In Vitro Bioequivalence Testing of Nasal Sprays Using Multiple Anatomically-Correct Nasal Airway Models

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VCU College of Engineering

Laleh Golshahi, Michele D Manniello, Sana Hosseini, Ali Alfaifi, Theodore A. Schuman, Michael Hindle, Worth Longest, and Dennis Sandell

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[1] FDA Draft Guidance (2003): Guidance for Industry (Draft).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

- Current *in vitro* BE tests are based on a rigorous weight of evidence approach, emphasizing on spray properties e.g. angle, width, or ovality ratios, but evaluated outside and independent of 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

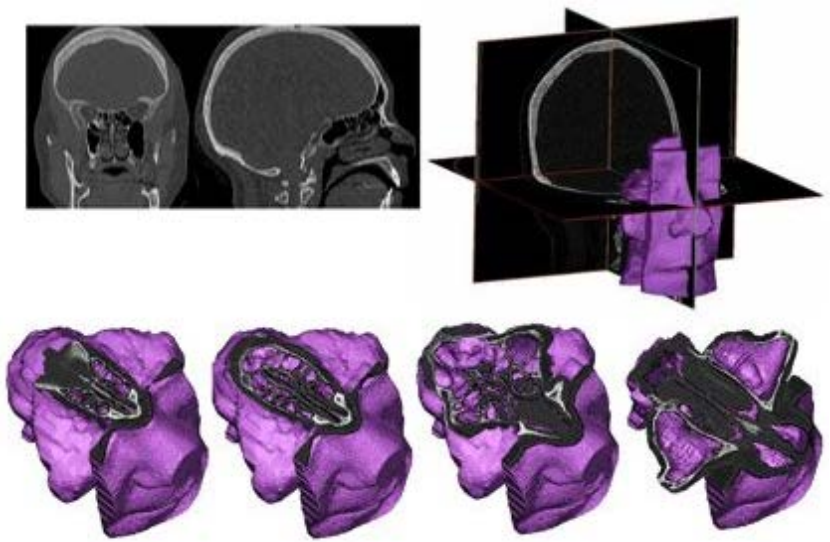
Objectives

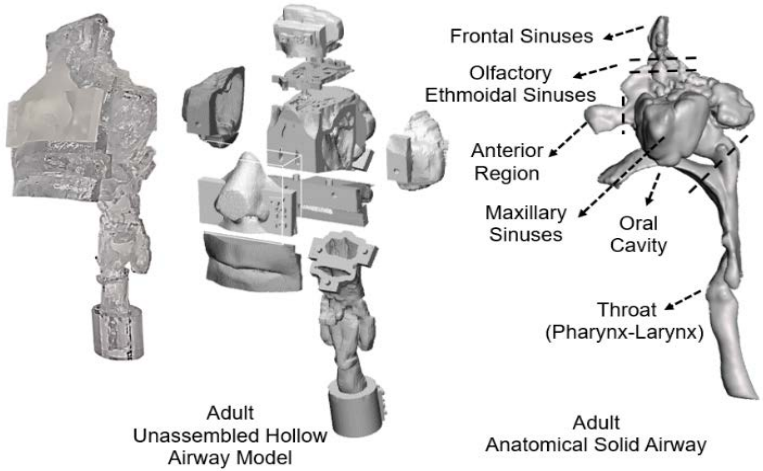
- Develop low cost and controlled *in vitro* test methods, closely replicating *in vivo* delivery of locally-acting drugs (e.g. corticosteroids), allowing comparison of test and reference products.

- Identify the range of posterior delivery efficiency (i.e. drug delivered to the region posterior to the nasal valve) using two nasal spray products with different spray properties administered to multiple anatomical nasal models.

- Rank and compare the ranking of nasal cavities based on their resulting posterior delivery using the two different products.

Anatomical Nasal Models

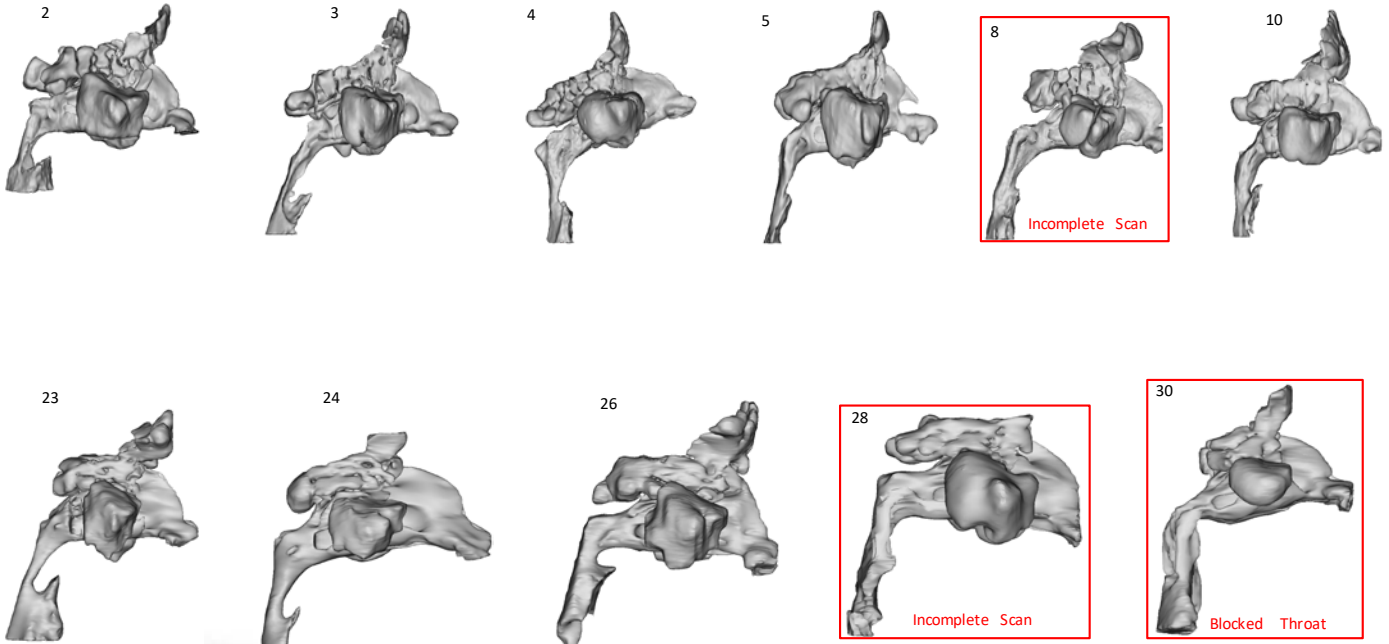




Anatomical nasal airway models have been considered as effective tools for determination of local deposition efficiency, so can contribute to identifying the range or variation in drug delivery to the region of interest.

