Cascade impactor stage groupings: Poor decisions from degraded data

Rejecting another bad metric

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The following is the second in 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 regulation of aerodynamic particle size distributions (APSDs) of orally inhaled products (OIPs). In the first of these articles,[1] we looked at the inability of the fine particle dose metric to detect size changes in APSD. Here, we turn our attention to the stage grouping metrics favored by the US Food and Drug Administration (FDA).[2] These articles are written to educate, to dispel common misconceptions, to raise awareness of risks and to encourage scientists to scrutinize current practices. These articles should not be mistaken for regulatory guidance documents.

Introduction

Guidance documents concerning the quality of OIPs from a number of major health authorities include cascade impactor stage groupings as a means for controlling inhaler aerodynamic particle size distributions (APSDs). Health Canada and the European Medicines Agency (EMA), for example, identify stage groupings as an option if the fine particle mass alone is insufficient to fully characterize the particle size distribution of the therapeutic dose.[3,4] The United States Food and Drug Administration (FDA) goes even further, recommending this methodology as the principal approach for APSD control in their current draft guidance for industry for the determination of quality for pressurized metered dose inhalers (pMDIs) and dry powder inhalers (DPIs).[2] Despite their prevalence, however, stage groupings are remarkably ineffective at observing differences between APSDs. In the following article, we explore the limitations of stage groupings, probing whether they are suitable for making batch disposition decisions based on inhaler performance testing.

Why stage groupings? ….Good question.

Chances are, if your lab releases OIPs for distribution, you have had to take cascade impaction data and reduce it to stage grouping metrics. Chances are, also, that this is the *only* instance in which you would treat the data in this manner. This is because the stage grouping metrics have no inherent value. There is no demonstrated correlation between these metrics and any measure of *in vivo* performance (such as lung deposition or clinical outcomes), and they offer little more than an obscured view of the product's APSD. Indeed, if you have ever had to investigate an out-of-trend or out-of-specification cascade impactor (CI) result for a commercial orally inhaled product (OIP), you have likely had to sift through huge volumes of CI data. Almost certainly, you have immediately discarded the stage grouping data and insisted that the testing lab provide you with the original CI data from which the stage groupings were derived. Only then can you begin to investigate the nature of the problem and diagnose the root cause. What then is the purpose of reducing CI data to stage groupings? What benefits do these metrics offer? You will have to ask someone else these questions, for we certainly do not have those answers. What we can offer you, though, is a compelling demonstration of how little the stage grouping metrics offer you as a scientist who strives to understand and control your product's APSD, and how little they do to ensure the delivery of safe and efficacious medicines to your patients. Hopefully, this will steel your resolve to keep asking those questions.

Attempting to control your APSD

To illustrate the shortcomings of stage groupings, let's walk through an example comparing different treatments of CI data and the information they offer. Note that this example focuses solely on the APSD as a measure of an OIP's performance. Imagine that you are a development scientist working on an OIP. The 201 distributions in Figure 1 summarize the recent historical performance of the product, including release and stability data from the batches used in pivotal clinical trials. The APSDs provided for this example are, in fact, development data from an actual OIP, drawn from the IPAC-RS blinded product database (see the sidebar at the end of this article for more information). Looking ahead to commercial production, you need to define specifications that the quality control (QC) lab will eventually use to make batch disposition decisions. To do so, the QC lab will need to assess whether the performance of a newly manufactured batch is sufficiently similar to that of the clinical batches. Now, imagine for a minute that you do not have any preconceived notions regarding health authorities' expectations for reporting APSD data. Imagine that your concern is simply to establish metrics, the bounds of which define a reasonable range around your target APSD, enabling batch disposition decisions.

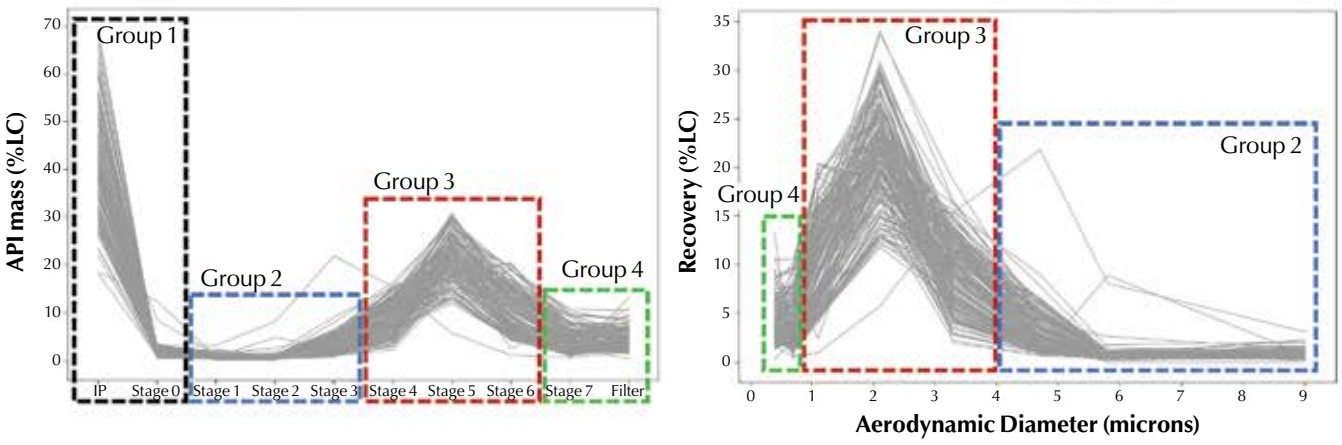
So how does one place appropriate limits on a product's APSD? A wide variety of metrics are available for describing cascade impaction data, however their utility for making batch disposition decisions varies widely. Moreover, the utility of a given metric depends heavily upon how it is applied and, in particular, with which other metrics it is used. *The key is to recognize that APSDs have two orthogonal dimensions, mass and size, and that APSDs can differ in either one, or both, of these dimensions*. For example, an irregular metering valve that delivers slightly more formulation than intended might impact only the mass dimension of a metered dose inhaler's APSD. Alternatively, a batch of the same product with less co-solvent than intended might deliver the same total mass of formulation, but with the distribution of the API mass shifted toward a finer aerodynamic diameter. Of course, there may also be changes in both dimensions of a product's APSD simultaneously, from either a single root cause or a combination of multiple causes. Regardless of the cause, though, *successful control of an APSD requires a system of metrics which is sensitive to changes in each of these two orthogonal dimensions.*

