Mechanistic Modeling and Realistic In Vitro Models to Facilitate Development of Generic Nasal Drug Products

SBIA 2022 – Advancing Generic Drug Development: Translating Science to Approval

Day 2, Session 6: Nasally Administered Drug Products

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Learning Objectives

- Describe the utility of computational fluid dynamics (CFD) and physiologically based pharmacokinetic (PBPK) modeling for nasal drug product development.
- Understand how CFD and PBPK modeling are used to identify potential relationships between in vitro metrics and drug delivery to the site of action for nasal drug products.
- Identify the value of CFD and PBPK modeling for development of nasal drug products with targeted nose-to-brain drug delivery.

Research for Mechanistic Modeling of Nasal Drug Products and In Vitro Nasal Models

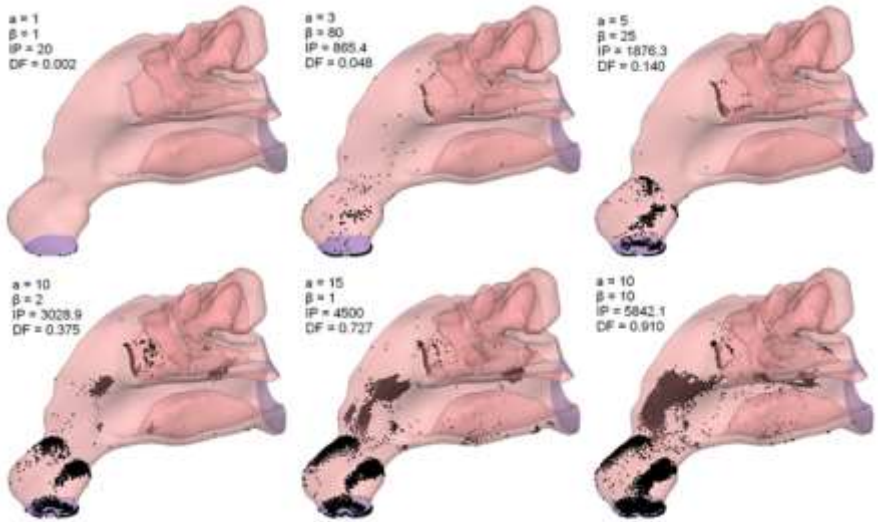
- Funded supported via Generic Drug User Fee Amendments (GDUFA)
- Six external grants and contracts (three ongoing)
  - Grant 1U01FD005201 (Applied Research Associates [ARA], 2014-2018)
  - Grant 1U01FD006537 (North Carolina State University [NCSU], 2018-2021)
  - Contract HHSF223201810144C (Virginia Commonwealth University [VCU], 2018-2021)
  - Contract 75F40119C10079 (ARA, 2019-present)
  - Contract 75F40120C00172 (VCU, 2020-present)
  - Grant 1U01FD007657 (University of Manchester, 2022-present)

Value of Mechanistic and In Vitro Models

- Product Development
  - Influence of device and formulation differences on regional deposition and absorption
  - Prediction of olfactory region absorption for nose-to-brain (N2B) delivery
- Bioequivalence (BE)
  - May be useful for alternative BE approaches for nasal drug products

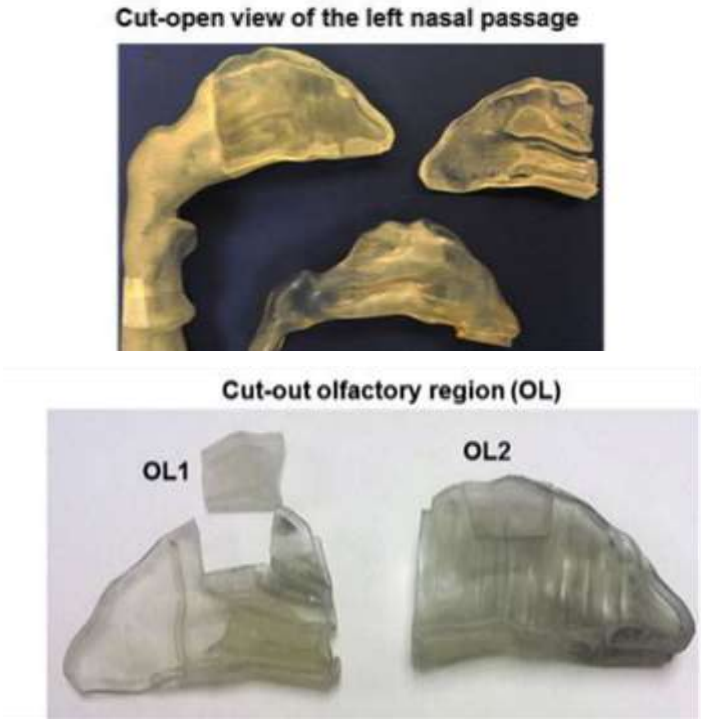
Computational Fluid Dynamics (CFD) Modeling of Nasal Drug Products

- Predict influence of device and formulation parameters on drug delivery to the site of action
  - Particle size distribution, spray angle, spray velocity
  - Regional deposition
    - Intersubject variability
  - Pharmacokinetic (PK) profile
    - Combined with physiologically-based pharmacokinetic (PBPK) modeling



Fiber deposition in nasal cavity, where a is the fiber radius in µm, β is the fiber aspect ratio, IP is the impaction parameter, and DF is the deposition fraction. (Fig. 13 from Dastan et al.[1])

