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Research Article

Product Lifecycle Approach to Cascade Impaction Measurements

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Abstract. Over the lifecycle of an orally inhaled product (OIP), multi-stage cascade impactor (CI) measurements are used for different purposes and to address different questions. Full-resolution CIs can provide important information during product development and are widely used but are time- and resource-intensive, highly variable, and suboptimal for OIP quality control (QC) testing. By contrast, Efficient Data Analysis (EDA) combined with Abbreviated Impactor Measurement (AIM) systems pertinent either for QC and—possibly—for adult Human Respiratory Tract (pHRT) has been introduced for OIP performance assessment during and post-development. This article summarizes available evidence and discusses a strategy for using either abbreviated or full-resolution CI systems depending on the purpose of the measurement, such that adequate, accurate, and efficient testing of aerodynamic particle size distribution (APSD) of OIPs can be achieved throughout the lifecycle of a product. Under these proposals, a comprehensive testing program should initially be conducted by full-resolution CI in OIP development to ascertain the product's APSD. Subsequently, correlations should be established from the selected AIM CIs to the corresponding full-resolution system, ideally developing specifications common to both techniques. In the commercial phase, it should be possible to release product using AIM/EDA, keeping the full-resolution CI for investigations, change control, and trouble-shooting, thus optimizing resources for APSD characterization throughout the product lifecycle. If an *in vitro–in vivo* relationship is established and clinically relevant sizes are known, an AIM–pHRT could serve as a quick indicator that clinically relevant fractions have not changed and also, in the management of post-approval changes.

KEY WORDS: abbreviated impactor measurement (AIM); Andersen cascade impactor (ACI); inhaler; lifecycle; quality control (QC).

INTRODUCTION

During development of an orally inhaled product (OIP), its full-resolution Aerodynamic Particle Size Distribution (APSD) and estimates of pertinent mass (size) fractions are fundamental ways to characterize the product's *in vitro* performance (1,2). The pharmacopeial eight-stage Andersen Cascade Impactor (ACI) or Next-Generation Pharmaceutical Impactor (NGI) are usually employed to obtain full-resolution cascade impaction (CI) measurements. These techniques, however, typically have high variability and require significant time, skill, and resources (3). Moreover, the full-resolution CI data may be unnecessary and even counter-productive for other purposes, *e.g.*, routine quality control (QC; 4), formulation, and device optimization or testing of add-on devices such as spacers and valved holding chambers where breath simulation is more appropriate to check on operation of inhalation and exhalation valves (5,6). QC testing used to confirm quality of a batch using APSD as critical quality attribute needs to be accurate, precise, and capable of high-throughput, so that the process can accommodate sufficiently large sample sizes to make more correct decisions about batch quality (7). Similarly, testing of OIP add-on devices needs to focus only on information relevant to the add-on-device performance, but from a sufficiently large number of devices to achieve acceptable resolution of changes in APSD metrics that might indicate the need for intervention based on the risk assessment for the device (8). Given the number of samples that might be involved to resolve small but potentially important changes in performance, it follows that it is highly desirable to capture this information as rapidly as possible without sacrificing accuracy and precision.

This article builds on the recently introduced Efficient Data Analysis (EDA) and Abbreviated Impactor Measure-

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ment (AIM) concepts (9) and discusses the role of these approaches, together with traditional CI measurements, in a product's lifecycle. Its purpose is to provide a guide for prospective users of AIM/EDA-based techniques.

CONSIDERATIONS FOR SELECTING AN AIM-BASED CI

There are many alternatives for building an AIM system (*e.g.*, modify an existing NGI or the eight-stage ACI by changing the number of stages, orifice dimensions, and operating flow rate, or purchase commercially available AIM systems from one of several vendors; 10). The three types of APSD measurement systems discussed later in this article in the context of an accuracy and precision study (11) are illustrated based (in this example) on the ACI (Fig. 1), where two of the configurations were modified to exemplify application of the AIM concept for use in product quality control (AIM–QC) and potentially for measurements predicting particle deposition in the human respiratory tract (AIM–pHRT). When building an AIM system, attention should be paid to the parameters such as total volume and flow profile (flow rate, flow acceleration). Depending on the purpose of the AIM system (*i.e.*, either best detection of changes to APSD profile or having fractions with perceived clinical significance), the physical configuration of the AIM system will likely depend on the specifics of the drug product being developed.

The exact stages that are selected for use in AIM–QC systems and consequently the exact size ranges used for such evaluations, depend on the size-deposition profile obtained for the product being tested (4). However, the particle size fractions (extra-fine and fine-particle fractions <1.1 and <4.7 μm aerodynamic diameter, respectively) that were chosen in the accuracy and precision study for the AIM–pHRT system are consistent with the current understanding of the relationship between particle size and deposition or clinical effects (12–14). However, it is recognized at the outset that much more work is needed to validate this approach in relation to clinical data on product efficacy, hence the use of the descriptor "possible AIM-HRT" (abbreviated to pHRT) for this system. AIM systems can also be custom-tailored to meet the current European regulatory requirements that focus on fine-particle dose based on a fixed boundary between coarse and fine fractions at 5 μm aerodynamic diameter (15).

There are currently several open debates related to establishing the clinical relevance of APSD measurements including the use of alternative induction port/throat geometries and breath simulators (16–18). In this work, we are not intending to demonstrate how clinically significant results may be obtained using abbreviated impactors. However, it is recognized that there is scope for further refinements to be considered in terms of abbreviated CI designs that more closely reflect the clinical situation (*i.e.*, by replacing the Ph.Eur./USP induction port with the idealized mouth–throat model of Finlay and colleagues) (19), and such improvements may be the subject of future experiments. In this article, we have reported on the pHRT-AIM as it was configured for the experiment comparing its precision with that of a full-resolution ACI (20).

The qualification of AIM-based systems against their full-resolution counterparts is an active and ongoing process, reflecting the increasing interest in the potential of abbreviated measurements within the community of stakeholders involved with inhaler APSD-related measurements. However, whichever design of abbreviated system is chosen for a given inhaler type/drug product, it is already known that attention should always be paid to eliminate particle bounce and re-entrainment (11). In addition, when evaluating pressurized metered dose inhalers (pMDIs), in which low volatile species such as ethanol are present in the aerosol plume, it is important to mimic the internal volume up to and including the first impaction stage of the reduced system (21). There is currently an initiative under way within the European Pharmaceutical Aerosol Group to define more inhaler-specific considerations for evaluating dry powder inhalers (DPIs) and pMDIs and nebulizers using AIM-based systems (22,23). In addition, recently published independent work with both pMDIs and nebulizers has confirmed that close agreement is possible between the NGI and fast screening impactor, an abbreviated system based on the design of the NGI pre-separator (24), in this instance with the cut-size between coarse and fine fractions set at 5 μm aerodynamic diameter.

