Efficient data analysis (EDA): Size, mass and common sense

A science-based alternative to fine particle dose and stage groupings

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This is the third of a series of articles by the Cascade Impaction Working Group of the International Pharmaceutical Aerosol Consortium for Regulation and Science (IPAC-RS) concerning the limitations of metrics commonly used in the assessment of aerodynamic particle size distributions (APSDs) of orally inhaled products (OIPs). In the first article, we explored the inability of the fine particle dose (FPD) metric to detect size changes in APSD [1]. In the second article [2], we examined the stage grouping (SG) metrics suggested by the United States Food and Drug Administration (FDA), the European Medicines Agency (EMA) and Health Canada [3-5]. Now, we take a broader view to discuss why we make quality control measurements such as inhaler APSD. Our view is that the decision-making framework that we use to demonstrate product quality consists of both the metrics themselves and the way they are used to make the decision. In the context of inhaler APSD, we contend that good decision-making requires independent assessments of each dimension of the APSD, namely size and mass, which we propose can be achieved via Efficient Data Analysis (EDA). These papers are written to educate, dispel common misconceptions, raise awareness of risks and encourage scientists to scrutinize current practices. The information provided should not be mistaken for regulatory guidance.

Introduction

We start by reminding the reader to ask the questions: "What is the purpose of quality control (QC)?" and: "What metrics should be assessed?" We hope the answer to the first question is that you perform QC to enable data-driven decisions regarding discrimination of product performance classification. We now hope that you would respond to the second question with the further related query: "What is the minimum number of appropriate metrics that is necessary to provide control of those product characteristics that are important for both patient safety and manufacturing sustainability (i.e., in the spirit of 'Quality by Design')?" [3]. In this context, we hope you will agree that employing additional metrics beyond this optimized minimum will not only increase the workload for QC personnel but also degrade the discriminating ability of the decision-making process. When considering which metrics should be measured, we contend that it is important to pose this final question: "Do these metrics inform you about the product's contribution to the patient and to its suitability for the target population?" [6]. Fundamentally, we maintain that the appropriate choice of QC metrics, combined with avoidance of measures that introduce unnecessary statistical "noise," improves our ability to discriminate product performance accurately. In this context, we previously demonstrated that either the commonly used single metric, FPD, or the use of SG, based on measures associated with three contiguous size range classes, are fundamentally flawed for making effective batch-disposition decisions based on product performance [1, 2]. Summarizing, we contend that the use of metrics that by themselves are either inadequate, as is the case for FPD, or that introduce statistical "noise," as is the case for SG, significantly degrades our decision-making ability.

How do we assess batch-to-batch changes in APSD to maintain proper control of our product?

From the foregoing, it is evident that we need to select metrics that not only assess APSD accurately *but are also sensitive to relevant changes in terms of the two independent variables defining APSD, namely mass of API and particle size, expressed as aerodynamic diameter.* In the first article in the series, we reminded readers that APSDs are two-dimensional in form and highlighted the risk of neglecting to follow each dimension independently [1]. Recall that we presented the reader with 201 mass-weighted APSDs from an OIP from the IPAC-RS database. Two hundred of these APSDs were presented as encompassing typical product performance, and one manifestly different APSD was introduced as a newly manufactured batch yet to be dispositioned. Looking at the cumulative APSDs, we showed that the mass median aerodynamic diameter (MMAD) for this new batch was well outside the range typically observed for the product, being more than 1 µm coarser than the other APSDs. However, when we attempted to use FPD to evaluate this APSD relative to the others, we saw that FPD could not discriminate between the unexpected performance of the newly manufactured batch and the typical product performance represented by the other 200 APSDs. We therefore concluded that the use of FPD by itself would not allow us to determine whether we had manufactured the product we had intended. This incongruity arises because FPD only assesses one of the dimensions (API mass) necessary to characterize an APSD; in other words, this measure is insensitive to changes in the size-dimension, described well by size-related metrics such as MMAD.

