Pathways to Establish Bioequivalence and Facilitate Development of Innovative and Generic Intranasal Drug Delivery Products: *In vitro* Anatomically-Correct Nasal Models

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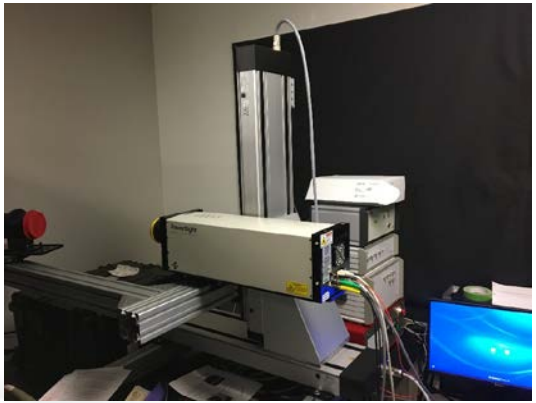


RARE Laboratory

In vitro-In vivo Correlations (IVIVC) for OINDP*

Current Main Areas of Research

- Nasal Drug Delivery
- Pulmonary Drug Delivery/Targeting
- High Flow Nasal Cannula (HNFC) Therapy

* OINDP: Orally-Inhaled and Nasal Drug Products

Objectives

- Provide an overview of nasal drug delivery and applications of anatomical nasal models in *in vitro* characterization of local drug targeting.

- Discuss some case studies of *in vitro* intranasal drug delivery to highlight the potential applications of nasal models in filling the gaps between nasal drug delivery device development (innovative or generic) and clinical studies.

Advantages of Intranasal Drug Delivery

- Relative ease of administration
  - Needle-free method of administration
  - No need to swallow

- Avoidance of gastrointestinal degradation and hepatic first-pass metabolism

- Providing rapid onset of action and less pain to the patient.

Applications of Intranasal Drug Delivery

- Locally-acting drugs (united airway concept CRS in CF)
- Vaccines
- Control of seizures and migraines
- Sedation and analgesia
- Delivery of opioid antagonists
- Nose-to-brain (N2B)

Intranasal Drug Delivery: Prevalence and Unmet Needs

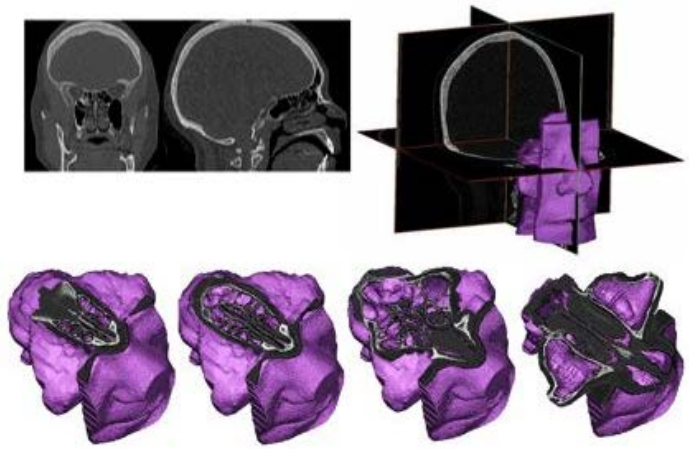
- Allergic Rhinitis (AR) is a very common problem.
  - 32% of all individuals with AR (60 million just in the US) are 17 years old and younger.
  - Onset of disease mainly in adolescence, but recent epidemiological studies show it's also common below the age of 6 years.

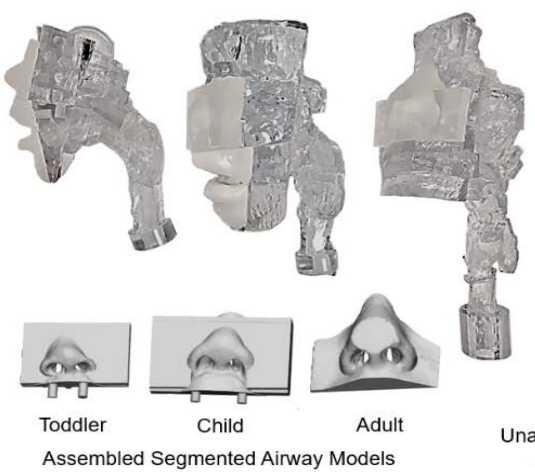
- Despite the prevalence of pediatric AR, the disease is inadequately treated (based on surveys of pediatric patients and parents of patients with allergy)
  - Undiagnosed or undertreated AR predisposes children to rhinosinusitis, asthma, and otitis media with effusion.
  - Treatment of AR will improve asthma outcomes.

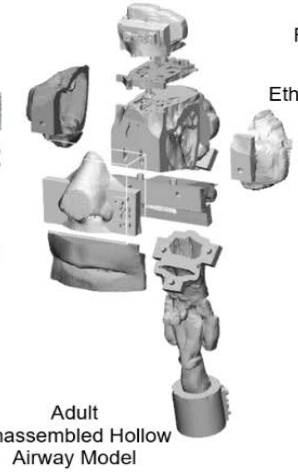
Pathway to Efficient and Subject-Specific Intranasal Delivery Technologies

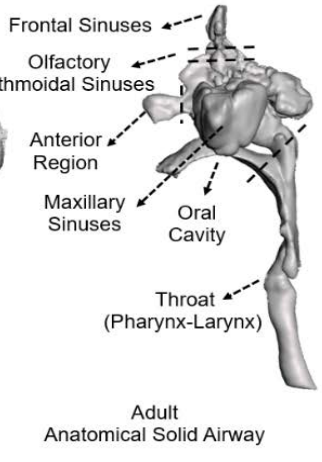
- Need to understand the local distribution of drug in the nasal airways of children with the consideration of
  - Nasal airway anatomy (detailed measurements of dimensions)
  - Aerosol plume characteristics, size distribution and velocity
  - Effect of administration protocols including the timing with reference to inhalation flow pattern (tidal volume, breaths per minute, I:E ratio, and breath hold)

Anatomical Nasal Models









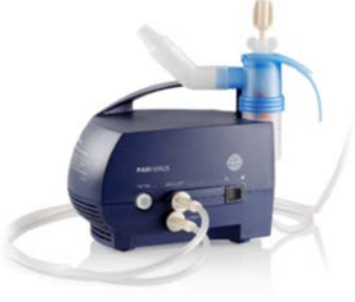
Anatomical nasal airway models have been considered as effective tools for determination of local deposition efficiency, so can contribute to identifying the range or variation in drug delivery to the region of interest.

