USP <601> and <1604> Give Different APSD Results

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Summary

Our study was designed to explore the discrepancy between cumulative aerodynamic particle size distributions (APSDs) prepared using methodologies described in normative chapter <601> of the United States Pharmacopeia (USP) prior to 2015 and current informative chapter <1604>. We applied a model smooth unimodal and log normal APSD with INPUT values of MMAD and GSD of 4.0 µm and 2.0 respectively to the entry to stage 1 of the NGI, configured 'out-of-the-box' without pre-separator. We disregarded the induction port as its aerodynamic characteristics are ill-defined and the mass of API deposited therein is assigned as non-sized by all methods. OUTPUT cumulative APSDs were subsequently derived using both methods. We found that the resulting mass median aerodynamic diameter (MMAD) values were 4.00 and 3.46 µm respectively. Fine particle fractions less than 5.0 µm aerodynamic diameter ($FPF_{< 5\,\mu m}$) were 0.626 and 0.722 respectively, comparing the cumulative APSDs using the pre-2015 chapter <601> and chapter <1604> methods. These differences represent a significant departure if performance of an orally inhaled drug product drug product has been developed using the pre-2015 <601> approach. By including the mass recovered from stage 1 as being greater than the cut-point size of that stage, the pre-2015 <601> method includes information that is missing altogether from cumulative APSDs determined using the chapter <1604> procedure. We conclude that further work is needed to evaluate the extent of the divergence fully.

Key Message

This article opens the "black box" to explore ramifications of a significant change in the calculational methodology for APSD-derived metrics (e.g., MMAD and FPF) associated with the recent launch of informative USP chapter <1604> compared with the practice in pre-2015 USP Chapter <601>.

Introduction

Aerodynamic particle size distribution (APSD) data describing the aerosol emitted from an orally inhaled product (OIP) is a critical quality attribute (CQA) required by regulatory agencies [1,2]. Multi-stage cascade impactors such as the next generation impactor (NGI), provide OIP developers a means to characterize OIP aerosol performance in terms of mass of active pharmaceutical ingredient (API) deposited on the size-fractionating components of the sampling apparatus. In the case of measurements made by NGI, the cumulative mass-weighted APSD is derived by progressive summation of recovered API mass from the collection cup associated with each stage, working from the micro-orifice collector towards the stage assigned as collecting the largest particles. These absolute mass values are then normalized by a factor representing the total mass sampled and expressed as a percentage of that chosen factor. Metrics representative of the APSD, such as mass median aerodynamic diameter (MMAD), geometric standard deviation (GSD), fine particle dose (FPD) and fine particle fraction (FPF), can subsequently be derived from the cumulative APSD using a variety of mathematical based approaches [3].

The driver for our investigation was the discovery that calculations of the cumulative APSD by the newly official USP Chapter <1604> [4] provide different derived metrics compared with those calculated using methodology in the USP Chapter <601>, official prior to 2015 [5]. Our presentation focuses on the NGI without pre-separator but is applicable with minor modifications to the configuration of the NGI with PS, and also to other multi-stage impactors, particularly the Andersen Cascade Impactor.

Methods

We undertook a theoretical study to assess the outcomes of evaluating NGI-measured APSDs using the two methodologies by generating, as INPUT, a smooth unimodal and log normal APSD with MMAD and GSD of 4.0 µm and 2.0, respectively. We mimicked presenting this model aerosol at the entrance to stage 1 of the NGI operated at 60 L/min to define the stage cut-point sizes in accordance with the archival calibration [6]. We disregarded the induction port as its aerodynamic characteristics are ill-defined and the mass of API deposited therein is assigned as non-sized by all methods. OUTPUT cumulative APSDs were subsequently derived using the methods in pre-2015 <601> [4] and <1604> [5]. We subsequently calculated MMAD and FPF following the procedures given in the relevant USP methodology.

Results

Figure 1 sets out diagrammatically and **Table 1 algebraically** how the stages of the NGI are evaluated to obtain the output APSD by Chapter <1604> and pre-2015 <601> respectively.