THE EFFICIENT DATA ANALYSIS (EDA) CONCEPT

Two Metrics Sufficient to Detect Quality Changes in APSD

In fundamental terms, changes in a mass-weighted APSD obtained from full-resolution CI measurements can be reduced to those associated with position of the mass distribution profile on the abscissa (size) scale and with its area under the curve or amplitude [position of the mode(s) on the ordinate (mass) scale, see Fig. 2].

Previous theoretical work (4) has shown that only two mutually independent metrics are necessary and adequate to detect these types of changes, namely the sum of large and small particle mass (LPM+SPM) and their ratio (LPM/SPM). The LPM-to-SPM boundary can be set on or nearby the value of mass median aerodynamic diameter (MMAD) determined from full-resolution CI data to maximize the sensitivity to change. The sum of LPM+SPM represents the impactor-sized mass (ISM) that reaches stages having an upper size limit, which are the only impactor deposition sites used in the calculation of MMAD. Thus stage 0 in the ACI would be excluded from ISM since its upper size bound is undefined (25). In this context, the recent experimental work with a commercially available pMDI product in the AIM precision and accuracy study has shown that ISM is highly correlated to total mass entering the impactor (impactor mass, IM; 26). In product lifecycle management, all of these metrics (as well as the particle fractions from which they are derived) would be chosen to maximize their sensitivity to quality changes in APSD. The data evaluation exercise undertaken by Tougas *et al.* (4) demonstrated that these metrics can detect unusual APSD data at least as well as the conventional approach based on stage groupings. However, it is important to note the advantage that, in contrast to the stage groupings approach, LPM and SPM are unconfounded, *i.e.*, they can detect changes in the APSD position and total area independently of each other, making them particularly sensitive to detect APSD changes in the context of a product quality-by-design environment. The unconfounded nature of these EDA metrics is also important relative to the current European regulatory

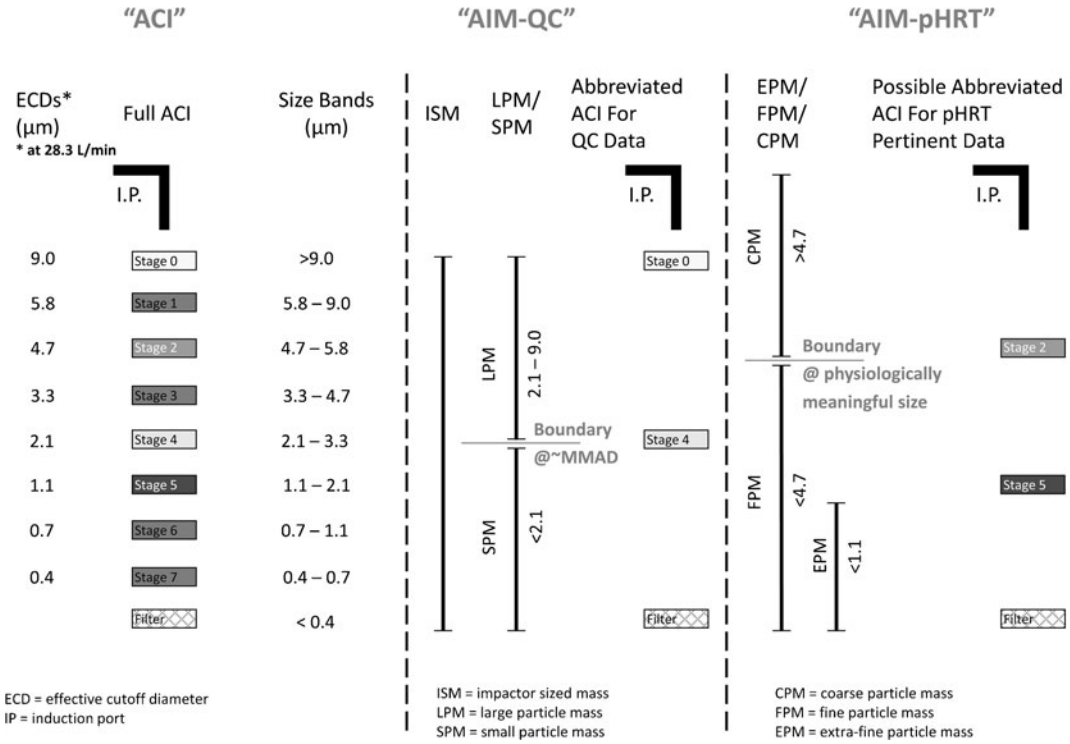

Fig. 1. Configurations of the full-resolution ACI and two possible AIM systems in the accuracy and precision experiment (flow rate 28.3 L/min) adopted from Ref. (11). *ACI* Andersen cascade impactor, *AIM* abbreviated impactor measurement, *AIM-pHRT* abbreviated impactor measurement system possibly relevant for adult human respiratory tract, *AIM-QC* abbreviated impactor measurement system for quality control, *CPM* coarse particle mass, *ECD* effective cut-off diameter, *EPM* extra-fine particle mass, *FPM* fine particle mass, *I.P.* induction port, *ISM* impactor-sized mass, *LPM* large particle mass, *MMAD* mass median aerodynamic diameter, *SPM* small particle mass, *pHRT* possibly relevant for adult human respiratory tract, *QC* quality control

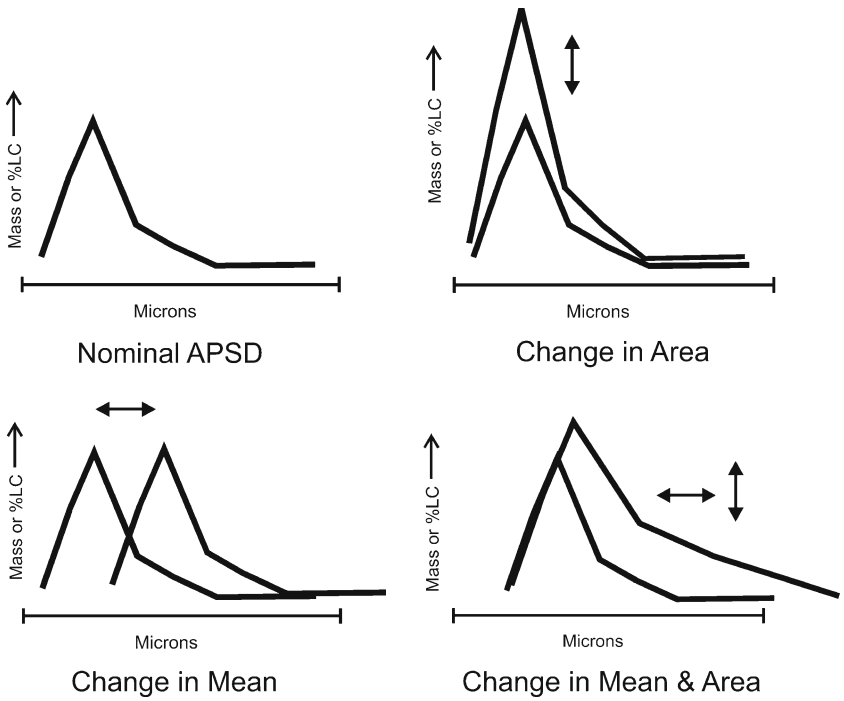

Fig. 2. Basic types of aerodynamic particles size distribution (APSD) changes: a shift in central tendency (mean), change of area under the curve (or AUC_{APSD}), and change in shape. (*LC* label claim) adopted from Ref. (4)

