The importance of human-realistic testing in inhaled and nasal drug product development

Proper testing is key to all pharma products, but especially so for orally inhaled and nasal drug products. What role can human-realistic testing play in ensuring inhalation-related treatments are as efficient and effective as possible?

By Joanne Mather and Lynn Jordan at Proveris Laboratories

Orally inhaled and nasal drug products are essential in treating respiratory conditions like asthma and chronic obstructive pulmonary disease (COPD).

The effectiveness of these combination products relies on the interplay between three key elements: formulation, device performance and patient use. Human-realistic testing encompassing hand studies, deposition studies and breathing studies are crucial for evaluating how these factors affect drug delivery in real-world scenarios.[1,2,3]

This article explores the importance of such testing in the development of inhaled and nasal drug products, focusing on the challenges and variables that arise when simulating patient use. It discusses current regulatory guidelines from agencies such as the US Food and Drug Administration (FDA) and European Medicines Agency (EMA), which emphasise the need for realistic performance assessments, and highlights recent research in the field. Additionally, the article looks ahead at the evolving landscape of inhaled and nasal drug products testing, including the role of personalised medicine and advanced simulation technologies in enhancing drug delivery precision. The findings underscore the necessity of integrating human-realistic testing to ensure that inhaled and nasal drug products meet efficacy standards across diverse patient populations and real-world conditions.

Orally inhaled and nasal drug products have revolutionised the treatment of respiratory diseases such as asthma, COPD and seasonal allergies. These products include metered-dose inhalers (MDIs), soft mist inhalers (SMI), dry powder inhalers (DPIs) and nasal sprays, which offer convenient and direct drug delivery to the lungs and nasal passages.

These devices present unique challenges due to their dependency on patient technique, device performance and formulation properties, all of which can significantly influence therapeutic efficacy.[4]

Unlike oral medications, where variability in drug absorption is relatively minimal, inhaled and nasal drug products can experience significant variability in dose delivery due to factors such as improper device use, airway obstruction and patient disease state. As a result, it is essential to conduct human-realistic testing to ensure that these products will deliver consistent and accurate doses in real-world conditions.

Human-realistic testing involves simulating actual patient use to assess product performance under typical conditions, which is often more variable than controlled lab environments.

The trifecta of formulation, device design and patient use

Inhaled and nasal drug products development requires careful consideration of three critical components: formulation, device design and patient usage. Each of these factors plays an essential role in determining whether the product will achieve its intended therapeutic effect.

Formulation considerations

The formulation of an inhaled and nasal drug product is one of the

factors that dictates how the drug will be aerosolised and how well it will reach the intended site of action in the lungs or nasal cavity. The particle size distribution of the active pharmaceutical ingredient (API) is a crucial factor in determining how well the drug will deposit in the respiratory system. Particles that are too large may not be able to reach the lungs effectively, while particles that are too small may be exhaled without proper deposition.

MDIs deliver the drug as a fine mist using a propellant in a pressurised system, whether the formulation is a solution or suspension. The size and uniformity of the aerosol droplets are critical in ensuring optimal lung deposition. For example, a study published in *Pharmaceutical Research* in 2021 demonstrated that formulations with a mean particle size of 1-3µm were the most effective for achieving high deposition in the lower respiratory tract, whereas particles of larger size were found to deposit more in the oropharyngeal region.[5]

SMIs deliver the drug as a soft mist. The drug is in a solution in the SMI and uses a mechanical method to deliver mist rather than propellent as is done with MDIs. The duration of the soft mist is longer than the duration of an inhaler, designed to alleviate some of the breathing coordination required with an inhaler.

DPIs in most devices rely on the patient's inspiratory effort to disperse the powder. The aerosolisation efficiency of a DPI can vary depending on the patient's ability to generate sufficient airflow to overcome the resistance of the DPI and trigger the dose.

Nasal sprays require careful consideration of droplet size and distribution to ensure effective intranasal deposition.

