Emerging Concepts and New Technologies for Bioequivalence of Orally Inhaled and Nasal Drug Products

Session L9: Generic Drug Development for Respiratory Products, U.S. Food and Drug Administration Update

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Disclosure to Learners

Financial Relationships with “ineligible companies” within the past 24 months:

- **None**

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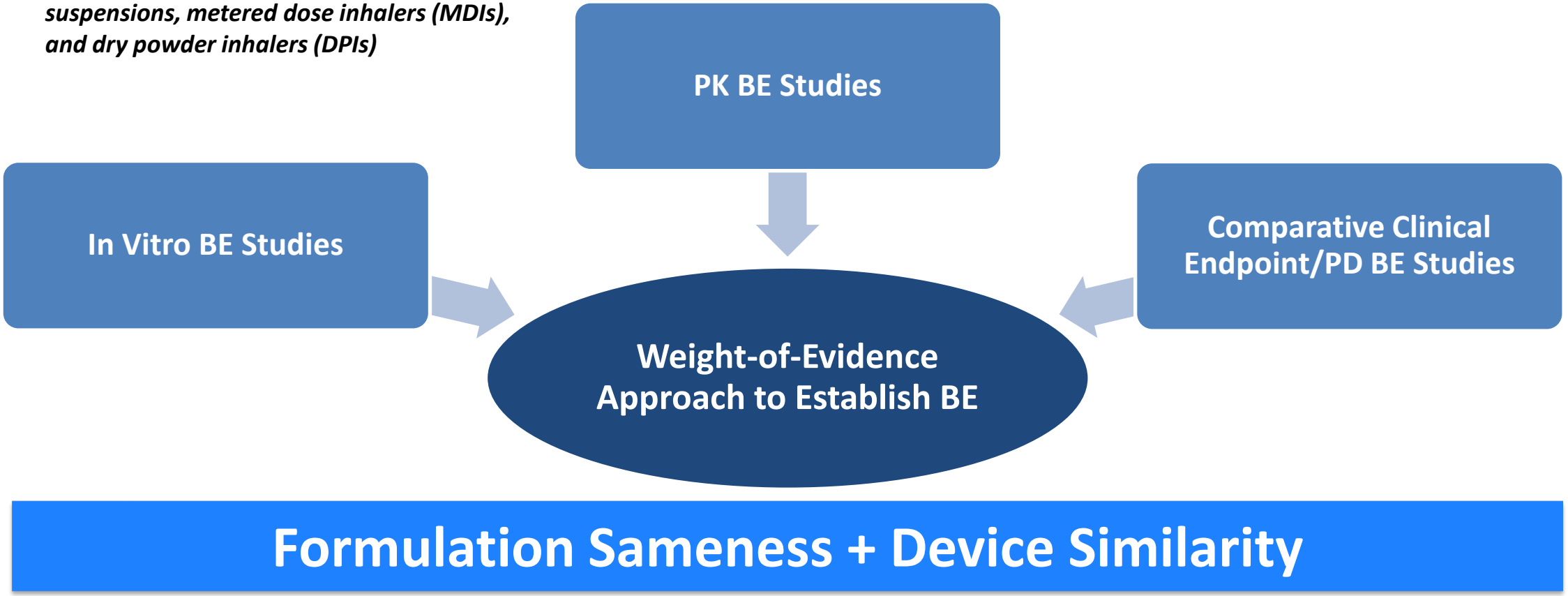
Outline

- Development of ***more biorelevant in vitro studies*** to better predict local deposition of **orally inhaled and nasal drug products (OINDPs).**
  - Generic Drug User Fee Amendments (GDUFA) Research Initiatives for OINDPs.
- Evaluation of ***in vitro anatomical models*** that incorporate **patient variation.**
  - **Study 1:** Evaluation of Aerodynamic Particle Distributions (APSDs) and Droplet Size Distributions (DSDs) after anatomical mouth-throat (MT) models from metered dose inhalers (MDIs).
  - **Study 2:** Development, Characterization, and Outcomes of Anatomical Models for Nasal Drug Products (NDPs).

Traditional Bioequivalence (BE) Approach for OINDPs

- **<u>BE – locally-acting OINDPs</u>:*** ***Absence of significant difference*** in which the drug becomes available at the ***site of action (i.e., lungs and nasal cavity).***

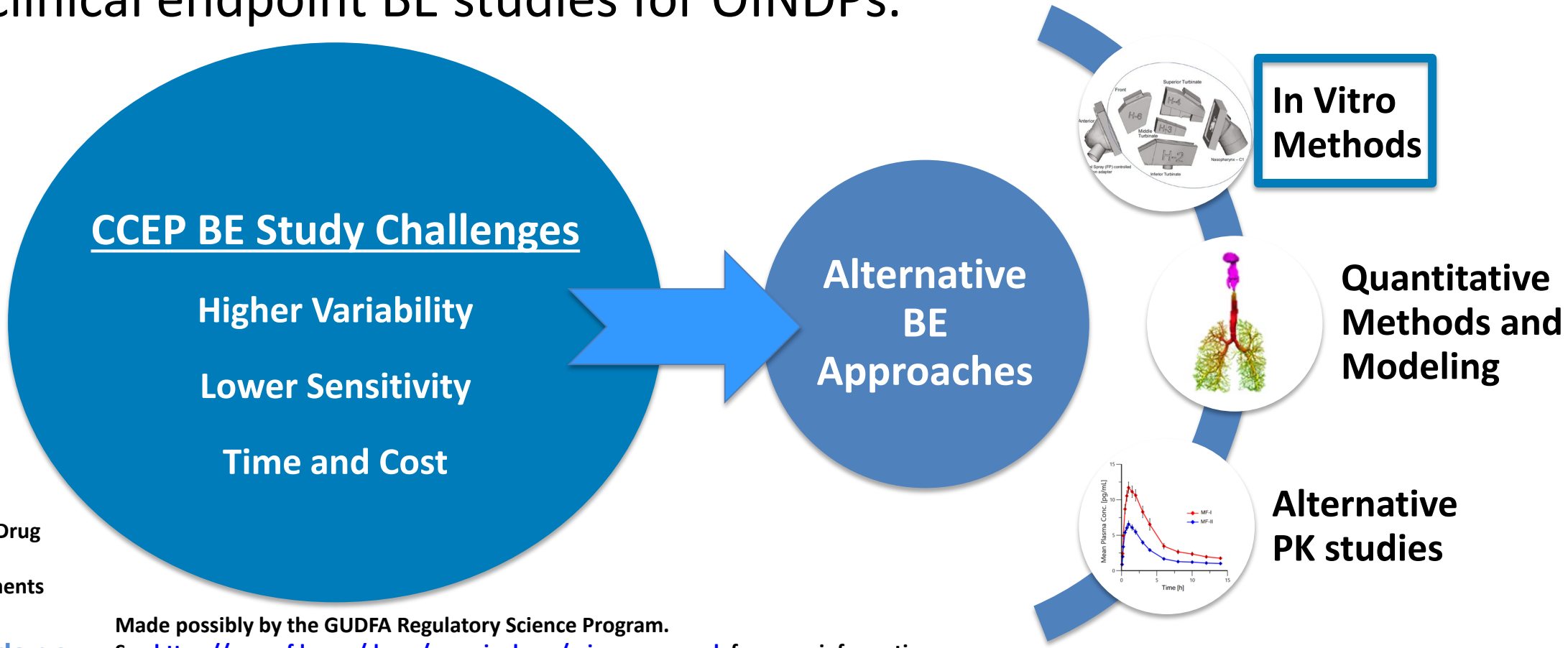
<u>Locally-acting OINDPs</u>: Locally-acting nasal suspensions, metered dose inhalers (MDIs), and dry powder inhalers (DPIs)