Solid Nasal Airway Models in STL

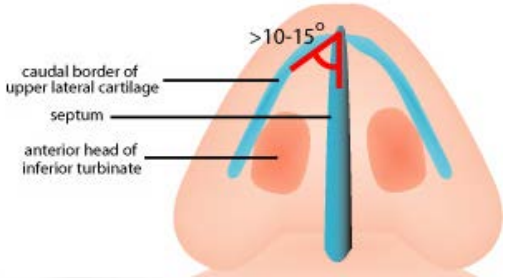
- 42 scans were screened to select the final 20 adult subjects with healthy nasal airways (50% female and 50% ≥50 years, age range 21–75 years old)



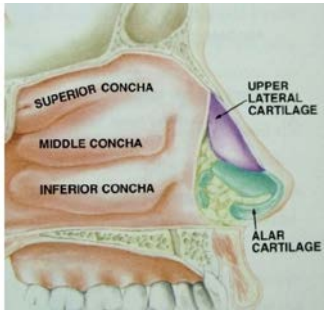
Identification of the Internal Nasal Valve (INV)

Initially, based on the rhinology literature,[1,2] an oblique coronal plane perpendicular to the bony nasal dorsum was intended to be used to define the internal nasal valve (INV) as the region in the cross-sectional plane just before the inferior turbinate on the right side of the patient starts appearing in the plane.

In order to consider the anatomical regions shown below, forming INV, and obtaining the minimum cross-sectional area (A_{min}), the process of cutting the anterior region had to be modified.



https://www.lamfacialplastics.com/

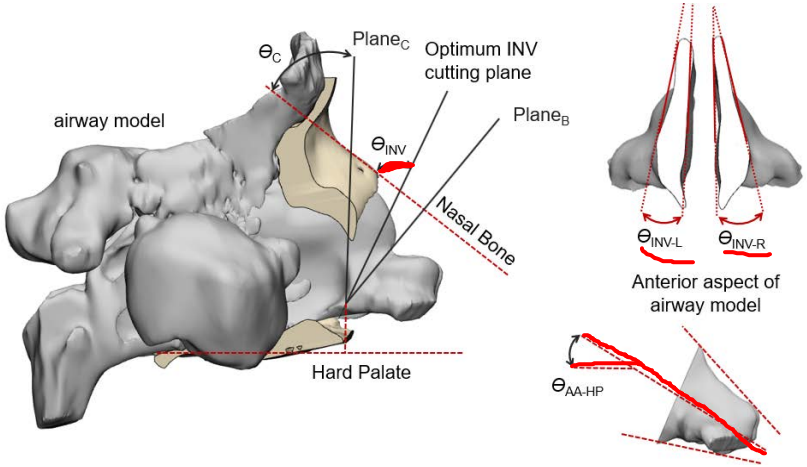


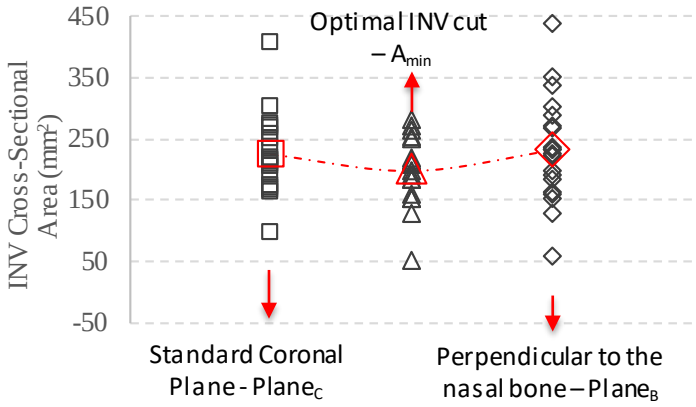
https://www.slideshare.net/godplaywei/surgical-anatomy-of-the-nose-2335808

1. Poetker et al. 2004, Computed tomography technique for evaluation of the nasal valve. *Arch. Facial Plast. Surg*.

2. Cakmak et al. 2003, Value of acoustic rhinometry for measuring nasal valve area. *Laryngoscope*.

Assessment of the Internal Nasal Valve (INV)



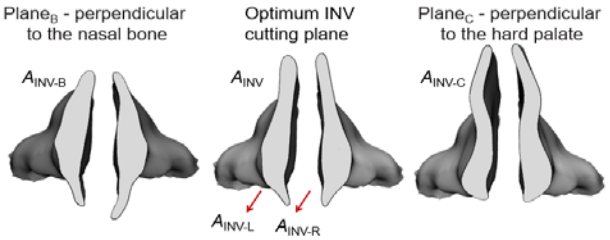


- Nasal Valve Angle (NVA): $\theta_{NVA} = 10.87 \pm 6.19^\circ$
  Poetker et al. (2004): $8.3 \pm 2.0^\circ$
  Classical range: 10-15°

  Poetker et al., Computed tomography technique for evaluation of the nasal valve. *Arch. Facial Plast. Surg.*

