Virginia Commonwealth University VCU

# Clinically Relevant *In Vitro* Tests for the Assessment of Innovator and Generic Nasal Spray Products

Mandana Azimi[1], P. Worth Longest[1, 2], Jag Shur[3], Robert Price[3] & Michael Hindle[1]

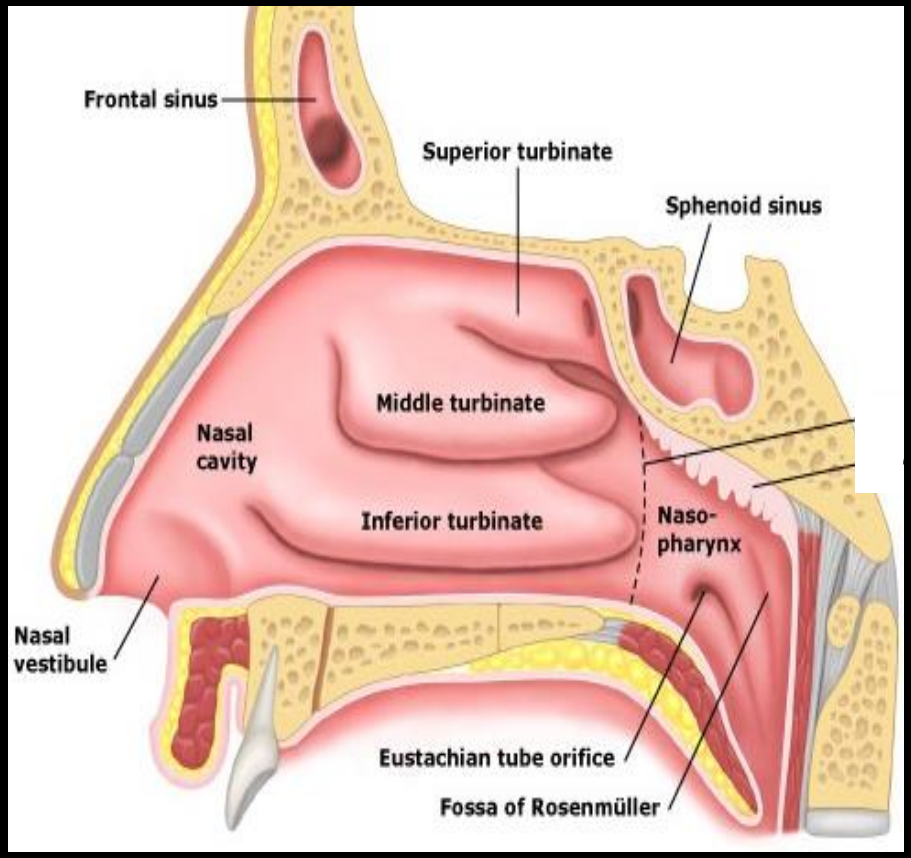
[1]Department of Pharmaceutics, Virginia Commonwealth University, USA

[2]Department of Mechanical and Nuclear Engineering, Virginia Commonwealth University, USA

[3]Department of Pharmacy and Pharmacology, University of Bath, UK

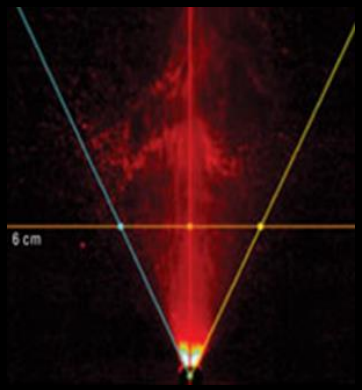
# Nasal drug delivery

- Can be used for local or systemic delivery
- Metered dose nasal sprays are the most commonly used devices
- Drug delivery efficiency depends on:
  - Nasal geometry
  - Patient use
  - Formulation and device combination



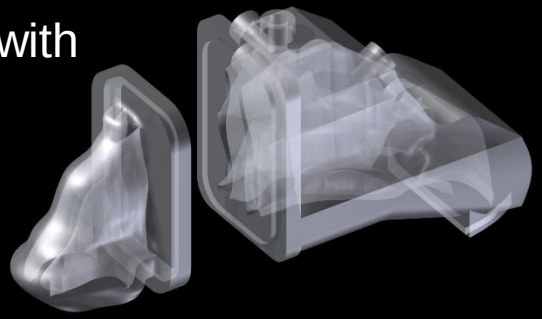
# *In vitro* testing: quality control vs clinically relevant methods

- Currently *in vitro* QC methods focus on device and formulation performance including methods to characterize spray plume and droplet size.




- The bio-relevance of these methods remains unclear.

- Nasal drug delivery efficiency and assessments of 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.

