A critical evaluation of the revised and new USP Chapters for Aerosols: <601> and <5> [Pharm Forum 2011; 37(4)]

This is the first of two articles, to be published by Inhalation, presenting opinions from representatives of IPAC-RS on the proposed revised and new USP Chapters for Aerosols <601> and <5>.

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Introduction

The United States Pharmacopeia (USP) and National Formulary (NF) play an important role in setting public standards for drugs and excipients, respectively. The USP standards are used in the United States and many other countries around the world to demonstrate identity, strength, quality and purity of medicinal substances and preparations. In USP's own words: *"The U.S. Federal Food, Drug, and Cosmetics Act designates the USP–NF as the official compendia for drugs marketed in the United States. A drug product in the U.S. market must conform to the standards in USP–NF to avoid possible charges of adulteration and misbranding. The USP–NF is also widely used by manufacturers wishing to market therapeutic products worldwide. Meeting USP–NF standards is accepted globally as assurance of high quality."* (From www.usp.org/USPNF/understandingUSPNF.html)

The legal standing of pharmacopeial standards is clarified in the USP General Notices and Requirements (see Table 1). Importantly, USP standards in chapters numbered below <1000> must be complied with 'if, and whenever' tested – even if tested numerous times, even if close to expiry date. On the other hand, the USP states that it is not an enforcement agency. The enforcement of USP standards falls, therefore, to other governmental agencies. In the United States, this role is played by the U.S. Food and Drug Administration (FDA), State Boards of Pharmacy, State and Municipal Departments of Health, etc.

In fact, the FDA refers to USP tests for regulatory purposes. For example, the 1998 Draft FDA Guidance *Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products Chemistry, Manufacturing, and Controls Documentation*[1] as well as the 2002 FDA final guidance *Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products - Chemistry, Manufacturing, and Controls Documentation*[2] reference the following USP Chapters:

<61> Microbial Limits;

<71> Sterility Tests;

<87> and <88> Biological Reactivity Tests;

<601> Aerosols (e.g., for the Unit-Spray sampling apparatus, and for the Leak-Test sampling plan);

<755> Minimum Fill; and

<905> Uniformity of Dosage Units.

Both guidances also mention that meeting USP-NF requirements may not always be sufficient, such as for controlling the quality of excipients: *"When a USP or National Formulary (NF) monograph material is used, the associated specifications may not always provide adequate assurance with regard to the assay, quality, or purity of the material or its performance in the drug product. In these cases, monograph specifications should be supplemented with appropriate controls (e.g., particle size distribution, crystal forms, amorphous content, foreign particulates) to ensure batch-to-batch reproducibility of these components."* (From page 8 of the FDA Nasal Guidance. Similar text can be found starting on page 9 of the FDA MDI/DPI guidance.)

For many years, general standards for orally inhaled and nasal drug products had been described in USP Chapter <601>, entitled *"Aerosols, Nasal Sprays, Metered-Dose Inhalers, and Dry Powder Inhalers"* (see, for example, USP 34 p. 218). The Chapter served its purpose reasonably well; there had been no indication that the standards or methods were outdated or required significant revi-

Table 1

Excerpts from General Notices and Requirements [from the 2010 Pharm.Forum 36(6)][12]
(Emphasis added by authors)

"2.30. Legal Recognition

The USP and NF are recognized in the laws and regulations of many countries throughout the world. Regulatory authorities may enforce the standards presented in the USP and NF, but because recognition of the USP and NF may vary by country, users should understand applicable laws and regulations.

In the United States under the Federal Food, Drug, and Cosmetic Act (FDCA), both USP and NF are recognized as official compendia. A drug with a name recognized in USP–NF must comply with compendial identity standards or be deemed adulterated, misbranded, or both. *To avoid being deemed adulterated, such drugs must also comply with compendial standards for strength, quality, and purity, unless labeled to show all respects in which the drug differs.* See, e.g., FDCA Sections 501(b) and 502(e)(3)(b); see also FDA regulations, 21 CFR 299.5. In addition, to avoid being deemed misbranded, drugs recognized in USP–NF must also be packaged and labeled in compliance with compendial standards, FDCA Section 502(g).