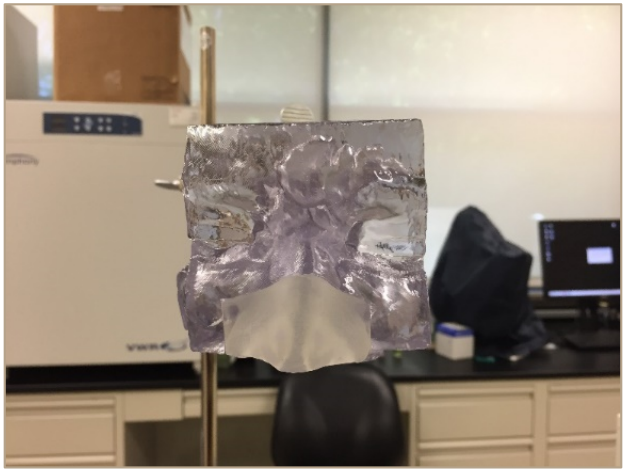
- Acoustic Axis: $\theta_{AA-HP} = 40.20 \pm 7.06^\circ$
  Cakmak et al. (2003): 45-55° for 25 healthy subjects

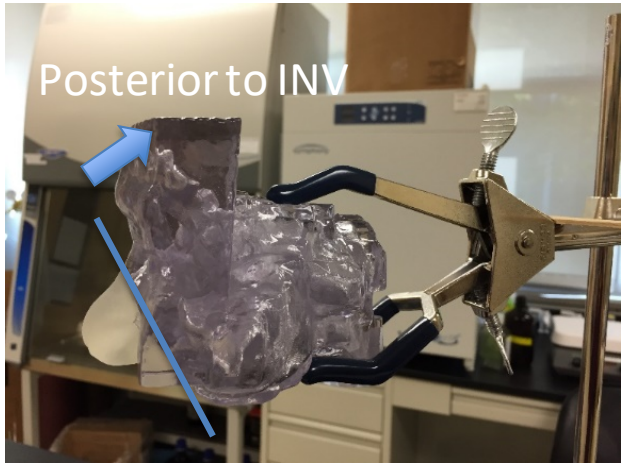
  Cakmak et al. Value of acoustic rhinometry for measuring nasal valve area. *Laryngoscope.*



Printed Nasal Models

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



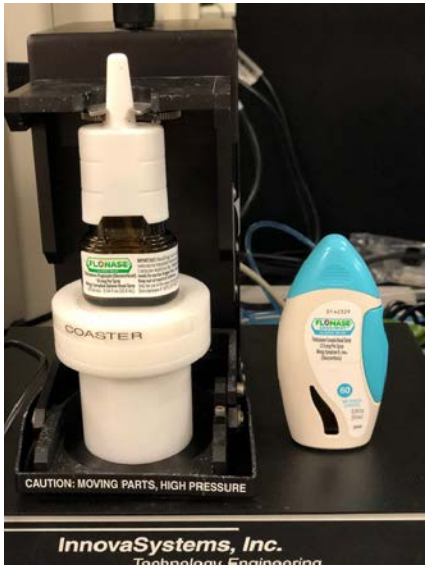


The front and side view of Model 1 in the final printed form in two pieces: anterior and posterior pieces.

Nasal Spray Products

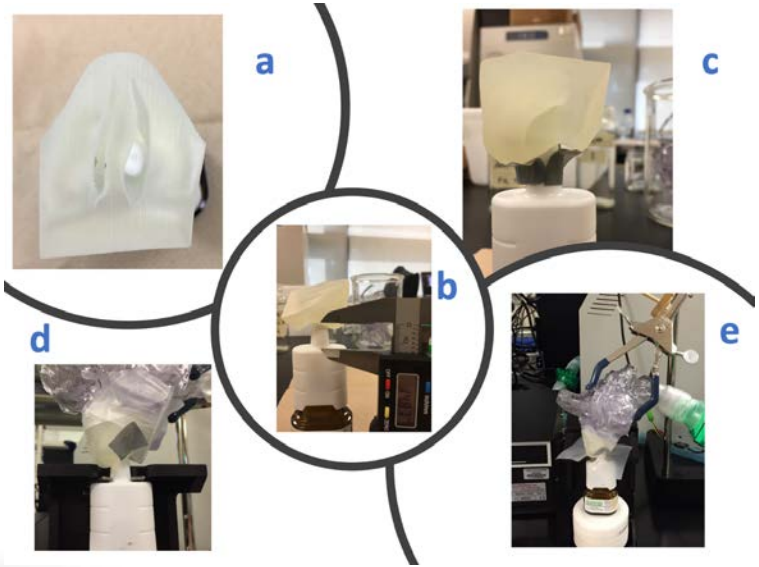
Flonase ®
API: Fluticasone Propionate (FP)
Nominal Dose: 50 μg of FP in each 100 mg Spray
Spray Volume: 100 μL
Recommended Dosage: 2 sprays per nostril once daily

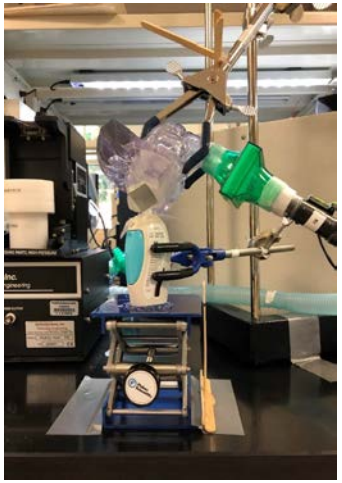
Flonase ® Sensimist ™
API: Fluticasone Furoate (FF)
Nominal Dose: 27.5 μg per spray
Spray Volume: 50 μL
Recommended Dosage: 2 sprays per nostril once daily



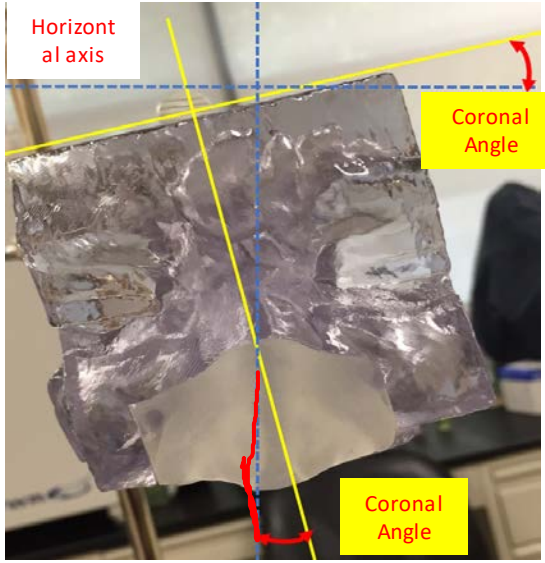
Insertion of Nasal Sprays through Nostrils

The mean (SD) of the insertion depth for Flonase was 15.1 (2.6) mm, whereas for Sensimist the nozzle, with the length of 12.5 mm, was inserted all in.