In the subsequent article [2], we discussed why cascade impactor stage grouping based on three contiguous size ranges is also ineffective at observing differences between APSDs consistently. Recall we showed for the product in question that SGs are incapable of reliable discrimination between APSDs, misclassifying as many as 62% of APSDs relative to simple limits on their size and mass dimensions. Although an individual group may have some ability to assess either dimension of an APSD, when all three stage groupings are used to evaluate *both* the size and mass dimensions, statistical "noise" emanates from the middle group in the set. Put simply, mass entering this middle group from either neighbor is exactly counterbalanced by mass leaving the neighbor and *vice versa. This statistical noise, combined with the simultaneous use of all three groups for evaluation, creates compounded misclassifications due to multiplicity that significantly degrade relevant discrimination and compromise decision capability.*

In this article, we complete the picture by demonstrating an intrinsically more discriminating way to control, simultaneously, both API mass and particle size while avoiding the noise introduced by capturing redundant information. At the same time, we argue that by virtue of not capturing such additional information, this approach does not introduce noise that results in multiplicity concerns. First, we remind the reader of the two key metrics that account for movements within either or both dimensions of an APSD; namely impactor-sized mass (ISM), defined as the mass recovered from the stages of the impactor whose upper-bound size is defined, and MMAD, which describes the central tendency of the mass distribution with respect to aerodynamic particle size. As an example of how this process might work, we now examine both ISM (expressed as mass of API as its percentage of label claim (LC)) and MMAD (µm) from real QC test results for a marketed product from the same IPAC-RS database (see sidebar for details). These metrics were calculated from Andersen 8-stage cascade impactor (ACI) data for each of the 201 batches of the product.

What does a metric offer?

Let's take a look at what each of these metrics offers cascade impactor (CI) practitioners. To do so, we introduce here a simple analysis that provides a clear, accessible view of both the nature of what an APSD metric reports and the level of discrimination it provides. In other words, it summarizes the utility of the metric, namely what you can and cannot do with it. To explain how this analysis is conducted, let us first focus solely on ISM. We begin by calculating the ISM for each APSD. Then, we assign a ranking to each APSD based on the value of its ISM, relative to the set of ISM values for the entire population of 201 APSDs. The rankings are expressed as percentiles, so the APSD with the largest ISM is assigned a rank of 100%, the APSD with the smallest ISM is assigned a rank of 0%, the APSD whose ISM is the median of the population is assigned a rank of 50%, and so on. As such, this ranking describes where each APSD's ISM value resides within a distribution of the entire population of ISM values for this product. The ISM rankings are then used to group the APSDs into four bins, with each bin representing a different portion of the total distribution of ISM values. Although we recognize that the ISM values may not always be normally distributed, for this exercise, the boundaries of the bins are chosen to represent increments based on multiples of a normally distributed population's standard deviation around the median value, as shown in Table 1. Bin 1

Table 1

Limits of binned distributions shown in figures

Bin No.	Lower	Upper
1	16%-50%	50%-84%
2	2.5%-16%	84%-97.5%
3	0.5%-2.5%	97.5%-99.5%
4	0%-0.5%	99.5%-100%

contains the APSDs whose ISM values therefore comprise the central 68% of the population, from the 16th percentile to the 84th percentile (± 1 standard deviation). Bin 2 contains the APSDs whose ISM values fall between the 2.5th percentile and the 97.5th percentile, excluding those in Bin 1 (those between 1 and 2 standard deviations from the median). The APSDs in Bin 3 correspondingly have ISM values between the 0.5th percentile and the 99.5th percentile, but outside the range of Bin 2 (i.e., between 2 and 3 standard deviations from the median). Finally, APSDs in Bin 4 have ISM values beyond the 0.5th percentile to the 99.5th percentile bounds of Bin 3 (i.e., those APSDs whose ISM values are more than 3 standard deviations from the median). Each bin is therefore symmetrically located about the median value and for clarity in presentation, the "upper" and "lower" halves are distinguished by color in the figures.