Device performance

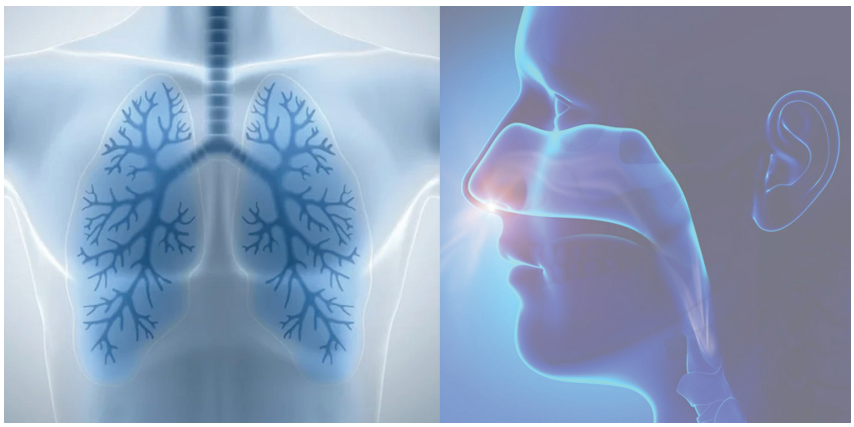
The performance of the inhaler or nasal device also plays a crucial role in ensuring consistent drug delivery. Variability in device performance can result from several factors, including the actuation technique, device resistance and actuation timing.In MDIs, the correct actuation technique is vital. Incorrect timing of actuation during inhalation can lead to poor lung deposition and suboptimal therapeutic outcomes. Breath-actuated inhalers have been developed to mitigate this issue by releasing the drug only when the patient inhales at the proper flow rate.

DPIs require the patient to generate sufficient inspiratory flow, which can be challenging for certain populations, such as the elderly or children. In these cases, low-resistance DPIs can improve usability and ensure more reliable drug delivery.

Nasal devices must be designed to deliver a consistent spray pattern to ensure that the drug reaches the nasal mucosa.

Patient-specific factors

Patient behaviour and technique are often the most significant sources of variability in inhaled and nasal drug products' performance.



