

# CROSS-INDUSTRY Organizations

## Abbreviated impactor measurement (AIM) and efficient data analysis (EDA) concepts: Current questions and future considerations: Discussions from the IPAC-RS workshop held during Respiratory Drug Delivery (RDD) Europe 2015



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### Background

Both abbreviated impactor measurement (AIM) and efficient data analysis (EDA) concepts have been in development for the past six years by the International Pharmaceutical Aerosol Consortium on Regulation and Science (IPAC-RS) Cascade Impactor Working Group (IPAC-RS CI-WG), amongst others, as more efficient tools for the assessment of orally inhaled products (OIPs), where it is necessary to determine and manipulate metrics related to aerodynamic particle size of the emitted aerosol as one of the critical quality attributes of these products.<sup>1-4</sup>

There has been some reluctance by industry to take up AIM and EDA adoption as a key component in OIP lifecycle management, although several validation experiments have been published relating to the AIM concept.<sup>5-7</sup> The rationale for adopting EDA has been explained on more than one occasion as a more sensitive measure of displacements of the aerodynamic particle size distribution (APSD), in terms of both size and mass concentration of the active pharmaceutical ingredient (API), than either determining fine particle dose in accordance with the European Pharmacopoeia method or the grouping of impactor stages into three or more parts related to likely deposition location in the human respiratory tract.<sup>2,3,8</sup>

A workshop was therefore organized at Respiratory Drug Delivery (RDD) Europe 2015. Its purpose was to explain the latest developments in both topics, as well as to build on the information published in book form on both concepts in 2013.<sup>9</sup> The workshop was organized as three repeat sessions, each lasting 45 minutes, during which the presentations listed in Table 1 were given, followed by question-and-answer (Q&A) discussions. These presentations can be found on the IPAC-RS website at: [http://ipacrs.org/assets/uploads/outputs/CI\\_RDD\\_Workshop\\_w\\_Notes\\_and\\_QnA.pdf](http://ipacrs.org/assets/uploads/outputs/CI_RDD_Workshop_w_Notes_and_QnA.pdf).

The content arising from a distillation of each Q&A session is the focus of this cross-industry organizations article. The questions and responses have been grouped into

Table 1

Authors	Presentation Title
Mitchell JP and Nichols SC	Abbreviated impactor measurement (AIM): Recent data and progress towards a European method
Patel R and Christopher JD	IPAC-RS CI-WG: Second experiment comparing AIM with full resolution Andersen 8-stage cascade impactor
Tougas TP	Why EDA?

several common topics, featured in the sessions, to identify the key issues of concern.