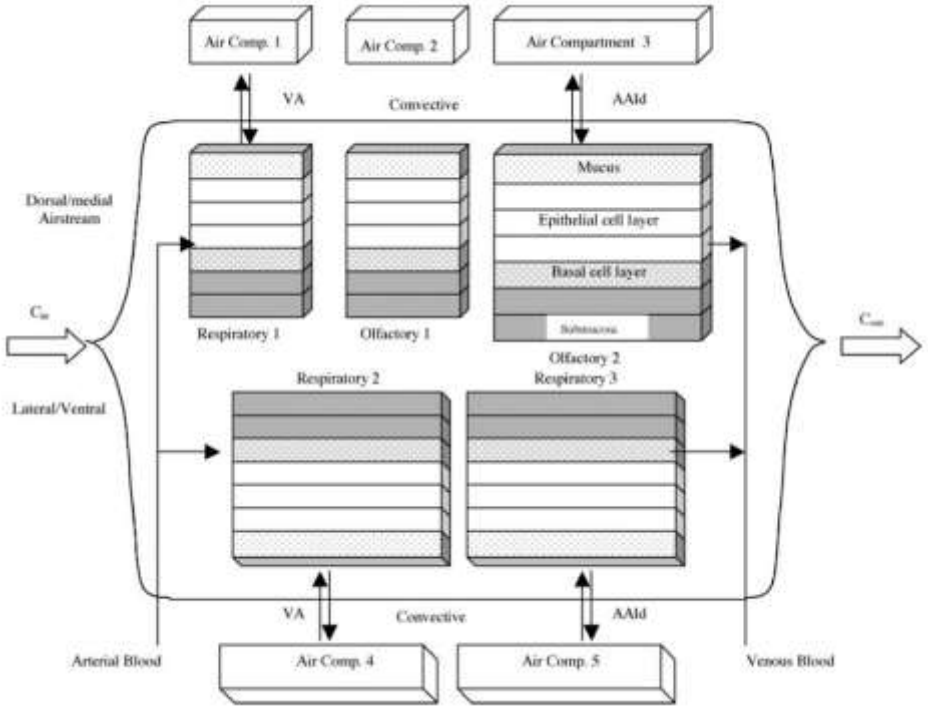
Nasal In Vitro Models



Nasal in vitro model that allows for measurement of olfactory region deposition. (Adapted from Fig. 1c of Xi et al.[2])

- Drug product is actuated into nasal model
- Deposited drug is measured from removable sections using high performance liquid chromatography (HPLC)
- Capable of evaluating intersubject variability

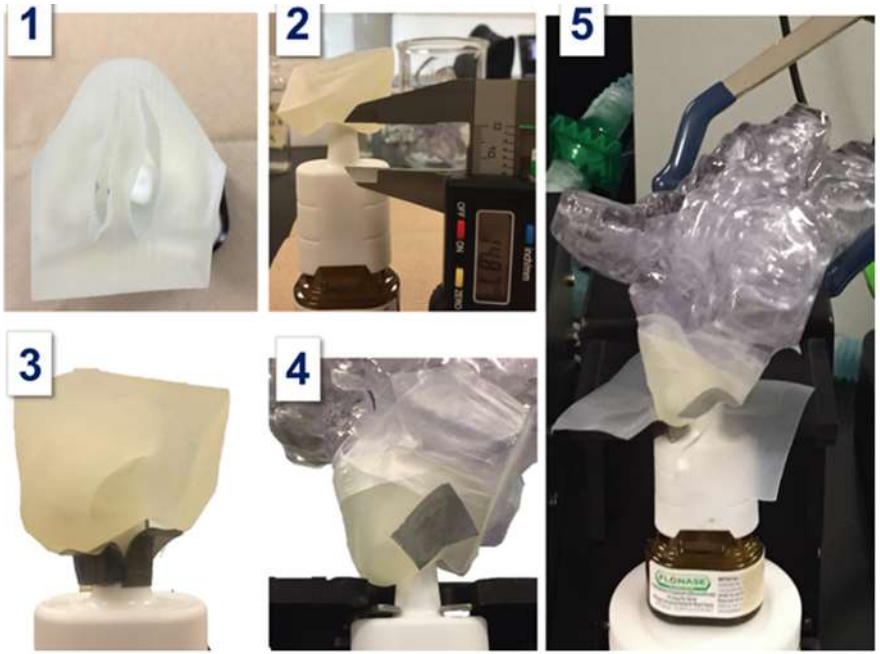
PBPK Modeling of Nasal Drug Products



- Compartmental model
- Regional deposition inputs (in vivo, in vitro, or in silico)
- Prediction of local and systemic PK
  - Dissolution in mucus layer
  - Absorption through nasal tissue
  - Metabolism in nasal tissue
  - Integration with systemic model
- Validated with in vivo systemic or tissue PK data

Nasal PBPK model structure as shown in Fig. 2 of Andersen et al.[3]

Regional Deposition Measurements

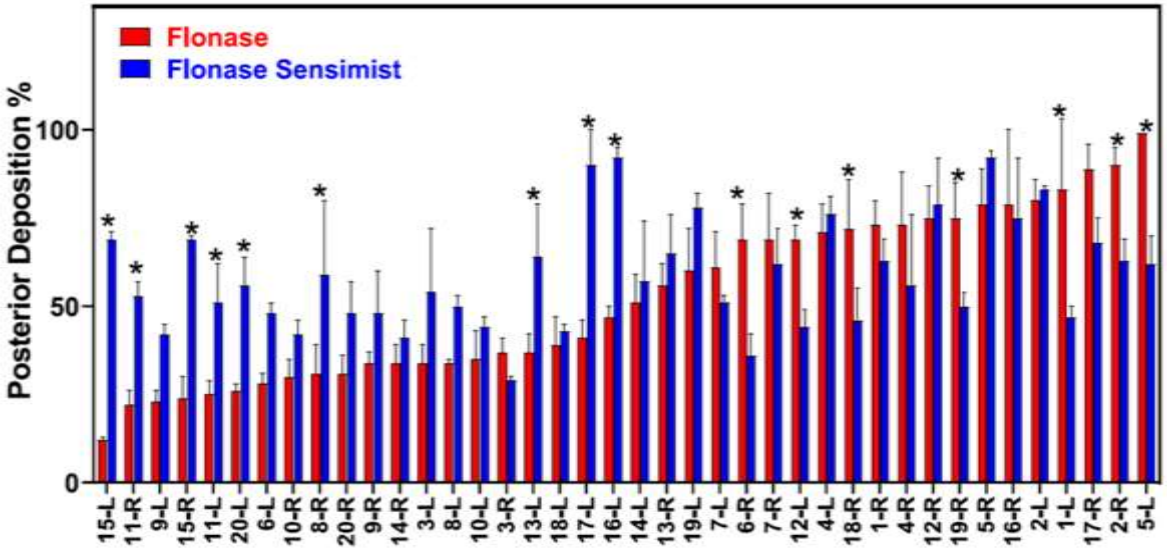


Experimental setup for measuring deposition following actuation of fluticasone propionate nasal spray. (Fig. 2 of Manniello et al.[4])

