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Mr. Mario Sindaco

Vice President, Science Operations

USP

Via email mys@usp.org

9 September 2019

RE: Responses to comments on the Stimuli Article **The Application of Abbreviated Impactor Measurement and Efficient Data Analysis in the Lifecycle of an Orally-Inhaled Product: A Roadmap** [Pharmacopeial Forum (PF), Vol. 44, No. 4]

Dear Mr. Sindaco,

Thank you for the opportunity to review and respond to comments submitted by the US Food and Drug Administration (FDA) Center for Drug Evaluation and Research (CDER) Branch Chief for Compendial Operations and Standards Branch, in the Office of Policy for Pharmaceutical Quality (REF: 09-18-022-J).

The stimulus article [1] was authored by the Cascade Impaction Working Group of the International Pharmaceutical Aerosol Consortium for Regulation and Science (IPAC-RS, http://ipacrs.org). IPAC-RS is a non-profit association committed to the advancement of science-based approaches to the development, manufacturing and regulatory assessment of orally inhaled products (OIPs) and intranasal drug products. Evaluating particle size of aerosols generated by these products is an important task for product design and development, as well as for subsequent quality control. Particle size distributions also play a role in establishing in-vitro bioequivalence of generic OIPs. Yet, current compendial methods for measuring particle sizes are complex, prone to human error, labor-intensive and time-consuming. Furthermore, there is currently almost no guidance in the US Pharmacopeia regarding analysis of the particle-size data most appropriate to a given context (e.g., early product development vs. commercial batch release vs. in-vitro equivalence comparisons of different products).

The stimulus article [1] explained how Abbreviated Impactor Measurement (AIM) and Effective Data Analysis (EDA) could be used to streamline particle-size measurements and context-appropriate data analysis. Both AIM and EDA concepts had been thoroughly researched through theoretical and experimental work, extensively reported on through peer-reviewed publications and in scientific conferences over a number of years starting in the mid-2000s, and have been used by experts in the field both among IPAC-RS member companies and the wider community.

Including AIM and EDA options would strengthen the US Pharmacopeia and would provide much-needed guidance to newcomers in the field.

IPAC-RS recognizes, however, that the practical and technical details of particle-size testing and data analysis may require a focused discussion of all interested stakeholders to be fully understood and appropriately applied. We are pleased, therefore, to provide detailed responses to the comments in the FDA/CDER letter referenced above. Furthermore, we encourage USP to convene a public meeting with participation of FDA, IPAC-RS, and other scientists and regulatory professionals, as a way to clarify any misunderstandings, facilitate wider adoption and standardization of AIM and EDA in appropriate situations (as explained in the stimulus article), and thereby to modernize pharmacopeial approaches to particle-size evaluation of orally inhaled products.

We looks forward to further dialogue with you and FDA CDER, including not only representatives from the Compendial Operations and Standards Branch but also those in CDER who review applications for brand-name and generic OIPs (New Drug Applications and Abbreviated New Drug Applications) and those who conduct research of in-vitro and quality control methods for pharmaceutical aerosols.

Sincerely,

[SIGNATURE edited]

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Cc:

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RESPONSES TO COMMENTS

1. In the INTRODUCTION,

a. TABLE 1 indicates that the applicability of AIM for product registration and commercial production in product QC is high. Current agency thinking is that the full resolution of APSD data is required for product registration and release/stability of commercial batches. Additionally, considerable evidence is needed before AIM could be considered for product registration, or QC. Therefore, we recommend that the applicability of AIM be changed to low for product registration and commercial production in product QC.

Response: We respectfully disagree with the Agency's comment that the applicability of AIM for product registration and/or QC is "Low". We understand that the Agency's current position is that registration and QC APSD data be collected using a "full resolution" CI and that the individual stage recoveries be combined to yield 3-4 groupings for control purposes. However, the aim of our stimulus article was, and is, to articulate how and when to best leverage the advantages offered by both AIM alone and AIM in combination with EDA during the lifecycle of an OIP.

