An overview of general chapter development for oral and nasal drug products (OINDPs) at the United States Pharmacopeia (USP): Part 2—Informative chapters <1601>, <1602>, <1603> and <1604>

This is the second article of a two-part series that provides an overview of the work currently undertaken by members of the Aerosols Sub-Committee at the USP, focusing on recent updates to the normative and informative chapters within the committee's remit.

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Introduction

A previous article[1] in *Inhalation's* April 2018 issue described the work of USP's Aerosols Sub-Committee of the General Chapters—Dosage Forms Expert Committee on the normative chapters <5> INHALATION AND NASAL DRUG PRODUCTS—GENERAL INFORMATION AND PRODUCT QUALITY TESTS, <601> INHALATION AND NASAL DRUG PRODUCTS: AEROSOLS, SPRAYS, AND POWDERS—PERFORMANCE QUALITY TESTS, <602> PROPELLANTS, <603> TOPICAL AEROSOLS, and <604> LEAK RATE.

As a reminder, USP's general chapters are subdivided into those numbered below <1000> that are generally normative (applicable) chapters and those numbered above <1000> that are informational chapters (Figure 1). This article is the second in the two-part series. It focuses on the informative chapters that are either official text or are in draft, and fall under the remit of the sub-committee:

- <1601> PRODUCTS FOR NEBULIZATION (official)
- <1602> SPACERS AND VALVED HOLDING CHAMBERS USED WITH INHALATION AEROSOLS—CHARACTERIZATION TESTS (official)
- <1603> GOOD CASCADE IMPACTOR PRACTICES (in draft)
- <1604> DATA INTERPRETATION OF AERODYNAMIC PARTICLE SIZE DISTRIBUTION MEASUREMENTS FOR ORALLY INHALED PRODUCTS (in draft)

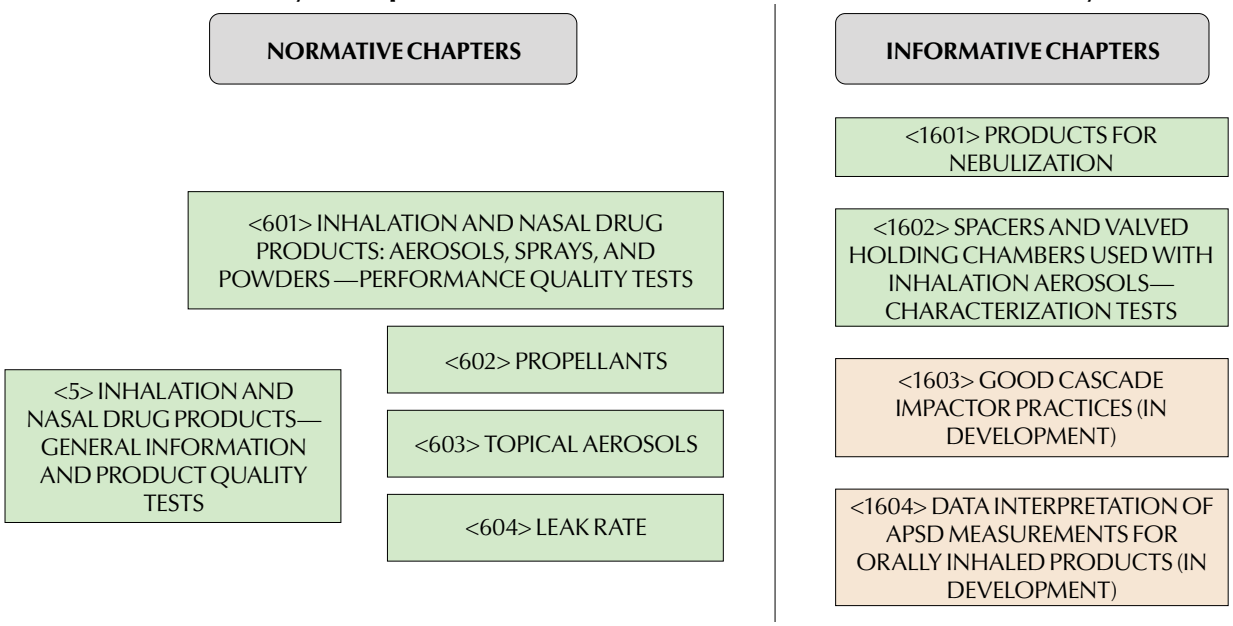
The information provided on draft chapters <1603> and <1604> is based on previously published *Stimuli* articles,[2,3] and should therefore be construed as only being indicative of likely content, given the USP reserves the right to change content, in particular to meet objectives in support of the United States Food and Drug Administration (FDA).

