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IPAC-RS Comments on
PF 45(6)[1] "<601> Inhalation and Nasal Drug Products – Aerosols, Sprays, and Powders – Performance Quality Tests"

IPAC-RS is a non-profit association of companies that develop, manufacture or market orally inhaled and intranasal drug products, with the goal of advancing science-based and data-based regulations, standards, and practices for these products. A list of current members, and further information are available at http://ipacrs.org. IPAC-RS appreciates the opportunity to provide comments on the revised USP chapter <601> "Inhalation and Nasal Drug Products – Aerosols, Sprays, and Powders – Performance Quality Tests".

General Comments

1. We commend USP for updating the text based on previous comments provided by IPAC-RS and others. In particular, we recognize as improvement the removal of references to data analysis, keeping the focus on analytical aspects of testing. We suggest that future revisions provide specific references to sources related to data analysis.

2. Another improvement is the removal of the specified air volume sample for inhalation aerosols and inhalation sprays. There are still instances, however (highlighted in the specific comments below), where this change has not been applied. Please update the text to align with the rest of the document.

3. IPAC-RS understands that there are still issues with stated specifications and other technical details, especially related to cascade impaction testing. Those comments were recently submitted to USP separately.

[1] Pharmacopeial Forum November 2019. Available (with free registration) at https://www.uspnf.com/pharmacopeial-forum/pf-table-contents.

Specific Comments:

Page numbers refer to the pdf of 49 pages.

Critical comments are highlighted in bold.

Location	*Original Language*	*Proposed Change*	*Justification*
Page 29 first paragraph in A.1.1.1 titled: Sampling the delivered dose from inhalation aerosols and inhalation sprays	**"The volume of air sampled per actuation should not exceed 2.0 L."**	**Delete this sentence**	**Setting a limit on the total volume of air sampled during delivered dose testing makes sense based on the way that DPI aerosols are generated since the energy to aerosolize the powder is provided by the patient inhalation airflow. However, such a testing requirement does not make sense for all inhalation aerosols and inhalation sprays, such as a press & breathe MDI. This requirement adds unnecessary testing variability since there would be a short duration (~4 seconds for a 2 L limit) where airflow is present through the test apparatus. If the testing analyst actuated the MDI prior to or near the end of the airflow, incomplete capture of the dose could occur. A 2 L volume limit might be applicable for DDU testing of a breath actuated MDI since the airflow is what triggers the delivery of the dose. However, a 2 L transient airflow is not appropriate as a requirement for all "inhalation aerosols and inhalation sprays" and it should be removed from section A.1.1.1. Further justification for removing the above sentences is that it appears to be in conflict with the following sentence that subsequently is included in section A.1.1.1 – "During tests of inhalation aerosols and sprays, air should be drawn continuously through the system to avoid loss of drug into the atmosphere."**
Page 29 Section A.1.1.1	**Figure 1a – inclusion of two-way solenoid valve and timer**	**Remove two-way solenoid valve and timer from Figure 1a.**	**Table 1 has been updated to put n/a against the two-way solenoid valve and timer as they are not required for all inhalation aerosols and inhalation sprays, such as a press & breathe MDI as constant flow is typically used (see General comment 2) therefore Figure 1a should be updated to remove these items and it will then align with the table and the proposed update in General comment 2.**

Location	*Original Language*	*Proposed Change*	*Justification*
Page 30 Figure 1b DDU sampling apparatus for inhalation powder	Sample collection tube	Sample collection tube (I) Change the design of sample collection tube since different dimension is reported in descriptions (table 1)	It misses the letter I that is reported in the table to describe the shape and dimension of sample collection tube for both apparatuses
Page 31 Table 1 DDU sampling apparatuses A and B	DDU Sampling Apparatus A (inhalation aerosols, inhalation sprays, and nasal aerosol)	DDU Sampling Apparatus A (inhalation aerosols, inhalation spray, nasal aerosol and nasal spray)	To align with figure 1a since the table 1 describe the components reported in the figure 1a
Page 34 A.3 Inhalation powders	Data are reported as amount delivered and as a percentage of target-delivered label claim	Data are reported as amount delivered and as a percentage of target-delivered dose (or of labelled delivered dose)	To align with A.3 Inhalation powders where it is reported that for inhalation powders, where the label claim is the pre-metered dose of drug, the target delivered dose is less than label claim. The new wording proposed avoid misunderstanding …
Page 37 C1.5 Table 3a,	The version of Stage 0 used at 60 and 90 L/min has external modifications, permitting another stage rather than the inlet adapter cone to be fitted above it. […]	The version of Stage 0 used at 60 and 90 L/min **(i.e. - 0)** has external modifications, permitting another stage rather than the inlet adapter cone to be fitted above it. [….]	Better understanding
Page 38 C1.5 Table 3b	Stage 3 cut-off at 30L/min: 3.97µm	Stage 3 cut-off at 30L/min: **3.99µm**	Could be a typo See JOURNAL OF AEROSOL MEDICINE 16 (3), p 311 (2003).
Page 38, C1.5 Table 3b	Stage 1 cut off at 30 L/min: 11.76 µm	Stage 1 cut-off at 30 L/min: **11.72** µm	Could be a typo See JOURNAL OF AEROSOL MEDICINE 16 (3), p 311 (2003).

Location	*Original Language*	*Proposed Change*	*Justification*
Page 40 C2.2 procedure-ACI without pre-separator	With the vacuum pump running, insert the mouthpiece/nosepiece into the mouthpiece/noisepiece adapter…	With the vacuum pump running, insert the mouthpiece/nosepiece of the inhaler into the mouthpiece/noisepiece adapter	To better and clearly describe this operative procedure
Page 45, Section 3.1	For operation at air flow rates of 60 and 90 L/min, use manufacturers' alternate stage configurations	It is now unclear which configuration to use when flow is in-between 28.3 and 60 L/min and in-between 60 and 90 L/min. Please specify if possible	To better and clearly describe this operative procedure