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Research Article

Improved Quality Control Metrics for Cascade Impaction Measurements of Orally Inhaled Drug Products (OIPs)

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Abstract. This study of aerodynamic mass-weighted particle size distribution (APSD) data from orally inhaled products (OIPs) investigated whether a set of simpler (than currently used) metrics may be adequate to detect changes in APSD for quality control (QC) purposes. A range of OIPs was examined, and correlations between mass median aerodynamic diameter and the ratio of large particle mass (LPM) to small particle mass (SPM) were calculated. For an Andersen cascade impactor, the LPM combines the mass associated with particle sizes from impactor stage 1 to a product-specific boundary size; SPM combines the mass of particles from that boundary through to terminal filter. The LPM–SPM boundary should be chosen during development based on the full-resolution impactor results so as to maximize the sensitivity of the LPM/SPM ratio to meaningful changes in quality. The LPM/SPM ratio along with the impactor-sized mass (ISM) are by themselves sufficient to detect changes in central tendency and area under the APSD curve, which are key *in vitro* quality attributes for OIPs. Compared to stage groupings, this two-metric approach provides better intrinsic precision, in part due to having adequate mass and consequently better ability to detect changes in APSD and ISM, suggesting that this approach should be a preferred QC tool. Another advantage is the possibility to obtain these metrics from the abbreviated impactor measurements (AIM) rather than from full-resolution multistage impactors. Although the boundary is product specific, the testing could be accomplished with a basic AIM system which can meet the needs of most or all OIPs.

KEY WORDS: aerosol; AIM concept; cascade impactor; inhaler; QC.

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NOTATIONS: ACI, Andersen cascade impactor; AIM, abbreviated impactor measurement; API, active pharmaceutical ingredient; APSD, aerodynamic particle size distributions; AUC_{APSD}, area under the APSD curve; CI, cascade impaction; CQA, critical quality attribute; DPI, dry powder inhaler; GSD, geometric standard deviation; HRT, human respiratory tract; IPAC-RS, International Pharmaceutical Aerosol Consortium on Regulation and Science; ISM, impactor-sized mass (defined as mass on all impactor components with a defined upper cutoff, i.e., from stage 1 to filter); LPM, large particle mass (defined uniquely for each product, from stage 1 to some defined boundary within the impactor); MDI, metered dose inhaler; MMAD, mass median aerodynamic diameter; MMF, Morgan–Mercer–Flodin; NGI, next generation pharmaceutical impactor; OIP, orally inhaled product; QC, quality control; RMSE, root mean square error; SPM, small particle mass (defined uniquely for each product, from some defined boundary within the impactor to the filter).

INTRODUCTION

OIP Quality Metrics Based on Aerodynamic Particle Size Distribution

The general goal of inhaler product QC testing is to provide additional assurance and confirmation that a batch of inhalers is of acceptable quality (1). Aerodynamic particle size distribution (APSD) measurements are undertaken by cascade impaction (CI) to quantify the aerosol particle size characteristics that affect delivery of drug to the respiratory tract. During product development, obtaining information about the full-resolution APSD profile is both practical and useful. By contrast, within a QC environment, faster, higher-precision, and higher-throughput methods would be more beneficial. Simplified APSD testing and associated metrics therefore might be sought to confirm that manufactured product is fit for its intended purpose. Several metrics have traditionally been applied for characterizing the APSD of OIPs, for example:

(1) Total mass of the active pharmaceutical ingredient (API) recovered from an impactor (also known as mass balance) (2–4)
(2) API mass below a specified particle size (e.g., fine particle dose, less than 5 μm) (3,5)

(3) API mass on individual stages or groups of impactor stages (5)
(4) Mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD) (3–5)

At a fundamental level, potentially significant changes to the size, location, and shape of OIP APSDs can be viewed in terms of two independent processes or a combination of these two processes (Fig. 1):

- A change in central tendency (usually characterized by the MMAD)
- A change in the area under the curve defining the differential (i.e., per micrometer of particle size) mass-weighted APSD

This logic has driven the selection of the two metrics considered in this study, with the following intent:

- Both metrics can be easily obtained.
- One metric is highly correlated with the mass-weighted mean of the APSD (represented customarily by the MMAD), but independent of the area of the APSD.
- The other metric is related to the area under the APSD, but independent of the mean of the distribution.

The large particle mass (LPM)/small particle mass (SPM) ratio would be expected to be related primarily to the central tendency of an APSD, while the impactor sized mass (ISM) (6) is a direct measure of the area under the curve of an APSD (AUC_{APSD}) (7), which can be obtained directly from full-resolution impactor experiments. Thus, a significant change from the typical mean aerodynamic particle size should be detectable as a change in the LPM/SPM ratio, and a significant change in the inhalable dose should be reflected in a change in the ISM. In addition, any significant change in the APSD impacting both the mean and the area under the APSD should be detectable as changes in both metrics.

ISM is defined for multistage impactors as the sum of the drug mass deposited on the terminal filter and all impactor stages except the uppermost. The mass of API on the initial/uppermost stage (e.g., stage 0 for a standard Andersen cascade impactor (ACI)) is excluded from the calculation of ISM because of the lack of a specified upper size limit for this stage, which by design is the norm for impactors. Thus, ISM includes the mass of API deposited on stage 1 through to the terminal filter in the full-resolution Andersen eight-stage cascade impactor that is widely used in OIP assessments (Fig. 2). As defined here, ISM is equal to the sum of LPM and SPM.

