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IPAC-RS Comments on USP Revised Chapter <604> "Leak Rate (of aerosol containers)" USP Pharm.Forum #48(6)

The International Pharmaceutical Aerosol Consortium on Regulation & Science (IPAC-RS) is an international association of companies focusing on orally inhaled and intranasal products. Member companies of IPAC-RS develop, manufacture and market both brand-name and generic products (see the list of members at https://www.ipacrs.org/about).

IPAC-RS seeks to advance the science, and especially the regulatory science, through joint research, consensus building, development of best practices, and collaborations among stakeholders. As such, IPAC-RS appreciates USP's publication of the revised chapter <604>, and would like to suggest further improvements . The IPAC-RS general and specific comments are provided below.

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

GENERAL COMMENTS

1. The removal of the alternate parameters and having a % of fill weight/yr rather than mg/year for small containers is disappointing as this is used for inhalation products (pMDIs). Whatever leak rate specifications are assigned to new products would be integrated with other product quality measures (QbD approach) therefore leak rate attributes of the product contribute to overall product design considerations and are defined appropriately. The USP criteria are used during development and application of criteria which are too punitive during the development phase may well impact novel products coming to the market. Particularly with the advent of novel propellants (HFA 152a and HFO 1234ze(E)), the fill weight of future products is under development and there is likely a need to define adjusted criteria amenable to future inhalation aerosols (pMDIs). The Note, 'For certain inhalation aerosol drug products (e.g. samples with low fill weight), an alternate acceptance criterion may be needed' raises questions – the definition of what constitutes 'samples with low fill weight' could be interpreted differently. Rather, we suggest there is a general exemption for **all** inhalation drug aerosol products, as by their nature they are low fill weights (10s of grams) compared to the larger types of aerosols which utilize the USP criteria (which can be 100's of grams). Inhalation products are subjected to in-line leakage testing and also have performance as well as fill weight

criteria applied throughout the shelf life of the product[1,2], therefore the leak rate of the product is scrutinized by additional means. The proposal to apply parameters for standard criteria across all aerosols (regardless of fill weight) is therefore inappropriate as additional criteria for performance will be applied holistically to ensure product quality. As such, there is a recommendation to re-instate the criteria that was in place for aerosols with a net fill weight of less than 15g, if it is required to present criteria in this general chapter for inhalation aerosols.

2. It is respectfully suggested that the criteria (specifications) for leak rate for inhalation aerosols can be removed from USP <604>. This suggestion is in alignment with Section 4.20 General Chapters of USP's General Notices and Requirements. In Section 4.20 it lists that general chapters may contain descriptions of tests and procedures for application through individual monographs. It is also mentioned that acceptance criteria may be presented in the monograph after the reference of the general chapter. The suggestion to remove the criteria for leak rate for inhalation aerosols also generally aligns with the initiative completed in August 2022 for removal of Performance Tests cited in inhalation aerosol monographs. In USP's Notice of Intention to Revise Inhalation Drug Product Monographs[3], it was supported by industry stakeholders and FDA that the performance tests are product specific / device specific. It was acknowledged in the notice that there may be differences among different manufacturers of the same drug product. The recommendations of the intent to revise inhalation drug product monographs can also be applied to the general specifications in the proposed revisions to USP<604> in PF 48(6). Specifications to ensure product quality are a part of the overall product control strategy adopted by the manufacturer for the specific inhalation aerosol drug product. It is not necessary and a regulatory burden to define a general specification for all inhalation aerosol drug products. If criteria are desired to be placed in the general chapter, it is recommended to reinstate the previous specification that was listed for aerosols with a net fill weight of less than 15 g. This could define the starting point for early development that should be later refined as additional product understanding is gained.

