Factors Influencing Plume Characteristics of Metered Dose Inhalers (MDIs) Following Passage through Bio-relevant Mouth-Throat Models

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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.*
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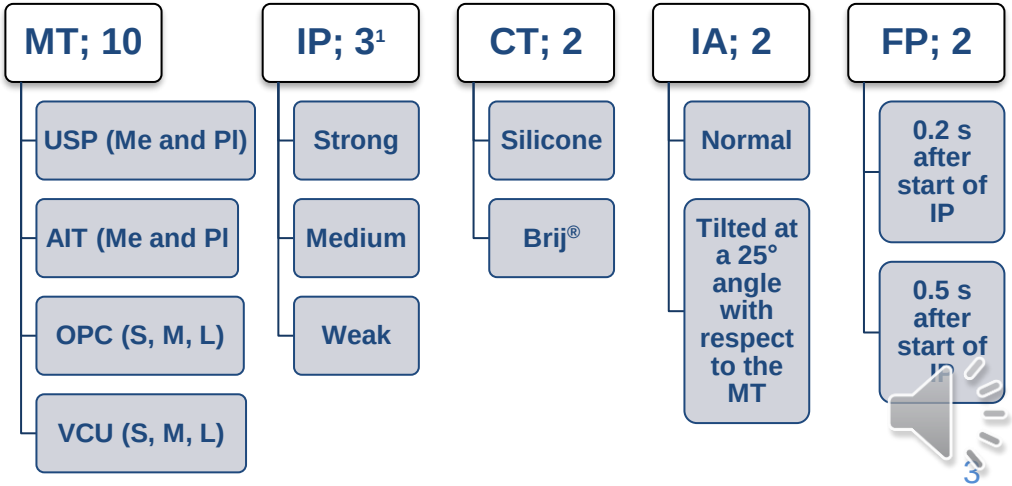
Introduction

- The goal of this Generic Drug User Fee Amendments (GDUFA)-funded research (75F40119C10154) is to understand how the **droplet size distribution (DSD)** of a MDI's emitted aerosol may change after passage through the mouth-throat in a realistic in vitro set-up.

- A systematic analysis of the effects of the following **factors** on the DSD of 3 **commercial MDIs** was performed using a reduced factorial design:

  - **Realistic Mouth-Throat (MT) Models**
  - **Inhalation Profiles (IP)**
  - **MT Model Coating Types (CT)**
  - **MT Model Insertion Angles (IA)**
  - **MDI Firing Points (FP)**



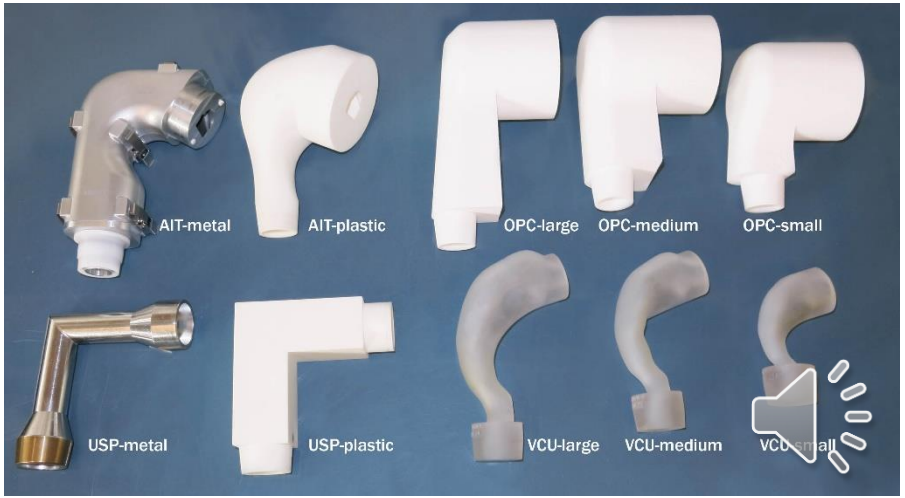
USP: United States Pharmacopeia induction port; AIT: Alberta Idealized Throat; OPC: Oropharyngeal Consortium; VCU: Virginia Commonwealth University; Me: Metal; Pl: Plastic; S: small; M: medium; L: large