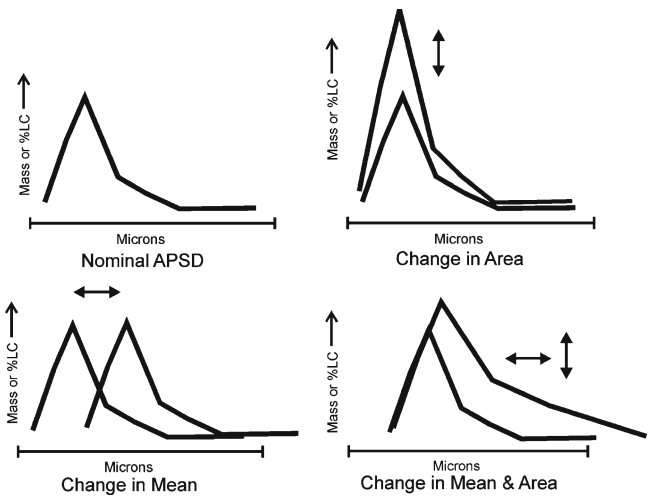

Fig. 1. A shift in central tendency, change of amplitude (or AUC_{APSD}), and change in shape are the basic types of APSD changes

Central tendency (location) and amplitude (AUC_{APSD}) of the APSD can be regarded as critical *in vitro* quality attributes (CQAs) for inhaler products (8). By contrast, the CI mass balance includes mass contributions from non-sizing components, such as the uppermost stage and throat (induction port). Changes in API deposition in the non-sizing components would most likely be accompanied by corresponding variations in ISM and therefore would be detected in the proposed approach, as well as more ideally by a separately undertaken and intrinsically more precise test for delivered dose uniformity. Moreover, CI mass balance measurements are to a large extent influenced by the choice of instrument and technique of the operator, rather than by product quality changes (9), and therefore, CI mass balance is arguably not a CQA but more of a verification of good analytical technique.

The use of a simple, accurate, and precise test for OIP quality would be particularly advantageous to detect rapidly any abnormal changes in the APSD so that the QC disposition of the batch can be determined correctly with optimum confidence. This article therefore explores whether two simplified aerodynamic particle size-related metrics, namely the ratio of LPM to SPM in conjunction with ISM, offer advantages over the conventional QC approach of quantifying drug mass deposited on three or four groups of impactor stages and comparing the results to limits for each grouping.

The aerodynamic particle size boundary differentiating LPM from SPM is selected purely on the basis of the shape of the APSD and is expected to vary depending on the product being tested; therefore, it does not have to be a fixed value suitable for all OIPs. Furthermore, it should not be considered as a necessity for it to have clinical significance, although it may be chosen to be related to a clinically meaningful particle size established in prior clinical trials on a particular product. Ideally, this boundary should be selected so as to maximize the sensitivity of these metrics to meaningful changes in APSD from the perspective of measuring product quality.

Abbreviated Impactor Measurement Concept

It is well understood that the collection of detailed information about API deposition on all stages of a multistage impactor to provide full-resolution APSDs is important during development to characterize a given OIP (2,5). However, it is unclear that such level of detail may always be necessary, especially for routine QC purposes. Full-resolution impactor testing is cumbersome due to high resource requirements and lengthy analysis times (9). Moreover, the high intrinsic measurement-to-measurement varia-

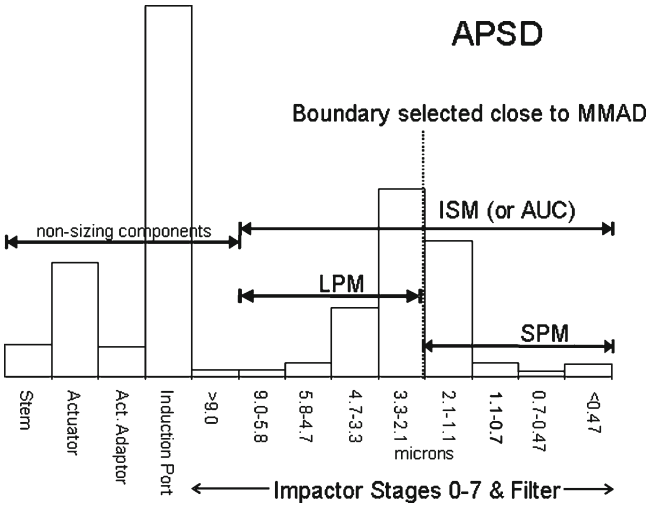

Fig. 2. Definition of OIP quality-related APSD metrics based on Andersen eight-stage cascade impactor measurements (at 28.3 L/min). The location of the LPM–SPM boundary depends on a particular product's APSD

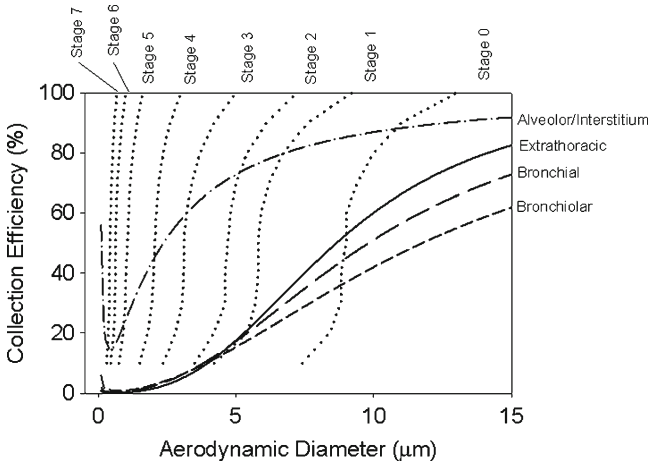

Fig. 3. Collection efficiencies of the ACI operated at 28.3 L/min and particle deposition profiles related to the morphological regions of the lung for a healthy male inhaling with peak inspiratory flow rate of 28.3 L/min (from (7))

bility (imprecision) of individual stage measurements, especially where little API collects, may make it more difficult to detect overall significant changes to the APSD. An alternative strategy is to make a so-called abbreviated impactor measurement (AIM), in which as few as two subfractions defining small (fine) and large (coarse) particle contributions to the overall APSD are directly measured. AIM-based systems by definition eliminate stages where little or no API collects, as the APSD is typically split into only two fractions, each of which contains an appreciable mass of API. Such AIM-based measurements therefore can be anticipated to possess relatively high precision by virtue of the fact that optimal performance of the analytical assays for API can be expected from a properly validated method. Although the multistage impactor is currently the tool of choice for the measurement the APSD of inhaler-generated aerosols, on the basis of an understanding that particle aerodynamic size (diameter) is related to the location of eventual deposition in the conducting airways and alveolar spaces, it is important to note that the impactor is not a perfect *in vitro* analog of the human respiratory tract (HRT) (7). This is because regional particle deposition profiles in the HRT are not sharply resolved into multiple size-related fractions, as is the case with the group of collection efficiency curves from the individual stages of the multistage impactor (Fig. 3), such as the Andersen eight-stage impactor and next generation pharmaceutical impactor (NGI) (7). In order for the impactor to be useful in this context, the assumption is therefore made that the size corresponding to the point at which 50% of the incoming mass of aerosol is collected by a given stage can be assigned as the representative aerodynamic diameter for that fraction collected by a given stage and that, in turn, this size can be related to an approximate deposition location in the HRT.

