

Effects of Realistic In Vitro Test Factors on the Aerosol Properties of Metered-Dose Inhalers (MDIs)

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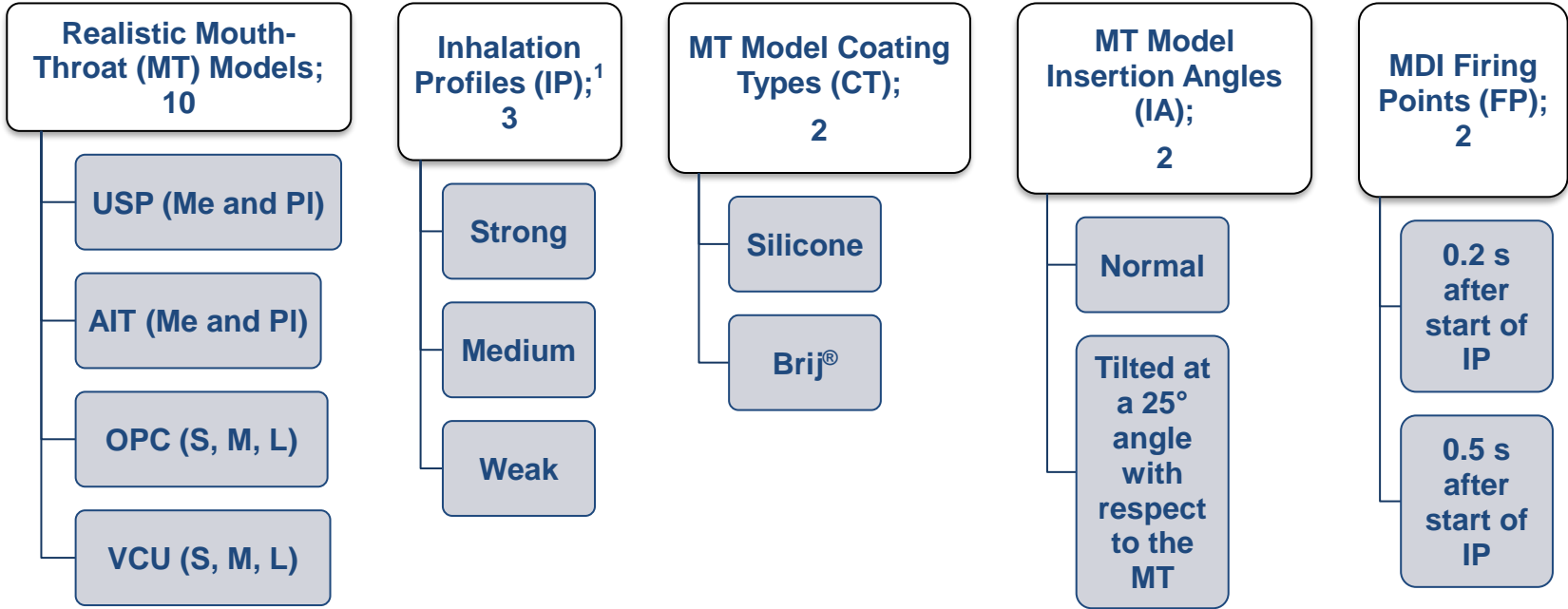
Disclaimer



- *This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.*

Introduction

- The goal of this Generic Drug User Fee Amendments (GDUFA)-funded research (75F40119C10154) is to 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 mouth-throat (MT) set-up.
- A systematic analysis of the effects from the following **factors** on the APSD of **3 commercial MDIs** was performed using a reduced factorial design:



