Comparing Nasal Suspension Products Using Realistic *In Vitro* Test Methods

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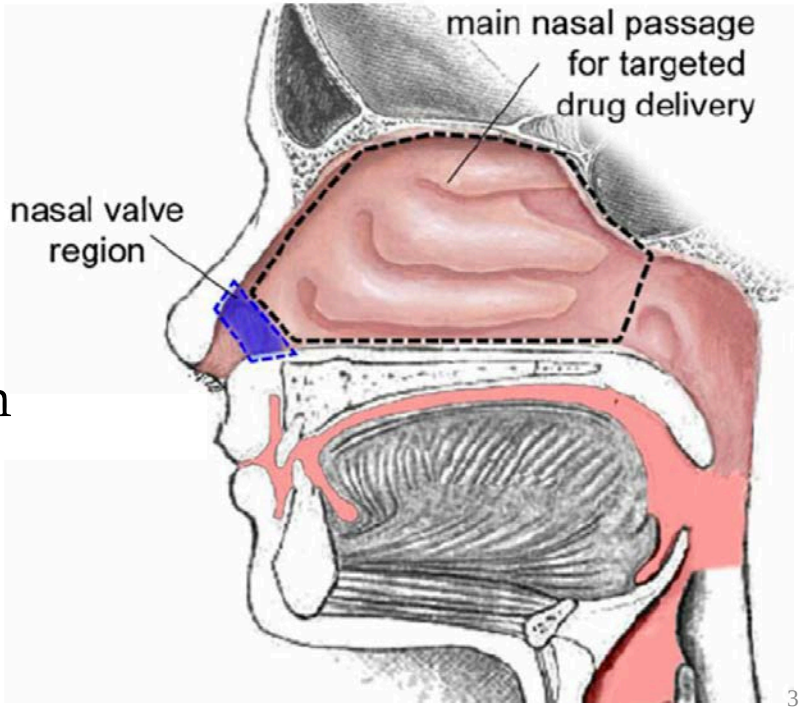
Goals

Development and evaluation of methods to characterize nasal spray products using realistic nasal airway models as more clinically relevant *in vitro* tools:

- Patient use variability
- Inter-subject variability
- Product variability

Nasal drug delivery

- Can be used for local or systemic delivery
- Metered dose nasal sprays are the most commonly used devices
  - Relatively poor delivery efficiency to the site of action in the middle passages
- Drug delivery efficiency depends on:
  - Patient use
  - Nasal geometry
  - Formulation and device combination



Nasal spray product characterization

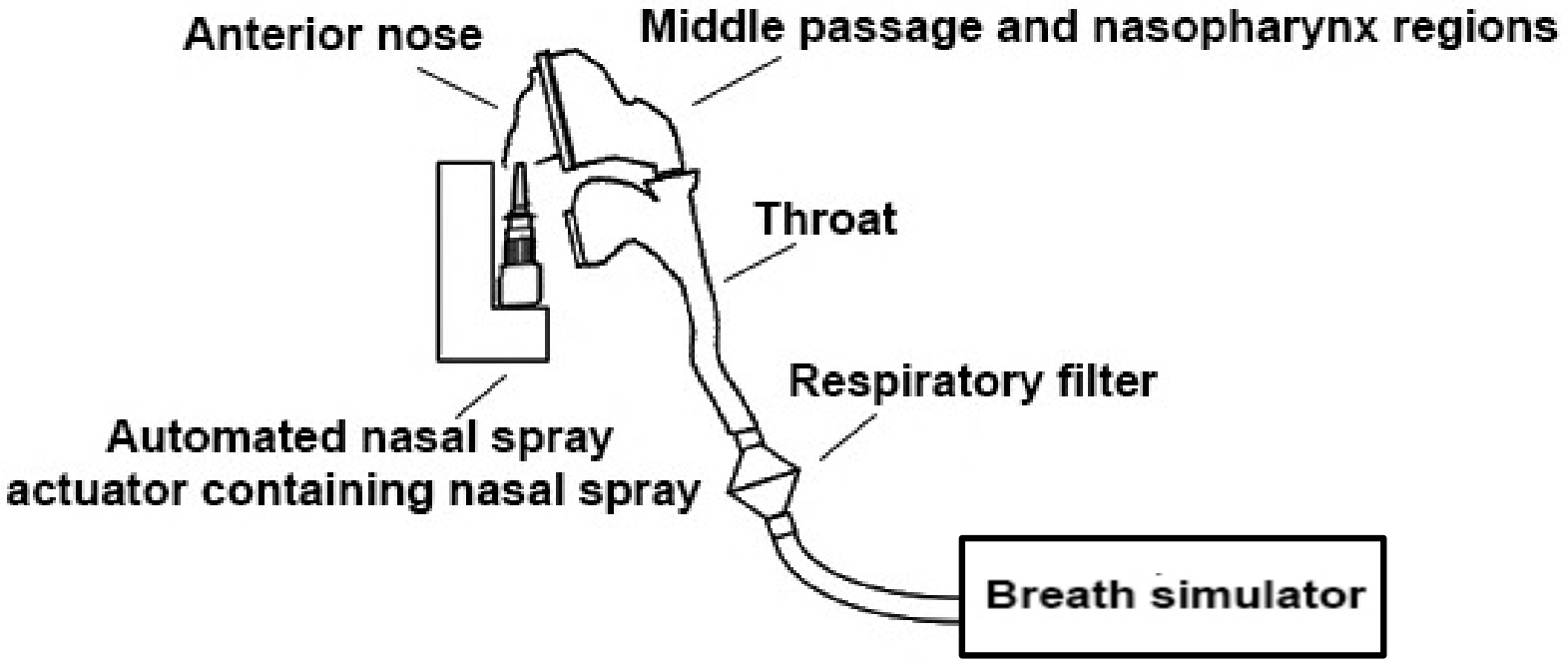
- Nasal drug delivery efficiency and assessments of bioequivalence currently use *in vitro* characterization methods that focus on the spray plume and droplet size characteristics of the nasal spray.

