# Implementing the AIM concept

## *Streamlining the testing of inhaled drug products by using an abbreviated impactor measurement method*

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*An article in the June 2009 issue of* Inhalation *introduced the concept of Abbreviated Impactor Measurement (AIM). Here, the authors examine its industrial relevance in greater detail, with particular reference to new data released by Pfizer.*

For orally inhaled drug products (OIPs), aerodynamic particle size distribution (APSD) as an *in vitro* indication of likely deposition behavior within the lung is a critical quality attribute. However, the productivity of multistage cascade impaction, the established method for APSD determination, is low. The current economic and regulatory environment has stimulated interest in abbreviated impactor measurement (AIM) methods that characterize the emitted dose using just two size contributions—coarse or large particle mass (CPM or LPM) and fine or small particle mass (FPM or SPM)—allowing for much higher productivity and better decision making based on mutually independent metrics instead of stage groupings from full resolution systems.

Multistage cascade impactors such as the Andersen 8-stage Cascade Impactor (ACI) and the Next Generation Impactor (NGI) give relatively detailed APSD measurements for the active pharmaceutical ingredients in OIPs. Although the precise correlation between particle size and *in vivo* behavior remains elusive, changes in APSD undoubtedly influence drug delivery deposition throughout the respiratory tract [1], making *in vitro* measurement essential during development and QC.

However, in certain circumstances such as design of experiment (DOE) studies in the initial stages of formulation where the aim is simply to identify parameters that have a beneficial impact on drug delivery, multistage impaction to measure a full APSD may be unnecessary [2]. In these cases, determining the relative size of the fine particle fraction (FPF), typically defined as the <5 µm dose, may be sufficient. In addition, for routine quality control (QC) that aims to ensure against the release to market of samples outside a defined specification, a full particle size distribution may provide more information than necessary and impose a high analytical burden.

### AIM's potential benefits

AIM's opportunity for increased productivity is its principal attraction; a simple comparison with the limited data now available suggests that AIM could offer a reduction in overall analysis times of at least 50% (Table 1). However, few companies to date have purchased AIM instruments or have attempted to optimize associated procedures, making accurate evaluation of time savings challenging. As companies streamline AIM procedures with multiple systems and analysts, AIM measurement times may well be reduced further, while multistage cascade impaction analytical times are already well understood and optimized within the existing constraints, so future productivity advantages for AIM could be even greater.

**Table 1**

**Time to make 6 measurements with the FSI (non-optimized) and the NGI (optimized set-up)**

| | Experimental | HPLC | Processing | Total |
|---|---|---|---|---|
| 6 FSI | 96 min | 40 min | 10 min | 146 min |
| 6 NGI | 120 min | 150 min | 20 min | 290 min |

Other important benefits offered by AIM include:

- Higher precision due to the removal of stages that collect very little material
- Simpler operation, less prone to operator variability
- Statistically more powerful metrics
- Simpler apparatus configurations better suited to automation
- Reduced solvent usage for the recovery of API during sample work-up [3].

## Establishing AIM's ability to capture changes in APSD

Users may acquire AIM data using conventional multistage cascade impactors by grouping the material collecting on different stages to form just two fractions for analysis or by using modified equipment. Commercially available instruments such as the Fast Screening Andersen (FSA) impactor from Copley Scientific, an abbreviated system based on the design of the ACI, and the Fast Screening Impactor (FSI) from MSP Corporation, a single-stage abbreviated system based on a modified NGI pre-separator, provide a convenient alternative. With any of these approaches, measurement sensitivity and an accurate reflection of full resolution APSD measurements are critical.

Splitting a dose into CPM and FPM by using a boundary of 5 μm may prove useful and intuitive for OIPs in terms of relevance to likely deposition in the human respiratory tract. However, recent work by a group within the International Pharmaceutical Aerosol Consortium on Regulation and Science (IPAC-RS) highlights the benefits of a more flexible approach to boundary setting. Selecting a cut-off figure to maximize sensitivity rather than on the basis of clinical relevance gives rise to two alternative but analogous fractions: large particle mass (LPM) and small particle mass (SPM).

The IPAC-RS study shows that impactor sized mass (ISM), the sum of LPM and SPM, and the ratio of these two parameters provide sensitive and independent metrics that can detect small changes in amplitude and/or position of the APSD [3]. Using just these two metrics, AIM can capture, in summary form, the core particle size information that underpins the decision making processes related to batch release.

