Considerations for Conducting More Realistic Aerodynamic Particle Size Distribution Testing for Orally Inhaled Drug Products

FDA-CRCG Workshop on Considerations for and Alternatives to Comparative Clinical Endpoint and Pharmacodynamic Bioequivalence Studies for Generic Orally Inhaled Drug Products

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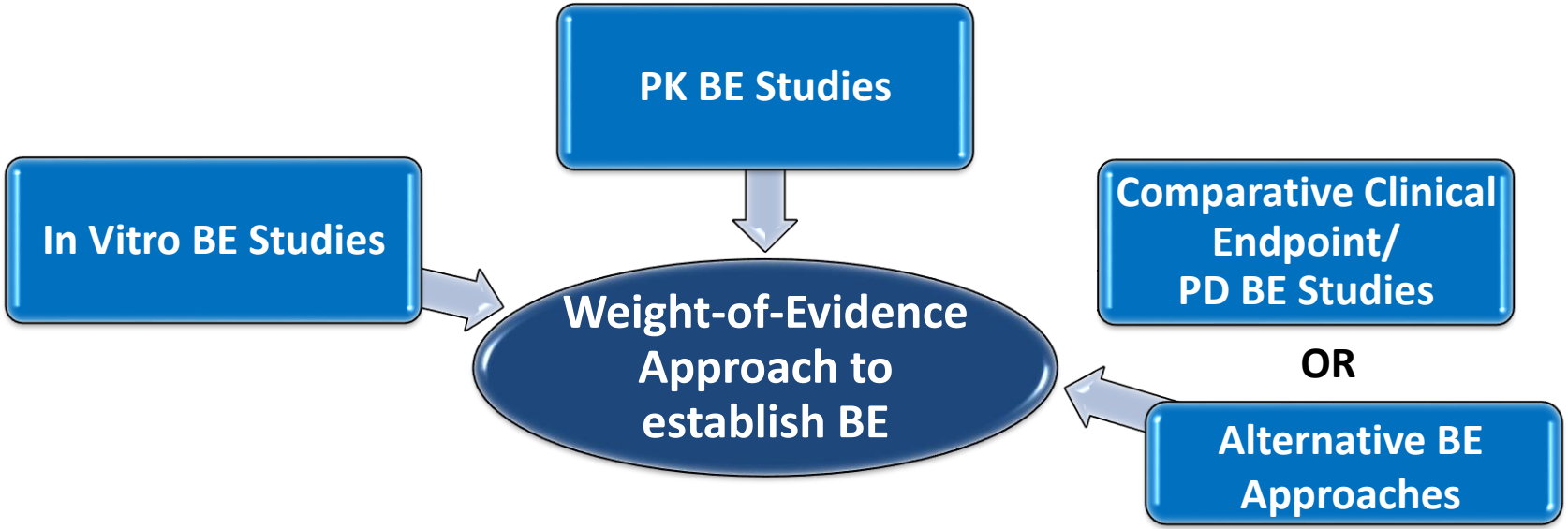
Weight of Evidence Approach for OIDPs

Bioequivalence (BE) recommendations for metered dose inhalers (MDIs) and dry powder inhalers (DPIs) include formulation sameness and device similarity, in addition to



OIDPs: Orally Inhaled Drug Products
PK: pharmacokinetic; PD: pharmacodynamic

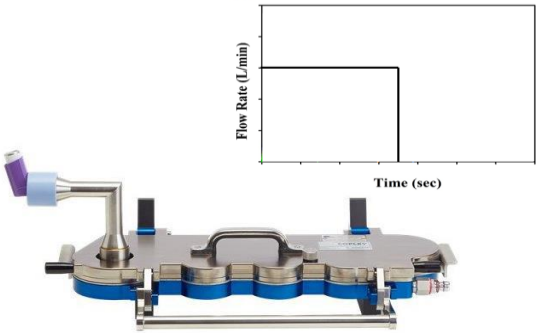
Suggested Studies for Alternative BE Approaches for OIDPs[1-4]

- Characterization of Emitted Sprays via velocity profiles and evaporation rates
- Morphology Imaging Comparisons of the full range of residual drug particle sizes
- **More Realistic APSD Testing using representative mouth-throat models and inhalation profiles**
- Dissolution
- Quantitative Methods and Modeling (e.g., Physiologically-based PK and computational fluid dynamics studies)
- Alternative PK BE Studies

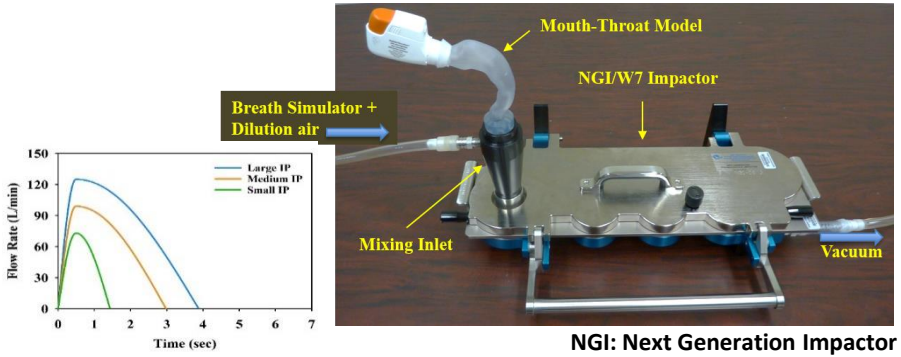
APSD: Aerodynamic Particle Size Distribution
PK: Pharmacokinetics