With AIM-based measurements, changes to the central tendency or amplitude of the underlying full APSD can be detected as variations in the magnitudes of both of the chosen simplified metrics already described (Fig. 4). The AIM concept is an evolution of earlier proposals to use a reduced Andersen cascade impactor stack approach in OIP quality assessment (10). However, AIM is not based on a single measurement technique but is a simplified measurement principle with flexibility to take into account the variety of OIP formulations and abbreviated impactor systems that are available or which might be developed to meet future needs. It has several practical advantages compared with full-resolution impactor measurements of APSD:

1. The time required to obtain the pertinent metrics that can be used to assess product performance in terms of APSD is greatly reduced.

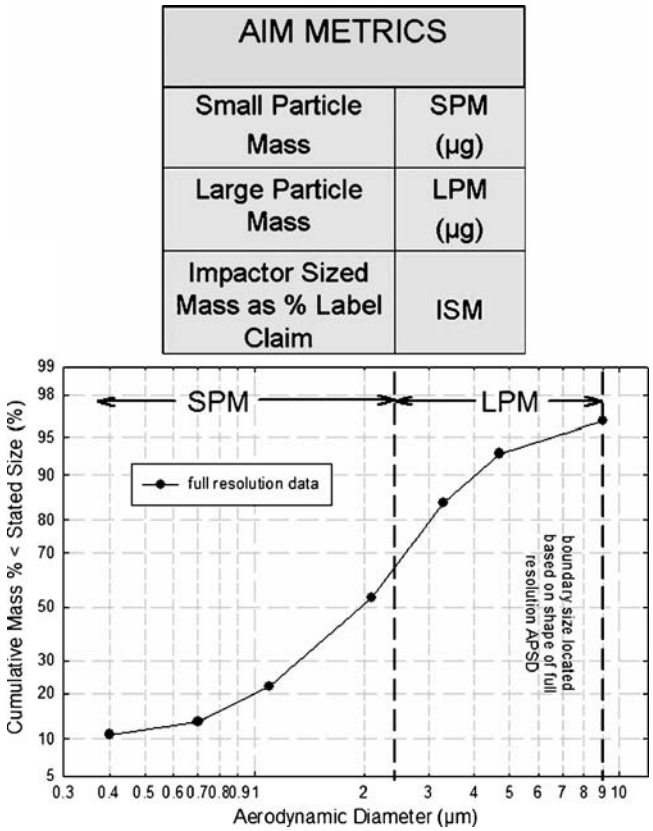

Fig. 4. AIM-based measurements of SPM and LPM and their relationship to full-resolution CI measurements

2. In the QC environment, the AIM approach should ideally have intrinsically improved overall precision by virtue of collecting higher API mass in each fraction and lacking any components that would capture little or no API. This advantage is expected to improve quality decisions, i.e., batch disposition.
3. The time savings associated with AIM systems may make it possible to develop more powerful study designs for assessing product quality by increasing the number of product units that can be evaluated from a batch within a fixed timeframe.
4. By reducing the number of manipulations required to make a measurement, AIM-based methods should decrease the chances of operator-related errors.
5. The use of less solvent for API recovery and quantitation, made possible by AIM, is more environmentally friendly and in line with the green chemistry principles.
6. AIM allows simpler apparatus configurations that are more amenable to automation (11).

METHOD

Verification of Concept by Analysis of OIP APSD Database

Data sets composed of individual impactor stage results from multiple APSDs determined on a variety of OIPs were examined in an effort to ascertain the ability of the AIM concept to be a sufficiently sensitive QC tool. These data were part of a comprehensive database collected in April 2000 through a collaborative effort of the International Pharmaceutical Aerosol Consortium (IPAC) and the AAPS Inhalation Technology Focus Group (12) which is now maintained by the International Pharmaceutical Aerosol Consortium on Regulation and Science (IPAC-RS). Although these results were obtained by full-resolution measurement techniques, the individual stage results were capable of being combined to obtain LPM, SPM, and other APSD metrics, as would have been obtained directly had AIM-based instruments been used. Moreover, the equivalency of fine particle dose by either summing individual stages or obtaining this directly through an AIM device has previously been established (11).

The ability to detect shifts in the size range occupied by an APSD was considered critical, since measurements of the AUC_{APSD} are directly obtainable as the sum of LPM and SPM. Size-related movements were evaluated by examining the ability of the LPM/SPM ratio to detect changes in MMAD. Eight diverse OIPs contained in the IPAC-RS database, including four from a previous study (8), were evaluated, encompassing the following major OIP categories:

- Hydrofluoroalkane (HFA)-solution metered dose inhaler (MDI)
- HFA suspension MDI
- Dry powder inhaler (DPI)
- Chlorofluorocarbon suspension MDI

Profiles of the APSDs for all eight products are depicted in Fig. 5. In this figure, each panel represents a product, and all individual profiles for a particular product are superimposed (up to 279 profiles, as indicated in column "*n*" of Table I).

Method for Data Analysis

MMADs were determined for each individual CI determination based on the Morgan–Mercer–Flodin (MMF) model (13) because it does not require assumption of the log-normal distribution and provides a better fit to the observed data than the United States Pharmacopeia method (14,15).