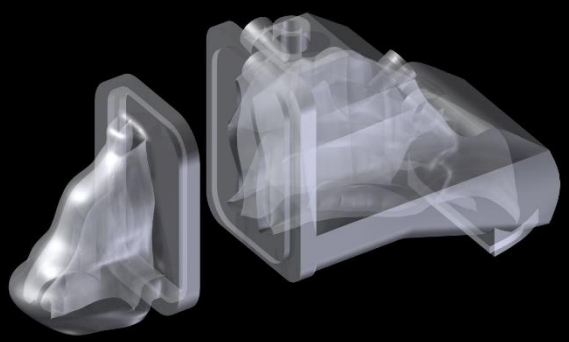


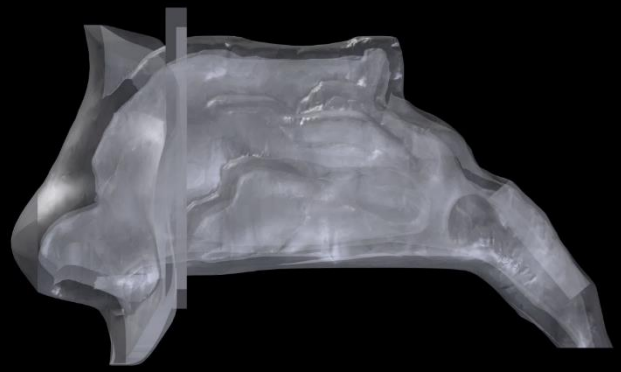
# Objective

To test the utility of a potential clinically relevant *in vitro* nasal deposition method and assess the effects of varying:

- Nasal geometry
- Patient use
- Formulation and device combination

# Nasal geometry





| 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 and 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) | 10832$mm^3$ | 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 |

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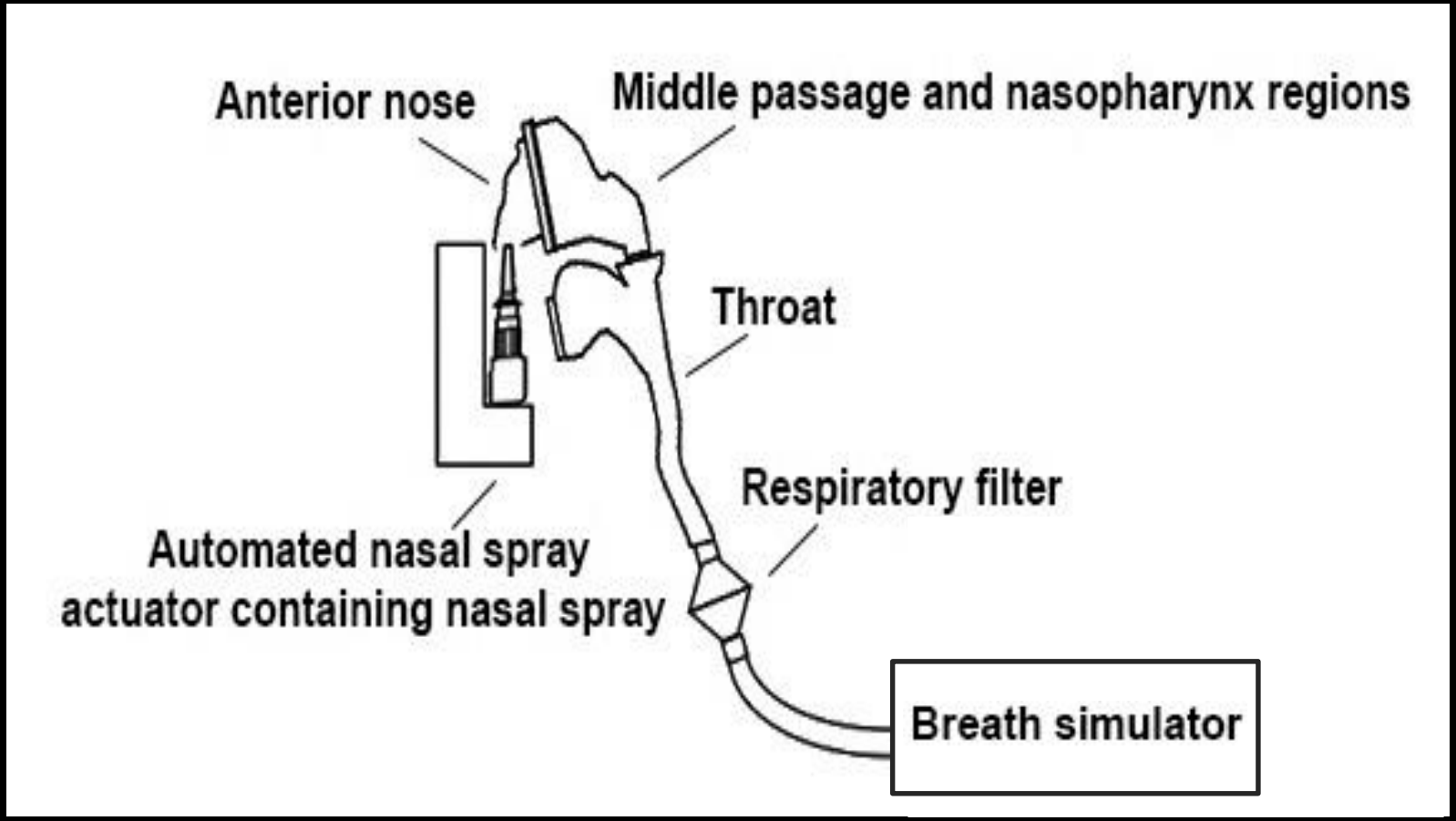
# Experimental setup