3. The calculation of percent of the net fill weight per year in USP <604> of PF 48(6) lists a requirement to determine the fill weight of each of 12 (up to 36) units by weighing the unit containing formulation and then weighing the components of each unit after the destruction of each unit. This net fill weight determination is used (W1-W3) for each container tested. It is recommended to retain the flexibility in the current version of <604> to allow the use the average fill weight (or target) when available. This assists the laboratory to reduce the number of canisters that need to be opened (safety and environmental benefits) and allows use of a net fill weight value already determined

[1] FDA Draft Guidance, Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products – Quality Considerations, April 2018.
[2] USP <5> Inhalation and Nasal Drug Products – General Information and Product Quality Tests, USP-NF.
[3] USP-NF. Notice of Intent to Revise. Inhalation Drug Product Monographs: Removal of Performance Tests. June 2021.

through other testing on the same batch. The non-destructive approach is also aligned with that in the Ph. Eur.

4. It is unclear why the USP are proposing to change the methodology and acceptance criteria for Leak Rate of Aerosol Containers. Evaluation of currently marketed US products against the revised acceptance criteria could result in many batches being out of compliance. The methodology and acceptance criteria currently applied were evaluated and endorsed by the US FDA during the review of these products and are deemed suitable for the intended use. We do not see any value in the proposed changes, and for those working with these products on a regular basis, experience shows that the test is discriminatory and broadly serves its purpose as-is.

   Furthermore, many non-US markets follow the USP, and this change would result in a broader compliance risk.

5. While it is understood that moving to acceptance criteria as % per year for all products, is intended to limit the allowed leakage based on the net fill weight of the product. However, for a product supplied in 2 sizes (e.g., 60 and 200 actuation) that utilizes the same valve and canister-crimp, the absolute (mg) leak rate will be the same and hence as a % will be higher for the smaller net fill weight presentation. Hence, retaining the currently approved USP acceptance criteria wherein products with net fill weight of 15 g or greater utilize acceptance criteria in %/year while products with net fill weight of less than 15 g utilize acceptance criteria in mg/year, is appropriate, and would eliminate the need for the note on alternate acceptance criteria for low fill weight samples.

6. We request that the note that allows the use of a previously determined average net fill weight in place of determining this each time the test is performed is reinstated. There is a high burden on QA staff to determine the fill weight each time the test is performed, for very little return in value.

7. Should the USP insist on changes to the methodology and acceptance criteria, USP should consider the following options:

   a) Define what is a low fill weight value and the associated acceptance criteria. It is suggested to maintain the current criteria for low fill weight presentations.

   b) Retain the note that allows the use of a previously determined average net fill weight in place of determining this each time the test is performed is reinstated.

   c) Reconsider the acceptance criteria proposed and base them instead on the performance of currently marketed products.

   d) In the Tier 2 testing criteria, the allowance to move to Tier 2 requires that the average leak rate is NMT 2.5% of the net fill weight. This requirement is not in the current <604>, and the need for this should be clarified.

1 **SPECIFIC COMMENTS**

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Section	*Original Language*	Proposed Changed Language	Justification of Proposed Change
Paragraph 1 sentence 2	*Conduct the test under the same constant humidity conditions'*	Remove this statement or amend to: 'conduct the test under the same constant humidity conditions if the product under test requires this control (e.g. plastic coated glass aerosol containers).'	The requirement to 'conduct the test under the same constant humidity conditions' is unclear and is not essential. The temperature of the environment drives the leakage from the containers. The humidity was previously mentioned for a specific aspect of the testing (where plastic coated glass aerosol containers are tested) therefore adding this statement to apply across any product is not applicable. If a comment for humidity is required, then it should be applicable only if the product being tested requires that the humidity be constant throughout the test
Sample Preparation Paragraph	*Previous version of USP <604> provided for use of average net fill weight. This option has been removed in the PF 48(6) version and should be reinstated.*	Reinstate the Note previously available as follows: [Note: If the average net fill weight has been determined previously, that value may be used in place of the value (W1-W3) above.]	It is recommended to retain the flexibility in the current version of <604> to allow the use the average fill weight (or target) when available. This assists the laboratory to reduce the number of tests involved (safety and environmental benefits) and allows use of a net fill weight value already determined through other testing on the same batch. The non-destructive approach is also aligned with the Ph. Eur.
Sample Preparation Paragraph	*'Weigh each container to the nearest mg, and record the weight, in mg, of each as W1. Allow the containers to stand in an upright position at a temperature of 25.0 ± 2.0° for*	Replace with: 'Weigh each container to the nearest mg, and record the weight, in mg, of each as W1. Allow the containers to stand in an upright position at a temperature of 25.0 ± 2.0° for NLT 3 days, and again weigh each container, recording the weight, in mg, of each as W2 and recording the date and time to the nearest half hour. Determine the time, T, in hours, during which the containers were under test.	For inhalation aerosols, it is important to retain the calculation indicated below: (365)(24/T)(W1-W2) The current USP <604> has the formula to determine the weight loss as a mg/year value which is then able to be calculated as % for larger containers using a net fill weight (actual or previously determined). The approach of