Returning to your specification setting task, you might then choose impactor-sized mass (ISM) and mass median aerodynamic diameter (MMAD) as orthogonal metrics to independently control the mass and size dimensions, respectively, of your product's APSD. ISM is the size-fractionated portion of the API mass captured by an impactor, and MMAD is the median aerodynamic diameter of the ISM.[5,6] These two metrics are widely accepted measures of the mass and size dimensions of an APSD. Note that these metrics include only the size-fractionated portion of the aerosol that is considered most directly related to pulmonary deposition.

Let's now look at how you might use these two metrics to control the product's APSD, as summarized in Figure 2. The left-hand plot presents the product's APSD data in terms of the two chosen metrics, with each point reporting the ISM (on the y-axis) and the MMAD (on the x-axis) of an individual APSD determination. Note that there is no correlation between the two variables, confirming the expected orthogonality of the two dimensions of the APSD (i.e., the amount of the API mass and its aerodynamic size are independent of each other).

Figure 1

APSD determinations (201 total) for a solution metered dose inhaler (MDI) from the IPAC-RS blinded product database (see sidebar for details). API mass (expressed in terms of percent label claim (%LC)) is plotted for each impactor component (left), and the size-fractionated mass is plotted vs. aerodynamic diameter (right). Typical stage groupings, as defined in Table 1, are shown on each plot.



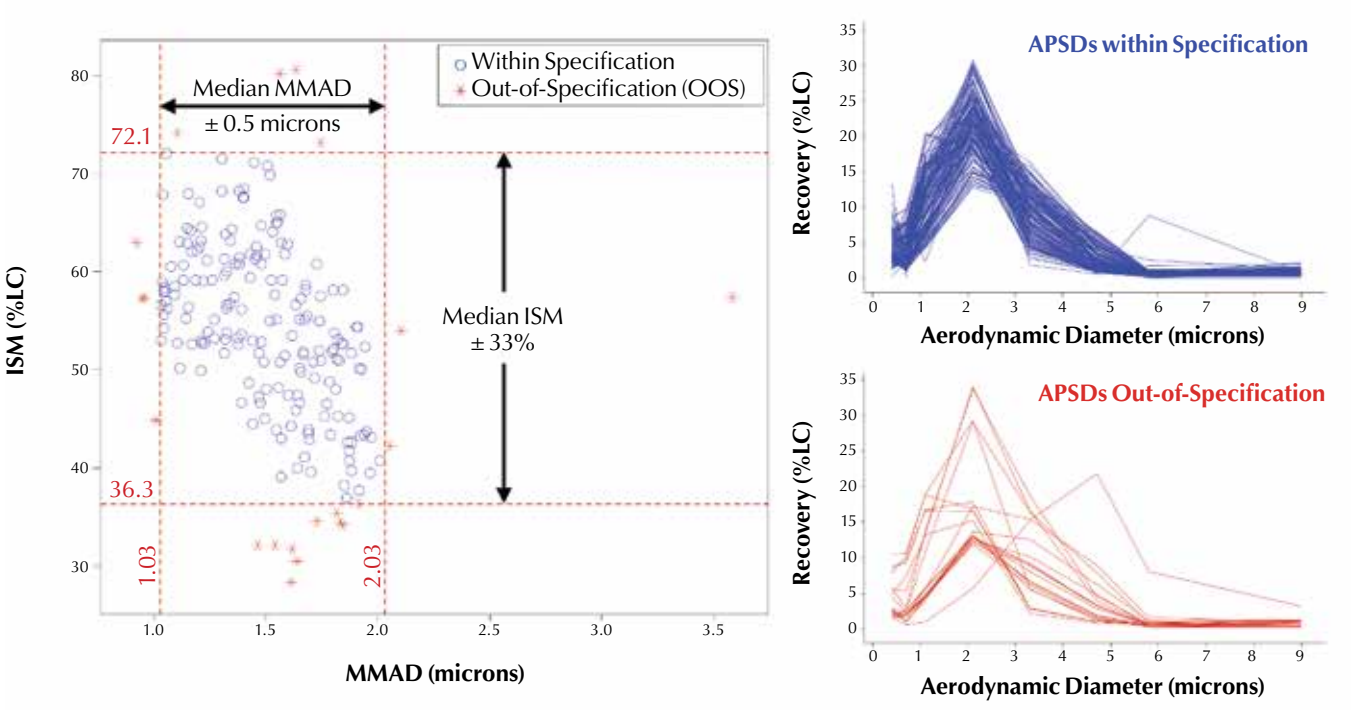
Although the actual specifications for this product are not known, we can still assign reasonable limits based on the spread of the data. To control the MMAD, we choose here to set upper and lower limits at ± 0.5 microns from the median MMAD value of 1.53 microns (at 2.03 microns and 1.03 microns, respectively). To control the ISM, we choose here to set upper and lower limits at ± 33% of the median ISM value of 54.2% label claim (LC) (at 72.1% LC and 36.3% LC, respectively). These ranges are chosen based on the authors' experience developing and characterizing OIPs in an attempt to define reasonable limits for this data set, allowing for realistic variability (inter- and intra-batch variability, inherent method variability, etc.). It is worth noting that the ± 33% range applied to the ISM would encompass approximately one standard deviation of a normally distributed population, and is consistent with specification limits of approved products.[7]

