PEER REVIEWED

The Role of Nasal Cast Testing in Drug Development

Nasal drug delivery has emerged as a major focus in pharmaceutical development because it combines convenience, rapid absorption, high bioavailability, and the potential for both local and systemic effects. Recent approvals and pipeline candidates for conditions including Alzheimer's disease, depression, migraines, diabetes, seizures, and opioid overdoses illustrate the expanding therapeutic scope of nasal delivery.

The nasal cavity is especially attractive because it provides a direct pathway to systemic circulation and, in some cases, to the central nervous system. This has opened opportunities for innovative nose-to-brain therapies. Similarly, nasal vaccines target the nasal-associated lymphoid tissue (NALT), stimulating mucosal immunity as a needle-free alternative to injections.[1,2,3]

A key challenge in nasal drug delivery is ensuring accurate and consistent deposition within targeted regions of the nasal cavity. This is complicated by natural anatomical variability and the many factors that influence spray performance, including device design and formulation properties.[4] Nasal cast testing has emerged as a valuable tool, providing developers with a rapid, cost effective, and reproducible method to evaluate deposition and guide optimisation early in development.[5,6]

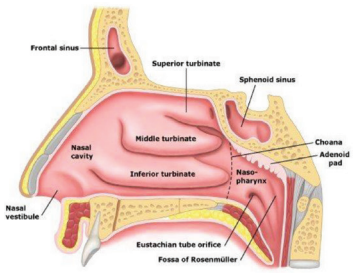


Figure 1: Nasal anatomy and spray deposition

This paper explores the importance of nasal cast testing, its regulatory relevance, and the specific benefits it offers in accelerating the development of effective nasal products.

The Problem:
Understanding Nasal Deposition

Drug efficacy for nasal delivery depends on where the spray deposits within the nasal cavity.

For example:

- Nose-to-brain delivery requires targeting the olfactory region and upper turbinates.
- Nasal vaccines benefit from deposition at the NALT region to trigger immune response.
- Systemic delivery relies on maximising deposition in the middle and lower turbinates for absorption.[7]

Traditional methods such as gamma scintigraphy and CT imaging have been used to study deposition.[8] These approaches provide detailed maps of distribution but are resource-intensive, costly, and impractical for iterative development. Early formulation and device screening requires a faster, safer, and more reproducible alternative.

The Solution: Nasal Cast Testing

Nasal cast testing fills this gap by using anatomically accurate replicas of the human nasal cavity to simulate drug delivery.

- Rapidly evaluate multiple device types (unit-dose vs. multidose, liquid vs. powder).
- Optimise formulation parameters such as viscosity, droplet size, mucoadhesion, and Spray Pattern.
- Systematically vary device settings such as spray angle, insertion depth, and actuation force.

These studies are reproducible and controlled, allowing developers to generate consistent data free from the inter-subject variability that complicates human trials. This enables rational decision-making earlier in development, reducing reliance on costly *in vivo* methods and accelerating go/no-go decisions.[9,10,11]

Regulatory Perspective

Although nasal cast testing is not a formal regulatory requirement, its relevance in regulatory science is steadily growing,

especially in the evaluation of locally acting nasal drug products. The FDA's 2003 Guidance for Industry on Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action outlines three foundational pillars for demonstrating bioequivalence: formulation sameness, device equivalence, and reproducibility of delivery.[12]

The guidance places strong emphasis on *in vitro* testing methods such as Spray Pattern analysis, Plume Geometry, Droplet Size Distribution, and Aerodynamic Particle Size Distribution (APSD). However, the FDA also underscores the importance of a mechanistic understanding of drug deposition and the reproducibility of actuation – areas where traditional *in vitro* tests may fall short.

This is precisely where nasal cast testing becomes invaluable. By using anatomically accurate models of the human nasal cavity, nasal cast testing provides direct insight into how and where the drug is deposited after actuation. It offers both quantitative and visual data that align with the FDA's call for deeper mechanistic understanding.