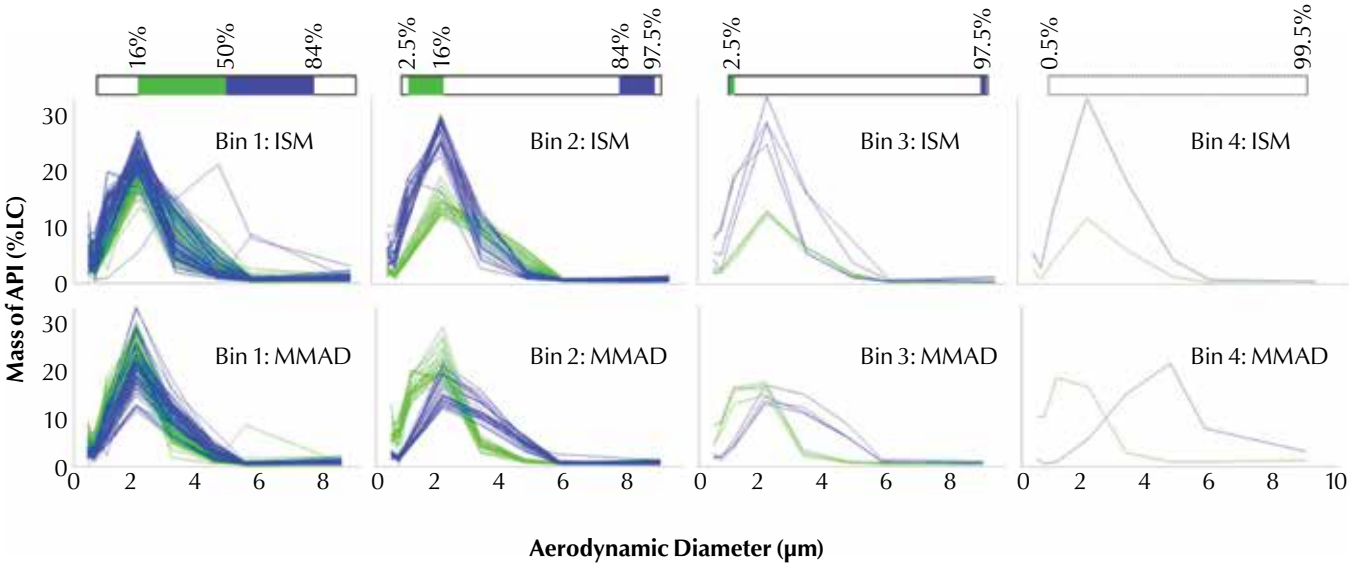
Now let's have a look at what this binning approach teaches us about what ISM offers as a metric. The plots in the top row of Figure 1 feature all 201 APSDs from the product, grouped according to their ISM bin. As previously mentioned, they are color-coded based on whether their ISM is greater than or less than the median ISM value. So, the left-most plot features APSDs whose ISM values are within the central 68% of the entire population.

Moving from left to right across the upper row of plots to Bins 2, 3 and 4, we see the APSDs whose ISM values are located further and further from the median. So what does this teach us about the utility of ISM as an APSD metric? Well, the increasing separation of the upper (blue) and lower (green) halves of each bin as we move outward from the median confirms that ISM can be used to discriminate between APSDs *that are visibly different in their mass dimension* (the y-axis). Although perhaps not surprising, this is an important demonstration of the evidence for meaningful, rationalizable discrimination between APSDs. This graphical presentation also confirms that ISM is incapable of discriminating between APSDs *based on their size dimension*. The collection of APSDs of widely varying size-based profiles classified by ISM alone, particularly in Bin 1 (upper row), highlights this fundamental limitation.

The lower row of plots in Figure 1 summarizes the same "binning by rank" analysis for MMAD. It is critical to understand that the ranking (and therefore the binning) for each metric is completely independent of other metrics. So, for example, a given APSD could reside in Bin 1 for ISM, but in Bin 4 for MMAD. Just as with the ISM binning, as we move further from the median MMAD value (from left to right across the row of plots) we see a clear, intuitive separation between the blue and green populations. This time, however, the separation is along the size dimension (the x-axis). This means that MMAD can be used to reliably discriminate between APSDs *based on the aerodynamic size of their API mass*. We further see a fundamental limitation of MMAD: that it tracks only the size dimension of the APSD and is insensitive to changes in the mass dimension.

Figure 1

201 APSDs from a single product are binned according to their ISM values (top row) and MMAD values (bottom row). Horizontal bars above each column showing the percentile ranges defining each bin are provided for reference. Within each bin, APSDs are further grouped based on whether the value of the specified metric is above (blue) or below (green) the population's median. Moving from left to right along a row of plots (i.e., away from the median) illustrates the discriminatory ability of a given metric. Each APSD is plotted as mass of API (expressed as a percent of label claim) vs. the effective cut-off diameter of the impactor stage.



Combining metrics for decision-making

Let's now take a look at how ISM and MMAD might be combined to support batch disposition decisions. In the left plot of Figure 2, each APSD is expressed as a single point, defined by its ISM on the y-axis and its MMAD on the x-axis. As indicated in the legend, the APSDs have once again been grouped into four bins. This time, however, each APSD is classified based on a *combined* assessment of ISM and MMAD. Specifically, we have classified each APSD based on the maximum of its individual ISM and MMAD bin assignments. For example, a Bin 2 assignment indicates that the APSD was assigned to Bin 2 for at least one of the two metrics, and that it was not assigned to Bins 3 or 4 for either metric. This approach is analogous to the simultaneous application of multiple specification limits. Since the mass and size dimensions of the APSDs are orthogonal, we observe clear boundaries between the four bins in this plot. Therefore, we see that there is a large central region (indicated by the red box) which encompasses all the APSDs assigned to Bin 1 (i.e., those whose ISM and MMAD each fall within the central 68% of their respective distributions) and, importantly, contains none of those APSDs assigned to other bins. We propose that simultaneously treating ISM and MMAD as described above can serve as the kernel of what is both necessary and sufficient to discriminate between batches based on product performance (APSDs).