Linear regression analyses were performed on plots of LPM/SPM *versus* MMAD, stage groupings *versus* MMAD, LPM/SPM *versus* ISM, and stage groupings *versus* ISM. All possible stage combinations were examined to determine the best boundary between LPM and SPM based on goodness-of-fit statistics. This optimum boundary and corresponding LPM/SPM ratios were used in subsequent modeling of LPM/SPM *versus* ISM. Stage groupings were selected based on the authors' prior experience with similar products and are consistent with Food and Drug Administration guidance documents (2). The goodness of fit of these models was evaluated by both the conventional coefficient of determination (R^2) and the root mean square error (RMSE) divided by the slope of the regression (b). The latter statistic projects the RMSE onto the abscissa and thus reflects the error in estimating MMAD values. These goodness-of-fit statistics were used to evaluate the relative performance of the QC metrics evaluated in this study.

RESULTS

The relationship between MMAD and the LPM/SPM ratio was approximately linear for every OIP type studied, illustrated by the magnitudes of the coefficient of determination and RMSE/b goodness-of-fit statistics (Table I). A small degree of systematic deviation from linearity was observed in some cases and is consistent with the expectations for the ratio metric, i.e., as MMAD approaches extreme small values, the LPM/SPM ratio should approach zero and as MMAD approaches extreme high values, the LPM/SPM ratio approaches infinity.

The results in Table I reflect outcomes for the LPM/SPM boundary placement that provided the best correlation between the LPM/SPM ratio and MMAD (denoted as optimum boundary in Table I). Figure 6 illustrates the nature and quality of these regressions for two cases (w9k001 and w9k901) listed in Table I. The 95% prediction bounds at the mean LPM/SPM ratio (Fig. 6) were projected onto the x-axis (microns). The difference between these projections of the upper and lower prediction intervals reflects the ability of the LPM/SPM ratio to detect differences in MMAD and indicate that changes of a few tenths of a micron are easily detected. Note that the goodness-of-fit statistic RMSE/b is directly proportional to the difference between the projected prediction bounds at the mean LPM/SPM ratio by a factor related to the selected confidence level.

While both goodness-of-fit statistics (R^2 and RMSE/b) are in general agreement about the quality of the correlation between LPM/SPM ratio and MMAD, they do not rank order the products in exactly the same order. For example, the two dry powder inhalers have the lowest R^2, yet the corresponding RMSE/b values are in the middle of the range of results 0.047–0.054 μm *versus* a range of 0.020 to 0.071 μm. This apparent discrepancy arises primarily from the survey nature of this study and the inherent characteristics of the