- VCU
  - PI: Laleh Golshahi
  - Contract #HHSF223201810144C (adult models)
  - Contract #75F4012000172 (pediatric models)
  - Develop two sets of models for adult and pediatric subjects (three models for each)
  - Intersubject variability for nasally inhaled corticosteroids
- Relationships of in vitro metrics of spray properties with regional deposition

Posterior Region Deposition Measurements

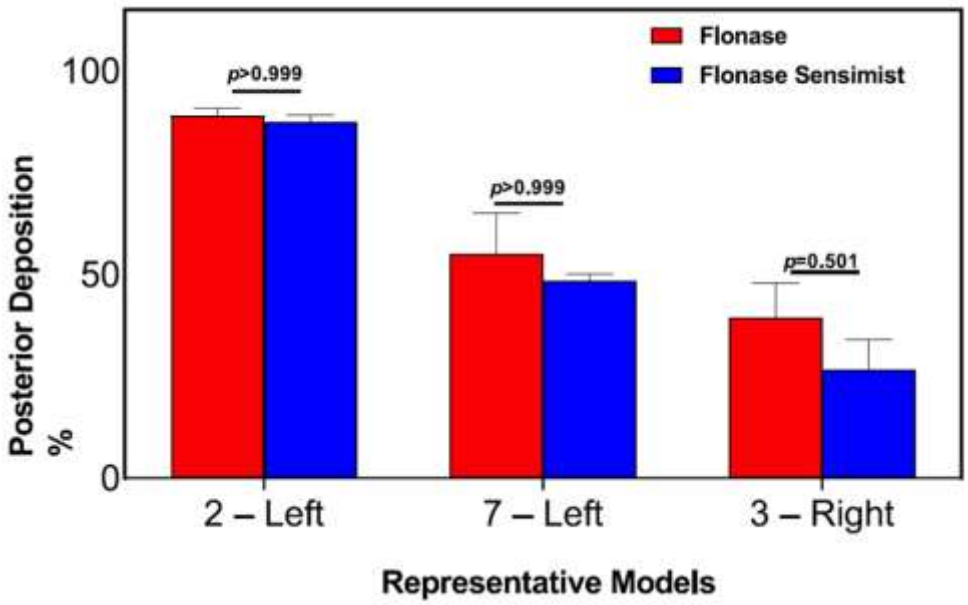
- Posterior regional deposition measurements in adult nasal models showed high variability
  - Range of 12-99% for fluticasone propionate nasal spray
  - Range of 29-92% for fluticasone furoate nasal spray
- In several cases there was a significant difference according to drug product



Posterior regional deposition in right side of 40 adult nasal airways (n = 5 for each model) of fluticasone propionate nasal spray (Flonase®) and hand-actuated fluticasone furoate nasal spray (Flonase Sensimist®). Significant differences between drug products are shown by "*." (Fig. 4 of Alfaifi et al.[5])

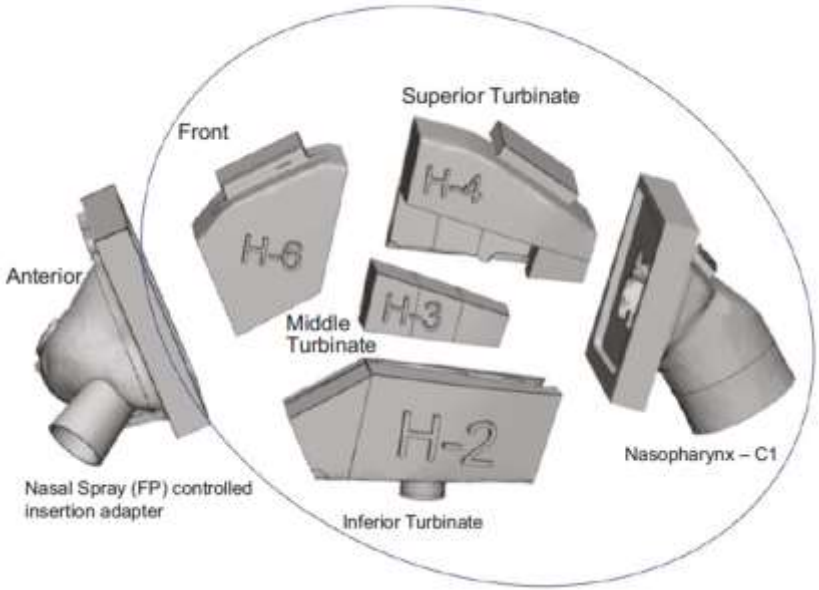
Nasal Model Selection

- Three adult nasal models have been selected to capture intersubject variability according to following criteria:
  - Low and high deposition models must differ by two standard deviations from the mean value of posterior deposition for all 40 models. The medium model should be not significantly different than the mean
  - No significant difference between drug products
  - Significant differences between low and medium models and between high and medium models



Posterior regional deposition in three selected models (n = 5 for each model) of fluticasone propionate nasal spray and hand-actuated fluticasone furoate nasal spray. (Fig. 7 of Alfaifi et al.[5])

