



U.S. Pharmacopeia
The Standard of Quality™

Explanatory Note Regarding Proposed Revisions to the *USP* and *NF* General Notices

An initial draft of USP's proposed revisions to the General Notices (Draft 1) was posted on the USP website in May 2007 for informal comments. Numerous comments were received on Draft 1. USP reviewed these comments and developed a second draft (Draft 2) of the proposed revision for formal notice and comment through *Pharmacopeial Forum* (*PF*). Because of the magnitude of some of the changes proposed in Draft 1 and the comments received, USP bifurcated the original proposal to allow presentation of some proposals in *PF* at a later date after additional consideration by USP and its stakeholders. Proposals that require additional consideration were found primarily in the Preamble and in sections 1 and 2 of Draft 1, and are mentioned below.

In order to aid the comment process on Draft 2 (as presented on the website and in *PF* 34(1)), this document describes some of the comments received on Draft 1 and details USP's preliminary views of those topics. Major (underlined) headings in this document reflect the major headings in Draft 1.

General Comments

Format

Several commenters said that the format change and the use of headings generally present improvements over the current text. Two commenters suggested additional changes to the structure, including moving the definitions section to the end of the General Notices.

Draft 2 incorporates many of the structural suggestions made by commenters. The definitions are now located near the end. Because USP is considering moving the Packaging and Labeling section to a general chapter, that text is presented as the final section of the General Notices. In this way, relocating that section will avoid a change to the numbering of other sections of the General Notices. USP welcomes comment on whether the Packaging and Storage section should remain in the General Notices or more properly belongs as a general chapter.

Amino Acids

One commenter advocated for including tests in the compendia that will help to ensure the quality of amino acids (e.g., tests for insoluble foreign matter).

USP is pleased to consider including such standards with appropriate supporting data and documentation, as described in the Guideline for Submitting Requests for Revision to the *USP-NF* (<http://www.usp.org/USPNF/submitMonograph/subGuide.html>).

Preamble

Inclusion of Other USP Compendia

Draft 1 proposed to apply a single General Notices to the *USP*, *NF*, *FCC*, Pending Standards, and SALMOUS. Draft 1 included text from the *FCC* General Provisions. Commenters felt that the inclusion of these other compendia in the General Notices made it more difficult to understand and apply each of the provisions.

USP has determined to continue discussions on this topic, and therefore is not proposing a “unified” General Notices covering all compendia at this time. References to *FCC* and its General Tests and Assays are omitted throughout the document. However, USP still believes that the *FCC* General Provisions and the *USP-NF* General Notices should be consistent, and that there is a strong need for a General Notices document to define the default conditions for Pending Standards and for SALMOUS. USP welcomes comments with views on how this can best be achieved. A proposal on this topic should be forthcoming late in 2008.

1. Title and Revision

Combining *USP* and *NF* General Notices

Commenters suggested that the General Notices for the *USP* and the *NF* should be combined, and that the references throughout the document should be made to “*USP-NF*,” rather than to *USP* and *NF* individually. Commenters also recommended deleting the text defining the current revision of the *USP*, and suggested that the General Notices refer to a single revision number (e.g., *USP-NF 32*, rather than *USP32-NF27*).

USP now is proposing in Draft 2 to combine the *USP* and the *NF* General Notices. Although we agree that this is unlikely to negatively affect the clarity of the document, we are soliciting comments regarding the effect of this proposal on the clarity of the distinction between *USP* and *NF* as separate compendia. To help maintain this distinction, and because certain provisions of the General Notices apply only to one of the two compendia, we are not using the reference “*USP-NF*” in the document.

We are not proposing to delete the text defining the current revision of the *USP*. Because the *USP* is currently in its 31st revision of the 1st edition, while *NF* is in its 26th edition, it is infeasible and inaccurate to combine them as a single revision or edition number. An alternative approach would be to identifying the compendia primarily by year (e.g. *USP-NF 2009*). USP welcomes comments on this approach.

Revision Bulletins

Several commenters discussed the provision stating that USP will give notice of Revision Bulletins directly to affected parties. Two commenters asked whether this statement is appropriate content for the General Notices, as it is administrative in nature. Another asked

how “affected parties” are determined. Another commenter suggested expanding the notice to relevant trade organizations.

USP agrees with the commenters’ suggestion that this administrative statement is not appropriate for the General Notices, and has deleted that sentence in the Draft 2.

Inclusion of Errata as a Type of Revision

Two commenters suggested including a sentence discussing Errata in the discussion of revisions to official text.

