Human-Relevant New Approach Methodologies (NAMs) for Nasal Drug Delivery to the CNS

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Why Human-Specific Nasal Targeted Delivery is Critical for CNS Applications

Section 1 —Motivation & Problem Statement

The brain is a protected compartment

The BBB and BCSFB block the majority of therapeutic candidates; the few small molecules that cross typically require systemic doses driving peripheral side effects.

The margin for error in CNS drug development is uniquely narrow

CNS drugs don't just fail on efficacy — off-target effects on mood, cognition, and behavior.

Animal models lack predictive validity for human nose-to-brain delivery

Animal modeling leads to lack of translation of pre-clinical testing of candidate treatment molecules (e.g., only 1 out of 500 got approved in the field of stroke).[4]

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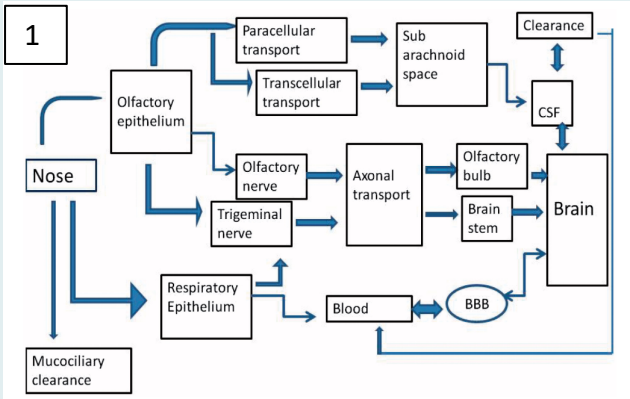

1&3. Selvaraj et al (2017), Artificial Cells, Nanomedicine, and Biotechnology, 46(8): 2088-2095.
2. Pardridge et al, J Cerebral Blood Flow & Metabolism, 32(11), 2012.
4. Chesselet MF, Carmichael ST. Neurotherapeutics. 2012 Apr;9(2):241-4.

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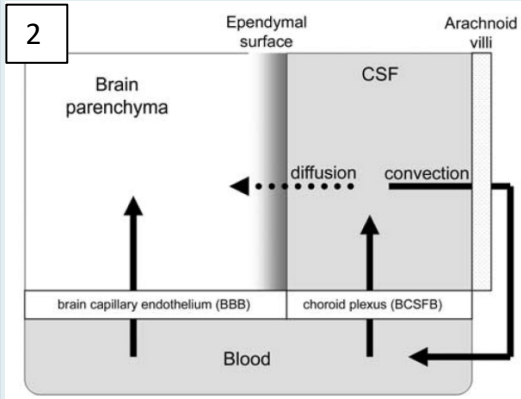

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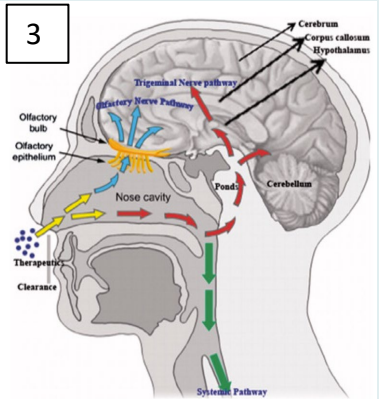
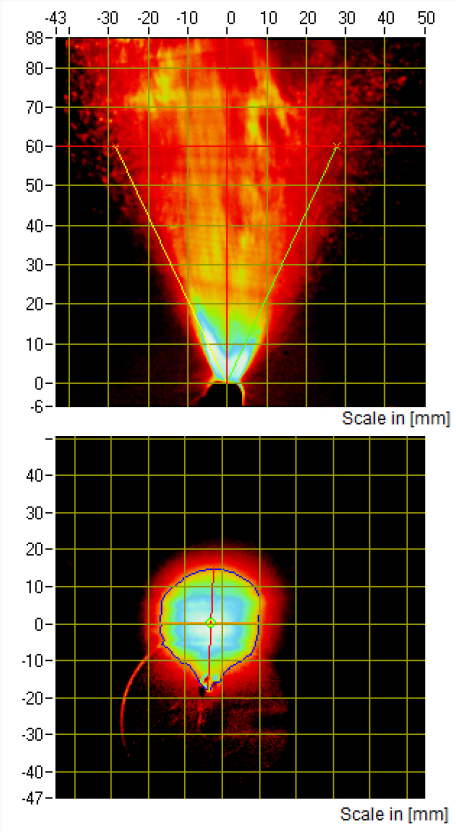


Framework Gaps Currently Limit Early-Stage Predictivity

CURRENT 2002/2003 DRAFT GUIDANCE FRAMEWORK

- Device performance is characterized without nasal context: All patients are essentially treated as having the same nasal anatomy.
- Growing use of single nasal geometry models to close the preclinical and clinical gap lack standardized context:
  - No defined source medical image quality and details
  - No established image-to-model conversion protocol
  - No standardized anatomical landmarks for regions of interest
  - No verification of health/disease status by specialists
  - No concurrent guidance on device positioning (administration is uncontrolled).

