

FIA – Where the AIM Is Quality Control

Successful inhalation products require rigorous quality control (QC) testing throughout the product life-cycle, including measurement of the total dose and fine particle dose (FPD) of the emitted aerosol. This long-term need for repeated measurements lends itself, in concept, to automatic equipment. However, automation of the FPD has proven extremely challenging, successfully accomplished by only very few pharma companies and at a substantial expense. FIA is now changing that equation together with its partners.



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Materials and Methods for AIM

"I was impressed when I first learned of FIA's proven approach to automated dosing equipment. The light bulb went on immediately – this is perfect for abbreviated impactor measurements (AIM)," says Dr. Daryl Roberts, co-inventor of the Next Generation Impactor (NGI) and now president of his own consultancy, Applied Particle Principles.

FIA's Automated Measurement System applied to the AIM concept has been worked out together with Dr. Mårten Svensson at Emmace Consulting and is based on established automation concepts.¹

The dose aerosol is separated into two size-fractionating components by two standard Fast Screening Impactors from MSP, Figure 1, that are mounted above a fritted glass collector, Figure 2, from which drug product can manually or automatically be recovered and quantified. These components are part of a complete automated dosing and analysis station manufactured by FIA. With proper choice of the size-fractionating components, the recovered drug product can be either the FPD or the large particle mass (LPM) or the small particle mass (SPM). Here we present the scientific rationale behind the AIM concept applied to a QC situation.



Figure 1. Two FSIs used alternating on top of the sampling apparatus in Figure 2.



Figure 2. Sampling apparatus for the emitted dose (principle as of reference 2); in the AIM concept the particles have passed through one of FSIs in Figure 1 before being collected in the apparatus.

Technical Rationale for the Adequacy of Having Two Size Fractions for Quality Control of Newly Approved Inhalable Drug Products

A key element underlying the technical adequacy of an 'abbreviated' impactor measurement is the question of WHEN to introduce the abbreviated measurement. The proper time is during the late stage of development, AFTER full resolution impactor measurements have adequately characterized the size distribution of the batches released for clinical trials. These batches should be released with Full Resolution Impactor (FRI) measurements AND with properly chosen AIM, specifically having just two size fractions. That way, when and if the clinical trial results show the desired safety and efficacy, the most cost-effective analytical method for the routine quality control tests for the release of commercial product will be the abbreviated measurements with the two size fractions.

The adequacy of measuring two size fractions alone to describe the safety and efficacy of an inhalable drug product was first articulated by Tougas, et al.³ These investigators show that the ratio of the LPM to the SPM produces a more sensitive measure of the mass median aerodynamic diameter (MMAD) than does the conventional method of grouping stages of a full-resolution impactor. The trick is to choose the definition of "large" and "small" so that the ratio of LPM to SPM ranges from approximately 0.8 to 1.2. The user is able, in fact, to make such a choice by examining the FRI measurements made during product development and is able to do so with only two size fractions (LPM and SPM must include only the "impactor-sized mass" – ISM – as discussed by Tougas, et al.).

The math itself is quite straightforward for finding the appropriate split between “large” and “small,” but surprisingly a graphical representation is also sufficient in many cases and can provide a more intuitive confidence in the chosen split. Figure 3 displays a logarithmic bar chart of the mass of active drug product on each stage of an NGI for a commercial metered-dose inhaler.⁴ The y-axis is the mass of active drug product on each stage (stages 1 to 7, right to left). Because of the unique logarithmic spacing of the NGI cut-points, each bar has the same width (same proportionality to the height). Therefore, the area of each bar is proportional to the mass on each stage. The proper split between “large” and “small” is therefore where the total bar area, less the area of the right-most bar (stage 1), is cut in half...and one’s eye can see that this split takes place roughly at 4.5 microns.

So, the two size fractions needed for quality control testing of this particular product would be approximately at 14 microns (the cut-point of NGI stage 1) and 4.5 microns. These size fractions yield either ISM and SPM or yield LPM and SPM, depending on the method of making the measurements (ISM is equal to LPM plus SPM, so only two of these three quantities are independent). These measurements can be made with several commercially available devices, provided that the collective efficiency curves are sharp, such as in the Fast Screening Impactor offered by MSP Corporation.⁵

Validation of any choice of two size fractionations will always need to be established, as described by Tougas et al.³ But once accomplished, the quality control testing for the batch release of commercial product will require only two size fractions, allowing for substantial cost saving over the 20-year to 30-year life of the drug product compared to full-resolution impactor testing, and fully meeting the expected safety and efficacy requirements.