Laying the limits for each metric (shown by the four labeled reference lines) atop the plot of ISM vs. MMAD in Figure 2 divides the plot into nine regions in a 3 x 3 grid. The central region defines those APSDs (shown in blue) that are considered acceptable by these specifications; both their ISM and MMAD are within the assigned upper and lower limits. APSDs falling in any of the eight peripheral regions (red data) are deemed unacceptable by these specifications, since either their ISM or their MMAD are outside the assigned limits. Each APSD is also provided in one of the two right-hand panels according to its classification (either within specifications or out-of-specification (OOS)), allowing readers to visually evaluate the suitability of the proposed specification limits. Comparing the red OOS APSDs in the lower plot to those falling within the specification limits (upper plot, in blue), one can easily rationalize the rejection of each OOS APSD. Each such distribution appears to deviate from the typical performance of the product in either one or both dimensions. In other words, the proposed MMAD and ISM limits appear as though they would perform as intended; they would allow the user to make sensible batch disposition decisions.

Let's recap briefly: we have taken 201 APSDs representing the performance of an inhaled product, and assigned realistic limits to both the mass and size dimensions of the APSD, resulting in the sensible rejection of those APSDs whose mass or size deviates from the product's typical performance. Although one can always debate the specific values of these limits, we contend that these are reasonable, realistic specifications and that they do the job they are intended to do. Specifically, these specifications would allow your QC laboratory to make sensible batch disposition decisions by discriminating between batches with APSD profiles

Figure 2

Control of the product's APSD by imposing limits on both the size and mass dimensions. The main plot expresses each APSD in terms of ISM vs. MMAD, with the labeled reference lines defining the proposed upper and lower limits for each metric. Blue and red symbols indicate whether APSDs fall within or out-of-specification, respectively. At right, the 201 APSDs are divided between two plots, allowing visual inspection of the proposed specifications' classification of APSDs as either within (top, in blue) or out-of-specification (bottom, red).



of consistent shape and size, and those exhibiting shifts in the distribution or total mass.

What would stage groupings make of these data?

Now, let's evaluate these same APSDs using the FDA-mandated stage groupings and see how well they perform. Essentially, we want to evaluate the utility of stage groupings when making batch disposition decisions. In other words, we want to assess the ability of stage groupings to determine how similar a given APSD is to a pool of reference APSDs. To do this, we begin by calculating stage groupings for each APSD. Based on the shape of the distribution, we have defined the groupings as shown in Figure 1 and detailed in Table 1. Group 1 contains the non-sized mass deposited in the induction port and on stage 0 and, as discussed earlier, is outside the scope of this article. The majority of the size-fractionated mass, deposited on stages 4, 5 and 6, is assigned to Group 3. The remaining mass comprising the coarse and fine peripheries of the size-fractionated mass are assigned to Group 2 (Stages 1, 2 and 3) and Group 4 (Stage 7 and the filter), respectively.

Having defined the stage groupings, we can now determine the relationship between each stage grouping and the two dimensions of the APSD data, as captured by the MMAD and the ISM, respectively. In Figure 3, each stage grouping is plotted against the corresponding distribution's MMAD (left panel) and ISM (right panel). Linear regression of each data set yields the trend lines provided on each plot for each stage grouping. These trend lines define the relationship between the stage groupings and the two dimensions of the APSDs; they capture the impact of changes in either MMAD or ISM on the stage grouping metrics. As such, the trend lines can now be used to project the previously assigned MMAD and ISM limits from each x-axis (shown with the vertical, black reference lines) onto the y-axes, yielding corresponding limits for each stage grouping (shown with horizontal, color-coded reference lines). In keeping with common practice,[7] both upper and lower limits are assigned for Group 3, whereas Groups 2 and 4 are each assigned only an upper limit. The limits for each stage grouping are provided in Table 2 alongside the MMAD and ISM limits from which they were trans-

Table 1

Typical stage groupings and their size ranges

Group	Andersen Cascade Impactor Components	Aerodynamic Diameter Range (microns)	
1	Induction Port	NA	Mass of Undefined Size
	Stage 0	> 9.0	
2	Stage 1	5.8 – 9.0	ISM: the size-fractionated mass that defines the APSD profile
	Stage 2	4.7 – 5.8	
	Stage 3	3.3 – 4.7	
3	Stage 4	2.1 – 3.3	
	Stage 5	1.1 – 2.1	
	Stage 6	0.7 – 1.1	
4	Stage 7	0.4 – 0.7	
	Filter	< 0.4	

Figure 3

Plots of stage groupings vs. MMAD (left) and ISM (right) illustrating the impact of changes to either MMAD or ISM on each stage grouping. Trend lines calculated via linear regression are used to translate the MMAD and ISM limits (vertical, black reference lines) to corresponding limits for each stage grouping (horizontal, color-coded lines).

