# CHALLENGES OF SIZING INHALER AEROSOLS: BRINGING THE METHODS INTO THE 21ST CENTURY

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## INTRODUCTION

- The multi-stage cascade impactor (CI) has been the traditional 'work-horse' for the aerodynamic size characterization of aerosols from orally inhaled products (OIPs)
- However, it is based on manual technology that is more than 50 years old
- There is an ongoing need for alternative techniques that are rapid and intuitive to use, whilst also being specific in terms of quantifying the mass of active pharmaceutical ingredient (API)
- In OIP development, it may be advantageous to obtain such data under conditions that are as clinically relevant as feasible
- No single technique currently meets all these criteria
- Guidance is given on current developments that offer more choice to stakeholders

## MODERNIZING SIZING METHODS

- The multi-stage cascade impactor (Figure 1) has withstood the test of time because:
  - recovery and assay can be made API-specific
  - particle size-related performance measures are scaled in terms of aerodynamic diameter, loosely correlated with deposition location in the human respiratory tract

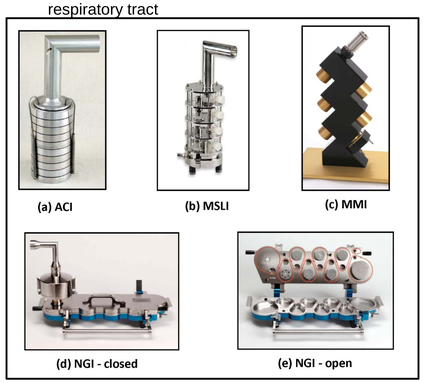


**Figure 1: Widely Used Cascade Impactors**
(from Good Cascade Impactor Practices, AIM and EDA for Orally Inhaled Products, Springer, April 2013)

- CIs ideally sample at a fixed flow rate that defines their stage cut-off sizes, a significant drawback to the development of more clinically appropriate methods
- Attempts to interface them with the continuously varying flow-time profile simulating the respiratory cycle have hitherto been complex and therefore not easy to standardize and validate
- At the present time, there are pressures to speed up both OIP development and quality control-related testing in production
  - Abbreviated Impactor Measurement (AIM)-based techniques may be more amenable to (semi)automation
- In addition, regulatory agencies, particularly for breath-actuated products, are increasingly looking for particle size-related measures that have been obtained under more clinically realistic conditions
  - Add-on devices such as valved holding chambers used with pressurized metered dose inhalers cannot be evaluated in terms of valve performance by a CI sampling at constant flow rate
- The challenges are therefore several-fold:
  - Modify existing impactor methods and data analysis to reduce complexity, thereby improving throughput and decision making; likely to be most applicable to the quality control environment (AIM-EDA concepts)
  - Adapt CIs to operate in conjunction with breathing simulators and more realistic representation of entry conditions than the USP/Ph.Eur. induction port; likely to be helpful in the provision of more clinically appropriate data in association with improved in vitro-in vivo relationships
  - Introduce alternative non-inertial techniques, such as microscopy-image analysis (MIA) combined with Raman chemical imaging (RCI)

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**This article is a summary of current thinking within the Cascade Impactor Working Group (CI-WG) of the International Pharmacopeial Aerosol Consortium on Regulation and Science (IPAC-RS) on how OIP aerosol sizing will develop in the next 5 years**

## AIM AND EDA CONCEPTS

- In the OIP lifecycle, the **Abbreviated Impactor Measurement** (AIM) concept offers several benefits compared with full resolution CI methods:
  - The opportunity to speed-up the measurement process
  - Reduce API recovery solvent use
  - Simplify data analysis, by reducing the number of impaction stages to the minimum needed to obtain metrics capable of discriminating changes in aerodynamic particle size distribution (APSD)
- Some full resolution CI measurements are still needed to provide benchmark APSDs

- The **Efficient Data Analysis** (EDA) concept can be used with both AIM-based and full resolution CI data:
  - The two EDA metrics comprise the ratio of large to small particle mass and impactor-sized mass (the sum of small and large particle mass)
  - These metrics alone offer improved discriminating ability for detecting APSD shifts compared with the stage groupings currently recommended by the USFDA

