IPAC-RS
International Pharmaceutical Aerosol Consortium on Regulation & Science

1500 K Street NW • Washington DC • 20005
Telephone +1 202 230 5607 • Fax +1 202 842 8465
Email info@ipacrs.org • Web www.ipacrs.org

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IPAC-RS Comments on USP <1604> "Presentation of Aerodynamic Particle Size Distribution (APSD) Measurement Data for Orally Inhaled Drug Products" *PF48(1)*

The International Pharmaceutical Aerosol Consortium on Regulation & Science (IPAC-RS, https://www.ipacrs.org/) commends USP for revising and publishing for comment informational chapter <1604> "Presentation of Aerodynamic Particle Size Distribution (APSD) Measurement Data for Orally Inhaled Drug Products" [PF48(1), January-March 2022]

IPAC-RS is an international association of companies that develop and manufacturer orally inhaled and nasal drug products (OINDPs). IPAC-RS seeks to advance the science, and especially the regulatory science, of OINDPs, through joint research, consensus building, development of best practices, and collaborations among stakeholders.

The IPAC-RS comments on USP <1604> are provided below. The IPAC-RS Cascade Impaction Working Group would be willing to discuss these comments with USP as needed. Please contact IPAC-RS Secretariat (at Svetlana.lyapustina@faegredrinker.com) for further information.

General Comments

1. The terms Inhaler, Mouthpiece, Adapter, MA and Patient Interface are used throughout the chapter (Pg.1 line 3, figure 1, pg. 2 line 26, figure 2, figure 3, figure 4) in a confusing and inconsistent manner and in a way that is also inconsistent with <601>. The term "patient interface" is particularly ambiguous and should be removed. The proposed changes are detailed below. It is important to recognize that the inhaler under test does not represent part of the aerosol sampling system itself. Furthermore, the inhaler typically contains a mouthpiece (inhaler mouthpiece) which retains drug and does not form part of the delivered dose (i.e. drug delivered to the patient) used in mass balance calculations. The adapter (mouthpiece adapter) interfaces with the mouthpiece and does form part of the aerosol sampling system, because it receives drug from the inhaler and constitutes part of the delivered dose. It is typical to include the drug mass deposited on the adapter with the induction port (or inlet). This approach is also consistent with the Data Analysis section of old versions of <601> (pre-USP 37) for which <1604> is intended to replace.

2. Page 2, Section: Deposition profile. The requirement to sum the inter-stage losses (wall deposition) as a separate assay is consistent with the latest <601>. However, this approach is rarely performed in practice, since older versions of <601> (pre-USP 37) required stage mass to be summed with corresponding collection plate mass, only in cases where inter-stage losses are shown during method development to be >5%. Whilst the latest approach makes more sense with regards to APSD accuracy, it causes issues with data reporting. This is especially applicable to most ACI users, when testing DPIs, which use older methods. If inter-stage losses are used in the analysis, they should be used only for purposes of mass balance determination and should not be part of the quantification of particle sizing.

3. Page 2, Section: Choice of CI… The requirement in <601> to test DPIs at a 4kPa pressure drop is described as if only a single inhaler is being tested. Where multiple inhalers of the same type are being tested, it is typical to test at an average flow rate that corresponds to a 4 kPa pressure drop over a range of inhalers of that type. All subsequent testing of that inhaler type is then performed at the average flow rate. This flow is rate is then built into the test method for that device type. This is to allow stage-wise drug mass comparison for devices of the same type. If devices are tested individually at a flow rate that yields a 4 kPa pressure drop then each device will almost certainly be tested at a slightly different flow rate. For some devices with inherently variable flow resistance, this flow rate variability can actually be quite high. This means that the cut-off diameters for each stage of the impactor will differ from test to test, rendering direct stage-wise drug mass comparison either inaccurate or impossible.