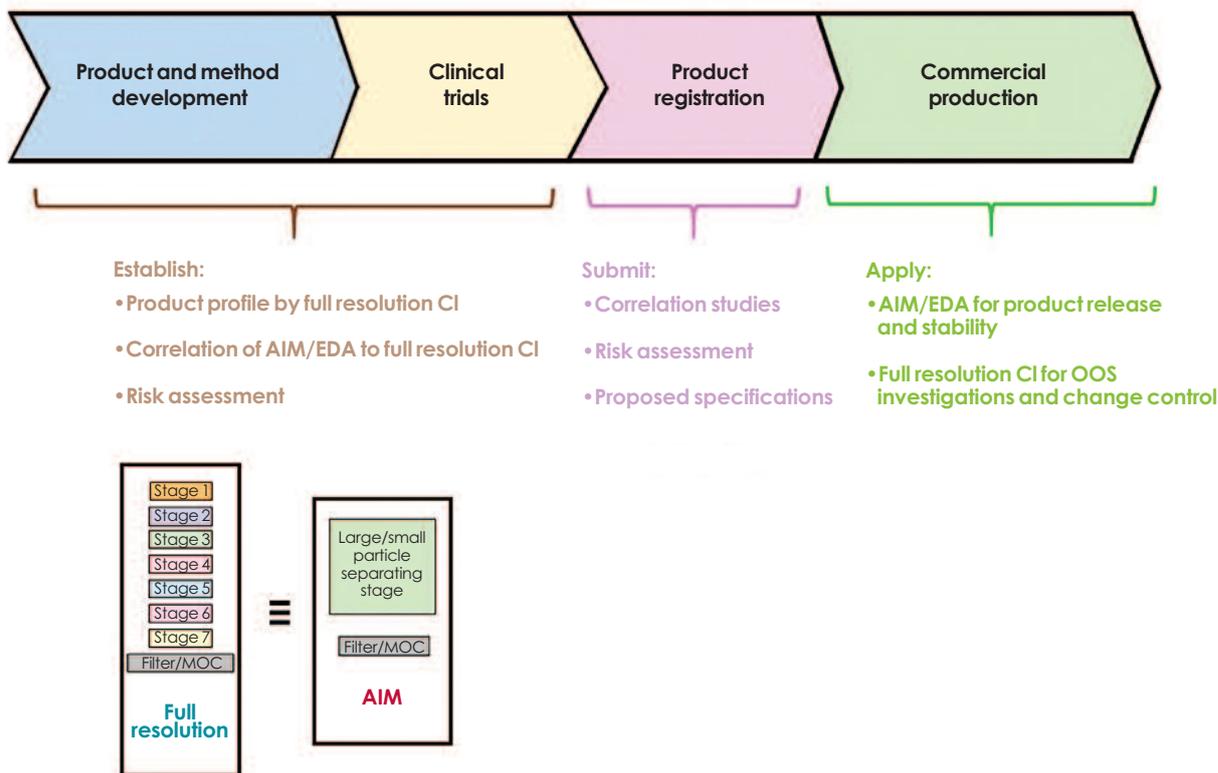
### The rationale for AIM/EDA

#### Q1.1: Why should we care about either AIM and/or EDA?

**A:** Either concept reduces waste of resources, which in turn helps control costs for patients and helps companies direct resources into more productive channels. The waste reduction comes from two principal sources: AIM allows a less complex experimental set up; while EDA allows more accurate decision-making concerning batch acceptance or rejection, with a lower rate of “false positive” errors compared to typical CI-based product quality control (QC) methods.<sup>4</sup> These advantages could be realized by applying either AIM or EDA alone. In combination, AIM and EDA reduce the unnecessarily excessive testing during routine QC as well as during investigation, and especially wasteful batch rejections stemming from the false positive error rate typical of current CI QC methods. While aiming to maintain consumer protection, AIM and EDA reduce producer risk.<sup>4</sup> Addi-

Figure 1

The role of AIM in the orally inhaled product lifecycle



tional savings would come from the harmonization of approaches in different countries (which is currently lacking), since a company’s manufacturing and testing operations could be standardized and streamlined around the globe.

**Q1.2: What was the historical justification for using either the mass fraction between 0.5 and 5.0 µm aerodynamic diameter or the mass < 5 µm as the fine particle mass (FPM), which is the focus of regulatory control?**

**A:** This selection was due to one (US) regulator’s mistaken emphasis on that portion of the distribution, based on industrial environmental testing practices. That regulator’s views have changed since then but the application of that fraction remained. For QC purposes, FPM by itself is a poor metric, since almost all current products have a large proportion of their mass in that fraction, however defined.

**The methodology**

**Q2.1: There are so many AIM apparatus. Which one to use?**

**A:** AIM will not completely replace full-resolution impactors in the product lifecycle (Figure 1). Establishing either equivalence or a stable correlation between the chosen AIM apparatus and the full-resolution impactor would be undertaken, where appropriate, during product development, with the results of the

correlation studies submitted to the regulatory agency as part of the registration package. The decision whether a stable correlation is acceptable, rather than a narrower definition for equivalence, is likely to be made by the sponsoring organization in discussions with the appropriate regulatory agency(ies) concerned with product registration. However, there is anecdotal evidence that at least one organization is developing their product using AIM with a stable correlation to their full resolution CI data. AIM would then be used routinely in commercial production, with the registered full resolution impactor data available as a reference point in the event of either an out-of-specification (OOS) event or as part of a change control process.