Case Study 1: Pediatric Nasal Drug Delivery

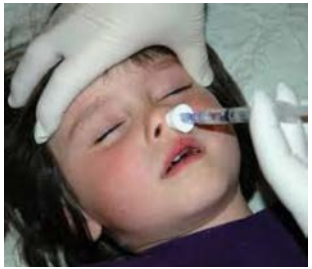
Comparative Study on Pediatric Intranasal Drug Delivery

- Nasal Sprays: Flonase®, Flonase® Sensimist™

- Nebulizers: PARI Sinustar™ and Sinus™ Pulsating Aerosol System



- Intranasal Mucosal Atomization Device (MAD Nasal™)

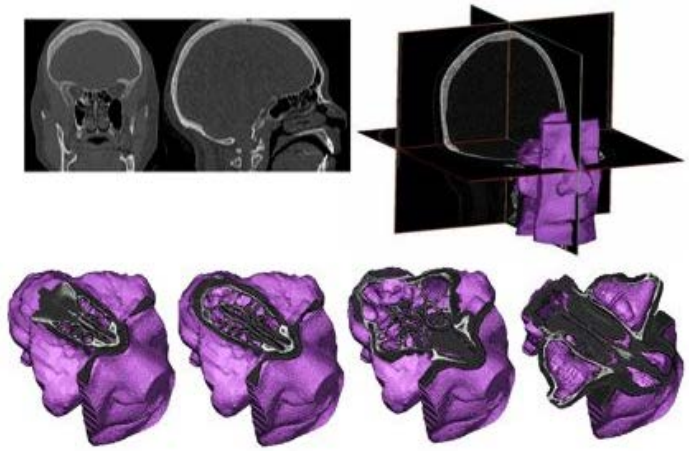


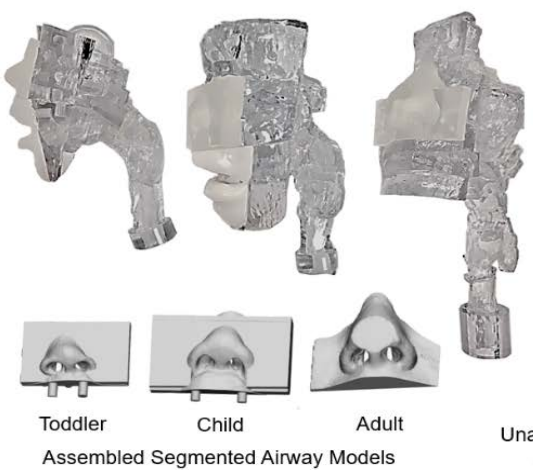
Active Pharmaceutical Ingredients (APIs)

- Flonase®: Fluticasone Propionate (50 ug per spray)
  Flonase® Sensimist™ : Fluticasone Fouroate (27.5 ug per spray)

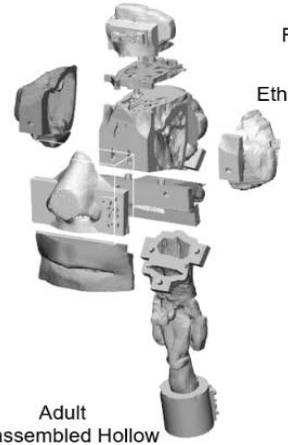
- PARI Sinustar™ and Sinus™ Pulsating Aerosol Systems: filled with albuterol sulfate (2.5 mg/ml), nebulized for 2 minutes

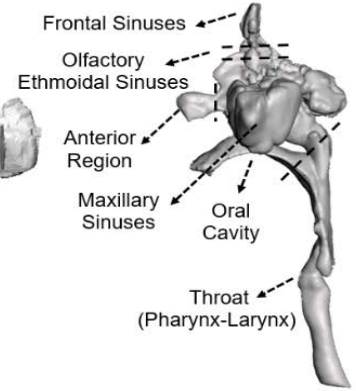
- MAD Nasal™: 0.5 ml of albuterol sulfate (50 ug/ml) in each nostril