General Chapter <1601> PRODUCTS FOR NEBULIZATION

The development of the content for this chapter originated with the Inhalanda Working Party of the Euro-

Figure 1

***USP–NF* General Chapters within the responsibility of the Aerosols Sub-Committee. Chapters shaded in green are official and chapters shaded in orange are in preparation for publication as Official Text through the *Stimuli* article process in *Pharmacopeial Forum*. APSD = aerodynamic particle size distribution; DDU = delivered dose uniformity.**



pean Pharmacopoeia in the period from 2005-2009, eventually appearing as Monograph 2.9.44: Preparations for Nebulisation. Chapter <1601> is an excellent example of chapters harmonized since its inception; it is almost identical to its European Pharmacopoeial counterpart.[4] The driving force was the realization that there had been little guidance in either of the pharmacopeias concerning quality testing of the widespread aqueous formulations available for use with nebulizing systems not linked with a specific drug product.

Chapter <1601> is comprised of two aspects of performance testing for nebulized products:

1. Drug substance delivery rate and total drug substance delivered per dose;

2. Aerodynamic assessment of nebulized aerosols.

These tests are analogous to the evaluation of delivered dose uniformity (DDU) and aerodynamic particle size distribution (APSD) in Chapter <601>. It is important to keep in mind that these tests standardize the approach for the assessment of the dose that would be delivered to a patient, but are not intended to provide an assessment of a given nebulizer device. Current International Standard ISO 27427:2013 covers nebulizer device testing and includes aspects that relate to the design verification of the device. It also discusses situations in which any solution containing drug product or a non-pharmaceutical tracer compound, such as sodium fluoride, can be used for that purpose.[5]

Nebulizers are commonly used by patients of all ages

Figure 2

Test configuration to determine drug substance delivery rate and total drug substance delivered from a nebulizing system.

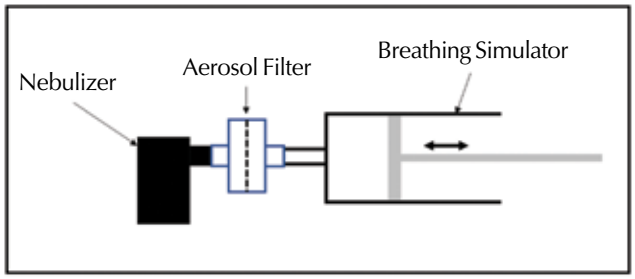


Table 1

Sinusoidal Tidal Breathing Patterns in USP Chapter <1601> to Determine Drug Substance Delivery Rate and Total Drug Substance Delivered from a Nebulizing System

Parameter	NEONATE	INFANT	CHILD	ADULT
Total Volume (mL)	25	50	155	500
Frequency (breathing cycles/min)	40	30	25	15
Inhalation/ Exhalation Ratio	1:3	1:3	1:2	1:1

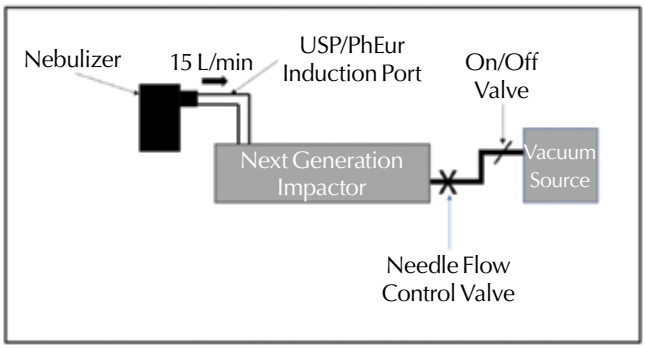
who are tidally breathing. The drug substance delivery rate and total drug substance delivered are therefore measured with the mouthpiece of the nebulizer connected to a breathing simulator via an aerosol filter (Figure 2). Adult breathing patterns (Table 1) were taken from a pre-existing European Standard,[6] while pediatric simulation breathing patterns were derived from a Canadian Standard.[7]

The droplet APSD is measured using the Next Generation Impactor (NGI) operated at a constant flow rate of 15 L/min (Figure 3), in conformity with the original European Standard.[6] The NGI has an archival calibration at this flow rate.[8]

Controlling evaporation of droplets produced by nebulizers may be critical to avoid bias in the droplet size assessment process.[9] Evaporation caused by heat transfer from the impactor metalwork to the droplet stream[10] can be prevented by pre-cooling the impactor to a temperature of about 5°C using a refrigerator or by operating the impactor in a climate-controlled chamber.