The first step in creating the cumulative mass distribution was to normalize the stage data. For pre-2015 <601>, this process involved dividing the mass data for each impactor stage by the total impactor mass, defined as sum of cups 1 to the MOC. This normalization process was similar applying the methodology in Chapter <1604> but used impactor sized mass (ISM), defined as the sum of mass on cups 2 to the MOC, as the normalizing factor instead.

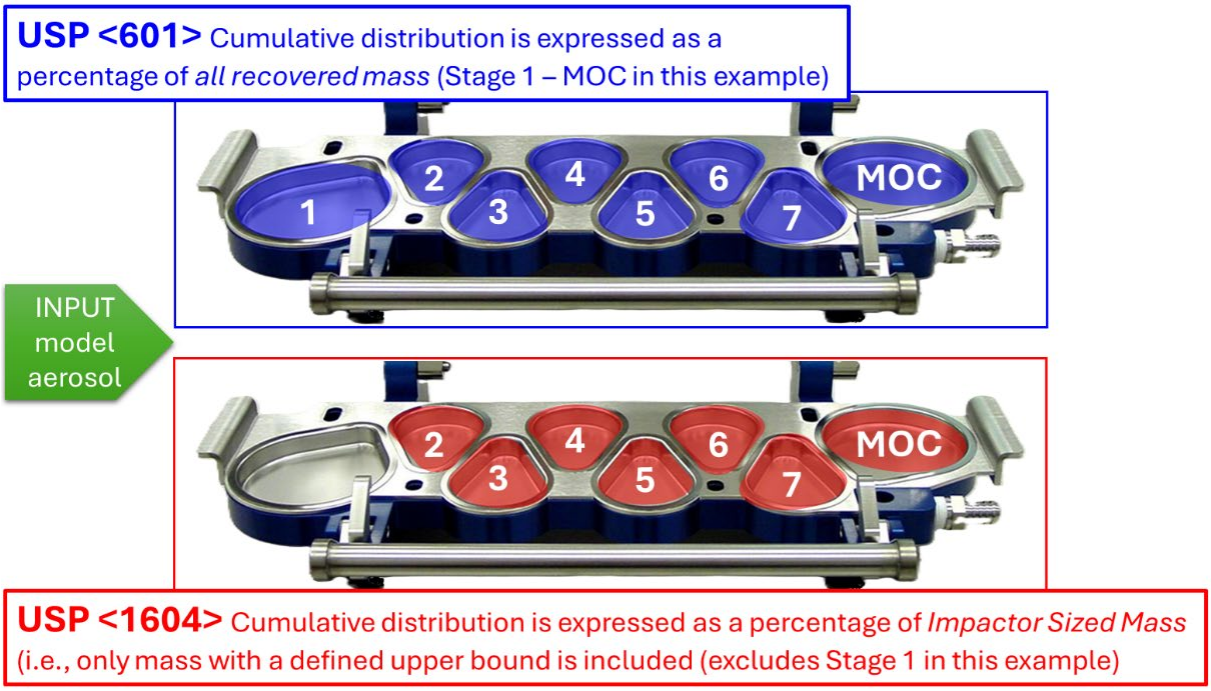

Figure 1: Diagram showing the method-dependent (pre-2015 <601> vs <1604>) masses used to assess derived APSD metrics for API collected by the NGI

The second step was to add sequentially for each stage the mass fractions from the prior stage(s) to the current stage, starting with the MOC and ending at stage 1 (**Table 1**).

Since our purpose was only to illustrate the divergence between methodologies, we did not go further and present the data in log probability format (sometimes referred as a log-probit plot), as this presentation tends to compress differences towards the central region of the APSD making it more difficult to demonstrate divergence.