At the outset, we would like to make clear that we are not proposing that AIM/EDA would simply replace all use of current CI-based measurement practices. As stated in the text of the Stimulus Article, we see significant opportunities for AIM *both* early in development (e.g., to facilitate formulation screening), and also for AIM/EDA in the QC setting, where APSD testing is performed solely for the purpose of making batch disposition decisions. We acknowledge the value and utility of using full-resolution CI techniques to *characterize* the APSD during development. However, it is critical to understand the distinction between these two different tasks: *characterization* (as needed during development) and *batch disposition* (as needed in the QC environment).

A considerable body of evidence has been published during the past decade explaining the theory and practice of AIM/EDA, and, importantly, consistently demonstrating the superiority of AIM/EDA over stage grouping metrics derived from conventional CI methods, for making batch disposition decisions in the QC environment.

Our position is that the conventional CI always offers value during product development, and, in addition, this configuration should be retained as an option to investigate OOS or OOT results in the QC environment. However, we maintain that, as a primary QC test, use of a conventional CI does not offer any additional value relative to AIM/EDA. This position has been carefully developed, and is by now is supported by a number of peer-reviewed publications. In particular, I would refer you to two key articles, the first focusing on the apparatuses, the second focusing on the metrics.

The first article [2] reports results from a rigorous, multi-laboratory experiment which ultimately demonstrates that an AIM apparatus is sufficiently sensitive to changes in the APSD of an OIP, that it can be used to make batch disposition decisions just as well as can a full-resolution CI. In this particular study, the OIP was a commercially available albuterol pMDI, the full-resolution impactor was an Andersen CI, and the AIM apparatus was a

reduced Andersen CI, both configured for measurements at 28.3 L/min. In summary, this work refutes the notion that data from more CI stages improves the ability to detect changes in the underlying APSD. We recognize that this example, by itself, does not ensure that all AIM methods are appropriate or adequate for control of all OIPs. As with any analytical method, the sponsor would need to demonstrate the suitability of a specific AIM method for control of an individual product.

The second article [3] focuses on the performance of stage grouping metrics vs. that of the EDA metrics for making batch disposition decisions. This exercise draws on a large database of APSD release and stability data from OIPs marketed by IPAC-RS member companies. The product identities were and are still blinded from members of the CI Working Group, and all the data were collected using conventional, full-resolution impactors. The conclusions of this work are clear and compelling: relative to the EDA metrics, the multiplicity introduced by using three stage groupings to control an APSD *increases risk to the consumer* (i.e., increased likelihood of releasing a batch inappropriately) *and increases risk to the producer* (i.e., increases the likelihood of rejecting a batch unnecessarily). The harm associated with increasing risk to the patient presumably needs no further discussion. It is worth considering, however, that the increased risk to OIP producers from unnecessary batch rejection also impacts patients as it ultimately hampers efforts to reduce costs and increase availability.

We appreciate that these references are dense, highly technical texts. While this level of detail is unavoidable if the analyses are to be conducted in a scientifically defensible manner, we do recognize that the complexity of the subject matter may limit the accessibility of the work. In an attempt to mitigate this limitation, our group has created a publicly available online tutorial comprised of narrated slide decks covering numerous aspects of CI theory and practice [4]. Module 5.2 of the tutorial focuses on the performance comparison of stage groupings vs. EDA (reference 2), and is intended to serve as a companion to the peer-reviewed article.

b. TABLE 2 (3) AIM Alone states "Sufficient for making decisions in QC setting…". Based on current agency thinking, full resolution of APSD data is needed for QC testing of commercial OIP.

Response:

As articulated in our response to comment 1a, we respectfully disagree with the Agency's position regarding the relative utility of AIM vs. full resolution CI for commercial QC.

It is also pertinent to appreciate that the Agency actually does not currently require full resolution APSD data for commercial QC testing, as stated above. Rather, in our experience, batch disposition decisions for the US market are made using stage grouping metrics. These groupings represent a considerable reduction in the resolution of the APSD from about 8 points down to 3-4 groupings. More significantly, however, the way in which the groupings are then used introduces multiplicity to the analysis, which leads to misclassification in batch disposition decisions. The use of three groupings to control the

size-fractionated portion of the APSD confounds the two orthogonal dimensions of the APSD, namely the total amount of drug and the size distribution of that drug.