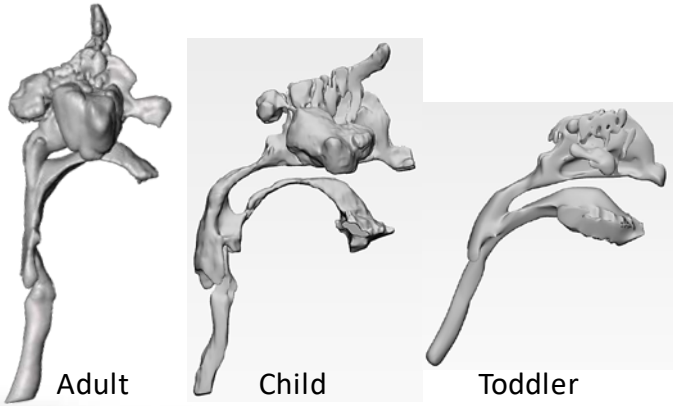


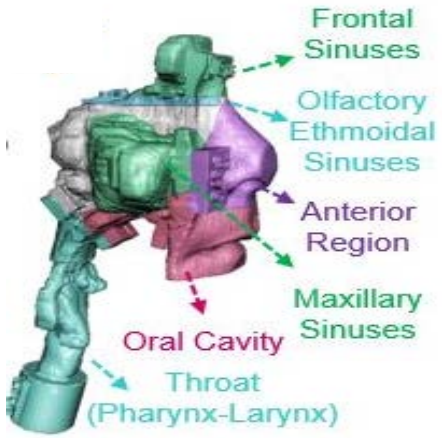
Assembled Segmented Airway Models


Adult
Unassembled Hollow
Airway Model



Adult
Anatomical Solid Airway

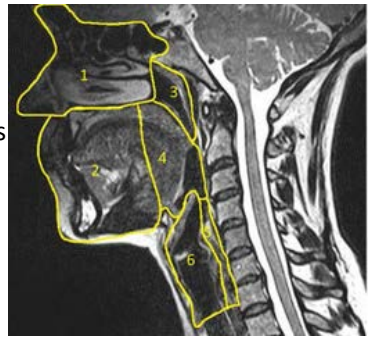




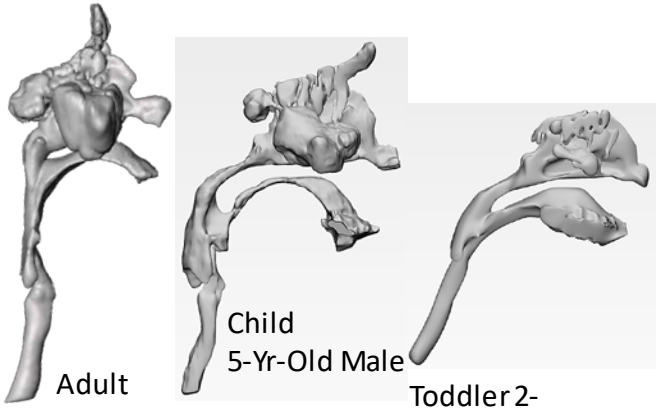
In Vitro Nasal Models in the Comparative Study

Regions	Adult		Child		Toddler	
	Volume	Surface area	Volume	Surface area	Volume	Surface area
	mm^3	mm^2	mm^3	mm^2	mm^3	mm^2
Anterior Region	2461	1713	672	871	703	789
Turbinates *	26419	27939	6484	9392	4992	9281
Olfactory	4251	5212	664	1702	359	863
Superior Turbinate **	4884	3279	3944	4654	707	1276
Maxillary Sinuses	43193	13057	14003	4887	1631	1283
Nasal Cavity ǂ	81209	51201	25770	21508	8394	13494
Throat (Pharynx-Larynx)	25942	14122	9628	5162	7013	3804
Oral Cavity	14460	7035	8263	4326	9673	3506

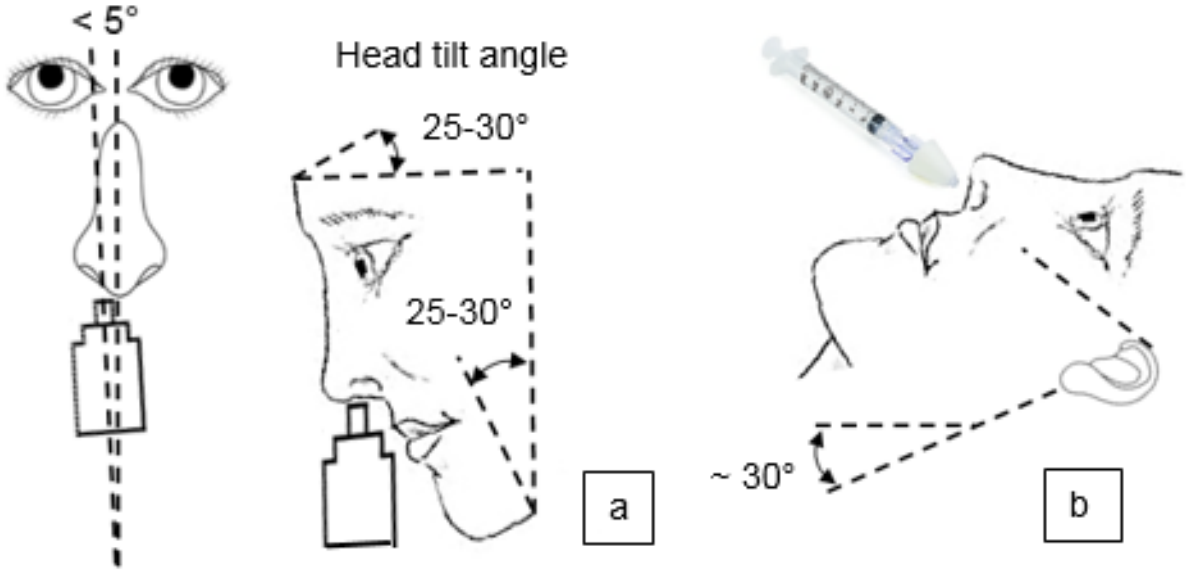
1. Nasal cavity and paranasal sinuses
2. Oral cavity
3. Nasopharynx
4. Oropharynx
5. Hypopharynx
6. Larynx



- The nasal airway models were cut into anterior region, turbinate, olfactory, maxillary sinuses, and superior turbinate including ethmoidal sinuses and frontal sinuses.
- All models were extruded 2-3 centimeters beyond the larynx



