Flow Rate-Rise Time Profiles from Model Dry Powder Inhaler (DPI) Testing of Abbreviated Impactor Systems Compared with Their Full Resolution Counterparts: Initial Experimental Data

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EPAG European Pharmaceutical Aerosol Group www.epag.co.uk

BACKGROUND:

- Flow rate-rise time profiles obtained when testing DPIs following procedures in the pharmacopeial compendia are important *in vitro* characteristics of likely clinical performance:
  - They affect both powder-to-aerosol generation and transport processes governing medication delivery efficiency
- Abbreviated cascade impactors (CIs) have been developed to simplify the testing of inhalers:
  - They can speed up early-stage product development when many tests may be needed to determine the optimum candidate formulations
  - They can also support full resolution CI measurements throughout product development

Commonly used abbreviated impactors

FSI

FSA

rNGI (filter at stage 3 of NGI)

STUDY PURPOSE AND GOALS:

- A previous EPAG cross-industry study* investigated flow rate-rise time profiles with full resolution CIs at target flow rates of 30, 60 and 90 L/min and with orifice plates representative of high-, medium-, and low-resistance DPIs
- Three of the nine original participating groups (blinded as the letters D, G and J) also tested abbreviated impactors
  - These data offer the opportunity to explore the impact of differing internal volume between reduced and parent full-resolution impactor,
  - This issue has been identified** as a potential source of discrepancies in measures of fine particle mass between at least one abbreviated and full resolution impactor system
- The study goal was to quantify how such differences may affect characteristic flow rate-rise time profiles

* Greguletz R, Andersson PU, Cooper A, Chambers F, Copley MA, Daniels G, Hamilton M, Hammond M, Mohammed H, Roberts DL, Shelton C, Versteeg HK, Mitchell JP *A cross-industry assessment of the flow rate-time profiles of test equipment typically used for dry-powder inhaler (DPI) testing: Part 1 –Compendial apparatuses.* Aerosol Sci Technol. 2020; 54(12): pp.1424-1447

**Copley M, Mitchell JP, Svensson M, Christopher JD, Quiroz J, Daniels G, Hamilton M, Russell Graham D. *Validating AIM- Based Instrumentation and Associated Measurement Techniques*. In: TP Tougas, JP Mitchell, SL Lyapustina (eds): Good Cascade Impactor Practices, AIM and EDA for Orally Inhaled Products, Springer, New York, NY, USA; pp. 283-358. 2013

MATERIALS AND METHODS:

- Participants D, G and J, of the main study provided measurements with reduced NGI (rNGI), Fast Screening Impactor (FSI) and Fast Screening Andersen impactor (FSA)
- The methodology followed closely the pharmacopeial procedure for APSD determination from DPIs:
  - Surrogate DPIs were constructed with aperture dimensions causing a 4-kPa pressure drop that simulated either a high-, medium-, or low-resistance DPI at the target flow rates of 30, 60, and 90 l/min

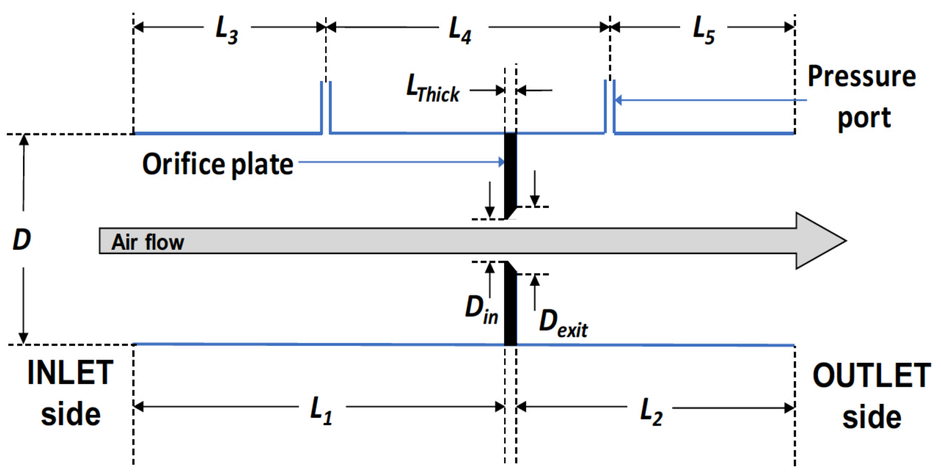

Figure 1: Surrogate DPI made from Orifice Plate with Well-Defined Dimensions

Table 1: Apparatus Configurations and Nominal Internal Volumes (all ±10 mL)