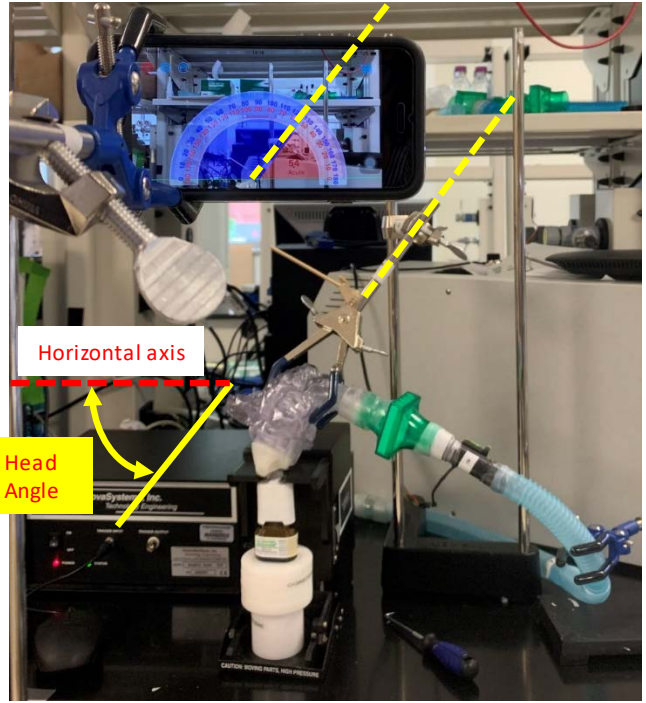




Administration of Sprays and Setup



Coronal Angle



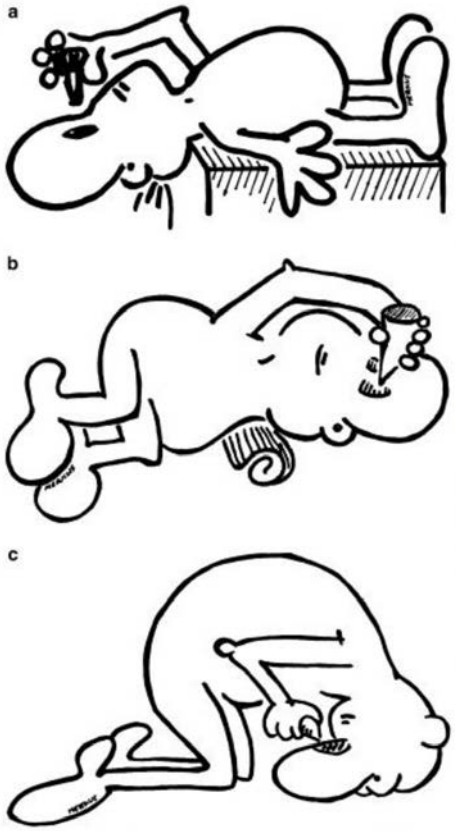
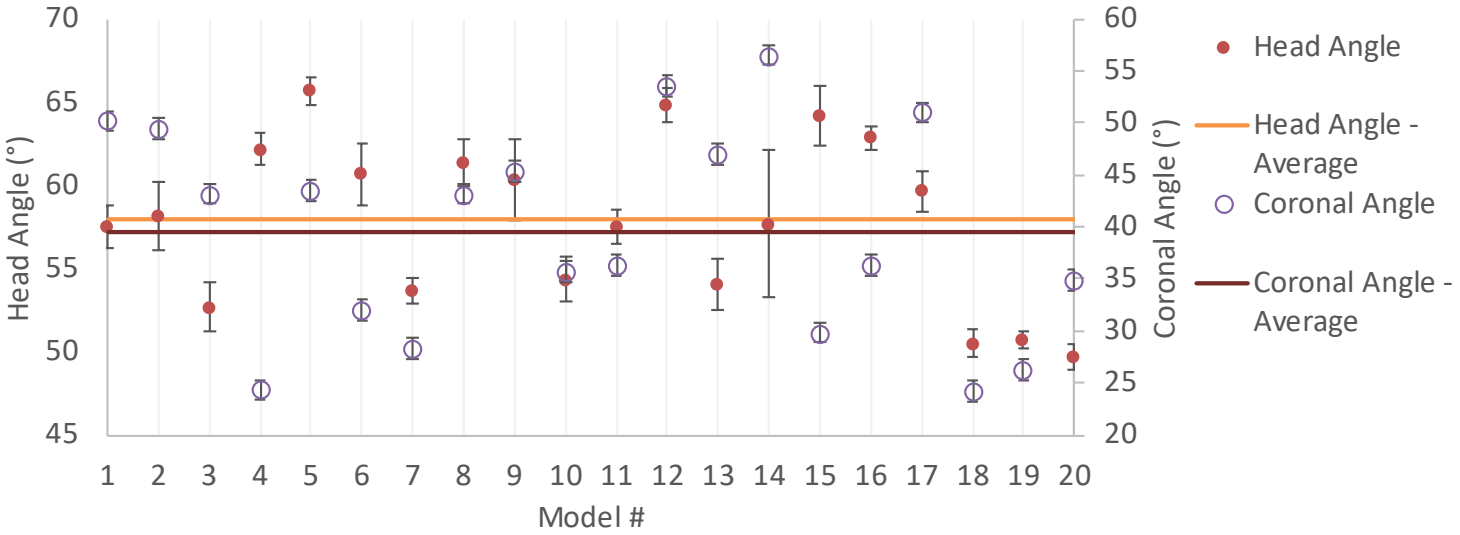