NGI Stage	Stage Mass	Cumulative Mass	a) <601> Cumulative Total Mass Fraction	b) <1604> Cumulative ISM Mass Fraction without Pre-Sep
MOC	sm_{MOC}	$cm_8 = sm_{MOC}$	cm_{MOC} / cm_1	cm_{MOC} / cm_2
Stage 7	sm_7	$cm_7 = + sm_7 + cm_8$	cm_7 / cm_1	cm_7 / cm_2
Stage 6	sm_6	$cm_6 = + sm_6 + cm_7$	cm_6 / cm_1	cm_6 / cm_2
Stage 5	sm_5	$cm_5 = + sm_5 + cm_6$	cm_5 / cm_1	cm_5 / cm_2
Stage 4	sm_4	$cm_4 = + sm_4 + cm_5$	cm_4 / cm_1	cm_4 / cm_2
Stage 3	sm_3	$cm_3 = + sm_3 + cm_4$	cm_3 / cm_1	cm_3 / cm_2
Stage 2	sm_2	$cm_2 = + sm_2 + cm_3$	cm_2 / cm_1	$cm_2 / cm_2 = 1.0$
Stage 1	sm_1	$cm_1 = + sm_1 + cm_2$	$cm_1 / cm_1 = 1.0$	

Table 1: Calculation of Cumulative Mass Fraction Using (a): Total Mass Summed from Stage 1-MOC (pre-2015 <601>; (b): Summed From stage 2-MOC when No Pre-Separator is Present (ISM <1604>)

The resulting OUTPUT cumulative APSDs for both the pre-2015 <601> and <1604> approaches are shown in **Figure 2** with the derived measures of MMAD and fine particle fraction < 5.0 μm aerodynamic diameter ($FPF_{< 5\ \mu m}$) presented in **Figure 3**.

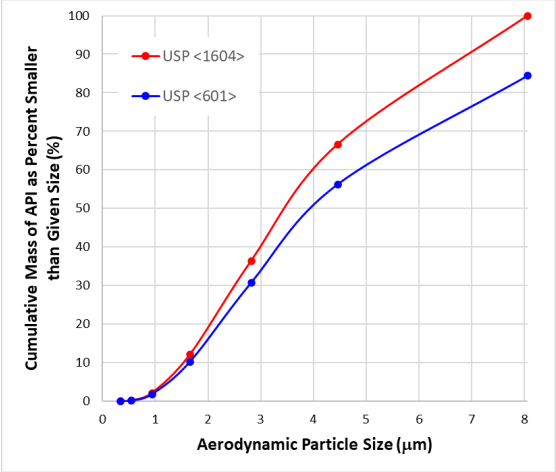

Figure 2: Cumulative mass distributions from each method (pre-2015 <601> versus <1604>) using a model input APSD with an MMAD of 4.0 μm and a GSD of 2.0

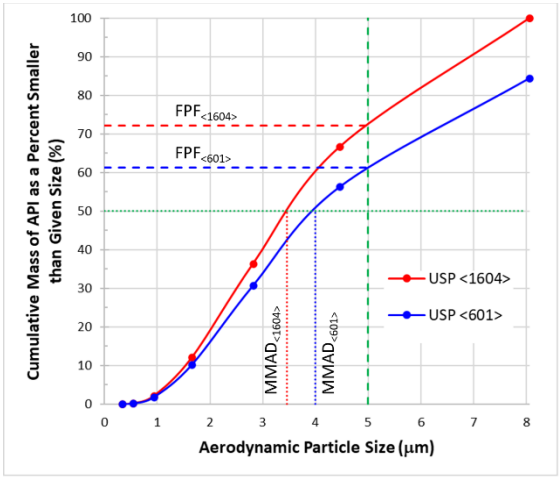

Figure 3: MMAD and FPF metrics derived from each method (pre-2015 <601> versus <1604>) using a model input APSD with an MMAD of 4.0 μm and a GSD of 2.0

We found that the resulting MMAD values were 3.46 and 4.00 μm respectively, comparing the cumulative APSDs using the chapter <1604> and pre-2015 chapter <601> methods respectively. Furthermore, the values of impactor-derived $FPF_{< 5\ \mu m}$ were 0.722 and 0.626 calculated by chapter <1604> and pre-2015 chapter <601> methodologies respectively.