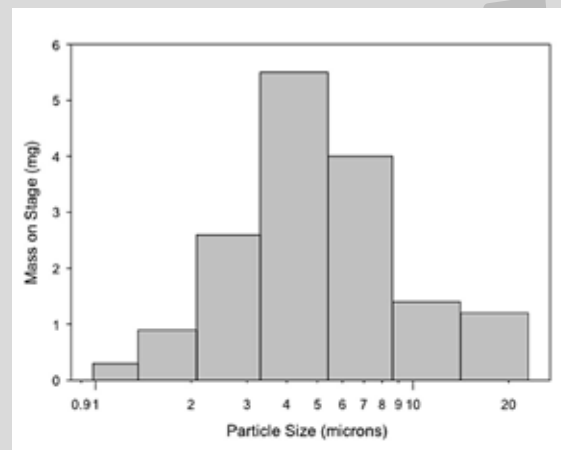


Figure 3 – Logarithmic Bar Chart of pMDI Data Collected with the NGI Operating at 15 L/min

Tougas and co-workers⁶ have shown more recently that particle sizing with two size fractionations is far more able to detect differences in particle size distributions than is the simple measure of FPD (defined in Europe as the mass of active drug product residing in particles smaller than five micron aerodynamic diameter). The main reason for this outcome is that a large fraction of the total mass of active drug is smaller than five microns in a typical commercialized inhalable drug product. Consequently, the FPD dose test is not much different than a total dose test, and therefore the size distribution can change substantially and not be detected at all. The AIM approach is thereby shown to be more sensitive to changes in the size distribution and is therefore a better quality control test than FPD.

References

1. Appelqvist, R., P. Andersson, H. Lundback, T. Löf, B. Olsson, “Automated Dose Measurement Stations – Valuable Players in the Development of Turbuhaler® Inhalers,” presented at 16th International Symposium on Laboratory Automation and Robotics, Boston, MA, October 18-21, 1998.
2. S. Hugosson, J. Lindberg, T. Löf, B. Olsson, “Proposals for Standardized Testing of Powder Preparations for Inhalation”, Pharm Forum, Vol 19, 3:5458-5466, 1993.
3. Tougas, T. P., D. Christopher, J. P. Mitchell, H. Strickland, B. Wyka, M. Van Oort, S. Lyapustina, “Improved Quality Control Metrics for Cascade Impaction Measurements of Orally Inhaled Drug Products (OIPs),” AAPS Pharm. Sci. Tech., 10 (4), 1276-85 (2009).
4. Beigton, J., A. Majid, L. Wojnarowicz, “The Determination of Aerodynamic Particle Size Distribution from a Metered Dose Inhaler Using the Next Generation Impactor,” Drug Delivery to the Lung XV, The Aerosol Society, London, England, December 9-10, 2004.
5. Roberts, D. L., F. J. Romay, “Design of the Fast-Screening Impactor Based on the NGI Pre-Separator,” Drug Delivery to the Lung XX, The Aerosol Society, Edinburgh, Scotland, December 9-11, 2009, part II, pp. 206-9.
6. Tougas, T. P., A.P. Goodey, G. Hardwell, J. Mitchell, S. Lyapustina, “A Comparison of the Performance of Efficient Data Analysis Versus Fine Particle Dose as Metrics for the Quality Control of Aerodynamic Particle Size Distribution of Orally Inhaled Pharmaceuticals,” AAPS Pharm. Sci. Tech., 18 (2), 451-61, 2017.



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Summary

FPD is typically the key quality measure for European regulatory authorities. LPM and SPM are the key measures for the so-called "efficient data analysis" that the US FDA is carefully considering as an adequate QC test for a registered drug product. Bringing together the engineering and quality assurance capabilities of FIA and combine that with the scientific and lab methodology support from APP and Emmace, the customer has the opportunity to implement the best AIM tools for individual customer drug products and to help customers explain to regulatory agencies the rigorous relationship of AIM to the QC necessary for product safety and

efficacy. We can provide a manual lab set-up for AIM as well as a fully automated combined delivered dose and AIM equipment, engineered for each customer's inhaler and choice of cut-off.

"We think customers will be increasingly successful getting regulatory approval of the abbreviated measures of particle size, when it comes to routine quality control testing," says Kjell Fransson, managing director of FIA. "Our equipment will play a key role in the long-term success of these products."

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