Draft 2 does not include this text because Errata are not revisions to official text. Rather, they are corrections that are necessary to conform published text to the official text approved by the Council of Experts.

2. Terminology

Statements about Legal Standing and Enforceability

A commenter suggested adding a section discussing the legal impact of *USP* and *NF* standards for drugs, dietary supplements, and compounded preparations. The commenter also suggested clarifying the legal enforceability of the compendia. Another commenter suggested discussing FDA’s role in enforcement of *USP-NF* standards.

Draft 2 does not include the commenters’ suggestions. The legal status of the compendia in the U.S. is covered in the Mission and Preface, but the adoption of the *USP* and *NF* in law varies in other countries. The use of “USP,” “NF” or another of USP’s marks is a visible manifestation of conformance to USP’s standards.

Consolidation of Text Relating to Compounding

A commenter suggested that the provisions relating to compounding should be presented in a separate section of the General Notices. Another suggested addressing these requirements in a general chapter.

The suggestion has not been incorporated into Draft 2. Compounded preparations are “official products,” and the ingredients used in them are “official substances.” Every provision applying to “official products” and “official substances” applies to compounded preparations. Placing the information specific to compounded preparations in a separate section may give the false impression that only that section applies to compounded preparations. We welcome comments from compounding professionals regarding the applicability of the General Notices to their practice and any challenges that they may face in applying these provisions.

Consolidation of Text Relating to Dietary Supplements

A commenter suggested that the provisions relating to dietary supplements should be presented in a separate section of the General Notices.

The suggestion has not been incorporated into Draft 2. Dietary supplements are “official products,” and dietary ingredients as well as other ingredients used in them are “official substances.” Every provision applying to “official articles,” “official products” and “official substances” applies to dietary supplements and their ingredients. Placing the information specific to dietary supplements in a separate section may give an incorrect impression that only that section applies to dietary supplements. USP welcomes comments from dietary supplement manufacturers regarding the applicability of the General Notices to their activities, and particularly any challenges that they may face in applying these provisions.

Official Text and Authorized Text

One commenter suggested that the proposed language to distinguish “official” general chapters from “authorized” general chapters, which would allow a general chapter to be included as official if “it includes other text that a USP Expert Committee considers necessary to perform compendial procedures or to assure product quality,” is too vague and requires interpretation. The commenter suggested stating instead that “official text has been determined by a USP Expert Committee to be necessary to perform compendial procedures or to assure product quality.” Another commenter suggested that many chapters with numbers above <1000> may need an additional round of public notice and comment before becoming enforceable, so that stakeholders may consider them more carefully.

Draft 2 does not strive to make a distinction between “official” and “authorized” general chapters, but instead maintains the current distinction between chapters numbered below <1000> and those numbered above <1000>. USP expects to continue discussions about the possibility of moving some general chapters into “authorized” status, and requests additional comment on the concept of moving some chapters to a book that is not part of the *USP-NF* (the “companion volume”). Further, USP requests additional comment on the chapters that should move to the companion volume, if it is created.

Official Substances

One commenter suggested, in relation to the definition of “official substance,” that dietary ingredients are not “official” in the same way that pharmaceutical ingredients are “official,” because *USP-NF* standards are voluntary for these ingredients.

Under the definitions presented in the current General Notices and Draft 2, any text that is contained in the *USP-NF* is official text, and any article for which a monograph is provided is an “official article,” whether or not the article complies with the compendial requirements.

Quality of Ingredients in Dietary Supplements

One commenter questioned the need for the statement that dietary supplements generally “are prepared from ingredients that meet *USP*, *FCC*, or *NF* standards.”

We retain the statement that dietary ingredients generally contain ingredients meeting these standards or, in the absence of such standards, meeting the requirements for food grade. We look forward to additional comment from the dietary ingredient and dietary supplement industry, as well as from consumer groups.

Information Monographs

One commenter suggested that a reference to information monographs as authorized text is confusing because no information monographs currently exist.

Although *USP* has not included the language about authorized text in Draft 2, we point out that *USP* has a number of information monographs available on the *USP* website at <http://www.usp.org/audiences/veterinary/?iama>.

3. Conformance to USP Standards

Use of Ingredients Meeting *USP-NF* Standards

Commenters pointed out that while official products should be required to use ingredients that meet *USP* or *NF* standards, such standards do not always exist for all ingredients.

Draft 2 clarifies that all ingredients must meet *USP* or *NF* monograph requirements, if such a monograph exists.