Whichever full-resolution impactor is used for full characterization, the same type of impactor should be used for AIM. Problems can arise if results from different type impactors are compared (e.g., full-resolution viable Andersen CI to AIM non-viable Andersen CI). The Fast Screening Impactor (MSP Corporation, St Paul, MN, US) has no obvious “parent” full resolution CI. However, it has been used in combination with the NGI by several groups with acceptable agreement in chosen metrics, in particular fine particle dose.<sup>10-12</sup> However, these investigations confirmed that dead-space, particle bounce and blow off, and other issues should ideally be matched between full-resolution and AIM apparatus. Note that AIM and EDA are not prerequisites of each other, so users have maximum flexibility.

**Q2.2: How to pick the boundary between large and small particles to apply EDA?**

**A:** The boundary between large and small particle mass fractions should ideally be somewhere on the rise portion of the cumulative APSD curve, close to the mass median aerodynamic diameter (MMAD). EDA will work best if the ratio metric based on large to small particle mass (LPM/SPM) is chosen close to unity (i.e., coincident with the MMAD), but it will also work well if the ratio of boundary size between LPM and SPM to MMAD ranges from 0.3 to 3.0.<sup>1</sup>

**Q2.3: What if the APSD is non-symmetrical?**

**A:** As long as the APSD is uni-modal, it does not matter whether the distribution is symmetrical, for the purposes of using AIM and EDA. If the true distribution is multi-modal, the full-resolution impactor will not “see” the separate modes because, with a maximum resolution of only 5 data points per decade of size,<sup>13</sup> its selectivity is insufficient to distinguish fine features, so the outcome will still be determined as uni-modal (perhaps with a significant tail). Either way, the AIM/EDA could still be validly used, but the sponsor might also wish to investigate the fine structure of the APSD with a technique, such as time-of-flight aerodynamic particle size analysis, having greater size-resolving power than CI-based methods.

**Q2.4: Are the non-aerodynamic sizing parts of the measurement apparatus (i.e., the uppermost impactor stage of the ACI, pre-separator and induction port [throat]) included in the analysis by EDA?**

**A:** EDA is appropriate to ascertain if shifts in the APSD have taken place, so by definition, only the components from the cascade impactor capable of providing size information (i.e., stages with a defined cut-off size assigned to them) are considered. In the case of the ACI, the upper size limit for stage 0 is undefined, so the mass fraction collected by this stage is part of the non-sized portion of the sampled aerosol. The non-sized portion is, however, controlled as a contributor to the delivered dose (DD) assay, which is currently a separate test in the pharmacopeias. However, in principle, a single AIM-based apparatus could be developed for measuring DD and APSD in a single test; one possible design is presented in Chapter 13 of the AIM/EDA Handbook.<sup>14</sup>

**Q2.5: Would EDA/AIM capture the geometric standard deviation (GSD) of the APSD?**

**A:** GSD is only meaningful if the APSD is uni-modal and log-normal. Even if these criteria are met, this measure of the spread of the distribution is unimportant as a metric for product QC. Note that the fine particle dose (FPD) metric by itself does not capture GSD either. **Post-workshop consideration:** If the width of an APSD changes, thereby altering GSD, then either impactor sized mass (ISM) or LPM/SPM or both metrics would be affected. Therefore EDA would detect a change in GSD.

**Q2.6: Has GSD been used at all (for regulatory purposes)?**

**A:** There is nothing to that effect published in the open

literature, although the Center for Devices and Radiological Health (CDRH) of the FDA, in 510(k) submissions, require reporting the sizes corresponding to the GSD (or the ratio of the 84th to 16th mass percentiles of the cumulative APSD (span)) for nebulizer-generated aerosols or for aerosols where a spacer/valved holding chamber is present.<sup>15</sup> In any case, controlling the APSD through either its GSD or span is not needed.<sup>16</sup>

**Application to specific orally inhaled products****Q3.1: Does AIM/EDA apply to nasal products?**

**A:** Droplets from nasal sprays are too large for CI characterization, and the purpose of testing them is different compared to orally inhaled products. Namely, the main concern is to prevent nasal products from having a respirable fraction. Nevertheless, it is possible to create AIM impactors with cut sizes in the range 5.0 to 10.0  $\mu\text{m}$  aerodynamic diameter without sacrificing significant size-selectivity because of gravitational sedimentation, so in principle, EDA could be applied.