- Statistical differences spray plume properties may not lead to changes in nasal drug deposition[1] which questions the clinical value of the current *in vitro* tests.

- Assessments of nasal drug delivery efficiency and bioequivalence may be aided by the use of more clinically relevant *in vitro* testing using physically realistic nasal airway models combined with simulated patient use parameters.

[1]Suman et. al, *J Aerosol Med*, 2006

Clinically relevant *in vitro* nasal testing



Regional drug deposition measured on:

i) Nasal spray device

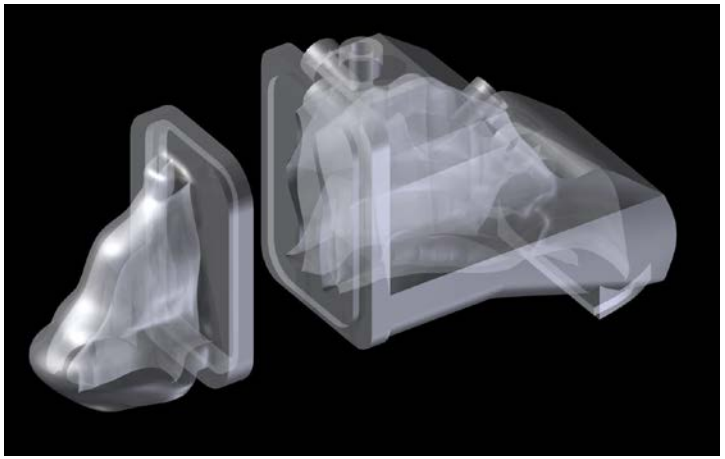
ii) Anterior nose region + drip

iii) **Middle passages + nasopharynx**

iv) Throat + filter

Innovator product: Nasonex ® Nasal Spray (mometasone furoate monohydrate) 50 µg/100 µl

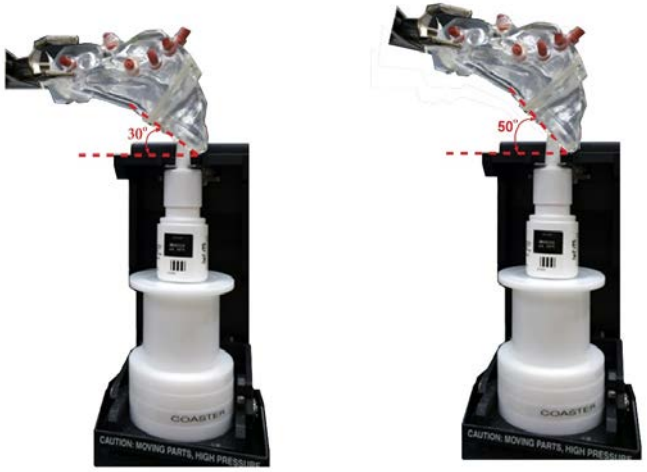
Nasal geometry: VCU nasal model 1



Data set	**Guilmette data, MRI scan of an individual - VCU Model 1**
Dh, nostril and nasopharynx	12.1 mm, 5.9 mm
Surface area (SA)	8024.2 mm^2
Volume (V)	10832mm^3
SA/V	0.7 mm^{-1}
SA of the nasal valve	1156 mm^2
Anterior nose volume	3.2 ml

