An overview of general chapter development for oral and nasal drug products (OINDPs) at the United States Pharmacopeia (USP): Part 1—Normative chapters <5>, <601>, <602>, <603> and <604>

This is the first 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

The Aerosols Sub-Committee (SC) of the General Chapters—Dosage Forms Expert Committee revises the United States Pharmacopeia (USP) chapters to reflect scientific developments and stakeholder input, as well as to align them with current and evolving regulatory requirements. The chapters within the responsibility of the Aerosols Sub-Committee are listed in Figure 1.

The general chapters of the *United States Pharmacopeia –National Formulary* (*USP–NF)* are subdivided. Those with numbers below <1000> are generally "normative" chapters, which have content that may be mandated in order to meet regulatory requirements. Chapters numbered above <1000> are "informative" and contain material that is useful to apply in performance testing but may not be mandatory with respect to use in regulatory submissions.

This article is the first of a two-part series in *Inhalation*, wherein sub-committee members will provide an overview of USP chapter content to help readers more clearly understand the purpose and application of each chapter. The focus of the present article is on the following 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
- <604> LEAK RATE

The second article is scheduled to appear in the December 2018 issue of *Inhalation* and will focus on the informative chapters in the <1600> series, which are currently undergoing significant changes.

Users of pharmacopeial chapters are strongly encouraged to discuss specific details concerning their product(s) with the appropriate regulatory bodies, including the United States Food and Drug Administration (US FDA), to establish precise requirements for testing, registration and quality control following approval.

General Chapter <5> INHALATION AND NASAL DRUG PRODUCTS—GENERAL INFORMATION AND PRODUCT QUALITY TESTS

Chapter <5> is one of several general chapters that cover General Requirements for Quality Tests and Assays for the different major dosage forms created in the 2010-2015 Council of Experts cycle. General quality tests are identified separately from the performance quality tests

that are more specific to OINDPs which appear in General Chapters <601> *INHALATION AND NASAL DRUG PRODUCTS: AEROSOLS, SPRAYS, AND POWDERS—PERFORMANCE QUALITY TESTS*, <602> *PROPELLANTS*, <603> *TOPICAL AEROSOLS*, and <604> *LEAK RATE*. These same performance quality tests also appear in the <1600> series of informative chapters that cover products for nebulization and spacers and valved holding chambers used with inhalation aerosols.

Table 1 defines the different forms of OINDPs and introduces the class definitions that appear in all other chapters associated with this dosage form. The terminology may not always be the same as class names in common use (e.g., *pressurized metered dose inhalers (pMDIs)* are referred to as *inhalation aerosols)*. However, these definitions were carefully developed to be highly specific for each OINDP class, as well as to avoid confusion where tests specific to each class of inhaler are specified in this and other chapters associated with OINDPs. This chapter mainly contains the standard quality tests listed for each of the OINDP classes and descriptions of each test. A few minor changes to these lists of tests have been made in the latest revision to <5> to ensure consistency across all the OINDP classes (Table 2).

General Chapter <601> INHALATION AND NASAL DRUG PRODUCTS: AEROSOLS, SPRAYS, AND POWDERS—PERFORMANCE QUALITY TESTS

Chapter <601> is primarily concerned with the determination of product Delivered Dose Uniformity (DDU) and Aerodynamic Particle Size Distribution (APSD). The chapter also addresses the use of laser diffractometry for the determination of droplet size distribution of spray and aerosol drug products. This *USP–NF* chapter is among the most commonly used by stakeholders involved with assurance of OINDP quality. Therefore, it has undergone several major revisions since 2010 to keep it up to date.