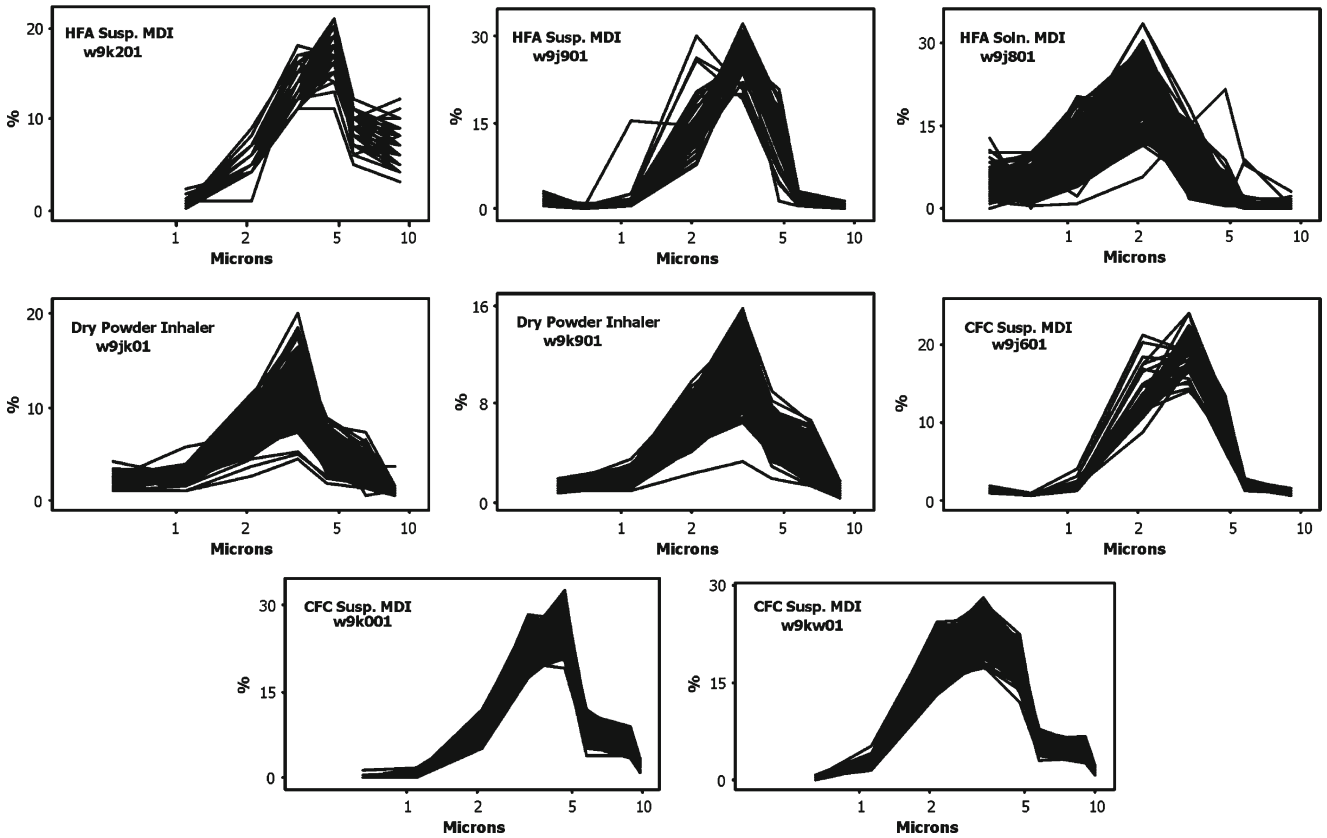

Fig. 5. APSD profiles of eight products used to evaluate LPM/SPM and ISM metrics

particular products included. Individual MMADs from these two products exhibited two of the three smallest variations in MMAD (interquartile range 0.133–0.159 μm) among all eight products (total range of the interquartile ranges is 0.133 to 0.444 μm). A narrower range of MMAD values leads to more uncertainty in the estimation of the regression parameters and hence poorer R^2 values for a given RMSE. Conversely, for a wider range of MMAD values with a similar RMSE, a better R^2 would result. Thus, at a given level of RMSE, R^2 is a function of the range of values in the dataset. In contrast, the RMSE/*b* statistic is a measure of the uncertainty in estimated MMAD values at the mean LPM/SPM of the particular data set. The RMSE/*b* values for both dry powder inhalers indicate that the LPM/SPM ratio is about average in performance with respect to detecting changes in MMAD. Based on these considerations, the RMSE/*b* statistic is believed to be the better predictor of the relative performance of the LPM/SPM ratio among the product types surveyed.

Similar analyses were performed on the assumed stage groupings for all eight products. These results are summarized in

Table I. Regression Analysis and Goodness-of-Fit Statistics for LPM/SPM Ratio *Versus* MMAD

Filecode[a]	Product type	CI runs (*n*)	Optimum boundary (μm)[b]	Average MMAD (μm)	Slope (*b*)	RMSE	Coefficient of determination R^2 (%)	RMSE/*b* (μm)
w9k201	HFA suspension MDI	80	4.7	3.91	0.4071	0.0162	96.4	0.040
w9j901	HFA suspension MDI	39	3.3	2.57	0.4959	0.0350	93.4	0.071
w9j801	HFA solution MDI	201	2.1	1.50	0.7155	0.0421	96.2	0.059
w9jk01	Dry powder inhaler	279	3.3[c]	2.66	0.4319	0.0201	83.0	0.047
w9k901	Dry powder inhaler	279	2.0[c]	2.59	2.3831	0.1278	84.3	0.054
w9j601	CFC suspension MDI	43	2.1	2.54	2.4548	0.0872	95.5	0.036
w9k001	CFC suspension MDI	272	3.3	3.54	1.6127	0.0330	97.3	0.020
w9kw01	CFC suspension MDI	272	3.3	2.86	0.7046	0.0198	95.8	0.028

CI cascade impaction, *MMAD* mass median aerodynamic diameter, *RMSE* root mean square error, *HFA* hydrofluoroalkane, *MDI* metered dose inhaler, *CFC* chlorofluorocarbon

[a] The filecodes are unique, randomly generated alpha-numerical labels assigned to specific products in the IPAC-RS database

[b] Here, optimum boundary is based on results from eight-stage Andersen impactor

[c] Modified Andersen impactor used for this product

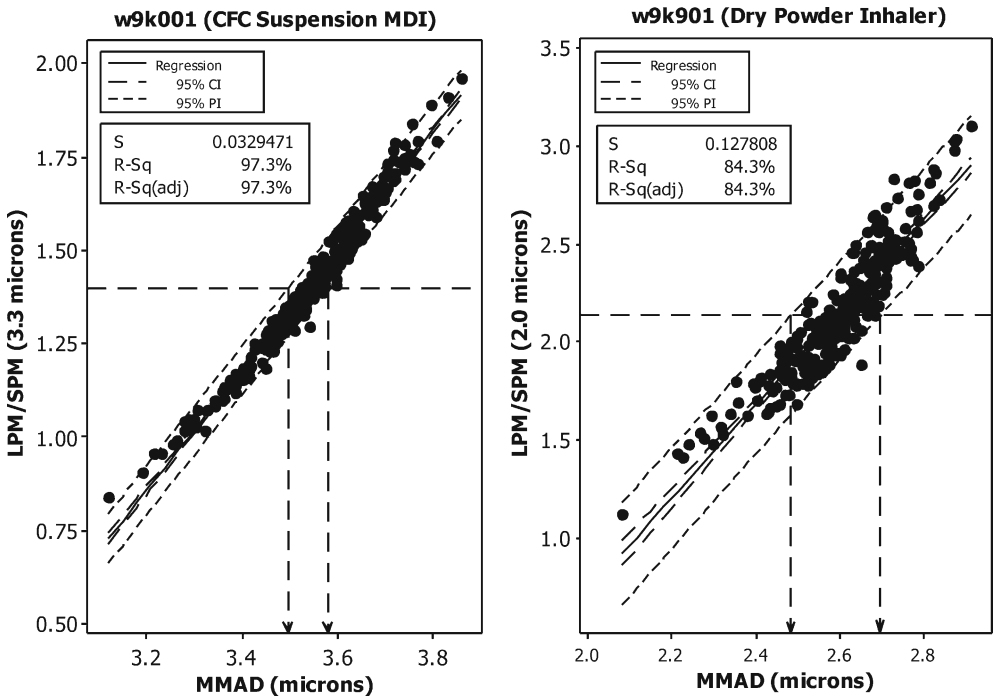

Fig. 6. Example regression plots for LPM/SPM ratio *versus* MMAD

Table II. In all instances, the first grouping contained all non-sized elements.

DISCUSSION

The slope of plots of the LPM/SPM ratio *versus* MMAD, with the LPM/SPM ratio as the directly measured dependent variable, reflects the sensitivity of this metric toward detecting changes in MMAD (the steeper the slope, the higher the sensitivity). Thus, slight changes in MMAD resulted in magnified variations in the LPM/SPM ratio when the slope was steep.

The LPM/SPM ratio is superior to using either the separate variables LPM, SPM, or grouped stages as individual metrics, since it removes the confounding influence of AUC_{APSD} in trying to detect changes in MMAD. In the proposed approach, changes in AUC_{APSD} are assessed simultaneously but separately through the ISM, which is the sum of LPM and SPM and is relatively independent of their ratio LPM/SPM.