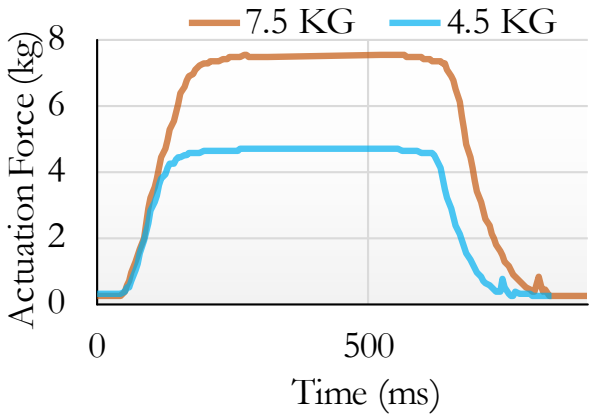
Patient-use variables and DoE design

Head angle: 30° or 50°

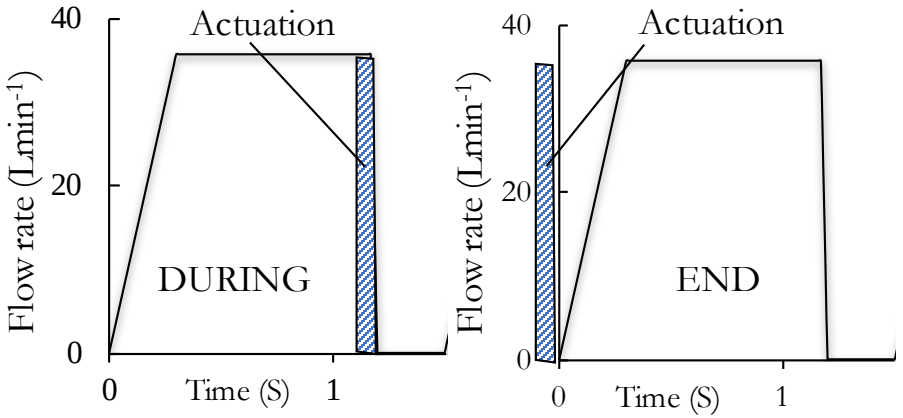


Position: 9 or 5 mm

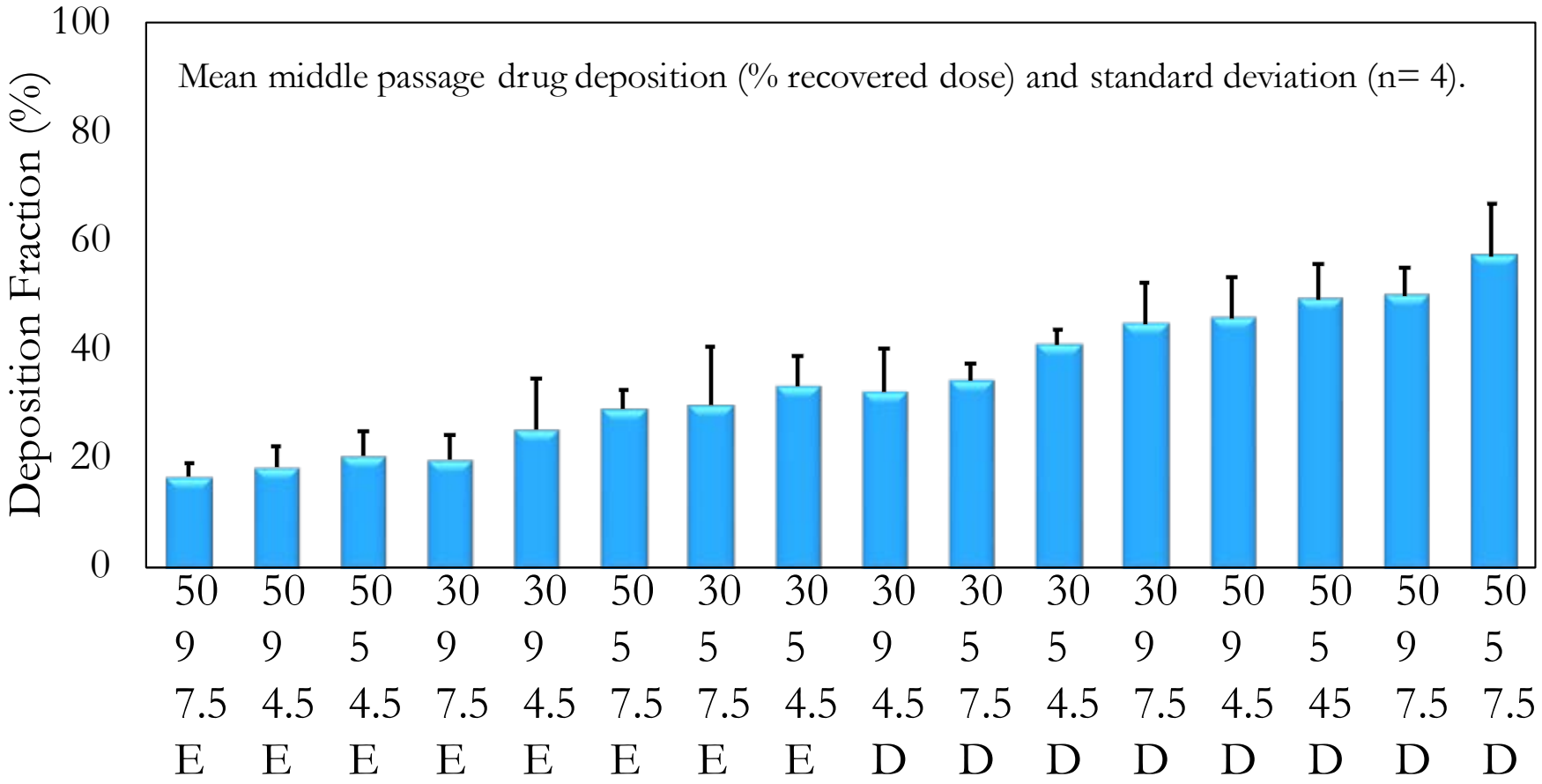
Actuation force: 4.5 or 7.5 kg



Timing: D or E

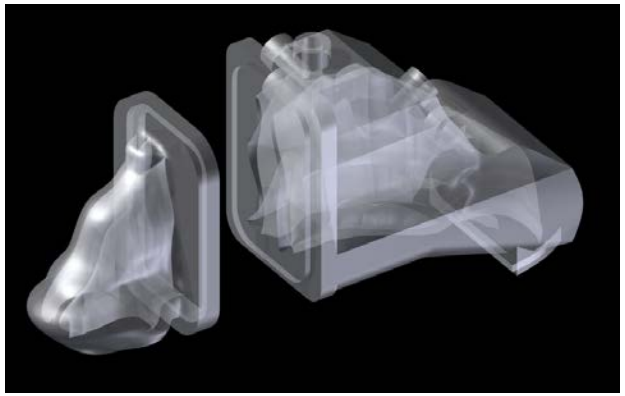


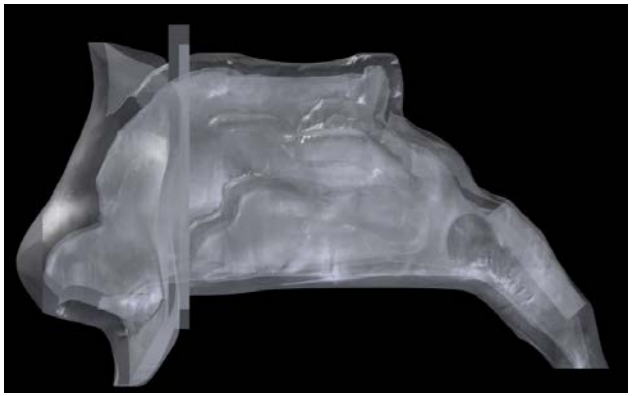
Middle passage deposition: Mometasone innovator product



- Nasal deposition varied significantly with changing patient use factors
- Significant main effect of nasal spray position within the nostril
- Significant interaction between inhalation timing & head angle