More Realistic APSD Testing

- Compendial in vitro APSD testing allows for **drug-specific particle size comparison** of formulations
- However, the currently recommended square wave testing provides limited information about clinical performance or the variability of lung delivery[5]
- In vitro APSD testing with realistic **mouth-throat (MT) models** and representative **inhalation profiles (IPs)** may be more predictive of in vivo deposition
  - Conventional APSD testing (with the USP induction port) has been shown to under predict MT deposition,[6] and would thus, overpredict lung deposition
- Results from more realistic APSD testing may be compared to the drug deposition reported in clinical literature to assess which in vitro method (e.g., MT models and/or IPs) offer the best in vitro to in vivo correlations[5]



Compendial in vitro APSD test setup[7]

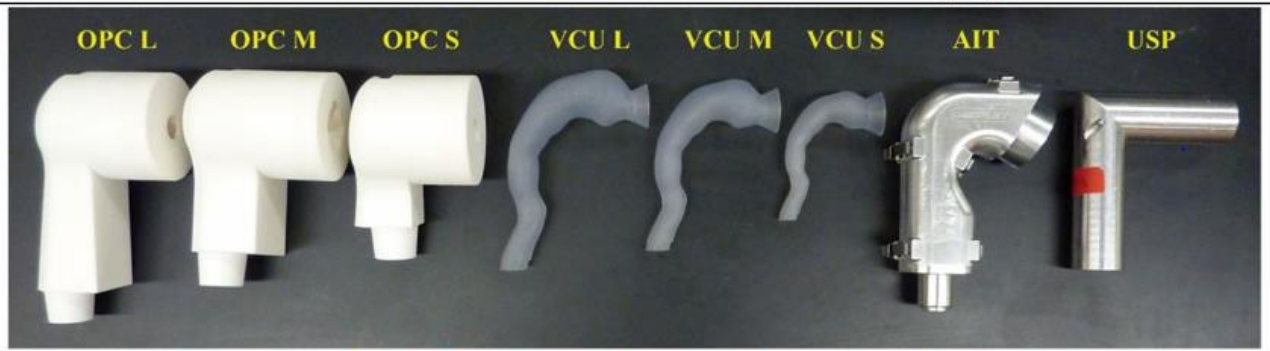
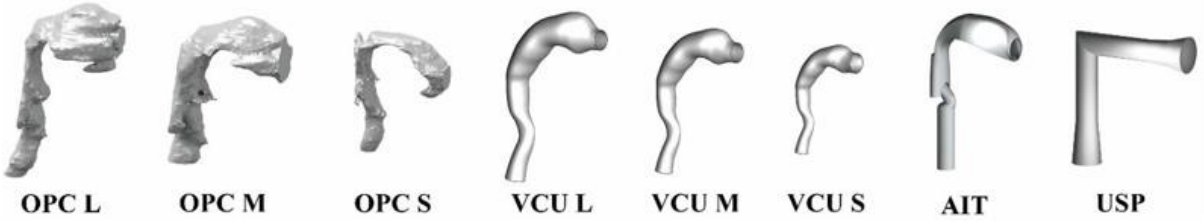


NGI: Next Generation Impactor

Realistic in vitro APSD test setup[8]

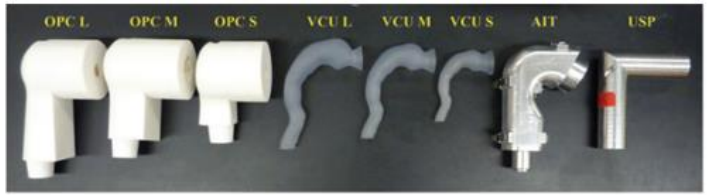
USP: United States Pharmacopeia

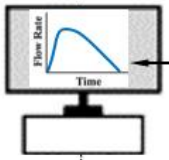
Commercially Available MT Models

Mouth-throat model	Oropharyngeal Consortium (OPC)			Virginia Commonwealth University (VCU)			Alberta Idealized Throat (AIT)	United States Pharmacopeia (USP)
Side view [9]								
Internal volume [10,11]	84.4 cm^3	91.7 cm^3	27.6 cm^3	96.1 cm^3	61.6 cm^3	26.6 cm^3	75.4 cm^3	67.3 cm^3
Internal geometry [9]								

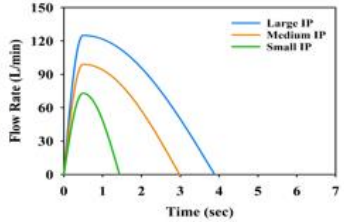
L: Large; M: Medium; S: Small

Example Experimental Test Setup





Inhalation Profile



Realistic Mouth-Throat Model

Breath Simulator

Exhale Release Port

Nephele Mixing Inlet

Control Valve

Pressure Regulator

Dilution air at constant flow rate

Next Generation Impactor

Control Valve

Vacuum at constant flow

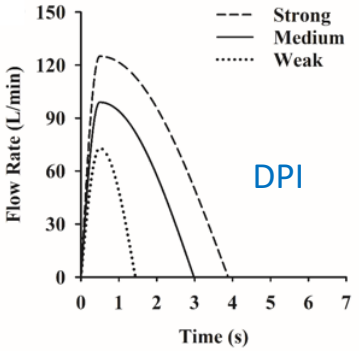
Schematic modified from Tavernini S, et al.[12]