Fig. 1 Three head positions: **a** Lying head back (*LHB*, chin as highest point), **b** lateral head low (*LHL*, lying on one side), and **c** head down and forward (*HDF*, "praying to Mecca")

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

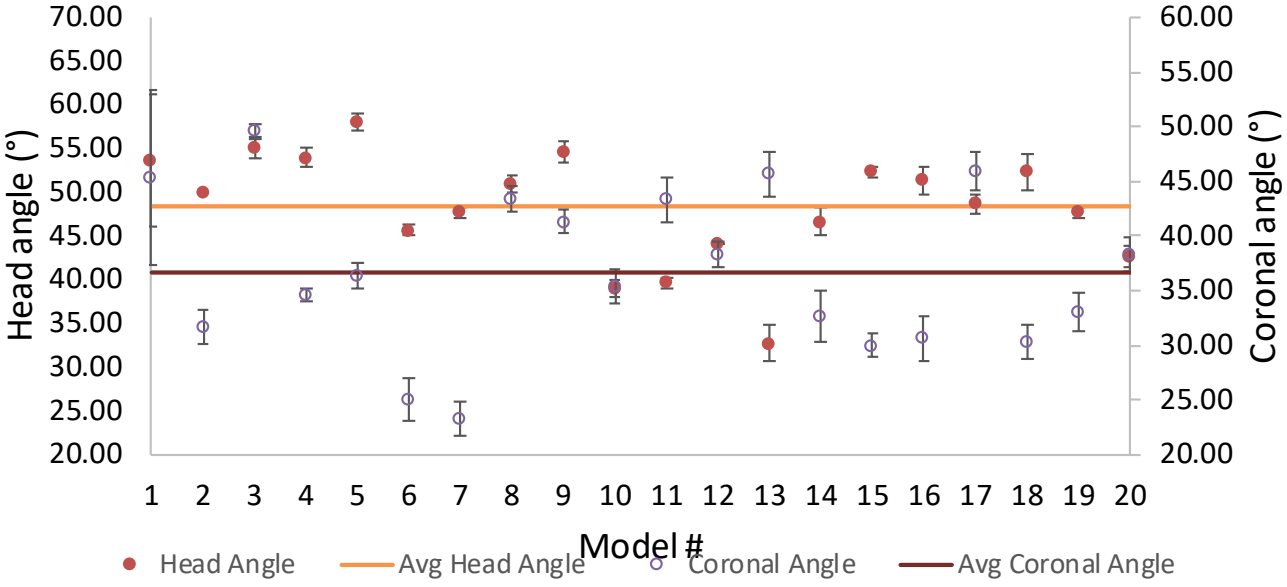
Head and Coronal Angles: Flonase®

The mean (SD) and range of head angles: 58 (5)˚ , 50-66˚
The mean (SD) and range of coronal angles: 39 (10)˚ , range 24-57˚



Head and Coronal Angles: Flonase® Sensimist™

The mean (SD) and range of head angles: 48 (6)° , range: 33-58°
The mean (SD) and range of coronal angles: 37 (7)° , range: 23-50°



Actuation of Sprays: Force Profile and Timing Relative to Breathing

Table 1

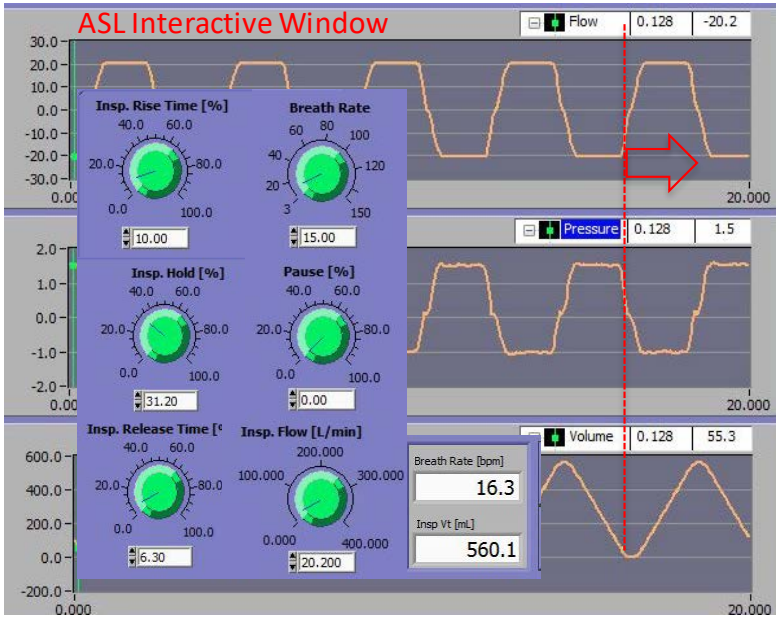
Inhalation parameters from breathing patterns of nine healthy adult volunteers with one nostril blocked and the breathing through one nostril following two types of instructions "breathe gently through your nose with your mouth closed" or to "breathe vigorously through your nose with your mouth closed" from Guo *et al* [12].

Breathing pattern	Tidal volume (mL)	PIF (L/min)	T_{max} (s)	T_d (s)	Slope (L/min s)
Slow (gently)	560.6±260.3	20.2±8.0	0.4±0.5	1.9±1.0	50.9±29.9
Fast (vigorously)	619.1±517.7	35.8±14.1	0.3±0.4	1.2±0.6	133.6±61.3

Table 2

Velocity- and Force-Controlled settings calculated from 20 adults hand data actuating Flonase ® by Doughty *et al* [11].