Administration of (a) Sprays and (b) MAD



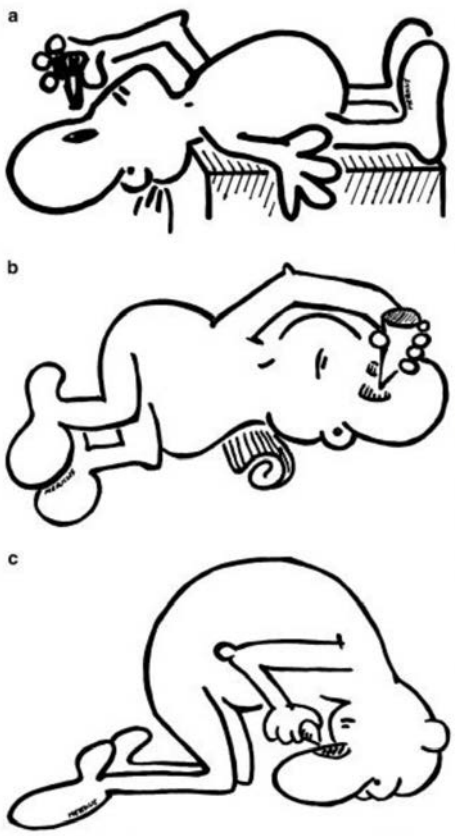
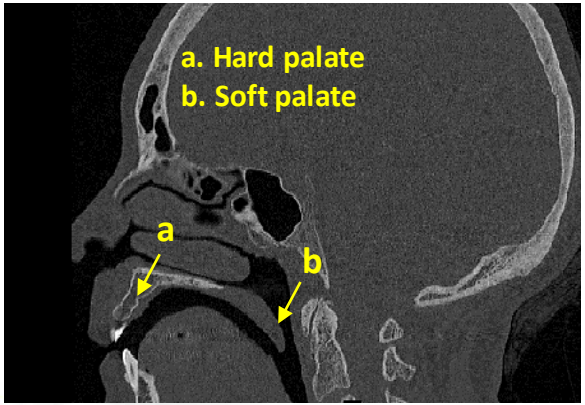


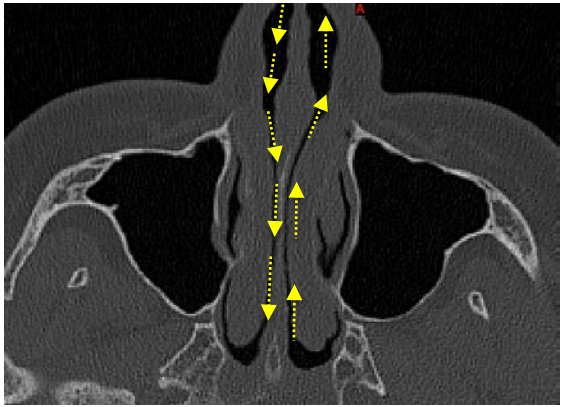
Fig. 1 Three head positions: a Lying head back (*LHB*, chin as highest point), b lateral head low (*LHL*, lying on one side), and c head down and forward (*HDF*, "praying to Mecca")

http://www.intranasal.net/DeliveryTechniques/default.htm

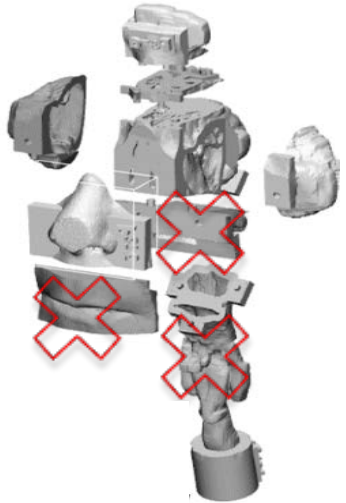
Administration of PARI Sinus™ Pulsating Aerosol System

- A secondary pulsating flow of 44.5 Hz with an amplitude of 24 mbar is superimposed to the aerosol stream in PARI Sinus™ Pulsating Aerosol System, which was disconnected to study the effect of pulsating flow.
- The contralateral nostril was semi-occluded and to simulate elevated soft palate in our *in vitro* tests, the back of nasopharynx was sealed instead of connecting the nasal cavity to the throat (pharynx-larynx) piece.
- No breathing was used with the PARI Sinus™ Pulsating Aerosol System.



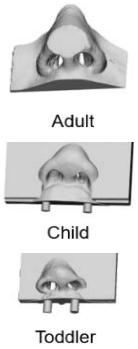


Elevated soft palate
Bidirectional breathing technique



Simulated Breathing Patterns

Subject	Gender	Age (year)	Sitting Awake			Resting (Sleeping)		
			V_t (L)	f (bpm)	$\bar{Q}$ (L/min)	V_t (L)	f (bpm)	$\bar{Q}$ (L/min)
Adult	Female	50	0.464	14	13.00	0.444	12	10.66
Child	Male	5	0.213	25	10.65	0.174	23	8.00

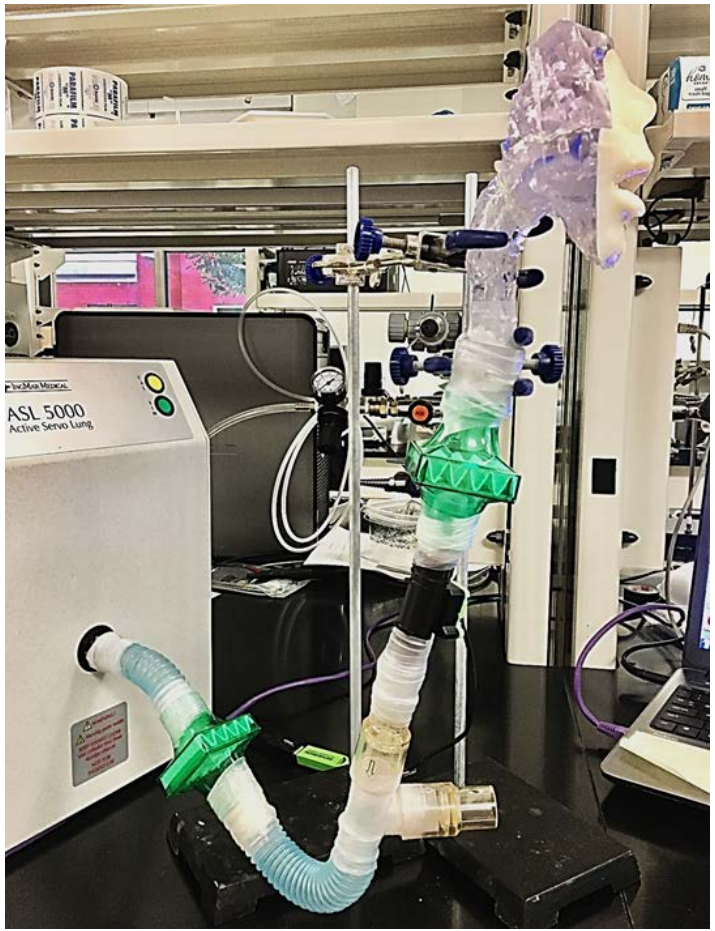


- The “sitting awake” pattern was used to test the nasal sprays and PARI Sinustar™ nebulizer.
- The “resting (sleeping)” pattern was used to test the MAD device.
- No breathing was used with the PARI Sinus™ Pulsating Aerosol System.