Figure 3

Arrangement for sampling nebulizer-generated aqueous droplets containing drug substance for the purpose of determining the APSD of the drug product.

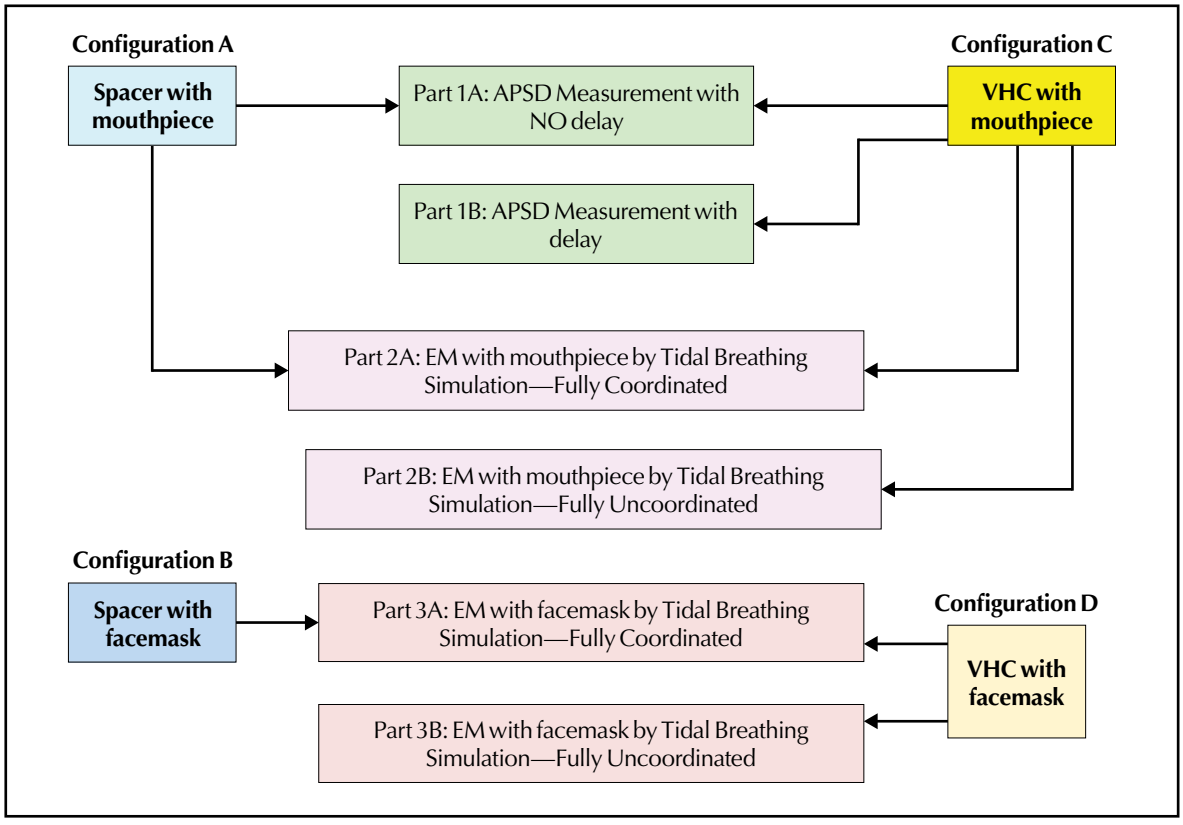


General Chapter <1602> SPACERS AND VALVED HOLDING CHAMBERS USED WITH INHALATION AEROSOLS—CHARACTERIZATION TESTS

The need for a chapter that covers commonly prescribed spacers and valved holding chambers (VHCs) for use with inhalation aerosols (pressurized metered dose inhalers) was identified in 2011 in a *Stimuli* article on the subject.[11] Spacers are open-ended tubes that are sometimes incorporated into the inhaler, with the primary purpose of increasing the distance from the actuator orifice to the patient, thereby reducing impaction of the high velocity particles that emerge from that location upon actuation of the inhaler. On the other hand, VHCs contain at least one valve that enables the resulting aerosol cloud to be retained within the chamber until

Figure 4

Decision tree to select type of performance testing for the four combinations of inhalation aerosol add-on device and patient interface. APSD = aerodynamic particle size distribution; EM = emitted mass; VHC = valved holding chamber.



the patient opens the valve by inhalation to receive the medication.[12] Some VHCs with a facemask patient interface also contain a separate valve that opens during exhalation, thereby permitting tidal breathing without requiring patients to remove the facemask from the face. Both types of add-on devices greatly modify the APSD of the inhaled aerosol, primarily by virtually eliminating the coarse particle mass fraction greater than about 5 µm aerodynamic diameter that would otherwise impact on surfaces of the oropharyngeal region.[12]

The content of chapter <1602> is structured so that the user is first asked to identify if the add-on device is either a spacer or VHC. This first step is important in that some of the subsequent testing would be inappropriate for spacers; for example, where a short delay is simulated following inhaler actuation and sampling of the aerosol since the emitted aerosol would merely escape into the local environment during the delay interval. A decision tree diagram is provided as an aid for this process (Figure 4).

