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IPAC-RS Comments on USP <601> "*Inhalation and Nasal Drug Products: Aerosols, Sprays, and Powders—Performance Quality Tests*" *PF48(4)*

The International Pharmaceutical Aerosol Consortium on Regulation & Science (IPAC-RS, https://www.ipacrs.org/) thanks USP for revising and publishing for further comment chapter <601> "Inhalation and Nasal Drug Products: Aerosols, Sprays, and Powders—Performance Quality Tests" [PF48(4), published July 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 are provided below. IPAC-RS also supports the comments submitted separately by Mark Copley (an IPAC-RS member).

Please contact IPAC-RS Secretariat (at Svetlana.lyapustina@faegredrinker.com) with any questions.

General Comments

1. Care should be made to make it clear that for **nasal spray products**, a DDU sampling apparatus (traditionally designed for pressurized metered dose inhaler devices) is not required for use in DDU workflows. An appropriate apparatus can be used in place of the DUSA or DDU sampling apparatus using a validated assay. This is in accordance with the language provided by the FDA in recent product specific guidance documents for nasal spray products.

Specific Comments

Location	***Original Language***	**Proposed Changed Language**	**Justification of Proposed Change**	**Type**
Page 2, A.1.1.1 Sampling the delivered dose from inhalation aerosols and inhalation sprays Paragraph below Figure 1a	*The volume of air sampled per actuation should not exceed 2.0 L*	Delete the sentence or state that this is not applicable to all inhalation aerosols and inhalation sprays	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	Critical

Location	*Original Language*	Proposed Changed Language	Justification of Proposed Change	Type
			tests of inhalation aerosols and sprays, air should be drawn continuously through the system to avoid loss of drug into the atmosphere." In addition, the solenoid and timer are listed as Optional in Table 1 for the Figure 1a configuration, which too conflicts the statement highlighted.	
Page 3, Caption for Figure 1a.	*DDU sampling apparatus…*	*Keep the original caption and ADD at the end of the caption*: "For nasal spray drug products, an appropriate apparatus can be used in place of the sample collection tube (I) outlined above for sampling of the delivered dose using a validated assay."	Traditionally DUSA tubes like what is outlined in Figure 1a and Figure 2 are not used for delivered dose uniformity with nasal sprays. This proposed addition is to minimize confusion on this topic and matches language seen in various FDA product specific guidance documents for different nasal sprays.	Critical
Page 4, Table 1, Under description for DDU Sampling Apparatus A and next to Item "Filter"	*25-mm glass fiber, stainless steel fiber, or microfiber polypropylene filter*	*Add a footnote or asterisk saying*: "not required for testing of delivered dose for nasal sprays"	Traditionally, nasal sprays are not actuated under flow conditions but rather into a closed container for delivered dose testing. Therefore, a filter is not required to perform this test.	Critical
Page 4, Table 1, Under description for DDU Sampling Apparatus A and next to Item "Filter"	*47-mm glass fiber filter, stain-less steel fiber filter, or (USP 1-Dec-2023) Microfiber polypropylene filter*	≥ 47-mm glass fiber filter, stain-less steel fiber filter, or (USP 1-Dec-2023) Microfiber polypropylene filter	In some cases, when trying to use the standard DUSA tubes described in USP 601, sufficient powder deposits on the filter such that air flow is restricted. This can result in significantly less than the target 2L actuation volume. In cases of this filter blinding/air flow restriction, an apparatus with a larger filter/area for air flow should be used. The use of 75 mm filters should alleviate this problem.	Critical
Page 4, Table 1, Under description for DDU	*A short length of suitable vacuum tubing……*	*Keep original language but add footnote or asterisk saying*: "not required for	Traditionally, nasal sprays are not actuated under flow conditions but rather into a closed container. Therefore, a	Critical

Location	*Original Language*	Proposed Changed Language	Justification of Proposed Change	Type
Sampling Apparatus A and next to Item "Vaccuum Tubing"		testing of delivered dose for nasal sprays"	vacuum tubing is not required to perform this test.	
Page 5, Table 1, Under description for DDU Sampling Apparatus A and next to Item "Flow meter or test product"	*Inhalation or nasal aerosol or spray products to be evaluated.*	*Remove* "nasal spray products"	Traditionally, nasal sprays are not actuated under flow conditions but rather into a closed container. Therefore, a flow meter is not required to perform this test.	Critical
Page 5, Table 1, Under description for DDU Sampling Apparatus A and next to Item "Vacuum Pump"	*Vacuum pump capable of drawing air…*	*Keep original language but add footnote or asterisk saying:* "not required for testing of delivered dose for nasal sprays"	Traditionally, nasal sprays are not actuated under flow conditions but rather into a closed container. Therefore, a vacuum pump is not required to perform this test.	Critical
Page 5, Table 1, Under description for DDU Sampling Apparatus A and next to Item "Sample Collection Tube"	*26.70-mm ID x 9.4-cm IL*	*Keep original language but add footnote or asterisk:* "For nasal spray drug products, an appropriate apparatus can be used in place of the sample collection tube (I) outlined above for sampling of the delivered dose using a validated assay"	Traditionally DUSA tubes like what is outlined in Table 1 are not used for delivered dose uniformity with nasal sprays. This proposed addition is to minimize confusion on this topic and matches language seen in various product specific guidance documents for different nasal sprays.	Critical
Page 5, Table 1, Under description for DDU Sampling Apparatus A and next to Item	*34.85-mm ID × 12-cm IL*	"Housing of sufficient diameter to accommodate the filter specified above."	In some cases, when trying to use the standard DUSA tubes described in USP 601, sufficient powder deposits on the filter such that air flow is restricted. This can result in significantly less than the target 2L actuation volume. In cases of this filter blinding/air flow restriction, an	Critical

Location	*Original Language*	Proposed Changed Language	Justification of Proposed Change	Type
"Sample Collection Tube"			apparatus with a larger filter/area for air flow should be used. The use of 75 mm filters should alleviate this problem.	
Page 8, A.3.1	*Perform this test under conditions of controlled temperature and humidity*	"Perform this test under conditions of monitored temperature and humidity"	The burden of controlling temperature and humidity will be too great for many products and unnecessary if demonstrated compliance of testing within a range	Critical
Page 8, Caption for Figure 2.	*DDU sample collection tube…*	*Keep original language with addition at the end of the caption.* "For nasal spray drug products, an appropriate apparatus can be used in place of the sample collection tube (I) outlined above for sampling of the delivered dose using a validated assay."	Traditionally DUSA tubes like what is outlined in Table 1 are not used for delivered dose uniformity with nasal sprays. This proposed addition is to minimize confusion on this topic and matches language seen in various product specific guidance documents for different nasal sprays.	Critical
Page 9, second line	*Procedure: To determine the content of drug substance in the discharged plume form a nasal spray, use DDU sampling apparatus A described above*	*Keep original opening sentence as written to the left but then add*: "For nasal spray drug products, an appropriate apparatus can be used in place of the DDU sampling apparatus described above, using a validated assay."	Traditionally, DUSA tubes like what is outlined in Table 1 are not used for delivered dose uniformity with nasal sprays. This proposed addition is to minimize confusion on this topic and matches language seen in various product specific guidance documents for different nasal sprays.	Critical
Page 18, Figure 7c / Table 5			Mislabeling of the "Vacuum Tubing Connecter" as "D" instead of "C"	Minor
Page 18, Figure 7c / Table 5			Misalignment of label "I" in the figure with the absence of "I" in Table 5	Minor