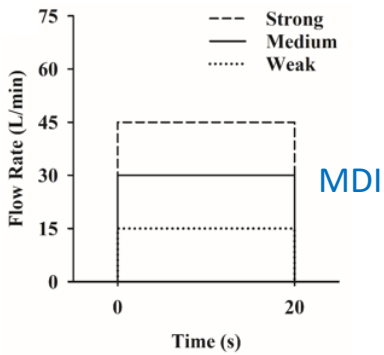
GDUFA Funded Research on Realistic MT Models and IPs

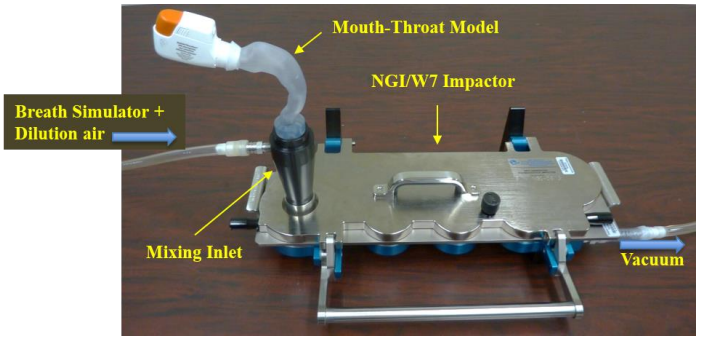
Study 1 - Influence of MT models and IPs on Total Lung Dose

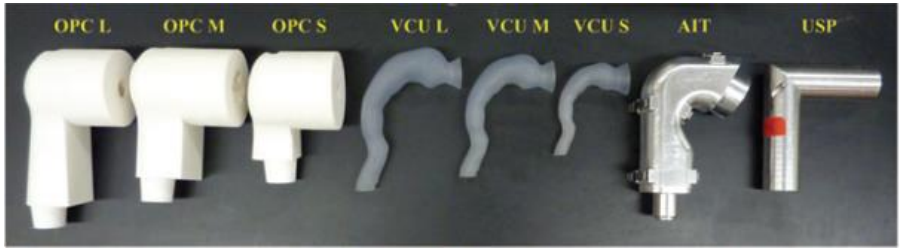
GDUFA-funded research: Virginia Commonwealth University (Principal Investigator, PI: Michael Hindle), Grant #1U01FD005231[9]

- Total Lung Dose in vitro = $TLD_{in\ vitro}$ = Drug mass exiting the MT model
- $APSD_{TLDin\ vitro}$ = the size distribution of drug mass exiting the MT model
- IPs simulated based on reported range of trained volunteers[13,14]
  - DPI: Budelin® Novolizer® (200 µg budesonide, Bud)
  - MDI: Ventolin® Evohaler® (100 µg albuterol as sulfate, AS)









Study 1 - Influence of MT models and IPs on Total Lung Dose

Budesonide (200 µg) DPI; weak-strong realistic IPs

- Overall, variance mostly due to **flow conditions**
- Across VCU models, $TLD_{in\ vitro}$ appeared to be less influenced by IP compared to OPC models
  - **MT model type** can be influential

Albuterol (100 µg as sulfate) MDI; 15-45 L/min

- Overall, variance mostly due to **MT models**
- Across VCU models, $TLD_{in\ vitro}$ appeared to be less influenced by flow compared to OPC models
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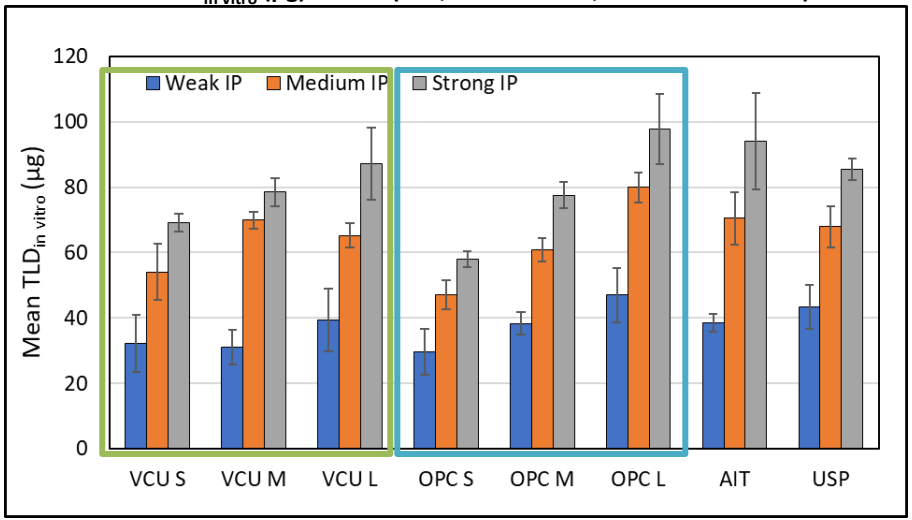
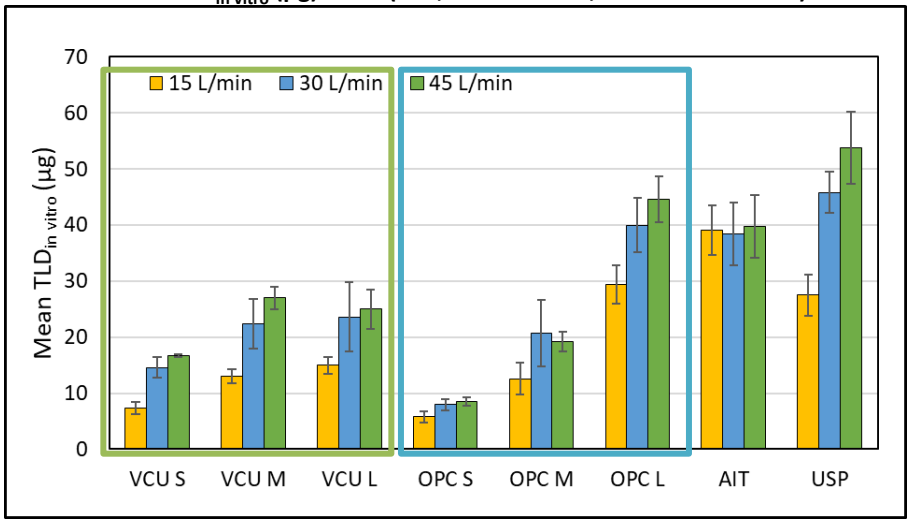
Mean $TLD_{in\ vitro}$ (µg) of Bud (n≥5; mean values, error bars are SDs)