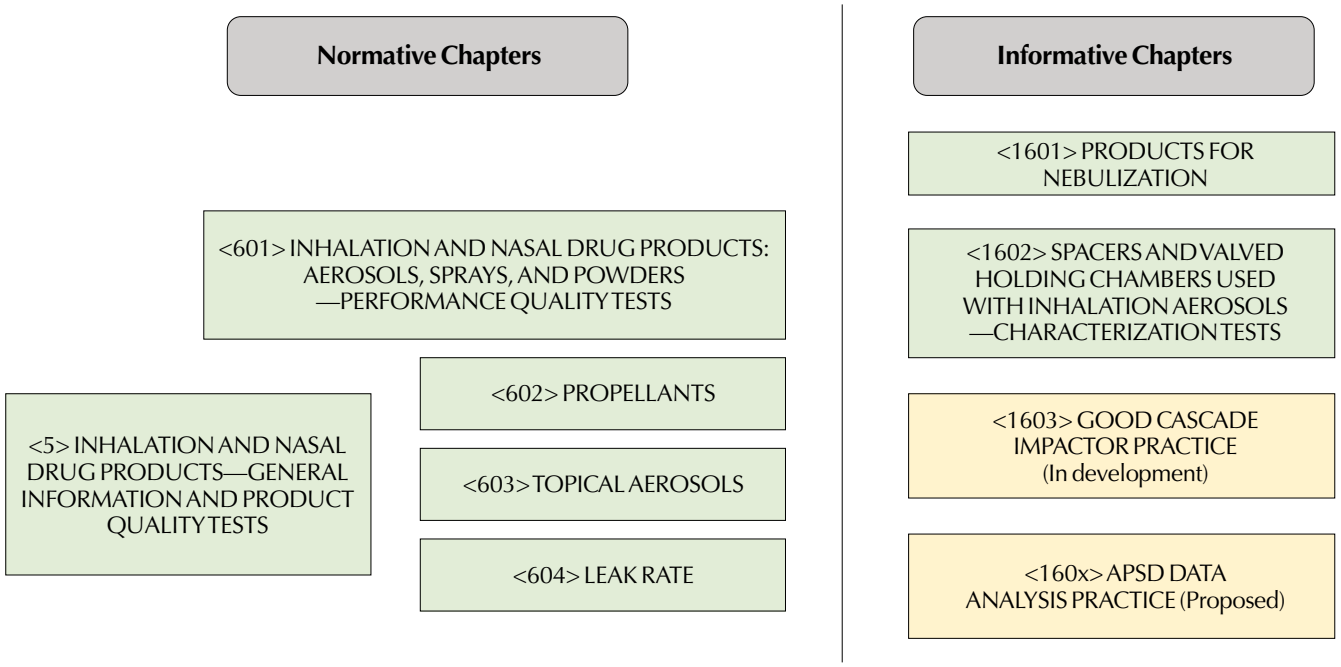
Significant changes have included eliminating the section that covers data analysis in association with APSD determination. In the near future, it is proposed to reinstate APSD-related data analysis as a new informative chapter (Figure 1, <160x>) that is more attuned to current FDA requirements.

The most recent *In Process Revision* of <601> took place in 2016, appearing in volume 42(6) of *Pharmacopeial Forum* (PF). This version received extensive public feedback, reflecting the importance that stakeholders have attributed to the content of this chapter. In response, the sub-committee made several changes to improve readability and consistency of the text associated with each section of the chapter. The sub-committee also took this opportunity to reorganize sections and subsections (Table 3).

- Section A, which covers DDU determinations, is largely unchanged from the version in the current official text. However, the illustrations of the dose collection apparatus configurations, (a) for use with inhalation powders and (b) for use with all other classes of inhalers, were clarified so that their captions align with the content of the corresponding tables that define each apparatus.

Figure 1

***USP–NF* General Chapters within the Responsibility of the Aerosols Sub-Committee. Chapters shaded green are official and chapters shaded in yellow are either in development or have been proposed through the *Stimuli Article* process in *Pharmacopeial Forum*. DDU = Delivered Dose Uniformity; APSD = Aerodynamic Particle Size Distribution**



- A new subsection, B.1.2, has been added in section B to address the issue of APSD measurements associated with nasal aerosols and sprays, where interest has been expressed in developing methodology to quantify the typically very small portion of the dose within the size ranges of existing cascade impactors. It should be noted that the recommendation given to follow the procedures in Section C associated with cascade impaction, is still rudimentary, because robust methodology specific to these classes of OINDP still needs to be developed.
- A new subsection, C.1.5, was added to section C, which brings together all cascade impactor descriptions with their stage cut-off diameters at various nominal flow rates associated with each configuration. Apparatuses 2 (Marple-Miller impactor) and 4 (Multi-Stage Liquid Impinger) are proposed to be removed from the options offered for APSD determination. This major decision was made to address requests to simplify available options, so that this section includes only methods currently used for FDA submissions, namely the Andersen Cascade Impactor with and without pre-separator, and the Next Generation Impactor, also with or without pre-separator. In addition, the previous references to apparatus numbers associated with this part of the chapter were eliminated to identify each of the remaining four apparatuses by their commonly used names.

These proposals will be published for public comment in *Pharmacopeial Forum* (*PF*), and the USP looks forward to stakeholder feedback on these proposed changes.

Chapters <602>, <603> and <604>

These three chapters contain material that is largely legacy in nature, which has not changed significantly in recent years. Chapter <602> provides requirements for establishing the boiling temperature, high boiling residues and water content for propellants used with inhalation and nasal aerosols, as well as a general sampling procedure. Chapter <603> describes methods for delivery rate and dosage amount for aerosol products designed to be delivered topically other than to the lungs. This includes dermatological foams and sprays. This chapter also describes tests for container pressure, minimum fill and leakage. Chapter <604> defines testing to establish the leakage rate from an aerosol container.