[…]

3.10. Applicability of Standards

Standards for an article recognized in a USP compendium are expressed in the article's monograph, *applicable general chapters*, and General Notices. Unless specifically exempted elsewhere in a compendium, the identity, strength, quality, and purity of an article are determined by the official tests, procedures, and acceptance criteria, whether incorporated in the monograph itself, in the General Notices, or in the applicable general chapters. […]

The standards in the relevant monograph, general chapter(s), and General Notices apply at all times in the life of the article from production to expiration. The manufacturer's specifications, and good manufacturing practices generally (including, e.g., Quality By Design initiatives), are developed and followed to ensure that the article will comply with compendial standards until its expiration date, when stored as directed (by the manufacturer, consistent with any applicable standards).

Thus, any official article is expected to meet the compendial standards if tested, and any official article actually tested as directed in the relevant monograph must meet such standards to demonstrate compliance. *Frequency of testing and sampling are left to the preferences or direction of those performing compliance testing,* and other users of USP-NF, including manufacturers, buyers, or regulatory authorities.

[…]

3.20. Indicating Conformance

When a drug product, drug substance, or excipient differs from the relevant USP or NF standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, *its difference shall be plainly stated on its label.*"

sion. However, in July 2011, Pharmacopeial Forum published an in-process revision of that Chapter, under a changed title *"Product Performance Tests—Nasal And Inhalation Aerosols, Sprays, And Powders,"* with significantly revised content and with a new companion Chapter <5>, entitled *"Inhalation and Nasal Drug Products—General Information and Product Quality Tests."* Both the revised Chapter <601> and the new Chapter <5> are accessible online upon free registration at www.usppf.com.

USP is a volunteer-based organization that revises its standards based on input received. Accordingly, the International Pharmaceutical Aerosol Consortium on Regulation and Science (IPAC-RS)[3] submitted comments on the proposed revised Chapter <601> and new Chapter <5>, and made plans to participate in the USP Aerosols Workshop on December 12-13, 2011.[4] (At the time of writing this article, this Workshop has not yet taken place). The remainder of this article highlights some of the problematic changes proposed by the USP. In a follow-up article to be published by *Inhalation*, one of the key challenges presented by the USP revisions – the changed specifications for delivered dose uniformity – will be discussed in more detail.

New Chapter <5> "Inhalation and Nasal Drug Products—General Information and Product Quality Tests"

The purpose of Chapter <5> is not entirely clear. The new nomenclature introduced in Chapter <5> for different types of inhalation products, as well as the listing of specific "product quality" tests for each product type, confuse the already complex web of regulatory and "standards" documents affecting orally inhaled and nasal drug products.

Taxonomy. The IPAC-RS' interpretation of the new nomenclature is presented in Tables 2 and 3. Among the challenges in nomenclature are "Solution for Inhalation" vs. "Inhalation Solution" (one of which needs to be diluted prior to use while the other does not), as well as "Suspension for Inhalation" vs. "Inhalation Suspension" (again, the differentiator is that one of these must be diluted, although the names are logically indistinguishable). Similarly, "aerosols," in the new USP taxonomy, would be limited to pressurized Metered Dose Inhalers (pMDIs) only. Upon encountering the word "aerosol," the reader should be careful to note the

Table 2

IPAC-RS Interpretation of the USP Chapter <5> Terminology for Inhalation Products
(*Bold Italics = assumed, as USP text is not specific*)

Inhalation Product Type (per USP <5>)	Dosage Form Sold As	Diluents	Dosage Form When Ready For Use	Administration	Other Information
Inhalation aerosol	Liquid or solid formulated with propellant and/ or co-solvent	None	Same as 'sold as'	Fine mist generated by a pressurized metered dose inhaler	Packaged under pressure
Inhalation solution	Water based ***solution***	None	Solution	Nebulization	
Inhalation suspension	Water based ***suspension***	None	Suspension	Nebulization	
Solution for inhalation	Water based ***solution***	Water	Solution	Nebulization	Dilute prior to use
Suspension for inhalation	Water based ***suspension***	Water	Suspension	Nebulization	Dilute prior to use
Drug for inhalation solution	***Soluble*** drug powder	Suitable vehicle ***solvent***	Solution	***Nebulization***	
Inhalation spray	Water based liquid formulations	None	Same as 'sold as'	Integrated spray pump unit	Unit or multi-dose device
Inhalation powder	Dry powder	None	Same as 'sold as'	Aerosolized powder(DPI)	Pre-metered or device metered