Discussion

The use of total impactor mass and ISM by the two different methods therefore directly impacts the derived APSD metrics. This outcome results in a number of consequences:

1. For this particular input APSD, both MMAD and $FPF_{<5.0\ \mu m}$ values derived from these compendial methods differed by about 14%. This magnitude represents a significant departure if performance of an orally inhaled drug product drug product has been developed using the 'pre-2015 <601> approach.
2. By including the mass recovered from stage 1 as being greater than the cut-point size of that stage, the pre-2015 <601> methodology includes information that is missing altogether from cumulative APSDs determined using the chapter <1604> procedure.
3. Additional study is required to understand how these values may further vary between the two methodologies as a function of variations of both INPUT aerosol parameters and impactor configurations. Such investigation should also include evaluation of the effect of flow rate

through the impactor, and perhaps more importantly, alterations to the apparatus configuration such as the addition of a pre-separator, which also performs as an inertial size fractionator and has its own cut-point determined in the archival calibration [6].

4. To the best of our knowledge, the change in APSD calculation methodology that we have evaluated from the pre-2015 <601> method, was not identified prior to the finalization of <1604>. We believe that the approach in the pre-2015 USP still represents today's standard industry practice. This realization leads directly to the question as to which method is better suited to produce metrics that are viewed as CQAs for inhaled products.
5. The USP chapter <1604> method is not harmonized to the European Pharmacopeial Chapter 2.9.18 [7] that is closely aligned to the pre-2015 <601> methodology. A further challenge here is the differing views from worldwide regulatory agencies, where some prefer use of drug mass summed across a number of pre-defined stage groupings, while others emphasize use of derived metrics such as MMAD and FPF.

Conclusions

Our investigation into the differences between the pre-2015 methodology in USP chapter <601> and that introduced by the recently official informative chapter <1604> has revealed that the latter method systematically underestimates MMAD and therefore overestimates $FPF_{<5.0\ \mu m.}$ Further work is needed to evaluate the extent of the divergence fully.

References

[1] United states Food and Drug Administration (FDA). Draft guidance: Metered dose inhaler (MDI) and dry powder inhaler (DPI) drug products--quality considerations. Silver Spring, MD. 2018. Available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/metered-dose-inhaler-mdi-and-dry-powder-inhaler-dpi-drug-products-quality-considerations. visited June 19, 2024.

[2] European Medicines Agency (EMA). Draft guideline on the pharmaceutical quality of inhalation and nasal medicinal products. 2024. Amsterdam, Netherlands. Available at: https://www.ema.europa.eu/en/pharmaceutical-quality-inhalation-nasal-products-scientific-guideline . visited June 19, 2024.

[3] Christopher JD, Dey M, Lyapustina S, Mitchell JP, Tougas TP, Van Oort M, Strickland H, Wyka B. Generalized simplified approaches for mass median aerodynamic determination. Pharm Forum. 2010; 36(3): 812-821.

[4] United States Pharmacopeial Convention. Chapter <1604>: Presentation of Aerodynamic Particle Size Distribution (APSD) Measurement Data for Orally Inhaled Products <1604>. In: USP–NF. Rockville, MD: 2024

[5] United States Pharmacopeial Convention. Chapter <1604>: Presentation of Aerodynamic Particle Size Distribution (APSD) Measurement Data for Orally Inhaled Products <1604>. In: USP–NF. Rockville, MD: 2024.

[6] Marple VA, Olson BA, Santhanakrishnan K, Mitchell JP, Murray SC, and Hudson-Curtis BL: Next generation pharmaceutical impactor (a new impactor for pharmaceutical inhaler testing). Part II: Archival calibration. J Aerosol Med. 2003; 16: 301–324.

[7] European Directorate for Quality in Medicines and Healthcare (EDQM). European Pharmacopoeia Monograph 2.9.18. Edition 11. Preparations for inhalation – Aerodynamic assessment of fine particles. Strasbourg. France, 2024