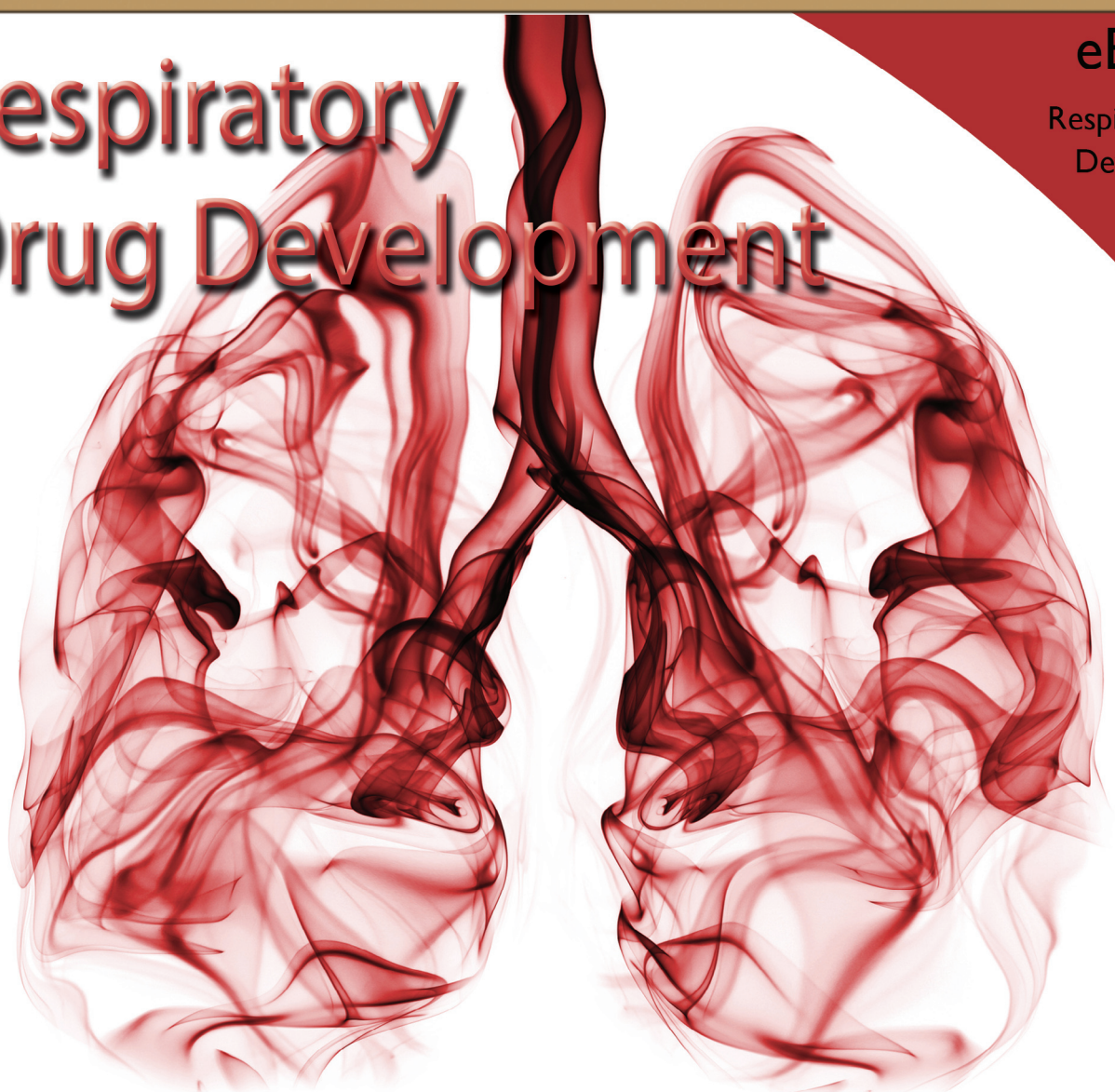
Drug Development & Delivery

Respiratory Drug Development



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Drug Development & Delivery®
2024 Respiratory Drug Development eBook

CDMOs Will Become More Essential to Inhalation Device Programs

By: Cindy H. Dubin, Contributor

The global market for inhalation drug delivery devices is expected to reach $20.7 billion by 2031, driven by rising prevalence of asthma, cystic fibrosis, and chronic obstructive pulmonary diseases (COPD) worldwide.[1] Contract development and manufacturing organizations (CDMOs) are playing a crucial role in inhaled device development. In fact, the inhalation CDMO market grew from $1.94 billion in 2023 to $2.08 billion this year and is expected to reach $2.7 billion in 2028.[2] Major trends to watch for going forward include increased demand for digital health solutions, biologic inhalation therapies, a focus on sustainable technologies, and increased collaborations and partnerships.