Chapter <1602> also covers two aspects of performance testing:

1. APSD determined by multi-stage cascade impactor operated at a constant flow rate;
2. Emitted mass (EM) determined by filter collection using a breathing simulator.

These tests are based on previously validated methods.[7]

The methodology for aerosol APSD determination is based on the method listed in Chapter <601> and incorporates a means of quantifying the short delay following inhaler actuation before sampling the aerosol by the impactor. An example of such a "delay" apparatus is illustrated in Figure 5. The shortest recommended delay interval is 1 second and example delay intervals of 2, 5 and 10 seconds are suggested.

The EM determination method uses a filter to collect the aerosol when it is sampled, simulating tidal breathing at the patient interface. The breathing patterns for the adult condition (Table 2) are slightly different from those in Chapter <1601>, reflecting the differing origins of the two chapters. Both spacers and VHCs intended for all sub-groups of patients are evaluated

Figure 5

Apparatus to create a delay between inhaler actuation and the onset of aerosol sampling from a VHC via multi-stage cascade impactor; the impactor operates at a constant flow rate throughout the measurement process.

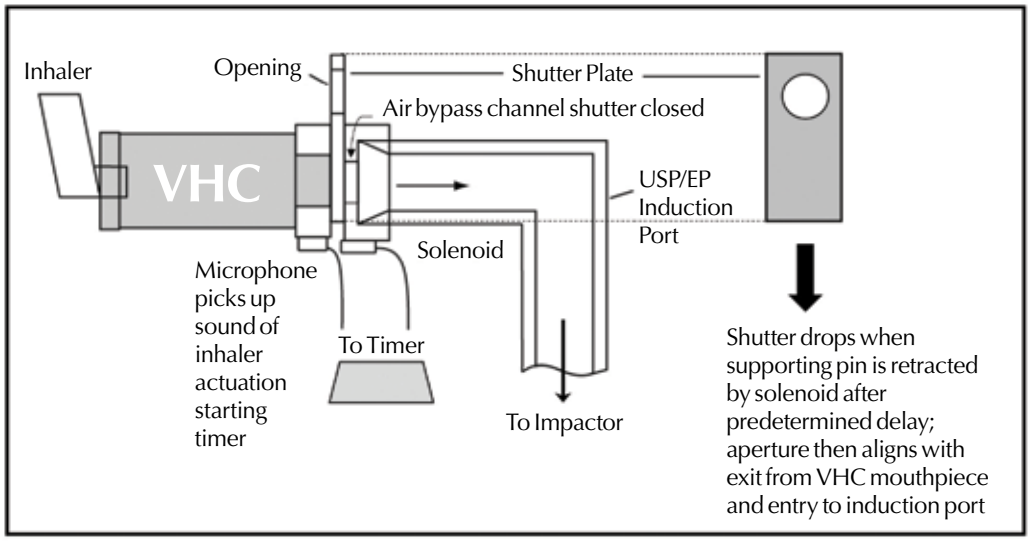


Table 2

Sinusoidal Tidal Breathing Patterns in USP Chapter <1602> for the Determination of Total EM from an Inhalation Aerosol with Spacer or VHC

Parameter	NEONATE	INFANT	CHILD	ADULT	
				Type 1	Type 2
Total Volume (mL)	25	50	155	770	500
Frequency (breathing cycles/min)	40	30	25	12	13
Inhalation/Exhalation Ratio	1:3	1:3	1:2	1:2	1:2

actuating the inhaler at the onset of inhalation, mimicking the ideal case of a fully-coordinated patient. VHCs are also evaluated actuating the inhaler at the onset of exhalation, to simulate the opposite condition in which the patient is uncoordinated.

