Limitations of metrics used in the regulation of aerodynamic particle size distributions (APSDs) of orally inhaled products (OIPs)

An interview with Adrian Goodey of the IPAC-RS Cascade Impaction Working Group on reactions in the inhaler community to a series of published articles

In 2020 and 2021, *Inhalation* published a three-part series of articles by the Cascade Impaction Working Group of the International Pharmaceutical Aerosol Consortium for Regulation and Science (IPAC-RS), written by authors Adrian Goodey, Jolyon Mitchell, Bill Doub, Dave Christopher and Ian Carter:

- The liability of fine particle dose (FPD)
- Cascade impactor stage groupings: Poor decisions from degraded data
- Efficient data analysis (EDA): Size, mass and common sense

The first and second articles discussed limitations of metrics commonly used in the regulation of aerodynamic particle size distributions (APSDs) of orally inhaled products (OIPs). The third article proposed using independent assessment of the dimensions of APSD (size and mass) by Efficient Data Analysis. The articles were written to educate, dispel common misconceptions, raise awareness of risks and encourage scientists to scrutinize current practices.

In this interview, *Inhalation* talks with author Adrian Goodey about reactions to the articles in the inhaler community since their publication.

Vicki Schuman, Editor and Publisher, Inhalation: The second article in the series exposed some significant problems with stage groupings, a common regulatory request for aerodynamic particle size distribution (APSD) control. What sort of reaction has this work precipitated since its original publication in August of 2020?

Adrian Goodey: Overall, we've been really pleased with the reaction to this article, as well as the other two articles in the series. When we discuss our findings with other scientists in the field, they're clearly somewhat shocked at first, and that usually prompts genuine interest. Once they understand the limitations of Stage Groupings and Fine Particle Dose, and how poor they are at discriminating between different APSDs, they want to know why they are still being asked to use these metrics. None of us like doing things that don't make sense to us, especially when you consider the investment made in cascade impaction testing and the importance of batch-disposition decisions. So, I'd say we have had a lot of positive feedback from our peers and that's always rewarding.

We've also gained some interest from health authorities and pharmacopeial organizations. At least, we've opened dialogues with a couple of groups, and their initial responses have been relatively promising. In general, whenever we've had the chance to discuss the work with our regulatory and/or pharmacopeial partners, they're quick to understand the problem

and readily acknowledge the shortcomings of the status quo. That said, any actual progress towards regulatory acceptance is imperceptible, which is obviously frustrating.

Inhalation: Why do you think that is?

Adrian: There may be multiple reasons, but ultimately, I think it's important for us to focus on what we can control. We can't force these groups to act, nor can we streamline their processes. What we can do is raise awareness of these issues within the orally inhaled and nasal drug product (OINDP) community. If drug development teams choose not to change their practices, or regulators choose not to change their requirements, that's up to them. What we can do is ensure—through education and communication—that their decisions are not made in ignorance. To that end, we will of course continue our efforts to publish and present on this topic and we are also exploring the possibility of organizing a forum to facilitate dialogue among stakeholders.

Inhalation: What advice or guidance would you offer to drug development teams facing this disconnect between scientific developments and regulatory expectations?

Adrian: First of all, I'd say, "don't lose hope." It's really easy to get demoralized when regulation lags behind science. We (the Cascade Impaction working group of IPAC-RS) are frequently dismayed to find that authorities are either utterly unaware of our work or simply choose to ignore it. We just keep advocating for what makes sense to us, and that's basically what I would offer as advice to development teams.

I believe that there are multiple ways to effect change and that industry has an opportunity to lead the way. The articles we published focused on the use of APSD metrics in the commercial Quality Control environment, on making batch-disposition decisions based on differences in APSD. However, the appropriate choice and use of APSD metrics is important throughout the development of a product. The fundamental problem with stage groupings and fine particle dose is that they tell you so little about your product's performance. So, for example, if you were to rely on fine particle dose or stage groupings to guide formulation and process development, you could end up in a real mess.

Scientists need clear, sensible feedback and that necessitates the use of other APSD metrics during development. Our hope is that more and more teams will monitor both size and mass throughout development and will ultimately propose size-based and mass-based APSD metrics at filing. We expect that as regulators encounter more and more real-world examples in which metrics are used to make sensible, rational distinctions between APSDs, they will become less and less comfortable maintaining the status quo. We have to believe that they will not be comfortable asking for things like stage groupings in the face of better science based on real-world evidence.

Inhalation: Both this article and the subsequent article contrast stage groupings to a system of metrics you refer to as EDA (efficient data analysis), where one simply monitors the size and mass of the APSD. How has this proposed approach to APSD control been received?

Adrian: Responses run the whole spectrum. Some people immediately understand the need to track both dimensions of the data and appreciate the simplicity of the approach. Others are just annoyed by the prospect of having to update their validated cascade impaction spreadsheet. Within the industry, there is definitely some trepidation about adopting an approach that has not yet received the blessing of health authorities. I think the important thing for teams to consider here is that incorporating EDA data into a regulatory submission is a relatively small investment. There is no additional testing or lab work; it's just a matter of calculating and reporting the necessary metrics (impactor-sized mass (ISM) and mass median aerodynamic diameter (MMAD), for example) from existing data.

We also encounter a lingering misconception that EDA necessitates the adoption of an abbreviated impactor measurement (AIM) method. I see where this idea comes from, but it's important to understand that the metrics and the test method are largely independent of each other. EDA, stage groupings and fine particle dose could each be calculated from either a full-resolution impactor or from abbreviated impactors. Similarly, our recommendation to use metrics sensitive to both size and mass applies equally to both full-resolution and abbreviated impactor data. They also represent different investments. Choosing to use EDA is a matter of calculating certain APSD metrics and using them to control your product's performance, regardless of your impactor configuration. In contrast, choosing AIM entails developing and validating an additional cascade impaction method using a reduced impactor configuration, which is a very different investment. I don't want to discourage teams from investing in AIM, because the potential benefits are significant, but it is not inherently linked with EDA. Most importantly, the value of EDA does not depend on the use of AIM; the value of EDA is in its ability to make rational distinctions between APSDs.

The three articles can be seen by clicking on the titles below and found in the *Inhalation* article archive: www.inhalationmag.com/articles

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We are also delighted to republish the stage groupings article on the following pages of this issue.

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