Applicability of Title

One commenter suggested clarifying the statement that “*USP*’s compendial standards apply equally to articles bearing names derived by transposing the definitive words of official titles...” to indicate that this applies only in the U.S.

The revised draft does not accept this distinction. Articles cannot avoid the requirements of the monograph merely by changing the order of the words in the title. This sentence addresses requirements that are a part of the *USP-NF* and are not dependent upon local law.

Text Discussing Title and Nomenclature

A commenter noted that the uses of monograph titles, and the appropriateness of using a use a name different from the monograph titles on an article, are discussed in a number of places in the General Notices. The commenter found the different discussions to be challenging to interpret and potentially contradictory. Another commenter suggested defining “official title.”

In Draft 2, the discussions of nomenclature and titles are consolidated and clarified in appropriate sections. Draft 2 also adds a definition for “official title.”

“Purports to Comply”

Commenters noted that the description that articles may use the designation “USP” or “NF” if the article “complies or purports to comply” with the standard to be unclear. They suggested that because an article either does comply or does not comply, the language about “purporting to comply” is unnecessary.

Although this language is included in the currently official General Notices, we have removed it in Draft 2. We request comments about known or potential uses of the “purports to comply” provision, however.

Label vs. Labeling

A commenter noted that the distinction between “label” and “labeling” was omitted from Draft 1. Another suggested defining these terms.

The official General Notices define “label” and “labeling” in the section discussing packaging and storage. That section has been reinserted in Draft 2. USP welcomes comment on the potential placement of the definitions of “label” and “labeling” in the event that the packaging and storage section is moved into a general chapter.

“USP-NF” on the Label

A commenter noted that the utility of the designation “USP-NF” on the label is unclear. The commenter states that, to his knowledge, no use is being made of the option to use the “USP-NF” on the label.

Because of the possibility that some products use the designation “USP-NF” on the label, and because it is longstanding policy, Draft 2 retains this option. Although it may not be used frequently, USP does not see a need for eliminating the option.

Applicability of Provisions

In the section headed “3.2.1. DRUG PRODUCTS AND DRUG SUBSTANCES,” one commenter questioned the omission of the terms “official article,” “official product,” and “official substance.”

The use of the terms “drug product” and “drug substance” in this section was intentional. In the definitions of “official substance” and “official product,” drug products and drug substances are defined as types of articles. Under US law, any drug, including any ingredient to be used in a drug, must comply with the relevant *USP* and *NF* standards. Other official articles, including dietary ingredients and dietary supplements, are not required to conform

unless they claim to conform. Omission of excipients from the heading was an oversight. Use of the term “any article” in that section was incorrect and has been changed.

Differences from the Compendial Standard

One commenter claimed that the provision allowing articles to differ from the compendial standards in strength, quality, or purity, provided that the difference is stated on the label, is incorrect because any article that does not meet compendial requirements is considered to be adulterated. The commenter also claims that this statement contradicts the statement that *USP* and *NF* standards apply to any article that uses the compendial name.

We do not agree with the commenter’s interpretation of U.S. law, and propose to retain this longstanding provision. We also do not believe that these two provisions are contradictory. The *USP* or *NF* standard applies to any article that uses the compendial title as its name, and differences from the standard in strength, quality, or purity are acceptable provided that the difference is described on the label.

4. Content of Compendia

Monographs/General Chapters

One commenter suggested that the basic information regarding monographs and general chapters has no value, and suggested its deletion.

Because the mission of the General Notices is to provide the basic assumptions for the use of the *USP* and *NF*, USP does not agree that the information has no value to the first-time user.

Monographs Describing Two or More Alternative Procedures

A commenter found confusing the description of monographs that allow for the use of one of two or more different procedures. The commenter asked how a user would know when they came upon such a monograph. Another commenter stated that manufacturers should not be required to examine a product for all possible impurities due to variations in synthetic routes.

Draft 2 clarifies this paragraph to make more explicit the language that will be used when a monograph describes more than one procedure, but requires the use of only one of the procedures. This language should prevent manufacturers from being required to test for “all possible impurities.”

Non-standardized Attributes

Two commenters pointed out that the discussion of non-standardized attributes from the *NF* General Notices may apply more broadly than originally written. One points out that it is equally applicable to some drug substances, and another suggests that some excipients are covered by *USP* monograph.

Draft 2 broadens this language, reflecting these comments.

