Description and Summary of Proposed General Notices Revisions Published for Comment in *Pharmaceutical Forum* 39(1) Jan-Feb 2013

Outlined below are brief descriptions and summaries of changes that are proposed for the next round of General Notices revisions; the text of the proposed changes is being published for public notice and comment in *Pharmaceutical Forum* 39(1) (Jan-Feb 2013). Following opportunity for public comment on the PF proposal, and consideration and adoption by the Council of Experts Executive Committee, these General Notices revisions are anticipated to be included in *USP 37-NF 32* (publishing November 1, 2013, official May 1, 2014).

1. TITLE AND REVISION

Publication of Accelerated Revisions/IRAs
With the switch to online publication of *PF* in January 2011, IRAs no longer "are published in *Pharmacopeial Forum.*" *PF* is used solely to publish proposed revisions for comment. This revision reflects that IRAs now are published initially on the USP website, and then incorporated into the next official publication.

2. OFFICIAL STATUS AND LEGAL RECOGNITION

2.10 Official Text: Clarify "Official" Status of Print and Electronic Versions of *USP-NF*
Increasingly, users of *USP-NF* are using the on-line rather than paper version of the compendia. At the same time, USP is making enhancements to its online product that will provide users with even greater functionality. Accordingly, there are growing reasons to revisit the issue of exactly what version of *USP-NF* should be considered "official," i.e. appropriate for use in determining compliance. To provide clarity going forward with the increasing focus on electronic versions, it is proposed that language be added to Section 2.10, acknowledging the status of both print and electronic versions, and specifying that in the event of any disparity, the electronic version will be deemed to apply.

2.30 Legal Recognition: Clarify Statutory Role of 'Official Compendium'
The means by which compendial standards are adopted into law in the United States under the Federal Food, Drug, and Cosmetic Act (FDCA) is by reference in particular FDCA sections (typically adulteration or misbranding provisions, such as sections 403, 501 and 502) to specific kinds of compendial standards in "an official compendium." For example, section 501(b) refers in the case of a drug "the name of which is recognized in an official compendium" to standards for "strength, quality, or purity," deeming any drug that does not conform to such standards to be adulterated. Accordingly, the definition of the term "official compendium" is critical. The term is defined in FDCA section 201(j) to mean "the official United States Pharmacopeia, . . ., official National Formulary, or any supplement to any of them." The proposed revised language clarifies the meaning and implications of the term, by more closely tracking the statutory language.

3. CONFORMANCE TO STANDARDS

3.10 Applicability of Standards: Clarify Applies to Both *USP* and *NF*.
There are two instances in the first and last sentences of the first paragraph where a specific compendium, *USP*, is referenced, instead of both *USP* and *NF*. However, the introductory text and Section 1 of *General Notices* makes clear that GN applies to both *USP* and *NF*. A change is proposed for clarity.

3.10.10 Applicability of Standards to Drug Products, Drug Substances and Excipients: Clarify Applicability of USP to OTC Drugs
The existing General Notices language is clear that USP standards apply to any articles marketed in the United States that are intended or labeled for use as a drug or drug ingredient, for humans or animals. Nevertheless, at times some have expressed uncertainty regarding the applicability to "over the counter" (non-prescription "OTC") drugs, though no such distinction is intended or expressed in the compendium (except where specifically stated). Under federal law, there is no fundamental distinction in the applicability of compendial requirements to Rx (prescription) and OTC drugs, other than the provision in FDCA 503(b) which provides for certain regulatory differences for drugs required to be dispensed by prescription (mainly involving exemption from certain misbranding and labeling requirements). Accordingly, new language is proposed to be added to this section to clarify the applicability of the compendia to OTC drugs, as well as drugs intended for animal use.

3.20 Indicating Conformance: Clarify Designation "USP" or "NF" Requires Compliance With Compendial Standards
Until the General Notices revisions published with USP 32, an article wishing to be designated "USP" had to be subject to a monograph, and also purport to comply "with all applicable USP standards." The current version starting with USP 32 retained the basic intent of this provision, but the language "complies with the identity prescribed in the specified compendium" (which was intended to be read in conjunction with the subsequent paragraph relating to compliance with standards for strength, quality and purity) has resulted in occasional questions about exactly what is required for use of the designation. To eliminate any ambiguity, it is proposed that the provision be revised to state that an article may use the designation "USP" or "NF" only if (1) there is an applicable monograph, and (2) the article complies with the identity prescribed in the compendium" **and** also complies with the standards for strength, quality and purity or labels any deviation from these standards.

4. MONOGRAPH AND GENERAL CHAPTERS

4.10.11 Dissolution, Disintegration, and Drug Release Tests: New Subsection Clarifying the Basis for Dissolution Tests
There continues to be misunderstanding and questions from stakeholders about the underlying basis for multiple dissolution tests in a monograph and associated labeling requirements. New proposed language is intended to help clarify these issues.

5. MONOGRAPH COMPONENTS

5.60 Impurities and Foreign Substances: Update Title of General Chapter <1086>
This section would be revised to accurately reflect the title of GC <1086>, which has been changed to "Impurities in Drug Substances and Drug Products."