approach, which requires control of the total dose fine-particle dose (FPD approach) or particles less than 5 μm (27). Here, the EDA metrics are capable of truly detecting changes to underlying particle size distribution (not only the fine-particle dose but the whole distribution), while the FPD approach only considers particles mass below 5 μm and therefore, would potentially be insensitive to changes affecting just the coarse size fraction. Furthermore, depending on the actual APSD of the product being tested, this approach may be completely insensitive to any shift within just the fine fraction of the dose captured by the CI, whether determined by a full-resolution or abbreviated system. In contrast, by virtue of its sensitivity to detect changes affecting the entire APSD, the application of EDA with an AIM–QC apparatus will detect changes in the fine-particle dose better than just a grouping of stages with sizes below 5 μm, making for a better decision-making tool (4).

It is therefore likely that by knowing precisely what is happening with the APSD—whether the change is in the total mass of impactor-sized particles (ordinate variable in Fig. 2) or in the location of the APSD in terms of aerodynamic particle size (abscissa variable in Fig. 2)—such outcomes will facilitate root cause identification much sooner and with more sensitivity than using a full-resolution ACI. In addition, when determined with an AIM-based CI, the time per measurement is reduced. In consequence, the testing of more samples from a lot is potentially possible within a given period (improved coverage), ultimately leading to more reliable quality assessments. The concept of measuring only properties related to two mass fractions may seem familiar to users of an earlier generation of simplified inertial size analyzers that include the Twin Impinger (28), but there are the following critical differences:

1. One of the QC metrics in the new approach is a ratio LPM/SPM rather than just the absolute amounts of large and small particle masses. By themselves, LPM and SPM are each confounded with the area under the curve (ISM). However, because they are (negatively) correlated, the LPM/SPM ratio is unconfounded with ISM and is more informative than considering LPM and SPM separately.
2. The boundary in a QC–AIM system is an adjustable parameter intended to maximize the detection of changes in the APSD of the product being tested. The boundary condition can be adjusted by either selecting different stages in the impactor or adjusting the flow rate.

From the foregoing, it follows that, for optimum measurement sensitivity, the product APSD characteristics should drive the selection of the LPM-to-SPM boundary. This necessary condition may lead to the need to have differently configured AIM systems for different products, however, in practice, there would only need to be a small number of such systems to capture all variety of products, given the limited overall range of applicability of aerosol particle size analysis (ca. 0.1–10 μm aerodynamic diameter) by CIs operated in accordance with the compendial monographs (29). It might be that as few as three different abbreviated CIs would be sufficient to cover all inhaled products, *e.g.*, choosing cut points around 1.5-, 2.5-, and 3.5-μm aerodynamic diameter. It should also be noted that the sampling flow rate is the other major variable that could be used to adjust the bound between LPM and SPM for a given abbreviated configuration to the desired boundary size (29) which may be appropriate for MDI and nebulizer testing but might be inappropriate for patient-driven DPI products since performance varies as a function of flow rate. However, whichever option is chosen, appropriate stages would have to be selected to create the abbreviated apparatus appropriate for each particular product/APSD of interest, and this selection process is foreseen as becoming part of that product's "method". It follows that it will also be essential to validate the AIM-based system chosen for a particular product, using the appropriate full-resolution CI to provide benchmark data before working with the reduced system on a routine basis. An experimental design published elsewhere (20,26) could be adopted for this purpose.

Justification for Abbreviated Impactor Measurements from Experimental Studies

We have shown that only the two fractions mentioned above need to be measured using an AIM–QC-configured apparatus in order to construct metrics that provide all the relevant information about OIP APSD for product QC purposes. However, when determining sizes related to likely particle deposition in the HRT, the analogous measurements of coarse (CPM) and fine (FPM) particle mass, respectively, are ideally augmented by measurements of extra-fine mass (EPM) <ca. 1.0 μm aerodynamic diameter as a sub-set of FPM. This is because this extra-fine fraction may be related to systemic absorption or such particulates may be exhaled before deposition can take place, particularly if a breath-hold at the end of inhalation is not practiced (30). Furthermore, assessment of CPM, FPM, and EPM may be sufficient to assess relevant *in vitro* APSD performance of add-on devices such as spacers and valved holding chambers used with pMDIs in accordance with a recently developed Canadian standard (31), without the need for full-resolution CI measurements. These developments may explain the increasing (22,24) interest in AIM systems from the community involved with drug delivery device development.

An important development setting AIM-based approach on a firm foundation took place in 2009, when a proof-of-concept experiment was undertaken with the purpose of comparing method precision between AIM systems and a full-resolution ACI, each operated at the manufacturer-stated nominal flow rate of 28.3 L/min for this system. One of the two AIM-based systems was configured to provide metrics pertinent to QC (QC system), and a second AIM-based configuration was evaluated as a candidate apparatus to provide possible indications of adult human respiratory tract deposition (pHRT system) (20,26). All systems were prequalified by stage mensuration to minimize CI-related bias and adjacent canisters were chosen from a lot of a US-commercially available HFA-albuterol (salbutamol) pMDI to minimize product variability. Measurements obtained with both abbreviated impactors were very similar in precision to that for the ACI for all evaluated measures of *in vitro* performance evaluated. However, one source of potential bias affecting EPM measurements by the pHRT system was traced to incomplete mitigation of particle bounce on the lower impaction state following migration of the surface coating away from immediately beneath the nozzle exits from preceding stage. In a follow-on study, this source of error was eliminated by the use of a glass microfiber filter soaked

with suitable surfactant to provide a tacky surface that could not be displaced by the divergent flow exiting from the previous stage. Similar experiments are now needed for other CI systems, in particular, those based on the NGI where data are currently limited and a formal comparison of precision has not to the authors' knowledge been undertaken. Comparative studies undertaken with the same degree of rigor as that adopted for the ACI-based apparatus comparison study (20,26) would greatly assist those involved with APSD-related assessments as part of developing plans for OIP lifecycle management by providing a greater range of choice of validated measurement equipment.

THE ROLE OF APSD IN OIP LIFECYCLE MANAGEMENT

APSD testing is used for a variety of purposes during the lifecycle of an OIP. In the various stages of development, the sponsor studies safety and efficacy of the product and establishes the target APSD with associated metrics and specifications. In commercial production, QC testing is meant simply to confirm whether the APSD is the same as that of the clinical batches. QC testing cannot be expected to repeat the detail required for safety and efficacy studies. The only reasonable and practical goal of QC testing is to ascertain that the APSD is within the specifications established for the product for release of the clinical batches.