Velocity-Controlled Settings	Mean (SD) adult settings	Force-Controlled Settings	Mean (SD) adult settings
Travel/Actuation length (mm)	5.6 (0.4)	Actuation Force (kg)	5.8 (1.4)
Compression velocity (mm/s)	41.9 (13.5)	Force rise time (s)	0.3 (0.1)
Velocity hold time (s)	0.2 (0.1)	Force hold time (s)	0.1 (0.0)
Release velocity (mm/s)	34.9 (8.9)	Force fall time (s)	0.2 (0.1)



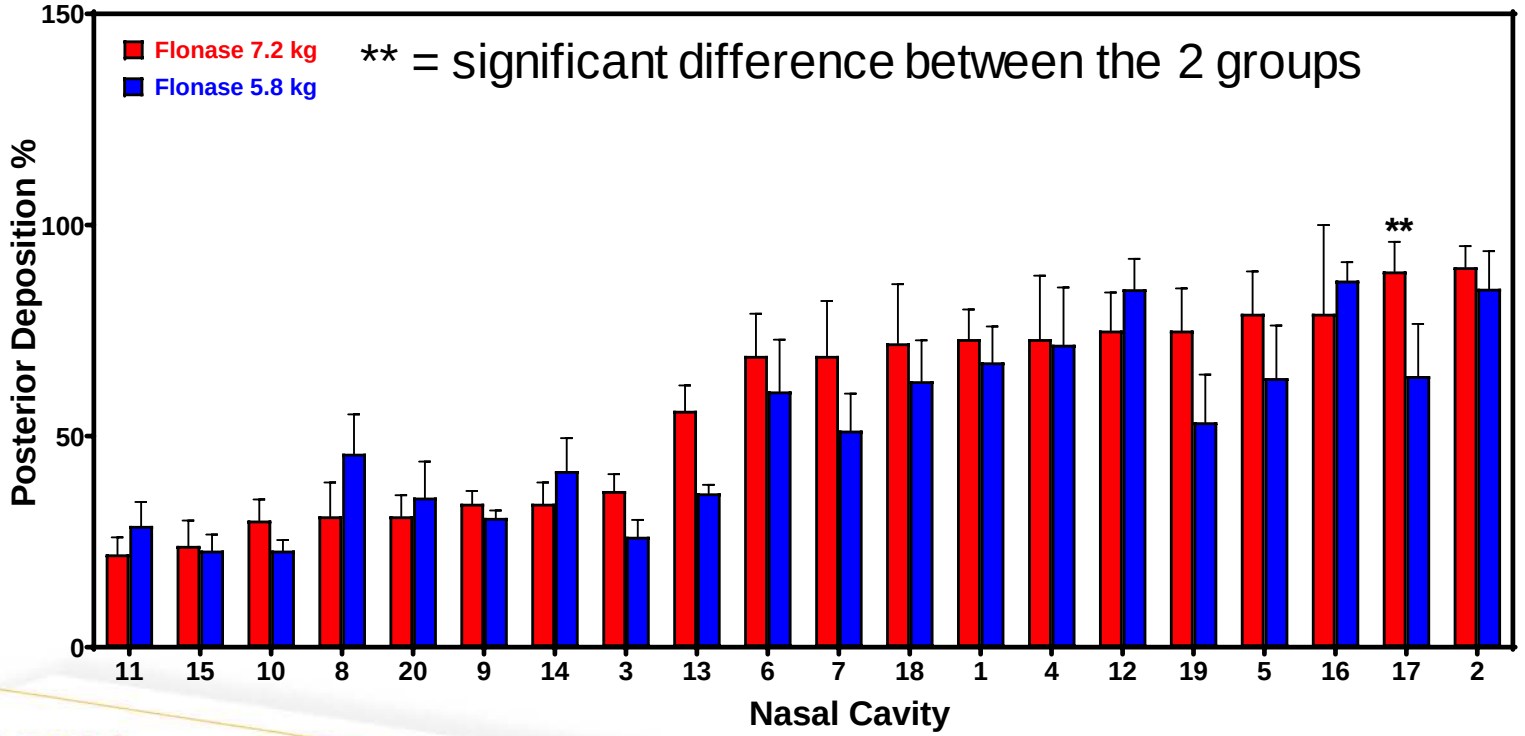
Doughty et al. *Drug Dev Ind Pharm* 2011, 37: 359-66.

Guo et al. *Pharm Res* 2005, 22: 1871-8.

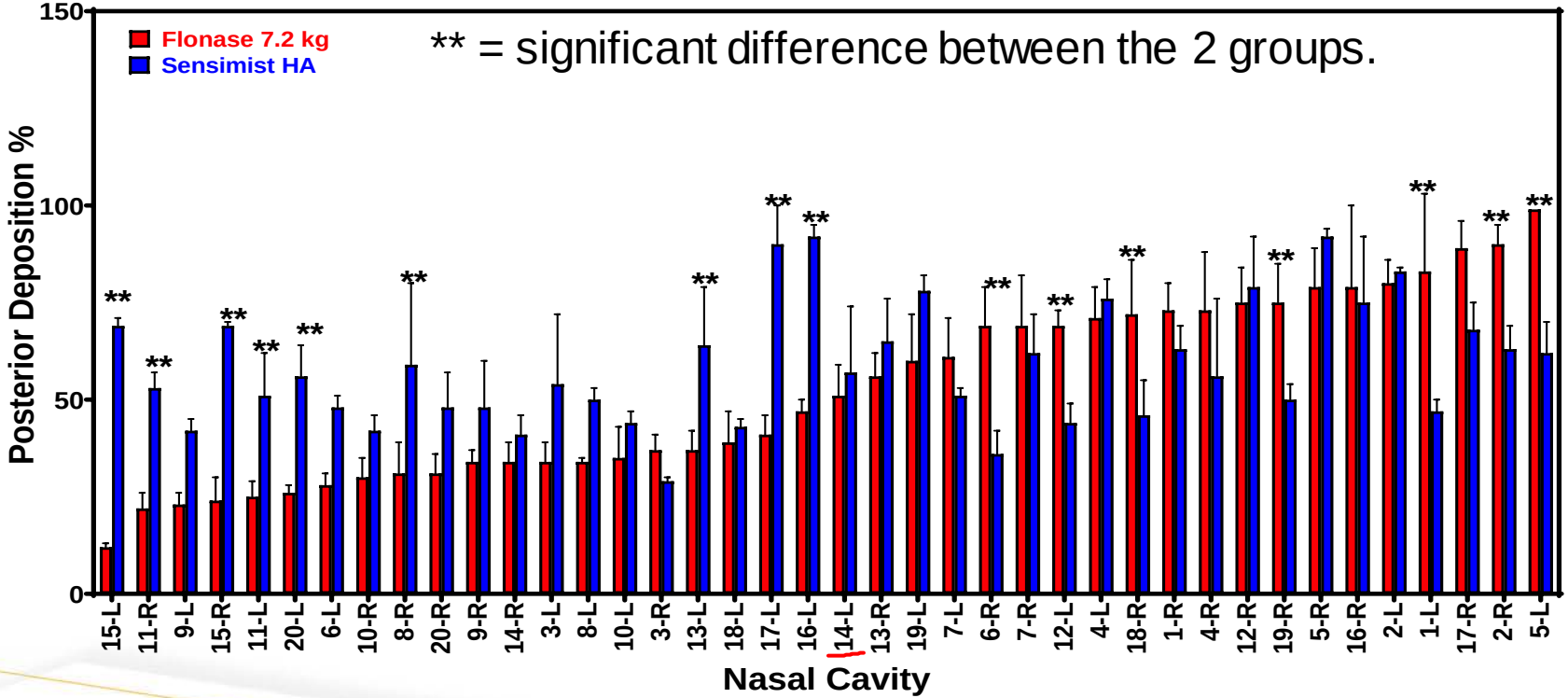
Average (standard deviation, SD) of total recovered dose as well as the average (SD) and range of posterior deposition