The testing of spacers and VHCs using a facemask as the patient interface poses a significant challenge. It is essential to achieve an effective seal between the facemask and entry to the measurement equipment at all times because once the propellant from the inhaler has evaporated, there is no energy source to move the aerosol towards the patient. Therefore, ambient air leakages via the facemask-to-face contact will preferentially take place over the inhalation valve opening, resulting in the potential for significant reduction in medication delivery.[13] This scenario is particularly important when delivering medication to neonates and infants, whose tidal volumes and inhalation flow rates are small compared to those of adults.[14] Chapter <1602> suggests the use of age-appropriate face models to act as an interface between the spacer or VHC, and facemask and the aerosol collection filter. An anatomically accurate upper airway (oro- or naso-pharynx) may also be part of the model, in which case the collected EM is indicative of the portion of the dose of medication per actuation capable of penetrating to the airways of the lungs. Currently, adult, child and infant face models are commercially available (Copley Scientific Ltd., Nottingham, UK).

Chapter <1602> lists the following attributes required for such a face model:

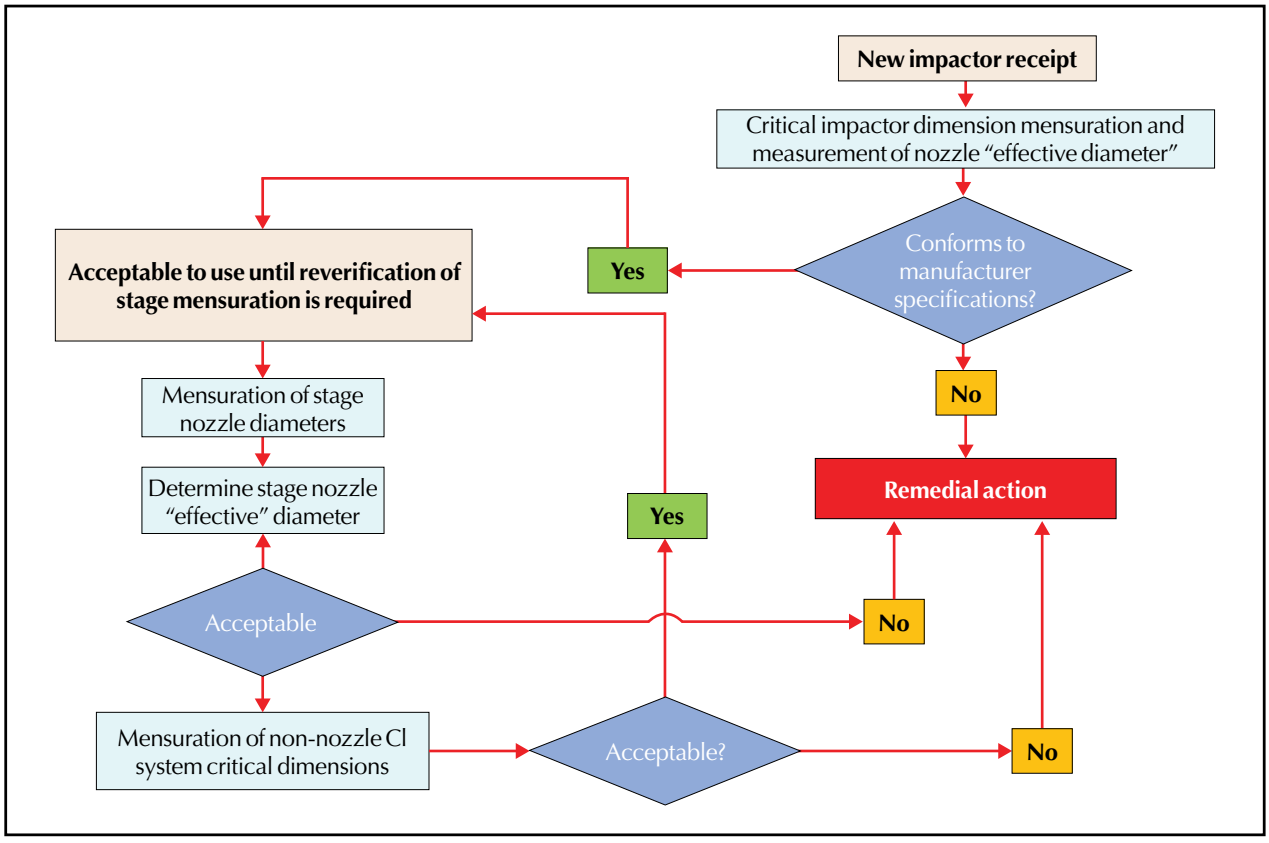
1. Appropriate facial dimensions for the intended user age range;
2. Ability to apply the facemask with the predicted amount of dead space when it is applied with a clinically appropriate force to the model;
3. Physiologically accurate soft facial tissue modeling around the chin, cheeks and nose where the facemask contacts the face;
4. Means of correctly mounting the spacer/VHC so that the facemask is oriented with the correct alignment to the face, as would occur when in use by a patient.