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

Methods

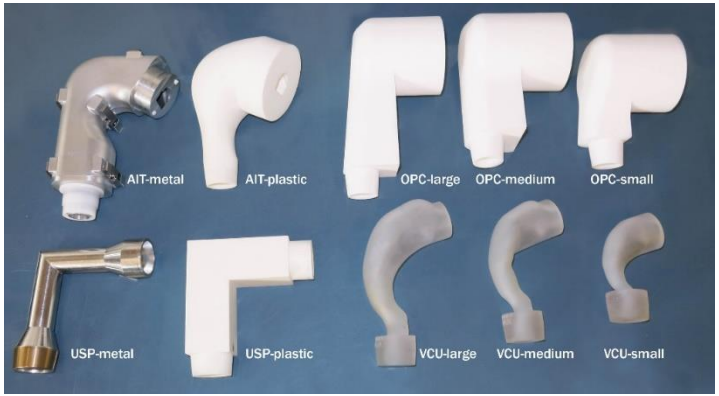
- Volumetric diameters (μm), **Dv10, Dv50, Dv90** and average transmission (**AT**, %) of the emitted aerosol were measured using a **Spraytec system** (Malvern Panalytical) with the inhalation cell connected to a breath simulator.
- Measurements were made at the exit of the inhaler actuator mouthpiece (i.e., **before the MT**) and again at the exit of the coated anatomical throat (i.e., **after the MT**).
- MDI products studied:

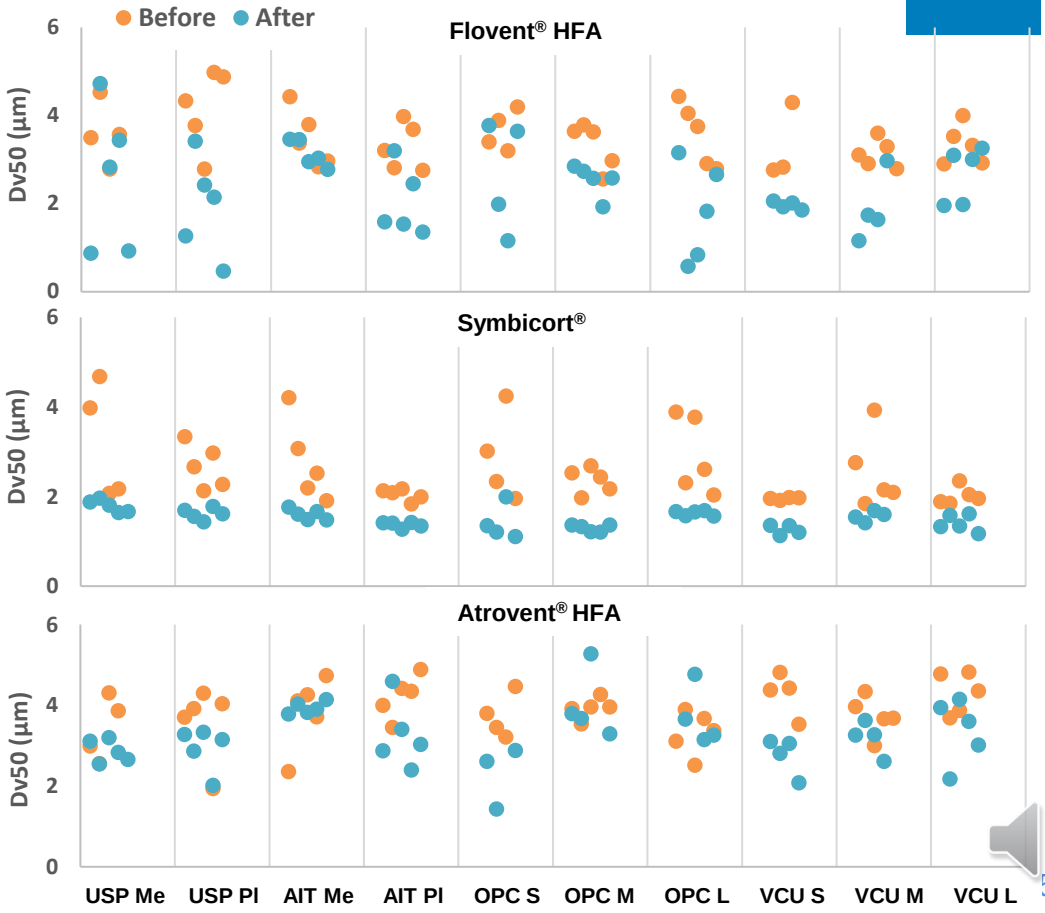
Product	API(s)	Formulation
Flovent® HFA	Fluticasone Propionate	Suspension
Symbicort®	Budesonide, Formoterol Fumarate Dihydrate	Suspension
Atrovent® HFA	Ipratropium Bromide	Solution