5. Standards and Acceptance Criteria

Applicability of Standards

Several commenters suggested that *USP* and *NF* standards apply not until “consumption” but to “time of use” or “expiration.”

Draft 2 reflects these comments.

Hypothesis Testing

Several commenters stated that much of section 5.1 (“Standards”) in Draft 1 is vague, uses unclear terminology, and is cumbersome. There was particular concern about the phrase “hypothesis testing.” The commenters suggested reverting to the current text.

This text has been clarified in Draft 2.

6. Terms and Definitions

Movement of Definitions to Monographs

One commenter noted that many of the definitions in the General Notices are “easy to overlook” and should be specified in the individual monographs when critical.

The General Notices provide the default conditions for the use of the compendia. The General Notices should always be used in conjunction with any monograph. *USP* considers all information presented in the General Notices to be “critical,” and declines to move these default conditions to monographs.

Odor Tests

A commenter suggests that odor tests should be removed from all monographs.

USP is working to provide updated methods for all monographs that contain odor tests, and requests assistance from industry in these efforts.

Pressure Measurements

A commenter suggested that the definition of “pressure” be made less specific to allow for measurements in Pascals rather than in mm of mercury.

USP is not prepared to change all existing pressure measurements to Pascals at this time. *USP* welcomes additional comment on the suggestion to omit mm of mercury from the

definition of pressure, in order to allow for use of Pascals or mm of mercury in new revisions, as appropriate.

Solutions

A commenter suggested adding a statement allowing for the adjustment of pH with “appropriate concentrations” when the concentration is not indicated.

Draft 2 includes a statement to this effect.

Specific Gravity

A commenter suggested adding the phrase “unless otherwise specified” back into the definition of specific gravity.

As specified in the preamble, all definitions in the General Notices apply unless otherwise specified in the monograph. It is not necessary to add “unless otherwise specified” in all definitions.

Temperatures

A commenter suggested changing the default condition that all measurements are to be made at 25 degrees to “ambient room temperature,” unless otherwise specified. The commenter suggested that this change would support efforts at international harmonization and reflects actual practice.

USP did not include this change, on the basis that clarity is best achieved by specifying a default temperature. Users may determine the range of temperatures that may provide appropriate results.

One commenter suggested that monographs should specify the instances in which tight temperature control is necessary. In all other cases, it could be inferred that tight control is not necessary.

This suggestion was not included in Draft 2 because it would require concurrent revision of many monographs. However, USP will consider this proposal at an upcoming meeting of the Council of Experts Executive Committee meeting as a proposed revision.

Time

A commenter noted that no default is given for time tolerances, and asked whether the 10% allowance applies to time as well as weights and volumes.

A new default condition has been added to clarify that the rounding rules apply to time.

Vacuum Desiccator

A commenter suggested including “vacuum desiccator” as a separate definition.

This comment is reflected in Draft 2.

Water

A commenter suggested revising the definition of water for use in the manufacture of official articles to eliminate the requirement that it meet EPA requirements. Instead, the water should be appropriate to the needs of the manufacturing process.

This requirement has not been changed in Draft 2. USP is aware, however, that FDA changed the GMP regulations while this proposal was in press to eliminate the requirement that water meet EPA standards. USP is willing to reconsider this requirement in light of the agency’s change, and requests additional comment on the topic.

A commenter asked about the distinction between water “as an ingredient” and water “in the manufacture of official articles.”

USP understands the current General Notices language to refer to two different uses of water: (1) water as an ingredient and (2) water used not as an ingredient but otherwise used in the manufacture of a compendial article. The headings in Draft 2 reflect the current official text in that way. USP requests comment on this distinction in practice.

Two commenters suggested that “water” (and its variations) should be defined only in the Reagents section of the *USP-NF*.

Because the General Notices are a mandatory section of the *USP-NF*, and because the definitions of water are intended to be mandatory throughout the compendia, it would not be adequate to include these definitions only in the informational Reagents section.

Several commenters asked whether USP intended to change the resistivity to 19 mohm-cm.

USP did not intend this change, and Draft 2 reflects the current requirement of 18 mohm-cm.

7. Equipment

A commenter suggested that the allowance for vessels of other dimensions or types is too broad and should be limited to only those vessels that are suitable for the intended use.

This suggestion has been incorporated into the proposal.

A commenter suggested that it may be difficult to determine and validate that an instrument provides “equivalent or better” sensitivity and accuracy than the instrument required by the

compendium. The commenter suggested that the text be revised to require that the instrument “provides appropriate” sensitivity and accuracy.