Partnerships with inhalation CDMOs is critical as they have the technological and regulatory expertise required to push these devices through to commercialization. This e-book highlights the various ways some leading CDMOs are approaching inhalation their programs. PPD, for example is focusing on spray characterization techniques, such as spray pattern (SP) and plume geometry (PG), for evaluating and testing innovator products. While SP is used as a quality control tool for actuators during product release, PG uses an automated actuator to precisely deliver the dose into the measurement zone. In this e-book, PPD stresses the importance of understanding the sources of variability and implementing appropriate controls and methods.

CDMO Vectura takes an off-the-shelf approach to develop devices across a range of platforms. The company partners with customers on inhalation programs from early discover through small-scale commercialization. Learn more in this e-book about how Vectura has contributed to 13 successful inhaled medications.

For its part, Bespak is committed to transitioning to climate-friendlier propellants and developing more sustainable pressurized metered dose inhaler (pMDI) manufacturing. This ebook highlights the company's efforts to increase capacity and an expand high-speed filling operations.

A report from Research and Markets also highlights the integration of artificial intelligence in inhalation devices. Earlier this year, Dr. Yu Feng of the Oklahoma State University (OSU) School of Chemical Engineering received funding from the University of Oklahoma Foundation for his project: "Artificial Intelligence (AI) Empowered User-Centered Smart Inhaler for Targeted Drug Delivery to Small Airways for Effective Lung Disease Treatment." The project aims to develop a groundbreaking smart inhaler that uses artificial intelligence. According to Feng, this technology has the ability to change the way lung diseases, such as COPD, will be treated. By using computational fluid-particle dynamics and machine learning/deep learning (ML/DL), the inhaler calculates the exact amount of medication needed and can deliver it to the small airways where it is needed most.

OSU doctoral student Mohammad Rashed Islam has a prominent role in developing the AI algorithm for the smart inhaler. The ML algorithm processes inputs like breathing profiles, disease status, and drug particle sizes to determine the optimal nozzle settings for drug release. These settings are then used by the inhaler's hardware system to adjust the nozzle, ensuring targeted drug delivery to specific lung sites while minimizing deposition on healthy tissues. The algorithm ensures more efficient delivery to the targeted areas, but also minimizes potential side effects – a significant advancement over traditional inhalation therapies, says Feng. The team plans to advance the algorithm with a broader range of particle-particle interaction mechanisms that can possibly influence medication transport and deposition in pulmonary airways.

We hope you find this fifth annual *Drug Development & Delivery* exclusive Respiratory e-Book valuable to your own project.

References

1. Global Inhalation Drug Delivery Devices Market $20.7 Billion by 2031, iHealthcareAnalyst, Inc., Dec. 19, 2023.
2. Inhalation CDMO Global Research Report 2024-2033: Integration of AI and ML Enhances Capabilities, Biopharmaceutical Inhalation Therapies Rapidly Expand, Patient-Centric Solutions Take Center Stage, Research And Markets, Apr. 25, 2024.

Bespak: Adapting to New Pressures: Leading the Transition to Climate-Friendly pMDI Propellants

By: Louise Righton, Head of Strategic Marketing, Bespak

Bespak, a leading contract development and manufacturing organization (CDMO) focused on orally inhaled and nasal drug-device combination products, has announced progress in its commitment to sustainable pressurized metered dose inhaler (pMDI) manufacturing. With initial capacity expansion already completed and allocated, and further expansion planned, Bespak is dedicated to supporting the transition to the new low global warming potential (GWP) propellants: HFA-152a and HFO-1234ze.

Propelling the Industry Into a More Sustainable Future

Climate-friendly propellants with lower GWP are vital to the long-term sustainability of the pMDI industry. The two most promising candidates are HFA-152a and HFO-1234ze. Respectively, these options provide an environmental impact that is 100 times and 1,000 times lower than that of currently used HFCs.