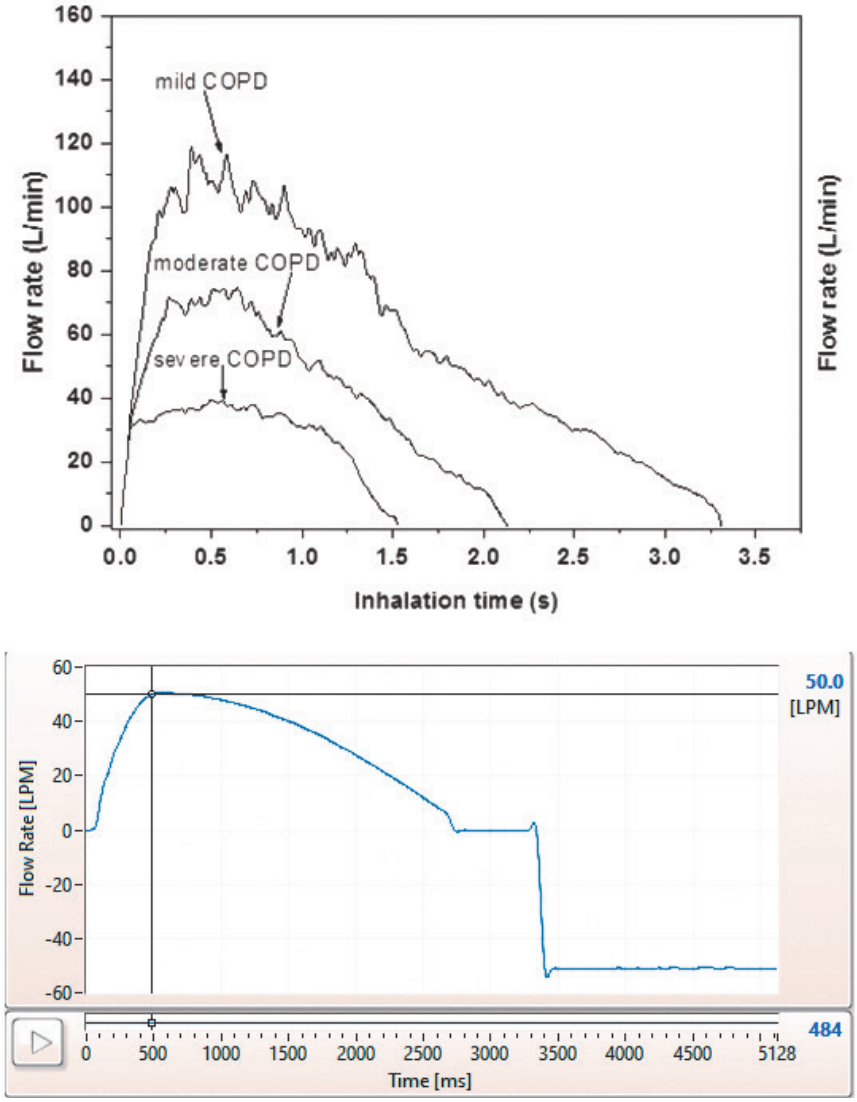


Figure 1: *In vitro* technologies enable testing on the full range of human breathing, including disease states, for the most accurate indication of *in vivo* performance

Age, disease state and cognitive or physical abilities all influence how well patients use inhalers and nasal sprays. For example, elderly patients may have difficulty with dexterity, grip strength or coordination, which can impair their ability to use inhalers or nasal sprays correctly.

There may also be differences in use with paediatric patients as well. It is important to study the intended patient demographic and focus on how they use the product in the development testing so the methods will be successful in clinical testing.

In a study published in *Respiratory Medicine* (2022), researchers found that over 40% of elderly patients using traditional MDIs had inhalation timing errors, resulting in inadequate drug delivery.

Similarly, children with asthma were shown to have difficulty using DPIs, as they could not generate the required inspiratory flow to activate the device.[6] Thus, testing under real-world conditions that replicate these challenges is necessary to determine if a product will work across a broad range of patients.

Human-realistic testing methods

To ensure that inhaled and nasal drug products perform as expected in real-world scenarios, human-realistic testing incorporates several techniques that evaluate how patients interact with the device, how the drug is deposited in the respiratory tract or nasal cavity, and how breathing patterns affect drug delivery.

Among the key methodologies are hand studies, deposition studies and breathing studies.

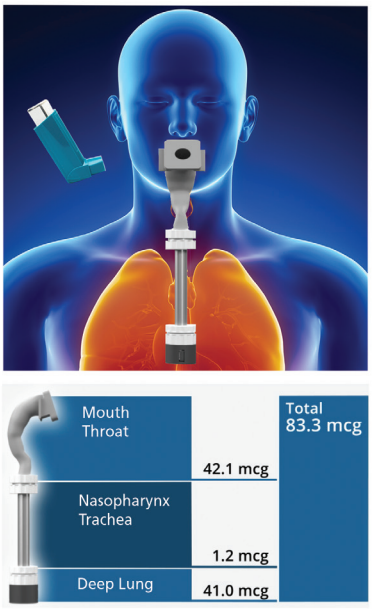
Hand studies: evaluating how the patient actuates the product

To understand how the patient demographic actuates the oral or nasal device, 'hand studies' can be done. For a hand actuation study, patients are given an overview of how to use the product and are allowed to do a few test actuations of the product under an extraction hood. Then they actuate multiple devices, again under an extraction hood, with a measurement device attached to the product. This provides data on how the patient actuates the device, and by testing many patients from the patient demographic, this results in the understanding of what are human achievable actuation parameters for this product. Hand studies help identify the patient usage parameters by simulating real-world usage scenarios.

