

BACKGROUND

Several metrics have traditionally been applied for characterizing aerodynamic particle size distributions (APSDs) of orally inhaled products (OIPs) in the context of product development, regulatory requirements and quality control (QC). Among such metrics are the total mass of the active pharmaceutical ingredient (API) recovered in a cascade impactor (CI) measurement, the aerodynamic mass median diameter (AMAD) (e.g. in a fine particle dose, $\leq 5 \mu\text{m}$), API mass on individual stages or groups of stages, mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD).

A systematic study of APSD data from several products has indicated that a simple metric conveying information from just fine (small) and coarse (large) particle size fractions of the API may be adequate to detect both abnormal control tendency and mass under the APSD curve (APSD) as an in-process control quality attribute (CQA) for these products¹. The use of a simple, accurate and precise size would be particularly advantageous for CI applications from an efficiency, speed and/or cost perspective. The use of a larger number of samples could be tested and thus, would greatly increase the understanding about the product. The poster explores whether the proposed simplified metrics in this case, small particle mass (SPM) and large particle mass (LPM) are applicable to a variety of APSD data sets including measured OIPs or simulated measured OIPs (MMODs) and dry powder inhalers (DPIs) from the IPAC-RS inhaler database. In particular, rates are explored for establishing the most appropriate link between small and large particles in relation to the overall APSD.

¹ FDA CDER (1998), "Drugs Guidance for Industry Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Product Chemistry, Manufacturing, and Controls Documentation" <http://www.fda.gov/cder/CDER2/28301a1.htm>

² P. Tougas 2008, "Capabilities of Aerodynamic Particle Size Distribution (APSD) Measurements based on Analysis of a Global Database", Respiratory Drug Delivery 2008, pp. 109-122

Abbreviated Impactor Measurement (AIM) Concept

- Regional particle deposition in the human respiratory tract (HRT) is not directly related into multiple size-related fractions, as simulated by typical full-resolution multi-stage CIs, such as the Andersen In-Stage Impactor (AI) and Next Generation Pharmaceutical Impactor (NGI).
- A single size boundary close to 5 μm aerodynamic diameter may be sufficient to enable in vitro data to provide adequate information that can be used to characterize fully developed and deposition in the HRT.
 - Large particle mass (LPM) – deposition dependent
 - Small particle mass (SPM) – dependent on receptors beyond the cartina
- Changes to the APSD would be detected as changes to the ratio of LPM / SPM or the sum of LPM and SPM.
- The concept can be modified to include extra-small particles (ESP) < 1 μm to characterize particles that might deposit in the lung periphery and/or be exhaled

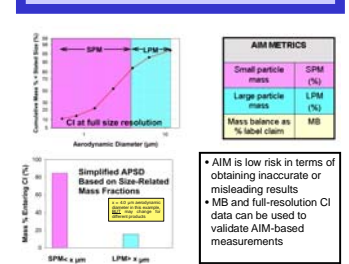
Advantages of AIM Concept

- Simplified system has intrinsically improved overall precision
 - Components that collect little or no API are eliminated
 - Signal to noise enhancement due to more mass (signal) collected on fewer stages (noise reduction)
 - Potentially better decision making capabilities
- Reduced labor and time per measurement
- Decreased opportunity for operator-related errors
- Capability of obtaining more determinations if needed
- AIM systems more amenable to automation

Application of the AIM Concept



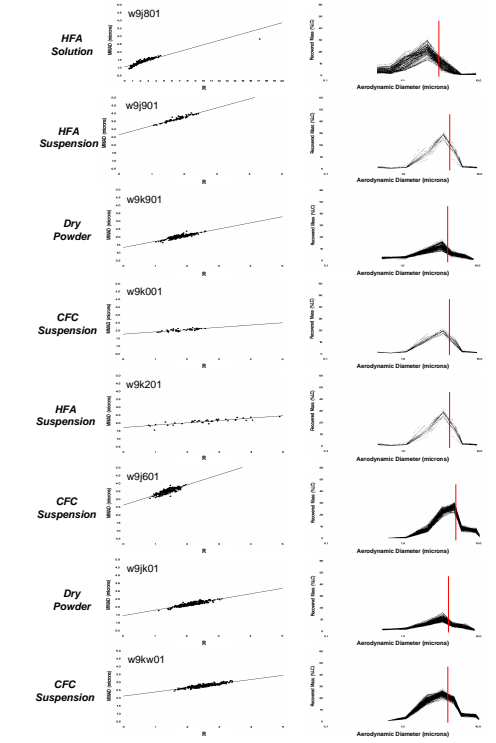
AIM - Deliverables



- AIM is low risk in terms of obtaining inaccurate or misleading results
- MB and full-resolution CI data can be used to validate AIM-based measurements

Large Particle to Small Particle Ratio versus MMAD and Impactor Sized Mass Profiles

Red Lines Indicate Separation of Stage Groups Used to Determine Small and Large Particle Mass



Role of Simplified Particle Size Metrics in Quality Control of OIP

Can APSD Measurements be simplified?