	Full Resolution			Abbreviated		
	Impactor	Pre-separator present	Total internal volume (mL)	Impactor	Pre-separator present	Total internal volume (mL)
D	NGI	Y	2000	rNGI	Y	1990
				FSI	N	1150
G	NGI	Y	1990	FSI	Y	1140
J	ACI (2)	Y	1180	FSA (2)	Y	630

- Each flow rate-rise time profile was recorded at 5-ms intervals upon actuation of a solenoid valve downstream of the CI-on-test to initiate the sampling and measurement processes
  - A model 4040 flow meter (TSI Inc., Shoreview, MN, USA) was used to capture the profile
  - Purpose-developed proprietary recording software recorded at 5-ms intervals
  - The resulting data enabled the calculation of characteristic rise time indicators
- t_{20}, t_{80}, and t_{90} (each in ms), representing times to attain 20%, 80%, and 90% of the steady-state target flow rate
- The primary measures were t_{90} and the slope of the profile ($slope_{t20/t80}$), calculated by linear interpolation between t_{20} and t_{80}

RESULTS:

A: Time to 90% of Steady-State Flow Rate (t_{90})

- rNGI t_{90} values at both target flow rates evaluated by participant D (30 and 60 L/min) very close to their reference value for the NGI with comparable internal volumes close to 2000 mL (**Figure 2**)
- In contrast, FSI and FSA t_{90} values were significantly shorter than corresponding data obtained with their full-resolution NGI and ACI configurations respectively

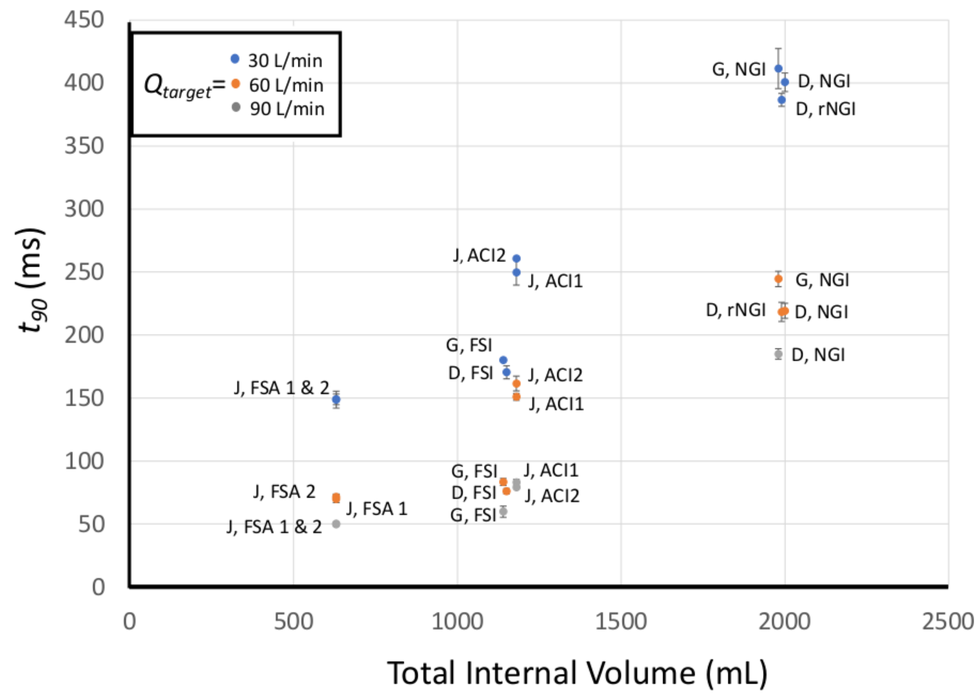

Figure 2: t_{90} Values (mean ± SD) For Abbreviated and Full Resolution Impactors

B: Slope of Rise Time Profile Between Times to 20% and 80% Flow Rate

- The smallest values of $slope_{t20/t80}$ were associated with the slowest flow rate-rise profiles **(Figure 3)**
- The values for the rNGI were very close to those for the NGI
- $slope_{t20/t80}$ for the FSI units were significantly larger than the corresponding values for the NGIs
- $slope_{t20/t80}$ for the FSA units at each target flow rate were very similar to each other, but significantly greater than equivalent values for the two parent ACIs

