

COMMENTARY– USP 32-NF 27

Revision proposals published in *Pharmacopeial Forum* often elicit public comments that are forwarded to the appropriate Expert Committee for review and response. In accordance with the Rules and Procedures of the 2005-2010 Council of Experts, revision proposals can advance to official status with minor modifications, as needed, without requiring further public review. In such cases a summary of comments received and the appropriate Expert Committee's responses are published in the *Commentary* section of the USP website at the time the revision becomes official. For those proposals that require further revision and republication in *Pharmacopeial Forum*, a summary of the comments and the Expert Committee's responses will be included in the briefing that accompanies each article.

The *Commentary* section is not part of the official text of the monograph and is not intended to be enforceable by regulatory authorities. Rather, it explains the basis of the Expert Committee's response to public comments. If there is a difference between the contents of the *Commentary* section and the official monograph, the text of the official monograph prevails. In case of a dispute or question of interpretation, the language of the official text, alone and independent of the *Commentary* section, shall prevail.

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No comments received for the following proposals:

General Chapters

<621> Chromatography
<1121> Nomenclature

Monographs

Albendazole
Alfadex
Allopurinol
Aminophylline
Arginine Capsules
Arginine Tablets
Betadex
Bupivacaine Hydrochloride
Chloroquine
Corn Syrup

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No comments received for the following proposals, continued

Monographs, continued

Curcuminoids
Curcuminoids Capsules
Curcuminoids Tablets
Diclofenac Potassium
Didanosine
Diethylstilbestrol Diphosphate
Diethylstilbestrol Diphosphate Injection
Disopyramide Phosphate
Dronabinol
Dyclonine Hydrochloride
Epinephrine
Erythorbic Acid
Estradiol
Eucatropine Hydrochloride
Eucatropine Hydrochloride Ophthalmic Solution
Fenofibrate Capsules
Flavoxate Hydrochloride
Fluconazole
Glyceryl Monooleate
Iopamidol
Iopamidol Injection
Isopropyl Alcohol
Ivermectin Tablets
Lecithin
Levalbuterol Inhalation Solution
Liquid Glucose
Meclizine Hydrochloride
Methoxsalen Capsules
Methyl Alcohol
Methylprednisolone
Naproxen Delayed-Release Tablets
Norethindrone Acetate and Ethinyl Estradiol Tablets
Norethindrone and Ethinyl Estradiol Tablets
Peg 3350 and Electrolytes For Oral Solution
Pentazocine Hydrochloride and Acetaminophen Tablets
Piperazine
Piperazine Adipate
Piperazine Citrate
Piperazine Dihydrochloride
Piperazine Phosphate

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No comments received for the following proposals, continued

Monographs, continued

Potassium Bromide Oral Solution, Veterinary
Powdered Soy Isoflavones Extract
Powdered Turmeric
Powdered Turmeric Extract
Propoxycaïne and Procaine Hydrochlorides and Norepinephrine Bitartrate Injection
Propylene Glycol Monolaurate
Pseudoephedrine Hydrochloride
Ralbumin Human
Salsalate Tablets
Sodium Bromide Injection, Veterinary
Sodium Bromide Oral Solution, Veterinary
Soy Isoflavones Capsules
Soy Isoflavones Tablets
Torsemide
Turmeric

General Notices

General Notices and Requirements/Section: *General Notices* and Requirements/All
No. of Commenters: 20

Note: The Council of Experts Executive Committee (CoE EC) is the decisional body for *General Notices*.

General Comments

Comment Summary: Several commenters expressed appreciation for the new format.

Comment Summary: Several commenters suggested omitting the section symbol before each section number, as this symbol has little meaning to users.

Response: Comment incorporated.

CoE EC-initiated change: The CoE EC changed the section numbering throughout, adding another digit to the second and third tier of section numbers. With this change, for example, section 2.2 becomes section 2.20, and section 3.1.1 becomes 3.10.10. This change allows for the future addition of new subsections between existing subsections without requiring changes to existing subsection numbers.

Preamble

Comment Summary: A commenter suggested that the preamble of the *General Notices* should be given a section number and/or a title (e.g., “Preamble”).

Response: Comment not incorporated. Generally, preambles are not given a heading.

Comment Summary: One commenter suggested changing the final sentence of the Preamble to indicate that a general chapter supersedes the *General Notices* in the event of a difference, whether or not the general chapter notes the difference.

Response: Comment not incorporated at this time. This concept is not included in the *General Notices* in *USP 31* and would require additional input before implementing.

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Section 1

Comment Summary: Several commenters suggested that the *USP* and *NF* should be identified using only the year in which the volumes become official, e.g., *USP-NF 2009*. The commenters feel that the revision and edition numbers are confusing and have little or no meaning to most users.

Response: Comment not incorporated at this time. This suggestion may be proposed in a future revision of the *General Notices*.

Comment Summary: One commenter suggested referring to “revision and edition” throughout this section because *USP* is published in an annual revision, while *NF* is published in an annual edition.

Response: Comment not incorporated. Because *USP* and *NF* both are revised from time to time, the term “revision” is appropriate.

Comment Summary: A commenter suggested omitting the official date from section one and noting instead that the official date is provided on the cover of the text.

Response: Comment not incorporated. The *General Notices* provide the basic assumptions, definitions, and default conditions for the interpretation and application of the *USP* and *NF*. The default official date is a basic assumption, and therefore belongs in the *General Notices*.

Comment Summary: Some commenters noted that official dates can be provided in content other than monographs and general chapters, and suggested changing the text regarding official dates accordingly.

Response: Comment incorporated.

Comment Summary: One commenter suggested clarifying that the official date specified in a specific portion of text only can become official on a date later than the default official date for the publication.

Response: Comment not incorporated. A specific portion of compendial text may have an earlier official date than the remainder of the compendium. For instance, a revision may be made official through a *Revision Bulletin* with a specific official date. That revision will be moved into the first available *USP-NF* or *Supplement* print publication, and the specified official date from the *Revision Bulletin* still applies. That official date may fall within the 6-month period that is provided for implementation of requirements after the publication of the *USP-NF* or *Supplement*, prior to the publication’s default official date.

Comment Summary: One commenter noted that official text can be published in a *Supplement* without previously appearing in *Pharmacopeial Forum*. For instance, text made official through a *Revision Bulletin* will appear directly in the *Supplement*. The commenter suggested noting such possibilities.

Response: Comment partially incorporated. The CoE EC eliminated the text discussing the process of moving material into the *Supplement*, as process is discussed in the *Mission and Preface*.

Comment Summary: One commenter suggested that *USP* should implement a specific publication schedule for *Revision Bulletins*. Another commenter noted that *Revision Bulletins* appear to be a method for correcting *Errata* and asked how industry should best monitor the *USP* website for compliance purposes.

Response: Comments not incorporated. *Revision Bulletins* are used when circumstances require immediate publication of official text, and therefore a specific

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timetable is not feasible or appropriate. *Revision Bulletins* are revisions to official text, while *Errata* are corrections. USP has initiated an email notice service to inform users of *Revision Bulletins* and other important material appearing on the USP website.

Comment Summary: Several commenters suggested that section one should include a discussion of *Errata*, as these changes are not otherwise mentioned in the *General Notices*. Commenters noted that it is important for users to be aware that corrections to incorrect text may appear and are effective immediately upon publication.

Response: Comment incorporated.

Comment Summary: One commenter requested the reinclusion of the text that appears in *USP 31* discussing the *Pharmacopeial Forum*.

Response: Comment not incorporated. The process for developing a standard is described in the *Mission and Preface*. While that information is essential for participation in USP's standards-setting activities, it is not a basic assumption, definition, or default condition for the interpretation and application of the *USP* or *NF*.

Section 2

Comment Summary: One commenter suggested specifying the sources of official text (*Revision Bulletin*, *Interim Revision Announcement*, etc.) in section 2.1.

Response: Comment incorporated.

Comment Summary: Two commenters suggested revising the statement in 2.1 regarding the circumstances in which content of general chapters numbered over 1000 may become mandatory. One of the commenters recommended making the statement more specific in order to be more accurate. The other suggested deleting the statement "or elsewhere in the compendia."

Response: Comment incorporated. The statement was made more specific.