So, from our perspective, although the Agency may require full-resolution CI *testing* to be performed, full-resolution CI *data* are not actually used for batch disposition in commercial QC. Perversely, this strategy of QC testing represents the worst of both worlds: it requires significantly more resources than AIM, but is inferior to AIM/EDA for making batch disposition decisions [3].

c. TABLE 2 (4) EDA with AIM states "Can detect APSD changes with sensitivity to those similar to those of other published methods". We suggest that a reference be provided to support this statement. Additionally, clarifying information should be provided about the other published methods.

Response:

As articulated in our responses to the previous comments, a number of peer reviewed works [e.g., 5, 6] demonstrate the ability of AIM/EDA to detect APSD changes with sensitivity similar to those of other APSD characterization methods. Specifically, here the authors were referring to conventional CI methods (e.g., Andersen or NGI based methods relying on either stage groupings or fine particle dose) [5].

d. TABLE 2 (5) EDA with Full-Resolution CI states "Sufficient for making decisions in QC setting…". Based on current agency thinking, considerable evidence is needed before EDA could be considered for use in QC settings.

Response:

The authors respectfully disagree with the Agency comment. Please refer to the response to comment 1a for detail.

e. TABLE 2 (5) EDA with Full-Resolution CI states "EDA offers fewer cases of incorrect rejection in batch release." We do not agree with this statement, although that EDA may offer fewer cases of incorrect rejection in batch release.

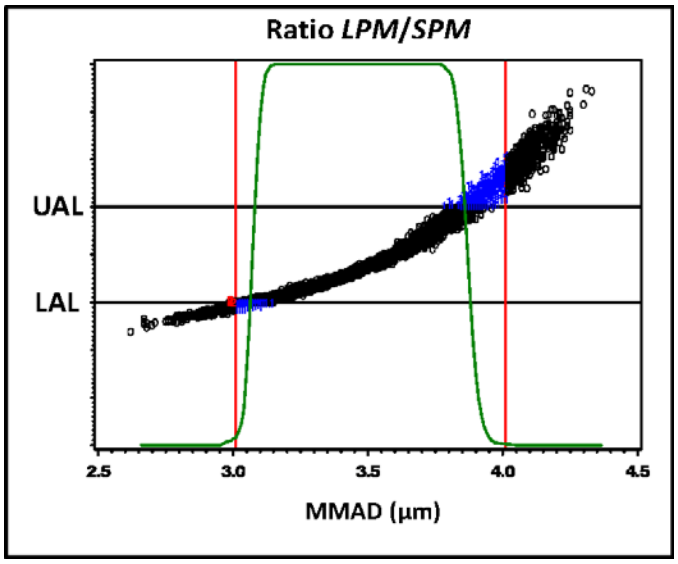
Response:

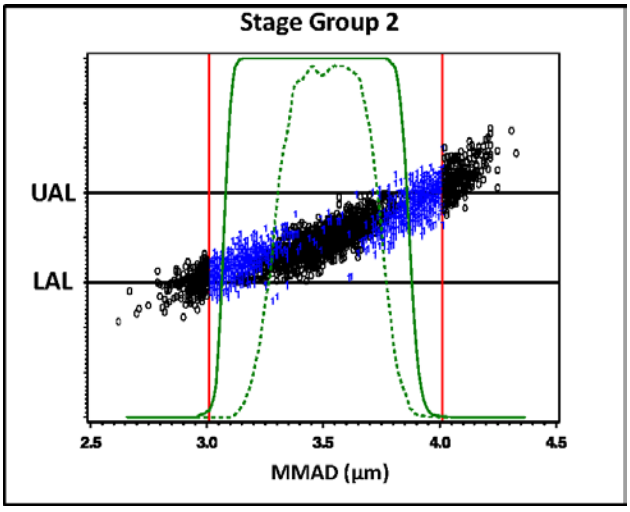
The authors respectfully disagree with the Agency comment. The basis of batch release depends on detecting changes in the underlying APSD, and EDA has been demonstrated to be more sensitive to changes in the APSD than stage groupings to such changes. Moreover, EDA has been demonstrated to have the ability to result in fewer instances of batch misclassification than stage groupings [3].