General Chapter <1603> GOOD CASCADE IMPACTOR PRACTICES

The concept of developing a guide for Good Cascade Impactor Practices (GCIP) originated from work by the US-based Product Quality Research Institute (PQRI).[15] In the early 2000s, PQRI was tasked with addressing the

Figure 6

Scheme for the application of stage mensuration as part of good cascade impactor practice (GCIP) to confirm suitability of use for compendial cascade impactor (CI) apparatuses; in-use mensuration check frequency is determined by amount of impactor use and product/solvent characteristics. CI = cascade impactor.



FDA recommendation concerning the role of the mass balance from cascade impactor measurements of APSD in the context of product quality control. There was an appreciation for the complexity of these APSD determinations in terms of the number of component parts that need to be managed throughout the measurement procedures and the likelihood for storage between uses. A formal development of GCIP was therefore considered useful to ensure that the cascade impaction equipment, including pre-separator, induction port, etc., is maintained system suitable throughout its lifetime.

The initial development of GCIP was largely focused on ensuring that the critical stage nozzles of the impactor remained within the manufacturer's specifications.[16] Nozzle diameter specifications for the multi-stage cascade impactor apparatuses are described in Chapter <601>. A *Stimuli* article on the topic in 2015[17] also helped provide momentum towards developing this new chapter. Figure 6 illustrates the processes recommended for the application of stage mensuration. Periodically, the nozzle diameters are individually measured by microscopy-image analysis and the "average" diameter, termed the effective diameter and calculated as described by Roberts,[18] is used to determine whether the stage remains suitable for continued use.

More recently, there has been a realization that Chapter <1603> needs to go beyond addressing this "maintenance" aspect and should include "in use" considerations. Table 3 summarizes the latest thinking on the topic and lists two aspects of good practice side-by-side.

Chapter <1603> is currently in draft. After completing the internal approvals process, it will be published as an In-Process Revision in the March-April 2019 issue of *Pharmacopeial Forum* (Volume 45(2)), providing the first opportunity to receive public comment.

General Chapter <1604> DATA INTERPRETATION OF AERODYNAMIC PARTICLE SIZE DISTRIBUTION MEASUREMENTS FOR ORALLY INHALED PRODUCTS

The original interpretation of cascade impactor measurements of inhaler aerosol APSD contained within Chapter <601> was removed several years ago, in response to advice that it did not conform to current FDA practices. Since that time, there has been significant stakeholder demand for advice on data interpretation, given the several metrics that can be established from a given set of APSD measurements (Figure 7).

Table 3

Components of GCIP Addressing Aspects that Relate to Maintenance and In-Use

MAINTENANCE	IN-USE
Stage mensuration, measurement traceability and mensuration interval	Assertion of correct assembly
Assertion of internal losses	Precautions to mitigate particle bounce and re-entrainment
Replacement of a damaged/deformed collection plate/cup	Precautions to mitigate bias arising from electrostatic charge
Replacement of a damaged stage/seal body	Precautions to mitigate leakage of the apparatus
	Assertion of correct flow rate
	Cleaning and storage
	Internal loss management

This has culminated in the recently issued revised draft guidance from the FDA for quality considerations relating to inhaled aerosol (MDI) and dry powder inhaler (DPI) products,[19] which states that, in the context of evaluating impactor-measured APSDs, "it can be appropriate to refer to the current USP chapter for APSD procedures."

