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

Christopher J Gruenloh[1], Ian Carter[2], J. David Christopher[3], Jamie Clayton[4], William H Doub[5], Adrian P Goodey[6], Svetlana Lyapustina[7], Jolyon P Mitchell[8], & Daryl L Roberts[9]

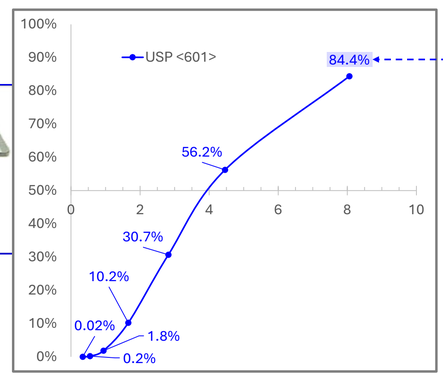
[1] PPD, Part of Thermo Fisher Scientific, Middleton, WI, USA, [2] PPD, Part of Thermo Fisher Scientific, Athlone, Ireland [3] Merck & Co. Inc., Rahway, NJ, USA, [4] Copley Scientific Ltd., Nottingham, UK, [5] OINDP In Vitro Analysis, St Louis, MO, USA, [6] Merck & Co. Inc., Rahway, NJ, USA, [7] Faegre Drinker Consulting, Washington DC, USA, [8] Jolyon Mitchell Inhaler Consulting Services Inc., London, Ontario, Canada, [9] Applied Particle Principles LLC, Hamilton, VA, USA

Key Message: This poster 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 common industry-practice aligned with pre-2015 USP Chapter <601>

USP <601> Cumulative distribution is expressed as a percentage of all recovered mass (Stage 1 – MOC in this example)

Impactor Stage	Cut-off diameter (um)	Recovered Mass (a.u.)	Cumulative Distribution
Stage 1	8.06	7.80	84.4%
Stage 2	4.46	14.08	56.2%
Stage 3	2.82	12.77	30.7%
Stage 4	1.66	10.24	10.2%
Stage 5	0.94	4.20	1.8%
Stage 6	0.55	0.81	0.2%
Stage 7	0.34	0.10	0.02%
MOC	0.14	0.01	

All Recovered Mass; Mass sized <8.06 um



$$\text{Cumulative \% Mass} < 8.06\ \mu m = \frac{\text{Mass sized less than 8.06 um}}{\text{All Recovered Mass}} = 84.4\%$$

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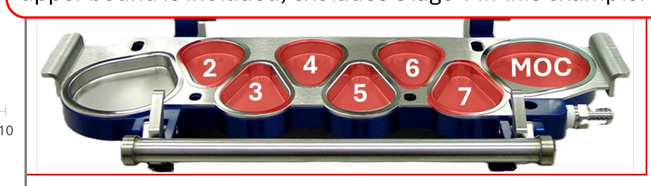
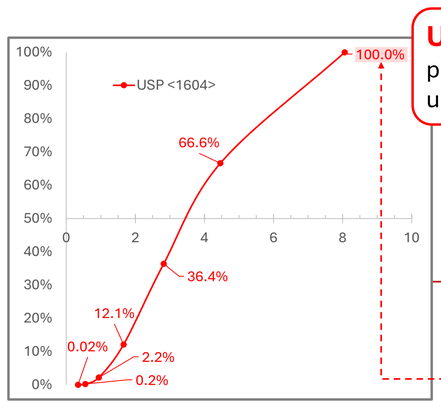
USP <1604> Cumulative distribution is expressed as a percentage of Impactor Sized Mass. Only mass with a defined upper bound is included; excludes Stage 1 in this example.



Impactor Stage	Cut-off diameter (um)	Recovered Mass (a.u.)	Cumulative Distribution
Stage 1	8.06	7.80	100.0%
Stage 2	4.46	14.08	66.6%
Stage 3	2.82	12.77	36.4%
Stage 4	1.66	10.24	12.1%
Stage 5	0.94	4.20	2.2%
Stage 6	0.55	0.81	0.2%
Stage 7	0.34	0.10	0.02%
MOC	0.14	0.01	

Impactor-Sized Mass; Mass sized <8.06 um



$$\text{Cumulative \% Mass} < 8.06\ \mu m = \frac{\text{Mass sized less than 8.06 um}}{\text{Impactor-Sized Mass}} = 100.0\%$$

Figure 1: Explanation of how a cumulative percent mass distribution is prepared as per USP <601> (at left, in blue) and USP <1604> (at right, in red). For each approach, an impactor image is used to illustrate which stages are included in the calculation. Accompanying data tables and plots explicitly show the two different treatments for the same impactor stage recoveries.