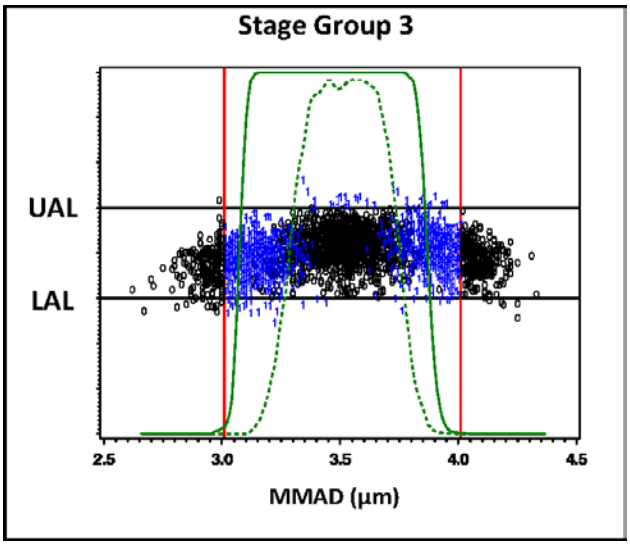
The following plots of operating characteristic (OC) curves and text from [3] provide the basis for our response. The first plot shows outcomes and the OC curve for EDA. In each

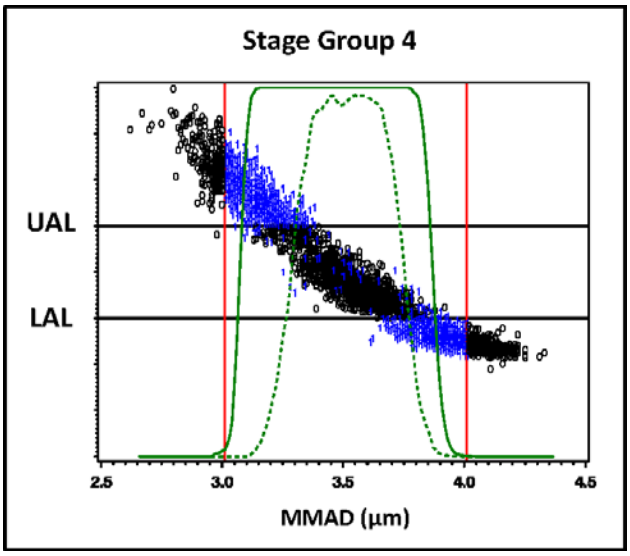
of the three-stage grouping plots the stage grouping outcomes and OC curve (dashed green curve) are based on the combined results of all three groups. The OC curve for EDA (solid green curve) is superimposed for comparison.

The blue plot symbols represent the instances of batch misclassification from incorrect batch rejection, quantified in Table 8.9 in [7] as 20.81% for EDA versus 48.04% for stage groupings, which show that stage groupings result in more than twice the rate of incorrect batch rejections. And as noted in the accompanying text, the nature of the incorrect rejections is reflected in the different shapes of the OC curves, which for stage groupings never reaches 100% at any point within the range of acceptable product characteristics.









Incorrect decisions which only occur near the boundaries of the acceptance region produce an OC curve with relatively steep sides and a flat top across the major portion of the acceptance region. This contrast can be observed in the figures by comparing the shapes of the OC curves and the pattern of incorrect decisions. The EDA ratio exhibits a broad flat curve with relatively steep sides compared to the Grouped-Stage OCC, which never attains 100% probability of passing even in the center of the acceptance region. The false rejection outcomes represented by the blue plot symbols occur consistently further away from the boundaries of the acceptance region, and even through the middle of the region for the Grouped-Stage approach than for the EDA ratio approach.

f. The FIRST PARAGRAPH following Table 2 states "…in the product QC environment, individual-stage data are seldom reported, and seldom needed." We note that this statement may not always apply, such as in the QC environment when an OOS occurs, individual stage data may be needed.

Response: The authors agree with this comment. Our position is that full-resolution CI should always supplement AIM/EDA in an investigation of OOS/OOT results.

g. The FIFTH PARAGRAPH following Table 2 states "All are unlikely, and should be explored during the development of a particular product." We recommend the removal of "All are unlikely".