**Q3.2: Would these methods work with a pressurized metered dose inhaler (pMDI)-spacer or pMDI-valved holding chamber (VHC)?**

**A:** Yes. It does not matter if a spacer/VHC is used as an add-on device to the inhaler. By eliminating most of the coarse mass fraction of the emitted aerosol, the spacer/VHC would shift the measured distribution to finer particle sizes, but it could still be analyzed using AIM and EDA, if necessary by selecting a cut-size between large and small mass fractions for the abbreviated impactor, that is more central to the emitted APSD.

**Future considerations****Q4.1: What are implications of AIM and EDA for generic pharma? Could these methods be used for bioequivalence (BE) testing?**

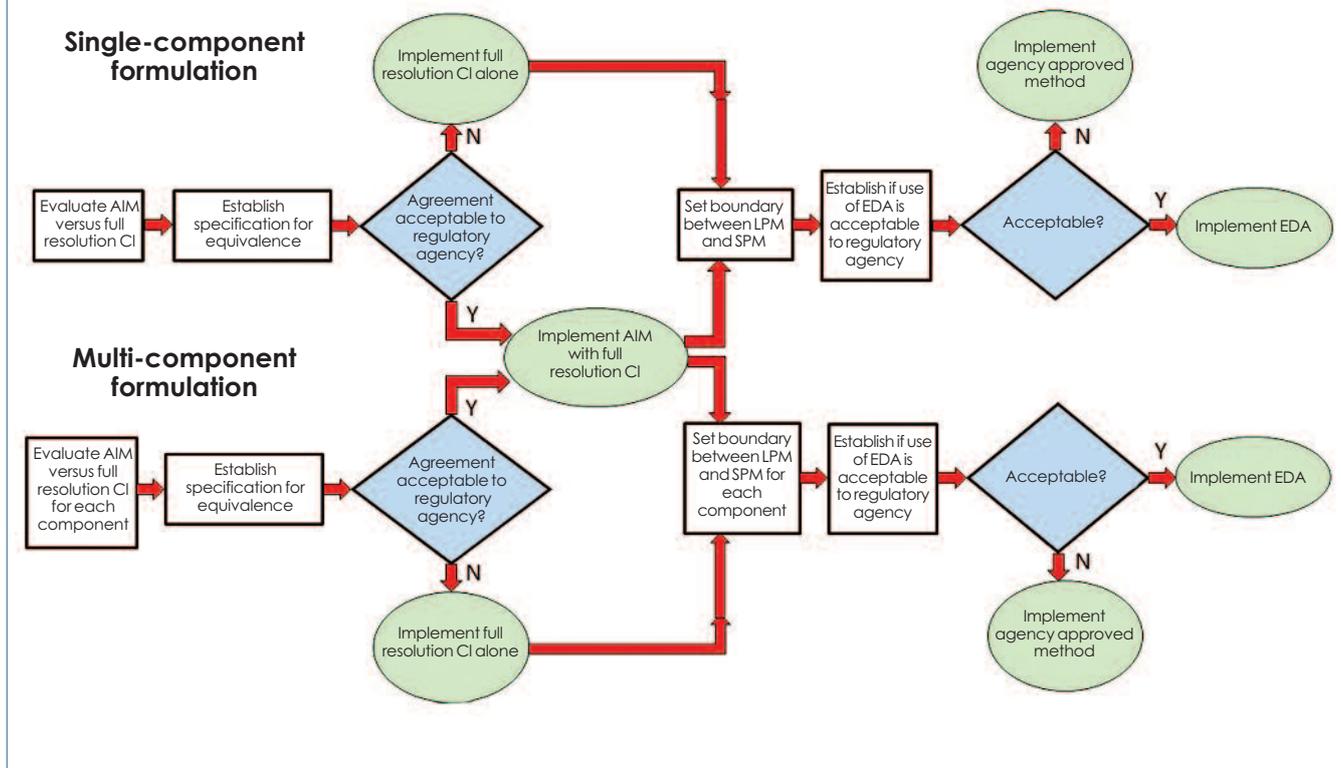
**A:** For BE testing, full characterization of APSD is required by both European and US regulatory agencies, and therefore EDA, by itself, would not be appropriate. If, however, at some stage in the future, there were greater regulatory freedom allowed with respect to the amount of size distribution data and assessment method, the AIM concept could be expanded to include extra-fine particles and a clinically relevant inlet such as the Alberta Idealized Throat (AIT). For QC testing, however, AIM and EDA could be used for generic products in the same way as for brand-name innovator products, with the same advantages and savings in time and resources.