Comment Summary: One commenter suggested that the inclusion of dietary ingredients and components of medical devices in the definition of official substance be qualified. The commenter also suggested that the inclusion of medical devices and dietary supplements in the definition of official product be similarly qualified. The commenter pointed out that these items are not required to comply with *USP* or *NF* standards unless they claim to comply.

Response: Comment not incorporated. These articles are "official articles" and either "official substances" or "official products" if they are recognized in the *USP* or *NF*, whether or not a particular manufacturer chooses to comply. Section 3.10 discusses the applicability of *USP* and *NF* standards to dietary supplements, medical devices, and their ingredients and components.

Comment Summary: One commenter suggested revising the language discussing the appropriate quality standards for ingredients in dietary supplements to omit reference to *USP*, *NF*, and *Food Chemicals Codex* because dietary supplements are not required by US law to meet these standards.

Response: Comment not incorporated. Although US law requires ingredients in dietary supplements to be only of food-grade quality, the *General Notices* set forth the requirements for conformance to *USP* and *NF* requirements. The CoE EC believes that it is appropriate that dietary supplements contain ingredients that meet *USP*, *NF*, or *FCC* standards when such standards are available.

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Comment Summary: Several commenters suggested adding a statement regarding the legal status of the *USP* and *NF*. They indicated that that the current text regarding legal status in the *Mission and Preface* could be easily overlooked and that a prominent placement of this information in *General Notices* is appropriate due to its importance.

Response: Comment partially incorporated. The *General Notices* have been revised to include a general statement about legal applicability of the *USP* and *NF*, with a reference to the more complete information in the *Mission and Preface*. The title of section 2 has been changed to include the new content.

CoE EC-initiated change: The CoE EC added a sentence to section 2.10 (formerly section 2.1) to clarify that general chapters numbered over 2000 apply to products intended for use as dietary ingredients and dietary supplements only, as a codification of a long-standing policy.

CoE EC-initiated change: The CoE EC moved text from the end of section 2.2 into section 3.1 (now 3.10). This text describes requirements for the ingredients used in official products and therefore belongs in the discussion of requirements for meeting standards in section 3 rather than in the definitions of official status in section 2.

Section 3

Comment Summary: One commenter suggested that section 3.1 be retitled “Applicability of Standards – General” and that the titles of sections 3.1.1 and 3.1.2 be expanded so that they may stand alone.

Response: Comment partially incorporated. The titles of sections 3.1.1 and 3.1.2 have been expanded. With those changes, the suggested change to the title of the parent section 3.1 is not appropriate.

Comment Summary: Two commenters suggested deleting the term “release” in the sentence, “The manufacturer’s release specifications, and current Good Manufacturing Practices (GMPs) generally, are developed and followed to ensure that the article will comply with compendial standards...”

Response: Comment incorporated.

Comment Summary: One commenter suggested adding the phrase “with applicable standards” to the last sentence of the second paragraph in section 3.1, so that “any article tested as directed in the relevant monograph shall comply with applicable standards.”

Response: Comment not incorporated because the relevant monograph, together with these *General Notices* and referenced general chapters, provides the applicable standards.

Comment Summary: One commenter requested that the *General Notices* define the number of units that must be tested for each batch.

Response: Comment not incorporated. This determination is left to the manufacturer and regulatory authority.

Comment Summary: Several commenters suggested the addition of language specifying that although articles must be able to meet compendial requirements if tested, routine testing is not the only means of demonstrating compliance, nor even necessarily the best means. They recommend language that makes clear that an item must be able to meet compendial requirements, as opposed to demonstrating

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compliance through routine testing. The commenters suggested including language that is similar or identical to the text in *USP 31* that expressly makes these points.

Response: Comment partially incorporated. The CoE EC has revised the proposed language to make clear that the *USP* and *NF* do not specify whether and how often testing must be performed. The CoE EC views these determinations as properly made by regulatory authorities and manufacturers.

Comment Summary: Several commenters found the third paragraph of section 3.1, comparing compendial standards and statistical sampling plans to be confusing. They requested clarification. One such commenter suggested incorporating language from the current *General Notices* to help clarify. Another commenter pointed out that the current language referring to the “singlet” has been omitted, and suggested including that text back into the *General Notices*.

Response: Comments generally not incorporated, but the CoE EC deleted one sentence to help avoid confusion.

Comment Summary: Several commenters objected to the proposal to remove the requirement that official substances be manufactured in accordance with good manufacturing practices. Some of the commenters suggested that the sentence should not only be retained, but also should be broadened to apply to all official articles.

Response: Comment partially incorporated. The existing text will be retained. The CoE EC notes that this text refers to “recognized principles of good manufacturing practice” and is not specific to the regulatory requirements of good manufacturing practices in any particular country. The suggestion to broaden this requirement to apply to all official articles, as well as suggestions of additional text that might be included, may be considered in a future revision of the *General Notices*.

Comment Summary: One commenter noted that the two discussions of the use of the “USP” and “NF” letters in sections 3.1.1 and 3.2 seem contradictory, and requested clarification.

Response: Comments incorporated. The text from section 3.1.1 was moved to section 3.2 and the language clarified to avoid confusion.

Comment Summary: A commenter noted that the reference to the United States in section 3.1.1 may cause some users to apply a more limited interpretation than may have been intended.

Response: Comment not incorporated. Section 3.1.1 (now section 3.10.10) addresses only the mandatory nature of the *USP* and *NF* in the US. Other sections, including sections 2.20 and 3.20, provide additional information relevant to users in countries that do not mandate compliance with the *USP* and *NF* in the same way.

Comment Summary: One commenter suggested moving the text regarding assay of compounded preparations from section 5.5 to section 3.1.2. The commenter also suggested including information regarding assay procedures from the general chapters on compounding.

Response: Comment not incorporated. The CoE EC will retain the existing text in section 5.5 as proposed, as it relates specifically to the Assay portion of monographs. The addition of text from general chapters may be considered in a future revision of the *General Notices*.

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Comment Summary: One commenter requested clarification regarding the circumstances in which an article is permitted to differ from the *USP* standard and state the difference on the label.

Response: Comment not incorporated because the proposed text is clear. Products may be labeled as “USP” or “NF” if they differ from the monograph requirements for strength, quality, or purity, and state the difference on the label. Products may not be labeled “USP” or “NF” if they differ from the identity specified by the monograph.

CoE EC-initiated change: In order to avoid referring to any particular regulatory regime, the CoE EC changed the reference to “current Good Manufacturing Practices (GMPs)” in section 3.10 to “good manufacturing practices.”

Section 4

Comment Summary: One commenter suggested adding a statement describing the circumstances in which a general chapter becomes mandatory.

Response: Comment not incorporated because this content is included in section 2.10 (formerly 2.1).

Comment Summary: One commenter suggested clarifying or deleting the statement relating to characteristics that are not standardized by the compendia. The commenter stated that it is difficult to understand the applicability of this statement.

Response: Comment incorporated. The statement has been clarified to indicate that it refers to characteristics that are not standardized by the compendial monographs. Particle size, for instance, often is not addressed by substance monographs. The text also has been clarified to refer to functional equivalence rather than performance equivalence.

Comment Summary: One commenter asked that the *General Notices* clarify how users should apply two different product monographs that both apply to a single drug product.

Response: Comment not incorporated. Specific examples of such situations would assist the CoE EC in responding in the future.

Comment Summary: One commenter suggested revisions to the final sentence of 4.1.1 because of concerns related to labeling requirements. The commenter did not specifically outline its concerns.

Response: Comment not incorporated. The CoE EC believes that the final sentence of 4.1.1 correctly states the requirements included in monographs.

Comment Summary: One commenter suggested that the sentence in section 4.1.2 allowing for an increase in the upper acceptance criterion for dietary supplements in certain cases also should apply to antibiotics and to formulations requiring overages.

Response: Comment not incorporated. Increases in the upper acceptance criterion are not appropriate for antibiotics or for articles requiring overages.

Comment Summary: One commenter suggested changing the phrase “good pharmaceutical practice” in section 4.1.2 to “good compounding practice” or similar.

Response: Comment incorporated, as the relevant paragraph clearly is discussing compounding practice.

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Comment Summary: One commenter suggested adding text in the description of general chapters to illustrate that some chapters cover compounding, dispensing, storage, and packaging.

Response: Comment incorporated.

Section 5

Comment Summary: One commenter requested clarification regarding the sections of the monograph that are required, as the reference to the >> symbol has been omitted.