BE: Bioequivalence; OINDPs: Orally Inhaled and Nasal Drug Products; PK: pharmacokinetic; PD: pharmacodynamic

GDUFA Research Initiatives for OINDPs

- Implement ***in vitro methods*** together with PK and certain other methods (e.g., in silico) as alternatives to the use of comparative clinical endpoint BE studies for OINDPs.[1]

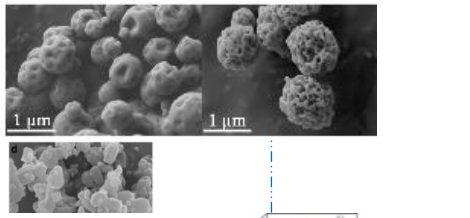


Generic Drug User Fee Amendments (GDUFA)

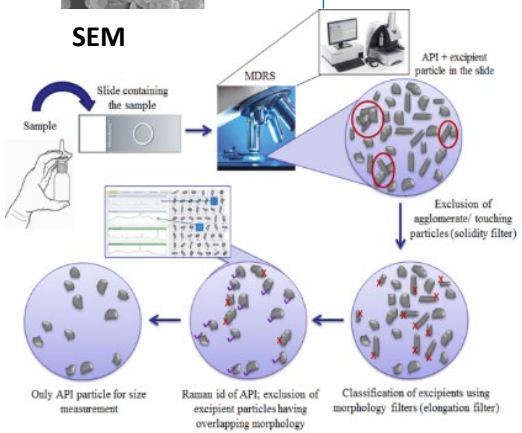
Made possibly by the GUDFA Regulatory Science Program.
See https://www.fda.gov/drugs/generic-drugs/science-research for more information.

GDUFA Research Activities for OINDPs

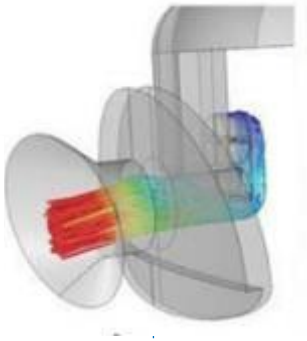
Formulation → Device → User Interface → ***Regional Deposition*** → Dissolution → Absorption



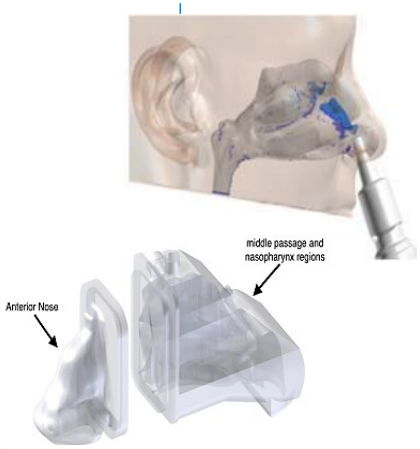
SEM



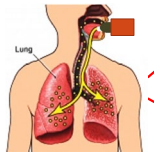
MDRS



HF CONSIDERATIONS



OUTCOME



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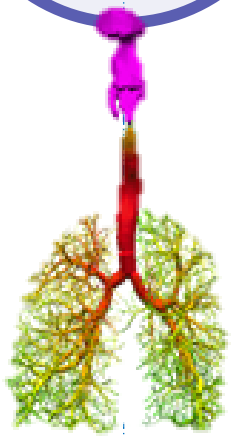
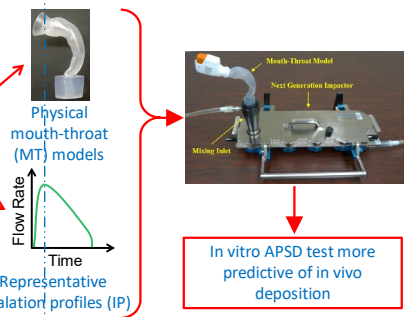
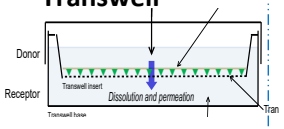