4. Given the content of General Comment 3 above, it is suggested that a statement to the following effect be inserted at the beginning of the chapter: "*The content of <1604> has been developed to provide informative guidance in the data interpretation in relation to measurements made using the procedures specified in <601>. In cases where inhalation powders are tested to determine aerodynamic particle size distribution, <601> specifies that measurements are to be made at the same pressure differential of 4 kPa. This requirement will require operating at different flow rates if the flow resistances of the inhalers differ slightly, a situation that can arise within a lot of the same inhaler type. For some passive inhalation systems (e.g., breath-actuated DPIs), it is difficult to make meaningful comparisons of aerosol metrics such as FPD, FPF, or MMAD between a measurements collected on an NGI vs. those collected using an ACI due to the differences in the two impactors internal volumes. The difference in internal volume alters the initial acceleration and aerosolization of particles emitted from the inhaler early in the profile before the peakflow rate is achieved. Additionally, the NGI and ACI differ because of different ECDs per stage, further prohibiting a direct comparison between the two impactors.* "

Line-by-Line Comments:

Location	*Original Language*	*Proposed Change*	*Rationale*	*Type*
Introduction (page 1)	This mass includes both (and is the sum of) the sized and non-sized fraction sampled from the patient interface …	This mass includes both (and is the sum of) the sized and non-sized fraction ~~sampled~~ emitted from the patient interface … ***Suggest making this substitution throughout the document.***	Clarifies language	Minor
Pg. 1, Line 4	**In the patient interface**	**On the mouthpiece**	**See general comment 1**	**Critical**
Pg. 1, Line 8	N/A	And nasal aerosols	completeness	Regular
Paragraph 4 (immediately above Figure 1)	'For determination of aerodynamic particle size distribution, the number of actuations should be minimized but sufficient to allow quantification of drug deposited on the stage with lowest deposition without overloading the stage with highest deposition. For details on performing the measurement, see <601>.	For determination of aerodynamic particle size distribution~~, the number of actuations should be minimized but sufficient to allow quantification of drug deposited on the stage with lowest deposition without overloading the stage with highest deposition.~~ ~~F~~and for details on performing the measurement, see <601>.	The monograph scope is data presentation not, sample analysis or method development. Recommend that text relating to the specifics of the methodology be removed and the reference to <601 be sufficient for methodology.	Regular
Figure 1, box in lower right corner	The stage numbering conforms to that for the NGI; other numbering applies for the various configurations of the ACI	The stage layout/numbering depicted for Sizing Components, conforms to that for the NGI	Better describes what is depicted in the figure.	Regular

Location	*Original Language*	*Proposed Change*	*Rationale*	*Type*
Figure 1 (p.1)		If possible, we suggest that the impactor stages be shown in one row.	Ease of reading	Minor
Top of page 2, second sentence	This chapter presents two pharmacopeial approaches that may be used evaluate the data obtained from CI analysis data, …	This chapter presents two pharmacopeial approaches that may be used evaluate CI analysis data, …	Removes redundant wording	Regular
Top of page 2, second bullet point	Assessment of the deposition profile by stage grouping of the delivered mass of drug product per actuation from the inhaler mouthpiece	Assessment of the deposition profile of the delivered mass of drug product per actuation from the inhaler mouthpiece by grouping CI stages	Better flow, better description of what is to be done	Regular
Top of page 2, last sentence	It might be appropriate to use one or more approaches.	It might be appropriate to use more than one approach.	Clarification	Regular
Pg 2, Section Choice of CI..	**However, when inhalers with different flow resistances are compared, measurements should be made at the same pressure differential, which will require operating at different flow rates.**	**However, when inhalers with different flow resistances are compared, measurements should be made at the same pressure differential, which will require operating at different flow rates. For some passive inhalation systems (e.g., breath-actuated DPIs), it is difficult to make meaningful comparisons of aerosol metrics such as FPD, FPF, or MMAD between a measurements collected on an NGI vs. those collected using an ACI due to the differences in the two impactors internal volumes. The difference in internal volume alters the initial acceleration and aerosolization of particles emitted from the inhaler early in the**	**See general comment 3**	**Critical**