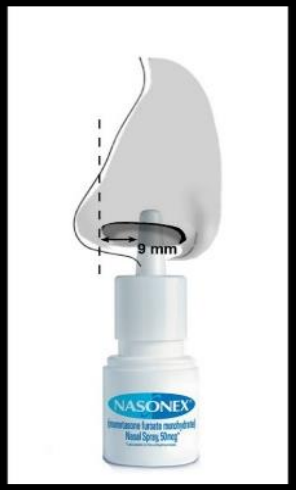

- Two actuations of Nasonex delivered into a single nostril
- Regional drug deposition was measured on:
  - i) Nasal spray device
  - ii) Anterior nose region + drip
  - iii) Middle passages + nasopharynx
  - iv) Throat + filter

# Patient use

## Head angle: 30º or 50º

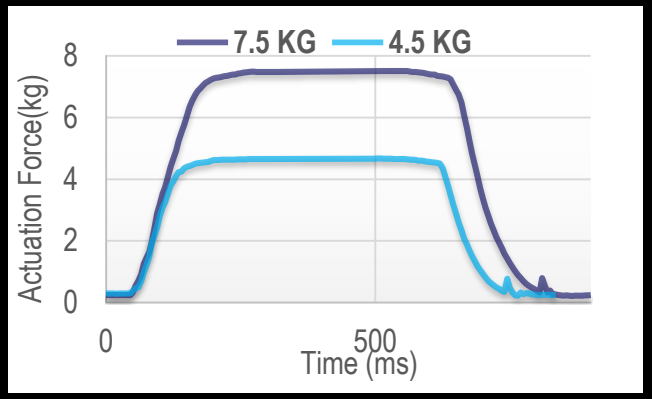


## Position: 9 or 5 mm

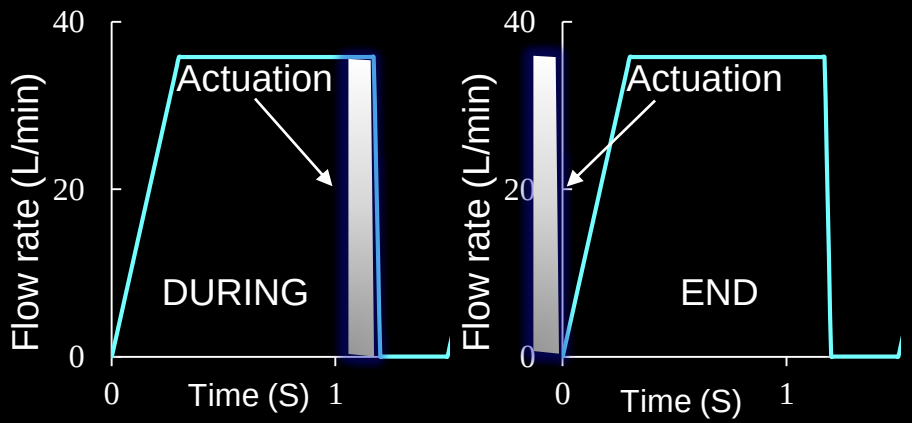




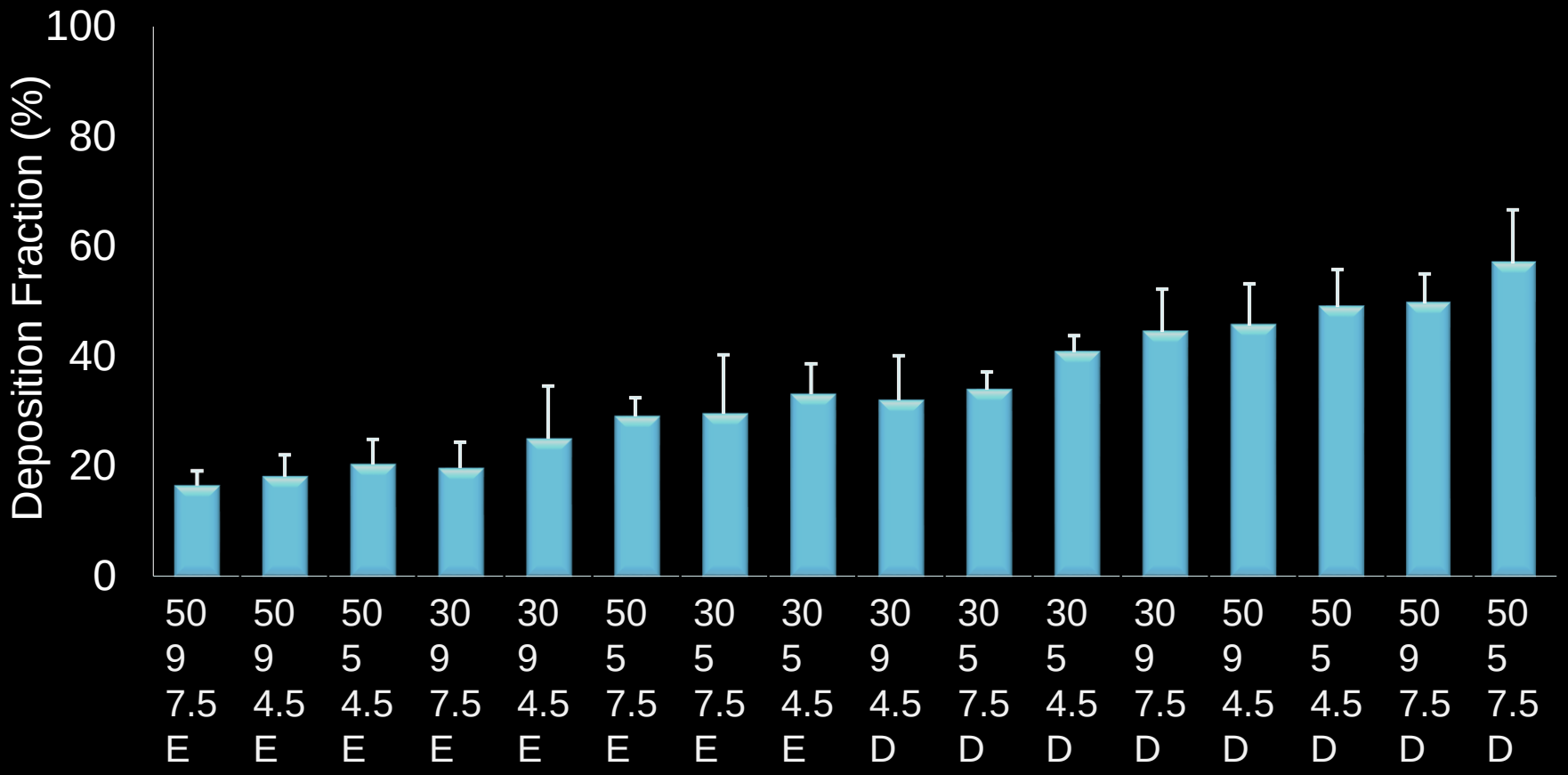