Table 1

Established Names and Definitions for OINDP Classes Given in *USP—NF* <5>

Delivery Mode	Class Name	Definition
ORAL	Inhalation Aerosol	A drug product for oral inhalation that is packaged under pressure and delivers a specified amount of therapeutically active ingredient(s) upon activation of an accurately metered valve system. Inhalation aerosols are more commonly known as metered dose inhalers or MDIs.
	Inhalation Powder	A drug powder for oral inhalation with the use of a device that aerosolizes and delivers an accurately metered amount of therapeutically active ingredient(s). Inhalation powders are more commonly known as dry powder inhalers or DPIs.
	Inhalation Spray	A non-pressurized, accurately metered, liquid drug dosage form for oral inhalation that is packaged in a container that delivers fine droplets of the formulation upon activation. Soft Mist Inhalers are included in this class.
	Inhalation Solution	A drug solution for oral inhalation with the use of a nebulization system
	Inhalation Suspension	A drug suspension for oral inhalation with the use of a nebulization system
	Solution for Inhalation	A drug solution for oral inhalation that must be diluted before it is administered with the use of a nebulization system
	[Drug] for Inhalation Solution	A drug powder that, upon the addition of a suitable vehicle, yields a solution that conforms in all respects to an inhalation solution
NASAL	Nasal Aerosol	A drug product for local application into the nasal passages that is packaged under pressure and delivers a specified amount of therapeutically active ingredient(s) upon activation of an accurately metered valve system
	Nasal Spray	A non-pressurized, accurately metered, liquid drug dosage form for local application into the nasal passages that is packaged in a container and delivers droplets of the formulation upon activation
	Nasal Solution	A non-pressurized, liquid drug dosage form for local application into the nasal passages
	Nasal Powder	Drug powder for local application into the nasal passages with the use of a device that delivers and aerosolizes an accurately metered amount of the therapeutically active ingredient(s)

Product monographs

Although some monographs relating to chlorofluorohydrocarbon-based pMDIs were previously available, until recently there were no monographs associated with orally inhaled products. However, the USP has published the following monographs relating to the following inhalation aerosol and inhalation powder products:

- Fluticasone propionate inhalation powder,
- Salmeterol inhalation powder,
- Fluticasone propionate and salmeterol inhalation powder,
- Fluticasone propionate inhalation aerosol,
- Fluticasone propionate and salmeterol inhalation aerosol.

Table 2

List of General Quality Tests Identified in *USP—NF* <5> for Each OINDP Class

Test Description	Inhalation Aerosol	Inhalation Solution	Inhalation Suspension	Solution for Inhalation	Drug for Inhalation Solution	Inhalation Spray	Inhalation Powder	Nasal Aerosol	Nasal Spray	Nasal Powder	Nasal Solution
Co-solvent Content (if present)	X							X			
Assay (strength and content uniformity)	X	X	X	X	X	X	X	X	X	X	X
Assay for Antimicrobial Preservative and Stabilizing Excipients (if present)		X	X	X	X	X			X		X
Content Uniformity for Pre-metered Dosage Forms		X	X	X	X	X	X		X	X	
Clarity and Color of Solution upon Dilution				X	X						
Elemental Impurities	X	X	X	X	X	X	X	X	X	X	X
Foreign Particulate Matter	X	X	X	X	X	X	X	X	X	X	X
Identification	X	X	X	X	X	X	X	X	X	X	X
Impurities and Degradation Products	X	X	X	X	X	X	X	X	X	X	X
Leachables	X	X	X	X	X	X	X	X	X	X	X
Leak Rate	X										
Microbial Limits	X						X	X	X	X	X
Net Fill Weight	X	X	X	X	X	X	X	X	X	X	X
Osmolality		X	X	X	X	X			X		X
pH		X	X	X	X	X			X		X
Primary Particle Size Distribution			X						X		
Plume Geometry						X					
Pump Delivery									X		
Reconstitution and Time (powder)					X						
Residual Solvent							X			X	
Spray Pattern	X							X	X		
Sterility		X	X	X	X				X		
Valve Delivery	X							X			
Viscosity									X		X
Water Content	X				X		X	X		X	
Weight Loss		X	X	X	X						