Results: Before and After MT

- Dv50 generally **decreased** after passage through MT models by 1.2-3-fold.





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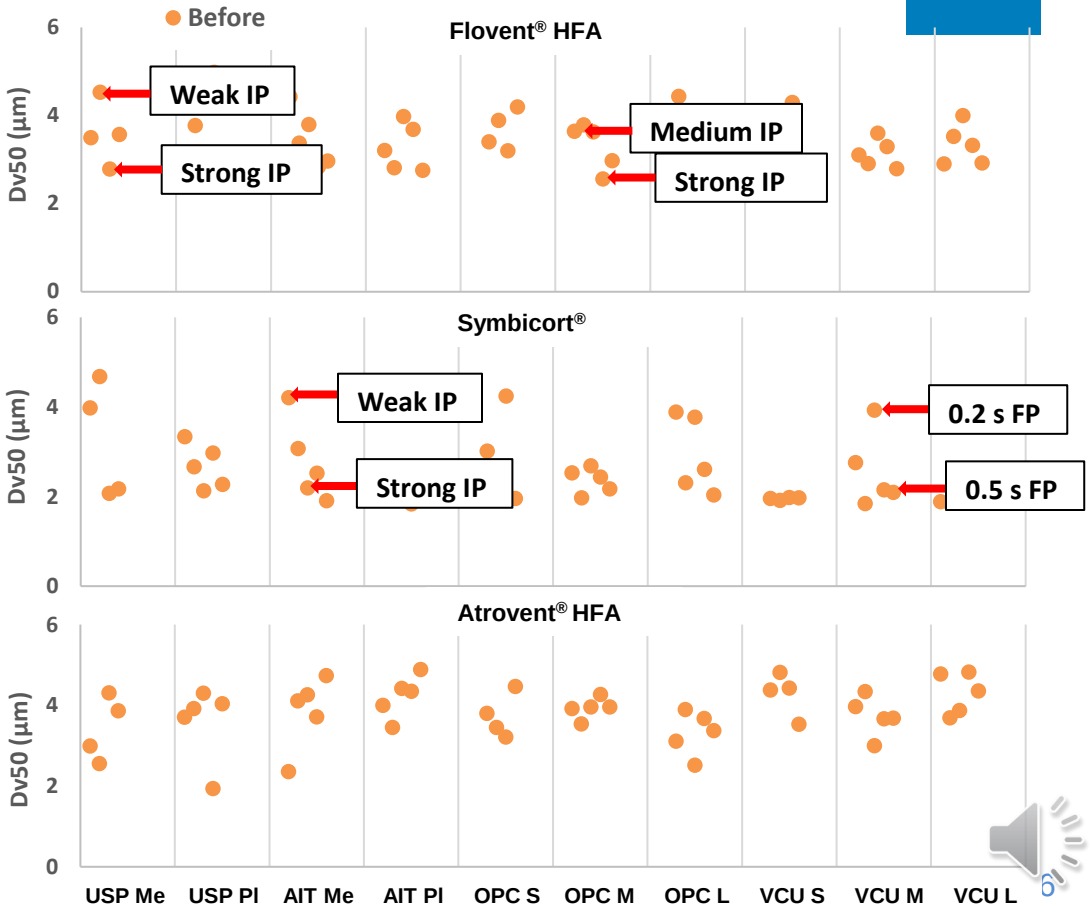
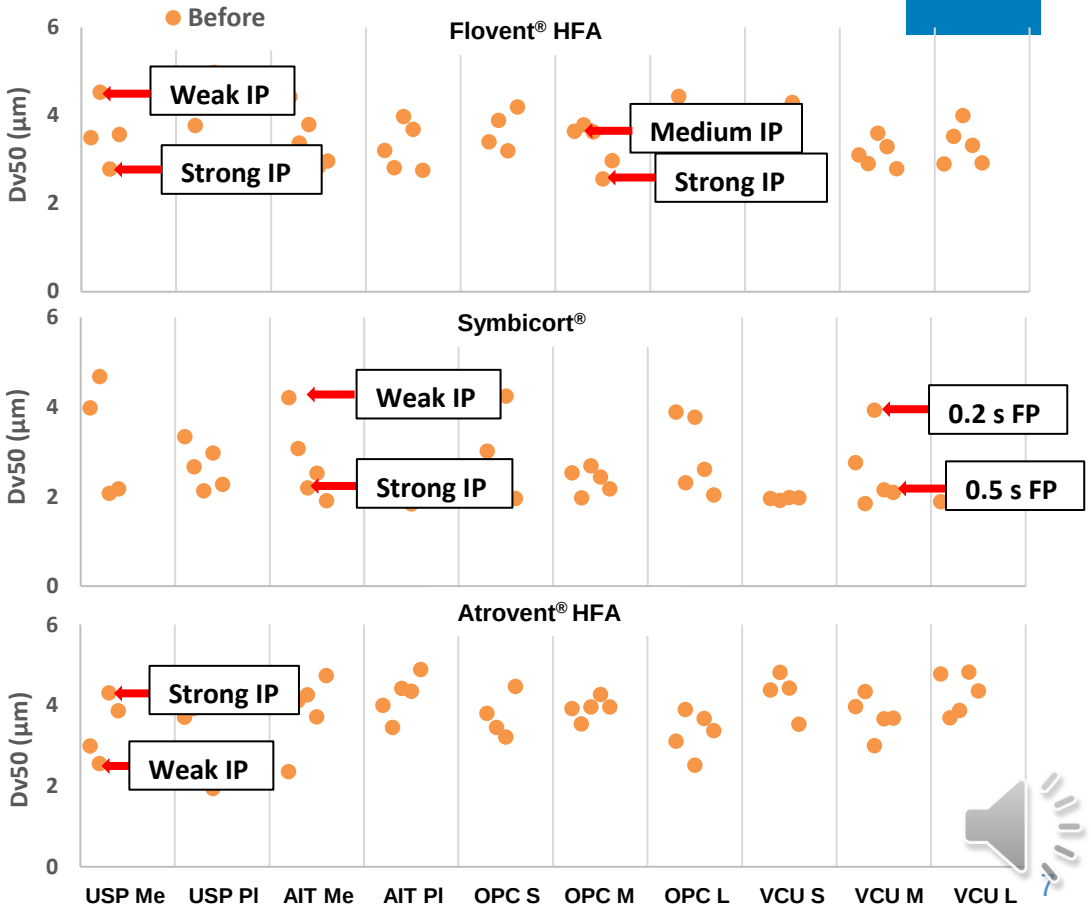
Results: Before MT