For innovators, this can reduce downstream risk, especially for nose-to-brain or vaccine applications, where demonstrating targeted delivery is critical. For generics, regulatory agencies expect bioequivalence to the reference listed drug (RLD). While APSD and *in vitro* actuation studies remain central, region-specific deposition maps from casts can provide valuable supportive evidence, strengthening equivalence arguments in borderline cases.

The European Medicines Agency (EMA) continues to emphasise the importance of pharmaceutical quality, device performance, and *in vitro* reproducibility for inhalation and nasal products.[13] The latest regulatory and scientific guidelines published in 2024 reaffirm that:

- Device performance is critical to ensuring consistent drug delivery.
- *In vitro* testing plays a central role in demonstrating therapeutic equivalence, especially for locally acting products.
- These principles are aligned with the FDA's approach, particularly in the context of bioequivalence and combination product evaluation.

Regulatory agencies across the globe are placing growing emphasis on actuation control in the evaluation of nasal drug products.

Figure 2: The Proveris Vereo® NSx Automated Actuator – an automated solution for actuating a variety of nasal sprays and syringes during in vitro testing.

Variability introduced by manual actuation, such as inconsistent force, angle, or timing, can significantly distort the assessment of a product's true performance. This inconsistency poses challenges not only for reproducibility but also for meeting the stringent expectations of agencies like the FDA and EMA which prioritise precision and reliability in both device and formulation characterisation.

Automated actuation platforms, such as the Proveris Vereo® NSx, offer a compelling solution to this challenge. These systems eliminate human variability by delivering consistent, programmable actuation parameters (stroke length, velocity, acceleration, and hold time), ensuring that each spray event is uniform and repeatable. When integrated with nasal cast testing, the result is a powerful, regulator-aligned methodology that generates anatomically relevant deposition data with high fidelity. This combination supports the mechanistic understanding of drug delivery and strengthens the overall data package submitted for regulatory review.

In essence, the pairing of automated actuation with nasal cast testing not only enhances scientific rigor but also aligns seamlessly with the FDA's and EMA's evolving expectations for data integrity, robustness, and reproducibility. It's a forward-looking approach that reflects the industry's commitment to precision and quality in nasal drug development.

Benefits of Nasal Cast Testing

Nasal cast testing delivers multiple advantages that address critical development challenges:

1. **Cost-Effectiveness –** Enables rapid, affordable screening of multiple formulation and device combinations before advancing to expensive *in vivo* or imaging-based deposition studies.

2. **Reproducibility –** Provides a controlled test environment, eliminating inter-subject variability and allowing systematic evaluation of key parameters.