Developers of add-on devices for OIPs rely on the already established safety and efficacy profiles of the approved drug product, so that their purpose of determining APSD-related data is related to the need to minimize the undesirable coarse particle mass that deposits in the oropharyngeal region while maintaining the amount of emitted fine particles ideally equivalent to that from the OIP device without add-on (15,32). There is therefore, in principle, no need to re-establish or re-test the entire detailed APSD profile in future measurements of *in vitro* performance, once the behavior of the add-on in this respect has been established by full-resolution CI.

Lifecycle Management Strategy

A strategy for optimizing the use of the different variants of CI measurements throughout a product's lifecycle is proposed, where the need for APSD-pertinent data is identified in relation to the following distinct but complementary processes (Fig. 3).

A. During Inhaled Product Development
   1. Use both the AIM–pHRT and the AIM–QC CIs as screening tools in early formulation development, noting that the AIM–QC system may provide greater sensitivity for detecting important changes in the APSD profile while taking advantage of higher throughput. The AIM–pHRT configuration could be used to obtain additional resolution if an IVIV relationship has already been established. Note, however, that once the formulation and delivery vehicle (pMDI, DPI, *etc.*) have been developed, the full-resolution CI would still likely be used to define product's APSD characteristics for the clinical batches.
   2. Establish the full-resolution APSD profile of the OIP with full-resolution CI-based measurements. This process would require multiple determinations representative of the product, for example, from different units, different batches, different life stages through individual inhaler content testing (as a minimum from beginning and end of unit), and at various times during stability testing, in numbers sufficient to obtain adequate statistical power.
   3. Choose LPM, SPM values, and correlate AIM–QC CI-based measurements of both metrics to their equivalents determined by full-resolution CI measurements after: (1) selecting an optimum particle size boundary between LPM and SPM; and (2) demonstrating that a relationship exists between LPM/SPM and MMAD. Note that:
      (a) The appropriate boundary between LPM and SPM must be determined by full-resolution CI.
      (b) The traditional coefficient of determination (R^2) may not be appropriate for all cases, when establishing the correlation between AIM- and full-resolution-based metrics. For instance, when the range of MMADs for a given product is narrow, the coefficient of determination may appear low relative to other products possessing higher MMAD variability, even though their correlation is just as good. This coefficient is therefore more appropriate for comparisons of distributions with similar ranges of MMAD, but not as an absolute indicator of goodness of fit. The root mean square error divided by the slope of the regression (b) is an alternative goodness-of-fit statistic that may be more robust in terms of predictive power (4).
      (c) Release batches against specifications based on LPM/SPM and ISM after correlation has been established and the target profile has been established. Establishing the correlation could occur either in development or after approval (depending on when a sufficient number of batches is available to justify the proposed approach—a sponsor company may make that decision based on its own risk assessment).
      (d) For the near term, determination of appropriate acceptance limits for the LPM/SPM ratio and ISM could be accomplished by developing limits that produce operating characteristic (OC) curves that match existing approaches (*i.e.*, groupings) with respect to type II error (consumer risk) consistent with limits for approved products, to achieve the same minimum acceptable quality standard. Details of this approach are the subject of ongoing work. Longer-term, "quality-by-design" drives the desire for limits driven by some relationship to product performance, *i.e.*, efficacy and/or safety.
      (e) Establish suitable precision for both LPM/SPM and ISM determinations (which is also necessary for full-resolution CI). Many replicate measurements by both full-resolution CI and

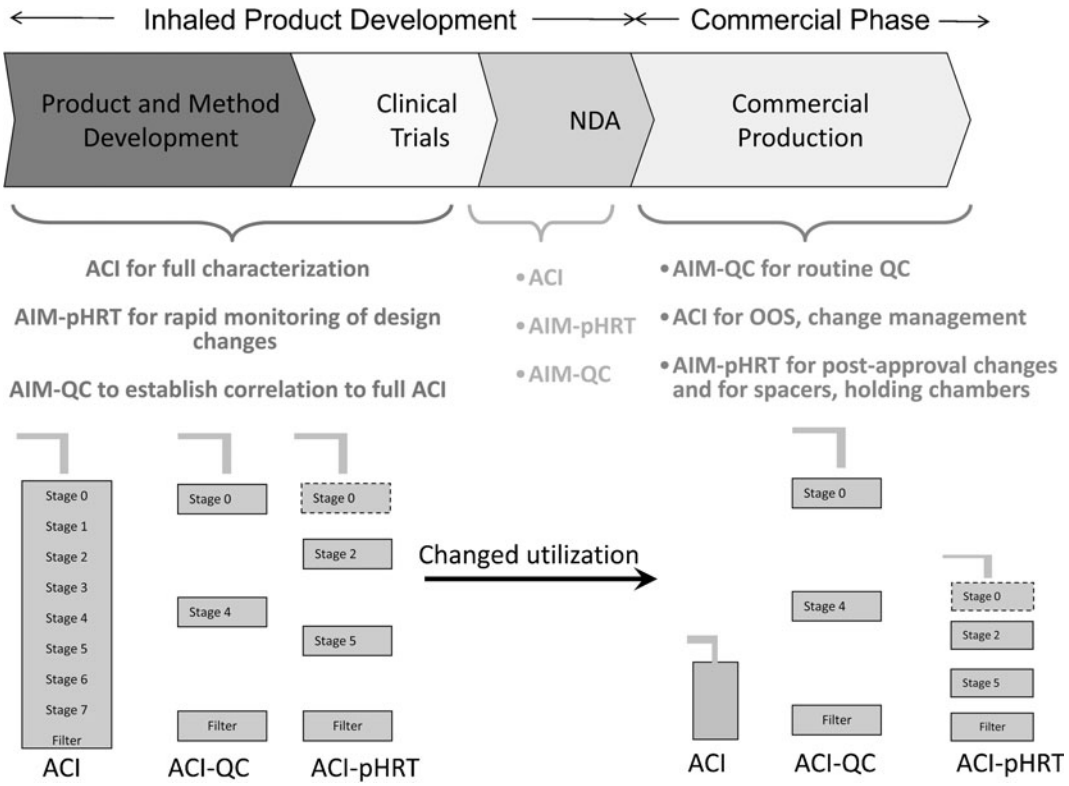

Fig. 3. Scheme illustrating appropriate purpose of various impactor configurations. *ACI* Andersen cascade impactor, *AIM* abbreviated impactor measurement, *AIM-pHRT* abbreviated impactor measurement system possibly relevant for adult human respiratory tract, *AIM-QC* abbreviated impactor measurement system for quality control, *OOS* out of specification, *pHRT* possibly relevant for adult human respiratory tract, *QC* quality control

AIM–QC system, ideally from several different batches or at minimum from widely spaced intervals during manufacture of a single batch, will be needed in order to assess how small of a change in MMAD and total mass entering the sizing part of the impactor can be detected by the EDA metrics for that particular product (20).