Further Sectioning of Adult Nasal Models



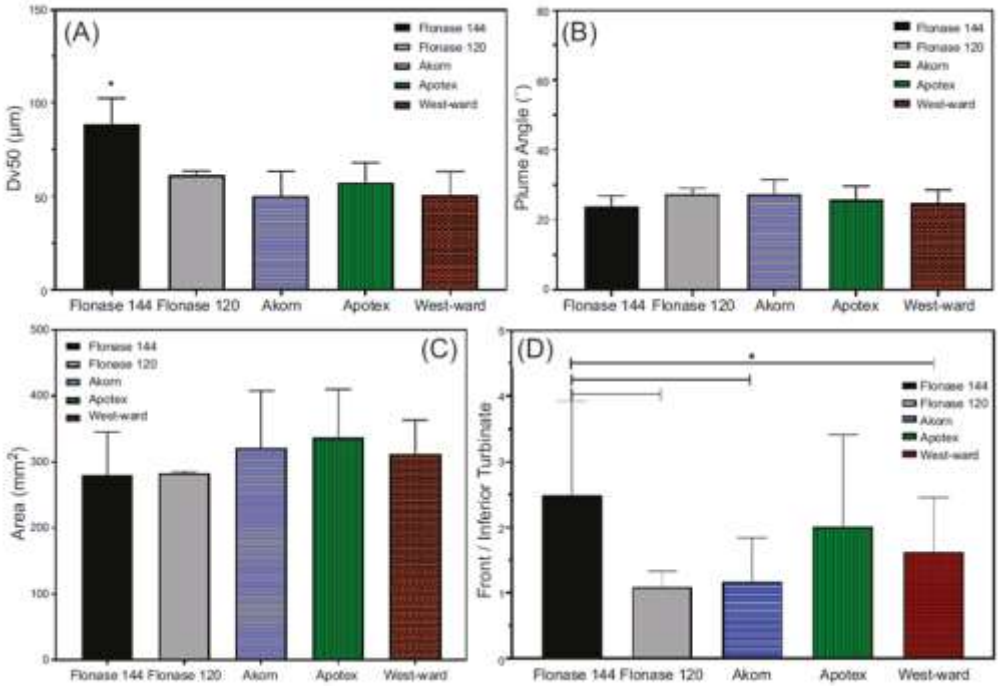
Computational rendering of high posterior deposition model sectioned into anterior, front, inferior turbinate, middle turbinate, superior turbinate, and nasopharynx regions. (Fig. 4 of Golshahi et al.[6])

Mean percentage of recovered regional deposition ± standard deviation in three selected models (n = 5 for each model) of fluticasone propionate nasal spray. (Based on Table 2 of Golshahi et al.[6])

	Posterior Deposition		
Posterior Section	**High**	**Medium**	**Low**
Anterior	23.2 ± 4.2	52.5 ± 0.8	64.1 ± 0.9
Front	37.9 ± 4.5	22.4 ± 1.1	15.8 ± 1.2
Inferior	32.4 ± 6.1	20.0 ± 2.1	17.2 ± 1.0
Middle	3.0 ± 2.4	3.0 ± 1.4	1.2 ± 0.5
Superior	1.6 ± 1.0	2.3 ± 1.1	0.0 ± 0.0
Nasopharynx	1.8 ± 0.2	0.0 ± 0.0	0.7 ± 0.1

Comparison of Different Products

- Relationships of in vitro metrics to regional deposition may be tested with three in vitro adult nasal models
- Three in vitro tests
  - Droplet size distribution
  - Plume geometry
  - Spray pattern
- Two brand-name fluticasone propionate nasal spray drug products (Flonase Allergy Relief® and Flonase) and three generic versions of Flonase (Akorn, Apotex, and West-ward)



Median droplet diameter (Dv50), plume angle, plume area at 6 cm, and ratio of front to inferior turbinate deposition across high, medium, and low models, for two brand-name fluticasone propionate nasal drug products (Flonase Allergy Relief [with 144 sprays] and Flonase [with 120 sprays]) and three generic versions of Flonase. * - significantly different. (Fig. 6 of Golshahi et al.[6])