Location	*Original Language*	*Proposed Change*	*Rationale*	*Type*
		profile before the peak flow rate is achieved. Additionally, the NGI and ACI differ because of different ECDs per stage, further prohibiting a direct comparison between the two impactors."		
Page 2, "System Suitability" section, second sentence	**However, where such losses are known to be ≤ 5% of the total delivered drug mass into the impactor, the procedure may be simplified by assaying only drug on the collection plates.**	**Where losses to non-collection areas within the impactor (walls) are known to be ≤ 5% of the total delivered drug mass into the impactor, the procedure may be simplified by assaying only drug on the collection pans/plates.**	**The two sentences that make up this section are not really related to each other. Perhaps a sentence in missing?** **The first sentence, which speaks to the mass balance being within the range of 85%-115% is a product quality requirement which, although based on the CI data, is not a testing requirement (i.e., dependent on the testing methodology). The second sentence discusses losses within the CI that are not assessable by what is recovered from the collection pans/plates.**	**Critical**
Page 2, Deposition Profile Section, 2nd sentence	Do not include the mass of the drug substance recovered from the interior walls of the CI, as the aerodynamic particle size of such deposits do not equate	Do not include the mass of the drug substance recovered from the interior walls of the CI, as the aerodynamic particle size of such deposits is undefined.	Clarification	Minor

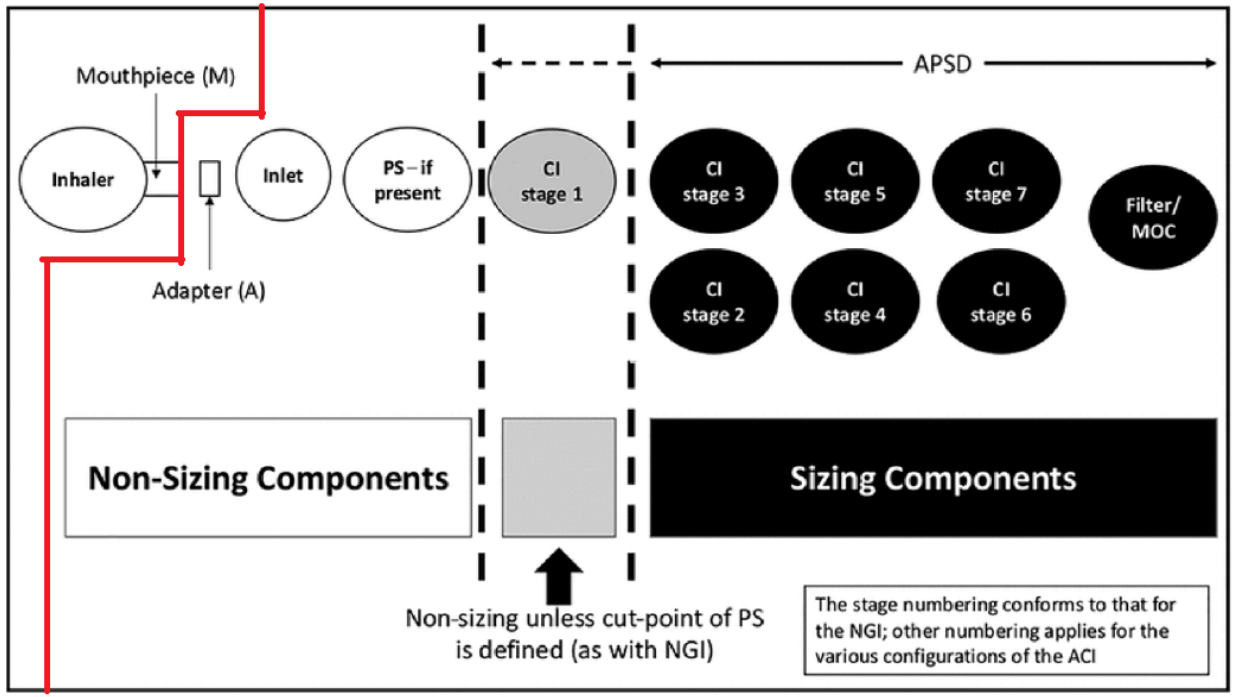
Location	*Original Language*	*Proposed Change*	*Rationale*	*Type*
	with the size ranges associated with each of the impaction stages.			
Figures 2-4 (pages 2-4).		The deposition on the adapter is here added to the deposition in the mouthpiece. It is more appropriate to add the deposition on the adapter to the deposition in the induction port, especially since adapter deposition is part of the calculation of mass balance and the fact that the drug already have left the device. We suggest that this be changed		
Pg. 4, Line 2	NOTE	N/A	Clarification required as to what that means in terms of the data and the result of no conformance	Regular
Page 4, The APSD … section, parenthetical following 1st sentence	[Note: Some distributions may not conform to the illustration in Figure 5.]	[Note: Some distributions may not conform to the illustration in Figure 5, which is specific to an NGI, due to differences in the configuration of the CI used to make the measurements.]	Also need to explain better whether the note refers to the X or Y axis of the figure	Regular
Page 4, The APSD … section, last sentence	In Contrast, when the PS is used with the NGI, mass on the initial stage 1 does …	In Contrast, when the PS is used with the NGI, mass on the initial stage (S1) does …	Clarification	Minor
Page 5, Stage groupings … section, 4th sentence	The groups for the purpose of the chapter can be defined, for example, in terms of four relative categories:	In the illustration provided for this chapter, the groups have been defined in terms of four relative categories:	Clarification	Minor
Page 5, Section "Stage grouping of	**"…substance emitted delivered from the inhaler"**	**Remove either "emitted" or "delivered"**	**Typo**	**Critical**