Mean $TLD_{in\ vitro}$ (µg) of AS (n≥5; mean values, error bars are SDs)



Study 1 - Influence of MT models and IPs on Total Lung Dose

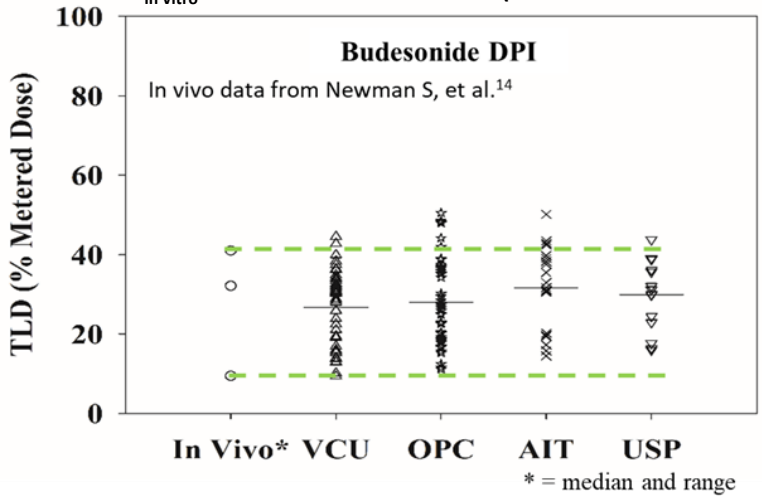
Budesonide (200 µg) DPI; weak-strong realistic IPs

- The four MT groups produced similar in vitro lung deposition to in vivo data (general population)

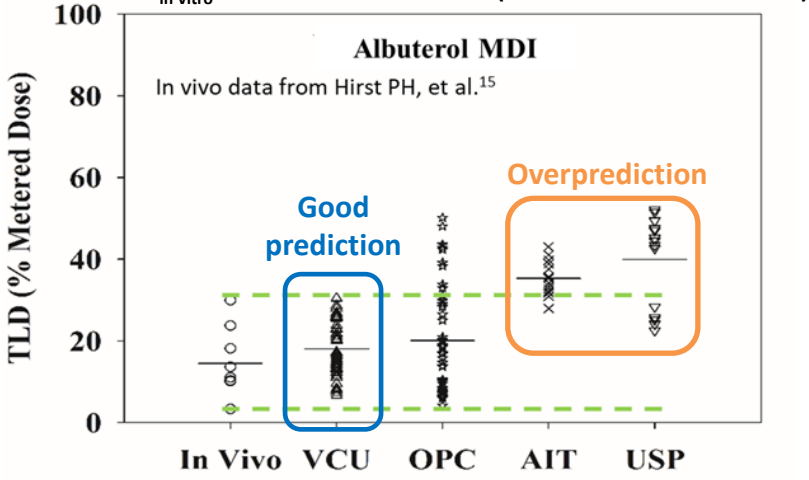
Albuterol (100 µg as sulfate) MDI; 15-45 L/min

- VCU models appeared to produce the most comparable range to the in vivo data

Individual $TLD_{in\ vitro}$ as % metered dose of BUD (solid lines are mean values)



Individual $TLD_{in\ vitro}$ as % metered dose of AS (solid lines are mean values)

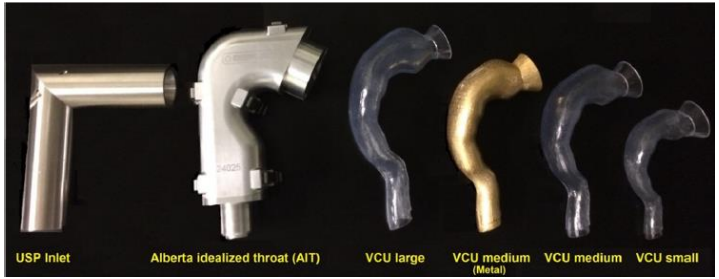


Product-specific results suggest the need to include various MT models (e.g., types and/or sizes) and IPs to capture patient variability