USP has not included this suggestion because it would allow for the use of instrumentation without determination of the instrument’s appropriateness in relationship to the compendial (public) standard. USP is in the process of developing a document to better define our expectations of showing equivalence to the *USP* procedures.

A commenter suggested that a number of definitions should be moved into General Chapters Volumetric Analysis <31> and Containers <661>.

The definitions have not been moved because the discussion of the appropriate chapter placement and text is still under consideration by the Committees involved. To avoid a void in the standard, we propose to retain these items in the General Notices until a revision to the appropriate chapters can be addressed.

8. Compendial Practices and Procedures

Alternative Procedures

A commenter suggested inserting text similar to the text in the European Pharmacopeia (EP) in place of the text describing the appropriate use of alternative methods and procedures. The commenter supported the inclusion of text that does not explicitly require validation of alternative methods. A commenter stated that the requirement that alternative procedures give equivalent results is problematic. Demonstration of equivalence may be impossible, especially where an alternative procedure is superior to the compendial procedure.

Although USP appreciates the commenter’s efforts toward harmonization of the major compendia, USP believes strongly that any method other than the compendial method must be validated before use and must be shown to be equivalent to or better than the compendial method. This approach is supported by FDA documents, as well. The language in Draft 2 has been modified slightly to account for both methods and procedures.

A commenter asked why an alternative procedure could be considered to be appropriate in cases of interference, when another section of the General Notices states that an article is not in compliance with the compendial requirements if added substances interfere with the compendial tests.

The commenter overinterprets the first statement. In Draft 2, that statement has been restated to read, “In some cases, the compendial procedure will not be appropriate for a particular manufacturer's article. In such situations, an alternative procedure need not be shown to be equivalent to the compendial procedure.” It remains the case that if an added substance interferes with a compendial test, the article is not in compliance with the compendial requirements.

A commenter suggested reinserting the currently official text discussing the interchangeability of methods between the *USP*, *EP*, and Japanese Pharmacopeia.

The text has been reinserted in Draft 2.

Solvent-Free Basis

Some commenters asked about the exclusion of residual solvents from the calculation for “solvent-free” basis.

Residual solvents are excluded from that calculation because these solvents are addressed through other compendial approaches.

Ignition to Constant Weight

Several commenters suggested that the definition of “ignite to constant weight” should be revised to harmonize with General Chapter <281>, or that the specific temperature for ignition should be specified in each monograph.

General Chapter <281> discusses ignition for specific purposes. As a default, however, 800° has been determined to be appropriate. As other temperatures are required, those temperatures will be addressed in the individual monograph.

Sample Preparation

One commenter suggested amending the description of “filtration” to allow for the common practice of discarding the first part of the filtrate. Another commenter requests that other means of separation should be allowed.

Draft 2 allows for discarding the first part of the filtrate. Other means of separation would be permissible as alternative procedures.

Test Solutions

One commenter pointed out that changes in a Test Solution may require validation.

Draft 2 reflects the commenter’s point.

Solution Adjustments

One commenter inquired whether solutions may be adjusted for reasons other than to adapt to the working range of the instrument. Another pointed out that any changes must be within the validated range of the instrument.

The text has been clarified to circumstances in which solutions may be adjusted, and to what degree. Draft 2 also indicates that the changes must be within the validated range of the instrument.

Units Necessary to Complete a Test

Commenters found the proposed language regarding a “good analytical result” to be confusing. One commenter also requested that USP reinsert the text allowing for the use of “proportionately larger or smaller quantities.”

The text in Draft 2 has been clarified. We believe that this statement allows for the use of proportionately larger or smaller quantities, but we welcome additional comment on the topic.

One commenter asks what use one makes of the weight of the selected tablets or capsules. The commenter also asked why other dosage forms are not addressed in a similar manner in the General Notices.

The specific use is specified in the monograph. Monographs for other dosage forms do not include similar requirements.

Good Manufacturing Practices

A commenter suggested adding new text stating that articles must be manufactured in accordance with current Good Manufacturing Practices (cGMPs) in order to be considered of *USP* or *NF* quality.

USP did not include this additional text because compliance with cGMPs is not necessary to conform to compendial requirements. In fact, in the US, compendial compliance is one aspect of compliance with cGMPs. The text from the *FCC* regarding compliance with GMPs has been omitted from Draft 2, along with the other *FCC* content.

9. Monograph Components

Added Substances in Official Substances

A commenter felt that the concept of “added substances” in “official substances” is confusing.