## Actuation force: 4.5 or 7.5 kg




## Timing: D or E



# Nasonex middle passage deposition
# VCU nasal model 1




- **Nasal deposition varied significantly with changing patient use factors**
- **Coordinating inhalation with actuation increased middle passage deposition**

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

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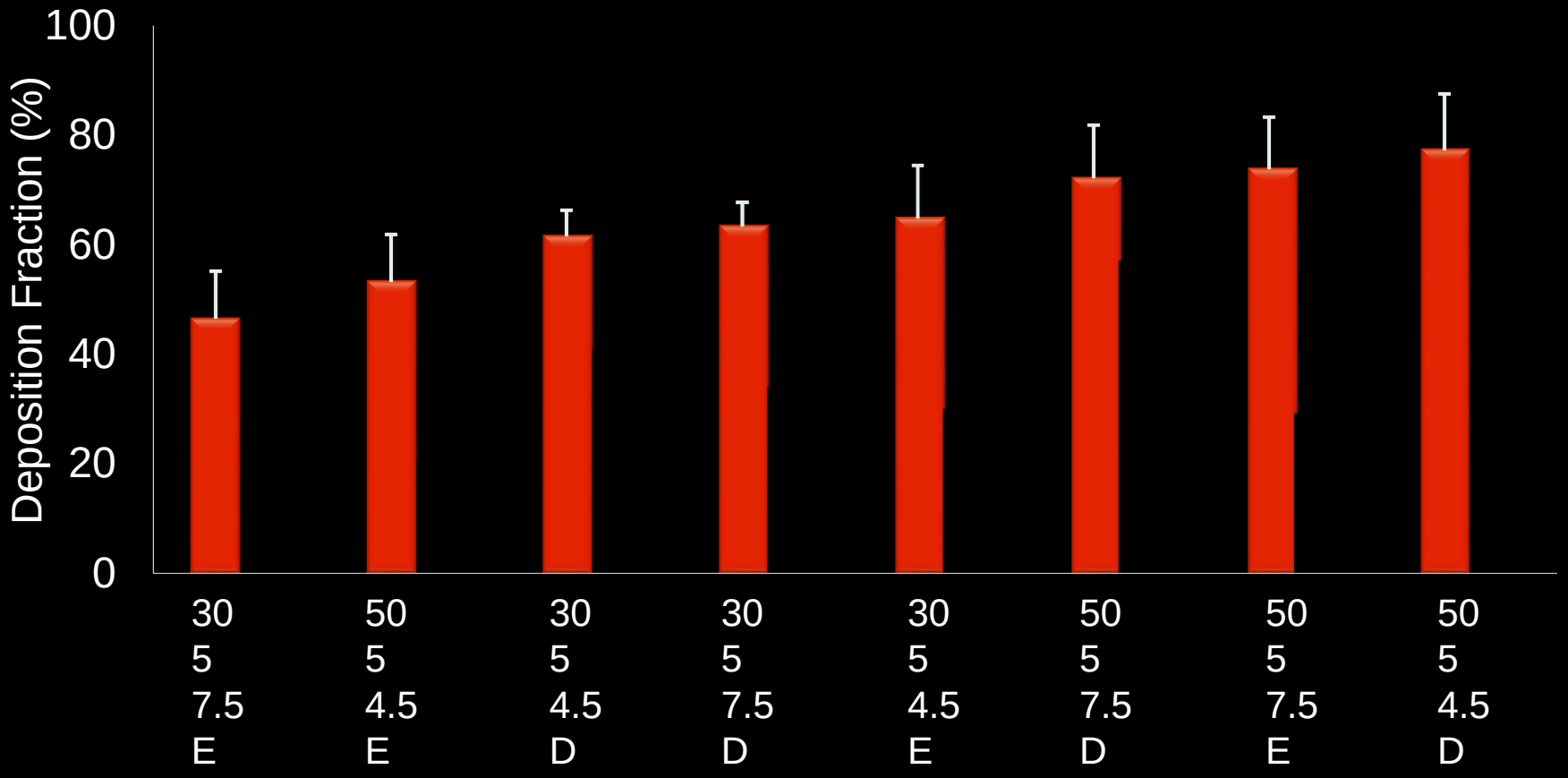
# Nasonex middle passage deposition
# VCU nasal model 2