Table 3

Content of Proposed 2018 Revision to *USP—NF* General Chapter <601>

Property	Section	Sub-sections		Content
DDU	**A**			**DELIVERED DOSE UNIFORMITY**
	A.1			**Inhalation Aerosols and Inhalation Sprays**
		A.1.1		Delivered Dose Uniformity of Inhalation Aerosols and Inhalation Sprays
			A.1.1.1	Sampling the Delivered Dose from Inhalation Aerosols and Inhalation Sprays
	A.2			**Nasal Aerosols and Nasal Sprays**
		A.2.1		Delivered Dose Uniformity of Nasal Aerosols and Sprays
			A.2.1.1	Sampling the Delivered Dose from Nasal Aerosols
			A.2.1.2	Sampling the Delivered Dose from Nasal Sprays
	A.3			**Inhalation Powders**
		A.3.1.		Delivered Dose Uniformity of Inhalation Powders
			A.3.1.1	Sampling the Delivered Dose from Inhalation Powders
	A.4			**Nasal Powders**
		A.4.1		Delivered Dose Uniformity of Nasal Powders
			A.4.1.1	Sampling the Delivered Dose from Nasal Powders
PSD and APSD	**B**			**DROPLET/PARTICLE SIZE DISTRIBUTION - NASAL AEROSOLS AND SPRAYS**
		B.1.1		Particle Size Measurement by Laser Diffraction
		B.1.2		Aerodynamic Particle Size Distribution (nasal aerosols and sprays) —Determination by Cascade Impaction
APSD	**C**			**AERODYNAMIC PARTICLE SIZE DISTRIBUTION: INHALATION AEROSOLS, SPRAYS AND POWDERS**
	C.1			**General Principles of Aerodynamic Particle Size Measurement**
		C.1.1		Stage Mensuration
		C.1.2		Inter-stage Drug Loss (Wall Losses)
		C.1.3		Re-Entrainment
		C.1.4		Mass Balance
		C.1.5		Procedure
	C.2			**Andersen Cascade Impactor without pre-separator for Inhalation Aerosols and Sprays, and Nasal Aerosols**
		C.2.1		Design—Andersen Cascade Impactor without pre-separator
		C.2.2		Procedure—Andersen Cascade Impactor without pre-separator
	C.3			**Andersen Cascade Impactor with pre-separator for Inhalation and Nasal Powders**
		C.3.1		Design—Andersen Cascade Impactor with pre-separator
		C.3.2		Procedure—Andersen Cascade Impactor with pre-separator
	C.4			**Next Generation Impactor without pre-separator for Inhalation Aerosols and Sprays, and Nasal Aerosols**
		C.4.1		Design—Next Generation Impactor without pre-separator
		C.4.2		Procedure—Next Generation Impactor without pre-separator
	C.5			**Next Generation Impactor with pre-separator for Inhalation Aerosols and Nasal Powders**
		C.5.1		Design—Next Generation Impactor with pre-separator
		C.5.2		Procedure—Next Generation Impactor with pre-separator

The USP Chemical Medicines Expert Committee is responsible for the content of product monographs. The Aerosols Sub-Committee's role is to be aware of the content in these monographs, given that the testing methodology contained in these monographs takes precedence over the procedures in the corresponding General Chapter(s). It should be noted that these product monographs each refer to the use of a specific induction port (throat) as inlet to the cascade impactor, even though this entry port is not included in <601>. It remains to be seen whether other OINDP manufacturers will offer text for future product monographs, given the precedent set by these additions to the *USP–NF*.

Conclusions

The Aerosols Sub-Committee continues the process of developing the General Chapters assigned by the parent General Chapters Committee, with the primary goal of supporting the needs of the FDA. The secondary goal is to harmonize methods with the other major compendia (European and Japanese Pharmacopeias) through the inter-compendial Pharmacopeial Discussion Group (PDG) process. Readers of this article are encouraged to maintain awareness and contribute to the public feedback process through *Stimuli Articles* and comments on *In Process Revisions* that appear from time to time in the *Pharmacopeial Forum* (*PF*), which has free online access, following a one-time registration, at http://www.uspnf.com/pharmacopeial-forum.

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 the *USP–NF* at http://www.uspnf.com/ for up-to-date information concerning chapter content.

Please watch for the second article in this series, scheduled for publication in December 2018. It will focus on the informative chapters in the <1600> series, which are currently undergoing significant changes.

References

USP. *USP 40–NF 35 S2*. <5> INHALATION AND NASAL DRUG PRODUCTS—GENERAL

INFORMATION AND PRODUCT QUALITY TESTS. Rockville, MD: United States Pharmacopeial Convention; 2017. p. 90-98.

USP. *USP 40–NF 35 S2*. <601> INHALATION AND NASAL DRUG PRODUCTS: AEROSOLS, SPRAYS, AND POWDERS—PERFORMANCE QUALITY TESTS. Rockville, MD: United States Pharmacopeial Convention; 2017. p. 472-498.

USP. *USP 40–NF 35 S2*. <602> PROPELLANTS. Rockville, MD: United States Pharmacopeial Convention; 2017. p. 498–499.

USP. *USP 40–NF 35 S2*. <603> TOPICAL AEROSOLS. Rockville, MD: United States Pharmacopeial Convention; 2017. p. 499–500.

USP. *USP 40–NF 35 S2*. <604> LEAK RATE. Rockville, MD: United States Pharmacopeial Convention; 2017. p. 500–501.

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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