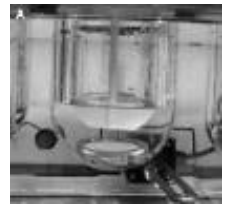


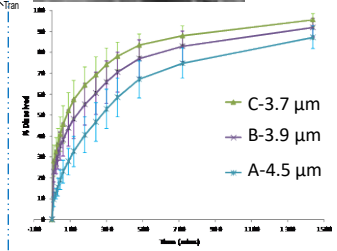
Transwell

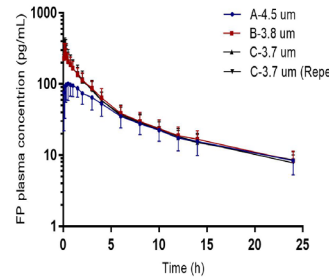


In vitro APSD test more predictive of in vivo deposition

Paddle Over Disk

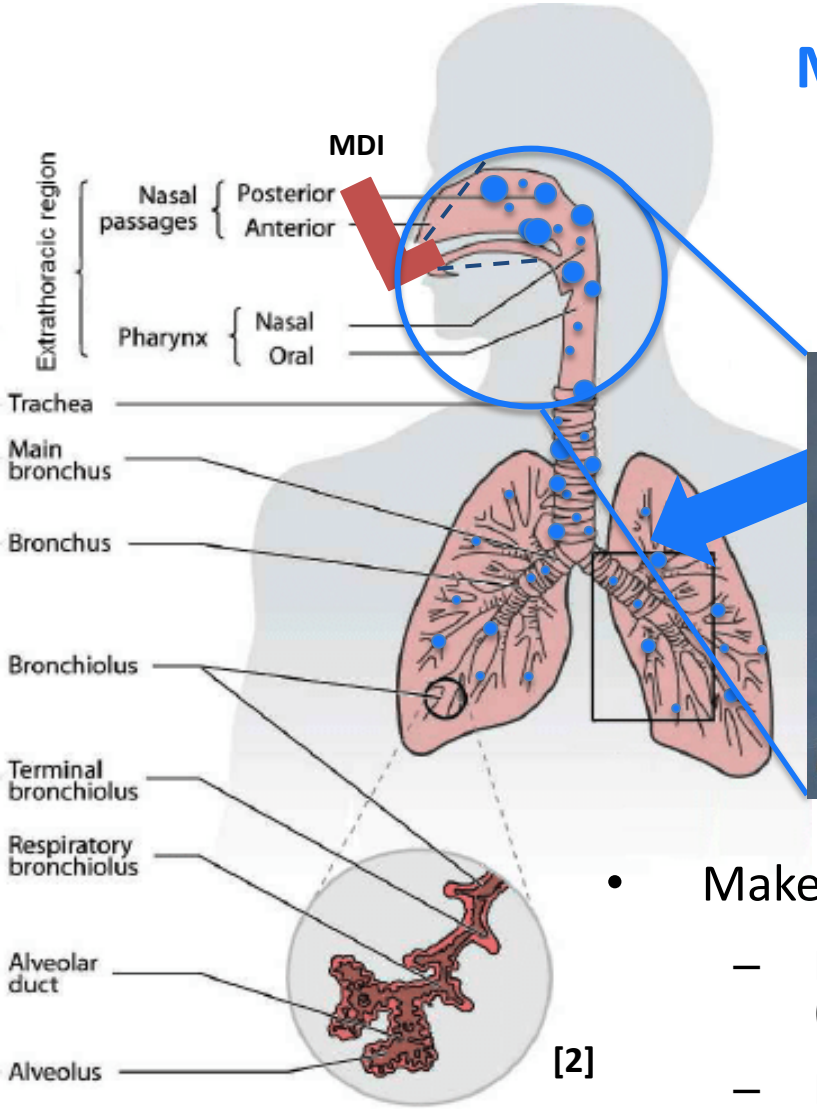






www.fda.gov

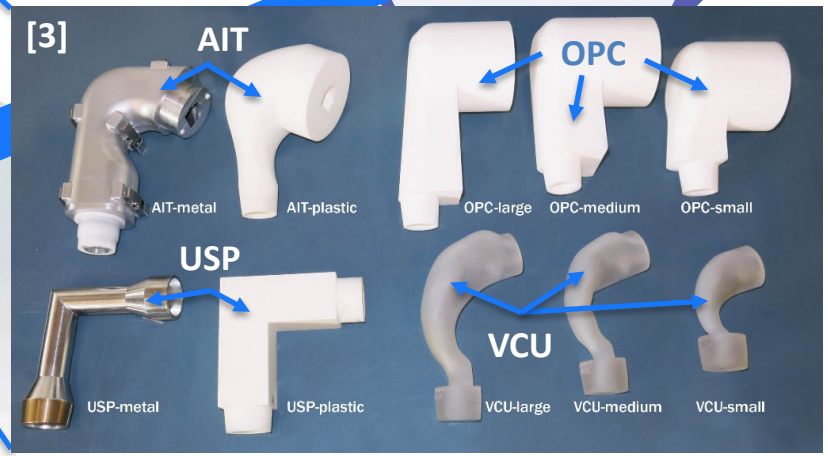
Research on Anatomical Models for OINDPs



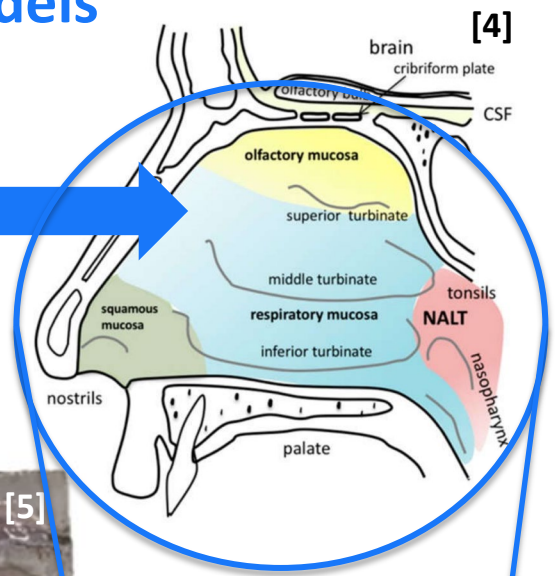
[2]

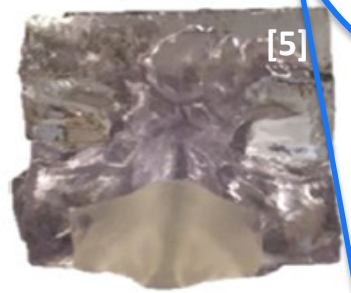
Mouth-Throat (MT) Models

Regional Deposition

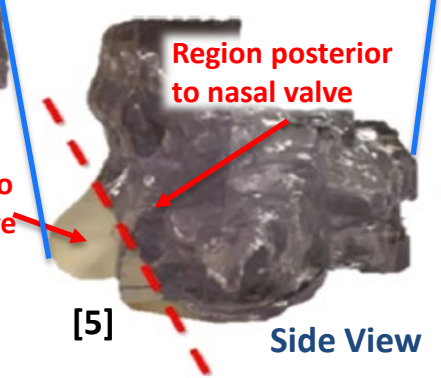


Nasal Models





Front View



3D-Printed Nasal Replica

- Make in vitro testing more ***patient-centric.***
  - Reflect more closely regional deposition seen in ***patients*** (capture variability seen in the clinical setting).
  - Help establish ***in vitro-in vivo correlations (IVIVCs).***

USP: United States Pharmacopeia induction port; AIT: Alberta Idealized Throat; OPC: Oropharyngeal Consortium; VCU: Virginia Commonwealth University

Study 1: Metered Dose Inhalers (MDIs)

Realistic Anatomical Models: Evaluation of Droplet and Aerodynamic Particle Sizes

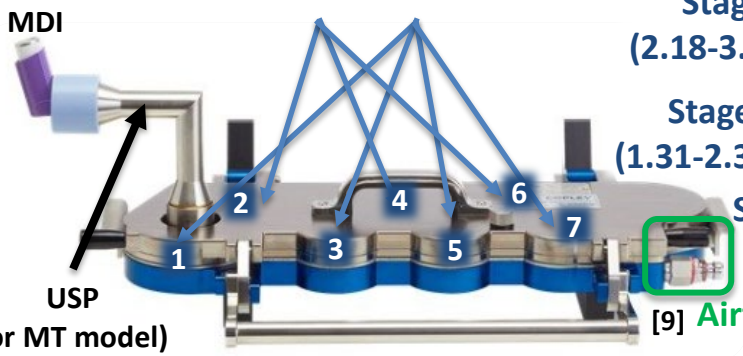
More Realistic In Vitro Particle Sizing of OIDPs

- **In vitro methods** ***more predictive*** of **in vivo deposition** by incorporating ***patient factors***.[7,8]

More Predictive/ Realistic APSD (rAPSD)

NGI: Next Generation Impactor

Aerosol fractions captured by impaction stages (Stage 1-Stage 7)



Each stage represents different region in the lung

Stage 1 (6.12-11.72 µm)

Stage 2 (3.42-6.40 µm)

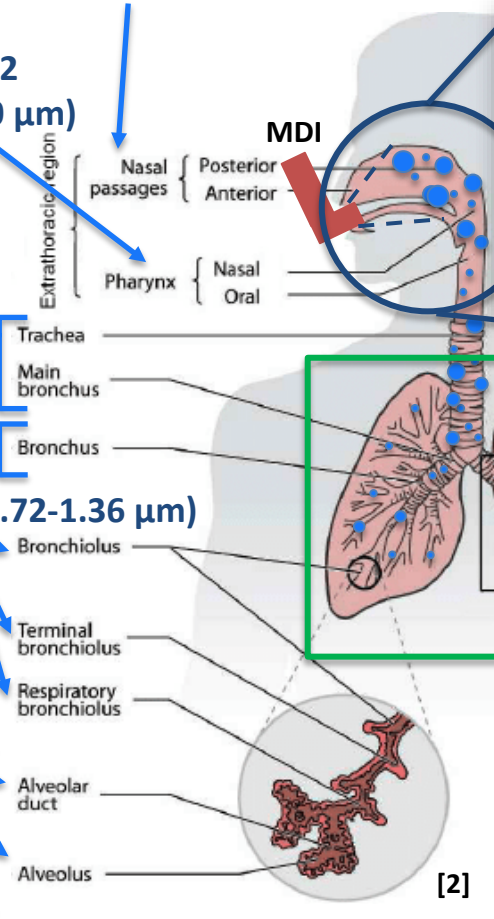
Stage 3 (2.18-3.99 µm)

Stage 4 (1.31-2.30 µm)

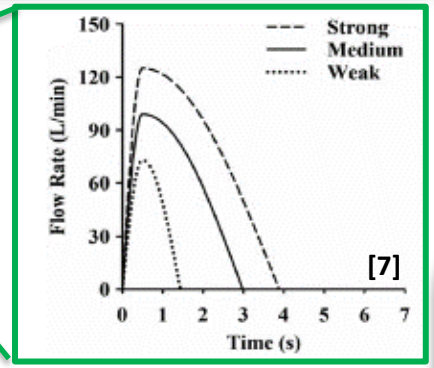
Stage 5 (0.72-1.36 µm)