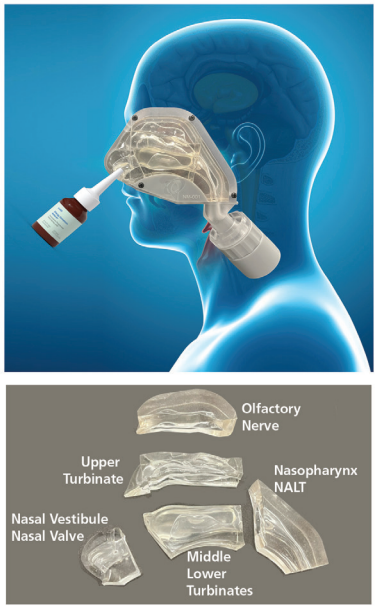
Deposition studies: understanding drug distribution

Deposition studies are essential for understanding how the drug reaches its intended target within the respiratory system. Factors such as particle size, device performance and breathing patterns influence where the drug will deposit in the lungs or nasal cavity. Deposition studies simulate these factors using *in vitro* models such as nasal casts or cascade impaction, and more advanced techniques like gamma scintigraphy and computational fluid dynamics (CFD).[7,8,9]

Research conducted in 2021 in the *European Journal of Pharmaceutical Sciences* found that modelling the deposition of inhaled aerosols in 3D-printed patient-specific lung models led to more accurate predictions of drug distribution in



In vitro respiratory model with representative breathing profiles provides indication of *in vivo* performance in a targeted region



In vitro nasal cast model with representative breathing profiles quantifies deposition in five different regions of the nasal cavity

the lungs. The study concluded that personalised deposition models could significantly improve dosing precision and reduce variability in clinical outcomes.[10]

Breathing studies: simulating real-world inhalation profiles

Breathing studies simulate how a patient's breathing profile influences drug delivery. These studies consider the inhalation flow rate, peak inspiratory flow rates (PIFR) tidal volume and breathing frequency, all of which affect how the aerosol is deposited in the lungs or nasal passages.[11] Breathing simulators, which replicate human inhalation patterns, are often used in combination with aerosol characterisation techniques to assess how the drug behaves under different conditions.

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A study in *Pharmaceutical Research* in 2023 showed that breathing simulators could predict the variation in lung deposition among different patient populations, including asthmatic and COPD patients.[12] By simulating low inspiratory flow rates, the researchers found that COPD patients received only 50-60% of the expected dose compared to healthy adults, highlighting the need for devices that account for disease-specific conditions (see **Figure 1**).

Regulatory expectations and actuation guidelines

Regulatory agencies, including the FDA, EMA and Health Canada, recommend extensive human-realistic testing to ensure the safety and efficacy of inhaled and nasal drug products before they can be approved. These agencies have established guidelines that mandate the inclusion of real-world patient factors in testing.

FDA and EMA guidelines

The FDA's Inhalation Drug Products for Systemic Use guidelines emphasise the importance of human-centred testing, requiring developers to conduct dose delivery studies that reflect typical patient actuation techniques.[13]

Similarly, the EMA's draft guidelines on MDIs and DPIs suggest that developers should include human factor testing to evaluate the impact of inhalation technique variability on clinical outcomes.

Moreover, agencies are increasingly focusing on personalised medicine and how devices should be tested for specific patient sub-populations.

The EMA's Scientific Advice Working Group has discussed the future of personalised inhaled and nasal drug products therapies, which will likely include more patient-specific deposition models and the incorporation of disease-modifying factors into testing protocols.[14]

Future directions in inhaled and nasal drug product testing

Technological advancements

As technology advances, the future of inhaled and nasal drug product testing lies in greater automation and personalisation. Smart inhalers that track patient usage patterns and real-time adherence could be used to provide feedback and improve technique. Machine learning (ML) algorithms may soon be integrated into inhalers to optimise drug delivery based on real-time data.[15]

Regulatory evolution

Regulatory agencies are likely to adopt more data-driven approaches in the future, emphasising the use of real-world evidence (RWE) and advanced modelling techniques. The development of dynamic personalised models that can simulate various patient-specific factors will be crucial in shaping the future of inhaled and nasal drug products testing.

Conclusion

Human-realistic testing is crucial for the development of inhaled and nasal drug products, as it helps ensure that these products will deliver consistent and effective doses in the real-world setting. The integration of hand studies, deposition studies and breathing studies is essential for understanding the complex interaction between formulation, device design and patient behaviour.