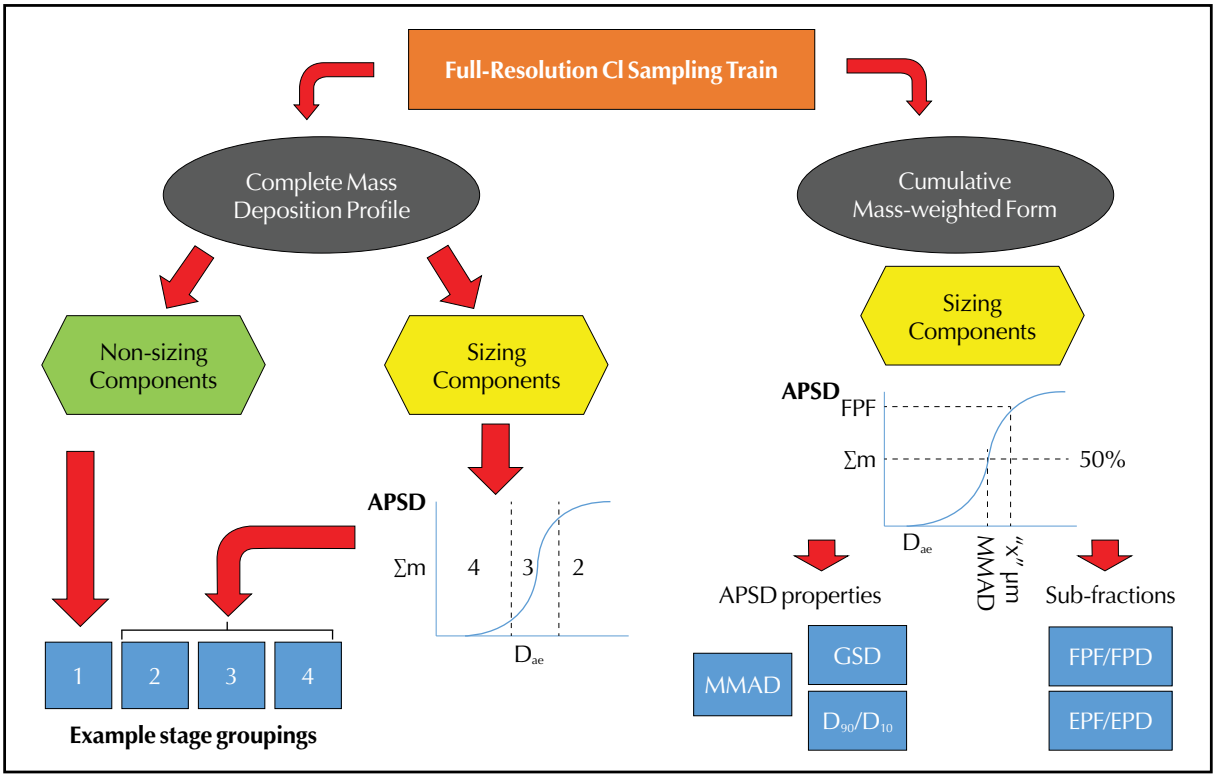
In response, a joint sub-committee involving statisticians and members of the Aerosols Sub-Committee was formed in 2016, tasked (among other work) with the development of a new informative chapter covering APSD analysis. Their thinking was crystallized in a *Stimuli* article published in 2017.[4] Chapter <1604> is also currently in preparation for publication as an In-Process Revision in the March-April 2019 issue of *Pharmacopeial Forum* (Volume 45(2)) with the deadline for public comment being May 30, 2019.

Conclusions

Four informative chapters relating to the quality testing of OINDPs have been published in *USP–NF* or are in draft form at the time this article was written. Their purpose is primarily to support the content of the normative chapters that were described in the first article of this two-part series.

Figure 7

Alternative approaches to the interpretation of multi-stage cascade impactor-measured inhaler aerosol APSD data. MMAD = mass median aerodynamic diameter; GSD = geometric standard deviation; D_{90} and D_{10} are the sizes corresponding to the 10th and 90th mass percentiles of the APSD respectively; FPF and FPD are fine particle fraction and fine particle dose (mass) respectively; EPF and EPD are extra-fine particle fraction and extra-fine particle dose respectively.



There are currently no plans to augment these chapters in the <160x> series, unless there is broad stakeholder demand to do so for a particular purpose, as inhaler technology develops. Feedback from these articles is welcome, preferably in writing. Please contact Dr. Kahkashan Zaidi, Principal Scientific Liaison at the USP; e-mail: kxz@usp.org; Tel.: +1-301-816-8269.

Disclaimer

This article is the work of the USP's Aerosols Sub-Committee and has been provided as a means of helping readers of *Inhalation* be aware of developments with *USP–NF* chapters that are of concern to the community involved with OINDPs. It does not represent official text and readers are advised to consult the current issue of *USP–NF* at http://www.uspnf.com for up-to-date information concerning chapter content.

References

1. Zaidi K, Curry P, Hickey AJ, Leiner S, Mitchell JP, Poochikian G, Suggett J. An overview of general chapter development for oral and nasal drug products (OINDPs) at the US Pharmacopeia (USP): Part 1—Normative chapters <5>, <601>, <602>, <603>, and <604>. Inhalation. 2018;12(2):21-27.

2. Nichols SC, Mitchell JP. A rational approach to cascade impactor mensuration in a good cascade impactor practice (GCIP) environment. Pharm Forum. 2014;40(1). www.uspnf.com/pharmacopeial-forum. Accessed May 5, 2018.