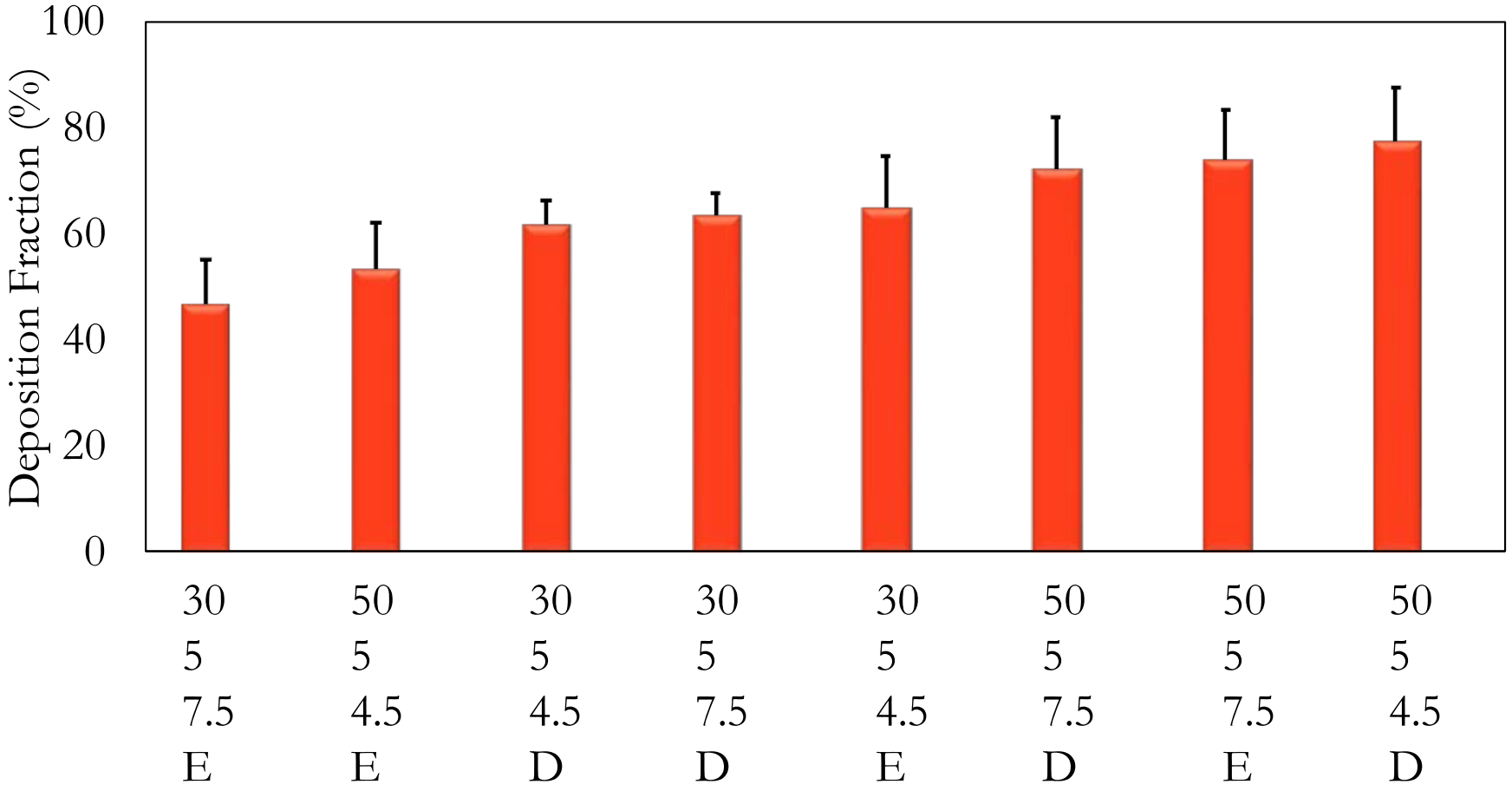
Inter-subject variability





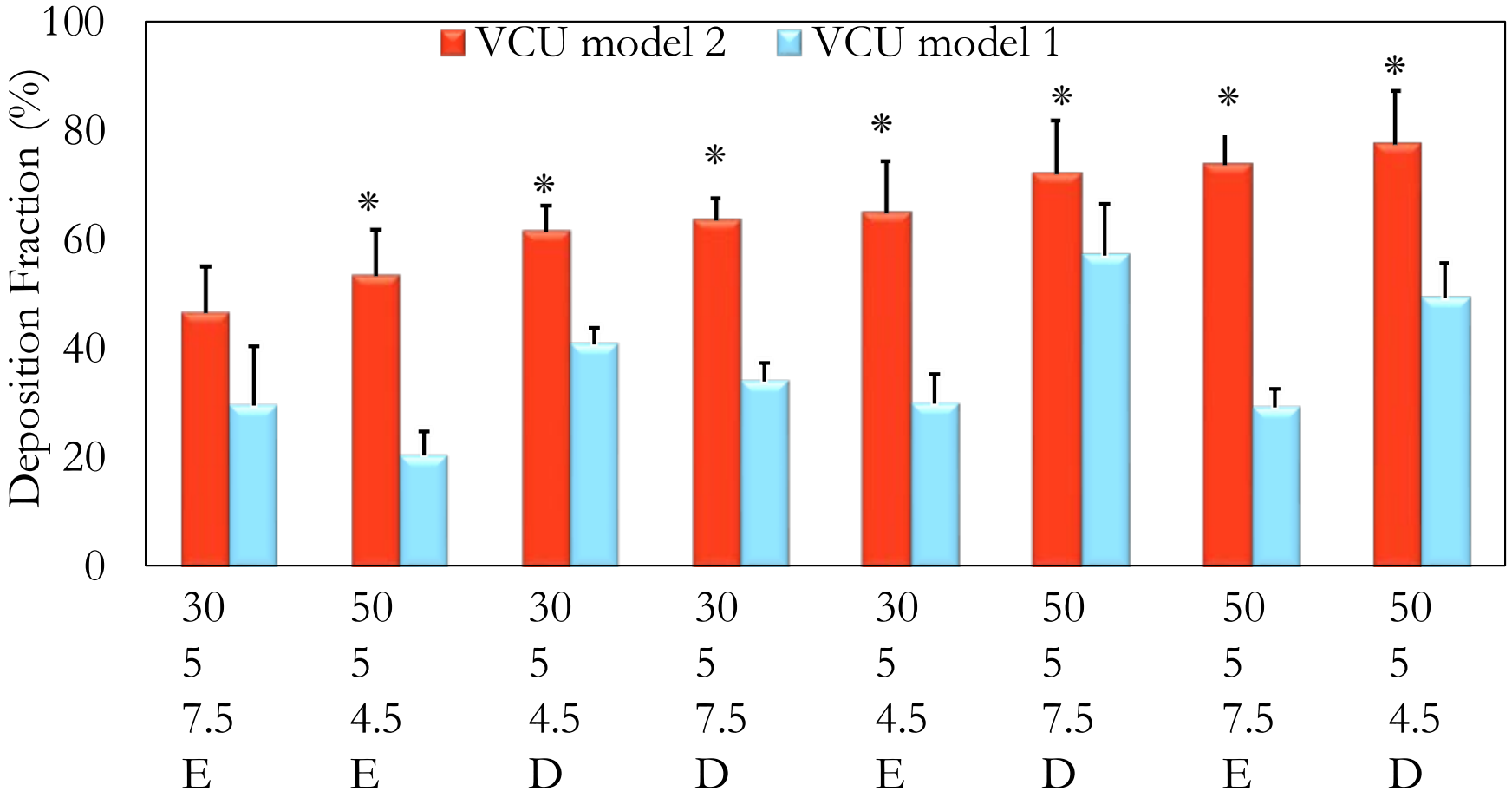
Data set	**Guilmette data, MRI scan of an individual - VCU Model 1**	**VCU Medical Center, CT scan of an individual - VCU Model 2**
Dh, nostril, nasopharynx	12.1 mm, 5.9 mm	10.6 mm, 4.5 mm
Surface area (SA)	8024.2 mm^2	6802.3 mm^2
Volume (V)	10832mm^3	5118 mm^3
SA/V	0.7 mm^{-1}	1.3 mm^{-1}
SA of the nasal valve	1156 mm^2	1493 mm^2
Anterior nose volume	3.2 ml	2.2 ml