- What is the greatest goal of QC tuning?
 - Provide additional assurance/confirmation that a batch of inhalers is of acceptable quality
 - What quality aspects are APSD measurements intended to control?
 - Assess particle size characteristics that impact delivery of drug to respiratory tract
 - Can simplified APSD testing and metrics detect abnormal drug product?
 - What type of changes need to be detected?
 - What constitutes a significant change?
 - How does the performance of the proposed metric (small & large particle fractions) compare with the currently accepted approach of a full stage approach?
 - What changes to APSD are we trying to detect?
 - Change in Amplitude
 - Change in Width
 - Shift in Mean
- Some or all of the above simultaneously

Verification of Concept: Analysis of IPAC-RS Database

Data sets composed of individual stage results from multiple APSDs determined on a variety of OIPs were examined in an effort to ascertain the ability of the AIM concept as a sufficiently sensitive QC tool. These data were part of a comprehensive database collected in connection with a collaborative effort of IPAC-RS and the APFS Inhalation Technology Focus Group. Although these results were obtained by full-resolution measurement techniques, the individual stage results could be combined to obtain SPM and other APSD metrics. The ability to detect shifts in the size range occupied by an APSD was considered critical, since measurements of the individual stage results could be combined to obtain the sum of SPM and LPM. Size-related movements were evaluated by examining the ability of the ratio of SPM/LPM (labeled as 'R') to detect changes in MMAD. It diverse OIPs products contained in the IPAC-RS database including four from a previous study¹ were studied to encompass the following major categories:

- HFA-solution MDI
- HFA-suspension MDI
- CFC-suspension MDI
- DPI

¹ "Initial Assessment of the ITRG/IPAC Aerodynamic Particle Size Distribution Database by the CMC Specifications Technical Team of the ITRG/IPAC Collaborator" (2008) https://www.cmc.gov.sg/Assets/CD/Products_CD/Verder_Sep2008_1.pdf

RESULTS

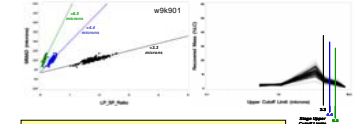
The relationship between MMAD and R was approximately linear for every OIP type studied, as is illustrated by the magnitudes of the correlation coefficients (see table above)

The gradient of plots of MMAD versus R, with R as the directly measured independent variable reflects the sensitivity of this metric towards detecting changes in MMAD. The slight changes in MMAD result in magnified variations in R when the gradient is small. Furthermore, a small gradient minimizes the impact of uncertainty in LPM and SPM on the prediction of MMAD.

The ratio 'R' is superior to using either LPM or SPM as individual metrics, since it reduces the influence of AUC/amplitude in trying to detect changes in MMAD (Note that AUC is determined simultaneously as the sum of LPM and SPM). Though not directly examined, this consideration should also be true comparing the ability of 'R' to detect small variations in MMAD versus metrics based on the mass of API contained in multiple stage groupings from a full-resolution APSD measurement.

The ratio 'R', in combination with the sum [LPM+SPM] may be superior QC metrics compared to full-resolution data that are typically employed today (e.g. mass of API collected by groups of individual CI stages). However, it does not replace the need to well characterize the APSD of a product during development through full-resolution, multi-stage CI measurements. The successful application of LPM- and SPM-based metrics is likely to depend on initial characterization of the full APSD of the OIP at product development, and the subsequent correlation of these simplified metrics. It should also be noted that full-resolution APSD determinations will likely be needed even during the commercial phase of an OIP as both an investigative tool as well as the reference method.

Influence of Cutoff Point on Sensitivity of R towards MMAD (Sensitivity is inversely related to slope of plot)



Filecode	Product Type	ICI	Correlation Coefficient	Slope Estimate	Standard Error of Slope
w9J01	HFA Suspension	20	0.915	1.97	0.186
w9J01	HFA Suspension	20	0.933	4.91	0.494
w9K01	CFC Suspension	27	0.984	2.26	0.072
w9K01	CFC Suspension	27	0.840	1.10	0.243
w9K01	HFA Suspension	30	0.957	1.62	0.056
w9J01	CFC Suspension	43	0.791	3.99	0.531
w9K01	CFC Suspension	27	0.877	1.87	0.465
w9K01	CFC Suspension	27	0.833	2.66	0.066

CONCLUSIONS

- Lean data analysis based on metrics derived from LPM and SPM should simplify OIP development and QC during its commercial phase, without compromising the ability to make control decisions.
- The proposed 'lean data analysis' is based on the Abbreviated Impactor Measurement (AIM) concept, and is not a single measurement apparatus or data interpretation strategy. As such, it may be implemented in a number of specific ways depending on the sponsor's data and agreements with regulators.
- The AI and NGI will continue to be needed as full-resolution APSD measurement techniques but more to provide reference data in product development and QC rather than as the primary technique for routine use.
- An additional APSD study to identify the most appropriate boundary between LPM and SPM for a given OIP may require an extra step in a product/method development program, but it has the potential to save significant resources during both Development and QC operations associated with commercial production.
- The transition to the AIM concept including lean data analysis will have to be gradual to ensure adequate acceptance by all involved. A preliminary presentation of the concept was made in June 2008 to the USP Aerosol Expert Committee in order to stimulate debate amongst stakeholders, and this poster continues and extends the process.

ACKNOWLEDGEMENTS

The authors appreciate the ongoing support of IPAC-RS Board for this project and technical advice from the European Pharmaceutical Aerosol Group (EPAG). We thank Copley Scientific Ltd., Westech Instruments and MSP Corp for their contributions to this poster. We also wish to acknowledge the technical advice from Matsen Svensson of AstraZeneca, Lund, Sweden regarding AIM options.