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%]

Posterior Deposition Sorted in Ascending Order for Flonase-7.2 kg vs Flonase-5.8 kg in the Right Side of Nasal Models



Posterior Deposition Sorted in Ascending Order for Flonase-7.2 kg vs Flonase Sensimist

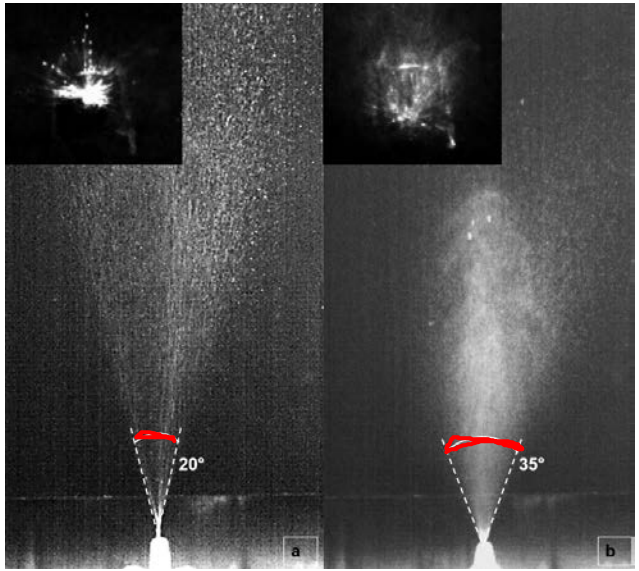


Droplet Size Distribution (DSD)

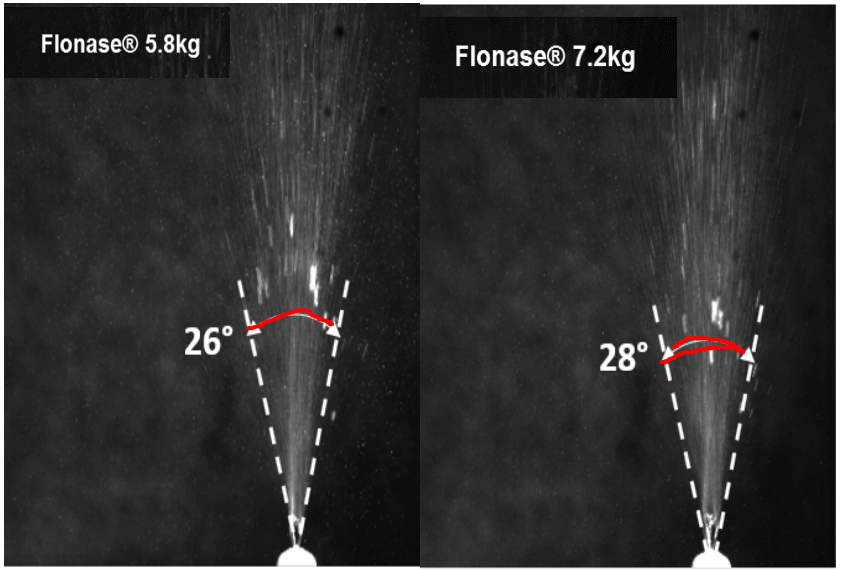
- Mie-based laser diffraction measurement, using Malvern Spraytec® (Malvern Instruments, Inc., Southborough, MA).
- D_{v50} at 6 cm < 3 cm (for both beginning and mid-life).
- D_{v50} at 7.2 kg < 5.8 kg for both 3 cm and 6 cm, but no significant difference in D_{v50} at the two actuation forces.
- D_{v50} Mid-Life< Beginning for both 3 cm and 6 cm.
- Flonase® Sensimist™ showed similar trends.

Product	Flonase			
Container Life	Beginning		Mid-Life	
Actuation Force	5.8 kg force			
Actuation Distance	3 cm	6 cm	3 cm	6 cm
D_{v50} (µm)	71.3 (1.1)	61.9 (2.2)	57.8 (11.1)	53.7 (3.4)
Span	1.3	1.2	1.4	1.4
Actuation Force	7.2 kg force			
Actuation Distance	3 cm	6 cm	3 cm	6 cm
D_{v50} (µm)	65.7 (2.6)	61.1 (2.2)	49.6 (5.4)	49.3 (5.5)
Span	1.4	1.3	1.5	1.4
Product	Flonase Sensimist			
Container Life	Beginning		Mid-Life	
Actuation Force	Hand Actuated			
Actuation Distance	3 cm	6 cm	3 cm	6 cm
D_{v50} (µm)	70.8 (1)	60.4 (2.9)	59.8 (2.1)	54.1 (0.2)
Span	1.2	1.2	1.3	1.3

Plume Angles using High Speed Imaging



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™ both hand-actuated (image not in scale).