The IPAC-RS group assessed the relevance of this "lean data analysis" (LDA) approach by comparing data sets composed of individual stage results from multiple APSD measurements from multistage cascade impactors. The database includes results for four major inhaled product groups: HFA solution MDIs, CFC suspension MDIs, HFA suspension MDIs, and DPIs. In each case, the LPM/SPM ratio detected changes in the mass median aerodynamic diameter (MMAD) of the order of just tenths of a micron when the boundary between the two fractions was set close to the MMAD [3].

The sensitivity of LPM/SPM for detecting movements in MMAD increases as the boundary value approaches the MMAD, although it is relatively robust across a range of sizes encompassing the central region of the APSD where the majority of the delivered mass lies. This outcome suggests that dedicated AIM instrumentation needs only to operate with the ability to cover a relatively small number of stage cut-off sizes to give good performance for all OIPs, an encouraging finding for the commercialization of new equipment.

## Solving the particle bounce problem

Proof of concept studies using the standard FSA and a slightly modified version developed by Trudell Medical International (TMI) with additional functional dead space before the first size-separating stage demonstrate the ability of these systems to provide data comparable to a full resolution ACI for pMDI-produced aerosols, although plate coating proved essential [4, 5]. Coating the collection surface minimizes particle bounce and re-entrainment, problems aggravated by AIM because of the increased inertia of particles that would otherwise collect on previous stages in a full resolution configuration.

More recent, as yet unpublished, studies at TMI show that simply coating the surface may not totally eliminate bounce since the force exerted by the air flow diverging below each impaction jet can displace the coating. A glass microfiber filter soaked in the coating media provided a better solution, with the glass fibers helping to stabilize the surface and prevent coating displacement.

## An FSI case study

Pfizer has studied the performance of a marketed DPI using an FSI with a 5 μm insert, comparing measured FPF values directly with equivalent data from NGI tests [1, 6, 7]. The analysts interpolated full resolution APSD results to <5 μm using log probability calculations, as the NGI has no stage with a cut-off at precisely 5 μm.

A first direct comparison showed reasonably good agreement between the two sets of data (Fig. 1). The FPF values measured by the FSI are slightly, but consistently, higher than those measured with the NGI, consistent with particle bounce and entrainment that tends to carry oversized material into the final filter, increasing the FPF classification. Coating the base of the pre-separator (PS) with a very thin layer of silicone oil largely corrects this discrepancy (Fig. 1).

Similar trials with other DPIs, using 5 µm inserts calibrated at different flow rates, confirm these findings, although the magnitude of discrepancies between the FSI and NGI results varies from product to product. One study to assess the potential of AIM for development work simulated a typical DOE by varying the percentage of fine excipient content and blend speed to prepare a series of five DPI formulations: A, B, C, D, and E (Fig. 2). Theoretically, FPF should increase with both blend time and fine excipient content, the latter being the dominant factor, giving a ranking of A, B, E, C, and D, with A giving the best performance.

The FSI results correctly identify the impact of excipient fine content, successfully ranking the formulations as expected (Table 2). Blend time shows no impact on performance, with no statistically significant difference between the results for A and B and C and D, pairs of formulations that are identical except for differences in blend time. The NGI results, on the other hand, fail to rank the blends as expected and show no statistically significant difference between blends A, B, and E.

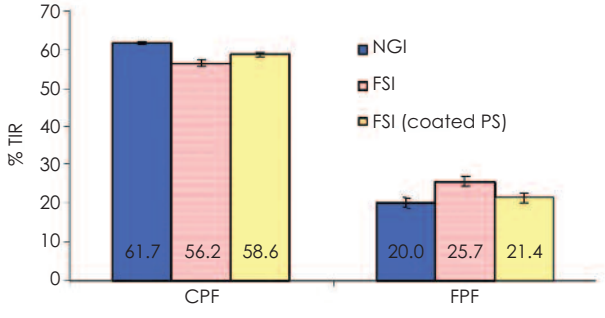
The two impactors produced statistically equivalent results only for blend E; the FSI predicts a higher FPF for all other blends. Although the results of the FSI appear positive since it successfully detects differences between blends with different percentages of fine content, this comparative study produced inconclusive results. A supplementary study involved a marketed device loaded with capsules of different fill weights to assess the tracking ability of the FSI in greater detail, this time over a much wider variation in FPF weight. A near 99% correlation between NGI and FSI data confirms that the abbreviated impactor tracks performance with excellent accuracy (Fig. 3).