Stage 6 (0.40-0.83 µm)

Stage 7 (0.24-0.54 µm)



Realistic mouth-throat (MT) models



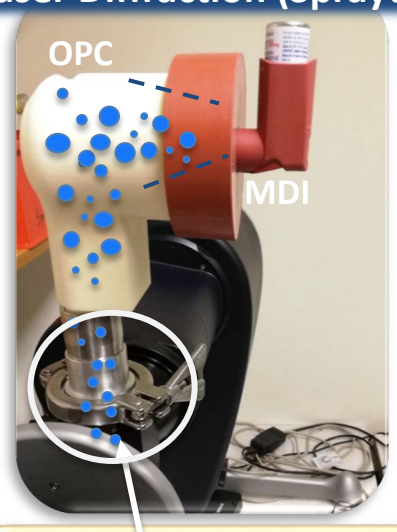
Patient Modeled Inhalation profiles (IPs)

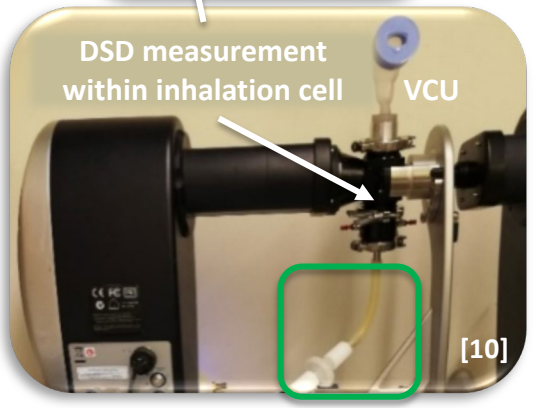
Breathing Profile Generator (not pictured)

rAPSD correlated to rDSD after MT model?

More Predictive/ Realistic DSD (rDSD)

Laser Diffraction (Spraytec)

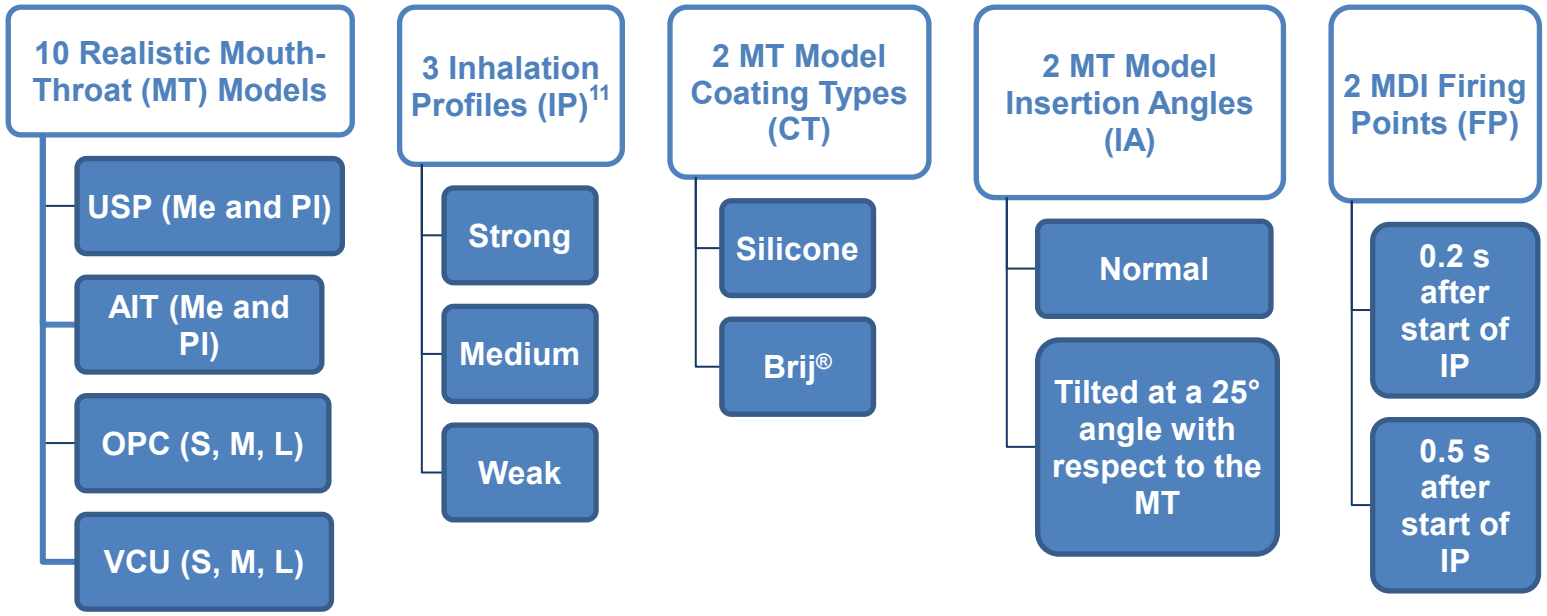




Evaluation of Ex-Throat Plume

Contract 75F40119C10154 "*Systematic Evaluation of the Ex-Throat Plume Properties of MDI Formulations.*" – University of Florida (Principal Investigator: Günther Hochhaus, PhD)*[,3,10]

- **Objective:** Understand how the ***aerodynamic particle size distribution (APSD)*** and the ***droplet size distribution (DSD)*** of a MDI's emitted aerosol may change after passage through a realistic in vitro anatomical mouth-throat (MT) set-up.
- **Design:** A systematic analysis of the effects from various factors (see below) on the ***APSD*** was performed using a reduced factorial design and compared to ***DSD by laser diffraction*** after anatomical MT for 3 U.S. commercial MDIs .



Commercial MDI Products

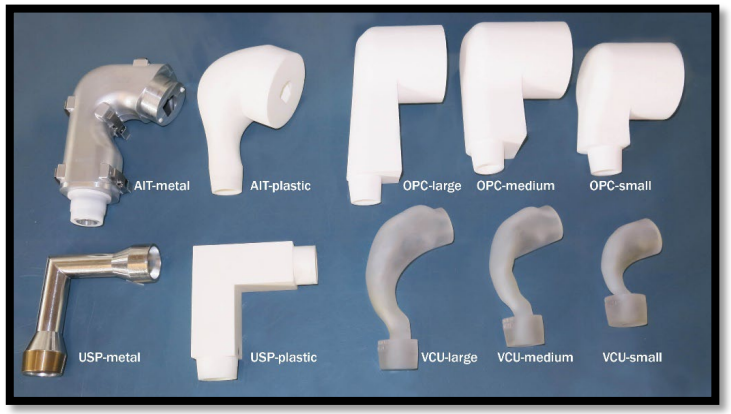
Product	API(s)	Formulation
FP MDI	Fluticasone Propionate	Suspension
Bud/FF MDI	Budesonide (Bud), Formoterol Fumarate Dihydrate (FF)	Suspension
IP MDI	Ipratropium Bromide	Solution

USP: United States Pharmacopeia induction port; AIT: Alberta Idealized Throat; OPC: Oropharyngeal Consortium; VCU: Virginia Commonwealth University; Me: Metal; Pl: Plastic; S: small; M: medium; L: large