Middle passage deposition: Mometasone innovator product



- **Lower impact of patient use factors on nasal deposition in VCU Model 2**
- **Significant effect of inhalation timing & head angle**

Middle passage deposition: Mometasone innovator product

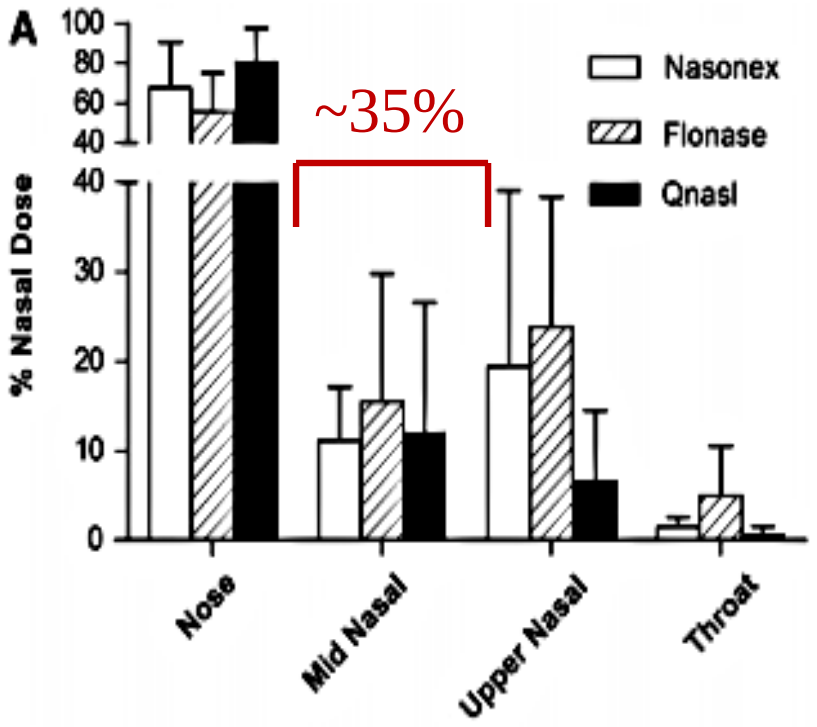


- **Higher middle passage deposition in VCU model 2 compared to VCU model 1**

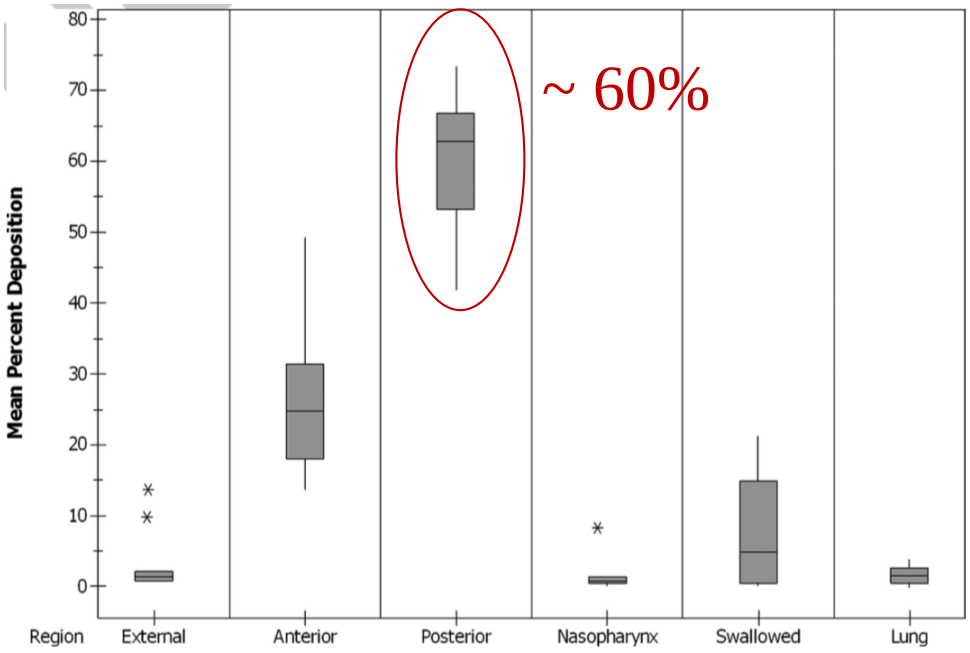
Mean middle passage drug deposition (% recovered dose) and standard deviation, n= 4. *p<0.05 (student t-test).