(f) Quantify the minimum number of batches required to achieve a statistically robust correlation. In line with the quality-by-design philosophy, the OIP sponsor will likely need data from many different batches (sufficient to represent adequately sources of variability in the manufacturing process, input materials, analysis, and stability effects), with multiple CI runs per batch (sufficient to assess within-batch variability) in order to get a good estimate of the target distribution (mean and variability), which would be representative of future production batches at release and for stability testing. The following outline provides an idea of what may be required:

f.1. Establish the APSD of the product, which will require a large body of full-resolution CI data.

f.2. In parallel, run AIM-based measurements to establish correlation between EDA metrics from both abbreviated and full-resolution systems to enable use of AIM for routine control later on.

In totality, the data required in part (f.2) will likely amount to hundred(s) of CI runs spread over numerous batches, reflecting different lots of API, device components, *etc.* However, the cost of this upfront work should be more than offset later by the regulatory freedom to use EDA in conjunction with AIM CI measurements in the QC environment. This sequence of events mirrors the principle underlying the quality-by-design approach, in which the full-resolution CI essentially maps out the "design space" for the product APSD, with the abbreviated CI working within the "control space". Such a regimen will also improve decision making by virtue of enabling more samples from the batch under consideration to be assessed for a given expenditure in terms of effort and equipment.

Nevertheless, despite the advantage of the approach just outlined, it is recognized that some companies may chose to collect these data only after the product has been approved. In such instances, the switch from full-resolution CI measurements with traditional data assessment to AIM-based CI determinations coupled with EDA could still take place. However, delaying this decision could be associated with some business risk because complete understanding of

the APSD-properties of the product in both measurement regimens (with sufficiently different batches) is also postponed.

4. Establish acceptable limits and associated acceptance criteria for ISM and LPM/SPM for the product with the same AIM–QC CI procedure that will be used later in product quality control.
5. In designed experiments undertaken during product and method development, use full-resolution CI data to identify possible *in vitro* failure modes (*i.e.*, establish ways that an APSD could change and their associated root causes, including aspects such as manufacturing dimensions of the device components, analytical instrumentation, method, *etc.*). Develop control strategies to mitigate identified risks/potential failure modes and evaluate the ability of the chosen QC metrics to detect significant changes. These insights would be helpful for setting product-appropriate specifications for the EDA metrics and later on, during commercial production, for out-of-specification (OOS) investigations.
6. Use full-resolution CI-based measurements as part of an in-depth investigation of any OOS results as well as when any changes are introduced.
   A developer of add-on devices or a pharmaceutical manufacturer interested in including add-on device information in their product label, would also determine characteristic values of coarse (CPM), fine- (FPM), and extra-fine (EPM) particle mass of the product ideally using an AIM–pHRT approach, using either the ACI or NGI as the full-resolution CI benchmark apparatus. Ultimately, it is anticipated that these metrics would be correlated to clinical response if an adequate *in vivo–in vitro* correlation (or an IVIV relationship) for product efficacy can be demonstrated, although it is recognized that such correlations are notoriously difficult to attain for OIP for a variety of reasons (33). In the absence of an established IVIV relationship, the add-on device developer would have to resort to correlating AIM–pHRT-based measurements with their equivalents obtained by full-resolution CI to provide baseline data for comparisons if any changes are introduced post-approval or if add-on devices are to be recommended with the OIP.

B. During the OIP Commercial Phase
   1. Release the commercial product against the already established QC specifications based on LPM/SPM and ISM.
   2. Continue stability testing of the product using the QC metrics and specifications for LPM/SPM and ISM.
   3. Bring in full-resolution CI measurements for an OOS investigation, *i.e.*, to explore the nature of a change that was detected by EDA or any time that unexpected or unusual trends are observed (*e.g.*, increase in variability). Note that since the EDA metrics have the ability to detect changes quickly they can serve as an efficient trigger for such action.
   4. Use full-resolution APSD measurements and possibly AIM–QC and/or AIM–pHRT systems as part of the change management process (*e.g.*, when substantial changes to the device, formulation, or manufacturing process are considered or introduced). The option and choice of the AIM system would be determined by the sponsor's risk assessment of the change.
   5. Use the AIM–pHRT system to manage uses with either bespoke or commercially available add-on devices (*e.g.*, spacers, valved holding chambers), which are well known to attenuate the oropharyngeal deposition of aerosol particles emitted from an OIP.

The strengths and limitations of each approach are listed in Table I, and the uses outlined above are summarized in Table II.

CI DATA FOR CLINICAL SIGNIFICANCE *VERSUS* QUALITY CONFIRMATION

In an AIM–QC CI, it has already been established that the location of the LPM-to-SPM boundary is set to maximize the ability of metrics LPM+SPM and LPM/SPM to detect changes in APSD. The question arises: Are these metrics and the detected changes clinically relevant? To the extent that the entire APSD profile is clinically relevant as all impactor-sized particles are likely to deposit somewhere within the respiratory tract (ignoring losses upon exhalation), the answer is a qualified "YES". However, it is important to appreciate that the underlying intent for these metrics is to provide best possible tools for confirming quickly and reliably in the QC environment whether a given OIP has an APSD within agreed specifications and in addition to provide assurance that the APSD of the clinical batches matches the target specifications. By themselves, therefore, these metrics and associated particle sub-fractions do not claim to be and do not need to be reflective of the drug deposition in precisely specified regions of the respiratory tract or of the ultimate clinical response due to drug-receptor interaction. In this context, it is worth noting the precedent that current APSD metrics based on grouped stages from full-resolution CI data have not been directly linked to clinical performance either. Given the large inter-patient variability in clinical trials to elicit dose–response relationships, in addition to the seldom considered added variability introduced with disease modifying patency of airways in the respiratory tract, small shifts in mass within the size ranges related to LPM and SPM sub-fractions are unlikely to have measurable clinical consequences. This situation may be true even when a convincing IVIV Relationship is established, as could be argued is potentially possible for some bronchodilator-based formulations (33). Put another way, the precision of existing CI-based methods for determining these QC metrics greatly exceeds the precision available to the clinician for the corresponding clinical metrics such as forced expiratory volume in one second (FEV_1), forced expiratory flow from 25% to 75% of vital capacity ($FEF_{25-75\%}$) and similar indicators of airway patency obtainable from well-established spirometric measurements to assess obstructive disease (34). The higher precision of *in vitro* methods is likely to become even more apparent for other therapeutic modalities such as anti-inflammatory products, where IVIV Relationships are not yet established with any confidence (33).