Deposition Measurements

- Following each experiment, the models were disassembled and assayed with known volumes of relevant solvents.

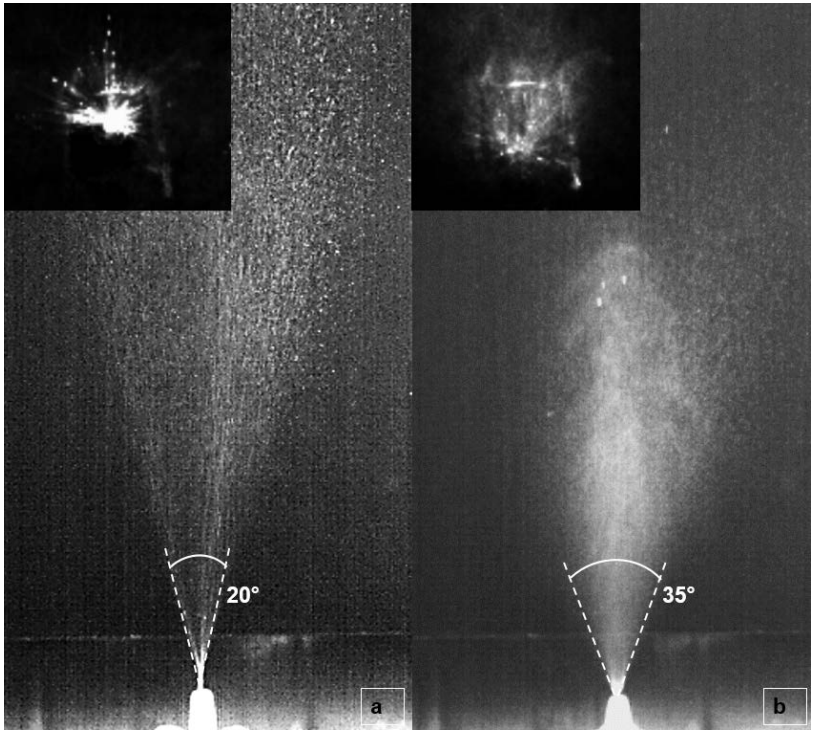
- The collected samples were analyzed by High Performance Chromatography (HPLC).



Measurement of Droplet Size and Velocity

- Size: Phase Doppler Particle Anemometry (PDPA) and Spraytec (Laser Diffraction).

- Velocity: High Speed Imaging and PDPA

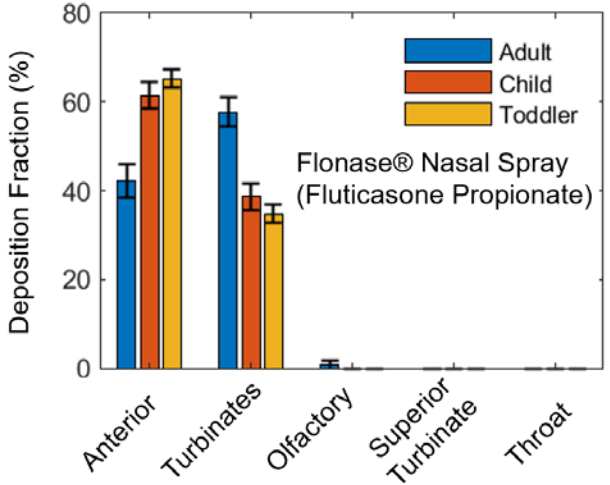


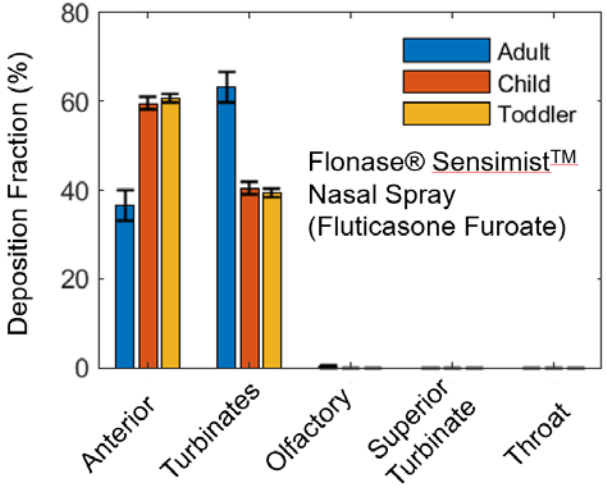
High-speed imaging of the nasal spray plume geometry and spray pattern (top-down view) at 3 cm from the spray nozzle tip a) Flonase® b) Flonase® Sensimist™ (image not in scale).

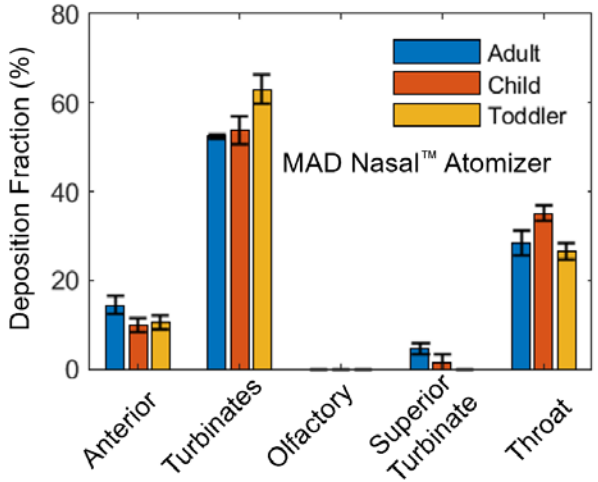
Volume-based Size Distributions of the Nasal Sprays and MAD Mean ± stdev (μm)