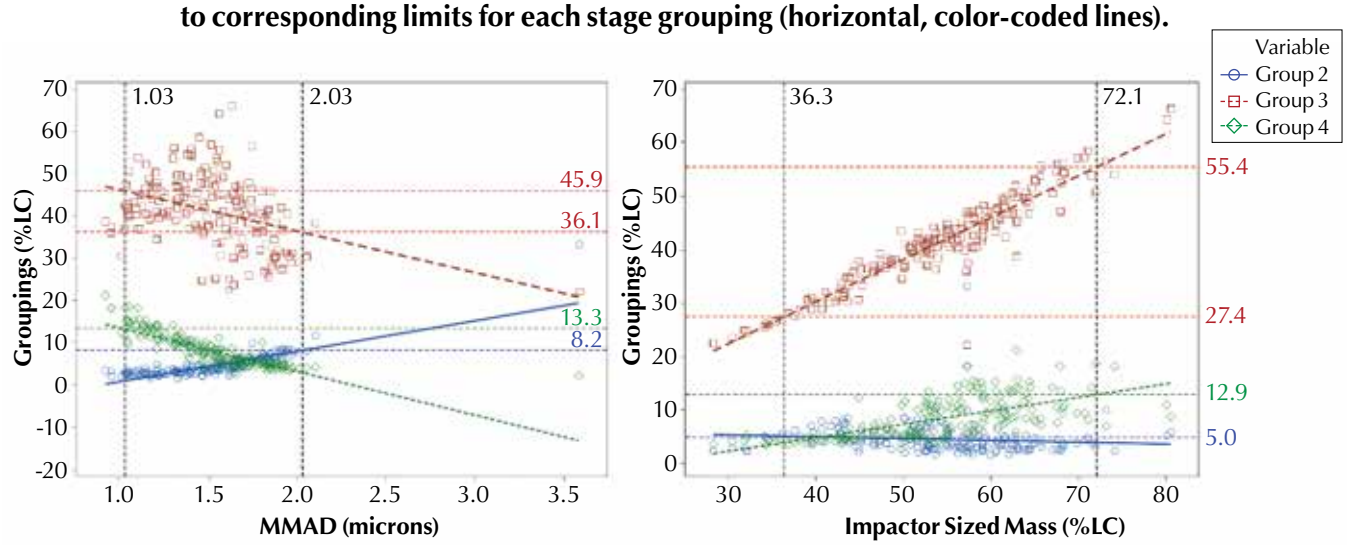


Table 2

Stage group limits as derived from the corresponding MMAD and ISM limits

Target Limits for MMAD and ISM			Stage Group Limits Translated via Linear Regression (%LC)		
			Group 2	Group 3	Group 4
MMAD (microns)	Lower Limit	1.03	--	**36.1**	--
	Upper Limit	2.03	8.2	**45.9**	13.3
ISM (%LC)	Lower Limit	36.3	--	27.4	--
	Upper Limit	72.1	**5.0**	55.4	12.9
Combined Limits:			**≤ 5.0**	**36.1-45.9**	**≤ 12.9**

lated. The bolded figures in Table 2 represent the combination of the most restrictive individual limits (i.e., the highest lower limits and the lowest upper limits) necessary to control both the MMAD and ISM using stage groupings.

Okay, now that we have defined the stage grouping limits, let's evaluate how well they control your product's APSD. In Figure 4, the product's APSDs are again expressed in terms of ISM and MMAD, and the previously assigned limits for each are shown with reference lines. Recall that the central rectangular region bounded by these limits defines the region wherein the APSDs meet both the MMAD and ISM specifications, and that data outside this region would be considered out-of-specification. As indicated in the legend, symbols report the classification of each APSD by the new stage grouping specification limits. Blue symbols indicate APSDs that were either "correctly accepted" (circles) or "correctly rejected" (stars). Meanwhile, red symbols indicate APSDs that were either "incorrectly accepted" or "incorrectly rejected." Incorrect classification means that the stage grouping limits failed to determine whether the MMAD and ISM conformed to their originally assigned limits. In other words, each incorrect classification represents an instance where the stage groupings are unable to detect whether there have been significant changes in either the mass or aerodynamic size of the APSD.

The pie chart provided in Figure 4 summarizes the performance of the stage grouping specifications relative to the MMAD and ISM limits. The results are appalling: the stage grouping limits misclassify 62% of the APSDs. For reference, this is worse performance than you would expect from a coin toss. The vast majority of the mis-classifications are rejections of APSDs with typical MMAD and ISM values, indicated by the red diamonds. There are no instances of incorrect acceptances in this example, which is beneficial to the patient, but due to the inherent limitations of the stage groupings approach, this benefit comes at a steep cost to the patient of the incorrect rejection of a massive proportion of suitable product.

Figure 4

Use of stage grouping limits to control the two dimensions of the product's APSD. Reference lines on the ISM vs. MMAD plot (left) show the original ISM and MMAD limits for reference. Classification of each APSD by the stage grouping limits is indicated in the legend. The pie chart (right) summarizes the performance of the stage groupings in discriminating between within specification and out-of-specification APSDs.