These new propellants represent a positive shift in the industry. However, their implementation may create challenges for individual pharmaceutical companies, such as the management of time-consuming and costly reformulations.[1]

Perhaps more concerning, the rapid adoption of sustainable low GWP propellants will place increasing pressure on global pMDI supply chains. This will inevitably worsen as more companies make commitments to switch to HFA-152a and HFO-1234ze propellants in the near future. It is expected that there will be a significant gap between demand and the available capacity for low GWP pMDI filling, potentially elongating time to market and restricting the availability of life-saving medication options to patients.[2] It appears likely that some companies will find it challenging to meet their own target timelines as capacity is quickly taken up as soon as it becomes available.

To relieve this scarcity of supply, CDMOs dedicated to extending their low GWP manufacturing capacity may offer a solution. The investments being made in pMDI filling capacity can help to alleviate supply chain concerns for developers and brand owners, while avoiding the shortage of trusted and affordable pMDI medications that patients rely upon.

Considerations When Choosing a Climate-Conscious CDMO

Some CDMOs are already investing significantly to support the industry in its switch to low GWP propellants. These organizations are committed not only to leading the transition to climate-friendly alternatives in pMDIs, but also driving sustainability throughout their entire operations.

In order to ease the transition to green propellants and reduce their carbon footprints, pharmaceutical companies should consider these CDMOs that have placed sustainability at the heart of their business. They should also look for a partner that can support clinical- and commercial-scale manufacturing with both new propellants to ensure the development of multiple formulation options can be pursued.

Bespak offers full-scale cGMP batch production of drug-device combination products, and specialist device manufacturing at any scale.

A collaboration partner capable of supporting the use of greener propellants can help drug developers breathe a little easier and may become a necessity as the industry evolves and agility becomes a competitive advantage.

Take Drug Development to the Next Level with a Market-Leading Partner

Bespak has recognized how the transition to greener propellants, and the resulting supply chain challenges, could impact its customers' ability to deliver life-changing drug products to patients in line with evolving global legislation. As such, the market-leading CDMO is proactively investing in its manufacturing capacity to relieve the scarcity of supply.

Reflecting its commitment to the production of low GWP pMDIs, Bespak is expanding its high-speed commercial filling operation in the UK. With one low GWP filling line fully allocated and installed, it has recently committed to further capacity expansion with an additional filling line placed on order.

Among the very first sites in the world to manufacture at scale with both sustainable propellant candidates, a key focus at Bespak is to support the transition of as many pMDI formulations to greener propellants as possible. The capacity expansion and overall investment highlights Bespak's dedication to transitioning to low GWP manufacturing to meet its customers' needs, ensuring essential and affordable pMDI products remain available for patients, and supporting a more sustainable industry.

With a long history in the development and commercial supply of pMDIs, Bespak supplies a major proportion of the world's pMDI dosing valves and actuators. And, with sustainability central to its vision, Bespak is committed to decarbonizing the inhaler industry. From development to delivery, Bespak can support accelerated commercialization of more sustainable pMDIs, helping to get them into the hands of the patients who need them most.

Learn more about low GWP propellants and sustainable pMDIs by reaching out to the experienced Bespak team here.

References

1. Pritchard, JN, Change is in the air – the new pressurized metered-dose inhaler propellants, Drug Delivery to the Lungs, Vol. 33, 2022.
2. Woodcock, A. et al., The environmental impact of inhaled therapy: making informed treatment choices, European Respiratory Journal, Vol. 60, 2022.

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by **Thermo Fisher Scientific**

Plume Geometry: Examination of Processing Schemes and Inter-Analyst Variability

By: Christopher J. Gruenloh, PhD, Research Fellow, Respiratory Products

About the Author

Christopher (Chris) Gruenloh is a Research Fellow at PPD, the clinical research business of Thermo Fisher Scientific, where he supports development and implementation of analytical solutions to meet the needs of clients who are developing orally inhaled and nasal drug products (OINDPs). His research interests include delivery of biologics to the respiratory tract and better controlling sources of variability in OINDP testing platforms. Chris is a member of the AAPS Inhalation and Nasal Community's Leadership Team and represents PPD as an Associate Member of IPAC-RS. Prior to PPD, Chris spent 16 years at GSK leading analytical and CMC teams focused on drug delivery including the development of dry powder inhalers, pressurized metered-dose inhalers, lung delivery of oligonucleotides and sub Q depot formulations of metabolic peptides. Chris has earned a B.S. in Chemistry from Saint Louis University and a Ph.D. in Analytical Chemistry from Purdue University.

Developing medicines that are delivered via the pulmonary and nasal routes for the treatment of local and systemic diseases is challenging. While the demonstration of safety, potency, and purity is a fundamental part of the marketing authorization process for all drugs, incorporation of a delivery device greatly increases the complexity of the drug development process.