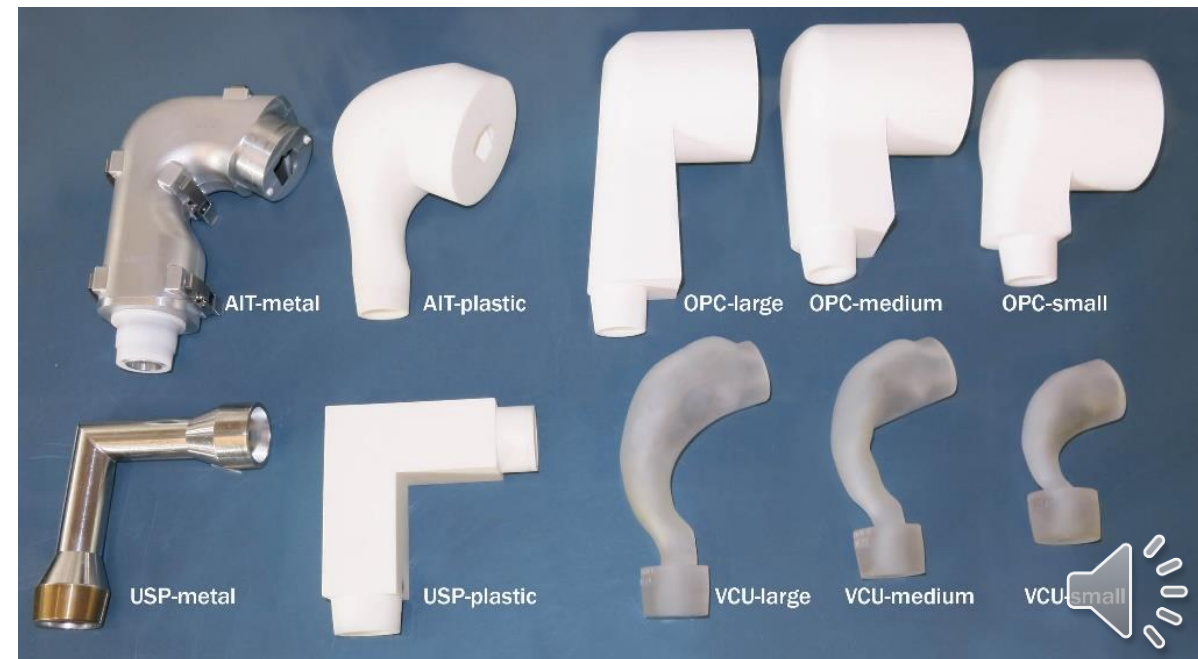
USP: United States Pharmacopeia induction port
 AIT: Alberta Idealized Throat
 OPC: Oropharyngeal Consortium
 VCU: Virginia Commonwealth University
 Me: Metal; PI: Plastic; S: small; M: medium; L: large

¹Delvadia et al. *J Aerosol Med Pulm Drug Deliv* 2016, 29: 196–206.

Methods

- **Fine particle fractions** of particles smaller than 5 μm (FPF < 5 μm ; fine particle dose divided by total emitted dose), **fine particle dose** of particles smaller than 5 μm (FPD < 5 μm), **mass median aerodynamic diameter** (MMAD) and **in vitro lung dose** (dose exiting the MT model) were determined from the next generation impactor (NGI) stage deposition.
- Correlations between APSD parameters and volumetric diameter (**Dv50**, μm) and average transmission (**AT**, %) measured using a **Spraytec system** were computed.
- MDI products studied:

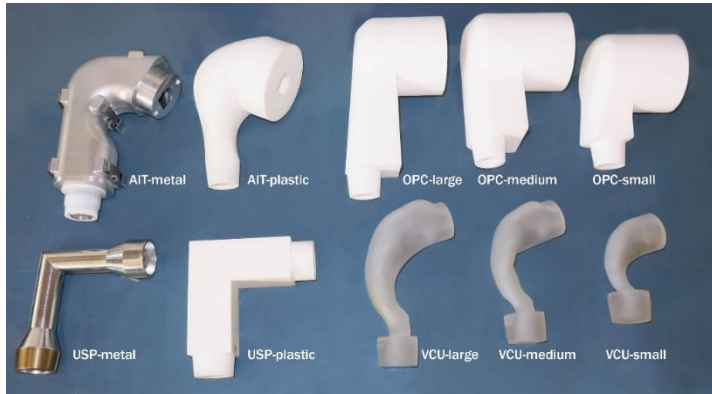
Product	API(s)	Formulation
Flovent [®] HFA	Fluticasone Propionate	Suspension
Symbicort [®]	Budesonide (Bud), Formoterol Fumarate Dihydrate (FF)	Suspension
Atrovent [®] HFA	Ipratropium Bromide	Solution