5.60.10 Other Impurities in USP and NF Articles: Clarify Control of Impurities in All Articles, Including Official Substances and Products
It has been brought to USP's attention that the current wording of this provision may introduce unintended ambiguity about the nature and extent of the intended control of impurities in all official articles, including official substances and official products. Proposed changes are intended to make clear that standards for impurities apply to all articles, unless otherwise stated in the monograph.

5.60.30 Elemental Impurities in USP and NF Articles: New Provision
The last round of General Notices revisions had proposed a new General Notices provision, to accommodate new General Chapters <232> Limits and <233> Impurities and make clear that these General Chapters will apply to all *official articles* recognized in *USP* and/or *NF*. Rather than calling out these new General Chapters in every *USP* and *NF* monograph, the approach chosen is to make them applicable through a General Notices provision, similar to that provided for Residual Solvents. The proposed revision was deferred, pending coordination with the completion of the chapters. On January 31, 2012, the Expert Committee approved the chapters for publication in USP 35 2nd Supplement, June 1, 2012, with a December 1, 2012 official date. ***However, the date when compliance with these general chapters effectively will be required would be May 1, 2014,*** when this new provision in General Notices, section 5.60.30, making chapters <232> and <233> applicable to all articles would become official. This approach is intended to allow users adequate time to come into conformance with the new chapters, while allowing implementation prior to that date if desired.

5.80 USP Reference Standards: Clarify that USP Reference Standards must be used for results to be conclusive
USP Reference Standards are considered an integral component of the compendial standards for which their use is specified; thus, only those results obtained using USP Reference Standards may be used to conclusively demonstrate conformance to or compliance with those USP standards for which the USP Reference Standard is specified. This understanding is reflected in section 6.30 for compendial tests, practices and procedures ("Only those results obtained by the methods and procedures given in the compendium are conclusive.") To clarify the applicability of this understanding to USP Reference Standards that are components of USP compendial standards, comparable language is proposed to be added to the Reference Standard provision.

6. TESTING PRACTICES AND PROCEDURES

6.50.20 Solutions: Add clarity re mixing equal parts of liquids and solids for solution preparations
A public USP stakeholder has observed that the existing language of this section is ambiguous about how exactly solids should be dissolved to make solutions, when proportionality is

required. The proposed revision clarifies the procedure for mixing liquids, and solids being dissolved in liquids.

6.50.20.1 Adjustments to Solutions: Reintroduce Language re Proportionately Larger/Smaller Quantities

Prior to the major General Notices revisions introduced in 2009 with USP 32, there was provision for allowing "Proportionately larger or smaller quantities than the specified weights and volumes of assay or test substances and Reference Standards" to be taken. See, e.g., USP 31 General Notices, Tests and Assays, 5th paragraph under "Procedures." Based on stakeholder comments regarding the usefulness of this provision, it is proposed that this language be reintroduced in the current Testing Practices and Procedures section, inserted as a new second sentence in the subsection on "Adjustments to Solutions" (6.50.20.1). Separately, at the beginning of the same subsection, it has been recommended that the reference to a solution of "molarity" delete the now-archaic parallel term "normality."

6.80.10.1 Equipment – Pipet /Pipette: Add provision for pipette

The current provision allows substitution of a suitable buret or volumetric flask, when a "pipet" is specified. The proposed revised language will also allow substitution of a "pipette" where properly specified.

6.80.30 Equipment: New Provision for "Temperature Reading Devices"

The General Chapters Physical Analysis Expert Committee accepted a subcommittee proposal at its February 23, 2011, meeting, to delete GC <21> *Thermometers*, and to concurrently incorporate the text into the USP General Notices. This would be accomplished by adding proposed text as a new GN 6.80.30.

8. TERMS AND DEFINITIONS

8.20 About: Update name of <41> *Balances*

Section 8.20 refers to Weights and Balances <41>, the name of which has recently been changed to Balances <41>.

8.240 Weights and Measures: Revise and expand chart of symbols commonly employed for SI metric units

Section 8.240 contains a chart of "Symbols commonly employed for SI [International System of Units] metric units and other units . . . ." A number of changes to the chart are recommended.

10. PRESERVATION, PACKAGING, STORAGE, AND LABELING

10.10 – 10.30.100 and 10.50 Storage- and Packaging-related provisions: Move Storage and Packaging Provisions to a new General Chapter <659>

The packing and storage provisions (10.10-10.30.100) are addressed in a new General Chapter <659> "Packaging Components and Storage Conditions" (published in USP 35, official May 1, 2012), and so may be omitted from General Notices, other than a brief provision proposed for section 10.10 applying <659> to articles (official products and official substances) recognized in

USP-NF. Included in the proposed text is a Note alerting users that these issues and related compendial requirements are addressed in that new General Chapter <659>. A related General Notices provision (10.50) originally intended to provide guidance to liaisons on packaging- and storage-related statements in *USP-NF* monographs is no longer needed or appropriate and is also proposed to be omitted. *Also note* with regard to the remaining Labeling-related provisions of General Notices section 10: these are also expected to be omitted in a subsequent revision, upon completion of a new General Chapter <7> that will address labeling-related information. In the meantime, these will be retained with unchanged section numbering (10.40 – 10.40.100.1).