Comparison of *in vitro* and *in vivo* deposition data for Nasonex® nasal spray product

Study 1 (Leach et. al , 2015)



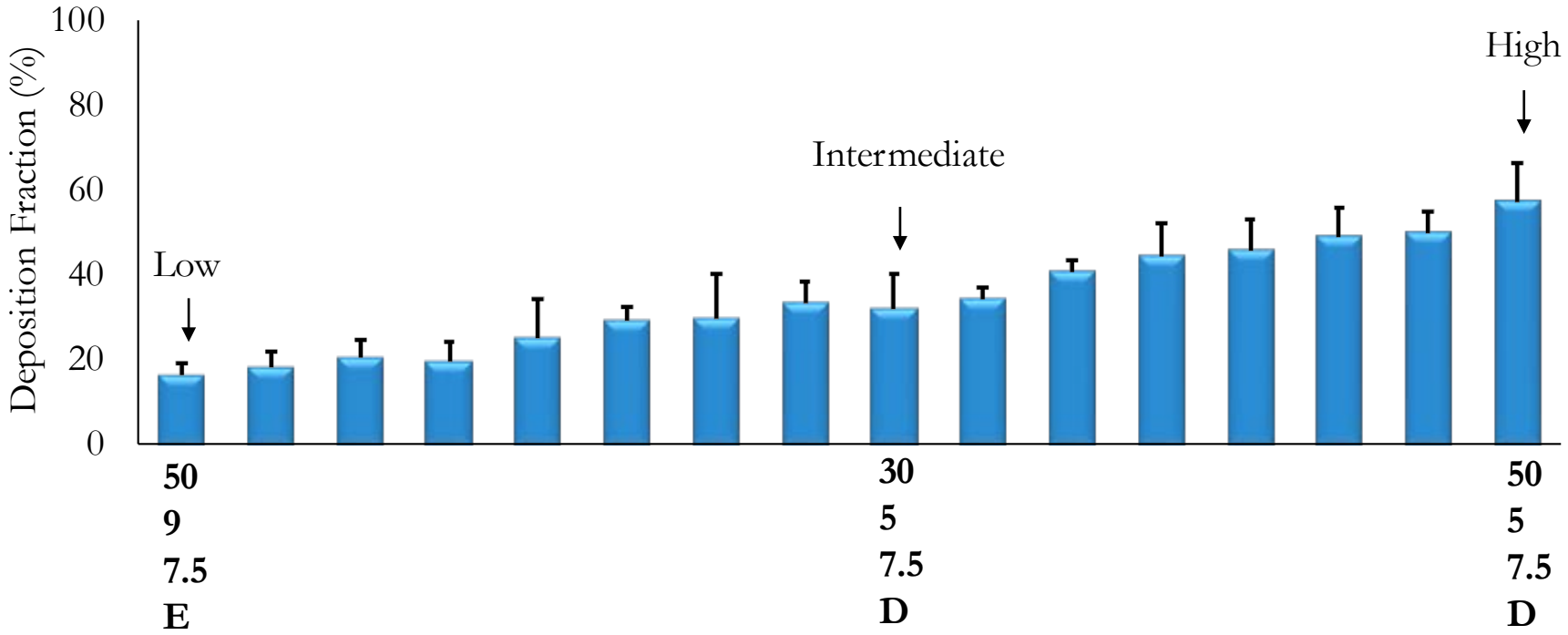
Study 2 (Shah et. al, 2014)



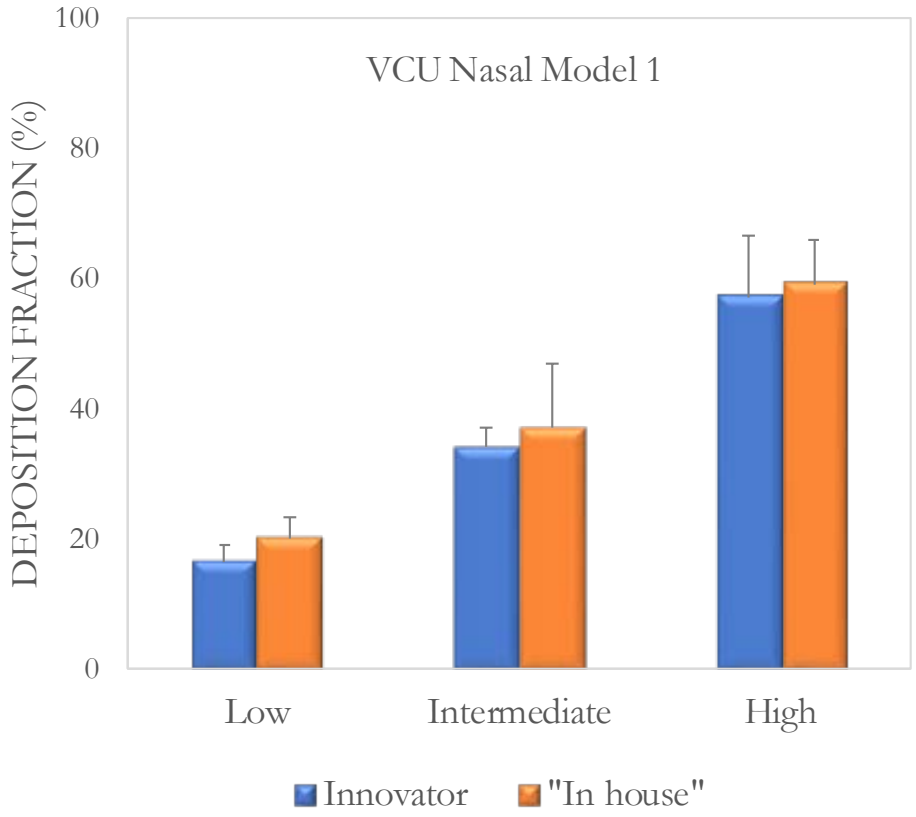
- **Mean (SD) middle passage deposition in VCU models 1 and 2 were 34.0 (13.6)% and 64.8 (12.4)%, respectively across all test conditions.**