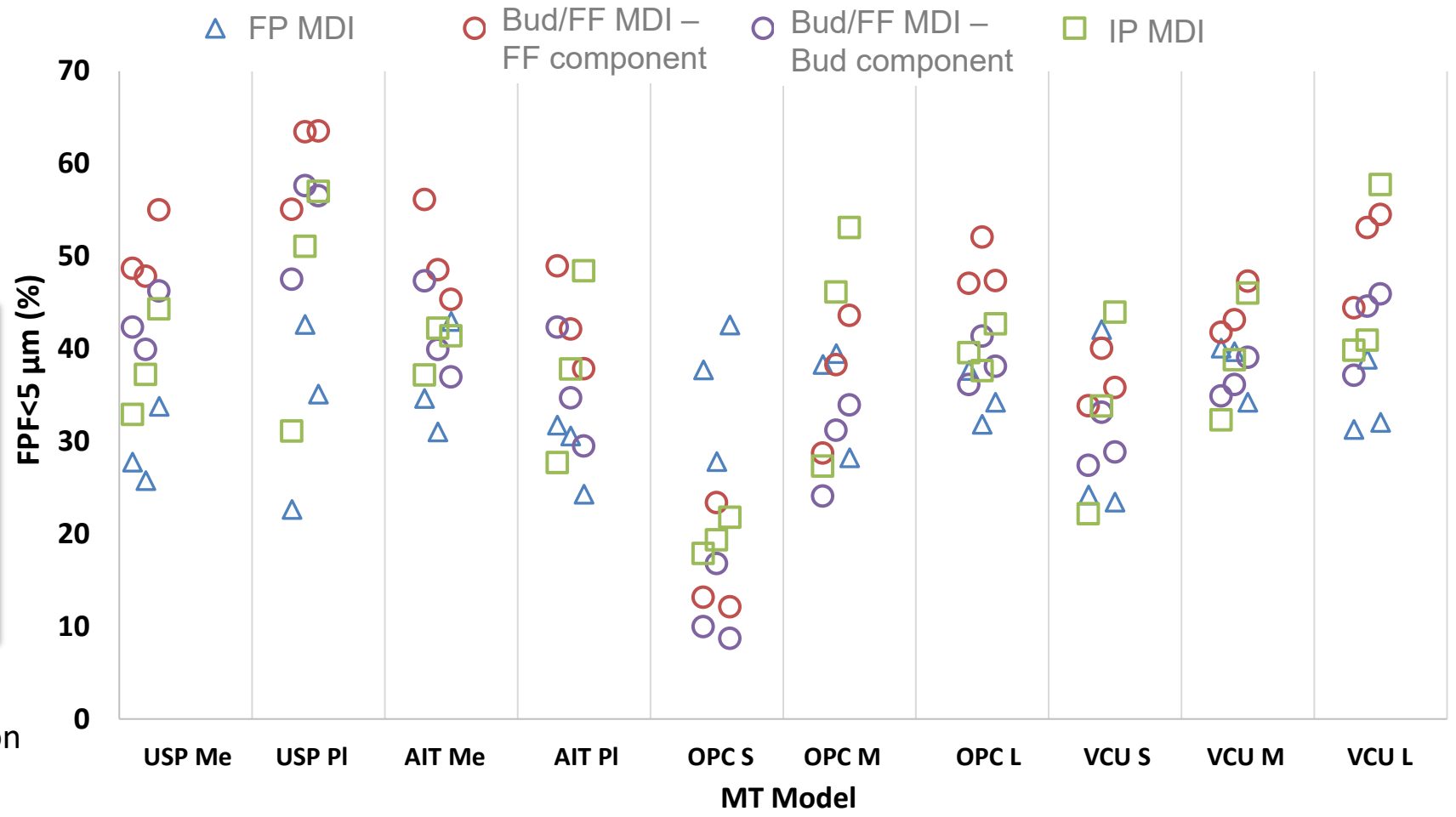
 ***in collaboration with Emmace Consulting AB and S5 Consulting**

rAPSD Results

- **rAPSD – FPF<5 µm**:[3] Statistical differences (p<0.05) found with…
  - **MT model choice**
  - IP (weak, medium, and strong)
  - FP (0.2 and 0.5 s after



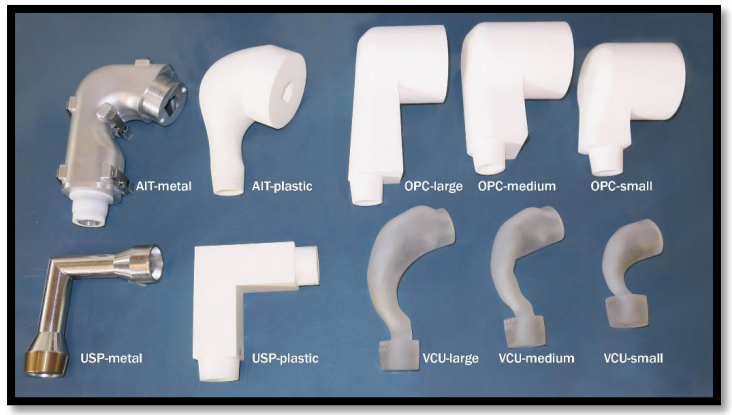
FPF<5 µm: ***Fine particle fraction*** of particles smaller than 5 µm (i.e., fraction of the aerosol that reaches the lungs)