Response: Comment not incorporated. That symbol has been omitted from the format for the redesigned monographs that will appear in *USP 33*. With that omission, *USP* and *NF* monographs make no distinction between required and informational content.

Comment Summary: Several commenters found the structure of section 5.2 to be unwieldy and suggested “flattening” the hierarchy to allow users to better navigate the section. They also suggested incorporating the text in 5.2.1 on official articles into section 5.2.

Response: Comment incorporated. We have removed several section headings.

Comment Summary: Commenters find the term “added substances” confusing and suggest using the terms “additive” and “excipient” instead.

Response: Comment partially incorporated. The CoE EC wishes to be as broad as possible in discussing the types of items that may be added to official substances and official products, and believes that “added substances” is the broadest term possible. Recognizing that excipients may be one type of substance added to official products, we have revised the title of this section to include excipients. We also have revised the section on official products to refer to “added substances or excipients.”

Comment Summary: One commenter suggested revising the first sentence of section 5.2, regarding the suitability of added substances, so that it is positive (“Substances are suitable if...”) rather than negative (“Substances are unsuitable unless...”), for the purpose of clarity. The commenter also suggested that the phrase “all substances” be changed to a phrase more consistent with the other terms in the section.

Response: Comments partially incorporated. The CoE EC deleted the word “all,” as the term “substances” is used throughout the section. The CoE EC agrees that the positive form of the sentence may be clearer, but notes that the current *General Notices* in *USP 31* use the negative form. The CoE EC continues to use the negative form because it encourages users to consider added substances carefully before use.

Comment Summary: Two commenters suggested deleting the requirement that added substances “not exceed the minimum quantity required” because they are uncertain how “minimum quantity required” is to be interpreted.

Response: Comment not incorporated. This requirement currently is official in *USP 31*.

Comment Summary: One commenter suggested that if section 5.2.2 intends that drug substance labels show the name and amount of each diluent, manufacturers would be required to provide proprietary formulation information.

Response: The CoE EC notes that the language in the proposal is essentially identical to the language in the *General Notices* for *USP 31*.

Comment Summary: Two commenters suggested that the CoE EC clarify the term “bases” in the listing of examples of substances that may be added to official products, in order to avoid confusion with “acids and bases.”

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Response: Comment incorporated. We have changed the term to “pharmaceutical bases.”

Comment Summary: Two commenters suggested further limiting the statement in 5.2.3.1.2 that “the proportions of the substances constituting the base in ointment and suppository products and preparations may be varied” under certain circumstances.

Response: Comment not incorporated. This language has been included in the *General Notices* for some time, and the CoE EC would need to further understand the implications of such a change before making it.

Comment Summary: One commenter suggested that section 5.2.3.2.1, discussing the use of ingredients on the dried basis, might apply to manufactured products as well as to compounded preparations.

Response: Comment not incorporated. The text applies only to monographs in the form of “recipes” that call for ingredients, and thus applies only to compounded preparations.

Comment Summary: One commenter suggested including the text from *USP 31* regarding description and solubility.

Response: Comment not incorporated. The text in section 5.3 is intended to cover the same content as the text in the current *General Notices*, although it has been tightened and rewritten from the current text.

Comment Summary: One commenter suggested including in section 5.3 a reference to the Solubility Table in the *Reagents, Indicators, and Solutions* section of the *USP-NF*. Another commenter suggested reincluding the Solubility Table into the *General Notices*, as this text is of particular utility to compounding professionals.

Response: Comment incorporated. We have added the Solubility Table back into the *General Notices*.

Comment Summary: One commenter pointed out that the discussion of uniformity of dosage units under “assay” in section 5.5 does not address the Assay per se.

Response: Comment incorporated. The discussion of uniformity of dosage units has been moved to a new section 5.70 on performance tests.

Comment Summary: One commenter suggested changing the phrase “good pharmaceutical practice” in section 5.6 to “good compounding practice” or similar. Two commenters suggested changing the phrase “processing methods” in this section to “manufacturing process.”

Response: Comments not incorporated at this time, as the CoE EC would need additional input before making these changes.

Comment Summary: One commenter suggested harmonizing the limit of any single “other impurity” in section 5.6.1 with the requirement in the *European Pharmacopoeia* at 0.10%, rather than the current 0.1%.

Response: Comment not incorporated at this time, but may be considered for a future revision of the *General Notices*.

Comment Summary: One commenter suggested clarifying whether the limit of total impurities applies to all ingredients and products.

Response: Comment not incorporated. The CoE EC believes that the language is adequately clear that the limit of total impurities of 2.0%, to include both monograph-detected impurities and other impurities, applies to all compendial articles.

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Comment Summary: One commenter suggested defining “other impurities.” Another commenter suggested pointing out that “byproducts of disinfection processes, e.g., chlorine” should be considered.

Response: Comment not incorporated. The text defines an “other impurity” as “an impurity present in the substance” that the “monograph procedure does not detect.” This would include byproducts of disinfection processes.

Comment Summary: Two commenters suggested changing section 5.6.2 on Residual Solvents to require that any method other than the methods provided in General Chapter <467> *Residual Solvents* must be validated.

Response: Comment not incorporated. Section 6.30, which provides information about the use of alternative methods, applies to methods alternative to those in General Chapter <467> *Residual Solvents* as it does to any other method.

Comment Summary: One commenter noted that the text in section 5.7 is different from the text in General Chapter <11> *USP Reference Standards*, and recommended simply referring to General Chapter <11> *USP Reference Standards* for instructions for use of USP Reference Standards. Another commenter suggested adding to section 5.7 text directing users to store USP Reference Standards as directed on the label.

Response: Comment partially incorporated. The CoE EC worked with the Reference Standards Expert Committee to develop appropriate language for inclusion in this section. The Reference Standards Expert Committee will revise General Chapter <11> *Reference Standards* to include text that is compatible with this text. Text relating to the storage of USP Reference Standards is appropriately included in General Chapter <11> *Reference Standards* and will be forwarded to the Reference Standards Expert Committee for their consideration.

CoE EC-initiated change: In section 5.6 (now 5.60), the CoE EC changed “current GMPs” to “good manufacturing practices” to avoid suggesting compliance with any particular regulatory regime.

CoE EC-initiated change: The CoE EC included in section 5.6.2 (now 5.60.20) text that had been proposed for deletion relating to the quality of solvents used during production.

Section 6

Comment Summary: One commenter questioned whether automated and manual procedures can be considered equivalent and suggested moving discussion of automated procedures into the following section on alternative methods and procedures.

Response: Comment not incorporated. The concept that automated and manual procedures are equivalent is included in the *General Notices* in *USP 31*.

Comment Summary: Two commenters suggested that the language in the second paragraph of section 6.3 on alternative methods may be open to unintended interpretations and may confuse users as they try to determine whether they may use an alternative method.

Response: Comment incorporated. The CoE EC believes that all potential situations are covered by the first paragraph, and thus is deleting the majority of the second paragraph. We retain the request for submission of alternative methods to USP as these methods can help us to improve the compendia.

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Comment Summary: One commenter suggested that *General Notices* allow for alternative methods to be submitted for USP for “inclusion of other parameters like the approval status of the product.”

Response: Comment not incorporated. The CoE EC does not fully understand the suggestion and would need additional input on such a proposal before implementing.

Comment Summary: One commenter expressed displeasure with the statement in section 6.3 that, where a difference appears between the *United States Pharmacopeia*, *European Pharmacopoeia*, and/or *Japanese Pharmacopoeia*, only the result obtained by the *USP* method is conclusive.

Response: Comment not incorporated. The CoE EC believes that it is important to clearly articulate the order of precedence in the event of a dispute between two or more standards.

Comment Summary: One commenter suggested that there are too many differences between fresh and dried materials for the language in section 6.4 to be appropriate. Specifically, the commenter objects to the language allowing test procedures to be performed on the undried or unignited substance, and the results calculated on the dried, anhydrous, or ignited basis, provided that the appropriate test is provided in the monograph. Another commenter suggests that the language in that section should allow the option of specifying the appropriate condition for testing under each monograph.

Response: Comments not incorporated. The CoE EC notes that the language in the proposed revision is essentially identical to the current text in the official *General Notices*. The appropriate conditions for testing are indicated in most monographs.