Table I. Purpose, Strength, and Limitations of Full-Resolution and AIM-Based CI Systems

Impactor type	Full-resolution impactor	AIM–QC system	AIM–pHRT system
Purpose	Measure overall shape of the full distribution with optimum size resolution for this inertial-based technique	Measures manufacturing and product changes quickly, efficiently, and without statistical confounding (*e.g.*, between changes in amplitude and shifts in size distribution)	Provides measurement of potentially clinically relevant fractions
Limitations	Time- and resource-intensive Prone to error and high variability of results	Only information specific to the purpose (QC or pHRT relevant) is obtained from experiments	
Strengths of approach	Different groupings can be easily calculated from the same set of data (*e.g.*, stage groupings for the US; fine particle dose for EU) The same impactor can be used with different flow-rates	Better characterization of the batch due to increased number of samples per batch within a given period of time Ability to conduct CI tests based on the patient dose(s) Compared with full-resolution ACI, AIM systems are quicker in use, require fewer resources, and potentially have higher analytical sensitivity [particularly important for high-potency/low-dose) products]	

Abbreviations used in Table I: *ACI* Andersen cascade impactor, *AIM* abbreviated impactor measurement, *AIM–pHRT* abbreviated impactor measurement system possibly relevant for adult human respiratory tract, *AIM–QC* abbreviated impactor measurement system for quality control, *CI* cascade impactor, *EU* European Union, *pHRT* possibly relevant for adult human respiratory tract, *QC* quality control, *US* United States

Table II. Uses of AIM-Based and Full-Resolution CIs in OIP Lifecycle Management: The Right Impactor for the Right Purpose

Impactor type/lifecycle stage (goal of APSD testing)	Full-resolution impactor	AIM–QC system with EDA metrics (LPM/SPM and ISM)	AIM–pHRT system (CPM, FPM, and EPM)
Product development (goal: establish a target APSD profile for a safe and effective product)	Define APSD of product for the clinical batches Identify failure modes for the APSD Use full-resolution for OOS investigations and justification of changes In order to prepare for routine use of AIM–QC, also conduct studies to select optimal boundary between LPM and SPM (*e.g.*, near MMAD, or to maximize sensitivity to significant failure modes)	Use as a screening tool in early development In order to prepare for routine use of AIM–QC, also conduct studies to: 1. Establish correlation of LPM and SPM to full-resolution APSD 2. Determine appropriate specifications for LPM/SPM and ISM (*e.g.*, as 90% confidence intervals on the LPM/SPM and ISM values observed with a representative sample of product).	Use as a screening tool in early development Conduct studies to establish correlation of CPM, FPM, and EPM to full-resolution APSD; this information will provide support for the subsequent use of the selected AIM–pHRT configuration by establishing an IVIV relationship
Commercial production (goal: confirm that the APSD of commercial batches is the same as that of clinical batches)	Use full-resolution APSD for OOS investigations	Use AIM–QC for routine quality control (release and stability)	
Post-approval changes (*e.g.*, supplier change) (goal: demonstrate sameness of APSD)	Use full-resolution APSD for complete justification of change	Use AIM–QC as a quick indicator of the same quality	Once an IVIV relationship has been established, use AIM–pHRT as a quick indicator that clinically relevant fractions have not changed.
Add-on device development (goal: minimize oropharyngeal deposition)	Provides baseline data to compare with OIP alone		Use AIM–pHRT to optimize add-on devices, ensuring clinically equivalent performance to that of OIP without add-on

Abbreviations used in Table II: *AIM–pHRT* abbreviated impactor measurement system possibly relevant for adult human respiratory tract, *AIM–QC* abbreviated impactor measurement system for quality control, *APSD* aerodynamic particle size distribution, *CPM* coarse particle mass, *EDA* efficient data analysis, *EPM* extra-fine particle mass, *FPM* fine particle mass, *ISM* impactor-sized mass, *IVIV in vivo–in vitro*, *LPM* large particle mass, *MMAD* mass median aerodynamic diameter, *OIP* orally inhaled product, *OOS* out-of-specification, *SPM* small particle mass

CONSIDERATIONS CONCERNING DETECTION OF APSD CHANGES BY EFFICIENT DATA ANALYSIS METRICS

In preliminary discussions with regulatory authorities, the authors were asked about the ability of EDA metrics to detect hypothetical changes in APSD when such changes are limited to an isolated portion of the profile in way that leaves both ISM and the LPM/SPM unchanged. After reviewing all possibilities, the authors believe that such narrow-range changes are physically unlikely, given the broad-spectrum nature of aerosol particle generation and detection processes in terms of impacts on a given APSD within the size range of interest (ca. 0.5–10 microns aerodynamic diameter (35)). Namely, all conceivable physical processes that would cause a change in particle deposition and recovery (*e.g.*, particle agglomeration or fragmentation, thermophoresis, diffusiophoresis, electrostatic charge, gravitational sedimentation, inertial impaction, turbulent diffusion, *etc.*) are not size selective on the scale relating to the span associated with single well-designed CI stages of the type incorporated into all compendia apparatuses, and their effects would always affect several stages and propagate throughout the entire profile, thereby affecting the LPM/SPM ratio or ISM or both. The only possible exception relates to Brownian diffusion, which may selectively remove the finest particles, resulting in a potentially smooth change within just the shape of the SPM portion of the APSD profile. In practice, however, such diffusional losses would likely take place to adjacent surfaces within the CI before reaching the back-up filter, resulting in a detectable decrease in ISM, if significant. Furthermore, this mechanism, is only pertinent for particles less than 0.5 μm in diameter, which for most products do not amount to much mass per determination. Erring on the side of caution, it is recognized that some solution pMDI formulations in which a significant proportion of the mass entering the CI is contained in sub-micron particles (36) may require further evaluation before AIM/EDA is applied to them. All the other types of physical changes in an APSD profile should be detected by the ISM, LPM/SPM ratio, or both.

CLINICAL RELEVANCE OF AIM–pHRT DATA

The particle fractions collected in an AIM–pHRT system are meant to provide clinically pertinent information about the dose depositing in the oropharyngeal region (CPM), in the airways (FPM) and alveolar compartments of the lung (EPM). The relationship between these deposition locations and the clinical effect of the drug depend on the action of the active pharmaceutical ingredient (API) in relation to appropriate receptors at different locations within the respiratory tract. Some drugs may need to penetrate deep into the periphery of the lung (37), although others may be better deposited in central or upper airways for maximum effectiveness (13). Because CIs are poor surrogates for modeling particle deposition in the respiratory tract (25), it can be argued that any further detail in terms of size resolution beyond the three fractions CPM, FPM and EPM, is superfluous from the clinical perspective. Not coincidentally, only three size fractions, oro- or naso-pharyngeal, tracheobronchial and alveolar deposition, are used in occupational health to describe the inhalation of potentially toxic particles (38). Furthermore, similar size fractions based on the mass of particulate matter <10.0, 2.5, and 1.0 μm aerodynamic diameter (PM_{10}, $PM_{2.5}$, and $PM_{1.0}$) define bounds for respiratory tract-relevant deposition fractions related to atmospheric environmental pollutants (39). Given this albeit indirect evidence from related fields of study involved with inhalation of potentially harmful aerosol particles, it can be argued that any more detailed fractionation of the APSD in the context of therapeutic drug delivery to the respiratory tract both dilutes the essential information to assess clinical safety and efficacy and has the potential to magnify intrinsic data variability.

The reduction in quality of decision making in relation to batch disposition (combined probabilities of accepting an out-of-specification batch and rejecting a good batch) is a less obvious but equally important aspect associated with the decreased coverage afforded if the number of samples that can be measured within a given time is reduced to make full-resolution APSD measurements.