Location	*Original Language*	*Proposed Change*	*Rationale*	*Type*
the deposition data", 2nd line				
Figure 5 (p.5)		It seems like the x-scale is more linear than logarithmic. Please check and correct if needed		
Figure 6 (p.5)	**Induction port**	**Induction port and adapter**	**Non-sizing component**	**Critical**
Figure 6 (p.5)		In the label for Figure 6 it says "Measure of spread*. *=GSD only if APSD is unimodal and log-normal". Should any measure of spread be used if this is not the case? If so, what measure?		
Figure 7, caption (p.6)	Curve fitting of cumulative mass-weighted deposition data to generate APSD as a CDP	Curve fitting using a Morgan-Mercer-Flodin model for the cumulative mass-weighted deposition data to generate APSD (see "Sized Fraction" section, below)	Clarification	Regular
Page 9	"The USP growth curve for calculating MMAD…"	The calculation of MMAD is now discussed under the Section "**Sized Fractions**" although MMAD is not a sized fraction. We suggest a new section for the MMAD calculations, e.g. "**APSD Shape Properties**" which is used in Figure 6 for MMAD and "measure of spread"		
Pg. 8, Table 2B (and all NGI tables)	Mass from preseparator, m_0	Mass from preseparator, m_p	Change 0 to p (for preseparator) to avoid confusion with a Stage 0 that does not exist in the NGI	Minor

Location	*Original Language*	*Proposed Change*	*Rationale*	*Type*
Page 9 Equation	$\frac{FPD_{<5\mu m}-F_3}{F_2-F_3}=\frac{5-4.46}{8.06-4.46}$	**In the equation where FPD<5 µm is calculated,** $\frac{FPD_{<5\mu m}-F_3}{F_2-F_3}=\frac{5-4.46}{8.06-4.46}$**, F_2 and F_3 are not defined. Please add that F_2 and F_3 are the cumulative dose up to stage 2 and 3, respectively, *i.e.* c_2 and c_3 are found in Table 2B. Please correct.**		**Critical**
Second sentence below the page 9 equation	'For best results, the CDP should be approximately linear in the region for the estimation.		Clarification requested on what is meant by 'approximately linear'	regular

Additional Changes Suggested for Figures

1) It is recommended that Inhaler and Mouthpiece be separated from the sizing components as they are not part of the aerosol sampling system, as indicated by the red line.



2) Figure 2,3,4 -> as per annotation above (see general comment 1)