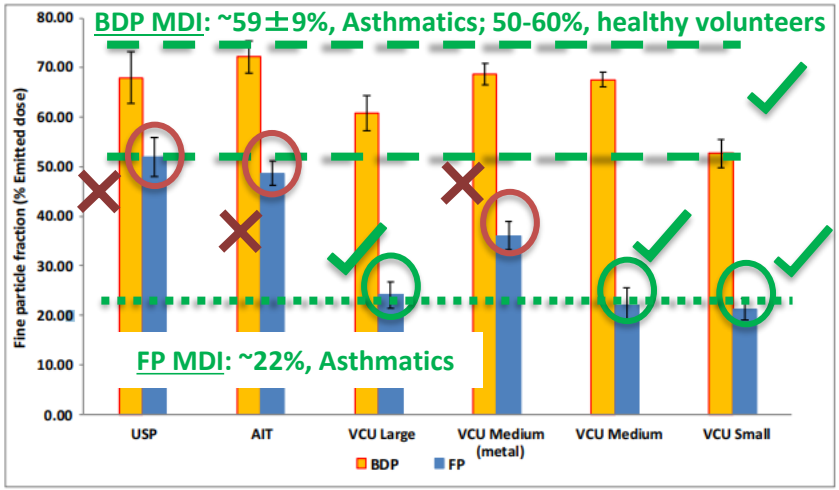
Study 2 - Influence of MT models on Solution and Suspension MDIs

Internal collaboration between OGD/ORS and the Office of Testing and Research in the Office of Pharmaceutical Quality[6]

- APSD testing with Andersen Cascade Impactor (ACI) at a constant flow rate of 28.3 L/min
  - Solution MDI: QVAR® (40 µg beclomethasone dipropionate, BDP)
  - Suspension MDI: Flovent® HFA (44 µg fluticasone propionate, FP)



FPF<5 µm as % emitted dose of BDP and FP (n=5; mean values, error bars are SDs)



FPF<5 µm: Fine particle fraction less than 5 µm

- Suspension-based MDIs like those containing FP appear to be much more sensitive to variations in MT model vs. solution-based MDIs, such as BDP MDI

MDI performance, as evaluated by rAPSD studies, could be influenced by many factors, such as the *type of formulation*, the *geometry*, *shape*, *internal space volume*, and the *material* used to make the MT models

Study 3 – Analysis of additional factors that influence APSD in MDIs

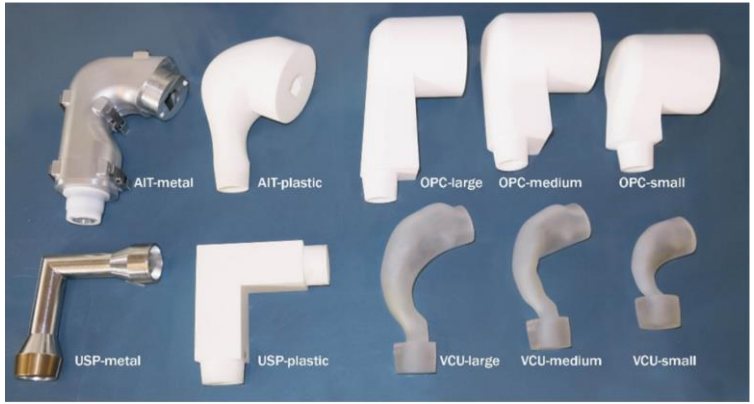
GDUFA-funded research: University of Florida (PIs: Günther Hochhaus, Jürgen Bulitta), Contract #75F40119C10154[17]

- **Realistic Mouth-Throat (MT) Models**
  - USP (Me and PI)
  - AIT (Me and PI)
  - OPC (S, M, L)
  - VCU (S, M, L)
- **Inhalation Profiles (IP)**[1]
  - Strong
  - Medium
  - Weak
- **MT Model Coating Types (CT)**
  - Silicone
  - Brij®
- **MT Model Insertion Angles (IA)**
  - Normal
  - Tilted at a 25° angle with respect to the MT
- **MDI Firing Points (FP)**
  - 0.2 s after start of IP
  - 0.5 s after start of IP

Me: Metal; Pl: Plastic

[1]Simulated IPs as described in Delvadia R, et al.[13]

Product	API(s)	Formulation
Flovent® HFA	Fluticasone Propionate	Suspension
Symbicort®	Budesonide (Bud), Formoterol Fumarate Dihydrate (FF)	Suspension
Atrovent® HFA	Ipratropium Bromide	Solution