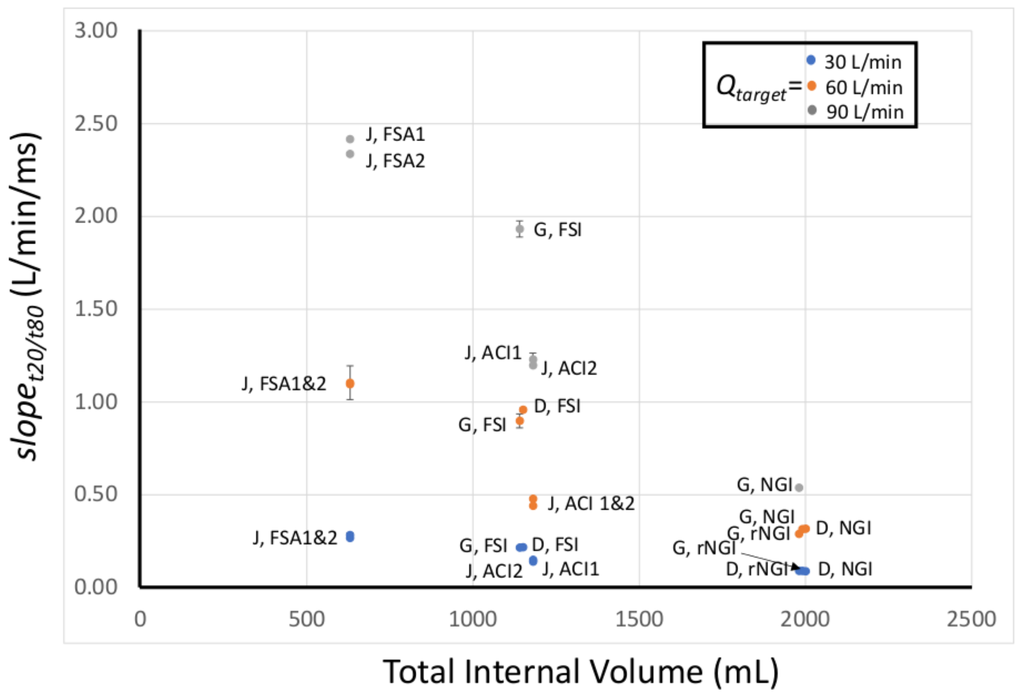

Figure 3: $Slope_{t20/t80}$ Values (mean ± SD) For Abbreviated and Full Resolution Impactors

DISCUSSION

- The results highlight the importance of apparatus internal volume in governing the shape of the flow rate-rise time profiles
  - This finding is supported by the predictions from a validated physical model# of the transient processes taking place when testing DPIs according to compendial methods
  - Changes in both t_{90} and $slope_{t20/t80}$ were directly associated with differences in the magnitude of the "trapped volume" behind the surrogate DPI
  - Changes in both t_{90} and $slope_{t20/t80}$ were directly associated with differences in the magnitude of the "trapped volume" (equivalent to the system total internal volumes in the present study)

Versteeg HK, Roberts DL, Cooper A, Chambers F, Copley M, Mitchell. JP *A cross-industry assessment of the flow rate-elapsed time profiles of test equipment typically used for dry-powder inhaler (DPI) testing: Part 2. –Analysis of transient air flow in the testing of DPIs with compendial cascade impactors.* Aerosol Sci. Technol. 2020; 54(12): pp. 1448-1470

- The results reported are a by-product of the much larger flow rate-rise time study* and are based on a very limited number of replicate measurements at each condition
- We have not addressed the role that apparatus resistance may play in determining the flow rate-rise time profile
- A designed experiment powered to enable statistical analysis of the comparisons between abbreviated and parent full resolution impactors should be undertaken to validate them and to address explicitly the contribution made by apparatus resistance

CONCLUSIONS

- Apparatus internal volume is a key determinant of flow rate-rise time profiles when evaluating DPIs in accordance with the methods for APSD measurement in the pharmacopeial compendia
- We have support for a proposal that in order to achieve improved agreement between abbreviated and full-resolution parent impactor:
  - Use systems with similar internal volume, such as the rNGI/NGI pairing **OR:**
  - Add sufficient internal volume to the abbreviated system to match that of the parent impactor