Spray pattern (SP) and plume geometry (PG) are spray characterization techniques used during the development of orally inhaled and nasal drug products (OINDPs), such as pressurized metered-dose inhalers, soft mist inhalers, and nasal sprays. Both techniques are required to evaluate test and innovator products in the generic approval pathway. While automated software routines have largely eliminated analyst subjectivity from SP, actions taken by the analyst, including the selection of both a single frame for image analysis and the location of the origin as well as placement of "arms" to indicate the outer limits of the plume in PG, continue to support perceptions of high variability and analyst subjectivity.

The plume geometry technique uses an automated actuator to precisely deliver the dose into the measurement zone. In short, a high-speed camera and a laser beam that has been expanded out to a 2-dimensional sheet are used, as illustrated in Figure 1. The camera is orientated orthogonally to the laser to capture a movie of the actuation event. Image processing starts with the analyst selecting an image or an average of multiple images on which the data analysis will be performed. If a single image is chosen, then convention suggests that the one with greatest intensity should be used. Second, the analyst assigns a location for the plume origin, and thirdly the analyst will place "arms" on either side of the plume that define the outer limits of the plume. Following these actions, the software can determine the plume angle and width.

A study was performed to examine analyst repeatability as a function of different processing variables for PG, including use of a single "snapshot" image (as directed by FDA guidance) versus a time-averaged image, location of origin (at mouthpiece vs at nozzle), and method by which arms are placed (intensity-based vs visual assignment) to indicate the outer limits of the plume. Results are provided in Figure 2 and indicate that both Flovent and Symbicort pMDI products gave similar PG spray angles regardless of dose strength. Placement of the origin at the nozzle gave a smaller spray angle than when placed at the edge of the mouthpiece using a time-averaged image, which makes sense from a purely geometric perspective (height of triangle with same width is reduced in the latter case, resulting in an increased angle). Spray angle further increases when comparing the single image result to the time-averaged one when the origin is fixed at the edge of the mouthpiece. Arguably, the most important observation from the figure is the increased variability associated with processing a single image via snapshot mode vs a time-averaged image. Analysis of tabulated data (not provided) indicates that inter-analyst variability was about 0.5 % RSD across both products and their strengths when a time-averaged image was used in comparison to about 3.2 % RSD when a snapshot image was used. Variability across analysts increased by another factor of 2 when analysts visually set the arms to define the outer limits of the plume.

With plume geometry, we see that the processing scheme will not only impact the magnitude of the reported spray angle result but also the associated variability. While inter-analyst variability can be greatly reduced using a time averaged image, snapshot mode is currently required per FDA guidance in support of *in vitro* bioequivalence studies.

In conclusion, PG results and associated variability will vary depending on the specific processing parameters utilized. It's important to understand the sources of variability and implement appropriate controls and methods. As a GMP laboratory solutions provider, we strive to reduce both inter-analyst and method-related variability, in order to increase confidence in the reported results for the product. For more information, contact us at https://www.ppd.com/our-solutions/ppd-laboratories/gmp-lab/.