Finally, given the purpose of AIM–pHRT systems is to provide size-fraction-based data that are clinically relevant, the use of the idealized mouth–throat model developed recently by Finlay's group at the University of Alberta, Canada, may be worth consideration in conjunction with such apparatuses, based on published data in connection with full-resolution measurements (19,40). This inlet has been designed to have similar deposition characteristics to an adult oropharynx, and provides a degree of standardization that is not possible with casts from individual upper airways from human subjects. It is conjectured that the incorporation of this idealized inlet should offset most of the consistent bias observed in CI measurements for beta-2 agonists (33). However, experimental data will be needed to substantiate this hypothesis, thereby enabling validated AIM–pHRT systems to be developed to their full potential. Such a study, though important as one of the next goals in the adoption of AIM/EDA principles in OIP testing, is beyond the scope of the present article. In this context, it should be noted as a further refinement towards the realization of clinical reality, a rigid induction port of this or any other design would not be able to reflect changes in particle deposition brought about by variations in oral cavity volume. Such effects happen with real patients if they use devices with different mouthpiece dimensions and are consequently opening their mouth wider or less wide (41). Although anatomically correct inlets having varying oral cavity volume are the obvious solution, use of such inlets has practical complications associated with them (*e.g.*, simulation of the mucosa, drug recovery from the complex geometries of the interior surfaces). The recent development of anatomically correct models developed from 3D magnetic resonance imaging (MRI) scans of live patients should provide at low cost aerosol transport conditions as close to those in reality as is possible for such *in vitro* systems (42). The relationships between respiratory tract size bands and their association with meaningful IVIV Relationships, however, continues to be a hotly debated area (43).

WHY SWITCH TO EDA/AIM MEASUREMENTS?

In the product lifecycle strategy proposed herein, it is apparent that moving away from stage groupings derived

from full-resolution CI measurements towards product-specific LPM/SPM and ISM metrics for routine quality control allows better decision making and also saves resources in the long run because of the following advantages:

- ➢ Easier operation of an AIM system;
- ➢ Similar sensitivity to APSD changes compared to current methods;
- ➢ Fewer false-positive results;
- ➢ Independent measures are available for peak size-location and magnitude (area under the curve of the APSD), leading to better diagnostic capability and predictability;
- ➢ Fewer inhaler actuations per CI measurement are possible due to the acquisition of sufficient mass in fewer sub-fractions, which has the potential to reduces errors, experimental uncertainty, and makes it potentially possible to test APSD with the prescribed dose, at least for moderate- and low-potency formulations;
- ➢ Less time is required per CI measurement, making it possible to design sufficiently powerful experiments for assessing product and CI method variability on a sound statistical basis.

CONCLUSION

An outline for comprehensive product lifecycle management strategy in terms of *in vitro* characterization of APSD has been described that is based on simpler, yet more statistically powerful efficient data analysis metrics. This approach is easily combined with abbreviated impactor measurements. The EDA/AIM approach could be adopted as the norm for inhaler development and quality control, but its effective implementation will need to be undertaken on a product-by-product basis. Although it can strongly be argued that full-resolution multi-stage CI testing is less than ideal for QC purposes, such measurements have their place in the initial product development process, as the first resort in the event of an OOS investigation and also in OIP change management when in commercial production.

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REFERENCES

1. European Directorate for Quality in Medicines (EDQM). European pharmacopeia 6.8, monograph 2.9.18. Preparations for inhalations: Aerodynamic assessment of fine particles. Strasburg, EDQM 2010.
2. US Pharmacopeial Convention. United States Pharmacopeia 33/National Formulary 28, Chapter <601> Aerosols, nasal sprays, metered-dose inhalers, and dry powder inhalers. Rockville, MD, 2010.
3. Christopher D, Curry P, Doub W, Furnkranz K, Lavery M, Lin K, *et al*. Considerations for the development and practice of cascade impaction testing including a mass balance failure investigation tree. J Aerosol Med. 2003;16(3):235–47. doi:10.1089/089426803769017604.
4. Tougas TP, Christopher D, Mitchell JP, Strickland H, Wyka B, Van Oort M, *et al*. Improved quality control metrics for cascade impaction measurements of orally inhaled drug products (OIPs). AAPS PharmSciTech. 2009;10(4):1276–85. doi:10.1208/s12249-009-9312-4.
5. Mitchell JP, Morton RW, Nagel MW. The influence of body geometry on spacer performance: a case study. In: Dalby RN, Byron PR, Farr SJ, Peart J, editors. Respiratory drug delivery-VII. Raleigh, North Carolina, USA: Serentec Press; 2000. p. 539–41.
6. Schultz A, Le Soeuf T, Looi K, Zhang G, Le Soeuf P, Devadason SG. Validation of methodology for recording breathing and simulating drug delivery through spacers and valved holding chambers. J Aerosol Med Pulmon Deliv., 2010;23: online in advance of publication.
7. Tougas T, Christopher D, Lyapustina S, Mitchell JP, Patel R. Capabilities of aerodynamic particle size distribution (APSD) measurements based on analysis of a blinded database. In: Dalby RN, Byron PR, Peart J, Suman JD, Farr SJ, Young PM, editors. Respiratory drug delivery 2008. Illinois, USA: Davis Healthcare International Publishing LLC, River Grove; 2008. p. 109–23.
8. International Organization for Standardization, Geneva, Switzerland. Aerosol drug delivery device design verification - Requirements and test methods. ISO 20072:2009.
9. Tougas T, Christopher JD, Mitchell JP, Lyapustina S. In: Dalby RN, Byron PR, Peart J, Suman JD, Farr SJ, Young PM, editors. Efficient data analysis and abbreviated impactor measurement concepts, respiratory drug delivery 2010. Illinois, USA: Davis Healthcare International Publishing LLC, River Grove; 2010. p. 599–603.
10. Mitchell JP, Nagel MW, Copley M. The abbreviated impactor measurement concept: a potentially faster and more precise way to assess quality of inhaled drug products. Inhalation. 2009;3(3):26–30.
11. Mitchell JP, Nagel MW, Avvakoumova V, MacKay H, Ali R. The abbreviated impactor measurement (AIM) concept: part 1—Influence of particle bounce and re-entrainment—evaluation with a "dry" pressurized metered dose inhaler (pMDI)-based formulation. AAPS PharmSciTech. 2009;10(1):243–51. doi:10.1208/s12249-009-9202-9.
12. Rudolph G, Kobrich R, Stahlhofen W. Modeling and algebraic formulation of regional aerosol deposition in man. J Aerosol Sci. 1990;21(S1):306–406.
13. Usmani OS, Biddiscombe MF, Nightingale JA, Underwood SR, Barnes PJ. Effects of bronchodilator particle size in asthmatic patients using monodisperse aerosols. J Appl Physiol. 2003;95:2106–12.
14. Usmani OS, Biddiscombe MF, Barnes PJ. Regional lung deposition and bronchodilator response as a function of beta-2 agonist particle size. Am J Respir Crit Care Med. 2005;172:1497–504.
15. European Medicines Agency (EMEA). Guideline on the pharmaceutical quality of inhalation and nasal products. EMEA/CHMP/QWP/49313/2005 Corr. 2006.
16. Newman SP, Chan H-K. *In vitro/in vivo* comparisons in pulmonary drug delivery. J Aerosol Med Pulmon Deliv. 2008;21(1):1–8.
17. Olsson B, Berg E, Svensson M. Comparing aerosol size distributions that penetrate mouth–throat models under realistic inhalation conditions. In: Dalby RN, Byron PR, Peart J, Suman JD, Farr SJ, Young PM, editors. Respiratory drug delivery 2010. Illinois, USA: Davis Healthcare International Publishing LLC, River Grove; 2010. p. 225–34.
18. Byron P, Delvadia RR, Worth Longest P, Hindle M. In: Dalby RN, Byron PR, Peart J, Suman JD, Farr SJ, Young PM, editors. Respiratory drug delivery 2010. Illinois, USA: Davis Healthcare International Publishing LLC, River Grove; 2010. p. 215–24.
19. Grgic B, Finlay WH, Heenan AF. Regional aerosol deposition and flow measurements in an idealized mouth and throat. J Aerosol Sci. 2004;35(1):21–32.