Methods: A Theoretical Study

Model Inputs: a smooth unimodal and log normal APSD with MMAD of 4.0 µm and GSD of 2.0.

- Aerosol presented to the entrance to stage 1 of an NGI operated at 60 L/min (without pre-separator) to define the stage cut-point sizes in accordance with the archival calibration.
- Induction port was disregarded as its aerodynamic characteristics are ill-defined and the mass of API deposited therein is assigned as non-sized by all methods.

Model Outputs: Cumulative APSDs derived using the methods in pre-2015 <601> and <1604>.

- **Figure 1** sets out diagrammatically and algebraically how the stages of the NGI are evaluated to obtain the output APSD by pre-2015 <601> and Chapter <1604>, respectively.
- Stage Data are normalized as follows:
  - **<601> (Pre-2015):** The mass data for each impactor stage is divided by the total impactor mass, defined as sum of cups 1 to the MOC.
  - **<1604>:** The normalization process was similar applying the methodology but used impactor sized mass (ISM), defined as the sum of mass on cups 2 to the MOC.
- **Figure 2** contrasts the cumulative distributions for the model aerosol resulting from each methodology and shows how the methods result in different values for MMAD and impactor FPF<5µm.

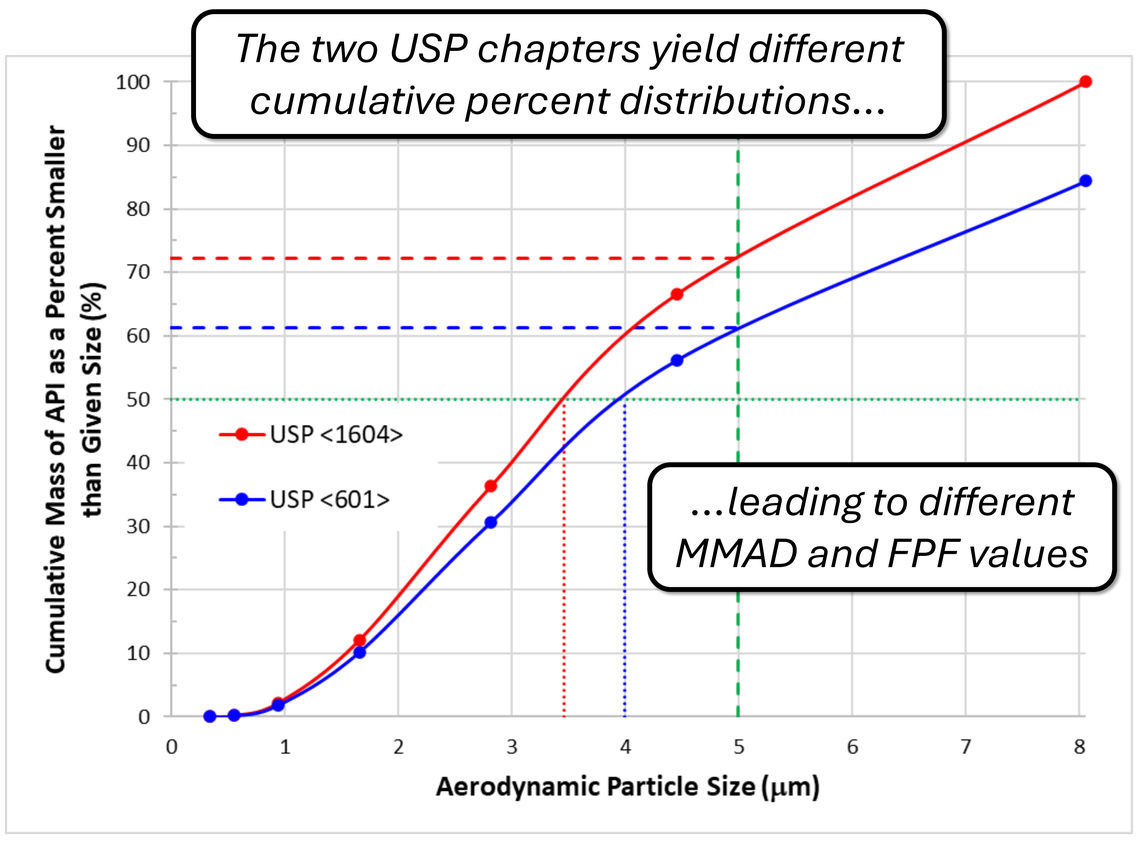


Figure 2: MMAD and FPF metrics derived from each method (pre-2015 <601> versus <1604>) using a model input APSD with an MMAD of 4.0 µm and a GSD of 2.0

Extension of Main Study: Subsequent work extended the study by exploring divergence between the methods as a function of:

1. Varying the MMAD of the input aerosol
   - Bland-Altman plot in **Figure 3** plots the output MMAD difference versus the average MMAD at the specified flow rate.
2. Varying the constant flow rate used for impactor sizing
   - Since dry powder inhaler (DPI) device resistance directly influences the flow rate required to achieve the compendial 4 kPa test condition, the divergence between methodologies was explored using a series of four flow rates with NGI stage cutoff diameters derived from the archival calibrations.