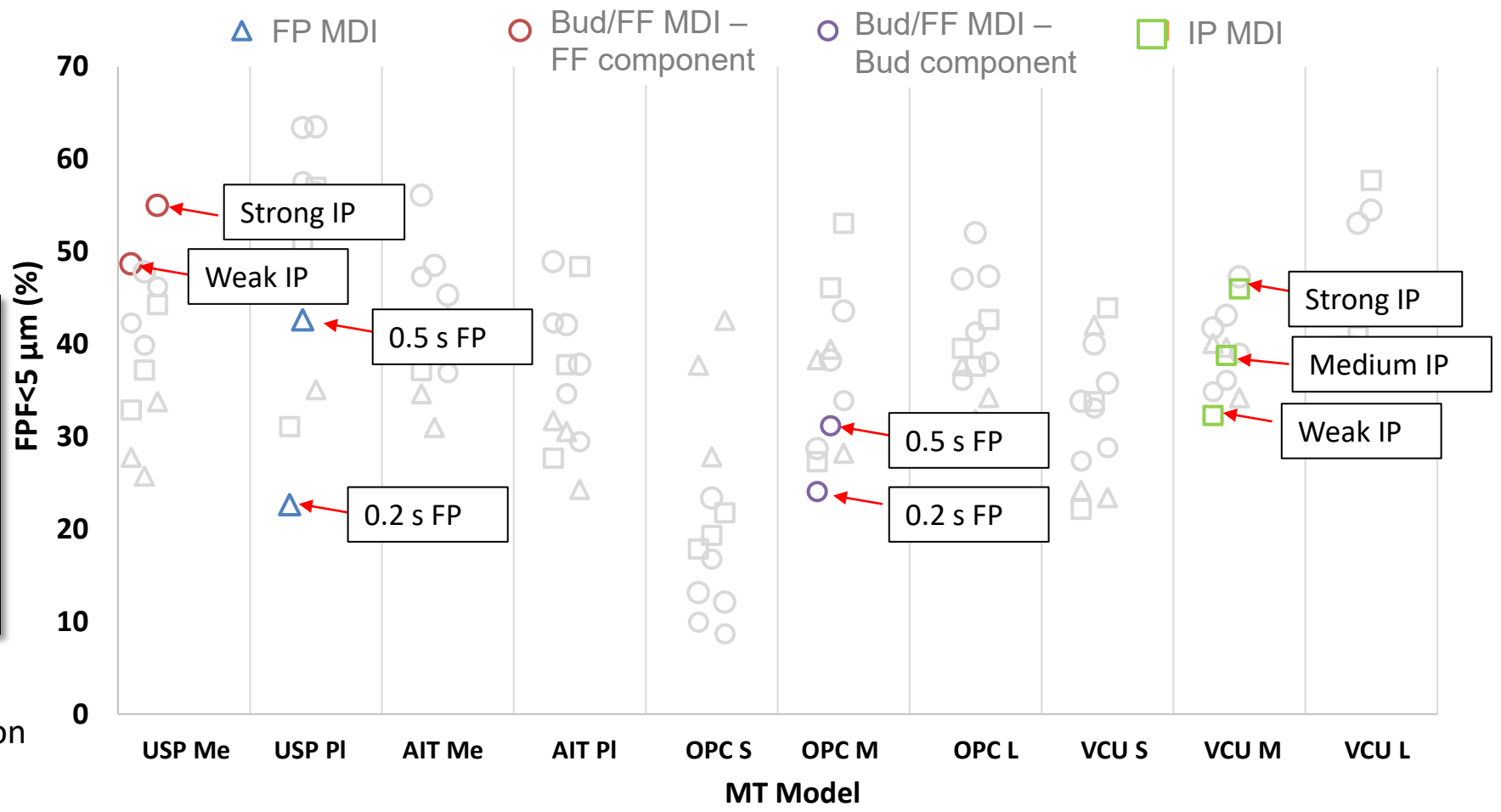


USP: United States Pharmacopeia induction port; AIT: Alberta Idealized Throat; OPC: Oropharyngeal Consortium; VCU: Virginia Commonwealth University

rAPSD Results cont.

- **rAPSD – FPF<5 µm**:[3] Statistical differences found with…
  - MT model choice
  - **IP (weak, medium, and strong)**
  - **FP (0.2 and 0.5 s after**





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USP: United States Pharmacopeia induction port; AIT: Alberta Idealized Throat; OPC: Oropharyngeal Consortium; VCU: Virginia Commonwealth University

rDSD by Laser Diffraction Results

- Choice of the **mouth-throat (MT) model** had the **strongest effect** on droplet size distributions (***Dv10***, ***Dv50***, ***Dv90)***, and average transmission (***AT***), followed by inhalation profile (***IP***).[10]
- Much **smaller** effects for ***insertion angle (IA)*** and ***firing point (FP)***.[10]

Eta-square values for each factor. Eta-square = 0.06 indicates a medium effect and eta-square = 0.14 indicates a large effect. Values ≥ 0.14 are shown in red and values ≥ 0.06 are shown in blue.[10]

Product	rDSD Parameter	eta-square				
		MT	IP	CT	IA	FP
FP MDI	Dv10	0.4336	0.0037	0.0830	0.0000	0.0065
	Dv50	0.1711	0.0311	0.1886	0.0237	0.0078
	Dv90	0.2210	0.0864	0.0569	0.0167	0.0025
	AT	0.2467	0.0039	0.1053	0.0000	0.0057
Bud/FF MDI	Dv10	0.0320	0.2264	0.0051	0.0179	0.0957
	Dv50	0.3266	0.0867	0.0005	0.0084	0.0256
	Dv90	0.4611	0.0577	0.0011	0.0000	0.0262
	AT	0.3357	0.0183	0.0183	0.0097	0.0168
IP MDI	Dv10	0.1962	0.0416	0.0210	0.1244	0.0041
	Dv50	0.3888	0.0622	0.0220	0.0251	0.0019
	Dv90	0.2353	0.1063	0.0143	0.0285	0.0213
	AT	0.5191	0.0256	0.0232	0.0151	0.0001

Large Effect ***Medium Effect***

Correlations between rAPSD and rDSD

- ***APSD measures (MMAD, FPF<5 µm, and FPD<5 µm)*** of **Bud/FF MDI (Bud component)** showed **highest** correlation ***(|r|>0.6)*** to Dv50.[3]
- ***Correlation*** were **insignificant** between ***rAPSD*** based parameters and ***rDSD*** parameters for other MDIs.[3]

MDI	rAPSD-derived parameters	Laser diffraction-based Dv50 (rDSD)	Laser diffraction-based AT (rDSD)
FP MDI	MMAD	0.21	0.34
	FPF<5 µm	0.12	0.17
	FPD<5 µm	0.10	0.10
	In Vitro Lung Dose	0.03	0.02
Bud/FF MDI – FF Component	MMAD	0.28	0.02
	FPF<5 µm	0.09	0.01
	FPD<5 µm	0.12	0.00
	In Vitro Lung Dose	0.01	0.00
Bud/FF MDI – Bud Component	MMAD	**0.75**	0.16
	FPF<5 µm	**0.67**	0.22
	FPD<5 µm	**0.75**	0.05
	In Vitro Lung Dose	0.58	0.01
IP MDI	MMAD	0.42	0.05
	FPF<5 µm	0.51	0.01
	FPD<5 µm	0.53	0.14
	In Vitro Lung Dose	0.27	0.01

MMAD: Mass median aerodynamic diameter
FPF<5µm: Fine particle fraction of particles smaller than 5 µm
FPD<5µm: Fine particle dose of particles smaller than 5 µm
In Vitro Lung Dose: Dose exiting the MT model

FP: Fluticasone Propionate; Bud: Budesonide; FF: Formoterol Fumarate; IP: Ipratropium Bromide
AT: Average Transmission (%)

Study 1 - MDIs: Summary of Outcomes

- **Realistic in vitro APSD** testing should consider the effect of different experimental conditions, particularly the type of ***MT model***, ***inhalation profile (IP)*** and MDI ***firing point (FP)*** on APSD of **solution or suspension MDIs**.[3]

- **Limited product-specific correlations** between the ***rAPSD-derived parameters*** and ***rDSD*** suggests that ***rDSD*** may serve as an additional ***supporting characterization method*** rather than an alternative to ***rAPSD testing***.[3]

Study 2: Nasal Drug Products (NDPs)

Realistic Anatomical Models: Development, Characterization, and Outcomes

In Vitro Anatomical Nasal Models

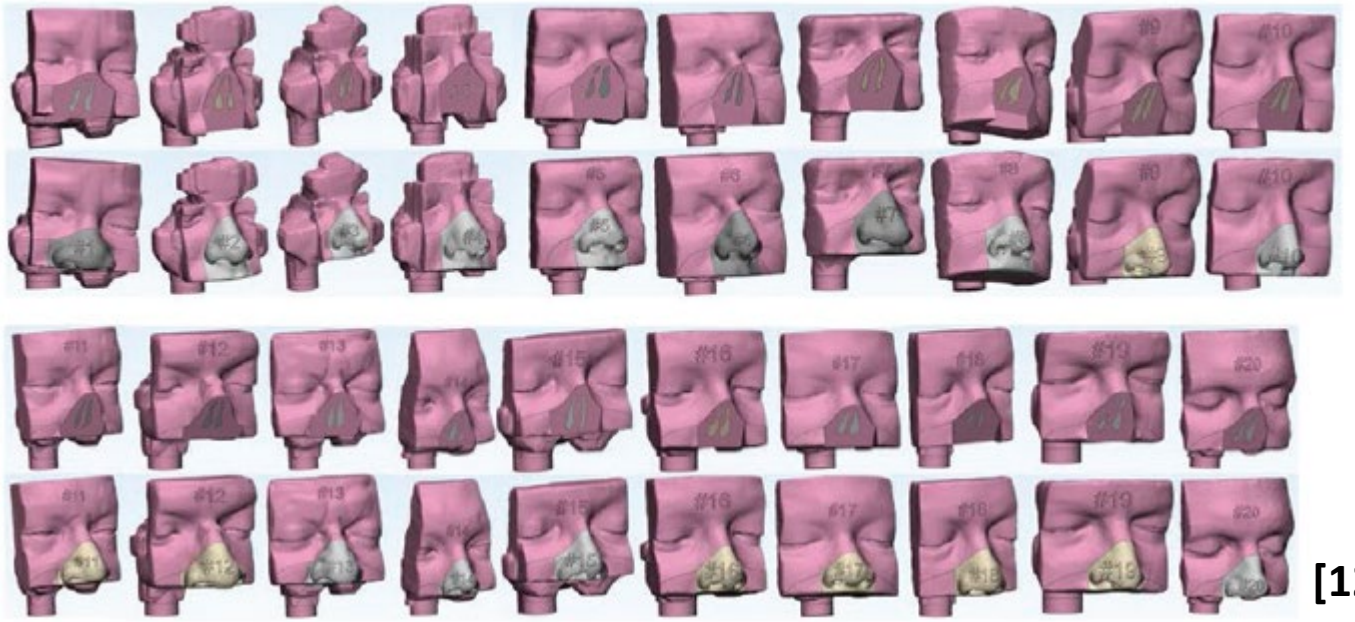
Contract HHS223201810144C *"Evaluating Relationships Between In Vitro Nasal Spray Characterization Test Metrics for Bioequivalence and Nasal Deposition In Silico and In Vitro"* – Virginia Commonwealth University (Principal Investigator: Laleh Golshahi, PhD)[5,12,13,14]