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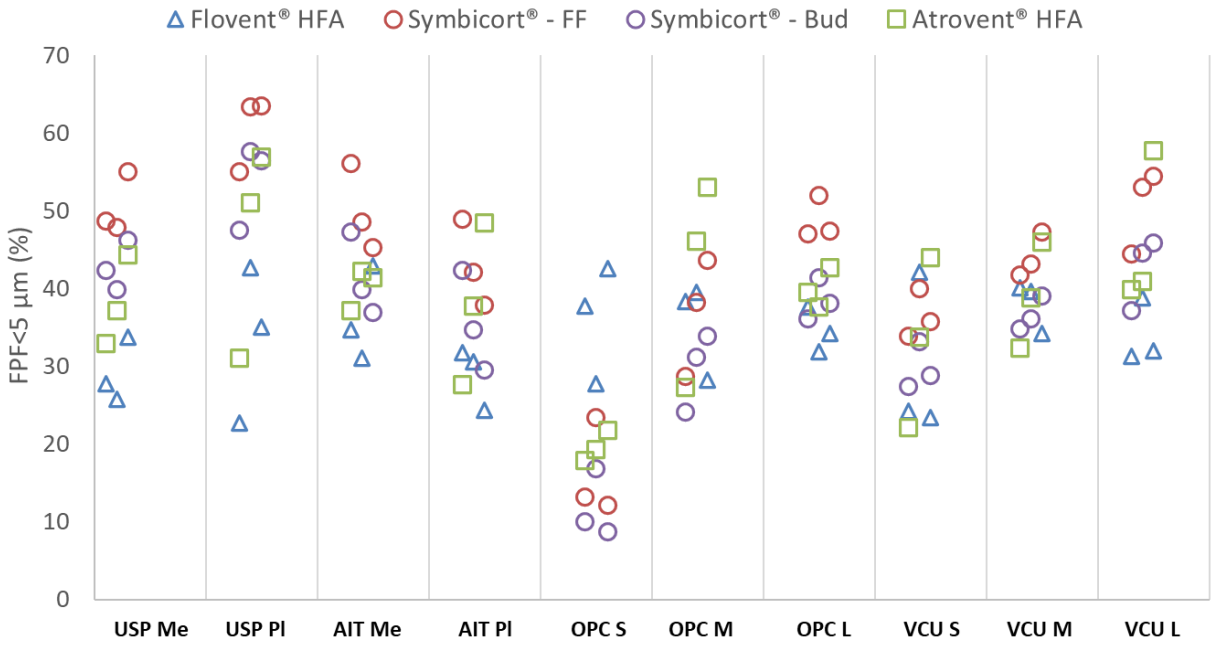
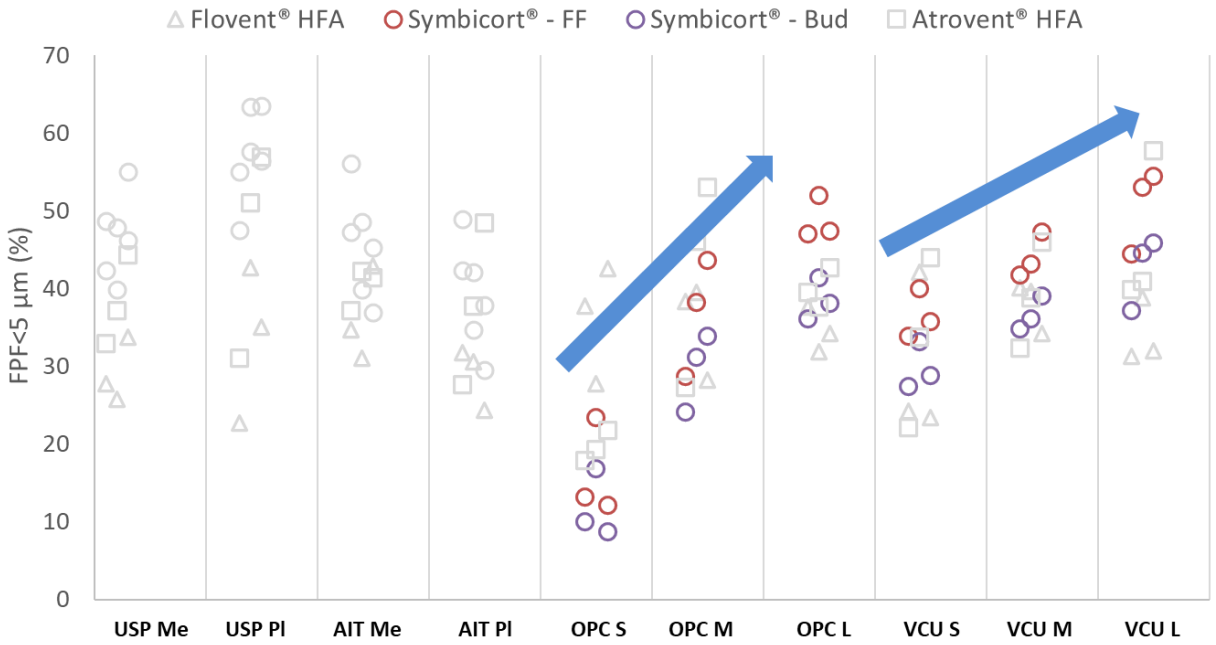