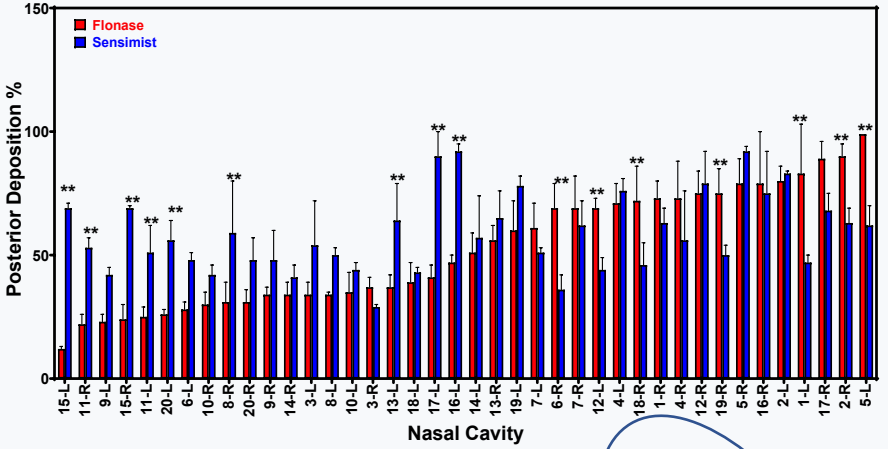


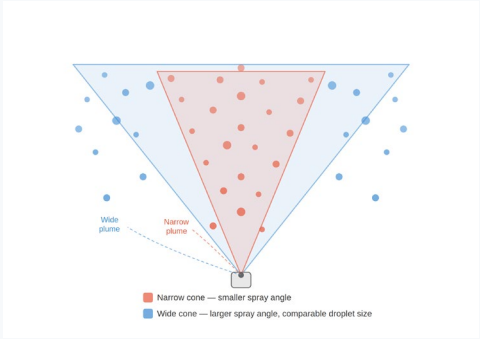
Inter- and Intra- Subject Variability Directly Impacts Regional Nasal Deposition

Significant Parameter Interaction, Inter- and Intra-subject Regional Variability

Parameter interactions and regional variability demand anatomy-informed strategies.

- Intersubject anatomical variability dominates deposition outcomes. Our library of 40 adult + 40 pediatric nasal casts demonstrates that no single model is representative.
- Device and formulation parameters interact with anatomy in ways that cannot be predicted from device characterization alone — underscoring the need for population-based, anatomy-informed BE frameworks.





Anatomically-Detailed Nasal Models Enable Human-Relevant Early-Stage Predictivity for CNS Delivery

ANATOMY-INFORMED APPROACH

Realistic Use Conditions

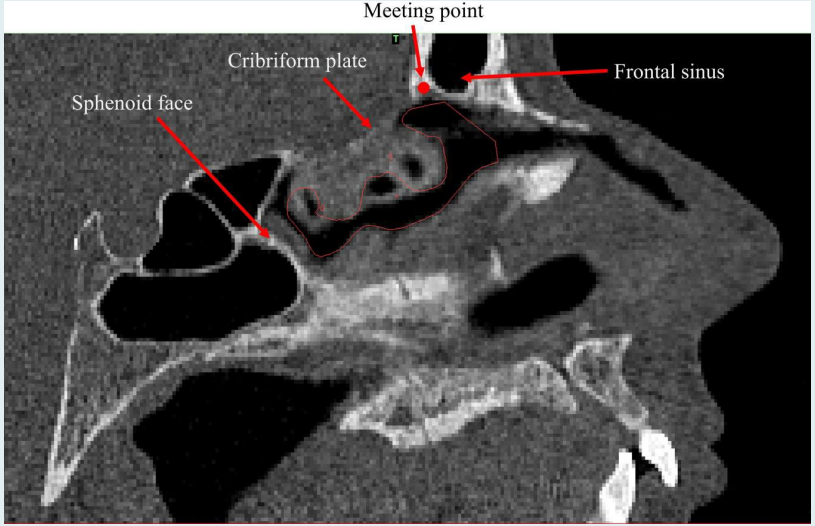
- Device output can be evaluated within the nasal airway.
- Device position can precisely be controlled within the nasal airway model.