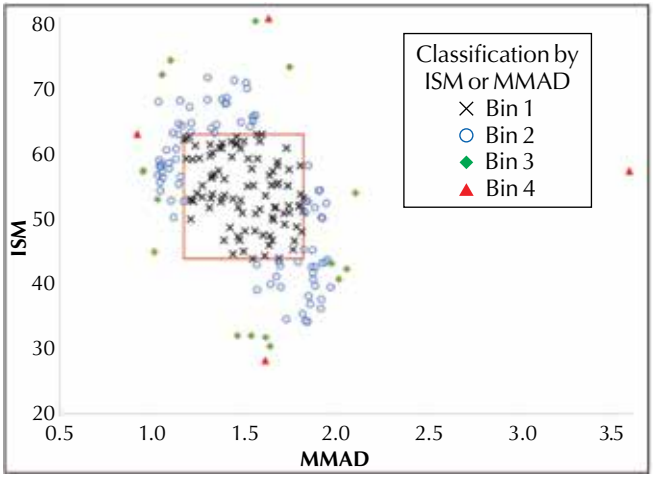
We have also conducted this same analysis using stage groupings, the results of which are presented in the right panel of Figure 2. In this plot, each APSD is classified based on the maximum of its three stage grouping bin assignments. In this example, Group 2 is defined as the mass on impactor stages 1 to 3 (3.3 µm-9 µm aerodynamic diameter), Group 3 represents the mass on stages 4 and 5 (1.1 µm-3.3 µm aerodynamic diameter) and Group 4 is the mass from stage 6 or beyond, including the filter (0 µm-1.1 µm aerodynamic diameter). Note that the filter is assumed to collect everything presented to it with 100% efficiency, so its lower bound size can be set to 0 µm aerodynamic diameter. The same red box from the left panel is provided for reference. In contrast to the prior example, classifications based on the combination of three stage groupings are nearly impossible to rationalize. For example, although we know the APSDs within the red box comprise a relatively narrow range of both ISM and MMAD, we see here that these same APSDs are now spread across four different bins. This suggests that specifications based on stage groupings may struggle to make meaningful discriminations between APSDs. Put simply, you may have limited ability to reconcile a visual comparison of two APSDs with your specification's assessment of the two distributions. We urge you to pause here and ask yourself whether you are comfortable with that.

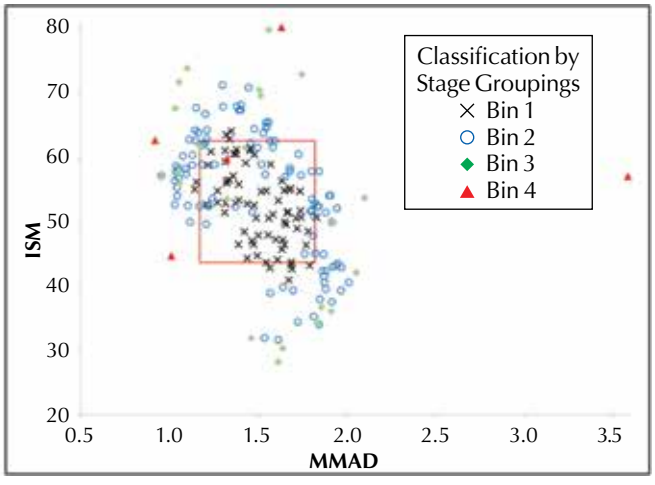
A closer look at APSD classification: Do your metrics pass the red face test?