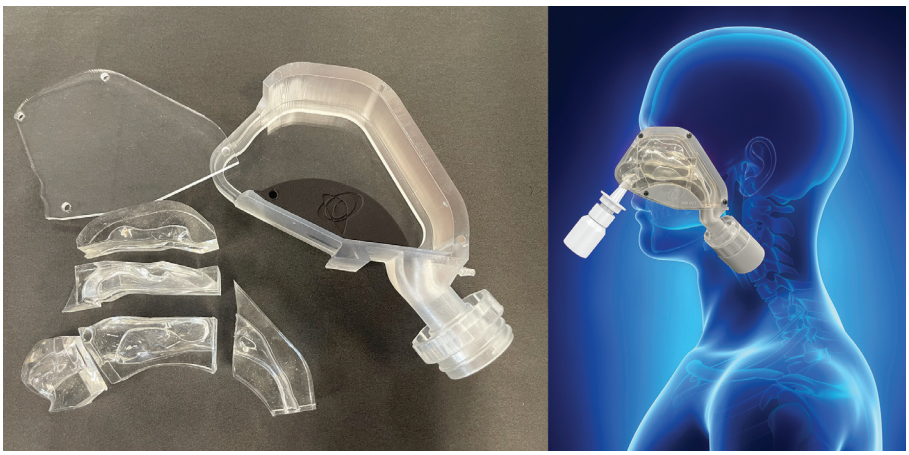
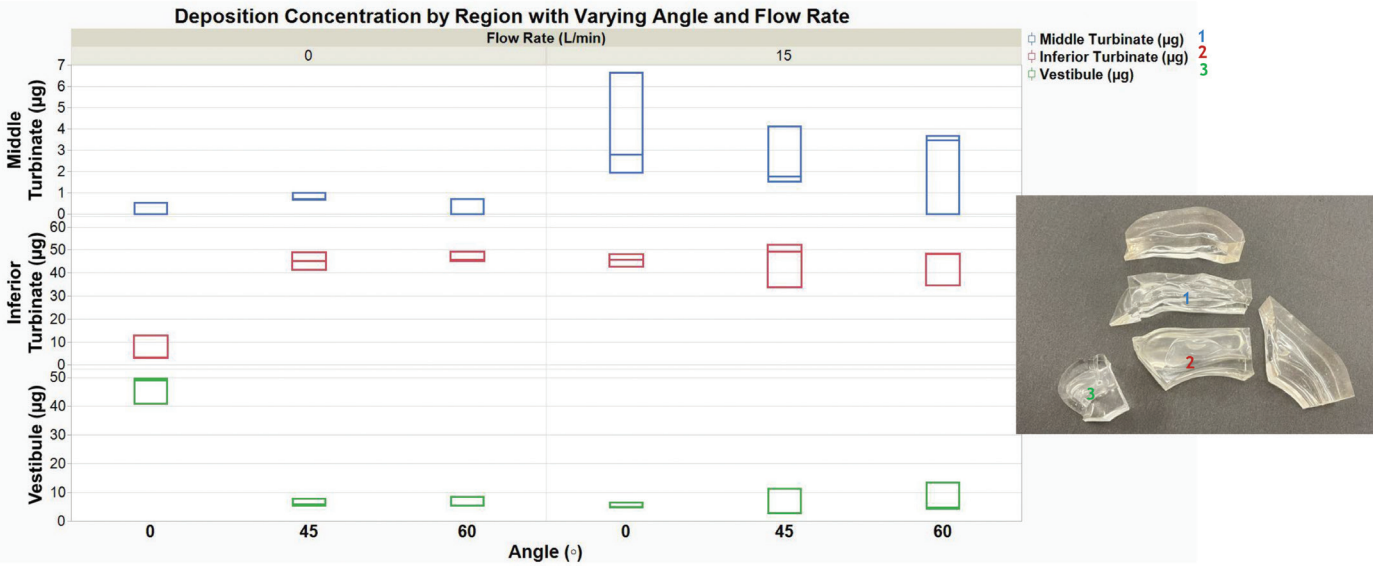


Figure 3: Proveris Nasal Cast – an anatomically accurate model of the human nasal cavity



		Angle (◦)					
		0		45		60	
		Flow Rate (L/min)		Flow Rate (L/min)		Flow Rate (L/min)	
		0	15	0	15	0	15
Vestibule (µg)	Mean	46.52	5.46	6.40	5.64	6.52	7.52
	RSD	10.3	18.5	19.0	86.9	27.8	68.3
Inferior Turbinate (µg)	Mean	6.43	45.59	45.15	45.09	46.69	43.87
	RSD	85.8	5.9	8.6	22.1	4.9	18.1
Middle Turbinate (µg)	Mean	0.17	3.79	0.79	2.48	0.23	2.38
	RSD	173.2	66.2	22.5	57.7	173.2	86.7

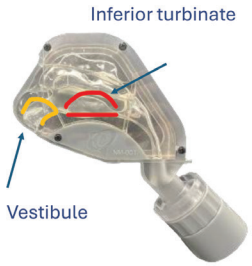


Figure 4: Deposition Concentration by Region with Various Angle and Flow Rate Conditions

3. **Targeted Insights –** Generates region-specific deposition data, essential for therapies that depend on precise targeting (olfactory region for CNS drugs, NALT for vaccines, turbinates for systemic absorption).