Measurement of plume angles using high-speed imaging of Flonase® at 5.8 and 7.2 kg actuations forces (image not in scale).

Measurement of Plume Geometry and Spray Patterns using SprayVIEW®

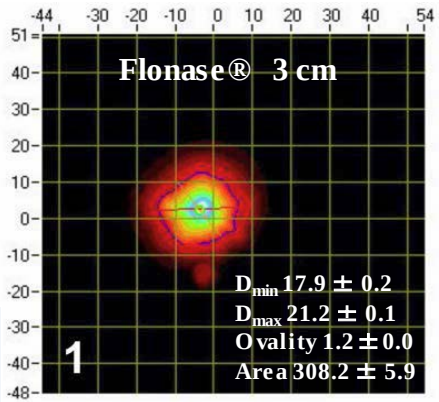
- SprayVIEW Measurement Systems
  - Equipped with Proveris Vereo® Automated Actuator Systems
  - Works with a velocity-controlled actuator, but deposition data with Flonase were taken using force-controlled actuations and Sensimist was hand-actuated.
  - All 250 images were captured at 500 Hz

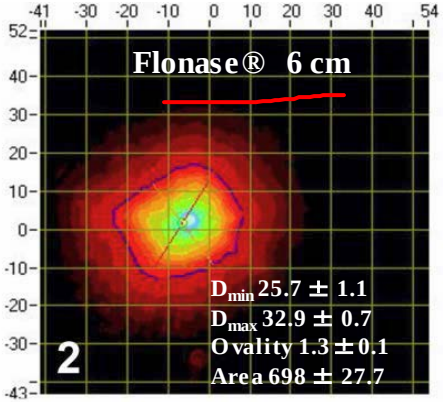
https://www.proveris.com/sprayview-measurement-systems/

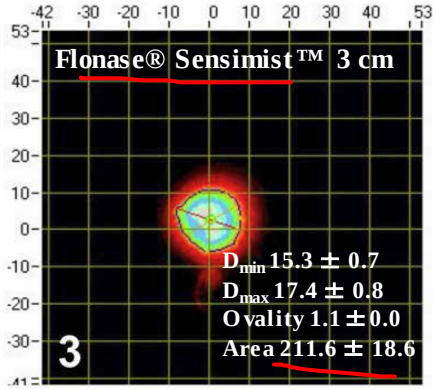
Results of SprayVIEW® Measurements: Spray Pattern

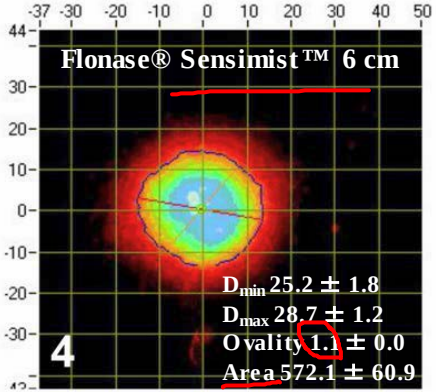
Flonase® vs Flonase® Sensimist™
at 7.2 kg actuation force.

Device	Force	D_{min} (mm)	D_{max} (mm)	Ovality	Area (mm^2)
Flonase	7.2 kg	45.6 ± 1.9	32.9 ± 0.7	1.3 ± 0.1	698.2 ± 27.7
Flonase Sensimist	7.2 kg	25.2 ± 1.8	28.7 ± 1.2	1.1 ± 0	572.1 ± 60.9

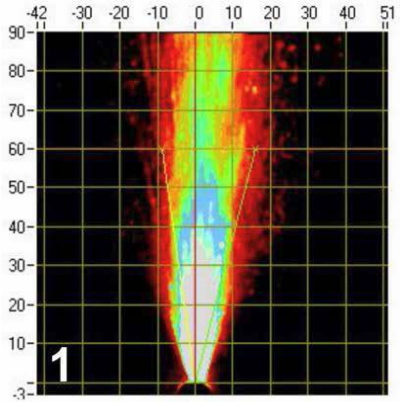
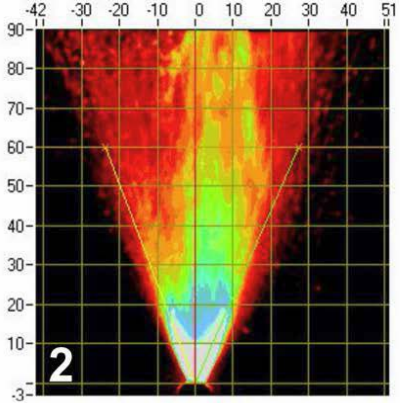
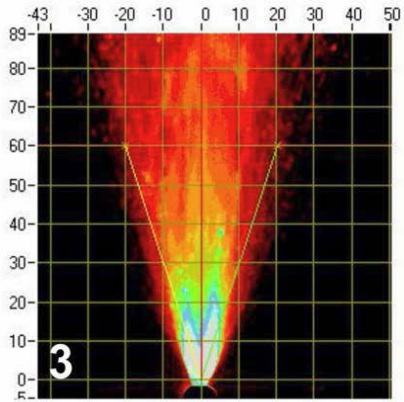








Results of SprayVIEW® Measurements: Plume Geometry

	Flonase® 5.8kg	Flonase® 7.2kg	Flonase® Sensimist™ 7.2kg
			
Angle (Degrees):	**24.3 ± 2.5**	**45.6 ± 1.9**	**36.3 ± 2.1**
Width (mm):	**25.9 ± 2.8**	**51.0 ± 1.5**	**39.3 ± 2.5**

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 to improve current *in vitro* BE test methods to make them more biopredictive for locally-acting drugs.

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