Let's now take a closer look at how the combination of three stage groupings classify these APSDs. The binning exercise used here is analogous to classifying via specification limits. Even without knowing the product's actual specification limits, we can assume that quality control of an APSD is based on the value of a chosen metric relative to a distribution of that metric's values, which represents typical or acceptable product performance. With this in mind, we will take a closer look at some of the consequences of attempting to control APSDs with SGs. In Figure 3, we highlight five examples of APSD classification by SGs that are

Figure 2

Both plots feature the same 201 APSDs from a single product, expressed in terms of their ISM values and MMAD values. The left plot shows binning by the maximum bin for ISM or MMAD. The right plot shows binning by the maximum bin for G2, G3 or G4. The position of the red box is the same for both plots (limits: ISM: 43.0-62.2 µg; MMAD: 1.16-1.77 µm).





difficult to rationalize. The main plot in Figure 3 is the same plot of 201 APSDs expressed in terms of their ISMs and MMADs (as shown in right plot of Figure 2), classified by the combination of the three SGs. Four regions on this graph are defined by red boxes, and the APSDs from each region are shown in the associated inset plots.

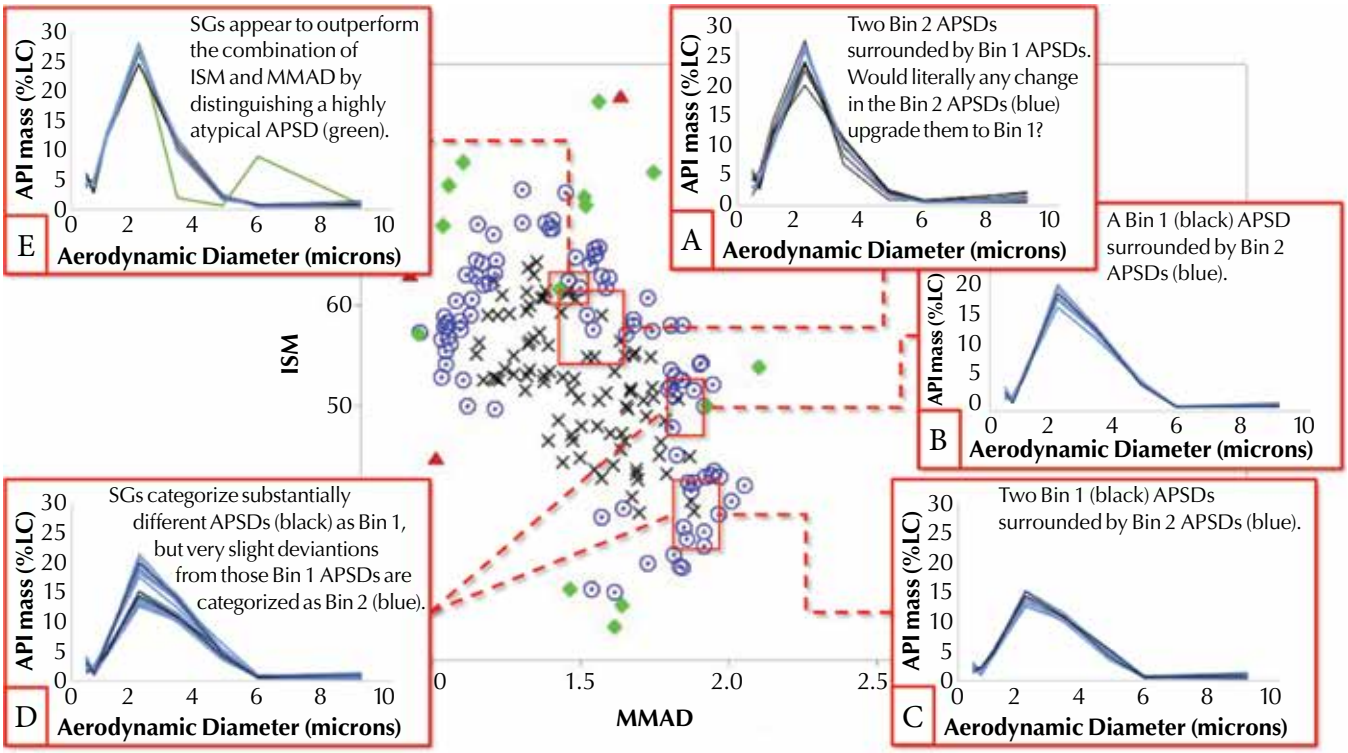
In panel A, a collection of nine APSDs presents a peculiar situation. As can be seen on the main plot, two APSDs classified as Bin 2 (in blue) are essentially surrounded by seven other APSDs from Bin 1 (in black). The Bin 2 assignment should mean that the blue APSDs are further from typical performance than the black APSDs assigned to Bin 1. It is difficult to know how to interpret this, though, for when you examine the APSDs in the inset plot, the blue APSDs appear to be well within the range spanned by the black APSDs. It almost appears that either an increase or a decrease in recovery on *any* impactor stage, would result in an upgrade for this particular APSD from Bin 2 to Bin 1. It begs the question: what is it about precisely these two APSDs that warrants distinguishing them from their highly similar neighbors? Surely, they do not represent some sort of sub-par performance that could be improved if they had more mass, or less mass, or were coarser or finer. What, then, is the classification by stage groupings telling us here?