Comment Summary: One commenter suggested that the *General Notices* clarify in section 6.4 the method for accounting for the solvents in the material, as the accuracy of the result depends on the method.

Response: Comment incorporated. The CoE EC has clarified that the methods in General Chapter <467> *Residual Solvents* are to be employed unless a test for the limit or organic solvents is provided in the monograph.

Comment Summary: Commenters suggested changing the definitions of “ignite to constant weight” and “dried to constant weight” in section 6.4 to require that the weighings differ by no more than 0.5 mg/g, rather than 0.50 mg/g of substance taken.

Response: Comment not incorporated at this time. This suggestion may be proposed in a future revision of the *General Notices*.

Comment Summary: One commenter suggested revising the title of section 6.5 to “Preparation of Solutions” to better reflect the content.

Response: Comment incorporated.

Comment Summary: Commenter suggested revising the direction relating to filtration in section 6.5.1 by adding “if appropriate,” as follows: “...the initial volumes of a filtrate may be discarded if appropriate.”

Response: Comment not incorporated. Statements in the *General Notices* using the term “may” rather than “shall” are understood to apply if appropriate.

Comment Summary: One commenter suggested noting in section 6.5.2 that volumes of solutions may not be additive and that each volume should be measured separately.

Response: Comment not incorporated. The *General Notices* assume that the reader has a basic level of knowledge about chemistry techniques.

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Comment Summary: One commenter suggested noting in section 6.5.2.1 that circumstances in which concentrations may differ by more than 10% are special cases.

Response: Comment incorporated.

Comment Summary: One commenter suggested adding back into the *General Notices* language allowing for the use of “proportionately larger or smaller quantities than the specified weights and volumes” under certain circumstances.

Response: Comment not incorporated. The text in section 6.5.2.1 (now 6.5.20.1) presents a revised version of the previous content and is intended to cover the same subject matter.

Comment Summary: One commenter suggested deleting the statement in 6.5.2.2 that Test Solution information is provided only as guidance.

Response: Comment incorporated.

Comment Summary: One commenter suggested that section 6.6, Units Necessary to Complete a Test, should be incorporated within section 3.1.

Response: Comment not incorporated. Section 3.1 discusses the applicability of standards, while section 6.6 addresses specific concerns in the performance of particular compendial tests.

Comment Summary: One commenter suggested that section 6.6 should specify a percentage of a lot that should be tested to ensure that the tested sample is representative of the lot.

Response: Comment not incorporated. The CoE EC believes that the language is specific enough to allow the entity conducting the testing to determine the appropriate number of units to test.

Comment Summary: One commenter pointed out that the proposal would change section 6.6.2 (Tablets) to refer to “any procedure,” rather than simply to the Assay. Section 6.6.3 (Capsules) was not proposed to be changed in the same way. The commenter asked whether the change was complete and whether it was intended.

Response: Comment incorporated. The direction to weigh and finely powder a specific number or tablets, or to remove as completely as possible the contents of a specific number of capsules, may appear in the Assay or in another portion of a monograph. The CoE EC has made the additional changes necessary for consistency.

Comment Summary: One commenter asked for clarification of the term “usually” in sections 6.6.1 and 6.6.2.

Response: Comment partially incorporated. The CoE EC deleted the reference to the “usual” number of tablets or capsules called for in specific instructions in monographs. It is not necessary to state this “usual” number because the actual number is specified in each monograph.

Comment Summary: One commenter suggested that the use of reagents meeting the specifications described in section 6.7 should be optional.

Response: Comment not incorporated at this time. The text proposed in *Pharmacopeial Forum* volume PF 34(1) imposes the same level of requirements as the current text in *USP 31*.

Comment Summary: One commenter suggested deleting the word “tubes” from the title of section 6.8.2.1, Chromatographic Tubes and Columns.

Response: Comment not incorporated because chromatographic tubes are specified in some compendial tests.

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Comment Summary: One commenter suggested that the definition of “water bath” in section 6.8.2.4 be revised to require “temperature control” rather than “vigorously boiling water,” because vigorously boiling water may not be needed and is altitude-dependent.

Response: Comment not incorporated at this time. This change may be considered in a future revision of the *General Notices*, with publication in *Pharmacopeial Forum* for comment.

Section 7

Comment Summary: One commenter suggested providing examples of rounding that are more applicable to limit tests. The commenter suggested that the examples are not appropriate because limit tests involve a very low range, e.g., parts per million.

Response: Comment not incorporated. The CoE EC points out that a rounding example is provided at the ppm level, but also notes that the examples are intended only to be examples and that the rounding rules apply equally without regard to the range.

Comment Summary: Several commenters suggested replacing “2.5 ppm” with “3.4 ppm” in the final rounding example.

Response: Comment partially incorporated. The CoE EC replaced “2.8 ppm” with “3.4 ppm” in the final example.

Section 8

Comment Summary: One commenter suggested revising the definition of “about” in section 8.1 to discuss the ranges acceptable for temperature and retention times specified in monographs because the relative retention times of known impurities are related to the specific retention time.

Response: Comment not incorporated at this time. This change would require additional input through a proposal in *Pharmacopeial Forum*.

Comment Summary: One commenter suggested revising the definition of “comcomitantly” in section 8.6 to include cases of identification in which the sample is measured, matched with the corresponding spectrum, and data back.

Response: Comment not incorporated. The CoE EC believes that the definition of “concomitantly” is adequate.

Comment Summary: One commenter requested that “low moisture content” in 8.7 be further defined.

Response: Comment not incorporated at this time. This change may be considered in a future revision of the *General Notices*.

Comment Summary: One commenter suggested that the definition of “negligible” should be deleted because it the term is used in few monographs. The commenter argued that “To warrant definition in the GNs, a term should have broad use or there should be some advantage in space savings or consistency.” Another commenter suggested that “negligible” should not be absolute, but should instead be based upon the total mass/content at issue.

Response: Comments not incorporated at this time. Appropriate revisions to the affected monographs may be proposed. If such revisions are made official, it may be possible to remove this definition from the *General Notices*.

COMMENTARY– USP 32-NF 27

Comment Summary: One commenter suggested revising the definition of “odor” in section 8.12 to allow the use of less than 25 g of material if appropriate considering the intended purpose and potency of the material.

Response: Comment incorporated in light of the safety concerns surrounding odor tests. The text is revised to allow the use of a suitable quantity.

Comment Summary: One commenter suggested deleting the reference to millimeters of mercury in the definition of “pressure” in section 8.15 to allow for references in Pascals.

Response: Comment incorporated. The monographs include the unit of measurement, so it is not necessary to designate mm of mercury as the unit of measure in the *General Notices*.

Comment Summary: One commenter requested clarification of the term “immediately” in section 8.16, Reaction time.

Response: Comment not incorporated at this time. This change may be considered in a future revision of the *General Notices*.

Comment Summary: One commenter suggested deleting the definition of “specific gravity” in section 8.17 and the definition of “moderate heat” in 8.18.

Response: Comment not incorporated. The *General Notices* provides basic definitions, of which “specific gravity” and “moderate heat” are two.

Comment Summary: One commenter suggested changing the definition of “temperature” in section 8.18 to require measurements to be made at “ambient room temperature” rather than at 25 degrees.

Response: Comments not incorporated. The *USP-NF* present a standard against which items may be measured. “Ambient room temperature” does not allow for such comparisons.

Comment Summary: One commenter suggested that the rounding rules should not apply to time, as specified in section 8.19.

Response: Comment not incorporated. Virtually all values in the compendia are subject to the rounding rules.

Comment Summary: One commenter suggested extending the definition of “transfer” in section 8.20 to include qualitative tests, such as identification tests in which quantitative transfer is not required.

~~**Response:** Comment not incorporated. “Transfer” is defined as a qualitative manipulation in the current *General Notices* in *USP 31*.~~

Amended Response: Comment not incorporated. “Transfer” is defined as a quantitative manipulation in the current *General Notices* in *USP 31*.

Note: Response was amended 05 March 2009 to correct “qualitative” to “quantitative” according to the *General Notices* published in *USP 31-NF 26*.

Comment Summary: One commenter suggested referencing kPascals as well as millimeters of Mercury in the definition of “vacuum” and “vacuum desiccator.”

Response: Comment incorporated.

Comment Summary: The Pharmaceutical Waters Expert Committee suggested changing the text in 8.23.1 to allow compliance generally with one of the water monographs in the *USP* or *NF*, or to include the titles of all water monographs in the *USP-NF*, for clarity.