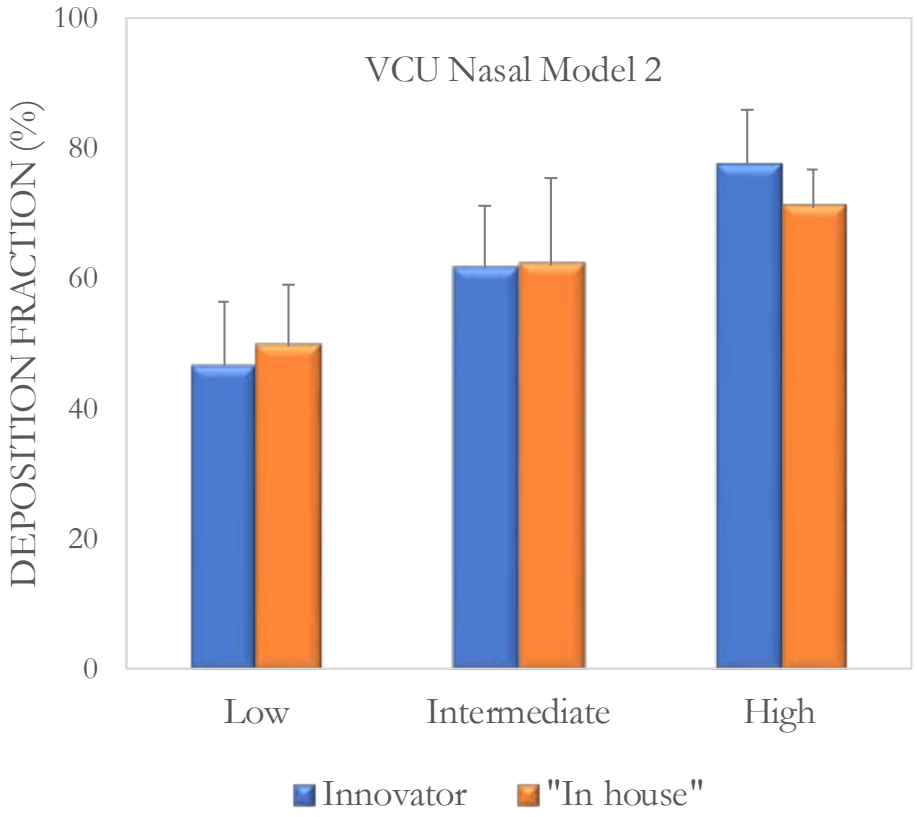
Regional nasal drug deposition of innovator & generic nasal spray products

- Formulation and device
  - Mometasone furoate: innovator vs "in house" (University of Bath) nasal spray
  - Fluticasone: innovator vs generic nasal spray
- Nasal geometry: VCU models 1 & 2
- Patient-use conditions: low, intermediate and high middle passage deposition