- ***Regional deposition*** may often be a good indicator of ***product performance*** of NDPs.
  - No standardized in vitro anatomical nasal models
- **Objective:** Develop a set of realistic adult nasal model replicas that capture inter-subject variability of regional deposition from suspension-based NDPs.

Anatomical Nasal Models: Development

- A set of 20 nasal model replicas based on subject-specific CT scan data were generated using rapid prototyping and divided into ***anterior and posterior regions*** using a method developed in Hosseini S. et al 2020.[12,14]

- Measure regional deposition for anterior and posterior regions of each side of nasal cavity (40 geometries).[13]
  - Target: **Posterior Deposition (PD)**, the entire region posterior to intranasal valve



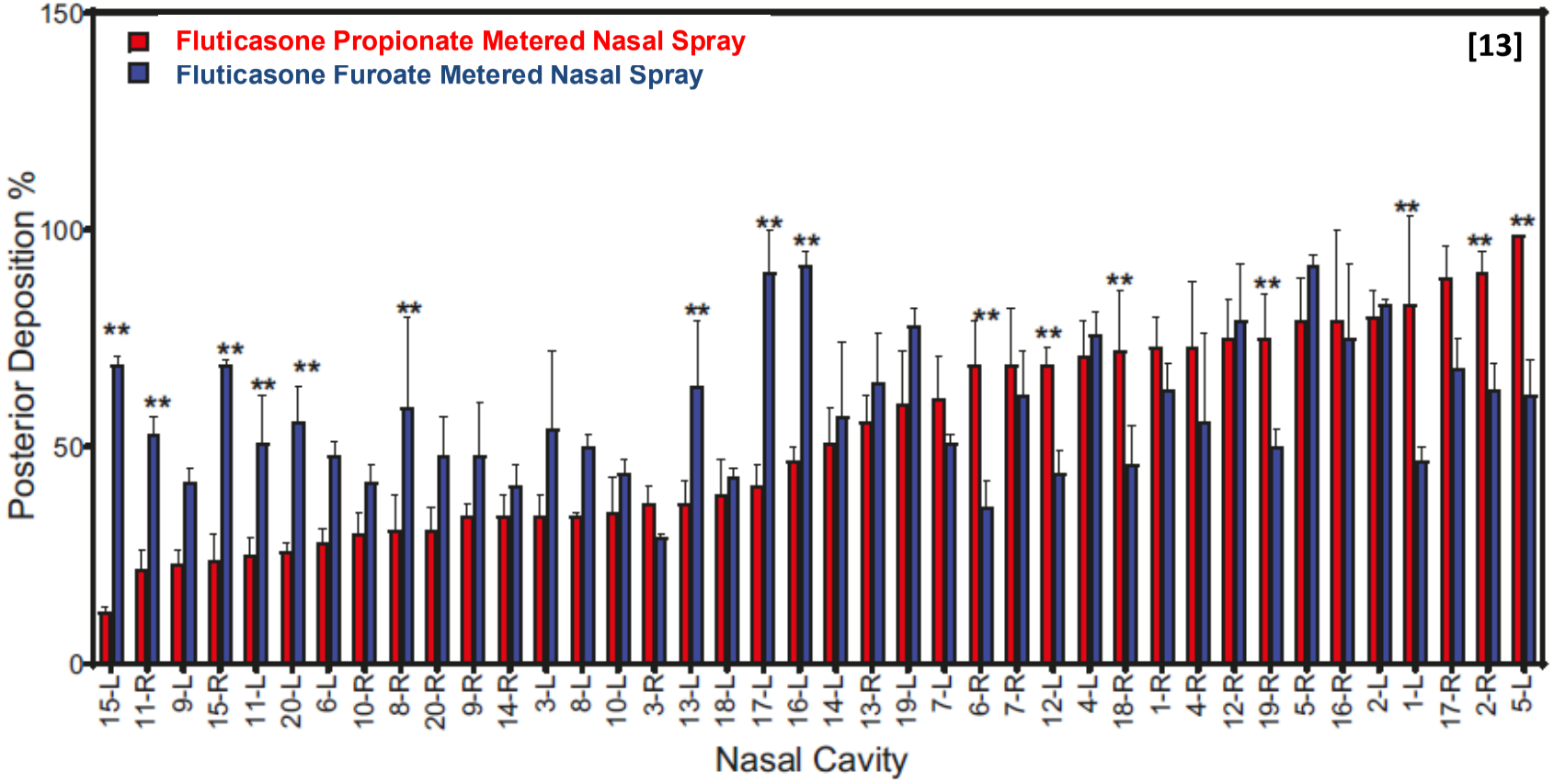
[12]

[5]

3D-printed Nasal Replica

Anatomical Nasal Models Evaluation

- **Posterior Deposition (PD)**
  [% total recovered dose][13]
  - **Fluticasone Propionate Metered Nasal Spray: 12-99%**
  - **Fluticasone Furoate Metered Nasal Spray: 29-92%**
  - Mean was comparable between the two drug products with a mean **~ 58%**



- ***Reduce number of in vitro experiments while representing a reasonable degree of inter-subject variability***
- ***Narrow down nasal models to represent a minimum, mean, and maximum PD***

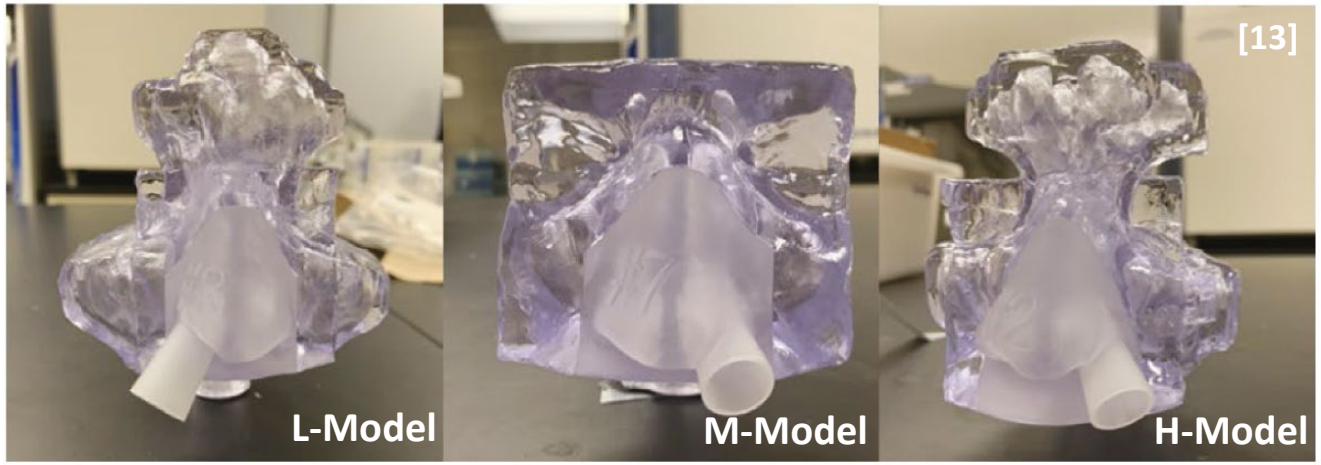
L-Model, M-Model, and H-Model

- Three models chosen representing minimum (**L-Model**), mean (**M-Model**), and maximum (**H-Model**) represent three distinct and statistically different levels of Posterior Deposition (PD).[13]