- **Low impact of patient use factors on nasal deposition in model 2**

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

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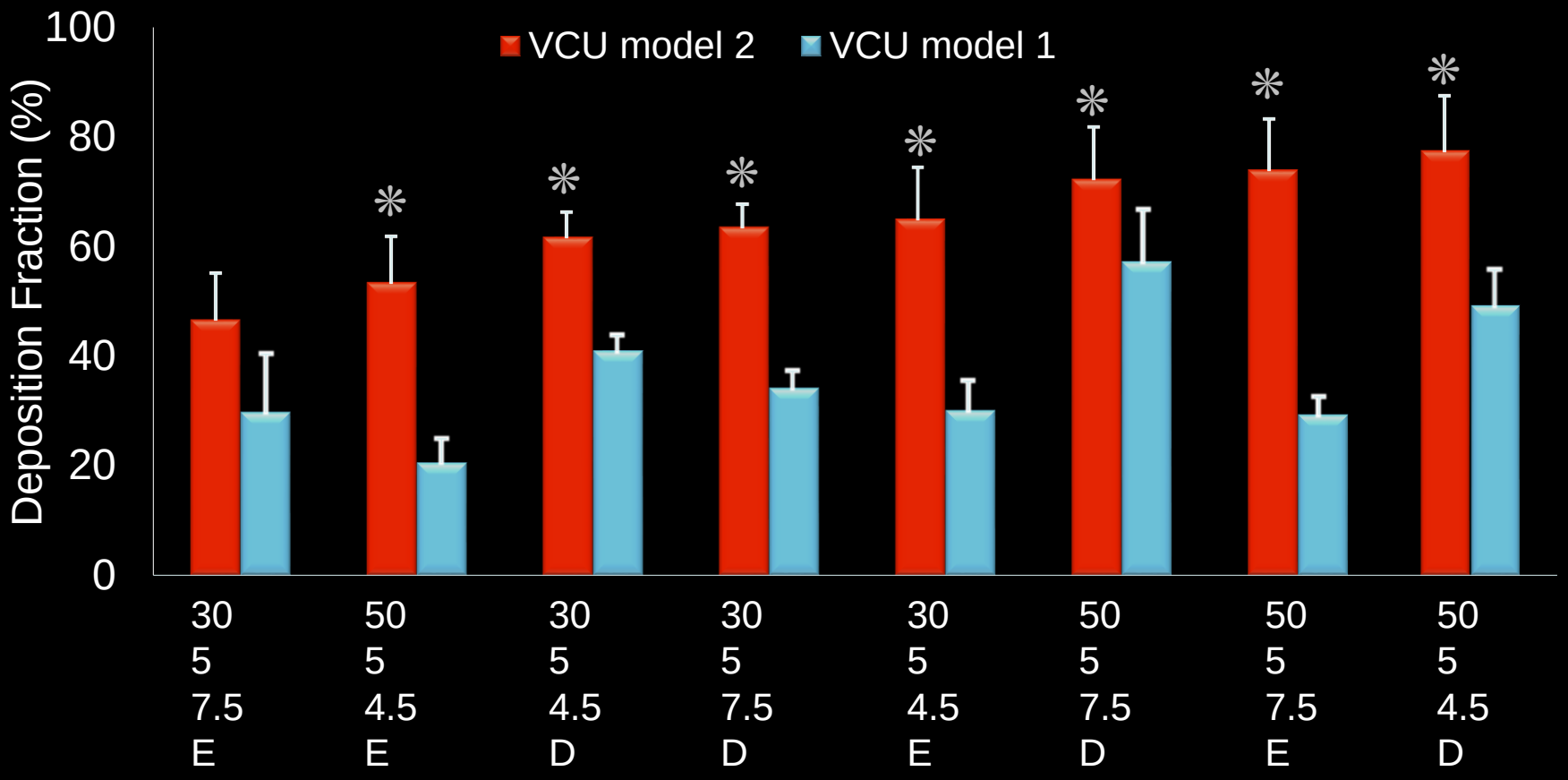
# Nasonex middle passage deposition
# VCU nasal model 1 and 2