Using LPM/SPM ratio rather than absolute values of LPM and SPM has a double benefit as a QC metric because, firstly, the ratio normalizes deposition values with respect to the total emitted mass, thus reducing variability, and secondly, APSD shifts within the sized portion of the profile are such that the LPM and SPM are negatively correlated (i.e., when one metric increases, the other decreases (a "seesaw effect")). As a result, the LPM/SPM ratio has a magnified sensitivity to shifts between LPM and SPM portions of the APSD, making the ratio highly sensitive to changes in the position and shape of an APSD. In contrast, the absolute values of LPM, SPM, or the metrics derived from grouped stages are each influenced by both changes in MMAD and AUC_{APSD}.

The lack of influence of AUC_{APSD} on the LPM/SPM ratio was verified by performing regression analysis of the LPM/SPM ratio *versus* ISM (equivalent to LPM + SPM). Table III summarizes the results of these regression analyses and compares goodness-of-fit statistics for the LPM/SPM ratios *versus* ISM to the ratios *versus* MMAD. The LPM/SPM *versus* ISM results exhibited poorer R^2 values and RMSE/*b* values that were 2–3 orders of magnitude larger (worse) than the corresponding RMSE/*b* results from the LPM/SPM *versus* MMAD correlations.

The good correlation between the LPM/SPM and MMAD and the absence of a correlation between LPM/SPM and ISM are further illustrated graphically by comparing representative plots of the LPM/SPM ratio *versus* MMAD and ISM (Fig. 7).

An important advantage of correlating LPM/SPM with MMAD is that the sensitivity of the LPM/SPM ratio can be optimized through the selection of the size boundary between LPM and SPM in cases where there is regulatory flexibility to do so. Under such circumstances, sensitivity would be expected to increase as the boundary approaches the true MMAD, which by definition represents the location of the center of the APSD, where the rate of change in particle mass per unit size width is at a maximum. In the present data analysis, as expected, the goodness-of-fit statistics trended toward a maximum approximately at an LPM/SPM ratio of unity (Fig. 8), where the coefficient of determination (R^2) for each selected boundary considered was plotted *versus* the average LPM/SPM ratio for that boundary. When the LPM/SPM ratio is unity, the boundary between LPM and SPM is located at the MMAD. Conceptually, this outcome should be expected since setting the size boundary at the MMAD by definition divides the mass of API equally between LPM and SPM.

At the same time, the LPM/SPM ratio was also relatively robust with respect to the exact location of the boundary between the two component fractions (Fig. 8), as long as it lay within the central portion of the distribution, which is

Table II. Regression Analysis and Goodness-of-Fit Statistics for Stage Groupings *Versus* MMAD

Filecode	Product type	Stage grouping	Slope (b)	RMSE	Coefficient of determination R^2 (%)	RMSE/b (μm)
w9k201	HFA suspension MDI	>9.0	22.1	4.69	48.2	0.212
		9.0–4.7	12.3	1.28	79.4	0.104
		4.7–2.1	−2.93	2.56	5.2	−0.874
		<2.1	−2.81	0.986	25.5	−0.351
w9j901	HFA suspension MDI	>9.0	3.25	5.72	0.5	1.760
		9.0–3.3	8.57	0.624	74.5	0.073
		3.3–1.1	11.3	3.55	13.6	0.314
		<1.1	0.096	0.767	0.0	7.990
w9j801	HFA solution MDI	>9.0	21.8	9.04	33.9	0.415
		9.0–3.3	5.21	1.08	67.0	0.207
		3.3–1.1	2.53	6.10	1.0	2.411
		<1.1	−24.1	3.28	82.5	−0.136
w9jk01	Dry powder inhaler	>8.6	−9.98	6.09	2.8	−0.610
		8.6–4.4	8.58	0.733	59.2	0.085
		4.4–1.1	13.1	4.42	8.5	0.337
		<1.1	0.391	0.960	0.2	2.455
w9k901	Dry powder inhaler	>8.6	0.990	5.85	0.2	5.909
		8.6–4.4	18.0	1.43	91.8	0.079
		4.4–1.1	−10.2	3.47	37.7	−0.340
		<1.1	−1.34	0.43	13.4	−0.317
w9j601	CFC suspension MDI	>9.0	2.02	8.93	0.1	4.421
		9.0–4.7	2.30	0.376	50.1	0.163
		4.7–1.1	0.09	4.03	0.0	44.778
		<1.1	−1.71	0.413	31.5	−0.242
w9k001	CFC suspension MDI	>10	11.3	3.78	12.0	0.335
		10–4.7	14.9	1.52	59.4	0.102
		4.7–2.1	−2.68	3.49	0.9	−1.302
		<2.1	−9.54	1.02	57.1	−0.107
w9kw01	CFC suspension MDI	>10	7.62	2.97	10.6	0.390
		10–4.7	9.65	1.01	62.3	0.105
		4.7–2.1	5.68	3.19	5.4	0.562
		<2.1	−18.0	1.29	77.9	−0.072

RMSE root mean square error, *HFA* hydrofluoroalkane, *MDI* metered dose inhaler, *CFC* chlorofluorocarbon

associated with the most mass of API within the impactor. These findings suggest that there should be acceptable sensitivity toward MMAD over a relatively broad range of LPM/SPM ratios. In practical terms, this outcome translates into the need for only a relatively small number of boundary options for all OIPs, thereby making it possible to design a set of AIM devices with a limited number of cutoff size options that should accommodate all user needs.