Method		Spraytec-3+	PDPA-3+	Spraytec-6
Flonase®	Dv_{10}	61.81 ± 1.22	72.34 ± 3.01	48.77 ± 2.04
	Dv_{50}	126.23 ± 2.90	116.99 ± 14.88	120.97 ± 4.89
	Dv_{90}	176.73 ± 5.67	167.78 ± 2.75	177.41 ± 7.16
Flonase® Sensimist™	Dv_{10}	22.46 ± 0.36	37.91 ± 6.55	24.45 ± 0.36
	Dv_{50}	57.11 ± 1.25	65.20 ± 9.59	46.46 ± 0.80
	Dv_{90}	101.85 ± 1.46	122.73 ± 24.27	91.62 ± 1.50
MAD Device	Dv_{10}	97.74 ± 2.70	-	-
	Dv_{50}	164.06 ± 4.53	-	-
	Dv_{90}	215.31 ± 1.89		-

Measurements at 3 cm from the spray tip	Flonase®	Flonase® Sensimist™	MAD Atomizer
High Speed Imaging	10.93 ± 2.34 m/s	9.48 ± 2.11 m/s	3.50 ± 0.27 m/s
PDPA-3	14.53 ± 1.80 m/s	14.43 ± 1.79 m/s	-







	Shot Weight (mg)	Percent Recovery (%)
Flonase®	93.64 ± 1.34	94.23 ± 1.82
Flonase® Sensimist™	54.84 ± 1.25	93.16 ± 2.34
MAD Nasal™	-	96.19 ± 1.73

Measurement of Droplet Size and Velocity

	PARI Sinus™ Pulsating Aerosol Nebulizer				PARI SinuStar™ Aerosol Nebulizer			
Measurement Method	D_{10}	D_{50}	D_{90}	GSD	D_{10}	D_{50}	D_{90}	GSD
	(μm)				(μm)			
Spraytec-3	0.86 ± 0.02	3.79 ± 0.03	8.95 ± 0.06	2.51 ± 0.02	1.07 ± 0.07	4.16 ± 0.03	9.26 ± 0.19	2.36 ± 0.07
PDPA-3	0.87 ± 0.04	3.77 ± 0.10	8.44 ± 0.43	2.33 ± 0.25	1.74 ± 0.04	4.36 ± 0.10	8.78 ± 0.36	1.95 ± 0.04
PDPA-NP-3	0.72 ± 0.22	3.56 ± 0.15	7.93 ± 0.45	2.54 ± 0.23	-	-	-	-
PDPA-6	0.62 ± 0.15	3.55 ± 0.19	7.93 ± 0.69	2.63 ± 0.14	-	-	-	-

PDPA-3	1.24 ± 0.05 m/s	0.53 ± 0.15 m/s
PDPA-NP-3	0.99 ± 0.18 m/s	-
PDPA-6	0.66 ± 0.03 m/s	-

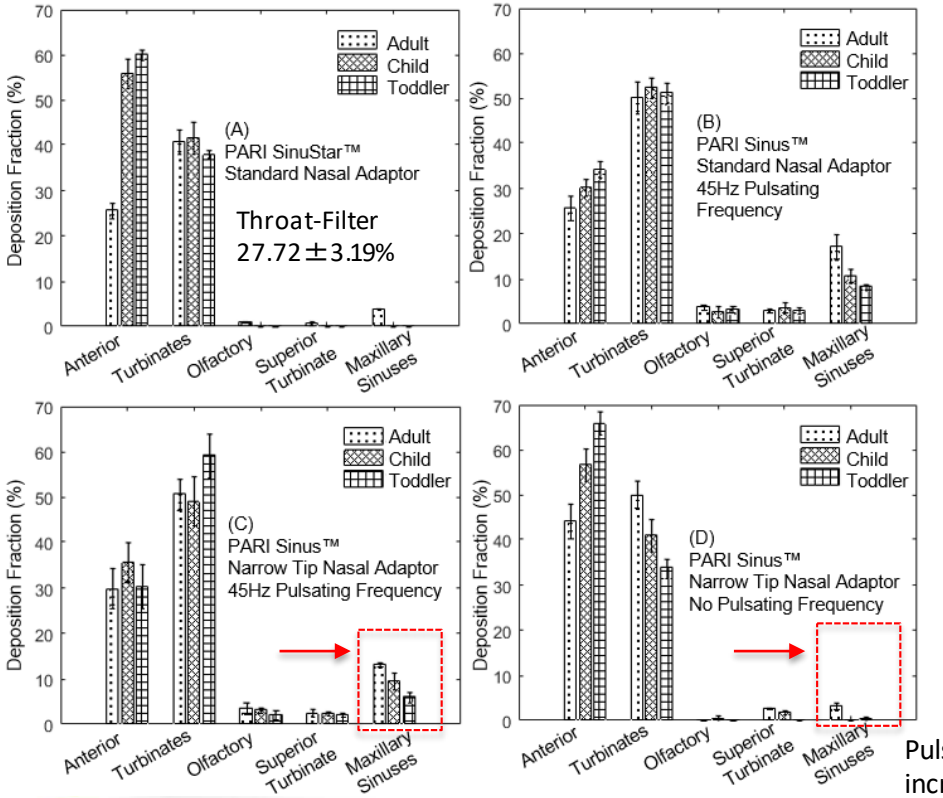
[I] Statistically significant differences between all components of particle size distributions of the two nebulizers (p<0.05).