- **High middle passage deposition in model 2 compared to model 1**

Mean regional deposition (% recovered dose) and standard deviation (n= 4). * - $p<0.05$ paired t-test

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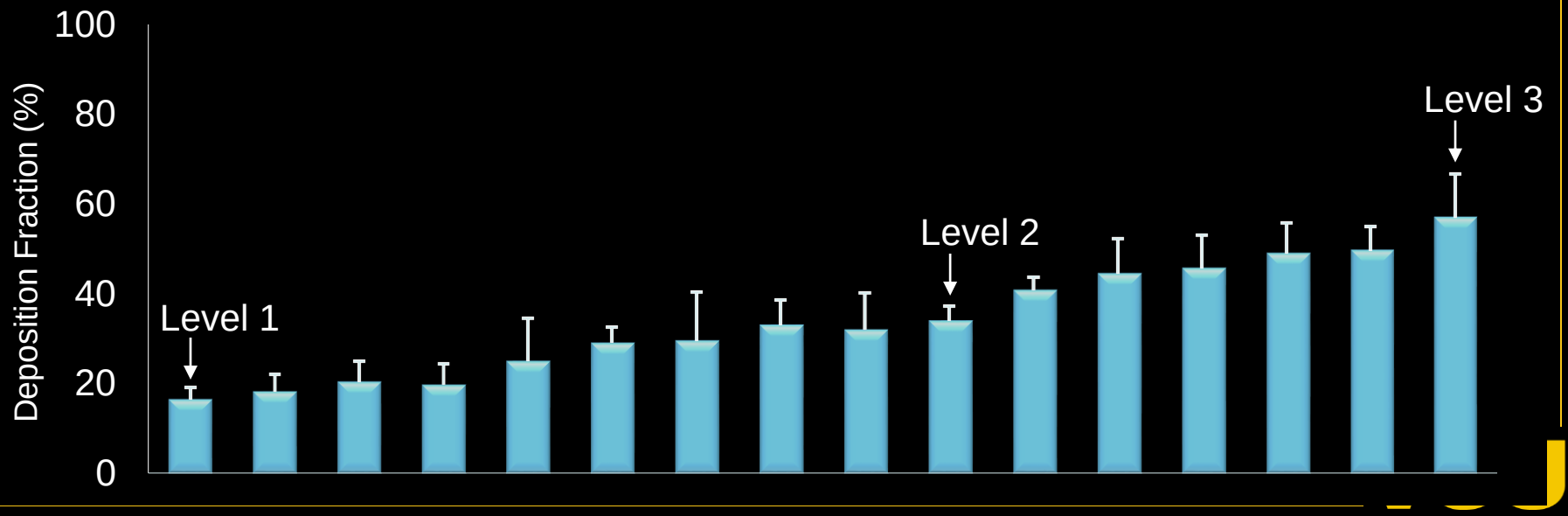
# Evaluation of realistic *in vitro* test method

- Formulation and device
  - Mometasone furoate: Nasonex vs “in house”
  - Fluticasone propionate: Flonase vs generic
- Nasal Geometry: VCU models 1 & 2
- Patient Use
  - Patient use conditions producing “low – level 1”, “intermediate – level 2” and “high - level 3” Nasonex middle passage deposition



# Patient use factors

| Expected middle passage drug deposition | Angle | Position (mm) | Force (kg) | Timing |
|---|---|---|---|---|
| VCU Model 1 | | | | |
| Level 1 ~ 20% | 50° | 9 | 7.5 | E |
| Level 2 ~ 40% | 30° | 5 | 7.5 | D |
| Level 3 ~ 60% | 50° | 5 | 7.5 | D |
| VCU Model 2 | | | | |
| Level 1 ~ 50% | 30° | 5 | 7.5 | E |
| Level 2 ~ 60% | 30° | 5 | 4.5 | D |
| Level 3 ~ 77% | 50° | 5 | 4.5 | D |