Table 3

IPAC-RS Interpretation of the USP Chapter <5> Terminology for Nasal Products

Nasal Product Type (per USP <5>)	Dosage Form Sold As	Diluents	Dosage Form When Ready For Use	Administration	Other Information
Nasal aerosol	Liquid or solid formulated with propellant and/ or co-solvent	None	Same as 'sold as'	Fine mist generated by a pressurized metered dose inhaler	Packaged under pressure
Nasal spray	Water-based liquid (solution or suspension) formulations	None	Same as 'sold as'	Integrated spray pump unit	1. Accurately metered 2. Local and/or systemic effects
Nasal powder	Dry powder	None	Same as 'sold as'	Aerosolized powder	Pre-metered or device metered
Non-metered nasal solution	Water-based liquid (solution or suspension) formulations	None	Same as 'sold as'	Integrated spray pump unit for local effect	1. Non-metered 2. Local effects

context. In most scientific articles and discussions, the term "aerosols" would include the aerosols generated by dry powder inhalers (DPIs) and even nasal or nebulizer systems. Not so if you are reading the revised USP Chapter, where the term would be restricted to pMDIs (and the terms pMDI and MDI are banished from general use). Confusingly, the term "aerosol" is nevertheless used in both <5> and <601> to describe particles emitted by "inhalation powders" (DPIs) as well as by "inhalation aerosols" (MDIs).

Furthermore, the new taxonomy does not distinguish between pre-metered DPIs and device-metered DPIs (calling them all "inhalation powders"), even though tests may need to be different for these two distinctly different types of products.

The new taxonomy also conflicts with other USP Chapters. For example, Chapter <5> differentiates Inhalation and Nasal Drug Products, while in Chapter <1151>,[5] inhalations include nasal products. An "Inhalation Spray" referred to in Chapter <601> can comprise (according to the Chapter <5> terminology) an "Inhalation Solution," "Inhalation Suspension," "Solution for Inhalation," "Suspension for Inhalation" or a "Drug for Inhalation Solution."

A relationship between USP "Product Quality" and FDA "Quality Control" Tests. What is the relationship between USP "Product Quality" and FDA "Quality Control" Tests? The short answer is "we don't know," and Chapter <5> does not shed any light on this question. On the surface, there is no relationship between the USP and FDA quality requirements. Regardless of the tests deemed appropriate by FDA for marketing a particular product, the tests listed in USP must also be applied (although there are no acceptance criteria in <5> and few test methods are given).

At a recent public workshop,[6] USP representatives emphatically stated that USP standards are not intended for batch release. Nevertheless, this clarification is currently absent from the USP text, inviting confusion between USP's "product quality tests" and FDA's "quality control tests" that are customarily understood to mean batch release tests. The distinction, however, is important: (a) qualitatively, the set of tests for batch release may be different from the USP lists (such as those in Chapter <5>), based on a given product's specifics and the agreed FDA requirements; and (b) quantitatively, for statistical reasons, the batch release specifications must be more stringent than the acceptance criteria listed in USP, in order to ensure a product's ability to meet USP specifications whenever tested (as required by law).

The distinction between USP "product quality tests" and batch release tests is particularly liable to misunderstanding outside of the US, where USP is extensively used.

The USP "product quality tests," moreover, seem to mix the tests appropriate for quality control with those appropriate for characterization or stability testing. For example, descriptions of tests for Plume Geometry and Spray Pattern mention "acceptance criteria," suggesting that the tests would be used for ongoing quality control, which far exceed the scope of these tests and are normally reserved for characterization and development studies.

The omissions of certain tests from Chapter <5> is equally confounding. For example, upon reading Chapter <5>, it could be concluded that USP no longer requires Aerodynamic Size Distribution or Delivered Dose Uniformity testing, because these tests are not mentioned.

Overall, the seemingly rigid approach of Chapter <5> begs the question regarding the application of concepts that have been developed within industry and the regulatory community over the past decade, such as Quality-by-Design, Risk Assessment and Risk Management, and the International Conference on Harmonization's approaches.