Middle passage deposition:
Mometasone innovator and "in house" products

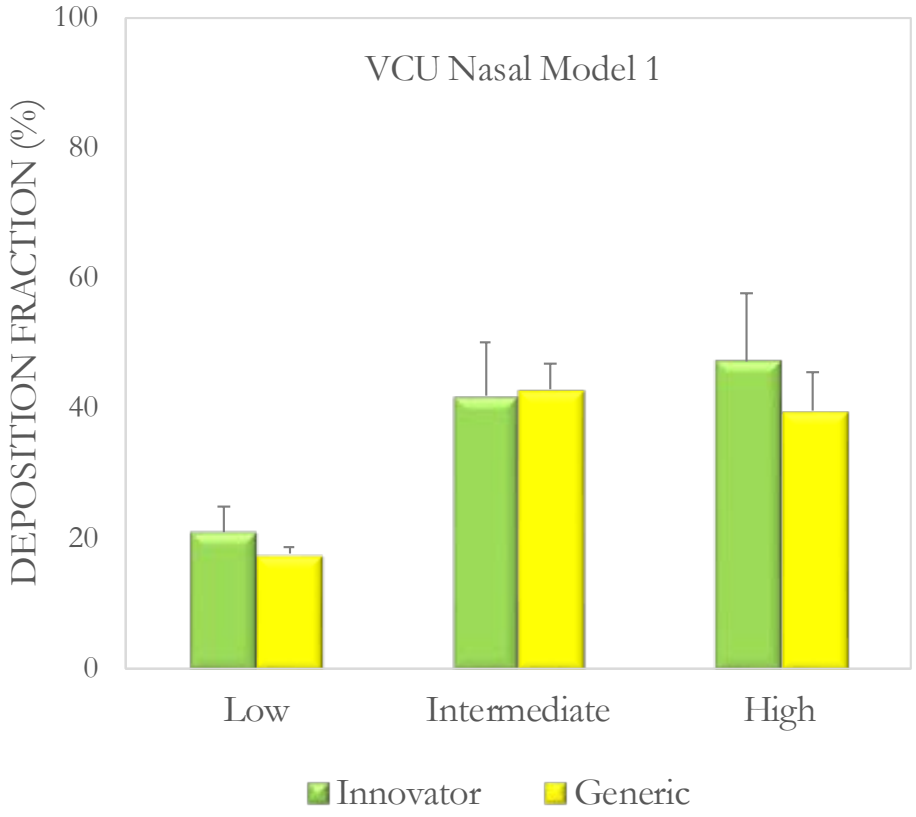


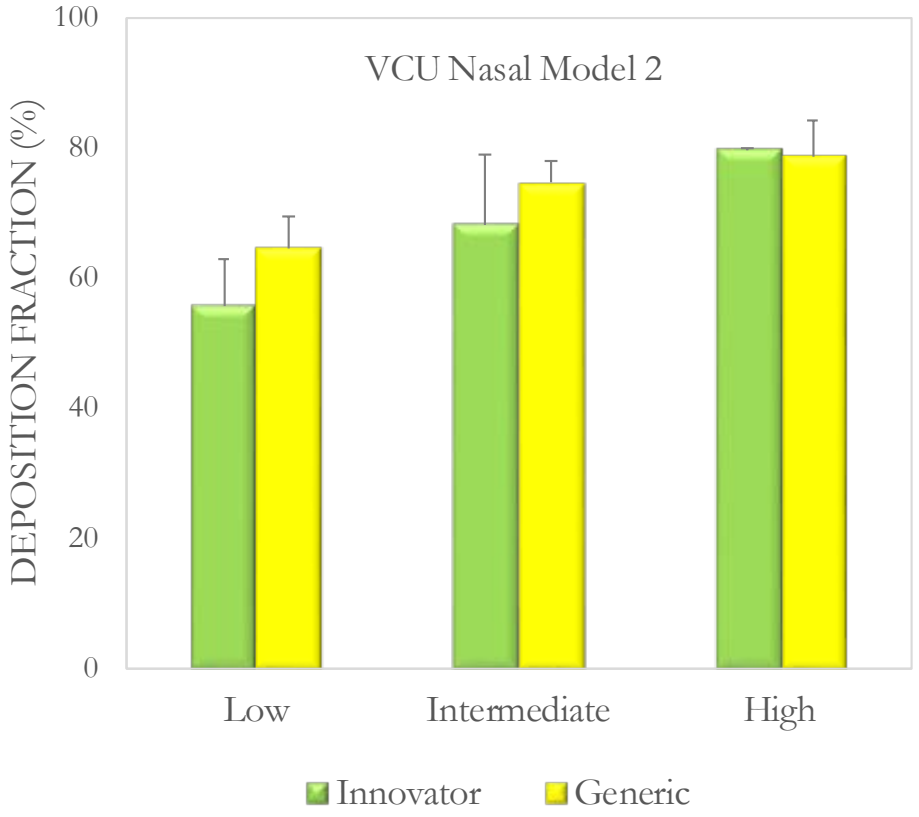


- **No statistical difference in the middle passage drug deposition for the two nasal spray products at each respective level**

Mean regional deposition (% recovered dose) and standard deviation, n= 4.

Middle passage deposition: Fluticasone innovator and generic products



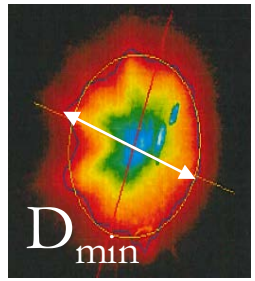


- **No statistical difference in the middle passage drug deposition for the two nasal spray products at each respective level**

Mean regional deposition (% recovered dose) and standard deviation, n= 4.

Regional nasal drug deposition of mometasone furoate nasal sprays with varying spray plume characteristics

- Formulations:
  - "In house" mometasone furoate nasal spray: Batch A
  - "In house" mometasone furoate nasal spray: Batch B
  - Mometasone innovator nasal spray: expiry Feb 2007
  - Mometasone innovator nasal spray: expiry Oct 2015 (in-date)
- Nasal Geometry: VCU model 1
- Patient-use conditions: Intermediate level



- FDA recommended *in vitro* tests for establishing BE for nasal spray products
  - Droplet size distribution (median volume diameter, Dv50) measured by Malvern Spraytec
  - Spray pattern (smallest diameter on spray plume image, Dmin) measured by SprayVIEW™

Mometasone furoate nasal spray middle passage deposition

Device	Dv50 (μm)	D_{min} (mm)	MP (%)
Batch A	35.6 (0.5)	28.3 (0.6)[a]	31.0 (8.5)[a]
Innovator 2007	36.3 (0.8)	23.8 (0.5)[a, b]	38.8 (3.8)[a]
Batch B	38.7 (3.0)	21.3 (0.2)	49.6 (8.8)
Innovator 2015	47.0 (1.0)	20.5 (0.2)	44.6 (7.6)

Mean (SD) for Dv50 and D_{min} for mometasone furoate nasal spray products and middle passage drug deposition (MP), expressed as % recovered dose, n = 3 and 4.

$P<0.05$, [a] compared to Batch B, [b] compared to Batch A

- **Lower middle passage drug delivery observed with larger plume diameters (D_{min})**

Mometasone furoate nasal spray middle passage deposition

Device	Dv50 (μm)	D_{min} (mm)	MP (%)
Batch A	35.6 (0.5)	28.3 (0.6)	31.0 (8.5)
Innovator 2007	36.3 (0.8)	23.8 (0.5)	38.8 (3.8)
Batch B	38.7 (3.0)[c]	21.3 (0.2)	49.6 (8.8)
Innovator 2015	47.0 (1.0)	20.5 (0.2)	44.6 (7.6)

Mean (SD) for Dv50 and D_{min} for mometasone furoate nasal spray products and middle passage drug deposition (MP), expressed as % recovered dose, n = 3 and 4.

$P<0.05$, [c] compared to Innovator 2015

- **Differences in plume geometries appeared to be more critical than droplet size in determining the deposition fate of the nasal spray**

Conclusions and Future Studies

- A realistic *in vitro* test was developed for nasal sprays incorporating realistic patient use conditions and airway nasal models
- Patient use factors and nasal model geometry were observed to have significant effects on middle passage drug delivery
- Innovator and generic nasal spray products were observed to have similar regional *in vitro* nasal deposition profiles

- Studies required to further understand relationship between *in vitro* spray characterization test metrics and nasal spray deposition.
- Develop nasal geometries that capture mean and high/low range of nasal spray deposition across the adult population.

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