Response: The authors respectfully disagree with the agency comment. Based on widely accepted mechanisms behind aerosol generation and transport, the listed scenarios are indeed highly improbable [8, 9]. We would welcome discussion on this topic if the Agency requires a more detailed explanation.

h. FIGURE 2 indicates AIM be used as the primary QC test, with ACI used as the secondary test to probe for OOS results. Based on current agency thinking, considerable evidence is needed before AIM could be considered in QC settings.

Response: The authors acknowledge the current Agency position. The purpose of the stimulus article is to offer the opportunity to improve the current practices of APSD characterization in the context of OIP quality control.

2. Comments on the AIM AND EDA IN THE PRODUCT LIFECYCLE section,

a. THIRD PARAGRAPH states "Shifts in APSD could be detected by using either EDA or the traditional measures of central tendency (i.e. MMAD) and spread [i.e., geometric standard deviation (GSD)…". Based on current agency thinking, MMAD and GSD are thought to be insensitive to detecting shifts in APSD and are not currently used by the agency to detect any APSD shifting.

Response: We understand that the Agency currently does not request MMAD and/or GSD for control of APSDs. Furthermore, we fully acknowledge that in the absence of other metrics, MMAD and GSD are, by themselves, insufficient for APSD control. However, we strongly disagree with the Agency's comment above that MMAD is insensitive to shifts in APSD. It is well understood and widely acknowledged that the MMAD of an aerosol is the single best metric for monitoring shifts in the *aerodynamic size* of the APSD (i.e., whether the APSD is finer or coarser). It tells us nothing about the *amount* of drug delivered (or, more specifically, the mass of drug captured in the impactor stages). However, if calculated appropriately, we contend that MMAD is highly sensitive to changes in the size of the aerosol particles/droplets.

As mentioned above, the orthogonality of the size and mass dimensions of the APSD necessitate the use of multiple metrics to adequately characterize or control the APSD. This same orthogonality of size and mass also contributes significantly to the sensitivity of the MMAD to size changes in an APSD. For example, mass-based metrics attempting to control the size of an APSD are inevitably subject to any variability in dose delivery. The MMAD, on the other hand, is independent of the total mass, and therefore does not fluctuate with delivered dose.

b. THIRD PARAGRAPH states "Later in the lifecycle, the methodology and supporting data for the validated AIM-based procedure are submitted to the regulatory agency(ies) for approval of the OIP as a key part of the in-vitro performance component of the dossier." Based on current agency thinking, considerable evidence is needed before AIM could be considered in QC settings.

Response: The authors acknowledge the current Agency position. The purpose of the stimulus article is to offer the opportunity to improve the current practices of APSD characterization and OIP quality control.

c. FOURTH PARAGRAPH states "Once the product is commercialized, it is envisaged that the approved AIM and/or EDA-based methodology would become the mainstay for batch release testing." Based on current agency thinking, considerable evidence is needed before AIM could be considered in QC settings.

Response: The authors acknowledge the current Agency position. The purpose of the stimulus article is to offer the opportunity to improve the current practices of APSD characterization and OIP quality control.

3. In the COMPENDIAL ACCEPTANCE OF AIM AND EDA CONCEPTS section,
a. THIRD PARAGRAPH states "By contrast, the US regulatory position concerning OIP quality standard measures seems more amenable to the adoption of AIM and EDA…" We currently do not use AIM or EDA based data for product registration, and there are no current plans to use this data in the near future. We are currently unable to support this statement without reference.

Response: The authors acknowledge the current Agency position. The purpose of the stimulus article is to offer the opportunity to improve the current practices of APSD characterization and OIP quality control.

4. General Comment:

The agency continues to have similar concerns related to the previous conveyed comments to USP related to the IPAC-RS for "Benefits of Alternative Cascade Impaction Techniques and

Measurements Related to the Quality Control (QC) Of Aerodynamic Particle Size Distribution (APSD) Of Orally Inhaled Drug Products (OIPS)".

Response: The authors acknowledge the current Agency position. The purpose of the stimulus article is to offer the opportunity to improve the current practices of APSD characterization and OIP quality control.

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