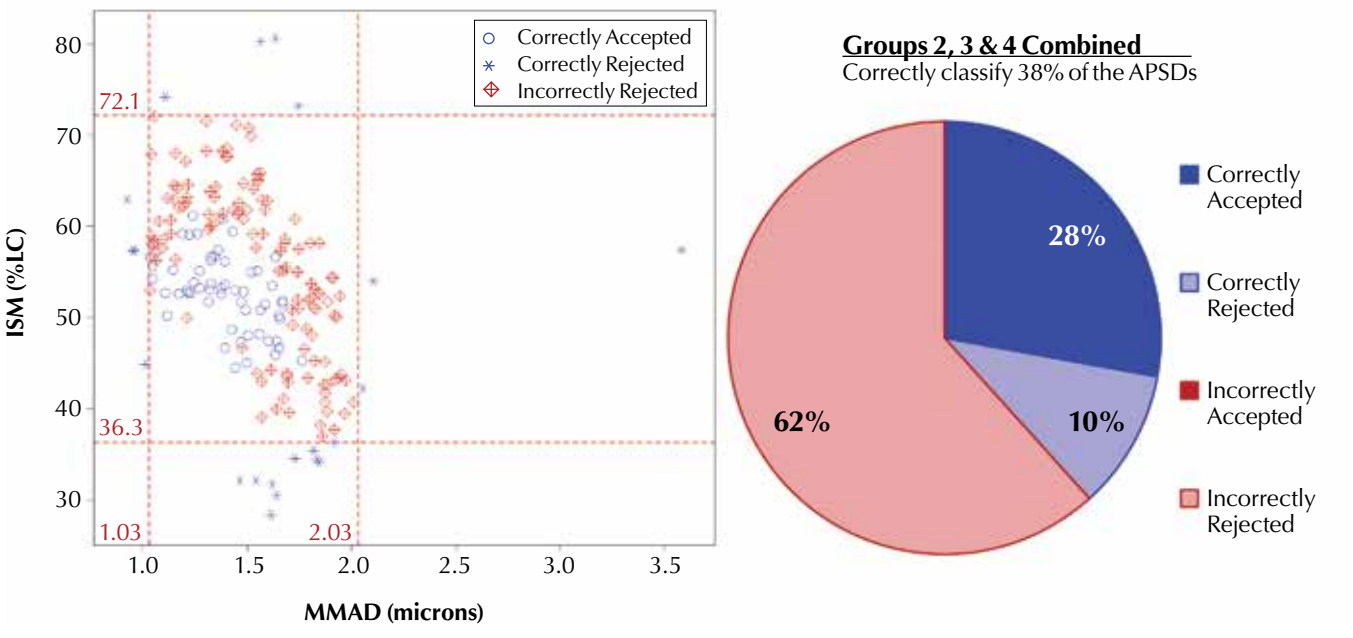


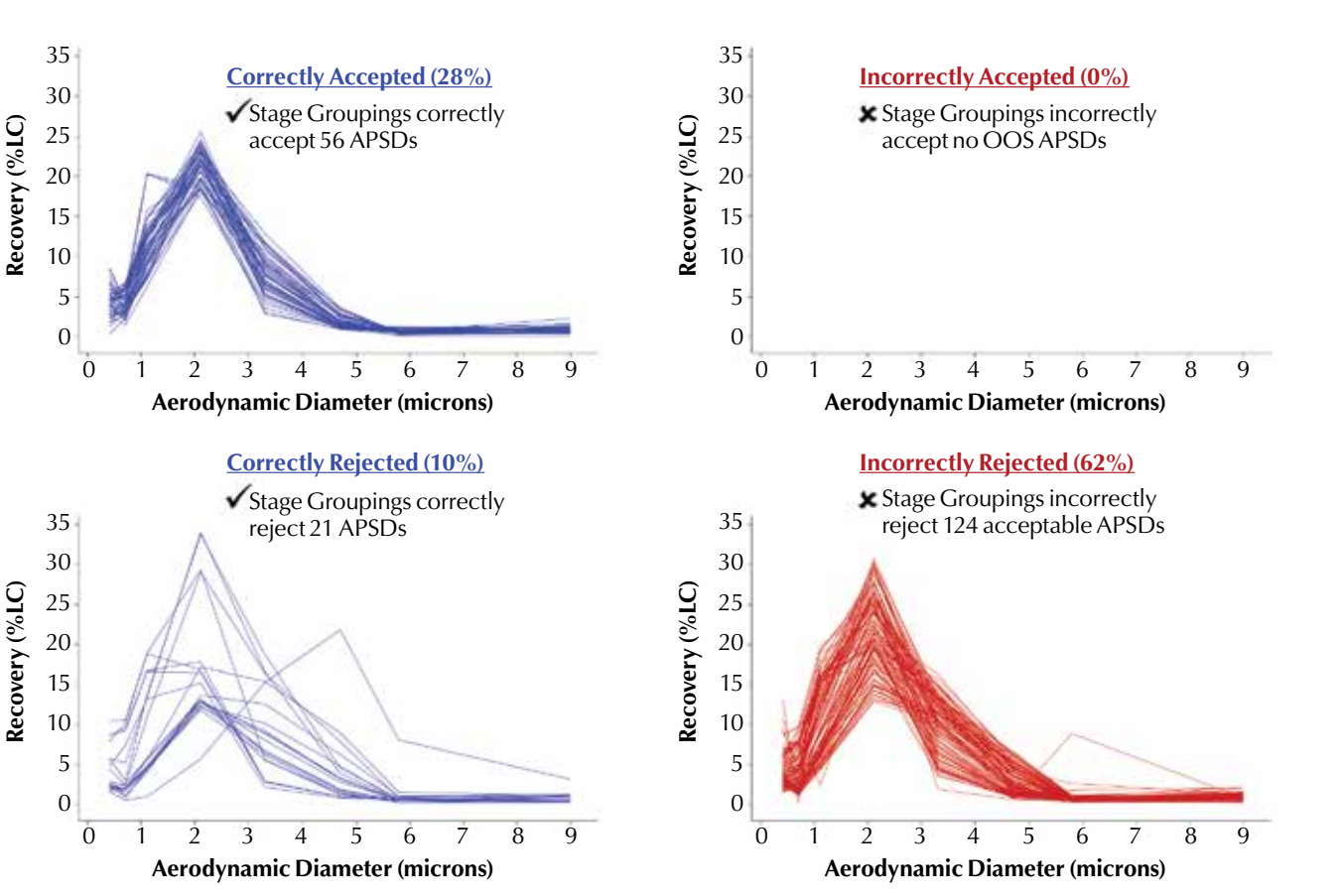
Figure 5 offers a closer look at which APSDs were correctly or incorrectly classified by the stage groupings. At a glance, the correctly classified APSDs in the two blue plots agree with our expectations. Relative to the correctly accepted APSDs, the correctly rejected APSDs appear to deviate from the norm in either their aerodynamic size or their total mass. However, a comparison of the incorrectly rejected APSDs (bottom right, in red) vs. the correctly accepted APSDs (top left, in blue) confirms that the stage groupings are not effective in making batch disposition decisions. It is very difficult to rationalize what makes these "incorrectly rejected" APSDs unacceptable, as it appears that many of them closely match the pool of accepted APSDs. Put simply, *the stage grouping specifications are not doing the job they are intended to do.*