COMMENTARY– USP 32-NF 27

Response: Comment incorporated. The text has been changed to require compliance with “the appropriate water monograph in the *USP* or *NF*.”

Comment Summary: One commenter suggested revising 8.23.2 to allow water used in manufacturing to meet US Environmental Protection Agency (EPA) requirements, the drinking water regulations of the European Union or Japan, or WHO guidelines for drinking water, to be consistent with the requirements in some of the water monographs. Another commenter suggested that this text be revised to require the use of water of a quality appropriate to the manufacturing process.

Response: Comments partially incorporated. The text has been revised to state that water meeting EPA drinking water requirements may be used, which is consistent with the current requirement in *USP 31*. This would allow for compliance with other appropriate regulations and is not inconsistent with the monograph text.

Comment Summary: One commenter suggested deleting all discussion of specific types of waters in section 8.23.3 because these waters are defined in general chapters. Another commenter suggested moving this text to the *Reagents* section of the *USP-NF*.

Response: Comments partially incorporated. The CoE EC worked with the Pharmaceutical Waters Expert Committee to develop more appropriate language, including references to general chapters rather than specific definitions.

Comment Summary: One commenter suggested rearranging the text in section 8.24 (weights and measures) slightly for a clearer result.

Response: Comment incorporated.

Comment Summary: One commenter suggested including the definitions of “molarity,” “molality,” and “normality,” which had been proposed for deletion. Another commenter suggested including the table of weights and measures, which had been proposed for deletion, because it is helpful in providing a complete resource.

Response: Comments incorporated. This content is included in section 8.24 (now section 8.240).

Section 9 (now section 10)

Comment Summary: Commenters suggested including the *NF* text regarding storage under nonspecific conditions. In the consolidation of the *USP* and *NF General Notices*, this text was omitted.

Response: Comment incorporated. This omission was inadvertent.

Comment Summary: One commenter asked why drug substances are exempted from the requirements of section 9.1

Response: The proposed text includes the same exemption that is provided in the *General Notices* in *USP 31*.

Comment Summary: Several commenters requested reincluding a direction to the Expert Committee regarding the appropriate language in monographs for excipients stable over a wide temperature range.

Response: Comment not incorporated. The *General Notices* present the basic assumptions, definitions, and default conditions for the interpretation of and application of the *USP* and *NF*. It is not the appropriate location for instructions intended only for Expert Committees.

COMMENTARY– USP 32-NF 27

Comment Summary: One commenter suggested clarifying the text in section 9.3.

Response: Comment not incorporated at this time. Section 9.3 includes the same text that currently is official in *USP 31*, pending potential future revision under the guidance of the Packaging and Storage Expert Committee.

Comment Summary: One commenter noted that the definition of “controlled cold temperature” had been omitted from section 9.3 and suggested that it be reincorporated.

Response: Comment incorporated as that omission was inadvertent.

Comment Summary: One commenter suggested that eliminating the decimal point and terminal zero in expressing the quantity of active ingredient, as specified in section 9.4.2, could affect the calculation of potency and widen the acceptance criteria.

Response: Comment not incorporated. The CoE EC notes that the text presented in *PF 34(1)* is the same as the text that is currently official in *USP 31*, and that the use of the decimal point and terminal following zero is not currently allowed by the *General Notices*. The CoE EC also points out that this text does not apply to acceptance criteria.

Comment Summary: One commenter suggested including the sentence in section 9.4.3 that had been proposed for deletion: “It is an established principle that Pharmacopeial articles shall have only one official name.”

Response: Comment incorporated.

Comment Summary: One commenter asks whether section 9.4.5 is to be interpreted as meaning that all botanical products must bear the statement relating to pregnancy.

Response: The CoE EC notes that the text in the *Pharmacopeial Forum* proposal is identical to the text in the currently official *General Notices*. The CoE EC also points out that the text applies only to products intended for use as dietary supplements and that the applicability of the *USP* and *NF*, including the *General Notices*, has been clarified in section 3.

Comment Summary: One commenter noted that section 9.4.10.1 does not address beyond-use dates for sterile preparations under the latest revision to General Chapter <797> *Pharmaceutical Compounding-Sterile Preparations*, and recommended revising the statement to align with that chapter.

Response: Comment not incorporated at this time. This change may be proposed in a future revision to the *General Notices*.

CoE EC-initiated change: The CoE EC made editorial changes to the first sentences of the temperature definitions in section 9.3 (now section 10.30) to form complete sentences.

Other Sections

Comment Summary: One commenter suggested including again the last paragraph of the current *General Notices*, which allows for the disregard of slight variations in volume due to variations in room temperature at the time of dispensing.

Response: Comment incorporated. This text has been added back into the *General Notices*, in a new section 9 on Prescribing and Dispensing. The numbering for the sections following has been changed accordingly.

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CoE EC-initiated change: The CoE EC has included again the text relating to the use of metric units in prescribing and dispensing. This text had been proposed for deletion. The CoE EC also included a clarifying sentence requested by the Safe Medication Use Expert Committee.

Monographs

Monograph/Section(s): Acetone/Multiple Sections

Expert Committee(s): Excipient Monographs 1

No. of Commenter(s): 2

Comment Summary #1: Commenter suggested the test for the water content be harmonized with the *European Pharmacopoeia* and USP's General Chapter <921> *Water Determination, Method 1a* instead of the proposed General Chapter method.

Response: Comment not incorporated at this time because the Committee determined that the *General Notices* allows for the use of alternate procedures to achieve equivalent or better results.

Comment Summary #2: Commenter suggested the test for related substances be harmonized with the *European Pharmacopoeia* to address the possible presence of methanol and benzene. The assay would then be calculated by subtraction of impurities present.

Response: Comment not incorporated at this time because the Committee determined that the *General Notices* allows for the use of alternate procedures to achieve equivalent or better results.

Comment Summary #3: Commenter requested the removal of the USP Reference Standards for Acetone and Methyl Alcohol and list as reagent grade.

Response: Comment not incorporated at this time because it is USP's policy to incorporate reference standards when appropriate to improve the quality of the monograph.

Comment Summary #4: Commenter questioned the reference to the S2 column packing for the water determination.

Response: Comment not incorporated. The Committee reviewed the column information submitted, Styrene divinylbenzene, with the revision along with the column designation recommendation and determined the designation indicates the column utilized.

Comment Summary #5: Commenter questioned the flow rate (40 mL per minute) in the water determination as seeming too great for a capillary system.

Response: Comment incorporated. The correct parameters for the acetone water test are now specified as follows: flow rate at 11 mL per minute; split rate at 50 mL per minute.

Comment Summary #6: Commenter questioned the purpose of using the same temperature for the injection port and the detector in the water determination.

Response: Comment not incorporated at this time. USP General Chapter <621> *Chromatography* has provisions that allow users to adjust parameter(s) to meet system suitability. Additionally, the monograph reflects the validated data supplied to the committee.

COMMENTARY– USP 32-NF 27

Comment Summary #7: Commenter requested the split ratio be adjusted to 1:250 from 1:400.

Response: Comment not incorporated at this time. USP General Chapter <621> *Chromatography* has provisions that allow users to adjust parameter(s) to meet system suitability. Additionally, the monograph reflects the validated data supplied to the committee.

Monograph/Section(s): Alfuzosin Hydrochloride/Multiple Sections

Expert Committee(s): Monograph Development – Pulmonary and Steroids

No. of Commenter(s): 1

Comment Summary #1: Commenter requested that the acceptance criteria for *pH* be changed from “between 4.0 and 5.5” to “between 4.0 and 6.0”.

Response: Comment not incorporated at this time. The proposed revision will be considered for incorporation into the official USP in the future.

Comment Summary #2: The commenter requested that the heading for the *Specific rotation* test should be changed to *Optical rotation*.

Response: Comment incorporated.

Comment Summary #3: Commenter suggested that their HPLC assay should replace the current potentiometric titration assay.

Response: Comment not incorporated at this time. The proposed revision will be considered for incorporation into the monograph in the future.

Monograph/Section(s): Bicalutamide Tablets/Multiple sections

Expert Committee(s): Monograph Development – Ophthalmics, Oncology, and Dermatology

No. of Commenter(s): 4

Comment Summary #1: Commenter suggested deleting the *Water* test because water content is formulation specific.