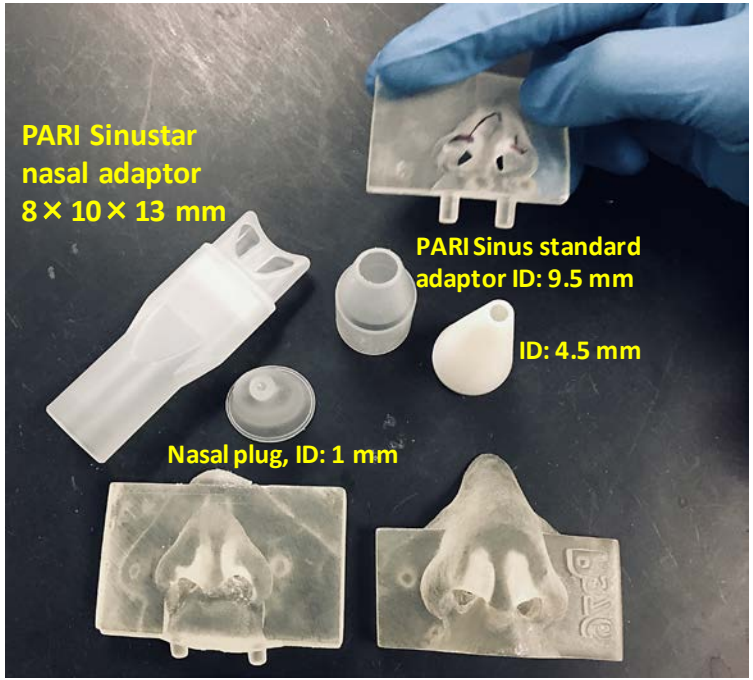
[+] Statistically significant differences between Spraytec-3 and PDPA-3 measurement methods for the PARI SinuStar™ nebulizer (p<0.05).

[†] Statistically significant differences between PDPA-NP-3 and PDPA-3 (p<0.05).

[‡] Statistically significant differences between PDPA-6 and PDPA-3 (p<0.05).

Results – Deposition Patterns





	Mass Output (mg)	Recovery (%)
A	1031.76 ± 79.46	5.19 ± 0.85
B	433.18 ± 17.26	10.35 ± 1.75
C	252.33 ± 13.67	68.41 ± 13.56
D	411.78 ± 14.81	31.42 ± 12.75

Pulsating airflow significantly increased maxillary sinus delivery values from zero to 9.61±1.92%, and 6.06±1.21% for pediatric models.

Conclusions

- Nasal sprays are not efficient for the pediatric population and they result in significant (~60%) anterior losses.

- MAD atomizer resulted in significantly less anterior deposition compared to the nasal sprays, but run off to the throat should be considered, which depends on the volume and viscosity of formulation.

- Paranasal delivery was significantly enhanced using pulsating nebulization under bidirectional breathing administration technique for all subjects.

Case Study 2: Intersubject Variability in Deposition of Nasal Sprays in Adults

Bioequivalence and Bioavailability of Nasal Sprays/Aerosols for Local Action

- *Bioequivalence (BE):* "the absence of a significant difference in the **rate and extent** to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes **available at the site of drug action** when administered at the **same molar dose under similar conditions** in an appropriately designed study."[1]

- *Bioavailability (BA):* "For drug products that are **not intended to be absorbed** into the bloodstream, bioavailability may be assessed by measurements intended to reflect the **rate and extent** to which the active ingredient or active moiety becomes **available at the site of action**."[1]

[1] FDA Draft Guidance (2003): Guidance for Industry (Draft). Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action.

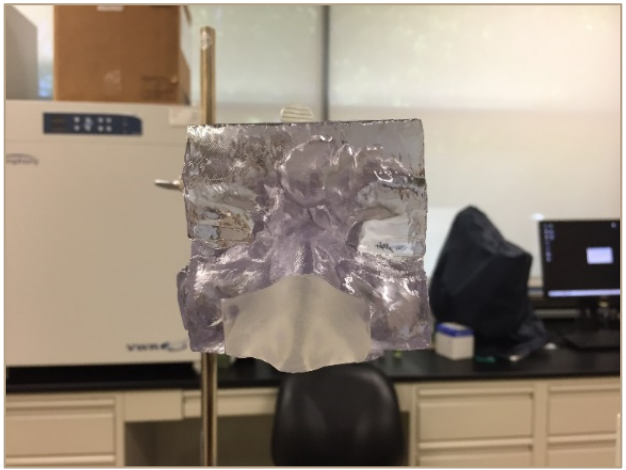
Pathway to a Biopredictive *In vitro* Bioequivalence Methods

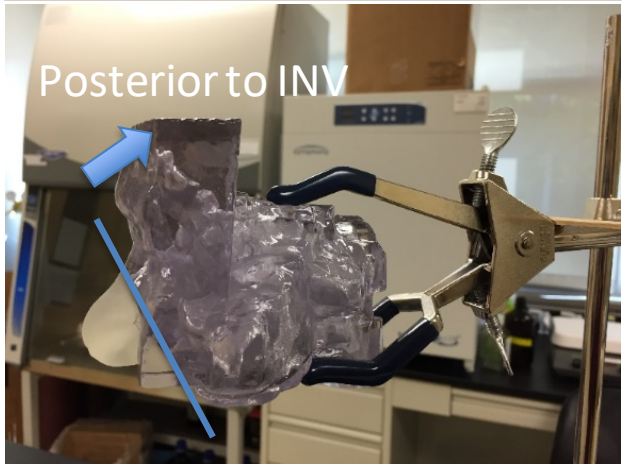
- Currently recommended *in vitro* BE tests are part of a rigorous weight of evidence approach, that emphasize spray properties e.g. angle, width, or ovality ratios, but are evaluated outside and independent of the nasal cavity.

- To make *In vitro* assessment predictive of *in vivo* local nasal deposition BE methods may need to incorporate
  - The critical interactions between device and nasal airways while accounting for patient use conditions (administration) and formulation
  - Inter- and intra-subject variability in airway anatomy and breathing

Printed Nasal Models

The posterior regions of the twenty nasal models printed in clear resin



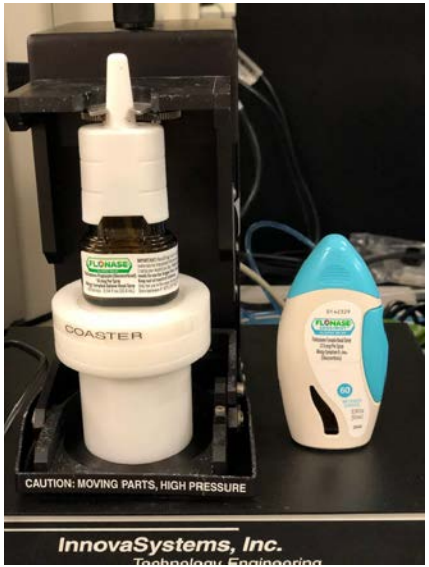


The front and side view of Model 1 in the final printed form in two pieces: anterior and posterior pieces.