4. **Formulation and Device Optimisation –** Facilitates side-by-side comparison of devices and formulations, enabling rational selection and refinement of both components of the combination product.

5. **Regulatory Alignment –** While not mandatory, cast studies complement regulatory requirements for device performance characterisation and bio-equivalence demonstration, providing supportive evidence for submissions to FDA and EMA.

Case Study:
Evaluating Deposition Using the Proveris Nasal Cast

The Proveris Nasal Cast was developed as one of the first *in vitro* tools to evaluate nasal spray deposition under physio-logically relevant conditions. Early models employed a water-indicating gel to provide photographic, qualitative visualisation of spray distribution. While useful for initial insights, these casts offered limited data.

The Proveris cast can be disassembled into six anatomically defined regions of the nasal cavity, enabling extraction and quantification of active pharmaceutical ingredient (API) deposited in each region. This advancement provides truly quantitative deposition profiles, aligning with the FDA's CMC guidance on characterisation and supporting more predictive assessments of product efficacy.

Automated actuation of devices into the nasal cast ensures highly consistent dosing, minimising operator variability and establishing reproducibility that is critical for regulatory acceptance. In addition to deposition mapping, Proveris Laboratories complements cast studies with metered shot weight determination – confirming delivered dose accuracy – and actuation force measurement, which provides insight into device usability and patient compliance.

In a recent case study, Proveris Laboratories evaluated deposition patterns of an over-the-counter, multi-dose nasal spray under varied testing conditions. The experimental setup used:

- 0° (device upright), 45°, and 60° insertion angles
- 0 vs. 15 L/min airflow to simulate nasal breathing (no-flow vs. flow conditions)
- 90% methanol extraction solvent
- 18 replicate actuations

Shot weight results confirmed robust dose delivery, indicating the methodology was sound and repeatable.

Deposition Outcomes

- **No-flow condition:** Deposition was highly sensitive to spray angle. At 0° (device upright), more drug deposited in the nasal vestibule. At 45° and 60°, vestibular deposition decreased, while deposition in the inferior turbinate increased. Across all angles without flow, very little API reached the middle turbinate.

- **Flow condition (15 L/min):** Deposition became less dependent on spray angle. Regardless of device orientation, the airflow carried particles deeper, reducing variability and promoting more consistent deposition patterns.

Regulatory and Clinical Implications:
These findings underscore several key points directly relevant to FDA and EMA expectations for CMC submissions:

1. **Clear dosing instructions –** Angle, insertion depth, and patient posture must be specified and justified, as they directly affect reproducibility of deposition.

2. **Inclusion of airflow simulation –** Since deposition is strongly influenced by breathing flow, *in vitro* studies should incorporate airflow to better mimic patient use.

3. **Validation of actuation methodology –** Low RSD values demonstrate robustness and reproducibility, supporting method validation under ICH Q2 principles.

4. **Patient and device relevance –** For rescue sprays like Narcan, patients may not be upright, highlighting the importance of deposition consistency under varied angles and flows. For vaccines or CNS drugs, ensuring delivery to turbinates or olfactory region is essential to therapeutic success.

In summary, the case study demonstrates how modern nasal cast testing, paired with automated actuation, generates robust, regulator-relevant data. It validates dosing instructions, strengthens product characterisation, and provides developers with confidence that their products can deliver consistent, targeted therapy across real world use conditions.

Conclusion
Nasal cast testing has become a cornerstone of nasal drug product development, bridging the gap between *in vitro* device characterisation and costly *in vivo* imaging studies. By enabling precise, reproducible, and cost-effective evaluation of deposition, nasal casts help developers optimise both formulations and devices to achieve reliable therapeutic outcomes.

Advanced models, such as the Proveris Human-Realistic Nasal Cast, when paired with automated actuation technologies like the Proveris Vereo NSx, accelerate development timelines, support regulatory submissions, and ensure that nasal products are delivered effectively and consistently to their intended target sites, ultimately advancing patient care and expanding therapeutic possibilities.