# Droplet size distributions

| | Dv10 (μm) | Dv50 (μm) | Dv90 (μm) | Span |
|---|---|---|---|---|
| **Actuation force of 7.5 kg** | | | | |
| Nasonex<br>50 μg (Merck & Co., USA) | 16.1 (0.6) | 44.5 (2.7) | 107.0 (5.4) | 1.4 |
| "In house" mometasone furoate<br>50 μg (University of Bath, UK) | 16.1 (0.7) | 47.2 (1.7) | 91.2 (1.7) | 1.6 |
| **Actuation force of 5.8 kg** | | | | |
| Flonase<br>50 μg (GlaxoSmithKline, USA) | 20.9 (1.1) | 70.8 (1.4) | 120.3 (1.6) | 1.4 |
| Generic fluticasone propionate<br>50 μg (Roxane Laboratory, USA) | 21.9 (0.2) | 69.4 (2.1) | 119.6 (0.9) | 1.4 |

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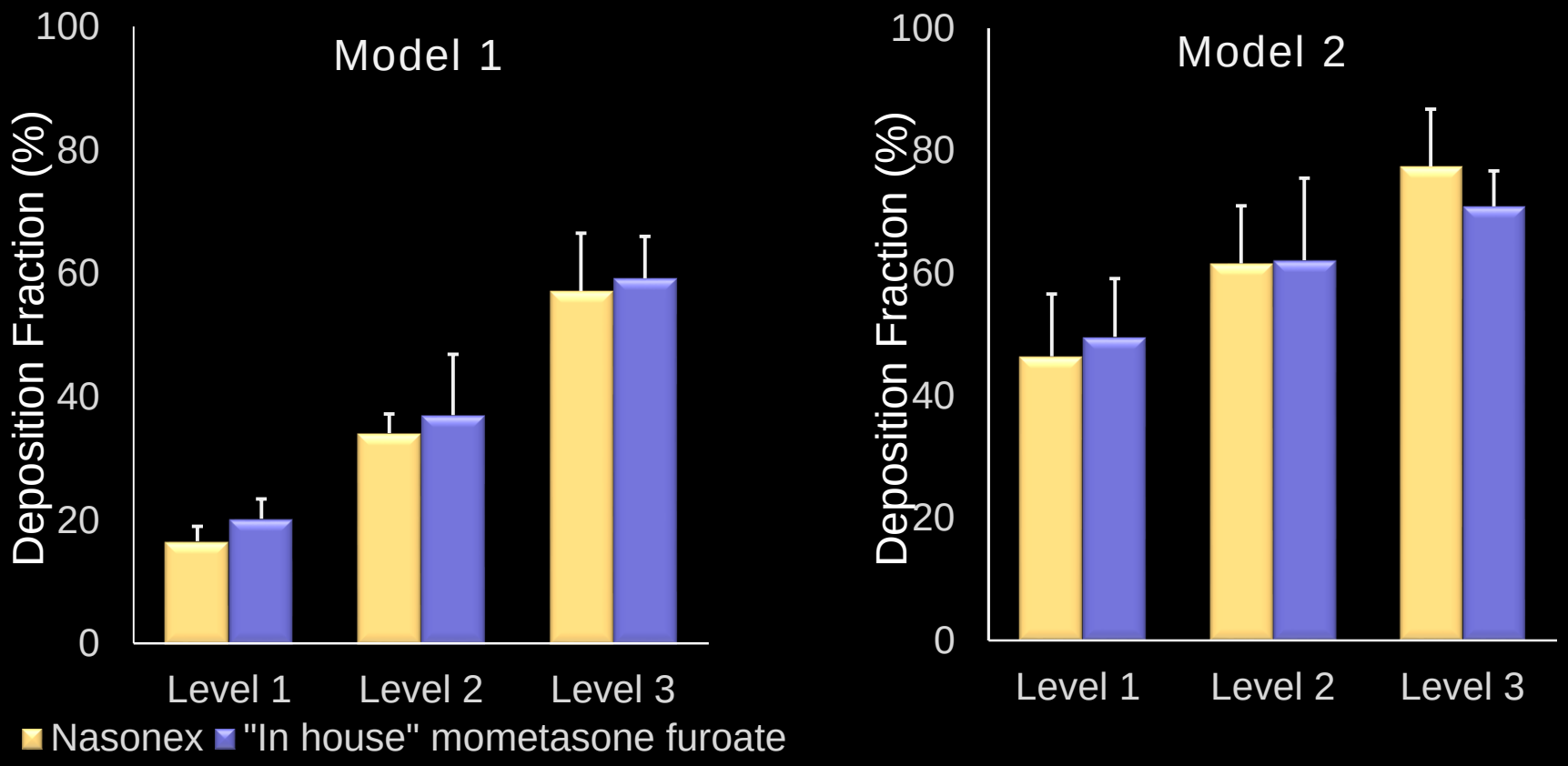
# Mometasone furoate middle passage drug deposition




- **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).