20. Mitchell JP, Nagel MW, Doyle CC, Ali RS, Avvakoumova VI, Christopher JD, *et al*. Relative precision of inhaler aerodynamic particle size distribution (APSD) metrics by full resolution and abbreviated Andersen cascade impactors (ACIs): part 1. AAPS PharmSciTech. 2010;11(2):843–51. doi:10.1208/s12249-010-9452-6.
21. Mitchell JP, Nagel MW, Avvakoumova V, MacKay H, Ali R. The abbreviated impactor measurement (AIM) concept: part 2—Influence of evaporation of a volatile component—evaluation with a "droplet producing" pressurized metered dose inhaler (pMDI)-based formulation containing ethanol as co-solvent. AAPS PharmSciTech. 2009;10(1):252–7. doi:10.1208/s12249-009-9201-x.
22. Stobbs B, McAulay E, Bogard H, Monsallier E. Evaluation of the fast-screening impactor for determining fine particle fraction of dry powder inhalers, drug delivery to the lungs-20. UK: Edinburgh; 2009. p. 158–61.
23. Copley M, Mitchell J, McAulay E, Russell-Graham D. Implementing the AIM concept, Inhalation, 2010;4 (1).
24. Sheng G, Zhang J, Simmons R, Watanabe W. Fast screening impactor (FSI) as a prescreening tool for MDIs and nebulizers. RDD. 2010;637-640.
25. Dunbar C, Mitchell JP. Analysis of cascade impactor mass distributions. J Aerosol Med. 2005;18(4):439–51.
26. Mitchell JP, Nagel MW, Doyle CC, Ali RS, Avvakoumova VI, Christopher JD, Quiroz J, Strickland H, Tougas T, Lyapustina S. Relative precision of inhaler aerodynamic particle size distribution (APSD) metrics by full resolution and abbreviated Andersen cascade impactors (ACIs). Part 2—Investigation of Bias in Extra-fine Mass Fraction with AIM-HRT Impactor. Accepted to AAPS PharmSciTech. 2010.
27. PharmEur 2.9.18 - details to come.
28. Hallworth GW, Westmoreland DG. The twin impinger: a simple device for assessing the delivery of drugs from metered dose pressurized aerosol inhalers. J Pharm Pharmacol. 1987;39:966–72.
29. Mitchell JP, Nagel MW. Cascade impactors for the size characterization of aerosols from medical inhalers: their uses and limitations. J Aerosol Med. 2003;16(4):341–77.
30. Leach C. Enhancing drug delivery through reformulating MDIs with HFA propellants—drug deposition and its effect on preclinical programs. In: Dalby RN, Byron PR, Farr SJ, editors. Respiratory drug delivery V. Buffalo Grove: IL. Interpharm-Press; 1996. p. 133–44.
31. Dolovich MB, Mitchell JP. Canadian standards association (CSA) standard Z264.1-02: a new voluntary standard for spacers and holding chambers used with pressurized metered-dose inhalers (pMDIs). Can Respir J. 2004;11(7):489–95.
32. Mitchell JP, Nagel MW, MacKay H, Avvakoumova VA, Malpass J. Developing a "universal" valved holding chamber (VHC) platform with added patient benefits whilst maintaining consistent *in vitro* performance. In: Dalby RN, Byron PR, Peart J, Suman JD, Young PM, editors. Respiratory drug delivery—Europe. Illinois, USA: Davis Healthcare International Publishing LLC, River Grove; 2009. p. 383–6.
33. Newman SP, Chan HK. *In vitro/in vivo* comparisons in pulmonary drug delivery. J Aerosol Med Pulm Drug Deliv. 2008;21 (1):77–84. doi:10.1089/jamp.2007.0643.
34. American Thoracic Society. Standardization of spirometry, 1994 update. Am J Respir Crit Care Med. 1995;152:1107–36.
35. Hinds WC. Properties, behavior, and measurement of airborne particles. 2nd ed. N.Y., USA: Wiley-Interscience; 1999. p. 75–110.
36. Leach C. Enhanced drug delivery through reformulating MDIs with HFA propellants—drug deposition and its effect on preclinical programs. RDD. 1996;133–144.
37. Gonda I. Aerosols for delivery of therapeutic and diagnostic agents to the respiratory tract, In: Critical reviews in therapeutic drug carrier systems, 1990;273-313.
38. Vincent JH. The inhalation of aerosols. In: Aerosol science for industrial hygienists, New York, Pergamon, 1995, pp 136–155.
39. Lundgren DA, Hlaing DN, Rich TA, Marple VA. PM10/PM2:5/PM1 data from a trichotomous sampler. Aerosol Sci Technol. 1996;25:353–7.
40. Zhang Y, Finlay WH, Matida EA. Particle deposition measurements and numerical simulation in a highly idealized mouth–throat. J Aerosol Sci. 2004;35(7):789–803. doi:10.1016/j.jaerosci.2003.12.006.
41. Daley-Yates PT, Parkins DA, Thomas MJ, Gillett B, House KW, Ortega HG. Pharmacokinetic, pharmacodynamic, efficacy, and safety data from two randomized, double-blind studies in patients with asthma and an *in vitro* study comparing two dry-powder inhalers delivering a combination of salmeterol 50 μg and fluticasone propionate 250 μg: Implications for establishing bioequivalence of inhaled products. Clin Thera. 2009;31(2):370–85. doi:10.1016/j.clinthera.2009.02.007.
42. Grgic B, Finlay WH, Burnell PKP, Heenan AF. *In vitro* intersubject and intrasubject deposition measurements in realistic mouth-throat geometries. J Aerosol Sci. 2004;35:1025–40.
43. Borgström L, Olsson B, Thorsson L. Degree of throat deposition can explain the variability in lung deposition of inhaled drugs. J Aer Medicine. 2006;19(4):473–83.