## The way forward

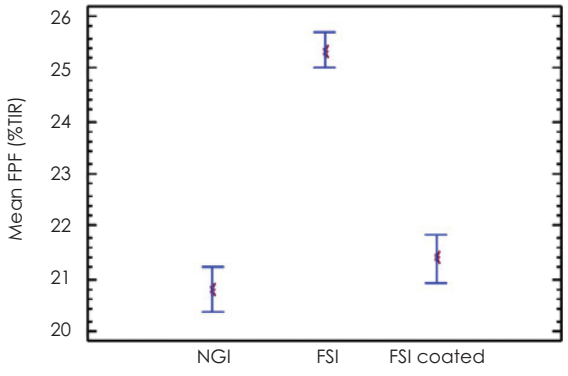
While multistage full resolution cascade impaction retains its place as the gold standard, research to date indicates the potential for good agreement between AIM results and full resolution results, suggesting possible adoption of AIM for routine QC on a formulation by formulation basis, with multistage

**Figure 1**

**DPI characterization with coating on collection surface of the FSI aligns the results for FPF (TIR = total impactor recovery)**




(a) Overall mean deposition




(b) Means and 95.0 percent LSD intervals

**Figure 2**

**Relationships of FPF and blend speed for blends A, B, C, D, and E**

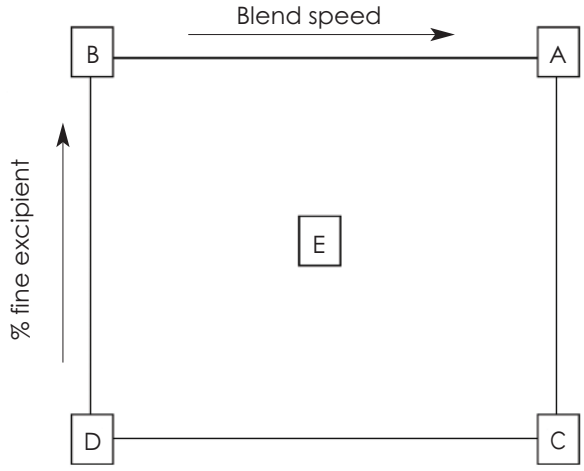



**Table 2**

**Impact of fine excipient content and blend speed on FPF using the FSI and NGI**

| | NGI | | FSI | |
|---|---|---|---|---|
| Blend | FPF (%TIR) | %RSD | FPF (%TIR) | %RSD |
| A | 26.9 | 4.9 | 30.2 | 3.8 |
| B | 26.1 | 4.5 | 29.8 | 4 |
| C | 21.2 | 13.4 | 25.5 | 3.1 |
| D | 23.6 | 3.7 | 25.4 | 3.6 |
| E | 26.2 | 6.8 | 27.7 | 6 |

cascade impaction retaining its place as a tool for more detailed investigation of out-of-specification batches. For now, unexplained anomalies remain in some of the studies, with AIM results more consistent with NGI data for certain marketed DPIs than for others, for example.

Commercially available AIM instruments have much reduced dead volumes relative to their conventional multistage counterparts, which might help to explain this behavior. Although the FSI and FSA maintain jet-to-plate separation distances where appropriate, they are smaller instruments with less internal space than the ACI and NGI. The impact of this difference on the flow characteristics of the device and on the rate of acceleration of the dose through the instrument is a key focus in ongoing studies within the European Pharmaceutical Aerosol Group (EPAG), particularly with respect to DPI characterization, since for these products, *in vitro* performance depends on inhaler resistance.

Finally, the reduction in thermal mass of certain AIM-based systems may increase their attractiveness for nebulizer characterization, where evaporation as a result of the thermal capacity of the impactor is known to be a significant problem [8]. Both the FSA and FSI have a much lower thermal mass than their multistage counterparts, reducing the potential for evaporation or, alternatively, making it much easier to chill the unit prior to operation and/or to maintain a low temperature during use. Further investigation to explore the use of AIM for nebulizer testing is warranted.

## References


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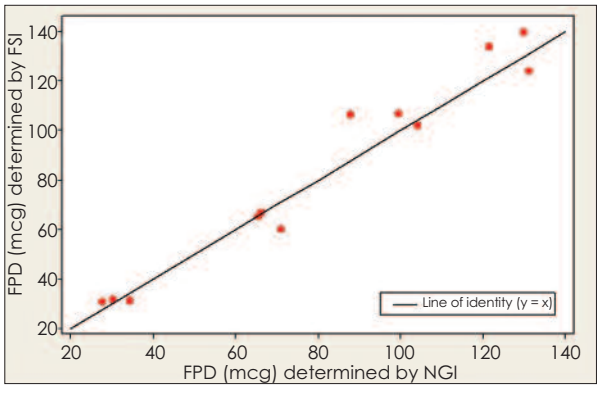
**Figure 3**

**Comparing the ability of the FSI and NGI to track changes in fine particle dose (FPD)**





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