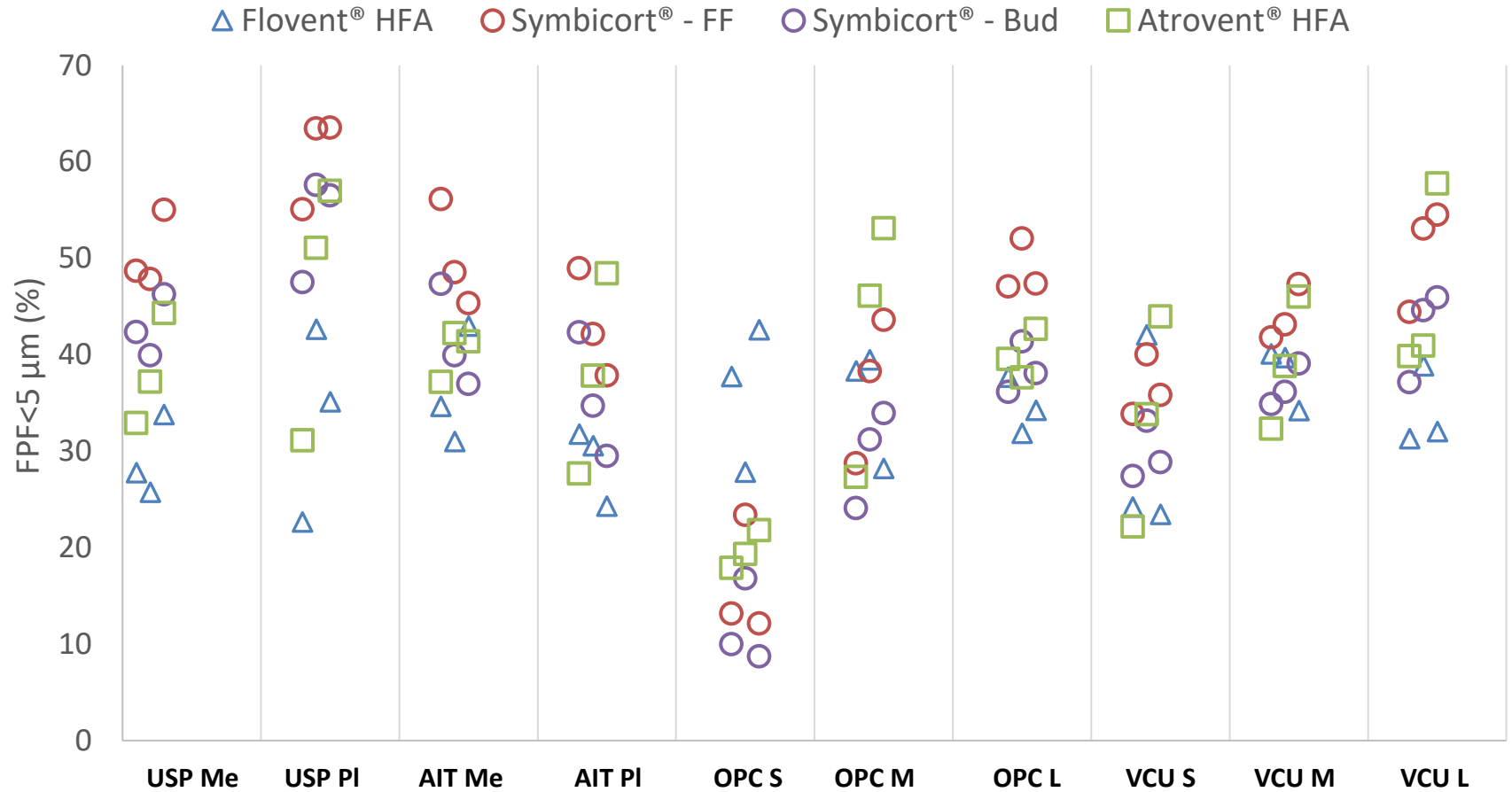
Results: FPF<5 μm



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



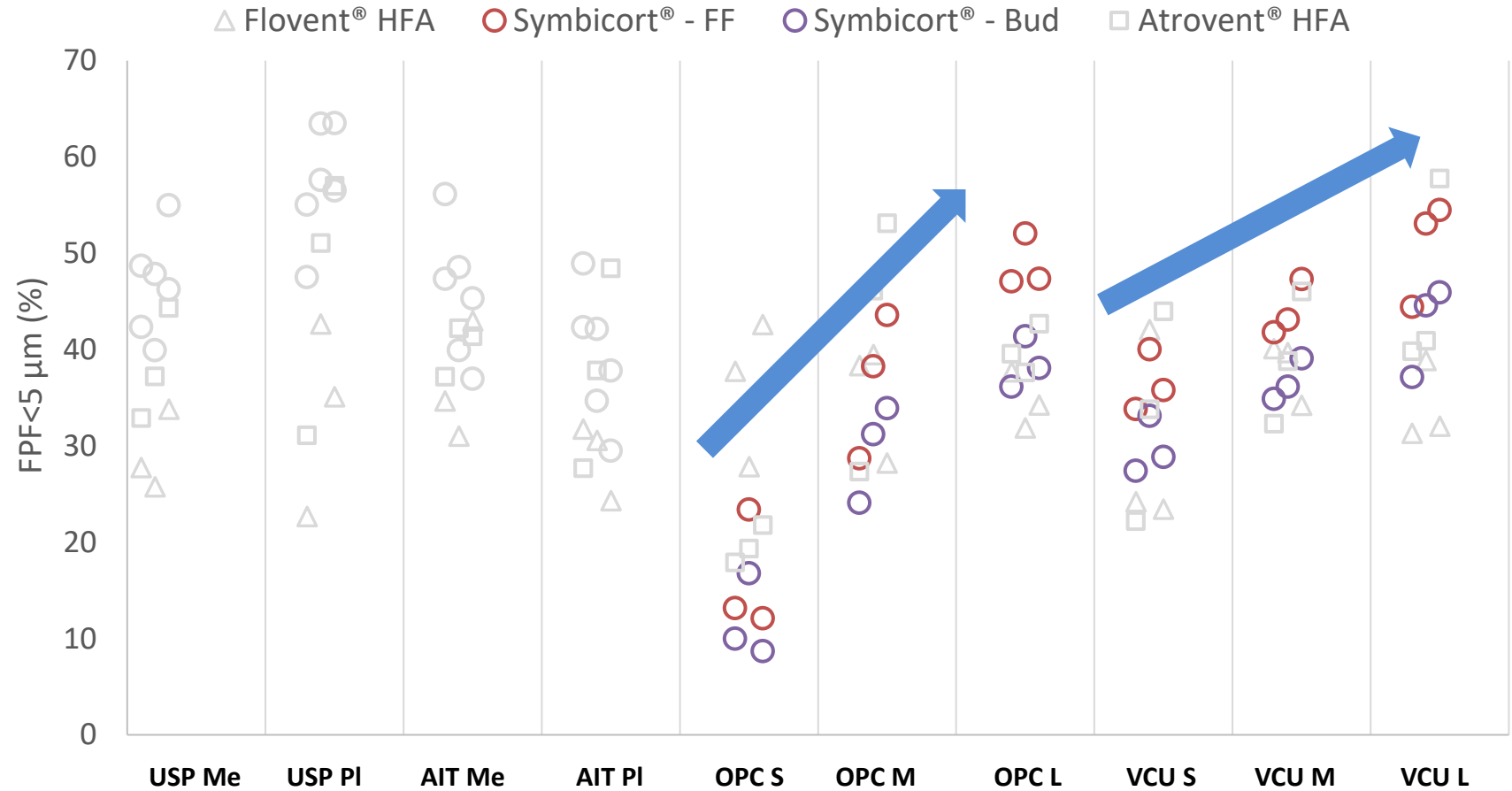
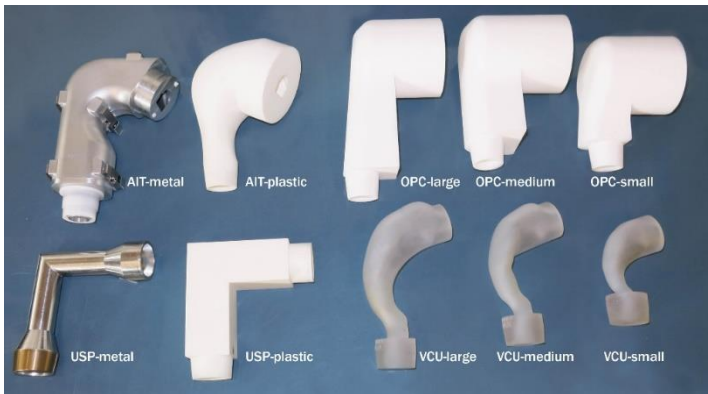
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Results: FPF<5 μm



- Increasing trend in FPF<5 μm observed with small, medium and large **MT models** for Symbicort- FF and Bud.