Why do stage groupings fail?

So, let's take a look at why stage groupings fail to track changes in MMAD and ISM and consequently are not well-suited for making sound batch disposition decisions. There are essentially two contributing factors: 1) the nature of the stage grouping metrics (i.e., how reliably they predict important changes in APSDs); and 2) their simultaneous application (a multiplicity issue that compounds the rate of incorrect decisions). Looking back at the plots in Figure 3, where each stage grouping is plotted vs. both MMAD and ISM, we can begin to understand the problem. If we first consider the dependence of each grouping on MMAD (left plot), we can see that Groups 2 and 4 exhibit a sensible correlation with MMAD. That is to say, as the aerosol coarsens, the mass in Group 2 (> 3.3 microns) increases and there is a corresponding decrease in Group 4 (< 0.7 microns). However, Group 3, containing the majority of the API mass, shows little correlation with MMAD. As such, when we attempt to use stage groupings to monitor the size of the aerosolized API, Group 3 contributes primarily noise to the process. You can think of the utility of a stage grouping as a function of both the slope of its response (i.e., the magnitude of the change in the stage grouping elicited by a change in the MMAD), as well as the variability around that trend line (i.e., how reliably does the stage grouping metric predict that change). In the case of Group 3 responding to changes in MMAD, the variability dwarfs the slope and drowns out any sensible response. In other words, by introducing noise, the inclusion of Group 3 impairs our ability to assess MMAD changes.

Figure 5

APSDs are grouped according to their classification by stage groupings, relative to the target ISM and MMAD limits. Correct assignments (blue, left) account for 38% of the APSDs. No APSDs were incorrectly accepted but 62% of all APSDs were incorrectly rejected (red, lower right).



Looking at the right-hand plot in Figure 3, where each group is plotted against ISM, we see the situation is reversed. Not surprisingly, Group 3 exhibits a relatively strong correlation with ISM (after all, it does contain the majority of the ISM). We see a large response in the Group 3 metric and the variability is relatively low. As such, we should expect Group 3 to reliably predict changes in the mass of the APSD. Meanwhile, the meager responses of Groups 2 and 4 relative to their considerable variability, mean that they contribute primarily noise to our effort to detect changes in ISM. So, when we are attempting to track changes in the mass dimension of an APSD, it is the inclusion of Groups 2 and 4 that degrade our ability.