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	NLT 3 days, and again weigh each container, recording the weight, in mg, of each as W2 and recording the date and time to the nearest half hour. Determine the time, T, in hours, during which the containers were under test. Empty the contents of each container tested by employing any safe technique (e.g., chill to reduce the internal pressure, remove the valve, and pour). Remove any residual contents by rinsing with suitable solvents, then rinse with a few portions of methanol. Retain as a unit the container, the valve, and all associated parts, and heat them at 100° for 5 min. Cool, weigh, record the weight as W3, and determine the net fill weight (W1 − W3) for each container tested. Calculate the leakage rate, in percentage per year, of each	Calculate the leakage rate, in mg/year, of each container by the formula: (365)(24/T)(W1-W2) For tests where the net fill weight is needed to determine the leak rate as a percentage per year, conduct the following: Empty the contents of each container tested by employing any safe technique (e.g., chill to reduce the internal pressure, remove the valve, and pour). Remove any residual contents by rinsing with suitable solvents, then rinse with a few portions of methanol. Retain as a unit the container, the valve, and all associated parts, and heat them at 100° for 5 min. Cool, weigh, record the weight as W3, and determine the net fill weight (W1 − W3) for each container tested. [Note—If the average net fill weight has been determined previously, that value may be used in place of the value (W1 – W3) above.]' Calculate the leakage rate, in percentage per year, of each container taken by the formula: 365(24/T)(W1 − W2)100/(W1 − W3)'	being able to measure individual aerosols canisters uses each aerosol canister as its own control for the weight loss over the studied time period. It avoids the destruction of units in order to determine a fill weight. A nominal fill weight is not required as the proposed approach directly measures the mass leaked and translates that value to an amount in mg per year. The mg/year leakage is a mass unit of measure to enable a QbD approach in the definition and control of release and stability fill weights required to ensure the adequate amount of product for patient dosing. As fill weight is a mass unit of measure, utilizing a mass unit of measure for leakage provides direct translation to the amount expected to be available at shelf life. This approach is commonly used for pMDI products approved by FDA. This approach for assessing the unit on a non-destructive basis is also used by Ph. Eur.

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	container taken by the formula: 365(24/T)(W1 − W2)100/(W1 − W3)'		
	Note, 'For certain inhalation aerosol drug products (e.g. samples with low fill weight), an alternate acceptance criterion may be needed'	~~Note, 'For certain inhalation aerosol drug products (e.g. samples with low fill weight), an alternate acceptance criterion may be needed'~~. If specification is required, please re-instate: 'For lower net fill weight inhalation aerosol products (e.g. all pMDIs), the requirements are met if the average leakage rate of the 12 containers is NMT 375 mg per year and none of the containers leaks more than 525 mg per year. If 1 container leaks more than 525 mg per year but NMT 750mg per year, determine the leakage rate of an additional 24 containers as directed herein. NMT 2 of the 36 containers leak more than 525 mg per year, and none of the 36 containers leaks more than 750mg per year. This test is in addition to the customary in-line leak testing of each container, is applicable at early phase development and is expected to be refined on a per product basis as further data are developed for that product.'	We request that USP remove the Note 'For certain inhalation aerosol drug products (e.g. samples with low fill weight), an alternate acceptance criterion may be needed' and consider removing the specifications entirely from this chapter, or re-instate the criteria that was in place for aerosols with a net fill weight of less than 15g, if it is required to present a criteria in this general chapter for inhalation aerosols. For justification, please refer to General Comment 1 above.

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