## INTERFACING THE CI WITH BREATHING SIMULATION

- The Miller aerosol mixing inlet appears capable of minimizing internal losses due to deposition on internal surfaces by aligning the converging continuously varying flow of clean air from the breathing simulator with the flow of particle-laden air being drawn by the vacuum to the CI, thereby mitigating localized turbulence at the merge-point (Figure 2)
- This type of system has the potential for use with either an abbreviated or full resolution CI, when APSDs are required, simulating patient-use of nebulizers or pMDIs with or without add-on devices, where tidal-breathing is the norm, especially for infants and small children
- However, there is a need for validation experiments to be undertaken to establish potential sources of bias and overall limitations to use in terms of breathing parameters.

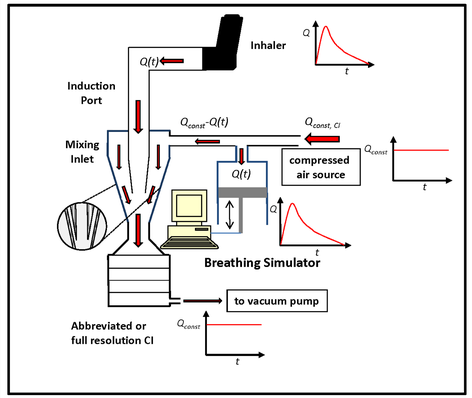


**Figure 2: Miller Inlet (Nephele Enterprises, through RDD Online, Virginia Biotechnology Research Park, VA, USA and Copley Scientific Ltd., UK) Enabling CI Operating at Constant Flow Rate ($Q_{const}$) to Interface with Breathing Simulator Providing Variable Flow Rate ($Q_t$) for pMDI Testing**

- The Electronic Lung™, developed by GSK (Figure 3), has been demonstrated to be effective in simulating patient-use of DPIs in conjunction, but is a relatively expensive technique that requires validation with other OIP types

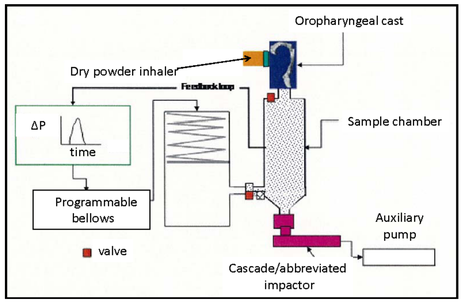


**Figure 3: Electronic Lung™ Used in the Testing of DPIs with Actual Patient Inhalation Flow Rate –Time Profiles**
(from Good Cascade Impactor Practices, AIM and EDA for Orally Inhaled Products, Springer, April 2013)

## NON-INERTIAL METHODS

- Alternatives to inertial-based particle size analysis are severely limited by the need for both API traceability and particle size scaled in terms of aerodynamic diameter
- Techniques based on light scattering, including laser diffraction, can only be applied to API solutions, and are therefore confined largely to assessments of preparations for nebulization
- Time-of-flight (TOF) analysis provided aerodynamic size but is non API-specific, and so may be limited to DPI products containing API without excipients
- Microscopy-Image Analysis combined with Raman Chemical Imaging (MIA–RCI) is a relatively new measurement modality that offers API selectivity, even with multi-component mixtures in suspension or solution
  - Particle geometric size is determined on a number-weighted basis, it is necessary to know the dynamic shape factor and density of the particle for size-conversion to aerodynamic diameter, and further error may be introduced by transforming the size distribution from a number- to mass-weighted basis, needed for direct comparison with CI data

## CONCLUSIONS

- The AIM concept provides a rapid alternative to full resolution CI measurements, but must be validated on a product-by-product basis
- EDA assessment of APSD metrics can be used with either full resolution or abbreviated CI-generated data, and appears to be more discriminating than stage groupings, as currently practiced in the US regulatory environment
- Aids, such as the Electronic Lung™ and the Miller mixing inlet could overcome many of the difficulties interfacing CI systems to breathing simulators
- MIA-RCI techniques, though relatively expensive compared with CIs, offer the opportunity to quantify API content as a function of particle geometric rather than aerodynamic size, and may therefore be useful in early stage product screening where API-specificity is important, but aerodynamic size properties may be less so

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