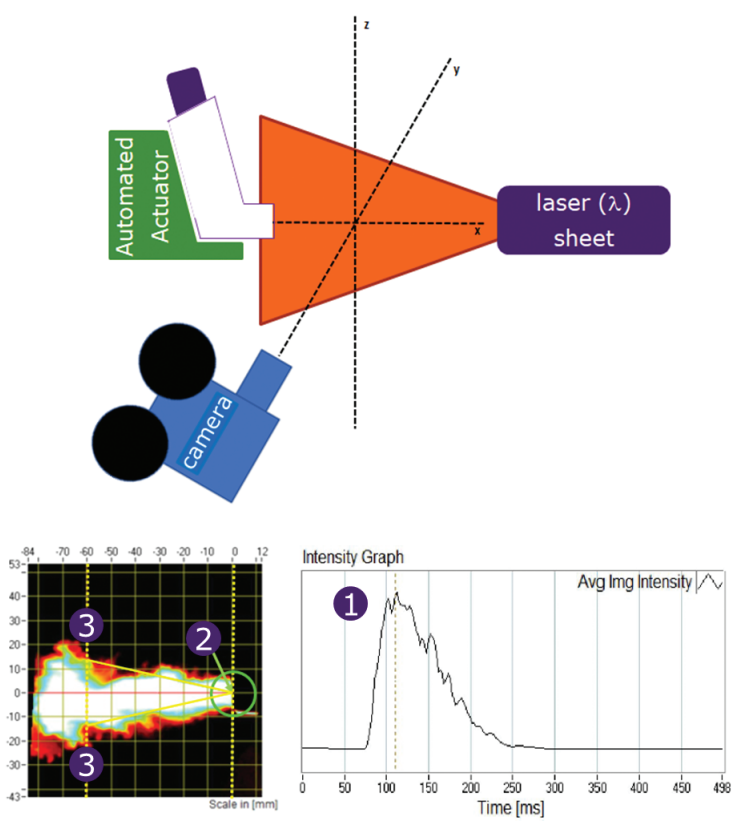

Figure 1. Schematic of Plume Geometry with a) image selection from the intensity graph, b) origin placement at mouthpiece edge or nozzle, and c) placement of "arms" used to indicate out limits of the plume.

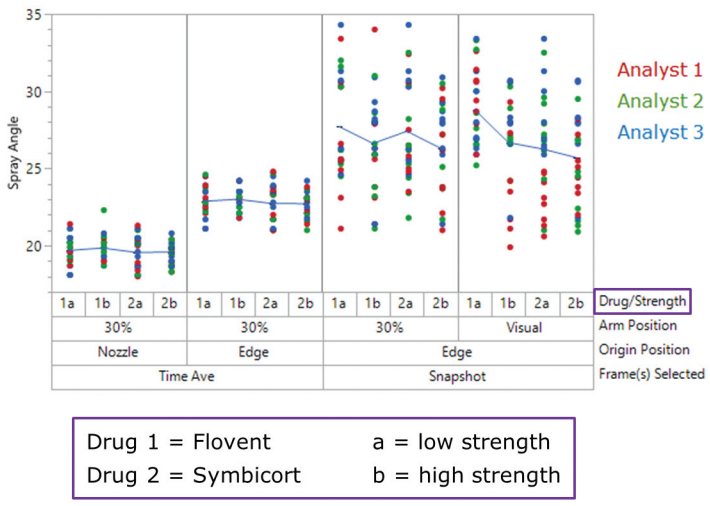

Figure 2. Plume Geometry spray angle results across three analysts as a function of different processing schemes.

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Vectura: Contributed to 13 Successful Inhaled Medicines

Vectura is a leading specialist inhalation contract development and manufacturing organization (CDMO) that provides innovative inhaled drug delivery solutions to enable its customers to bring their medicines to market.

With differentiated proprietary technology and pharmaceutical development expertise, Vectura has the device, formulation, and development capabilities to deliver a broad range of complex inhaled therapies. Vectura has contributed to the success of 13 inhaled medicines launched by its partners and licensees.

Being able to provide customers with a single partner for preclinical inhalation toxicology services, formulation, device and manufacturing services offers real benefits in terms of continuity, shortened timelines and reduced costs.

Technical Services

- Preclinical Toxicology Services
- Inhaled Formulation Development & Optimization
- Commercially-Validated Device Platforms (DPI, pMDI & smart nebulizer)
- Comprehensive Analytical Services
- Process Development & Scale-Up
- Product Manufacturing
- Regulatory Services

Major Products/Services

Vectura has development expertise across a range of delivery platforms, including nebulizers, DPIs (capsule and blister formats), pMDIs, and intranasal. This allows a "device agnostic" approach to best meet the needs of customers, their development programs, and ultimately, the patient. We provide flexibility by offering services that utilize 'off-the-shelf' devices and Vectura's expertise in spray-drying, advanced powder blends, and liquid formulations can help in the development of a wide range of small molecules, biologics, and complex combination therapies.

With integrated services including advanced inhalation analytics, GMP product manufacturing, and device assembly, customers can partner with Vectura to progress inhaled programs from early discovery through all clinical phases to small-scale commercialization.

If you would like to find out how your inhaled development program could progress with Vectura's capabilities, contact businessdevelopment@vectura.com.

Vectura's DPI range includes the Gyrohaler®, F1P, LOMI (Lever-Operated Multidose Inhaler) and OIC (Open-Inhale-Close).

The FOX® handheld, breath-activated, battery-powered vibrating mesh nebulizer. It is CE-marked and is suitable for the delivery of small molecules and biologics, formulated as solutions or nano-suspensions.

Vectura conducts extensive inhaler testing and analysis.

Having all the disciplines required for a development program under the same roof can really help to solve the particularly tricky challenges that are always present in inhaled product development.

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