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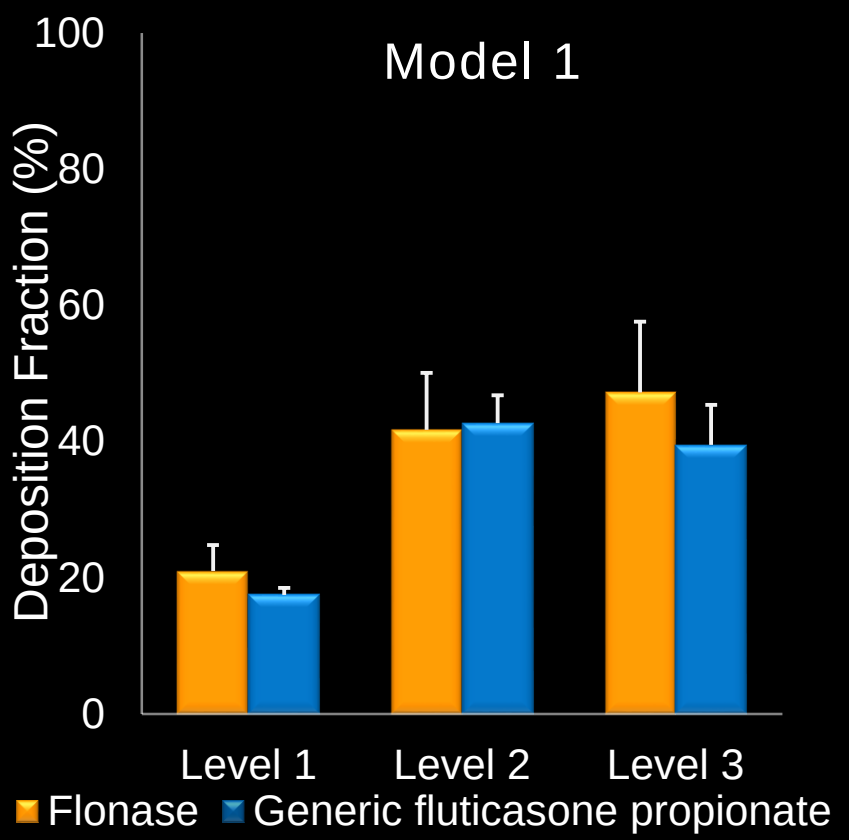
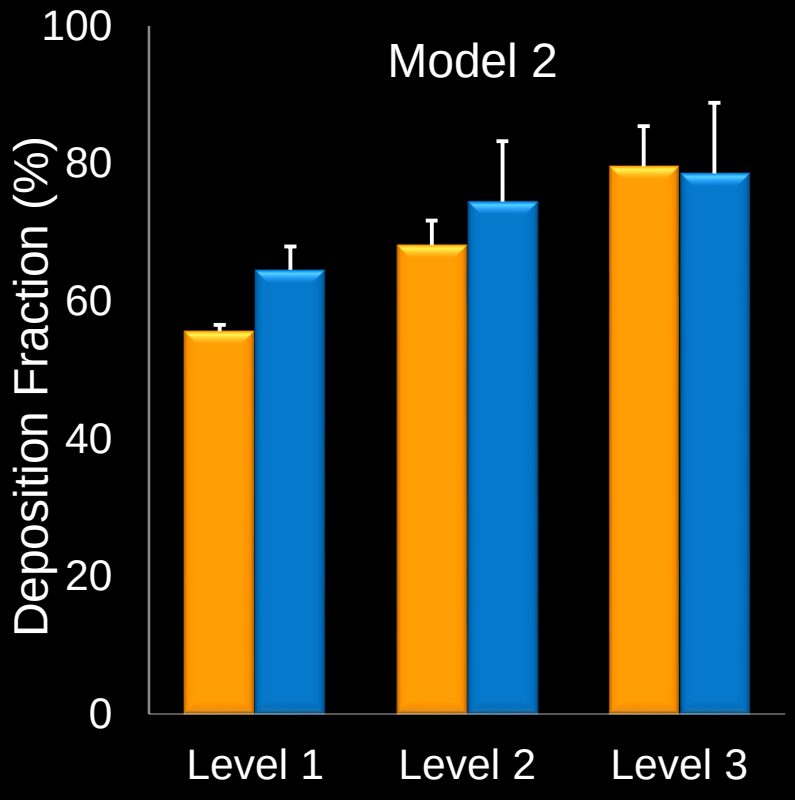
# Fluticasone propionate middle passage deposition




- **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).

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# Conclusions

- Realistic *in vitro* test methods could have utility as an inexpensive tool for early evaluation of regional nasal deposition
- *In vivo* validation will be needed before this method will be accepted as a technique for evaluating bioequivalence of nasal spray products
- The effects of patient use factors and geometry of the nasal cavity were found to have significant effects on middle passage drug delivery

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