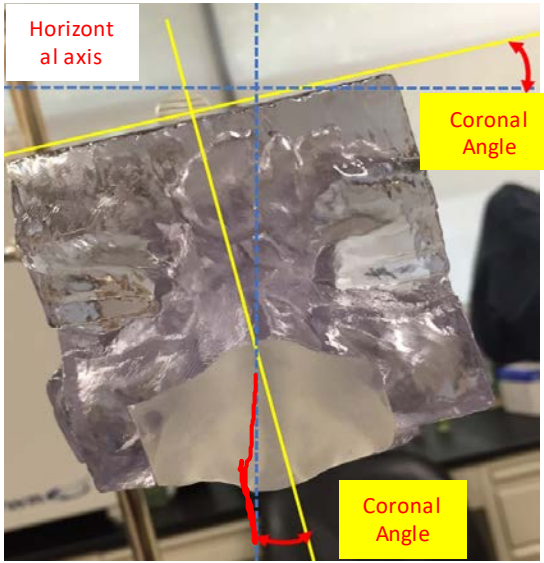
Nasal Spray Products

Flonase ®
API: Fluticasone Propionate (FP)
Nominal Dose: 50 μg of FP in each 100 mg Spray
Spray Volume: 100 μL
Recommended Dosage: 2 sprays per nostril once daily

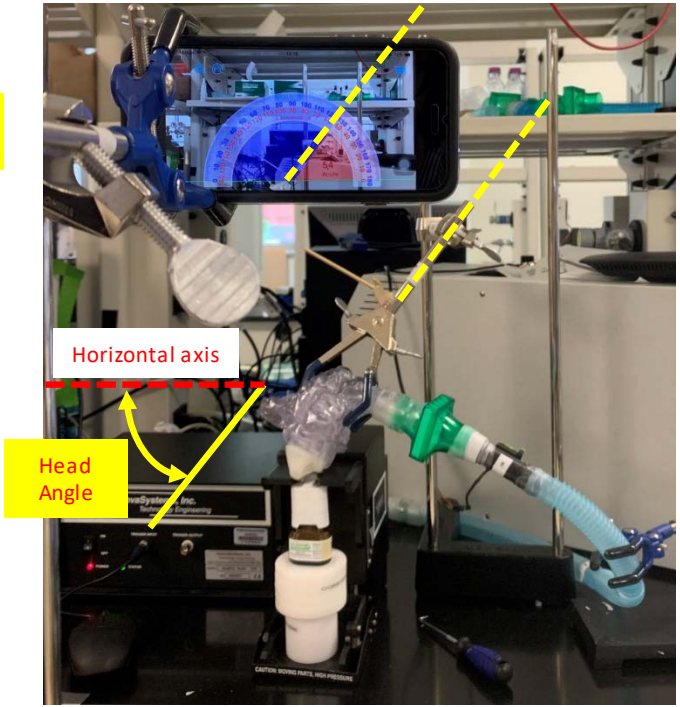
Flonase ® Sensimist ™
API: Fluticasone Furoate (FF)
Nominal Dose: 27.5 μg per spray
Spray Volume: 50 μL
Recommended Dosage: 2 sprays per nostril once daily



Administration of Sprays and Setup



Coronal Angle



Average (standard deviation, SD) of total recovered dose as well as the average (SD) and range of posterior deposition

Side of Septum in 20 Subjects	Left		Right		
Nasal Spray	Flonase	Flonase Sensimist	Flonase		Flonase Sensimist
Actuation Force (kg)	7.2 kg	N/A	5.8 kg	7.2 kg	N/A
Total Recovery (% Labeled Dose)	94.4 (3.2)	94.4 (5.2)	95.6 (3.8)	93.4 (3.7)	89.4 (4.6)
Posterior Deposition (% Recovered Dose)	47.7 (23.3)	61.3 (16.0)	52.1 (21.2)	57.1 (23.7)	57.8 (15.9)
[Range]	[12-99%]	[42-92%]	[23-87%]	[22-91%]	[29-92%]

Conclusions

- A wide range of posterior delivery was observed using both Flonase and Flonase Sensimist.

- The results show the importance of the nasal airway anatomy in determining the fraction of delivered dose reaching the region posterior to the nasal valve.

- Anatomical airway geometries and interaction of device with anterior region may need to be considered in order for currently recommended BE test methods to be more biopredictive with respect to locally-acting drugs.

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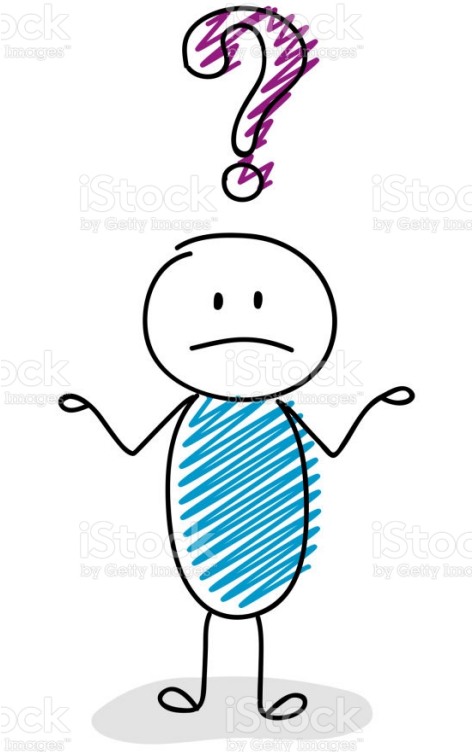

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For consulting, collaborations, and any questions please do not hesitate to contact me at LGOLSHAHI@VCU.EDU or (804) 827-3742.

Thank you!