REFERENCES

1. Nose-to-brain drug delivery: from bench to bedside | Translational Neurodegeneration | Full Text
2. First-in-human positron emission tomography study of intranasal insulin in aging and MCI - Sai - 2025 - Alzheimer's & Dementia: Translational Research & Clinical Interventions – Wiley Online Library
3. Nguyen, L. T.-T., & Duong, V.-A. (2025). Nose-to-Brain Drug Delivery. Encyclopedia, 5(3), 91. https://doi.org/10.3390/encyclopedia5030091
4. Gao M, Shen X, Mao S. Factors influencing drug deposition in the nasal cavity upon delivery via nasal sprays. J Pharm Investig. 2020;50:251–259. https://link.springer.com/article/10.1007/s40005-020-00482-z
5. Pathak YV, Yadav HKS, eds. Nasal Drug Delivery: Formulations, Developments, Challenges, and Solutions. Cham: Springer; 2023. Accessed September 9, 2025. https://link.springer.com/book/10.1007/978-3-031-23112-4
6. Xi J, Yuan JE, Zhang Y, Nevorski D, Wang Z, Zhou Y. Visualization and Quantification of Nasal and Olfactory Deposition in a Sectional Adult Nasal Airway Cast. Pharm Res. 2016;33(6):1527–1541. Accessed September 9, 2025. https://link.springer.com/article/10.1007/s11095-016-1896-2
7. Yadav HKS, Lim-Dy A, Pathak YV. An Overview of the Anatomy and Physiology of Nasal Passage from Drug Delivery Point of View. In: Pathak YV, Yadav HKS, eds. Nasal Drug Delivery: Formulations, Developments, Challenges, and Solutions. Springer; 2023:1–13. Accessed September 9, 2025. https://link.springer.com/chapter/10.1007/978-3-031-23112-4_1
8. Newman SP, Illum L. Radionuclide imaging studies in the assessment of nasal drug delivery in humans. Am J Drug Deliv. 2004;2(2):101–112. Accessed September 9, 2025. https://link.springer.com/article/10.2165/00137696-200402020-00003
9. Gondhale-Karpe P, Bhope S, Puri M, Manwatkar S, Mahajan B. Analytical Tools for the Characterization of Nasal Spray Drug Products. In: Kulkarni S, *et al.*, eds. Biosystems, Biomedical & Drug Delivery Systems. Springer; 2024. Accessed September 9, 2025. https://link.springer.com/content/pdf/10.1007/978-981-97-2596-0_4
10. Kimbell, J.S., *et al.* (2007). Deposition of inhaled particles in the human nasal airway: Effects of airway geometry and particle size. Aerosol Science and Technology, 41(5), 408–423. https://doi.org/10.1080/02786820701282677
11. Per G Djupesland, John C Messina & Ramy A Mahmoud (2020) Role of Nasal Casts for *In Vitro* Evaluation of Nasal Drug Delivery and Quantitative Evaluation of Various Nasal Casts, Therapeutic Delivery, 11:8, 485-495, DOI: 10.4155/tde-2020-0054
12. U.S. Food and Drug Administration. Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action: Guidance for Industry. April 2003. Accessed September 9, 2025. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/bioavailability-and-bioequivalence-studies-nasal-aerosols-and-nasal-sprays-local-action
13. European Medicines Agency. Guideline on the Pharmaceutical Quality of Inhalation and Nasal Medicinal Products (Revision 1). EMA/CHMP/QWP/49313/2005 Rev. 1. Accessed September 9, 2025. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-pharmaceutical-quality-inhalation-nasal-medicinal-products-revision-1_en.pdf

Joanne Mather

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.

Alyssa Rubino

Alyssa Rubino drives product marketing at Proveris Laboratories, where she helps communicate the value of tools and services that support development of orally inhaled and nasal drug products (OINDPs). With a background in life sciences and regulatory strategy, she brings a unique perspective that connects scientific innovation with customer needs. Alyssa works closely with both internal teams and industry partners to share how Proveris can help improve product performance, streamline development, and support regulatory success.