By contrast, in the European Pharmacopeia, only delivered dose or fine particle dose are listed as aerosol-specific quality tests (with the term "aerosols" generally applicable and not limited to pMDIs). The need for any other specialized tests in Europe is determined by the regulatory authority based on product specifics. The USP approach seems more complex and any benefit – at the cost of harmonization – is unclear. The loss of pharmacopeial harmonization also contradicts FDA's global initiative that aims to establish a better exchange of risk information between agencies. A meaningful exchange and common assessment are only possible if the standards are comparable and, thus would be endangered by the proposed USP new and revised Chapters.

Revised Chapter <601> "Product Performance Tests—Nasal and Inhalation Aerosols, Sprays, and Powders"

The revised Chapter <601> significantly changes requirements for Aerodynamic Particle Size Distribution (APSD) testing and the Delivered Dose Uniformity (DDU) specifications. The second article in this two-part series will discuss the new USP DDU requirements, to which many of the currently marketed orally inhaled products (OIPs) may not be able to conform routinely. Following, is a review of the other relevant aspects of the revised <601>.

A significant restriction is proposed for the mass balance criterion (from 75-125% to 85-115% of the label claim). A comparison of these limits with the DDU requirements suggests that a batch may well pass the DDU test yet fail this mass balance requirement. There have been several publications[7, 8] highlighting the inher-

ent variability of the mass balance measurement and placing its value only as a "system suitability" test (with appropriate limits). An explanation for the USP revised limits appears to be warranted.

For the testing of "inhalation powders" (which means DPIs in the USP newly proposed taxonomy), the volume of air for APSD testing is now restricted to 2 liters. Interestingly, the volume may be 4 liters – depending on which specific part of <601> is referenced, although 2 liters is more prevalent. A total flow volume of 2 liters of air would be inappropriate for APSD measurements due to the dead volume of cascade impactors.

The revised <601> prescribes the use of a pre-separator for all "inhalation powders," not taking into account the fact that not all DPIs require a pre-separator. For example, engineered dry powders that do not use large carrier particles do not need a pre-separator.

Moreover, Chapter <601> leaves the impression that using the Andersen Cascade Impactor (ACI) at flow rates other than 28.3 LPM is unacceptable, ignoring publications and technical data on ACI use with lower and higher flow rates.[9, 10]

Another missed opportunity for clarification and improvement relates to the calculation of mass median aerodynamic diameter (MMAD). A 2010 stimulus article explained the bias due to assumption of log-normality necessary for the current pharmacopeial procedure and proposed a more generalized method for MMAD determinations.[11] The log-normal distributional assumption is rarely valid.

In addition to the new terminology in Chapter <5>, there are further new terms in revised Chapter <601>. The linguistic confusion can lead to very practical, not academic, problems. For example, "inhalation powder" and "aerosol" have replaced DPI and MDI, respectively, which has resulted in difficult-to-understand phrases such as the following, to name a few:

"…drugs leaving the mouthpieces of inhalation aerosols and sprays or inhalation powders,"

"multiple-dose assemblies of pre-metered dose units," and

"a loaded, drug-free device (with previously emptied packaging)."

In several instances, <601> seems to suggest that APSD is a function of formulation only, not of the device/formulation combination, e.g.: *"For formulations with a significant fraction of particles not captured by the micro-orifice collector…."* Finally, there is no definition of the term "drug," and its meaning seems to shift throughout the Chapter. For example, in such phrases as *"target-delivered dose…reflects the expected mean* drug *content"* and *"formulated as …solutions of* drug*,"* the term "drug" probably refers to the active pharmaceutical ingredient (API), while in phrases "drug *packaging modifies the product's resistance to airflow"* and *"aerodynamic size distribution of the* drug *aerosol leaving the product,"* the term "drug" probably refers to the entire formulation, including potential excipients, carriers, etc.

Conclusion

USP standards play an important role in setting public and legal expectations for the quality of orally inhaled and nasal drug products. Equally important is the role that industry and subject matter experts confer. These industry experts and academicians should scrutinize the proposed changes/updates to the USP for these product types and comment accordingly. From the perspectives of the authors, it appears that not all proposed USP revisions are warranted and justified. A broader public dialogue is therefore recommended before USP proceeds with its revisions. Such a dialogue could address, for example, whether and how the USP process takes into consideration safety aspects, efficacy questions and the manufacturing capabilities of orally inhaled and intranasal drug products – preferably based on data. It might be worth considering, in a broad public forum, an appropriate way to arrive at realistic pharmacopeial standards.

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