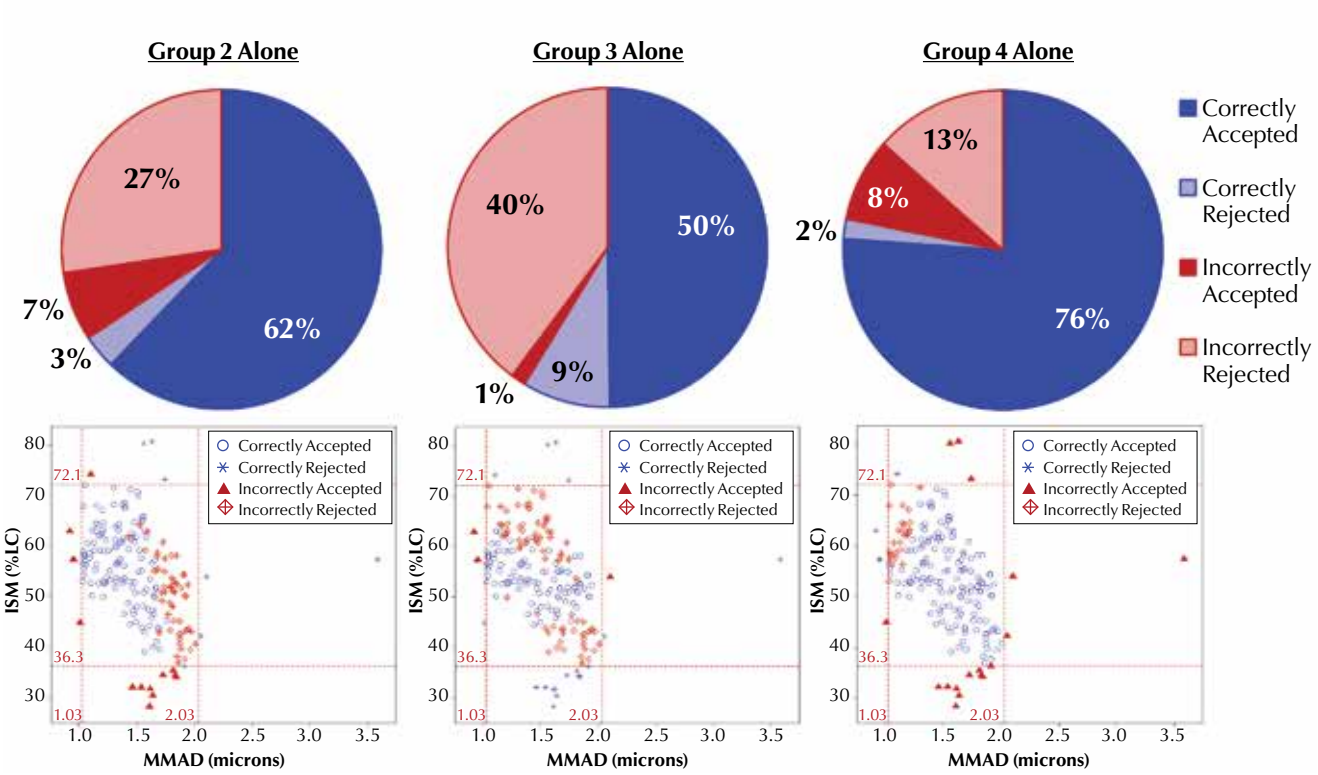
As an analogy, if you want to keep an eye on the stars in the night sky, and also on microbes in the soil, it sounds intuitively good to keep both a telescope and a microscope on hand. This would indeed be a good choice of tools, unless of course, you use *both* the telescope *and* the microscope to evaluate *both* the stars *and* the microbes. That is to say, if you viewed the stars through both the microscope and the telescope, and then gave equal weight to the view provided by each instrument, you would likely have difficulty making sense of the stars. Similarly, your evaluation of microbial life would be rendered worthless if you used both the telescope and the microscope, and then considered the view offered by each when making your assessment. This analogy may sound absurd, but this is essentially what you do each time you use all three stage groupings to evaluate both the size and mass of an APSD.

This is at the heart of the multiplicity issue. One might assume that since you have one metric that correlates well with ISM (Group 3) and another two that appear to track MMAD (Groups 2 and 4), that the combination of these metrics would successfully track both ISM and MMAD. This sounds intuitively good, but when used in combination, *the incorrect decision rates for each individual metric are compounded to yield a much higher incorrect decision rate based on combined outcomes.* This is a prime example of multiplicity, a well-understood concept essential to measurement science and a central consideration in the design of clinical trials.

To illustrate the importance of avoiding multiplicity, let's examine its impact on your product in a batch-disposition scenario. The standard application of stage grouping limits is so detrimental to APSD control that it would actually improve if we relied on any one stage grouping individually, abandoning the rest of the APSD data. This point is illustrated in Figure 6 where we examine the performance of each stage grouping applied individually. You may be shocked to learn that any individual stage grouping outperforms the combined groupings by a dramatic margin. Even the use of Group 3 alone classifies almost 60% of the APSDs correctly, despite its poor correlation with MMAD. Meanwhile, Group 2 performs slightly better (65% accuracy) and Group 4 correctly classifies 78% of the

Figure 6

APSD classification by individual stage groupings. Pie charts summarize each group's individual performance in correctly classifying APSDs based on their size and mass, as shown in the lower plots of ISM vs. MMAD.



APSDs. In this example, the conventional use of all three stage groupings is also outperformed by any combination of two stage groupings. This means, that if you only had stage grouping data with which to monitor your product's APSD, the conventional application of all three stage groupings would actually be the worst of your seven possible options. So, if each time you came to disposition a batch, you chose at random which combination of stage groupings to use, six out of seven times (> 85% of the time) you would end up with a better option than what is typically asked of your lab. *Clearly, the simultaneous application of the three stage groupings profoundly degrades your ability to monitor and control APSD changes*.

Context and implications

So what do all these shocking performance figures actually mean? The answer is simple: they mean that the typical practice of using stage grouping limits to control APSD data is deeply flawed and ineffective. That said, the performance figures reported in Figure 4 do not mean that the use of the mandated stage grouping limits will cause you to discard 62% of the batches you manufacture. The reason for this is that the approach taken here (deriving stage grouping limits from MMAD and ISM limits) yields more restrictive stage grouping limits than would likely be chosen for a given product. Additionally, inhaler QC testing often has mitigation strategies such as tiered testing to accommodate analytical variability and limited sample sizes. Does this then mean that the example presented here is irrelevant due to the selection of more restrictive limits? Not at all. Rather, this means that so-called "realistic" stage grouping limits (i.e., those that would not reject a huge percentage of batches) have extremely limited ability to monitor APSD changes. In other words, if stage groupings are used, their limits must be set so wide that they have very little meaningful utility.

