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***Re: IPAC-RS Comments on "Proposed Revisions to the General Notices and Requirements" in Pharm.Forum 41(1) [Jan.–Feb. 2015]***[1]

Dear Mr. Sindaco,

The International Pharmaceutical Aerosol Consortium on Regulation and Science (IPAC-RS) commends USP for attempting to clarify the "*Applicability of Standards*" as presented in section 3.10 of part "3. *Conformance to Standards*" of the *General Notices and Requirements*.[1] We have, however, some comments and concerns, as explained below. The main concern is that current revisions amplify confusion about the meaning of USP tests rather than clarify how USP tests should be used and understood by innovator and generic industry, regulators and the public.

IPAC-RS is an international association of pharmaceutical companies that develop, manufacture and market orally inhaled and intranasal drug products. The mission of IPAC-RS is to advance consensus-based, scientifically driven standards and regulations for orally inhaled and intranasal drug products, with the purpose of facilitating the availability of high-quality, safe, and efficacious drug products to patients worldwide. Current IPAC-RS members are 3M, Actavis, AstraZeneca, Boehringer Ingelheim, Catalent, Chiesi, GlaxoSmithKline, Hovione, Lupin Pharmaceuticals, MannKind Corporation, Merck & Co., Mylan, Novartis, Sunovion, Teva, and Vectura.

The comments in this letter refer to the following language in section 3.10 of the *General Notices and Requirements* (emphasis in bold added):

> *<<The standards in the relevant monograph, general chapter(s), and General Notices and Requirements apply at all times in the life of the article from production to expiration. It is also noted that the manufacturer's specifications, and manufacturing practices (e.g., Quality by Design, Process Analytical Technology, and Real Time Release Testing initiatives), generally are developed and followed to ensure that the article will comply with compendial standards until its expiration date, when stored as directed. Every compendial article in commerce shall be so constituted that when examined in accordance with these assays and test procedures, it meets all applicable pharmacopeial requirements (General Notices and Requirements, monographs, and general chapters). Thus, any official article* ***is expected to meet the compendial standards if tested,*** *and any official article*

[1] http://www.usp.org/proposed-revisions-gen-notices-pf-41

> *actually tested as directed in the relevant monograph must meet such standards to demonstrate compliance.*
>
> *Some tests, **such as those for Dissolution and Uniformity of Dosage Units**, require multiple dosage units in conjunction with a decision scheme. These tests, albeit using a number of dosage units, are in fact one determination. These procedures should not be confused with statistical sampling plans. Repeats, replicates, statistical rejection of outliers, or extrapolations of results to larger populations, as well as the necessity and appropriate frequency of batch testing, are neither specified nor proscribed by the compendia; such decisions are based on the objectives of the testing. **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**.>>*[1]

The above-quoted language does not really clarify how industry (as well as other stakeholders) should understand and use USP tests, especially those in general chapters with acceptance criteria, such as in chapter <905> (about uniformity of dosage units, referenced in the above passage). Moreover, the combination of precise acceptance criteria on a sample (as in chapter <905>) and an open-ended testing schedule (as per section 3.10) creates an illusion of a common public standard, which in reality is either unattainable or is representing a wide range of quality levels and thus not serving as a standard at all.

Simple statistical calculations can show that the minimal required quality of a product's batch (expressed, for example, as its mean and standard deviation), will be vastly different if the condition for batch acceptance is "meet criteria in <905> once" *versus* "meet criteria in <905> ten separate times" *versus* "meet criteria in <905> any number of times" (hence resulting in a range of "qualities"). Most importantly, this last situation (meeting criteria of <905> whenever tested, with zero failures) would require such batch quality levels that may be technically and practically unachievable for many products.

In addition, the current revision of section 3.10 removed the sentence that "*in all cases, statements about whether the compendial standard is met apply only to the units tested.*" With that removal, it becomes now unclear what it means if a sample fails the USP criteria. Does that failure reflect on the untested units in any way? Does it have any implications for the batch? Or does it mean that a second sample may be tested to demonstrate product's compliance with USP?

The original test in chapter <905> may have worked when used once per batch (as has been widely practiced in the past). With the current emphasis both by USP and FDA on NOT using USP tests for batch release, only two options seem workable for moving forward:

1. For general chapters that currently have specifications, such as <905>, USP should determine characteristics of the distribution of a population of units (a "batch" of some typical size) such that if tested once against <905> (as historically accepted in the past), that "batch" has nearly 100% probability of acceptance (because that's what being a "standard" means). USP should put thus-calculated population characteristics into <905>, which would then work with the language in section 3.10 of the *General Notices and Requirements*. By focusing on population characteristics, the chapter would also become independent of a sample and therefore will avoid the ambiguity around the meaning of failing a sample.

OR

2. USP should remove all acceptance limits from general chapters such as <905>, and leave it to individual product monographs to spell out acceptance criteria for specific products (as was done for chapter <601>). This option could also allow the considerations of efficacy and safety for a given product to be included in the quality specifications for that product.

Both options have significant challenges and will require further in-depth discussion within USP and in the broader stakeholder community including regulators, innovator and generic industry, and other USP users.

Moreover, we agree with USP that "*Repeats, replicates, statistical rejection of outliers, or extrapolations of results to larger populations, as well as the necessity and appropriate frequency of batch testing, are neither specified nor proscribed by the compendia; such decisions are based on the objectives of the testing.*" We would add, however, that acceptance criteria and statistical design of the test should also depend on the objectives of testing. Testing objectives and, consequently, requirements vary widely throughout a product's lifecycle, starting from early discovery and development, through to validation, routine quality control, investigations, etc. Focusing on population characteristics rather than a fixed sample would provide a pathway for maintaining consistent standards throughout a product's lifecycle.

A more detailed discussion of the topics raised in this letter would be of great value, and could be included in section 3.10 and/or as a special "Informational Chapter". We also look forward to the USP webinar on chapter <905> scheduled for April 21, 2015, which plans to "*discuss the application of USP–NF General Chapter <905> to various dosage forms*".[2]

We understand that historically, USP evolved as a compendium of tests for "products on the shelf", without consideration of drug development or manufacturing processes. In the modern environment, however, ignoring the relationship between units on the shelf and the rest of the product only multiplies the confusion and increases misapplication of USP tests.

In summary, if USP chooses to adhere to its philosophy of only concerning itself with "**products on the shelf**", the only way to avoid the conflict between the intent and practical use of pharmacopeial standards would be to remove all specifications from general chapters leaving only test methods there, and to rely on individual product monographs for acceptance criteria and specifications (as was done for aerosol products).

The stated purpose of the *General Notices and Requirements* is to present "*the basic assumptions, definitions, and default conditions for the interpretation and application of the United States Pharmacopeia (USP) and the National Formulary (NF).*"[1] The revised language in section 3.10 "*Applicability of Standards*" does not achieve that goal because it does not clarify the assumptions, definitions, conditions or interpretation of USP tests which have acceptance limits.

Sincerely,

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Susan Holmes, Chair, IPAC-RS Board of Directors

[2] http://www.usp.org/meetings-courses/courses/uniformity-dosage-units-usp-nf-general-chapter-905