If an abbreviated approach is chosen as part of OIP product development, it is foreseen that the sponsor would select the LPM–SPM boundary size that provides the most sensitivity to the LPM/SPM metric and would subsequently

Table III. Regression Analysis and Goodness-of-Fit Statistics for the LPM/SPM Ratio *Versus* ISM

		Regression analysis: LPM/SPM ratio *versus* ISM				Goodness-of-fit LPM/SPM ratio *versus* MMAD (at optimum boundary)	
Filecode	Product type	Slope (b)	RMSE	Coefficient of determination R^2 (%)	RMSE/b (μm)	Coefficient of determination R^2 (%)	RMSE/b (μm)
w9k201	HFA suspension MDI	0.005	0.082	7.4	16.4	96.4	0.040
w9j901	HFA suspension MDI	0.003	0.136	1.0	45.3	93.4	0.071
w9j801	HFA solution MDI	−0.012	0.185	27.2	−15.4	96.2	0.059
w9jk01	Dry powder inhaler	0.003	0.045	15.0	15.0	83.0	0.047
w9k901	Dry powder inhaler	0.039	0.263	33.9	6.8	84.3	0.054
w9j601	CFC suspension MDI	0.017	0.406	2.9	23.9	95.5	0.036
w9k001	CFC suspension MDI	0.003	0.202	0.4	67.3	97.3	0.020
w9kw01	CFC suspension MDI	−0.003	0.096	1.7	−32.0	95.8	0.028

LPM large particle mass, *SPM* small particle mass, *ISM* impactor-sized mass, *RMSE* root mean square error, *HFA* hydrofluoroalkane, *MDI* metered dose inhaler, *CFC* chlorofluorocarbon

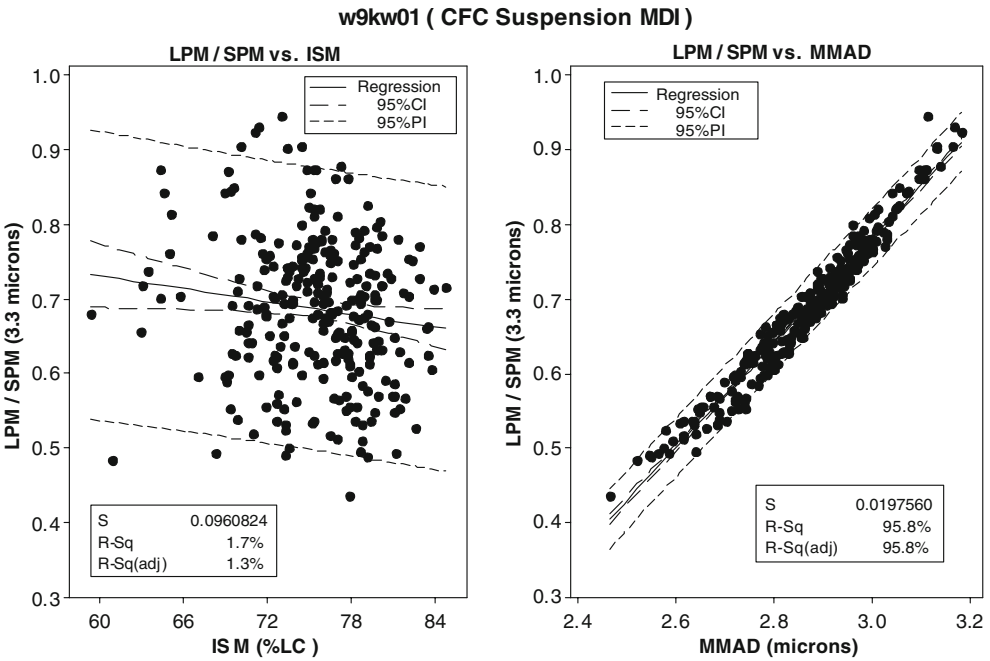

Fig. 7. Example regression plots for LPM/SPM ratio *versus* ISM and MMAD (w9kw01, CFC suspension MDI)

establish acceptance criteria based on this choice. As discussed above, the location of this boundary need not imply clinical significance. Since its location is likely to be governed by the APSD shape, it will need to be chosen on a product-by-product basis. It is also anticipated that the boundary position may be dependent upon the flow rate that is typically used to characterize the aerosol emitted from that specific product. For example, it is possible that the boundary might be located at a relatively large value of aerodynamic diameter for OIPs that are intended to be tested simulating medication delivery during calm, tidal breathing (peak inspiratory flow rates typically <60 L/min). On the other hand, products that are evaluated by simulating a rapid inhalation maneuver at higher flow rates (e.g., DPIs at flow rates ≥60 L/min, or pressurized MDIs which contain a significant ballistic component) might have their boundary assigned at a smaller size. Ultimately, however, the precise acceptance criteria adopted for the LPM/SPM ratio should be based on the sponsor's assessment of the significance of particular changes in APSD in terms of product performance.

Overall, these investigations of OIP APSDs have shown that the LPM/SPM ratio appears to be capable of detecting small changes in MMAD on the order of tenth(s) of microns. This finding is reflected in the magnitude of the goodness-of-fit statistic, RMSE/*b*, obtained for regressions of the LPM/SPM ratio *versus* MMAD reported in Table I. In contrast, the performance of regressions of stage groupings *versus* MMAD reported in Table II was significantly inferior with respect to this statistic. The results in Table II reflect the performance of the current practice of constructing stage groupings based on empirical inspection. Besides exhibiting inferior correlation with MMAD, there is no apparent approach to selection of stage groupings that optimize this correlation or is even predictive of positive or negative correlation.

Furthermore, because the data used here were derived from individual stage results from full-resolution multistage impactors, they represent worst case conditions. Less variability might be anticipated if measurements of LPM and SPM were made directly using a two-stage AIM-based device due to the avoidance of increased API analytical variability associated with stages containing API mass close to or at the limit of detection.