3. Mitchell J, Sandell D, Suggett J, Christopher JD, Leiner S, Walfish S, Curry P, Zaidi K. Proposals for data interpretation in the context of determination of aerodynamic particle size distribution profile for orally inhaled products. Pharm Forum. 2017;43(3). www.uspnf.com/pharmacopeial-forum. Accessed June 25, 2018.

4. European Directorate for the Quality of Medicines (EDQM). Preparations for nebulization. European Pharmacopeia, 9th ed. Strasbourg, France: EDQM.

5. International Standards Organization (ISO). Anaesthetic and respiratory equipment—Nebulizing systems and components. ISO 27427:2013.

6. European Committee for Standardisation (CEN). Respiratory therapy equipment—Part 1: Nebulising systems and their components. Ref: EN 13544-1:2006.

7. Canadian Standards Association (CSA). Spacers and

holding chambers for use with metered-dose inhalers. Ref: Z264.1-02:2008.

8. Marple VA, Olson BA, Santhanakrishnan K, Roberts DL, Mitchell J, Hudson-Curtis BL. Next generation pharmaceutical impactor: A new impactor for pharmaceutical inhaler testing. Part III. Extension of archival calibration to 15 L/min. J Aerosol Med. 2004; 17(4):335-343.

9. Dennis J, Berg E, Sandell D, Ali A, Lamb P, Tservistas M, Karlsson M, Mitchell J. Cooling the NGI—An approach to size a nebulised aerosol more accurately. Pharmeur Sci Notes. 2008;2008(1):27-30.

10. Stapleton KW, Finlay WH. Undersizing of droplets from a vented nebulizer caused by aerosol heating during transit through an Anderson impactor. J Aerosol Sci. 1999;30(1):105-109.

11. Mitchell JP, Poochikian G, Hickey AJ, Suggett J, Curry PD, Tougas TP, Zaidi K. In vitro assessment of spacers and valved holding chambers used with pressurized metered-dose inhalers: The need for a USP chapter with clinically relevant test methods. Pharm Forum. 2011;37(4). www.uspnf.com/pharmacopeial-forum. Accessed June 25, 2018.

12. Dolovich MB, Ahrens RC, Hess DR, Anderson P, Dhand R, Rau JL. American College of Chest Physicians; American College of Asthma, Allergy, and Immunology. Device selection and outcomes of aerosol therapy: Evidence-Based guidelines. Chest. 2005;127(1):335-371.

13. Esposito-Festen J, Ates B, van Vliet F, Hop W, Tiddens H. Aerosol delivery to young children by pMDI-spacer: Is facemask design important? Pediatr Allergy Immunol. 2005;16(4):348-353.

14. Mitchell JP, Dolovich MB. Clinically relevant test methods to establish in vitro equivalence for spacers and valved holding chambers used with pressurized metered dose inhalers (pMDIs). J Aerosol Med Pulm Drug Deliv. 2012;25(4):217-242.

15. Christopher D, Curry P, Doub B, Furnkranz K, Lavery M, Lin K, Lyapustina S, Mitchell J, Rogers B, Strickland H, Tougas T, Tsong T, Wyka B. PQRI Particle Size Distribution Mass Balance Working Group. Considerations for the development and practice of cascade impaction testing including a mass balance failure investigation tree. J Aerosol Med. 2003;16(3):235-247.

16. Nichols SC, Mitchell JP, Shelton CM, Roberts DL. Good cascade impactor practice (GCIP) and considerations for "in-use" specifications. AAPS PharmSciTech. 2013;14(1):375-390.

17. Nichols SC, Mitchell JP. A rational approach to cascade impactor mensuration in a good cascade impactor practice (GCIP) environment. Pharm Forum. 2015;41(4). www.uspnf.com/pharmacopeial-forum. Accessed June 25, 2018.

18. Roberts DL. Theory of multi-nozzle impactor stages and the interpretation of stage mensuration data. Aerosol Sci Technol. 2009;43(11):1119-1129.

19. US Food and Drug Administration (FDA). FDA Guidance for Industry: Metered dose inhaler (MDI) and dry powder inhaler (DPI) products—Quality considerations. Draft Guidance, Revision 1 (April 2018). www.fda.gov/downloads/drugs/guidances/ucm070573.pdf. Accessed June 25, 2018.

The relationship between the United States Pharmacopeial Convention (USP) and the US Food and Drug Administration (FDA) dates back to the 1906 Pure Food and Drug Act, which deemed the *United States Pharmacopeia* and the *National Formulary* official compendia under federal law. For more information about the relationship between the FDA and USP, please visit: http://www.usp.org/about/public-policy/usp-fda-roles.

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