- **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 Dv50.
- **Decreasing trend** in Dv50 observed with weak, medium and strong IPs for Flovent® HFA and Symbicort®.



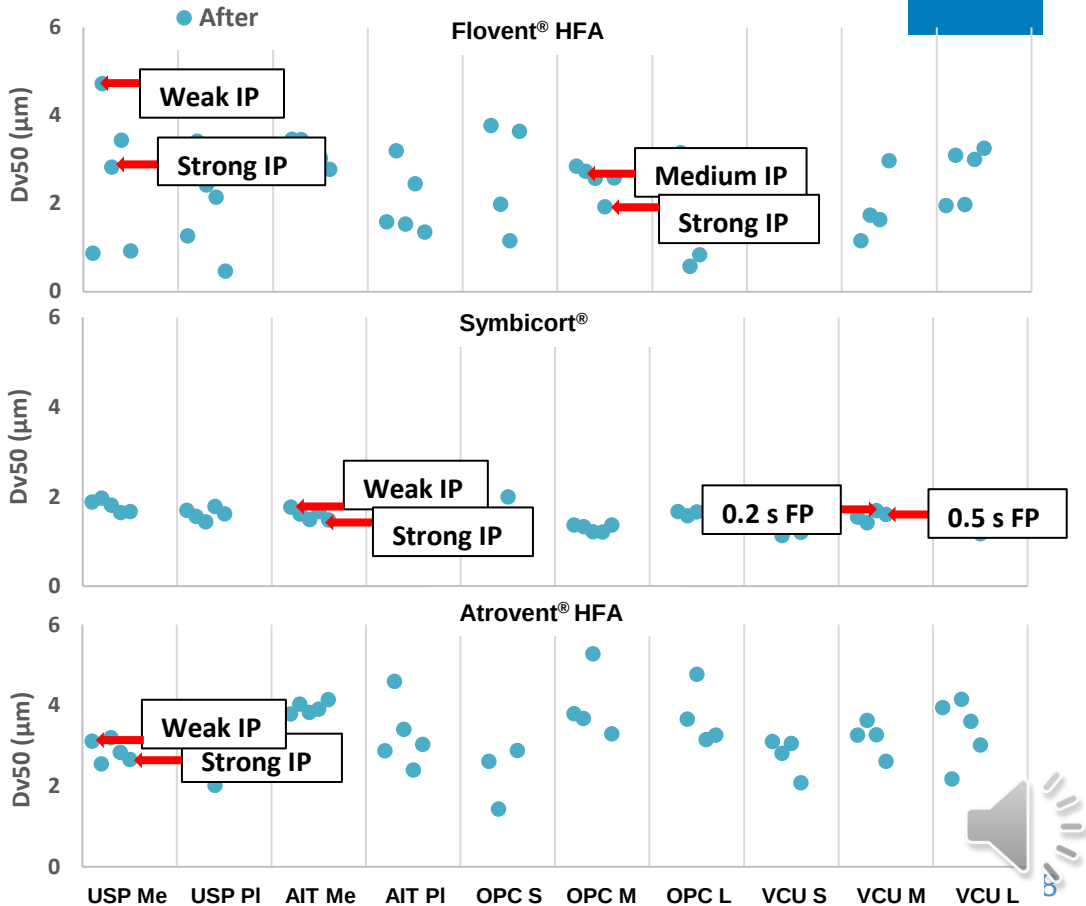
Results: Before MT

- **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 Dv50.
- **Decreasing trend** in Dv50 observed with weak, medium and strong IPs for Flovent® HFA and Symbicort®.
- **Increasing trend** in Dv50 observed with weak, medium and strong IPs for Atrovent® HFA.



Results: After MT

- **Large range** of Dv50 as a result of different IP, CT, FP, and IA, particularly for Flovent® HFA and Atrovent® HFA.
- Less effect of experimental conditions on Symbicort®.
- Effect of **different sizes of MT** appear **product specific**, but more prominent for OPC than VCU.
- Significantly ($p<0.05$) higher (10-40 %) Dv50 for metal version of AIT (**AIT Me**) as compared to plastic (**AIT Pl**).



Results: After MT

- Choice of the **MT model** had the **strongest effect** on Dv10, Dv50, Dv90, and AT, followed by IP.
- Strong effect of **CT** on Dv50 of **Flovent**; silicone consistently resulted in a higher Dv50 as compared to Brij®.
- Much smaller effects for IA and FP.

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.

MDI	Parameter	eta-square				
		MT	IP	CT	IA	FP
Flovent® HFA	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
Symbicort®	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
Atrovent® HFA	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

Conclusions

- **Inhalation profile** and **firing point** had strong effects on volumetric diameters before the mouth-throat (MT).
- The **mouth-throat geometry** had the strongest effect on plume properties after the MT of the investigated commercial MDIs, followed by **inhalation profile**.
- Overall, the effect of different factors on the droplet size distribution (DSD) was found to be **product specific** and was inconsistent within the **formulation type** (i.e., **suspension or solution**).
- Future studies are planned to explore the effect of these factors on aerodynamic particle size distribution (APSD) parameters and the correlation between DSD and APSD parameters.

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Questions?

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