With increasing emphasis on patient-specific factors and real-world evidence, the future of inhaled and nasal drug products development

Measurement device attached to a multi-dose nasal spray captures data on how the patient actuates the pump

will require more sophisticated testing methods that integrate personalised medicine and advanced simulation technologies.

References:

1. *Mehta PP et al (2023), 'Editorial: Advances in orally inhaled and nasal drug products (OINDPs)', Frontiers in Pharmacology, 14, 1185609*
2. *Amini E (2022), 'Advancing bioequivalence assessments of orally inhaled and nasal drug products (OINDPs) through in vitro, in vivo, and in silico approaches', Doctoral Dissertation, University of Florida, US*
3. *Visit: fda.gov/media/111304/download*
4. *Spencer T et al (2024), 'Best Practices in Device Design for Orally and Nasally Inhaled Products (OINDP)', presented at Drug Delivery to the Lungs (DDL) Conference 2024*
5. *Pinto JT et al (2021), 'Spray-congealing and wet-sieving as alternative processes for engineering of inhalation carrier particles: Comparison of surface properties, blending and in vitro performance', Pharmaceutical Research, 38(6), 1107-1123*
6. *Bourbeau J et al (2022), 'Inhaler technique in elderly patients with asthma and COPD: A systematic review', Respiratory Medicine, 191, 106678*
7. *Cheng YS (2014), 'Mechanisms of pharmaceutical aerosol deposition in the respiratory tract', AAPS PharmSciTech, 15(3), 630-640*
8. *Djupesland PG (2013), 'Nasal drug delivery devices: characteristics and performance in a clinical perspective – a review', Drug Delivery and Translational Research, 3(1), 42-62*
9. *Zhang Y, Kleinstreuer C (2023), 'Effect of nasal inhalation on drug particle deposition and size', Annals of Biomedical Engineering, 51(2), 345-360*
10. *Smith JD et al (2021), 'Modeling the deposition of inhaled aerosols in 3D-printed patient-specific lung models', European Journal of Pharmaceutical Sciences, 158, 105678*
11. *Ghosh S et al (2017), 'Peak Inspiratory Flow Rate in Chronic Obstructive Pulmonary Disease: Implications for Dry Powder Inhalers', J Aerosol Med Pulm Drug Deliv, Dec, 30(6), 381-387*
12. *Erdelyi T et al (2023), 'Modeling of pulmonary deposition of agents of open and fixed dose triple combination therapies through two different low-resistance inhalers in COPD: a pilot study', Pharmaceutical Research, 40(5), 1065072*
13. *Visit: fda.gov/regulatory-information/search-fda-guidance-documents/metered-dose-inhaler-mdi-and-dry-powder-inhaler-dpi-drug-products-quality-considerations*
14. *Visit : ema.europa.eu/en/human-regulatory-overview/research-development/scientific-advice-protocol-assistance*
15. *Visan AI, Negut I (2024), 'Integrating artificial intelligence for drug discovery in the context of revolutionizing drug delivery', Life, 14(2), 233*

Joanne Mather is a scientific marketing leader with many years of experience in the analytical science space. As senior director of Marketing at **Proveris Scientific**, she focuses on translating complex scientific and regulatory challenges into practical solutions that help companies in the OINDP space accelerate development and ensure product quality. With a strong background in analytical science and a customer-centric approach, she is dedicated to supporting the industry in bringing effective and reliable aerosolised drug products to market.

Lynn Jordan is the senior applications manager at **Proveris Laboratories**, bringing extensive experience in orally inhaled and nasal drug products (OINDPs). In her role, she leads scientific initiatives that support pharmaceutical companies in addressing complex challenges associated with OINDP development. Her deep expertise enables her to provide valuable insights and solutions that enhance product performance and regulatory compliance. Lynn's commitment to advancing scientific understanding in the field contributes significantly to the successful development and commercialisation of inhalation and nasal drug products.