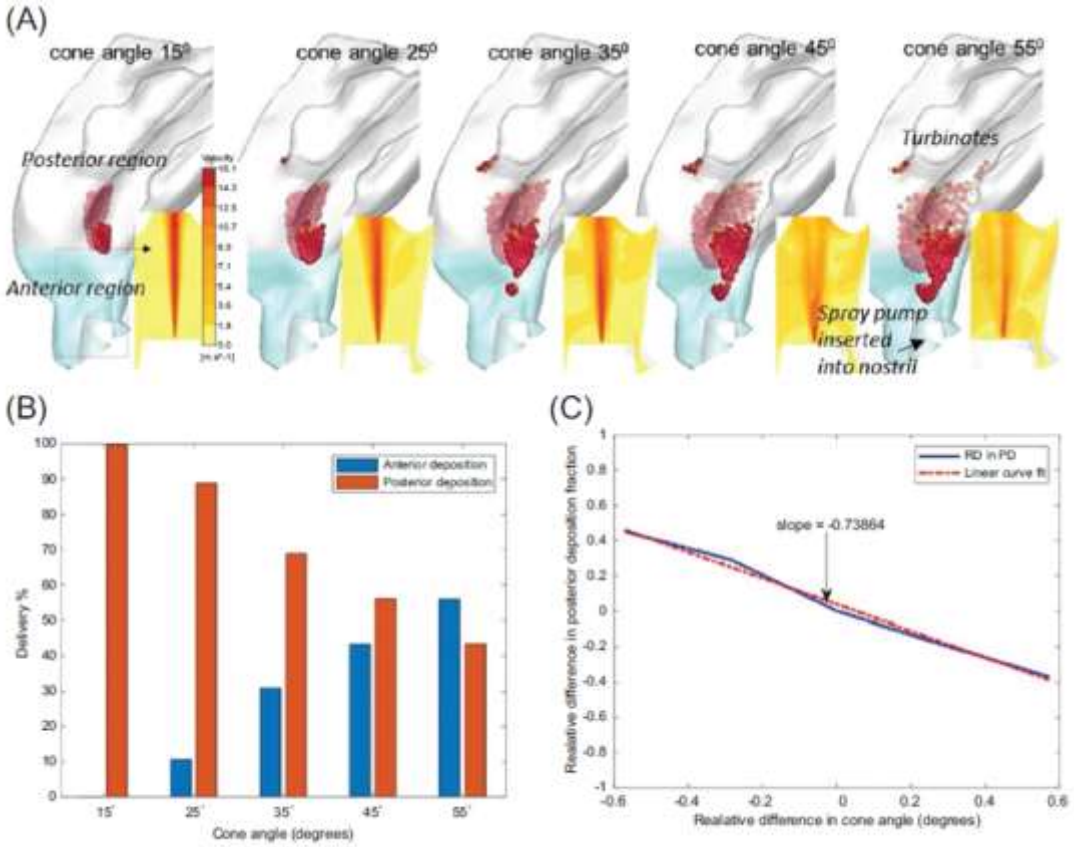
CFD Model Validation

Deposition predictions using two CFD methods with fluticasone furoate nasal spray and fluticasone propionate nasal spray as compared with in vitro data (n = 5). (Based on Table 6 of Kolanjiyil et al.[7])

	Fluticasone Furoate		Fluticasone Propionate	
	Anterior (%)	Posterior (%)	Anterior (%)	Posterior (%)
CFD quasi two-way coupling	93.4	6.6	89.5	10.5
CFD one-way coupling	92.6	7.4	94.0	6.0
In vitro	94.1 ± 1.9	5.9 ± 1.9	85.8 ± 5.4	14.2 ± 5.4
Relative error (quasi two-way coupling) (%)	0.7	11.9	4.3	26.1
Relative error (one-way coupling) (%)	1.6	25.4	9.6	57.7

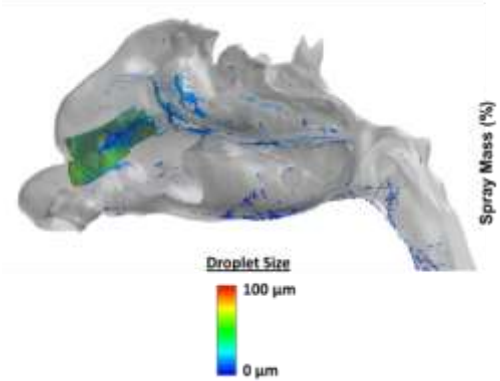
- Model credibility should be established before using model for intended purpose
- One adult nasal model (medium) from Manniello et al.[4] was used to develop CFD model
- Two methods used to couple fluid and particle motion
- Results compared to in vitro data
- Improvement of predictions may be possible by considering spray-wall interaction and post-deposition liquid motion[8]

Influence of Spray Cone Angle

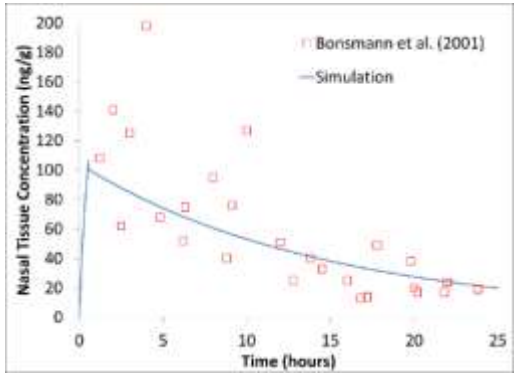


CFD simulation results with medium nasal model and fluticasone furoate nasal spray, shown as (A) variation in spray cone angle input parameter, (B) anterior and posterior deposition percentage predictions, and (C) relative difference (RD) in posterior deposition fraction (PD) as varied by relative difference in spray cone angle (baseline of 35°). (Fig. 1 of Kolanjiyil et al.[9])

Hybrid CFD-PBPK for Nasally Inhaled Corticosteroids



CFD predictions for deposition locations of fluticasone propionate droplets, from Kimbell et al.[10]



PK predictions of fluticasone propionate nasal spray, from Schroeter et al.[11]

- Applied Research Associates, Inc.
  - Grant #1U01FD005201: 2014-2018
  - Contract #75F40119C10079: 2019-present
  - Principal Investigator (PI): Jeffry Schroeter
- Fully 3D CFD model predicts deposition
- PBPK model for nasal absorption
- CFD results serve as inputs to the PBPK model
  - Models are run independently
  - Constant mucociliary clearance (MCC) velocity
- Investigation of device and usage parameters

In Vitro Metrics – Input Parameters

- CFD modeling was used to examine impact of various in vitro parameters on regional deposition predictions
- Input parameters were varied by ± 10% and ± 20% to understand parameter sensitivity

CFD input parameters for several brand name drug products (Based on table produced by ARA for contract 75F40119C10079)

Spray	Spray Cone Angle (degrees)	Dv50 (µm)	Span
Fluticasone Propionate	63.3 ± 4.2 [a]	46.4 ± 2.1 [b]	2.04 ± 0.32 [b]
Triamcinolone Acetonide	55.9 ± 0.9 [a]	43.8 ± 2.8 [a]	1.99 ± 0.27 [a]
Mometasone Furoate	20.0 ± 0.5 [c]	41.4 ± 1.1 [b]	1.91 ± 0.25 [b]
Budesonide	59.4 ± 18.3 *	29.4 ± 1.7 [b]	2.42 ± 1.23 [b]
Fluticasone Furoate	35 ± 2.1 [d]	57.1 ± 1.3 [d]	1.39 ± 0.01 [d]

[a] Next Breath report, Kimbell R01[12]

