhalation flow rate and volume, and real-time patient feedback on the inhalation manoeuvre ensure maximal drug delivery throughout the lungs. This can be crucial for innovators aiming to demonstrate proof-of-concept for a therapy in early development.

Smart Nebulization in Early Development

Smart nebulization as a strategy to accelerate programs to the clinic has many benefits and, using phase-appropriate technologies, allows clinical trials to be initiated and proceed in a timely fashion while preserving the flexibility to progress to commercial launch on the same platform or move to an alternative.

For more information about FOX® or any of Vectura's inhaled product development services, contact enquiries@vectura.com.

Helping you bring inhaled medicines to market

See how our inhaled development **expertise,** formulation **science** and device **technology** can accelerate your programme

Visit **www.vectura.com** to find out more

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