Response: Comment incorporated.

Comment Summary #2: Commenter requested changing the Assay acceptance criteria from 90.0-110.0% to 95.0-105.0% because the new specification would be consistent with their specification.

Response: Comment not incorporated because the assay limit for the approved marketed product is 90.0-110.0%.

Comment Summary #3: Commenter requested replacing the isocratic HPLC assay by a gradient HPLC assay.

Response: Comment not incorporated. The Expert Committee reviewed the information provided and concluded that the current method is suitable for its intended purpose and the proposed gradient procedure offers no clear advantage to the current method.

Comment Summary #4: Commenter requested revising the Assay procedure to achieve better separation of bicalutamide peak from the impurities which would eliminate the need for the related compound B resolution requirement.

Response: Comment not incorporated. The Expert Committee reviewed the information and determined that the current Assay procedure is suitable.

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Comment Summary #5: Commenter requested replacing the UV procedure with an HPLC procedure for *Uniformity of Dosage Units*.

Response: Comment not incorporated. The Expert Committee reviewed the information and determined that the current UV test procedure is suitable for its intended purpose.

Comment Summary #6: Commenter requested revising the test for *Limit of 4-amino-2-(trifluoromethyl)benzonitrile* to monitor the process impurities.

Response: Comment not incorporated because the process impurities are monitored and controlled in the drug substance monograph.

Monograph/Section(s): Butylated Hydroxytoluene/Related Compounds

Expert Committee(s): Excipient Monograph 1

No. of Commenter(s): 1

Comment Summary #1: Commenter suggested that since there are no known National Formulary (NF) grade suppliers for BHT, what the purpose the addition of related compounds test is.

Response: Comment not incorporated because the Committee reviewed all information and comments received and determined that proposed change is consistent with the *European Pharmacopoeia's* Butylatedhydroxytoluene monograph, and furthers USP's efforts to harmonize NF excipient monographs with *European Pharmacopoeia* Excipient monographs intended for use in a pharmaceutical dosage form.

Monograph/Section(s): Cabergoline/Specific Rotation

Expert Committee(s): Monograph Development – Psychiatric and Psychoactives

No. of Commenter(s): 1

Comment Summary #1: The commenter requested tighter *Specific rotation* limits.

Response: Comment not incorporated because the current specifications are consistent with marketed product.

Comment Summary #2: The commenter requested adding *Heavy metals* and *Residue on ignition* tests.

Response: Comment not incorporated because no supporting data for these tests were provided.

Monograph/Section(s): Carbomer 934, Carbomer 934P, Carbomer 940, and Carbomer 941/Multiple Sections

Expert Committee(s): Excipient Monographs 2

No. of Commenter(s): 2

Comment Summary #1: Commenter questioned the title notes of Carbomer 934, Carbomer 934P, Carbomer 940, and Carbomer 941 because the official date for the monograph of Carbomer Homopolymer is listed January 1, 2007 but the monograph title will not apply to the Homopolymer monograph until January 1, 2011.

Response: Comment not incorporated. The committee concluded that current "Carbomer Homopolymer" will become an official monograph starting 01-Jan-2007. However, the title " Carbomer Homopolymer" becomes official January 01, 2011. If the

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monograph is not official, or to be official, USP makes a notification at the end of the monograph.

Comment Summary #2: Commenter recommended revising the “NOTE” section for Carbomer 934, Carbomer 934P, Carbomer 940, and Carbomer 941 to read as follows: [NOTE— Effective January 1, 2011, the heading of this monograph will no longer constitute the official title for Carbomer 934 manufactured without the use of benzene. When benzene is not used in the manufacturing process, the name of the article will be Carbomer Homopolymer and will meet the requirements of the Carbomer Homopolymer monograph.]

Response: Comment incorporated.

Comment Summary #3: The commenter proposed maintaining the original viscosity test requirements of $25 \pm 0.2^{\circ}$ rather than the revised requirement of $25 \pm 0.1^{\circ}$.

Response: Comment not incorporated because the committee will like to standardize the procedure according to a newly revised General Chapter <911> *Viscosity* that will appear in *Pharmacopeial Forum* volume PF 34(6).

Monograph/Section(s): Carbomer Copolymer, Carbomer Homopolymer, Carbomer Interpolymer/Labeling

Expert Committee(s): Excipient Monographs 2

No. of Commenter(s): 0

Expert Committee-initiated Change: The Expert Committee changed the *Labeling* section from "giving the type of viscosity parameter" to "giving the viscosity measurement parameters" for clarification.

Monograph/Section(s): Cefdinir/Multiple sections

Expert Committee(s): Monograph Development – Antibiotics

No. of Commenter(s): 2

Comment Summary #1: Commenter requested changing the *Residue on ignition* limit from 0.1% to 1.0%.

Response: Comment not incorporated. The Expert Committee is willing to consider future changes to the monograph upon receipt of supporting data.

Comment Summary #2: Commenter recommended including an X-ray diffraction test to distinguish between polymorphic forms.

Response: Comment not incorporated because the current IR procedure in the *Identification* test and the test for *Water* adequately distinguishes the different polymorphic forms.

Comment Summary #3: Commenter recommended adding impurities to the *Related compounds* test.

Response: Comment not incorporated. The Expert Committee is willing to consider future changes to the monograph upon receipt of supporting data.

Comment Summary #4: Commenter requested the monograph include alternative columns for the *Assay* and *Related compounds* test.

Response: Comment not incorporated. The Chromatographic Reagents information is not official text. Alternative column information can be provided as a reference if there is adequate data demonstrating column equivalency.

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Monograph/Section(s): Cefdinir Capsules/Multiple sections
Expert Committee(s): Monograph Development - Antibiotics
No. of Commenter(s): 1

Comment Summary #1: Commenter requested clarification of the instructions to prepare Buffer Solution B in the Related compounds test. The reagent used to prepare this buffer should be Potassium phosphate monobasic, not Sodium phosphate monobasic.

Response: Comment incorporated.

Comment Summary #2: Commenter requested the *Standard* and *Test* solutions section of the *Related compounds* test be revised to indicate the diluent is Phosphate buffer Solution C.

Response: Comment incorporated.

Comment Summary #3: Commenter requested clarification regarding the concentration of the solutions used in the *Dissolution* test because the concentrations indicated in the *Pharmacopeial Forum* proposal seem too high to obtain accurate results.

Response: Comment not incorporated because the concentrations mentioned in the *Dissolution* test are based on validated data.

Comment Summary #4: Commenter requested *Related Compounds* tests for *Cefdinir Capsules* and *Cefdinir for Oral Suspension* monographs be revised to clarify the relative response factors.

Response: Comment incorporated.

Monograph/Section(s): Cefdinir for Oral Suspension/Multiple sections
Expert Committee(s): Monograph Development - Antibiotics
No. of Commenter(s): 1

Comment Summary #1: Commenter requested clarification of the instructions for preparing Tetramethylammonium hydroxide solution for the *Related Compounds* test.

Response: Comment incorporated.

Comment Summary #2: Commenter suggested that *Phosphate buffer Solution C* be used to prepare the *Standard* and *Test* solutions in the *Related compounds* test.

Response: Comment incorporated.

Comment Summary #3: Commenter requested clarification regarding the concentration of the solutions used in the *Dissolution* test because the concentrations indicated in the *Pharmacopeial Forum* proposal seem too high to obtain accurate results.

Response: Comment not incorporated because the concentrations in the current test are based on validation information.

Comment Summary #4: Commenter requested *Related Compounds* tests for *Cefdinir Capsules* and *Cefdinir for Oral Suspension* monographs be revised to clarify the relative response factors.

Response: Comment incorporated.

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Monograph/Section(s): Dimethyl Sulfoxide/Multiple sections
Expert Committee(s): Monograph Development – Ophthalmics, Oncology, and Dermatology

No. of Commenter(s): 3

Comment Summary #1: Commenter suggested the flow rate in the *Related compounds* test should be 1.7 mL per minute.

Response: Comment incorporated.

Comment Summary #2: Commenter suggested changing the limit for the *Limit of nonvolatile residue* test from 0.002% to 0.01%.

Response: Comment incorporated.

Comment Summary #3: Commenter requested changing *Limit of nonvolatile residue* test to match the current method specified in the ACS Reagent Chemicals Handbook.