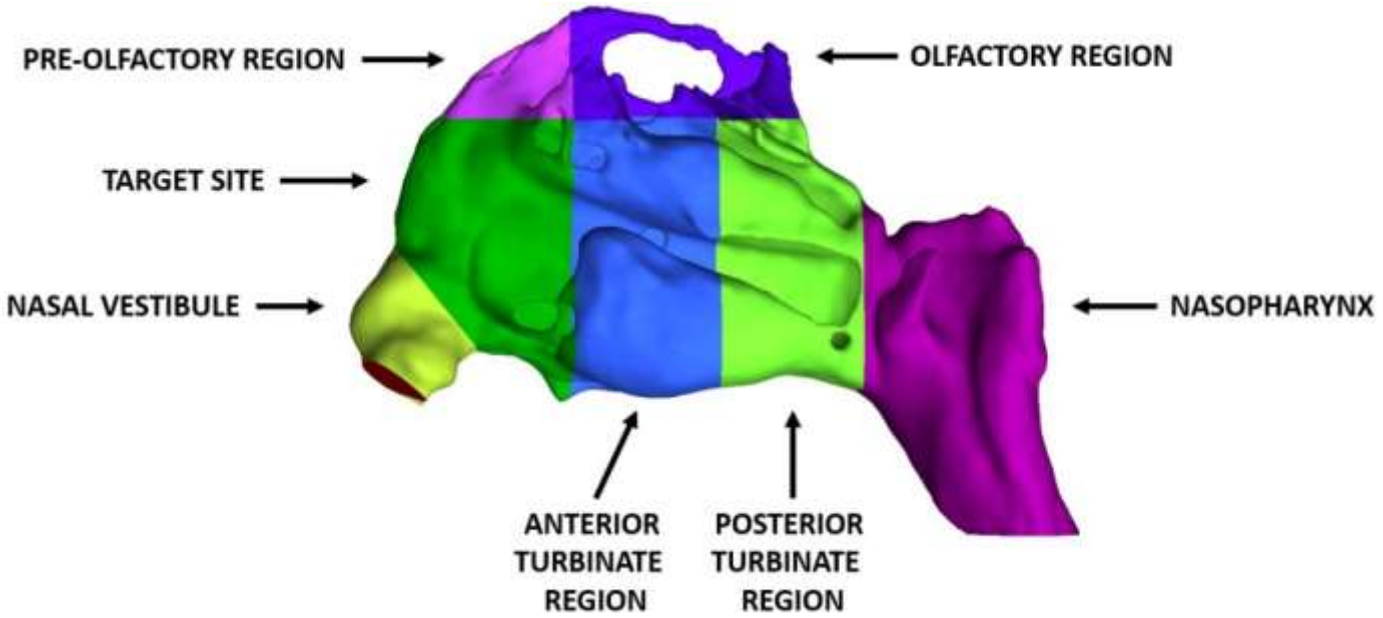
[b] Schroeter et al.[13]

[c] Xi et al.[14]

[d] Hosseini et al.[15]

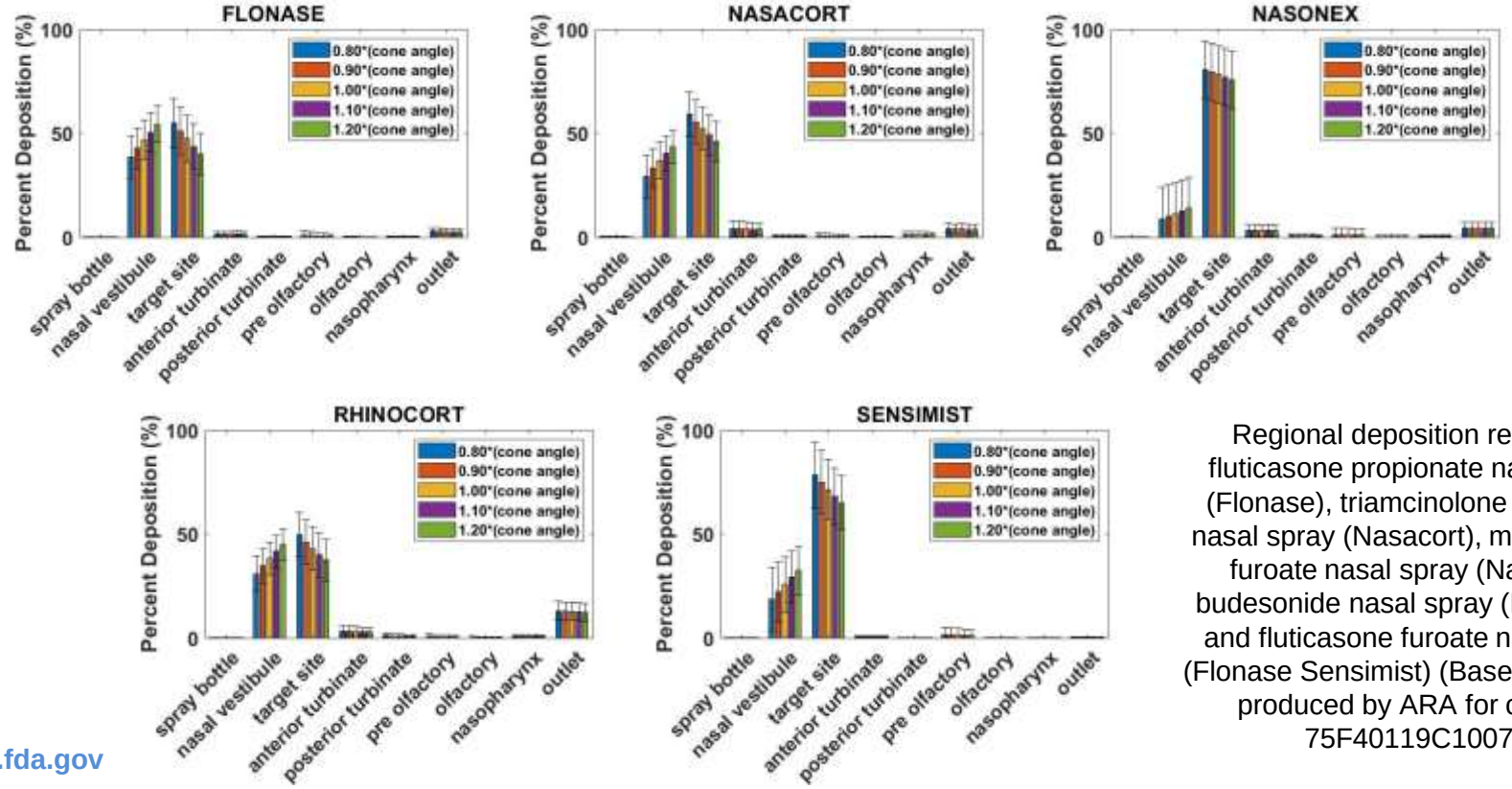
* Estimated valued based on Shrestha et al.[16]