Posterior deposition (PD) of Fluticasone Propionate (FP), Fluticasone Furoate (FF), and Mometasone Furoate (MF) from three suspension nasal spray products.[13]

Posterior Deposition (PD)	Replica – Nostril	Age	Gender	Mean ± SD PD (% Recovered Dose FP)	Mean ± SD PD (% Recovered Dose FF)	Mean ± SD PD (% Recovered Dose MF)
Low (L)	3 – Right	63	F	36.5±4.0	28.8±1.0	24.5±3.9
Mean (M)	7 – Left	35	M	60.5±10.0	51.4±2.0	46.7±7.6
High (H)	2 – Left	22	F	80.3±6.0	83.5±1.0	72.7±2.4

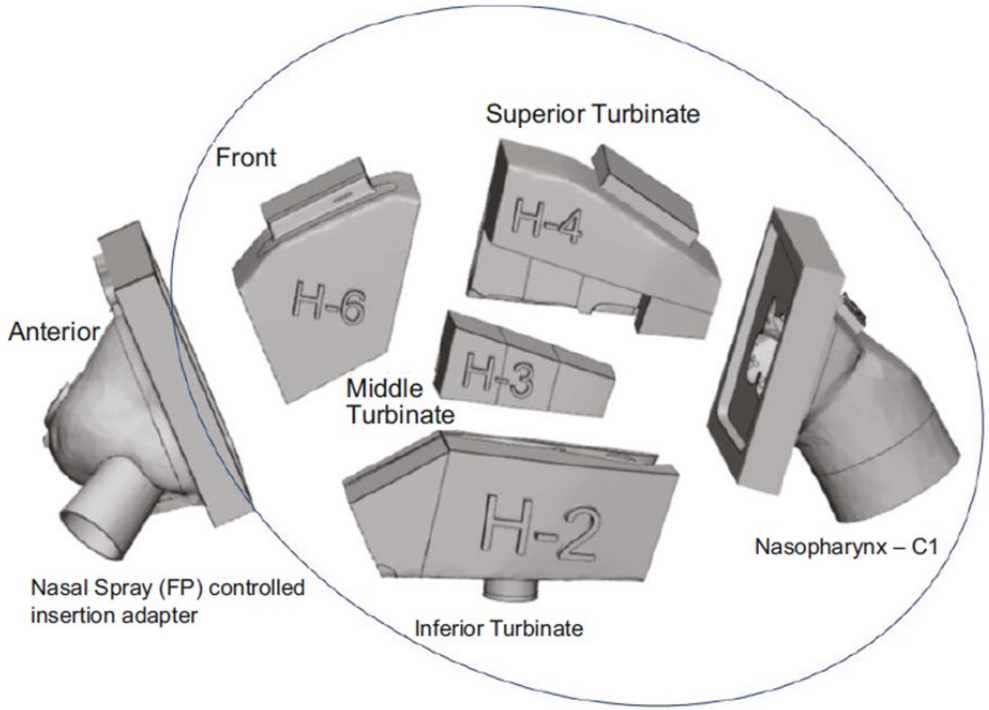
Rapid prototyped anatomically-accurate nasal airway replicas with nozzle holders



- **In Vitro to In Vivo Comparisons – Mometasone Furoate Metered Nasal Spray – PD**
  - Nasal Models: **22-75%**
  - In vivo (literature):[15] **53-67%**
- **Differences**
  - Uncontrolled patient administration in vivo
  - Dosing
  - Patient populations
  - Discrepancies between defining anterior vs. posterior regions

Deeper Dive into Posterior Deposition

- Further exploration of posterior deposition (PD) by dividing into five smaller subregions: ***front, nasopharynx, superior-, middle-, and inferior-turbinate.***[13]



The anterior cavity of the H-Model is shown with a nozzle holder for Flonase and its posterior region (circled) segmented to regional sections to provide a more detailed picture of local drug distribution.[13]

Regional Nasal Deposition of Fluticasone Propionate (FP) from an FP Nasal Spray.[13]

Posterior Section	Mean ± SD PD (% Recovered Dose FP)		
	L-Model	M-Model	H-Model
Anterior	64.1±0.9	52.5±0.8	23.2±4.2
Front	**15.8±1.2**	**22.4±1.1**	**37.9±4.5**
Inferior	**17.2±1.0**	**20.0±2.1**	**32.4±6.1**
Middle	1.2±0.5	3.0±1.4	3.0±2.4
Superior	0.0±0.0	2.3±1.1	1.6±1.0
Nasopharynx	0.7±0.1	0.0±0.0	1.8±0.2

>90% drug deposits in the front and inferior-turbinate regions, despite common notion that middle-turbinate should be the main target for locally-acting steroids.[13]

Study 2 - NDPs: Summary of Outcomes

- **Successful development** of three nasal models (***L-Model, M-Model, and H-Model***) that represent low, mean, and high posterior nasal cavity deposition.
- Early indications that the nasal models are capable of ***capturing posterior deposition*** within the range seen for ***in vivo deposition.***
- ***>90%*** drug deposits in the ***front and inferior-turbinate regions***, despite common notion that middle-turbinate should be the main target for locally-acting steroids.

Ongoing Work

- ***In vitro-In vivo Correlations*: Understand how in *vitro spray characteristics* may correlate to *regional nasal deposition*.**
- ***Continued in silico modeling efforts***
  - ***Hybrid CFD-PBPK models* to predict PK outcomes in the low, medium, and high delivery models.**
- ***Follow-on contract (75F40120C00172) to extend work for development of *anatomical nasal models of children.***

Conclusions

- More biorelevant in vitro tests with ***anatomical models*** that consider ***patient anatomical features*** may ***better predict local drug deposition*** and, thus, support **alternative approaches** to the **comparative clinical endpoint BE studies** recommended for **OINDPs**.
  - **MDIs:**
    - ***Realistic APSD*** testing is able to **incorporate patient variability** (via anatomical MT models and IPs) so that APSD may be more predictive of in vivo deposition. However, the ***effect of experimental conditions*** (e.g., ***MT model***, ***inhalation profile*** and MDI ***firing point)*** must be considered and optimized for testing.
    - ***rDSD by laser diffraction*** **may not be an alternative** for ***rAPSD measurements***, rather complementary and supportive characterization and, perhaps, useful for in silico modeling.
  - **NDPs:**
    - Successful **development**, **optimization**, and **testing** of ***adult nasal anatomical models.***
    - Continued testing to possibly establish ***in vitro – in vivo correlations*** ***(in vitro spray characteristics*** impact ***regional nasal deposition)*** (ongoing).
    - May be useful for inputs and optimization of ***in silico models*** (ongoing).
    - Extension of nasal models specific to the nasal anatomy of ***children*** (ongoing).

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