Response: Comment incorporated.

Comment Summary #4: Commenter suggested adopting the *European Pharmacopoeia* test method for *Related compounds*.

Response: Comment not incorporated because the procedure in the *European Pharmacopoeia* test for *Related compounds* uses a packed column gas chromatography procedure and the Expert Committee concluded that the capillary GC column in the proposed revision is a more suitable technique

Expert Committee-initiated Change: The Expert Committee added a split ratio of 33:1 in the *Chromatographic system* section of the *Related compounds* test as well as a note allowing adjustment of the split ratio in order to optimize the performance.

Expert Committee-initiated Change: The Expert Committee revised the *Assay* calculation by subtracting the results from the tests for *Limit of nonvolatile residue* and *Related compounds*. A note was added to indicate the correction for water is not applied to the result.

Monograph/Section(s): Dipivefrin Hydrochloride/Assay

Expert Committee(s): Monograph Development – Ophthalmics, Oncology, and Dermatology

Expert Committee-initiated Change: The Expert Committee changed the *Assay* formula from “ $100(Cs/Cu)/(ru/rs)$ ” to “ $100(Cs/Cu)(ru/rs)$ ” for clarification.

Monograph/Section(s): Ethyl Acrylate/ and Methyl Methacrylate Copolymer Dispersion/Limit of Monomers

Expert Committee(s): Excipient Monographs 2

No. of Commenter(s): 2

Comment Summary #1: The commenters requested the addition of a calculation formula for the percentage of each monomer in the polymer dispersion.

Response: Comment incorporated. Calculation section is revised in “Limit of monomers”.

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Monograph/Section(s): Flavoxate Hydrochloride Tablets/Packaging and Storage, Assay

Expert Committee(s): Monograph Development – Psychiatric and Psychoactives

No. of Commenter(s): 1

Comment Summary #1: Commenter requested changing the *Packaging and storage* section from “Preserve in well-closed containers protected from light” to “Preserve in well-closed containers, protected from light”.

Response: Comment incorporated.

Comment Summary #2: Commenter requested changing the Assay procedure to add acetonitrile before filtration.

Response: Comment incorporated.

Monograph/Section(s): Formoterol Fumarate/Assay, Water content, Heavy metals

Expert Committee(s): Aerosols

No. of commenter(s): 3

Comment Summary #1: A commenter suggested tightening the assay limits to harmonize with *European Pharmacopoeia*.

Response: Comment incorporated.

Comment Summary #2: A commenter suggested lowering the limit for *Water content* because the drug is a dihydrate.

Response: Comment incorporated.

Comment Summary #3: A commenter suggested eliminating the *Heavy metals* test from the monograph.

Response: Comment not incorporated because other suppliers could have different methods of synthesis that could result in higher heavy metal content.

Comment Summary #4: A commenter suggested including *European Pharmacopoeia*'s HPLC method for the test for content of related compound I (diastereoisomer).

Response: Comment incorporated.

Comment Summary #5: A commenter suggested adding specification for “total of unspecified impurities”.

Response: Comment incorporated.

Comment Summary # 6: A commenter suggested revising the response factors to harmonize with *European Pharmacopoeia*.

Response: Comment not incorporated because the sponsor provided information indicating that these response factors were determined using impurity standards of very high purity.

Monograph/Section(s): Foscarnet Sodium/Multiple sections

Expert Committee(s): Monograph Development – Antivirals and Antimicrobials

No. of Commenter(s): 1

Comment Summary #1: Commenter proposed (1) replacing the multiple assay and impurities tests with a single proposed HPLC procedure and (2) retaining the existing GC procedure used in the test for the *Limit of foscarnet related compound D*.

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Response: Comment not incorporated. The Expert Committee reviewed the information and concluded that the proposed procedure is more appropriate as an alternate procedure.

Comment Summary #2: Commenter proposed replacing the *Limit of phosphate and phosphite* HPLC with UV detection procedure with an ion-exchange HPLC procedure with conductivity detection.

Response: Comment not incorporated because the proposed instrumentation is not readily available to all laboratories.

Monograph/Section(s): Granisetron Hydrochloride /Multiple sections
Expert Committee(s): Monograph Development – Gastrointestinal, Renal, and Endocrine

No. of Commenter(s): 2

Comment Summary #1: Commenter requested USP to add the test for *Heavy metals*.

Response: Comment incorporated. Based on the information received from several manufacturers, the test for General Chapter <231>*Heavy Metals, Method II* with the limit of NMT 20 ppm is added to the monograph.

Comment summary #2: Commenter suggested that the use of the terms “Test 1” and “Test 2” in the *Related compounds* test could be interpreted to mean that this is a flexible monograph and that only one of the tests needs to be performed. The commenter suggested that renaming Test 1 as “*Limit of Granisetron related compound E*” would eliminate the potential confusion.

Response: Comment incorporated.

Monograph/Section(s): Levalbuterol Hydrochloride/Specific solvents

Expert Committee(s): Aerosols

Number of commenter(s): 3

Comment Summary: Commenters suggested harmonizing with the International Conference on Harmonization by removing specific solvents and by referencing General Chapter <467> *Residual Solvents*.

Response: Comments incorporated.

Monograph/Section(s): Levothyroxine Sodium Tablets /Definition

Expert Committee(s): Monograph Development – Gastrointestinal, Renal, and Endocrine

No. of Commenter(s): 1

Comment summary #1. Commenter requested USP to extend the effective date of this revision which is October 3, 2009. The Commenter does not manufacture Levothyroxine Sodium Tablets for the US market, but does manufacture this product in a number of territories worldwide, and many of these markets have a local regulatory commitment to observe the USP. The Commenter indicated that within the currently defined timelines, it will not have a marketable product that conforms to the revised specification.

Response: At this point, the Monograph Development-Gastrointestinal, Renal, and Endocrine Expert Committee agreed not to change the implementation date of October 3, 2009, which corresponds to 24 months after the FDA notice, and wait for additional comments from the manufacturers outside of the US. The Committee will also take a

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proactive step and reach out to the USP users outside of the US, to assess possible impact of this change on the worldwide market.

Monograph/Section(s): Lisinopril and Hydrochlorothiazide Tablets/Assay

Expert Committee(s): Monograph Development – Cardiovascular

No. of Commenter(s): 1

Comment Summary #1: The commenter requested the related compound A resolution statement in the chromatographic system of the Assay test be changed from “... related compound A is not less than 3.0” to “... related compound A is greater than 3.0.”

Response: Comment incorporated.

Monograph/Section(s): Meclizine Hydrochloride Tablets /Related compounds

Expert Committee(s): Monograph Development – Gastrointestinal, Renal, and Endocrine

No. of Commenter(s): 1

Comment Summary #1: Commenter indicated the 4-chlorobenzophenone impurity has a response factor of 0.72, and requested the concentration of the *Sensitivity solution* be reduced to 1.25 µg per mL, to ensure that the 4-chlorobenzophenone impurity is detectable at the reporting limit of 0.1%.

Response: Comment incorporated.

Monograph/Section(s): Meradimate/Assay

Expert Committee(s): Monograph Development – Ophthalmics, Oncology, and Dermatology

No. of Commenter(s): 0

Expert Committee-initiated Change: The committee added a note for the split ratio in the *Chromatographic system* to allow adjustments in order to optimize performance.

Monograph/Section(s): Mirtazapine Orally Disintegrating Tablets/Multiple Sections

Expert Committee(s): Monograph Development – Psychiatric and Psychoactives

No. of Commenter(s): 2

Comment Summary #1: Commenter requested that the sample preparation procedure in the *Identification* test by IR be modified to allow better extraction of mirtazapine. The request was to delete the use of *Diluent* and to dissolve the article first in water followed by extraction with n-hexane.

Response: Comment incorporated.

Comment Summary #2: Commenter requested the range for the *Loss on Drying* test be modified to from NMT 5.0% to NMT 2.5%.

Response: Comment not incorporated because water content is formulation-dependent. The Expert Committee removed the test for *Water* from the monograph to accommodate various product formulations.

Comment Summary #3: Commenter indicated that two impurities specified in the *Related compounds* test are manufacturing impurities and do not need to be monitored.

Response: The Expert Committee decided to delay adoption of the *Related compounds* test until this issue is resolved. The use of *USP Mirtazapine Related*

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compound A RS has been deleted from the USP Reference Standards section to reflect the delay in the adoption of the *Related compounds* test.