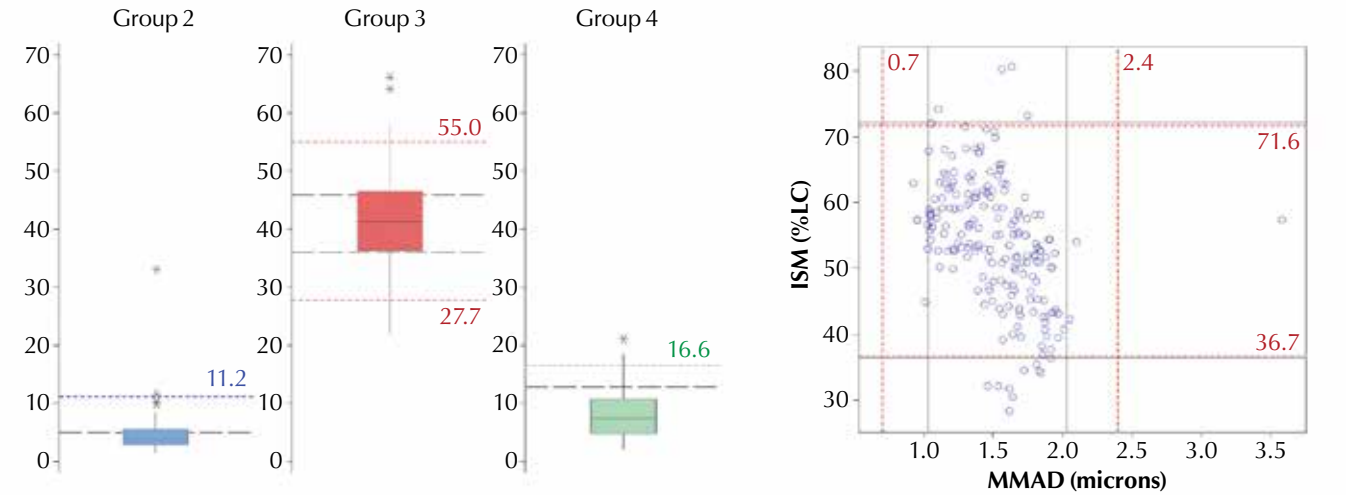
To appreciate what this would mean for the APSDs we have been working with, consider the plots in Figure 7. The left-hand panel presents the stage grouping data as box-and-whisker plots, with two sets of limits indicated by the horizontal reference lines. The black lines show the limits for each group, which were previously translated from the MMAD and ISM limits (see Table 2). The colored reference lines show an alternative set of limits, this time derived directly from the stage grouping data, as would be more typical for OIP specification development. Note that these limits were derived in accordance with publicly provided examples of stage grouping limits,[7] with Group 3 limits set at ± 33% of the Group 3 median, and limits for Groups 2 and 4 set at 20% and 30% of the Group 3 upper limit, respectively.

One can immediately see that the limits derived directly from the stage grouping data are considerably wider than those translated from the MMAD and ISM limits. Indeed, many readers might observe that the limits imposed by our translation exercise (shown in black) are not a good match for these stage grouping data. The Group 3 limits are essentially at the quartiles of the population, therefore excluding half of the APSDs, and the Group 2 upper limit is even more restrictive. The result of this mismatch between these data and their imposed limits is, of course, the huge number of rejected APSDs, as shown in Figure 4.

On the other hand, the limits designed to accommodate the stage grouping data (color-coded and labeled) at least appear as though they would exclude a more reasonable portion of the APSDs. If, however,

Figure 7

At left, stage grouping data from the 201 APSDs are summarized in the box and whisker plot, showing the median and quartiles for each. Colored reference lines show limits proposed for control of the stage groupings. Black reference lines show the previous limits translated from the MMAD and ISM limits. At right, ISM is plotted vs. MMAD for each APSD, illustrating the impact of deriving limits from stage grouping data (dashed red lines) compared to the original MMAD and ISM limits (black lines).



we look at the right-hand plot in Figure 7, we can see that these alternative limits leave much to be desired if your aim is to control the product's APSD. As before, the APSDs are represented here in terms of their two dimensions, ISM (mass) and MMAD (size). In addition to the original limits assigned to each metric (solid, black reference lines), the ISM and MMAD limits corresponding to the alternative stage grouping limits are shown via dashed, red lines. Although the wider stage grouping limits certainly result in the rejection of fewer APSDs, it is interesting to note that the ISM limits are essentially unchanged. In other words, our decision-making ability with respect to the mass of the distribution remains the same. In contrast, though, the MMAD limits have widened to the point that, aside from a single extremely coarse APSD at MMAD of 3.5 microns, all APSDs fall within the MMAD limits by a comfortable margin. In other words, by adopting these more "realistic" stage grouping limits, we have essentially sacrificed our ability to discriminate based on the size of the APSD. So, regardless of whether you set the limits intended to control the APSD (as in Figure 4) or only to control the stage groupings themselves (as in Figure 7), you quickly arrive at the same conclusion: stage grouping limits are not suitable for making batch disposition decisions based on changes in your product's APSD.

Conclusions

The use of stage groupings to control cascade impaction data is fundamentally flawed and ineffective. The individual stage groupings do not adequately account for both dimensions of the size-fractionated mass comprising the APSD, and their combined use compounds this weakness to dramatic effect. Clearly, stage groupings cannot be relied upon for batch-disposition decisions and are therefore a liability to the guarantee of safe and efficacious medicine for the patient.

In the first two articles of this series, we have scrutinized the two most common approaches to APSD control: fine particle dose and stage groupings. Neither approach was found to satisfactorily detect changes in APSD. Neither approach can be relied upon to observe atypical product performance. The continued preference for these metrics by health authorities is somewhat curious, for they do not benefit the patient, the payer, the regulator or the producer. Moreover, there are alternatives to fine particle dose and stage groupings that reliably report APSD changes. In our third and final article in this series, we will recommend such metrics and demonstrate their ability to detect changes in either the size or mass of an APSD, thus enabling the user to make batch-disposition decisions based on the performance of their product.

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

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