Two of the other highlighted regions in Figure 3 (panels B and C) feature examples of the opposite scenario. This time, Bin 1 APSDs (in black) are located in the midst of Bin 2 APSDs (in blue). The eight APSDs in panel B appear to be highly similar, but for some reason, stage groupings have identified one of them as preferred relative to the others. Similarly, in panel C, two of the ten APSDs in this region are somehow distinguished by SGs from the eight Bin 2 APSDs that surround them. When you examine these APSDs, can you rationalize the distinctions made here?

Panel D showcases a baffling peculiarity of APSD classification by stage groupings by superimposing the plots from panels B and C. If you consider the three black Bin 1 APSDs, you can see that there is significant latitude concerning what constitutes typical product performance. The taller black APSD from Panel B comprises roughly one and a half times the mass of the two black APSDs from Panel C, but all three are classified as Bin 1. Such a range may well be appropriate for a given product and does not necessarily stand out as being peculiar. That said, what we struggle to comprehend is the following paradoxical situation. Either

Figure 3

Five panels (A-E) provide APSDs drawn from the four regions indicated by red boxes on the background plot. The background plot is the same ISM vs. MMAD representation of the 201 APSDs, with the symbols indicating the combined stage grouping bin, as previously shown in Figure 2 (right panel). Inset APSD plots show API mass (as a percent of label claim) vs. effective cut-off diameter of the impactor stage. Bin 1: Black X's, Bin 2: Blue circles; Bin 3: Green diamonds; Bin 4: Red triangles.



the higher mass APSD from panel B or the lower mass APSDs from panel C are apparently suitable for assignment to Bin 1. However, despite the considerable range between these Bin 1 APSDs, small deviations from these APSDs, in *any* direction, leads to a different classification. Are these specific APSDs discrete examples of preferred performance, isolated like islands in a sea of inferior APSDs? Instead of defining individual acceptable APSDs and outlawing the spaces in between, in the real world, the only logical practice is to define acceptable performance over a continuous range.