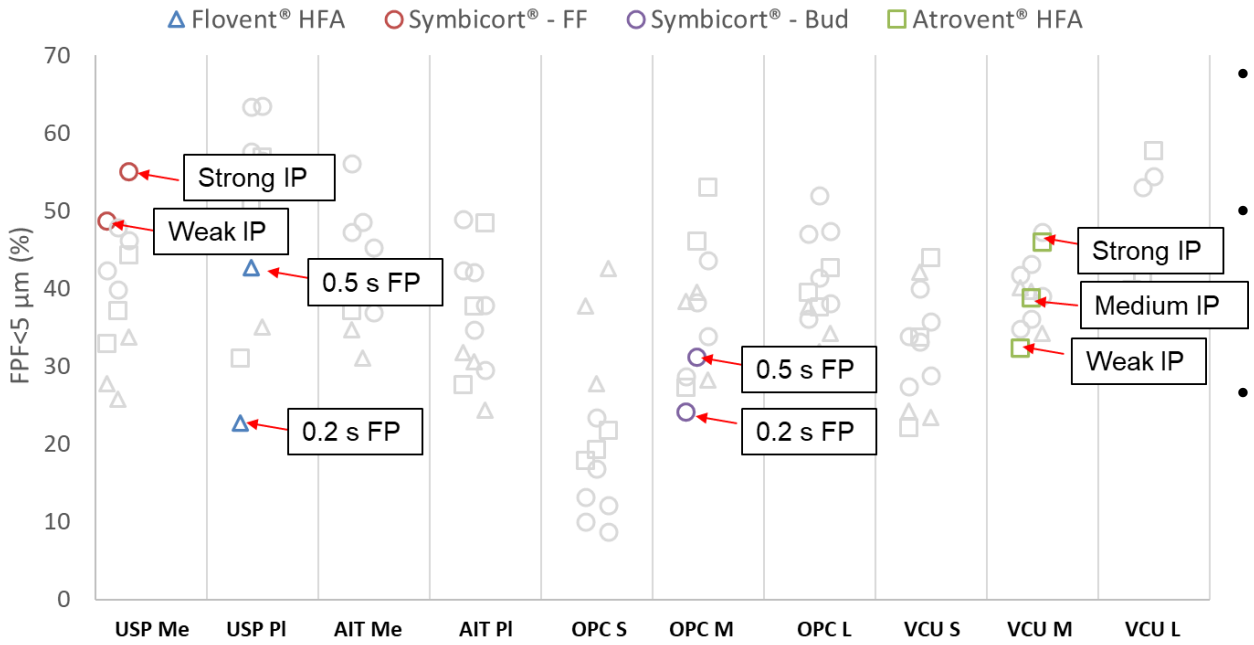
- Significant differences in the FPF <5 µm obtained with different MT models

Study 3 - Analysis of additional factors that influence APSD in MDIs



- Significant differences in the FPF <5 µm obtained with different MT models
- Increasing trend in FPF<5 µm observed with small, medium and large MT models for Symbicort- FF and Bud

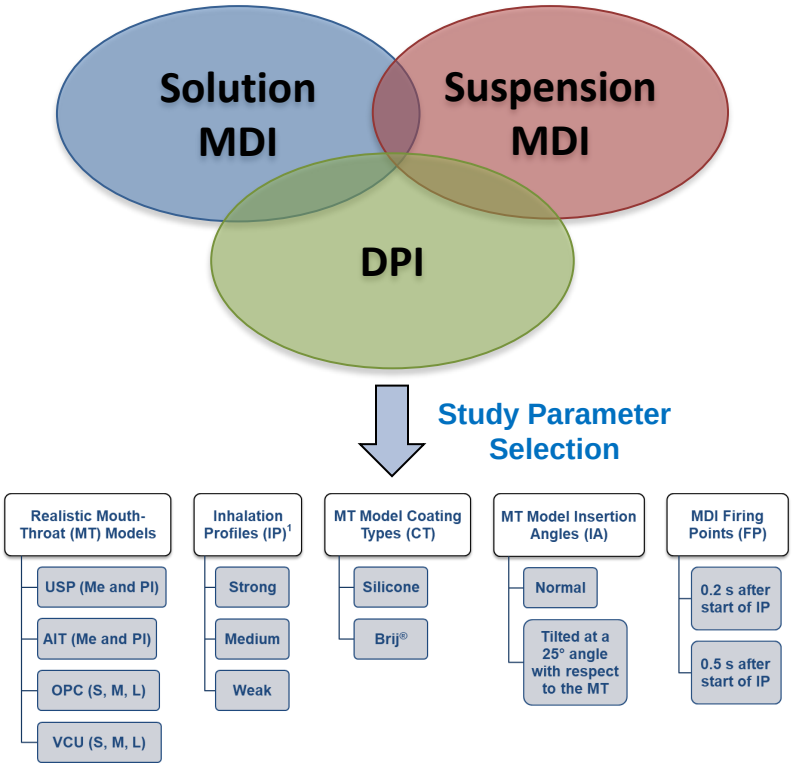
Study 3 - Analysis of additional factors that influence APSD in MDIs



- Significant differences in the FPF <5 µm obtained with different MT models
- Increasing trend in FPF<5 µm observed with small, medium and large MT models for Symbicort- FF and Bud
- IP (weak, medium and strong) and firing point (FP) (0.2 and 0.5 s after the start of IP) showed significant ($p<0.05$) effects on FPF<5 µm

Realistic APSD testing should consider the effect of different experimental conditions, particularly the type of MT model, IP and MDI firing point

Considerations for More Realistic APSD Testing – Method Development



Lessons Learned:

- Overall, realistic APSD results are **product-specific**
- Formulation differences can affect results
- Multiple study method parameters can affect results:
  - IPs, MT model materials, MDI firing point