Regional Definitions for Nasal Models



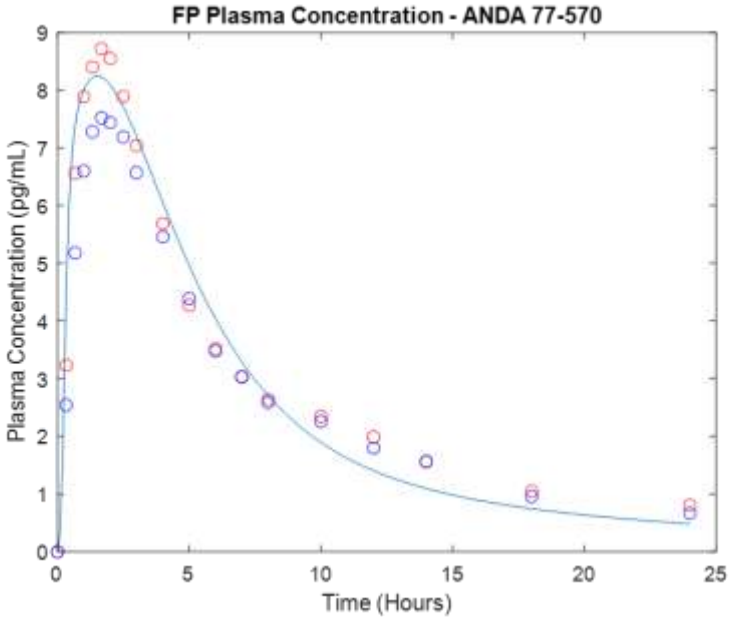
Regional definitions for healthy subject model MCW002 (Figure produced by ARA for contract 75F40119C10079)

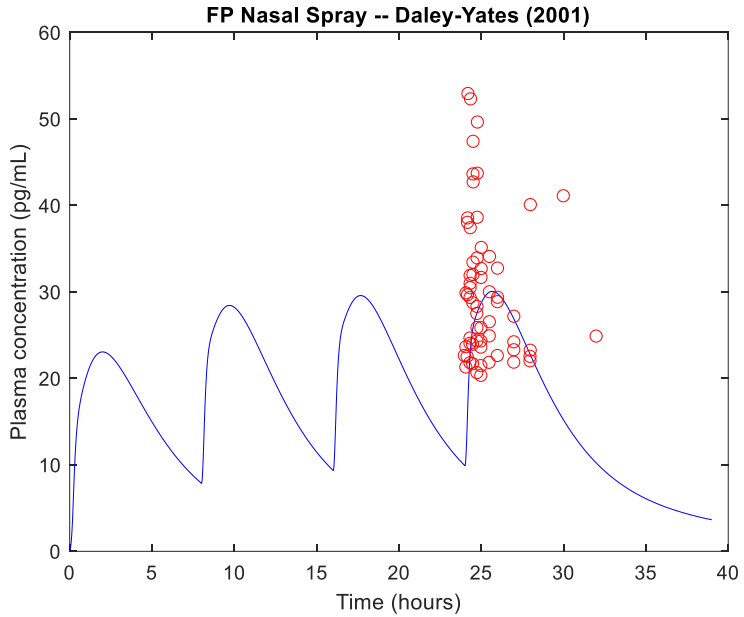
Sensitivity of Regional Deposition to In Vitro Metric Variation



Regional deposition results for fluticasone propionate nasal spray (Flonase), triamcinolone acetonide nasal spray (Nasacort), mometasone furoate nasal spray (Nasonex), budesonide nasal spray (Rhinocort), and fluticasone furoate nasal spray (Flonase Sensimist) (Based on figures produced by ARA for contract 75F40119C10079)

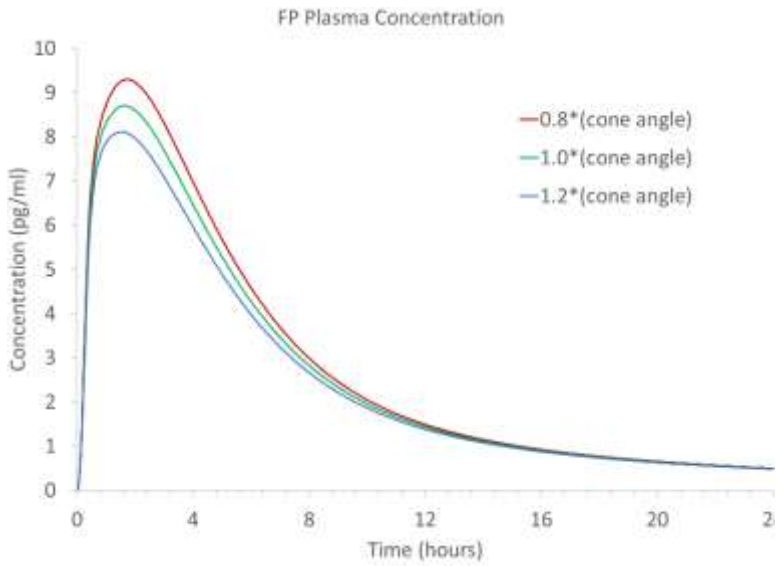
PBPK Model Validation for Fluticasone Propionate Nasal Spray