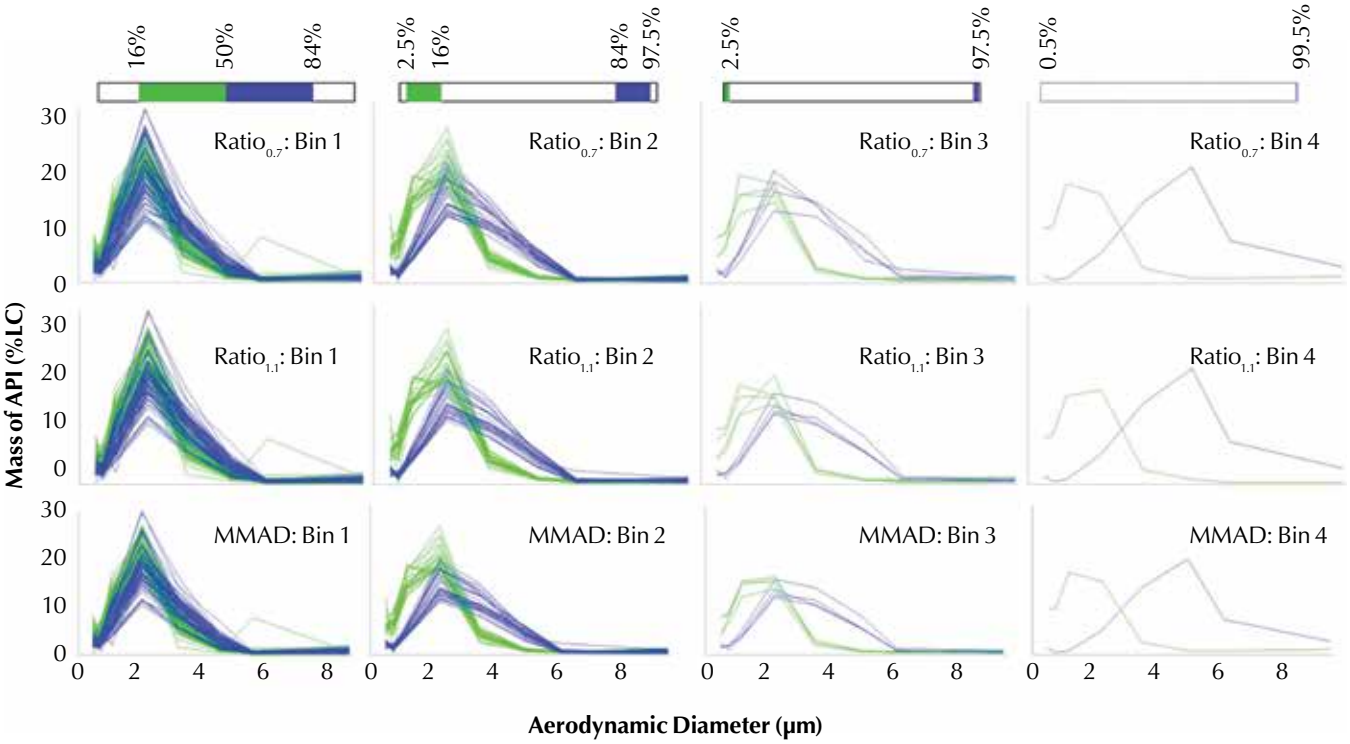
Finally, the example highlighted in panel E also warrants examination. Here, we have six APSDs all within a narrow range of ISM and MMAD values. Five of the six APSDs appear highly similar, although SGs have categorized some as Bin 1 and others as Bin 2 (in black and blue, respectively). The remaining APSD (in green) is visually distinct, apparently bimodal, and is categorized as Bin 3 by SG-based analysis. Interestingly, though, the combination of ISM and MMAD assigns all six of these APSDs to Bin 1, and this is simple enough to rationalize: all six APSDs have ISMs between 60.6% and 62.4% LC, and the range of MMAD values is less than 0.1 µm. Does this data set represent a scenario in which SGs perform better than EDA? We contend that this is not the case, because the degree of bimodality observed in panel E is exceedingly unlikely to represent the underlying APSD. Consider for a moment what realistic phenomena could possibly yield an aerosol with two modes so close together (~4 µm), and furthermore, whether such bimodality could actually be resolved by an ACI. As previously noted by Mitchell, et al. [7], even a genuinely bimodal APSD is unlikely to be observed by the inherent low resolution combined with overlapping stages of this apparatus [8]. Experienced CI practitioners reading this article may have already assessed that the far more likely origin of this atypical APSD is an accidental switching of impactor stage recoveries, either during extraction of the API from the stages or in the labeling of HPLC vials. Specifically, the recovery from stage 4 appears to have been inadvertently inserted between the recoveries from stages 1 and 2. Further scrutiny reveals that there is, in fact, a replicate APSD determination for this sample included in the IPAC-RS database, consistent with our speculation that the observed bimodality is owed to laboratory error. Ultimately, then, rather than a failure of the ISM and MMAD approach, we contend this is nothing more than an immediately identifiable lab error that has created the illusion of a highly improbable APSD.

From insufficient to sufficient and efficient

Hopefully, we have convinced you that you must measure differences in *both* size and mass to discriminate

Figure 4

201 APSDs from a single product are binned according to their $RATIO_{0.7}$ values (top row), $RATIO_{1.1}$ values (middle row), and MMAD values (bottom row). Horizontal bars above each column illustrate the bounds of each bin. Within each bin, APSDs are further grouped based on whether the value of the specified metric is above (blue) or below (green) the population's median. Classification of the product's APSDs by the EDA Ratio (with either a 0.7 or a 1.1 µm cut-off) is remarkably similar to classification by MMAD.



meaningfully between APSDs (i.e., that FPD and SGs are insufficient). Hopefully, we have also convinced you that you need *only* measure differences in size and mass to discriminate meaningfully between APSDs (i.e., that ISM and MMAD are sufficient). If we are aligned on those points, the next pertinent question is: "Are there more efficient ways to make batch disposition decisions that are still based on both the mass and size dimensions of a product's APSD?" In other words: "Are we investing more than is required for the information returned to us?" We conclude that the answer is "yes;" that the same comparisons can be made, and the same decisions reached, in a far more efficient manner. In support, we refer to Tougas et al. [8], who showed that use of ISM and the ratio of the large particle mass (LPM) to the small particle mass (SPM) within the ISM (RATIO) are all that is needed to characterize comprehensively movements in the mass and/or size directions of the underlying APSD. *Importantly, Tougas, et al. demonstrated that the "RATIO" metric is strongly correlated with MMAD, provided the boundary between LPM and SPM is within 0.3 and 3 times the MMAD value.* It is important to appreciate that the boundary between LPM and SPM is product-specific and should therefore be determined as part of the development process using data acquired from a full resolution impactor. In this context and by convention, RATIO is given a subscript that indicates the upper stage boundary chosen to define SPM. Use of these metrics (ISM and either MMAD or RATIO) to describe APSD is conveniently referred to as Efficient Data Analysis (EDA).