USP retains this language in Draft 2. In many excipients and some drug substances, a material is added to aid in the stability, processability, or consistency of the material. These added substances are generally inert, but may affect the final value received in the Assay. An example is Titanium dioxide. TiO_2 is typically ground to a very fine particle size. This material has a tendency to re-aggregate with significantly affects its effectiveness. Therefore, manufacturers will often add other inorganic oxides in small quantities to reduce aggregation.

A commenter suggested adding “color” as a type of substance that may be added to official substances.

Colors are addressed separately and permitted in certain official products. They are not included as added substances permissible in official substances because colors will often interfere with monograph tests and procedures.

A commenter suggested that this section allow for the addition of information based on the guideline on the Composition Profile for Excipients that is being developed by the International Pharmaceutical Excipients Council (IPEC).

USP looks forward to reviewing the IPEC guidance.

Added Substances in Official Products

One commenter pointed out that some of the text in this section discussed both official substances and official products. Another commenter suggested deleting most of the criteria relating to the appropriate use of added substances, including the requirements that they “be harmless in the amounts used,” “do not exceed the minimum quantity required,” and “do not interfere” with compendial tests.

The section on added substances has been reorganized in Draft 2 to clarify that certain text does apply to both official substances and official products. The requirement that the ingredients be “harmless in the amounts used” has been deleted, but the other requirements have been retained in this draft. Although other sections of the General Notices also may specify that added substances may not interfere with compendial requirements, USP does not believe that it is necessary to remove that statement in this context. USP also continues to believe that added substances should be used in the minimum quantity required to achieve the intended purpose and has not been presented with evidence of situations in which more than the minimum quantity is necessary.

A commenter pointed out that the term “added substances” can be replaced with the term “excipients” when referring to official products.

“Added substances” is retained because it is broader. Although “excipients” is appropriate in relation to most official products, some official products will not include traditional excipients. A commenter suggested adding “usefulness” as a reason for which substances may be added to official products.

USP did not add this term because we view the existing term “efficacy” as covering the same topic.

Two commenters pointed out that inert gases may safely be used in articles intended for other than parenteral administration. Two commenters also suggested that argon be added to the list of acceptable inert gases.

USP has deleted the parenteral use limitation in Draft 2, but welcomes comment about situations in which inert gases may not be appropriate. Draft 2 includes argon in the list of gases.

A commenter asks why the discussion on the alteration of the proportions of substances in official products applies only to compounded preparations and only to ointments and suppositories.

This text applies only to compounded preparations in the current General Notices. We welcome comment about the potential impact of extending this statement to cover (1) manufactured drugs in addition to compounded preparations and (2) dosage forms other than ointments and suppositories.

Identification

Several commenters felt that the role of the identification test in establishing identity was unclear in the draft.

Draft 2 has clarified that the identification test is required, but not necessarily sufficient, to establish identity.

Assay

Several commenters opposed the inclusion of a default upper assay limit.

Draft 2 omits the default limit. An upper limit is included in each monograph.

Impurities

A commenter suggested reverting to the current text discussing impurities and foreign substances.

Draft 2 is based on the current text.

Other Impurities

A commenter suggested further dialogue to address “other impurities” and “ordinary impurities.” Another commenter suggested that this section be completely revised to align with ICH Q3A and Q3B.

USP is open to additional comments and discussion on this topic.

A commenter asked whether a policy should be developed to address toxic components that cannot be detected by the compendial method, but can be identified by an alternative method. The commenter also asks whether all toxic components should be declared in the labeling.

Another commenter suggested that if ICH concepts are used, the statement about toxicity is not needed.

Toxic impurities and genotoxic impurities form a very important ongoing discussion in the USP. Where toxic impurities are known to exist, FDA and manufacturers that know of these issues have a responsibility to propose revisions to the *USP-NF* standard to minimize risks to the patient. The concept of labeling toxic impurities is an interesting topic that USP will discuss further. The ICH concepts do not adequately limit or eliminate toxic impurities in a comprehensive way. Therefore, the use of ICH will not address this problem. However, discussions on the best ways to include or emphasize the ICH impurity standards in USP monographs are ongoing.

10. Test Results

Rounding Rules

A commenter pointed out that where a limit is expressed in ppm, the results also should be expressed in ppm. Another commenter suggested deleting the table.

The rounding table has been changed in Draft 2 to reflect the first comment. It is retained because it is believed to be useful to those less familiar with the compendia.