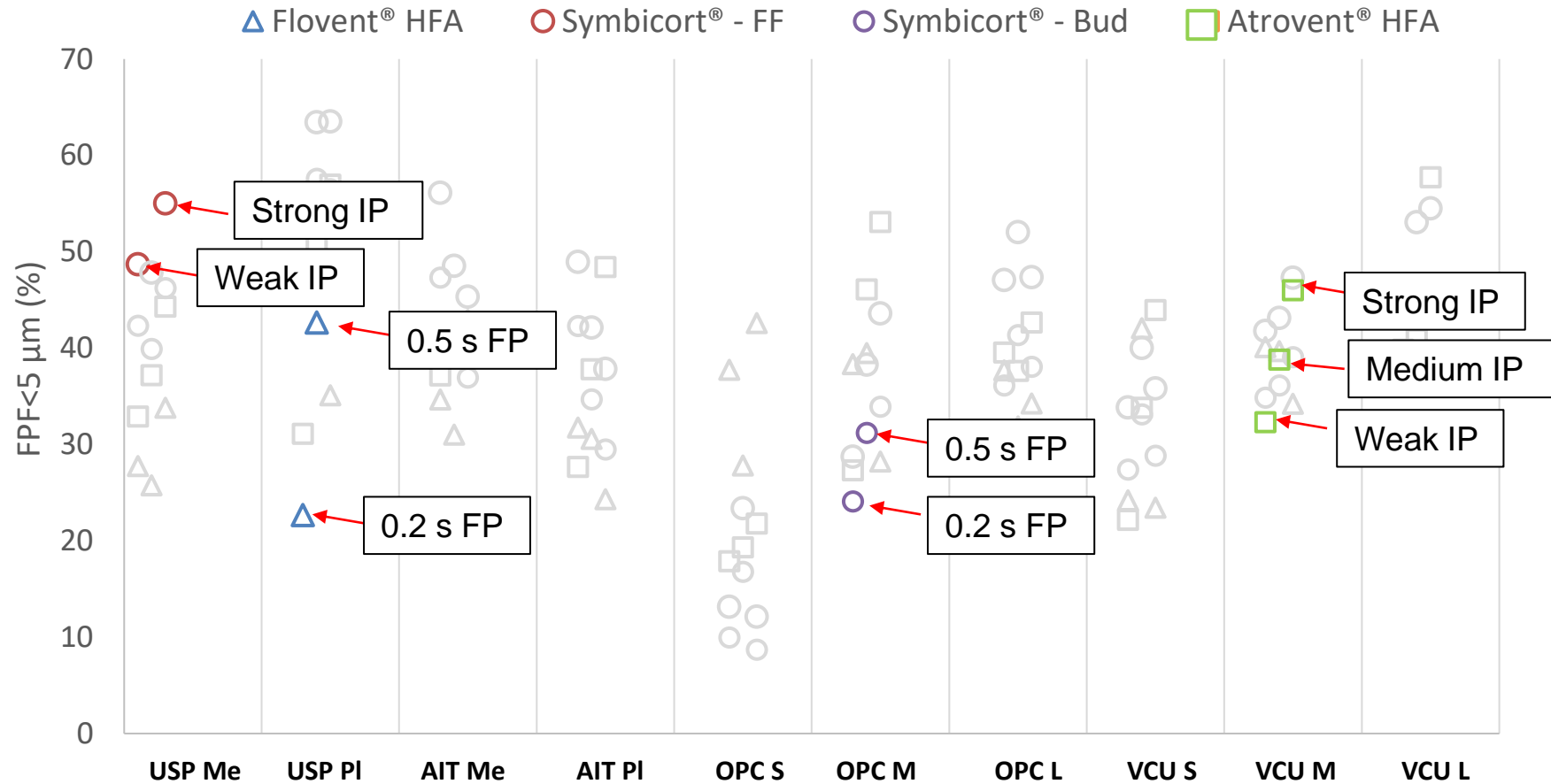
USP: United States Pharmacopeia induction port; AIT: Alberta Idealized Throat; OPC: Oropharyngeal Consortium; VCU: Virginia Commonwealth University; Me: Metal; PI: Plastic; S: small; M: medium; L: large



Results: FPF<5 μm



- **IP** (weak, medium and strong) and **FP** (0.2 and 0.5 s after the start of IP) showed significant ($p < 0.05$) effects on FPF<5 μm.



Results: Correlation between APSD and DSD



- MMAD, FPF<5 μm and FPD<5 μm of Symbicort® (Bud) showed highest correlation ($|r|>0.6$) to Dv50
- Correlation were insignificant between APSD based parameters and DSD parameters for other MDIs.

MDI	APSD-derived parameters	Laser diffraction- based Dv50	Laser diffraction-based AT
Flovent® HFA	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
Symbicort® - FF	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
Symbicort® - Bud	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
Atrovent® HFA	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

Conclusions

- Realistic in vitro APSD testing should consider the effect of different experimental conditions, particularly the type of **MT model**, **IP** and MDI **FP** on APSD of solution or suspension MDIs.
- Limited and product-specific correlations between the APSD-derived parameters and DSD suggests that laser diffraction may serve as an additional **supporting characterization method** rather than an alternative to cascade impactor-based realistic in vitro methods.



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