Population Relevance

- Intersubject variability across populations, age, and disease can be captured.

Improved Endpoints

- Direct measurement of regional deposition (beyond indirect weight-of-evidence) will be enabled.



The Challenge: identification of olfactory region from superior turbinate.

- Olfactory region and superior turbinate are anatomically adjacent — difficult to separate
- Must define anatomical boundaries with precision and reproducibility

Concurrent Device–Anatomy Evaluation: The Path to Actionable, Human-Relevant Drug Product Development

Administration Conditions Can be Optimized for Regional Targeting

- Products sharing identical plume characteristics can produce different regional deposition profiles.
- Administration angles and insertion depth, and anatomy interact to shift drug toward or away from the target regions of action, i.e. the olfactory epithelium.
- Optimizing these parameters provides a mechanistic path to BE demonstration beyond matched device outputs.

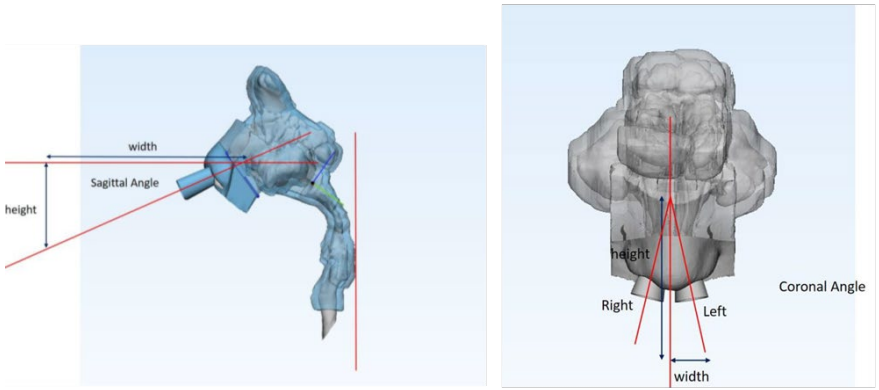
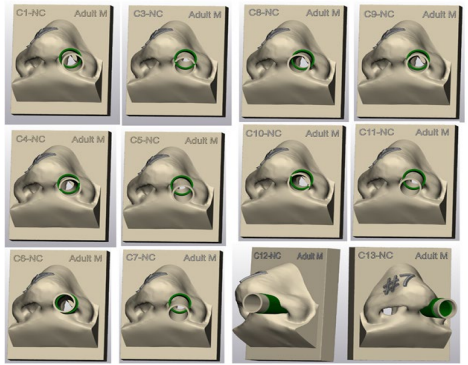
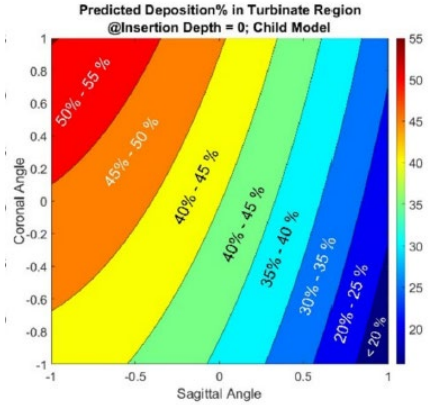


Figure 8 – Sagittal and Coronal angles



Hejazi M, et al. Pharm Res 2026; 666: doi: 10.1007/s11095-026-04066-8



Contours of predicted drug deposition percentage, illustrating the effect of varying administration parameters.

Key finding: Two products with same plume & droplet size ≠ same deposition. Two products with different specs can achieve equivalent deposition with optimized administration.

Research Priorities for GDUFA Science: Establishing NAMs for Nose-to-Brain Drug Delivery

1. Develop human-relevant NAMs to enable predictive early-stage assessment of nasal drug products designed for olfactory targeting.

2. Apply NAMs to characterize the range of various drug modality delivery at the nasal epithelium across different populations, enabling drug product design that accounts for dose variability.

3. Extend NAMs to predict permeation across the olfactory epithelium, providing a mechanistic foundation for regulatory guidance on growing nose-to-brain drug delivery products.

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