**Q4.2: Could industry's reluctance to adopt AIM and EDA be due to concern that deviations from log-normality would go unnoticed?**

**A:** The concern is misplaced, since having a log-normal distribution, in itself, has no clinical relevance. What would be important are deviations from the approved APSD of a product at registration (log-normal or not)

Figure 2

Flow diagram showing how AIM and/or EDA might be implemented during the development phase of the product lifecycle. The precise criteria for acceptability would be agreed upon on an individual product basis between the sponsor and the regulatory agency.



used in clinical trials. Such deviations, either as changes to mass concentration of API and/or aerodynamic size of the emitted particles), would be detected by EDA.

#### Q4.3: How long would it take for regulatory agencies to adopt AIM and EDA?

**A:** Several regulatory agencies have already indicated their readiness to consider product applications based on AIM and EDA concepts. Industry now needs to take the initiative and prepare such submissions. An existing (legacy) product could offer a lower-risk (relative to a New Chemical Entity) way to introduce AIM and/or EDA via a method change supplement. **Post-workshop note:** In the case of a generic product registration, that submission would also have to make use of full resolution CI measurements rather than an AIM-based approach, if the originator product had been fully characterized in that way beforehand. This consideration would likely also apply for release specifications.

#### Q4.4: We need more guidance on how to apply AIM and EDA. How can these goals be achieved?

**A:** Industry requests flexibility but also guidance from regulators. The balance could be achieved if regulatory guidance documents set forth general principles while the detailed how-to considerations are worked out and published by industry consortia; e.g., in the form of white papers, voluntary consensus guidelines and best practices. Figure 2 sets out a flow-chart outlining a logical process for the implementation of AIM with or with-

out EDA, depending upon the outcomes of establishing method equivalence (for AIM) and regulatory agency acceptability (for both AIM and EDA).

#### Where next?

The questions raised during the workshop indicate that, although there is a basic understanding of both AIM and EDA concepts, through the foundation laid by previously published articles, and in particular the book: “Good Cascade Impactor Practices, AIM and EDA for Orally Inhaled Products,” there is still room to create additional “how-to” documentation for each concept, while recognizing there are a number of considerations that need to be carefully evaluated on a product-by-product basis before implementing an AIM-based approach.

To further assist product- and method-developers, the IPAC-RS Cascade Impaction Working Group is currently completing the following manuscripts for peer-reviewed journals, as well as a poster to be presented at RDD 2016:

- Discriminating Ability of AIM to Detect Changes in MMAD (Results of a Second Series of IPAC-RS Experiments);
- Use of Efficient Data Analysis Compared to Fine Particle Dose (FPD) as a Quality Control Tool;
- A Roadmap for Developing and Applying AIM and EDA in Practice;

- The Abbreviated Impactor Measurement Concept as a Stand-Alone Alternative to the Full Resolution Cascade Impactor from the Perspective of Their Calibration Traceability Chains.

These upcoming publications will add to the growing literature demonstrating advantages of EDA against current methods of interpreting CI-derived APSD data (e.g., fine particle dose <5  $\mu\text{m}$  aerodynamic diameter (FPD<sub><5 $\mu\text{m}$</sub> ) in Europe; stage groupings in the US), and will further clarify the “why” and “how” of adopting either or both concepts in the OIP lifecycle. Furthermore, the IPAC-RS CI-WG is working on a set of web-based educational materials for stakeholders, presenting the background and practical aspects of impactor data testing and analysis (including AIM and EDA) in an easily accessible format. All of these activities are part of a conscious shift in the CI-WG focus, from laying down a solid scientific foundation to facilitating a wider understanding and adoption of the AIM and EDA approaches by the OIP Industry.

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