Comment Summary #4: Commenter requested replacing the *Related compounds* procedure, which requires a 160-minute run time, with another procedure that has a 40-minute run time.

Response: Comment not incorporated because the *Related compounds* test will not become official in *USP32-NF27*. A revision proposal detailing the alternate (shorter run time) procedure will be published in a future *Pharmacopeial Forum*.

Comment Summary #5: Commenter suggested the addition of an alternate sample preparation in the Assay to lessen the amount of variability observed.

Response: Comment incorporated.

Monograph/Section(s): Mupirocin Calcium/Related Compounds, Assay

Expert Committee(s): Monograph Development – Antibiotics

No. of Commenter(s): 1

Comment Summary #1: Commenter suggested that the limit for any other unspecified impurity in the *Related compounds* test should be changed from 1 to 1.0.

Response: Comment not incorporated because the currently approved product limit is 1%.

Expert Committee-initiated Change: The *Chromatographic system* in the Assay was revised to indicate that the peaks generated in the *Resolution solution* are rearrangement products and not hydrolysis products.

Monograph/Section(s): Polyvinyl Alcohol/Multiple Sections

Expert Committee(s): Excipient Monographs 2

No. of Commenter(s): 4

Comment Summary #1: A commenter observed that the IR-Identification test methods and acceptance criteria for polyvinyl alcohol differs from the *European Pharmacopoeia*. Specifically, the Polyvinyl Alcohol IR-Identification test requires comparison to *USP Polyvinyl Alcohol RS*, whereas the *European Pharmacopoeia* lists absorption maxima at 2940 cm^{-1} and 2920 cm^{-1} . In addition, the commenter asked whether the USP Polyvinyl Alcohol Reference Standard is partially or fully hydrolyzed. Lastly, the commenter additionally requested the release date of the associated reference standard (USP Polyvinyl Alcohol Reference Standard).

Response: Comments not incorporated. The USP Polyvinyl Alcohol monograph and its associated RS meet United States manufacturing requirements for partially hydrolyzed polyvinyl alcohol. The Expert Committee acknowledges the *European Pharmacopoeia* polyvinyl alcohol monograph definition is broader than USP's. USP Polyvinyl Alcohol Reference Standard was released in March 2008.

Comment Summary #2: Commenter suggested that the monograph limits for methanol and methyl acetate, conflict with the residual solvent limits requirements in the USP General Chapter 467> *Residual Solvents* and in the International Conference on Harmonization Guideline Q3C(R3): Impurities: Guideline for Residual Solvents .

Response: Comment not incorporated. Methanol and methyl acetate limits are included in the Polyvinyl Alcohol monograph because they are outside the scope for General

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Chapter <467> *Residual Solvents*. Residual solvent limits in General Chapter <467> *Residual Solvents* apply only to finished drug products.

Comment Summary #3: Commenter suggested the “Limit of methanol (methyl alcohol) and methyl acetate” test include capillary columns that are equivalent to the glass column required in the monograph.

Response: Comments not incorporated due to inadequate supporting data.

Expert Committee-initiated Change: The Expert Committee reworded the *Labeling* section from "giving the type of viscosity parameter," to "giving the viscosity measurement parameters" for clarification.

Monograph/Section(s): Prednisolone Sodium Phosphate/Related compounds and Assay

Expert Committee(s): Monograph Development – Pulmonary and Steroids

No. of Commenter(s): 2

Comment Summary #1: Commenter requested that the concentration of prednisolone sodium phosphate in the *Related compounds* test standard solution be changed from “0.1 mg per mL” to “0.001 mg per mL” to reflect the concentration used in testing the current approved marketed product.

Response: Comment incorporated.

Comment Summary #2: Commenter requested that the relative response factor provided for free prednisolone in the *Related compounds* test should be changed from “F=0.75” to the reciprocal “1/F=1.3” because the test formula provided uses the reciprocal to calculate the limit of this impurity.

Response: Comment incorporated.

Comment Summary #3: Commenter suggested that prednisone sodium phosphate, a known impurity, be included in the *Related compounds* test with a limit of NMT 0.5%.

Response: Comment incorporated.

Comment Summary #4: Commenter requested that the preparation of the *Mobile phase* in the *Assay* be clarified to indicate the components are added by weight (w/w).

Response: Comment incorporated.

Monograph/Section(s): Propofol Injectable Emulsion/Multiple Sections

Expert Committee(s): Monograph Development – Pulmonary and Steroids

No. of Commenter(s): 3

Comment Summary #1: Commenter requested the *Assay* acceptance criteria be changed from “90.0 to 105.0% on the as-is basis” to “90.0 to 110.0%” to accommodate currently marketed products.

Response: Comment incorporated.

Comment Summary #2: Commenter requested that the storage statement provided in the *Packaging and storage* section be changed from “Store between 4° and 22°” to “Store at controlled at room temperature” to accommodate the storage conditions for currently marketed approve products.

Response: Comment incorporated.

Comment Summary #3: Commenter requested that the specification for the *Globule size distribution* test in lipid injectable emulsions be changed from referencing General Chapter <729> *Globule Size Distribution In Lipid Injectable Emulsions* to using the

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commenter's procedure because General Chapter <729> *Globule Size Distribution In Lipid Injectable Emulsions* is not intended for small-volume parenteral sedative-hypnotic agents but rather for large-volume parenteral emulsion products used for supplemental nutrition. The commenter's procedure has a mean globule size acceptance criteria of NMT 0.55 µm.

Response: Comment not incorporated. The Expert Committee is willing to revise the monograph in the future if evidence is provided to demonstrate that the requirements of General Chapter <729> *Globule Size Distribution In Lipid Injectable Emulsions* do not apply to this product.

Comment Summary #4: Commenter requested that the weight of stearic acid used for the Blank titration in the *Limit of free fatty acids* test be corrected from "142.3 g" to "142.3 mg".

Response: Comment incorporated.

Comment Summary #5: Commenter requested that the limits of propofol related compounds A and B in the *Related compounds* test be changed from NMT 0.25% and NMT 0.1%, respectively to NMT 0.5% for both of the related compounds. This change reflects the limits approved for currently marketed product.

Response: Comment incorporated.

Comment Summary #6: Commenter requested that a limit of NMT 0.1% for the largest unknown impurity and a limit of NMT 0.2% for total unknown impurities be added to the *Related compounds* test to reflect the limits approved for currently marketed product.

Response: Comment not incorporated. The proposed unknown impurity limits will be published in a future edition of *Pharmacopeial Forum* to allow manufacturers appropriate review and comment time before the limits become official.

Comment Summary #7: Commenter suggested that a test for Glycerin with limits of 90.0-110.0% and a test for egg phosphatides with limits of 90.0 – 110.0% be added to the monograph.

Response: Comment not incorporated. The proposed tests for the excipients are to be published in a future volume of the *Pharmacopeial Forum* to allow manufacturers appropriate review and comment time before the tests and acceptance criteria become official.

Expert Committee-initiated Change: The Expert Committee deleted the phrase "to the second inflection point" that appears under Sample titration in the *Free fatty acids* test because inclusion of this phrase suggests only the second inflection point is determined potentiometrically.

Monograph/Section(s): Tamsulosin Hydrochloride/Multiple sections

Expert Committee(s): Monograph Development – Gastrointestinal, Renal, and Endocrine

No. of Commenter(s): 3

Comment Summary #1: Commenter indicated that two specified impurities eluting before tamsulosin are not separated by this method and should be integrated together to determine compliance.

Response: Comment incorporated. A *Note* was added to clarify that these two impurities should be integrated together.

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Comment Summary #2: Commenter requested to change the sample weight in the titration assay from “700 mg” to “350 mg”, to be consistent with the *European Pharmacopoeia* monograph for Tamsulosin Hydrochloride.

Response: Comment incorporated.

Comment Summary #3: Commenter requested to clarify the term “disregard limit”.

Response: Comment incorporated. The term is changed to the International Conference on Harmonization term “reporting level for impurities”.

Comment Summary #4: Commenter requested USP raise the limit for the optical isomer under *Enantiomeric purity* from “NMT 0.1%” to “NMT 0.3%”. The Commenter indicated that there is no toxicity concern associated with the S-isomer, and the increased limit will not adversely affect the safety of the drug.

Response: Comment incorporated.