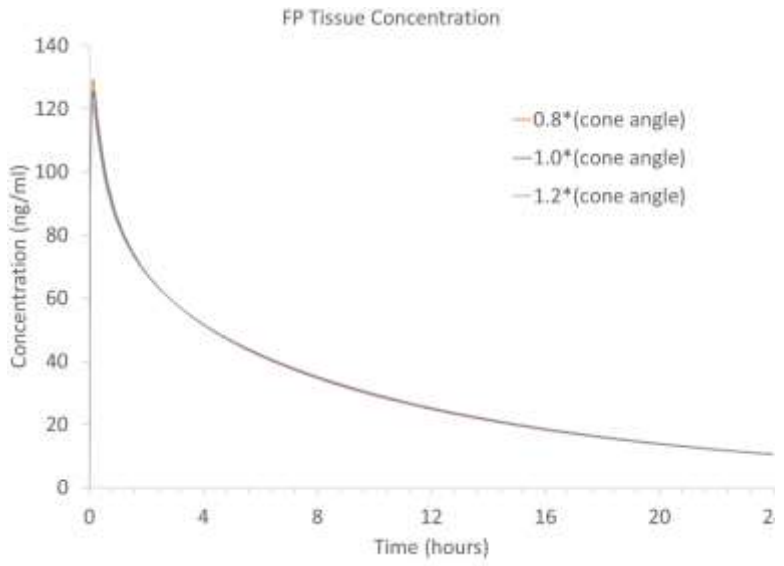




PBPK model validation following administration of fluticasone propionate nasal spray with a dose of 200 µg, as given in publicly available review for abbreviated new drug application (ANDA) 77570 with test and reference products,[17] and a dose of 800 µg given four times as given in Daley-Yates et al.[18] (Based on figures produced by ARA for contract 75F40119C10079)

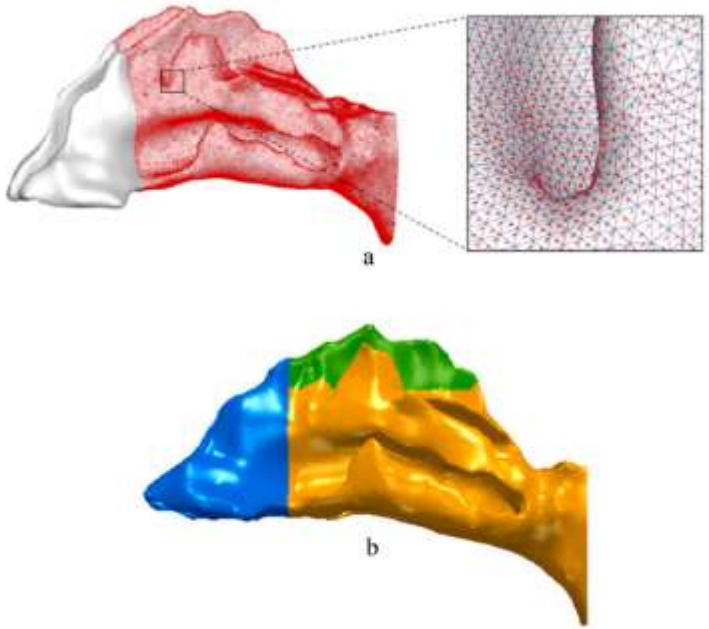
Impact of Spray Cone Angle on PK





Systemic and tissue PK predictions for fluticasone propionate (FP) nasal spray based on differences in spray cone angle (Based on figures produced by ARA for contract 75F40119C10079)

Nasal Modeling to Predict Nose-to-Brain Drug Delivery



Nasal MCC model features, including a) 6 mm/min mucus velocity vectors in mucus layer and b) regional definitions including olfactory (red), nasal vestibule (blue), and nasal cavity (orange) regions. (Fig. 1 of Chari et al.[19])

- North Carolina State University
  - PI: Clement Kleinstreuer
  - Grant #1U01FD006537: 2018-2021
  - 3D CFD model is used to predict regional deposition of nasal drug products
  - Nasal MCC model predicts transit, dissolution, and absorption simultaneously
  - Can be used for predicting nose-to-brain drug delivery
- Other models (e.g., ARA and VCU) may be used for nose-to-brain drug delivery provided effect of mucociliary clearance is not expected to be pronounced
- PBPK model for nose-to-brain drug delivery is focus of new award to University of Manchester (Grant #1U01FD007657, PI: Kayode Ogungbenro, 2022-present)

Challenge Question #1

Which of the following statements is NOT true?

A. Nasal in vitro models may be sectioned to allow for measurement of regional deposition using high performance liquid chromatography (HPLC).

B. Computational fluid dynamics (CFD) modeling is a physics-based method that allows for prediction of fluid and particle transport only in simplified geometries.

C. Physiologically based pharmacokinetic (PBPK) modeling is a compartmental method that allows for prediction of pharmacokinetics (PK) following drug administration.

Challenge Question #2

Nose-to-brain drug delivery is achieved by targeting which nasal region?

A. Nasal vestibule

B. Olfactory

C. Nasopharynx

D. Inferior turbinate

Conclusions

1. GDUFA supports several external research grants and contracts for enhancing generic nasal drug product development.

2. Mechanistic CFD and PBPK models and realistic in vitro nasal models are being developed to investigate relationships between in vitro test metrics and regional drug delivery and to better understand regional delivery of drugs that target nose-to-brain drug delivery.

3. Mechanistic modeling and realistic in vitro nasal models may facilitate development and potentially approval of nasal drug products.

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- FDA/CDER/OPQ/ONDP
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- University of North Carolina
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  - William (Bill) Bennett
- North Carolina State University
  - Clement Kleinstreuer
  - Sriram Chari


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