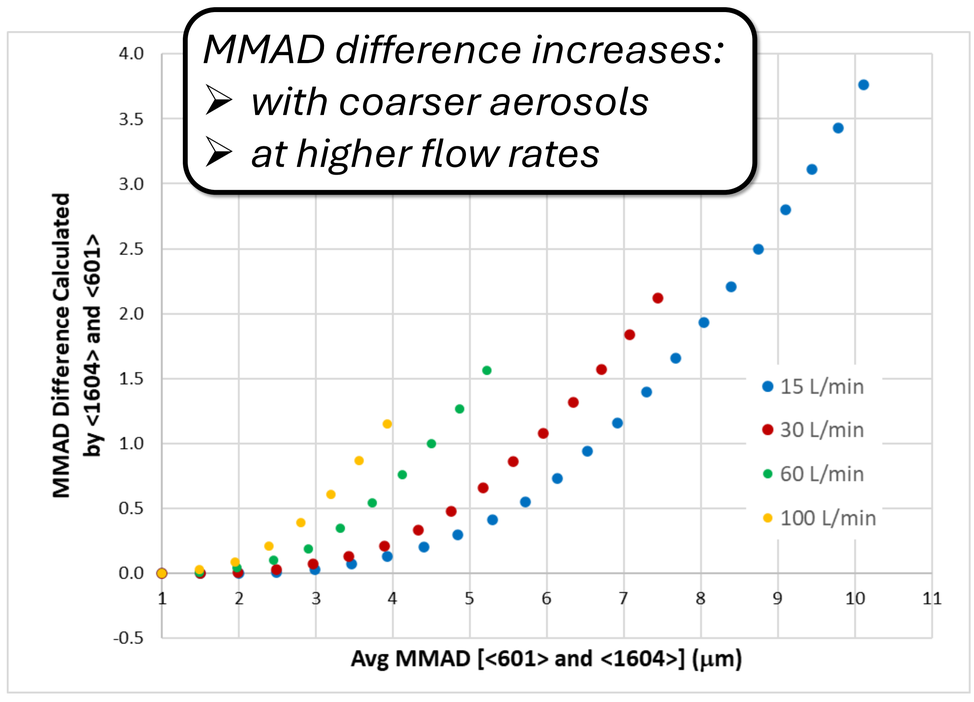


Figure 3: Bland-Altman plot of MMAD difference vs average MMAD with colored series Illustrating the impact of using flow rates from 15 to 100 L/min

Discussion

The use of total impactor mass in USP <601> versus using ISM in USP <1604> directly impacts the derived APSD metrics with multiple consequences:

1. The pre-2015 <601> Methodology for calculating APSD includes the mass recovered from stage 1, assigning it as greater than the cut-point size of that stage. The mass on stage 1 is not included in APSD calculations using the <1604> procedure.
2. For an INPUT APSD with 4 um MMAD and GSD of 2.0, both OUTPUT MMAD and $FPF_{<5.0\ \mu m}$ derived from <601> and <1604> differed by about 14%. This magnitude represents a significant departure if performance of an OIP has been developed using the 'pre-2015 <601> approach.
3. The divergence in MMAD observed between <1604> and <601> increases as the input aerosol coarsens since more mass is predicted to be observed on stage 1.
4. The divergence in MMAD is flowrate dependent with collections at higher flow rates (**Figure 3**) giving larger differences than those at lower flow rates. Specifically regarding DPIs, the divergence for a low resistance device operated at a higher flow rate will therefore be greater than for a high resistance device operated at a lower flow rate.
5. To the best of our knowledge, the change in APSD calculation methodology that we have evaluated from the pre-2015 <601> method, has not previously been studied. We believe that the approach in the pre-2015 USP is still a prevalent approach within the industry. This realization poses the question as to which method is better suited to produce metrics that are viewed as CQAs for inhaled products.
6. The <1604> method is not harmonized to the European Pharmacopeial Chapter 2.9.18 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 the recently official informative chapter <1604> has revealed that the methods diverge significantly when examining MMAD and FPF<5.0 µm. Further work, including head-to-head comparisons using data from a range of OIPs, is needed to fully evaluate the practical extent of these differences both within and across common impactor configurations.