Figure 4 features a comparison of the APSDs sorted according to the rankings for MMAD, $RATIO_{0.7}$ and $RATIO_{1.1}$. Here, we observe that each of the ratio plots tracks movement away from the central tendency of size in a manner that is nearly identical to that observed for MMAD by itself, confirming the observation of Tougas, et al. [8] respecting the non-critical nature of the boundary location between SPM and LPM fractions.

Since we have seen from the evidence presented here that both ISM and RATIO describe *independently* movements in both the size and mass defining the underlying APSD, it follows we can confirm that these metrics (which constitute EDA) are both necessary and sufficient to enable good decisions to be made regarding product quality for OIPs.

Further support for the use of EDA was provided by Christopher, et al. in a multi-laboratory study probing the decision-making ability of EDA [9]. Analysis of albuterol metered dose inhaler (MDI) APSDs collected using both conventional and abbreviated impactors (AIM) revealed that the uncertainty in MMAD prediction by the EDA RATIO metric was approximately 0.1 µm. In other words, splitting the APSD into eight fractions with the conventional ACI did not allow better decision-making than simply splitting the APSD into two fractions, large and small. Moreover, the same study also demonstrated that a conventional ACI was no more capable of making batch disposition decisions than an abbreviated form of the same impactor.

Pause here for a moment to reflect on the implications of this: a ten-component ACI was reduced to a 4-component AIM apparatus, without degrading decision-making ability. If you were asked to modify a QC method such that it would take twice as long, consume twice as much solvent, increase the variability, and make it more prone to user error, would you not expect that this could only be justified by a dramatic improvement in your ability to disposition batches of your product? Granted, the conventional impactor offers a higher resolution (albeit, only 7- or 8-point) sampling of your product's APSD and could be a useful tool for investigating any atypical results. For routine QC testing to support batch disposition, though, it is difficult to rationalize such an investment without a significant return.

Conclusions

In this article, we initially provided additional evidence regarding the inadequacy of commonly used APSD metrics. We then established that ISM and MMAD, which independently track movements in the mass and aerodynamic size, are an appropriate minimum set of metrics for effective decision-making. We further demonstrated that a simple RATIO of LPM to SPM offers the same sensitivity to changes in APSD size as achieved with MMAD determinations. In combin-

The IPAC-RS APSD Database

The APSD data used in this manuscript originate from QC testing of actual OIPs. The blinded IPAC-RS database includes APSD data for 34 OIPs, which are either commercially marketed or in late development (Phase IIB or later), from seven manufacturers. To ensure blinding and confidentiality, APSD data were submitted to the IPAC-RS secretariat. For each product, the APSD data consist of API recoveries from individual impactor components (e.g., induction port, stages, filter, etc.) expressed as a percent of the product label claim. More information regarding the database can be found at: https://wayback.archive-it.org/7993/20170405182408/https:/www.fda.gov/ohrms/dockets/ac/00/techrepro/3609_rpt2.pdf.

ing ISM and RATIO, EDA therefore improves APSD discrimination relative to conventional metrics such as FPD and SGs. Moreover, since ISM and RATIO can be acquired using abbreviated impactor methods, the AIM/EDA combination can be leveraged to dramatically improve efficiency without sacrificing decision-making ability, as previously demonstrated.

In our opinion, an improved approach to APSD quality control is clearly needed and long overdue. Fortunately, improvement is well within our reach. The proposed APSD control strategy represents a simple, incremental improvement. Implementation of EDA to make batch-disposition decisions does not require the development of new methods or the purchase and qualification of new instrumentation. Extending EDA to incorporate an AIM apparatus, if desired, would represent only a minimal change in laboratory procedures while harnessing enormous gains in efficiency. The strategy is straightforward, intuitive and the supporting science is well documented. As such, EDA aligns perfectly with the stated intent of the FDA's Emerging Technology Program. In light of the evidence presented, we hope readers will question whether their current practices are sufficient (i.e., whether they serve their intended purpose), and also consider their efficiency (i.e., whether their investments are justified by the returns).

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