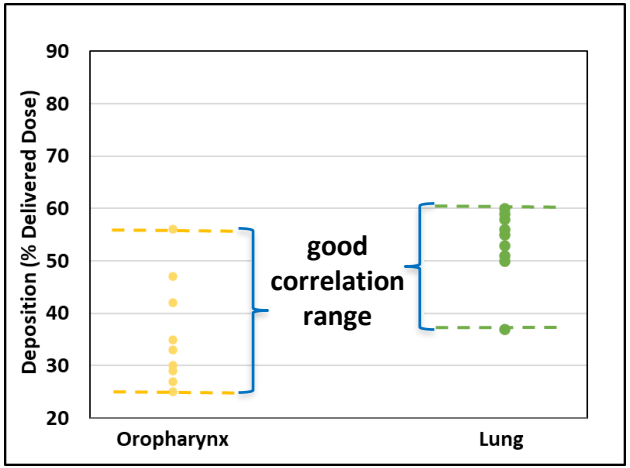
Ongoing Questions:

- Are there optimal study design parameters for each dosage form?
- Does the method parameter selection depend on how realistic APSD study will be used (i.e., standalone method or input for in silico methods)?

Considerations for More Realistic APSD Testing – Assessing Patient Variability

- Selection of MT models and IPs should consider how these will **correlate with in vivo performance** (if available)
  - In vitro data should target in vivo range for good correlation
- Ideally, IPs should be based on **patient population**
  - Comparative clinical endpoint/pharmacodynamic study is conducted on patient population

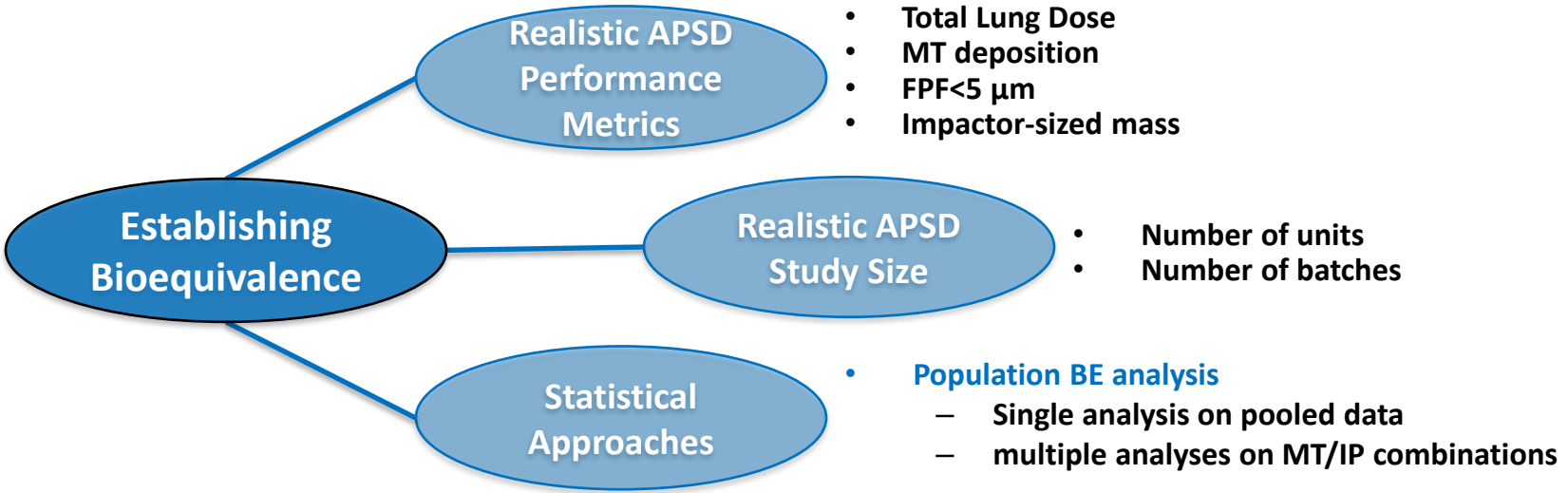
In vivo oropharynx and lung deposition as % delivered dose of BDP in asthmatic adults (mean values)[17-21]



Ongoing Questions:

- Is there an optimal method for selecting which MT type/size and IPs to use? Is in vivo data always needed or can other information be used?
- Is the MT type/size more critical to capture for evaluating patient variability as compared to IP? Does this matter based on the dosage form?

Considerations for More Realistic APSD Testing – Appropriate Statistical Methods



Ongoing Questions:

- What realistic APSD parameters are the most correlated with in vivo performance?
- What statistical method is appropriate?
- Is there a minimum study size that is sufficient for establishing BE? Does this depend on the study purpose (i.e., standalone method or input for in silico methods)?

Summary

- Realistic in vitro APSD testing is currently part of the recommended alternative to a CCEP BE study approach for solution MDIs
- Compared to current compendial methods, realistic APSD can provide a ***better prediction*** of deposition of inhaled particles in the lungs and capture patient variability
- Research has demonstrated the importance of ***product-specific*** realistic APSD for DPIs and MDIs
  - Formulation type, IPs, MT models (including model material) and MDI firing point have been shown to affect test results
- There are still ***ongoing questions*** regarding realistic APSD method development, patient variability assessment and the appropriate statistical method to use to establish bioequivalence.

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