Whether or not changes in MMAD on the order of tenth(s) of microns are significant with respect to OIP clinical performance is outside the scope of this investigation. However, in the context of product development and QC assessment, the present analysis demonstrates the sensitivity of the LPM/SPM ratio that is readily measurable

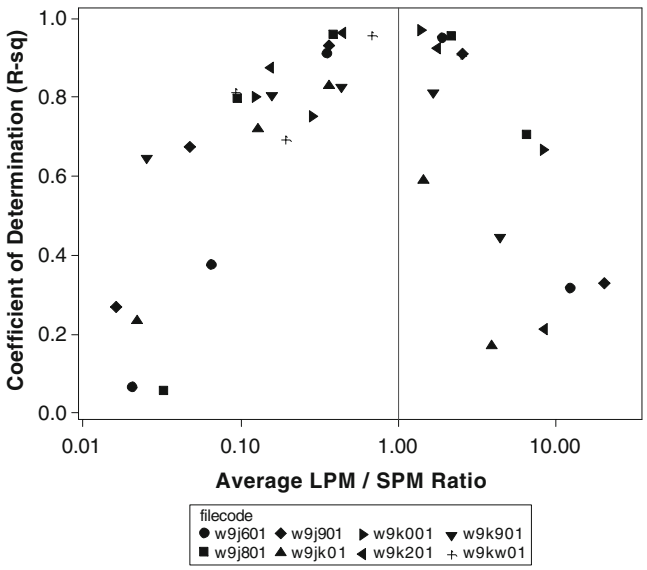

Fig. 8. Analysis of the goodness-of-fit statistics as a function of boundary size

and which can detect small variations in APSD characteristics affecting MMAD.

In addition to the demonstrated sensitivity to APSD shifts, the LPM/SPM ratio has also shown high intrinsic precision compared with equivalent data derived from stage groupings obtained from full-resolution impactor measurements. Thus, the LPM/SPM ratio, in combination with the sum [LPM + SPM = ISM], may be superior QC metrics compared to those typically employed today (e.g., mass of API collected by groups of individual impactor stages). However, such superiority in the context of determining product QC does not replace the need to create benchmark data for the OIP and characterize its APSD during development by full-resolution, multistage impactor measurements. The successful application of LPM/SPM-based metrics will therefore likely depend on initial high-resolution characterization of the APSD of the OIP at an early stage of product development and the subsequent correlation of the simplified metrics to the reference APSD data. High-resolution measurements may also be occasionally needed during the commercial phase, e.g., for investigation, reference, or troubleshooting of AIM-based measurements.

It is recognized that a limitation in the foregoing discussion is that markedly skewed APSDs were not considered. However, such situations appear to be rare occurrences for OIPs, judging from the large variety of products represented in the IPAC-RS database (see, for example, the APSD profiles of the eight products examined for this work and depicted in Fig. 5).

For relatively symmetric APSDs, two extreme cases can be envisaged:

- A "spiked" APSD, i.e., a monodisperse distribution where the GSD approximates to unity, with almost all of the mass located within a few percent of the MMAD value. Under these circumstances, *R*-squared values will be low unless the boundary between LPM and SPM is fixed at the MMAD.
- The opposite case of a "flat" APSD, in which the rate of change of mass with size is a constant throughout the entire size range encompassed by the APSD, which may be more than 1 order of magnitude (i.e., GSD>2.5 for an overall size range from 0.1 to >20 μm aerodynamic diameter). Here, the LPM–SPM boundary could be fixed at almost any size, with little impact on the *R*-squared value.

In reality, all OIP APSDs lie between these two extremes. The boundary should therefore be chosen as close as possible to the MMAD value determined from full-resolution CI methods. Preferably, MMAD should be determined via a method that does not assume a log-normal data distribution, such as Chapman–Richards, MMF, or two-point interpolation methods described elsewhere (14,15).

Even though the boundary between LPM and SPM is potentially unique to every OIP, the impaction equipment used for the proposed testing need not be unique to every product. If the abbreviated impactor system can be used at different flow rates, the boundary between LPM and SPM can be adjusted using the simple and well-defined relationship between flow rate through the system and stage cutoff size (16). Equally important, the proposed method is relatively robust to the choice of the boundary, as previously discussed (Fig. 8). Additionally, the range of possible MMADs (and therefore boundaries) is not large for inhalation products since they are all intended to target the lung. Among the eight products analyzed here, which were purposely selected to be as diverse as possible, only three different boundaries (2.1, 3.3, and 4.7 μm aerodynamic diameter; see Table I) needed to be used in the analysis. If these locations are suitable for all potential OIPs, only two or three versions of an AIM-type instrument/method would be sufficient to meet needs in this respect. The most important aspects of applying abbreviated (lean) data acquisition and analysis strategies for OIPs are the initial determination of the full-resolution APSD profile for each product in a robust manner and subsequent confirmation that an AIM system with a particular chosen boundary between LPM and SPM provides acceptable predictive capability for MMAD.

While this study used exclusively ACI results, there is no fundamental reason why similar correlations would not apply to any other multistage impactor, including the NGI. The only difference would likely be in the choice of the boundary size between LPM and SPM because of the different cutoff sizes associated with another multistage system. The equivalence of ACI, NGI, and AIM alternatives for inhaler APSD measurements has been studied and established by several groups (17–20). The intent of the present study was to use a large existing database of ACI results to make inference about a feasible approach for using AIM devices and simple metrics as QC tools for monitoring APSD. When this approach is applied in practice, a correlation between the AIM results and a full-resolution impactor used by the sponsor would need to be established.

In summary, the proposed set of simpler APSD metrics for routine QC has two key advantages compared with full-resolution CI measurements:

- The recommended approach is less subject to method variability, and as a consequence, a sponsor will have a better chance to detect true product quality changes and less chance to fail product due to method variability.
- Abbreviated impactor measurements may substantially reduce time and resource requirements associated with the batch assessment process.

CONCLUSIONS

A systematic study of APSD data from several OIPs has indicated that a simple metric comprising information from fine (small) and coarse (large) particle size fractions of the API may be adequate to detect meaningful changes in both the location of the measure of central tendency (MMAD) and the area under the APSD curve (equivalent to impactor-sized mass). Abbreviated, or lean, data acquisition and analysis should simplify both OIP development and QC, without compromising the ability to make correct decisions concerning the disposition of product. The proposed approach is aligned with the AIM concept, which may be implemented in a number of specific ways depending on the sponsor's data and agreements with regulators. If an AIM-based QC methodology is to be introduced for a given OIP, a small additional study specifically designed to establish full-resolution APSD in a robust manner would be needed to identify the most

appropriate boundary between LPM and SPM; this small additional effort in a product/method development program has the potential to save significant resources later, during both development and QC operations associated with commercial OIP production.

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