



USP General Notices Revision Project

Web Posting of Proposed Version for PF 36(1) January-February 2010

The *General Notices and Requirements* section of the *United States Pharmacopeia* and the *National Formulary (USP-NF)* were most recently revised in *USP 32-NF 27*. In the past several years since those revisions were originally undertaken, a number of new issues have been identified, as well as renewed interest in addressing previously considered issues. Outlined below are proposals for ten revised and one new *General Notices* provisions.

A previous version of this document was posted on USP's Web site for informal comments from interested stakeholders, from July 1, 2009 through August 31, 2009. In response to comments, for example, the proposed deletion of GN §10 has been withdrawn, until it can be coordinated with forthcoming new General Chapters that will address packing and storage (GC <659>) and labeling (GC <7>). The introductory sections below summarize the rationale for each proposal, including selected responses to comments received in response to the informal web posting. The proposed revisions highlighted in yellow below will be published in PF 36(1) on January 1, 2010. Final revisions are expected to be preposted on the USP website in July 2010, followed by publication in *USP 34-NF 29* in November 2010, with an official date for most revisions (except for any that might have a specified deferral date) of May 1, 2011.

Changes are Proposed for the Following General Notices Sections

- 2.30 *Role of USP in Federal Law*
- 3.10 *Encourage Early Adoption of Revised Standards*
- 3.10 *Concept of "Will Pass If Tested"*
- 3.10 *Good Manufacturing Practices*
- 3.10.10 *Applicability to Articles Recognized in Compendium;
Synonymously Named Compounded Drugs*
- 4.10.10 *Appropriate Test Procedure*
- 5.20 *Added Substances - Eliminate Double-Negative Wording*
- 5.40 *Clarify Role of "Identification" and "Identity" Tests*
- 5.60.30 *Clarify scope of control of elemental impurities (metals)*
- 5.80 *Monograph Components – Reference Standards*
- 7.10.05 *Add definition for "nominal" in Test Results section*

Note – changed & additional text on following pages highlighted in yellow.

2.30 Role Of USP In Federal Law

The current *General Notices* (2.30) does not address the basis for the recognition or legal status of USP compendial standards under U.S. law. There is only a reference to the Mission and Preface (which itself currently has limited information on the role of USP in law). Section 3 “Conformance To Standards” has targeted subsections on drugs (3.10.10) and devices and dietary supplements (3.10.20), but they pertain only to the application of the USP standards. While one commenter urged that USP leave the interpretation of Federal law to others, on balance it appears useful and appropriate to include some basic information about USP and Federal law in the *General Notices*, including clarity about the role of identity standards in particular. (Similarly, the “Indicating Conformance” section, 3.20, concerns use of the USP designation from a compendial perspective, not a legal perspective). Such clarity would be helpful, for example, in better understanding the role of related Reference Standards, and in providing the foundation for various compendial initiatives now in preparation or under consideration (such as Performance Based Monographs).

<p>Current</p> <p>2.30. Legal Recognition</p> <p>The <i>USP</i> and <i>NF</i> are recognized in the laws and regulations of many countries throughout the world. Regulatory authorities may enforce the standards presented in the <i>USP</i> and <i>NF</i>, but because recognition of the <i>USP</i> and <i>NF</i> may vary by country, users should understand applicable laws and regulations. More information about the legal status of the <i>USP</i> and <i>NF</i> is provided in the <i>Mission and Preface</i>.</p>	<p>Proposed</p> <p>2.30. Legal Recognition</p> <p>The <i>USP</i> and <i>NF</i> are recognized in the laws and regulations of many countries throughout the world. Regulatory authorities may enforce the standards presented in the <i>USP</i> and <i>NF</i>, but because recognition of the <i>USP</i> and <i>NF</i> may vary by country, users should understand applicable laws and regulations. More information about the legal status of the <i>USP</i> and <i>NF</i> in the United States is provided in the <i>Mission and Preface</i>.</p> <p>In the United States under the Federal Food, Drug, and Cosmetic Act (FDCA), both <i>USP</i> and <i>NF</i> are recognized as official compendia. A drug with a name recognized in <i>USP-NF</i> must comply with compendial identity standards, or be deemed adulterated, misbranded, or both. To avoid being deemed adulterated, such drugs must also comply with compendial standards for strength, quality, and purity, unless labeled to show all respects in which the drug differs. See, e.g., FDCA Sections 501(b) and 502(e)(3)(b); also FDA regulations, 21 CFR 299.5. In addition, to avoid being deemed misbranded, drugs recognized in <i>USP-NF</i> must also be packaged and labeled in compliance with compendial standards, FDCA Section 502(g).</p> <p>A dietary supplement represented as conforming to specifications in <i>USP</i> will be deemed a misbranded food if it fails to so conform. FDCA Section 403(s)(2)(D).</p> <p>Enforcement of <i>USP</i> standards is the responsibility of FDA and other government authorities, in the U.S. and elsewhere. <i>USP</i> has no role in enforcement.</p>
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3.10 Allow Early Adoption of Revised Standards

When new or improved standards have been published as final but not yet made official (particularly in situations where additional time is provided to facilitate or accommodate implementation), USP wishes to make clear that early adoption is allowed (indeed encouraged), and that such adoption will not preclude the user from being deemed in compliance, or being able to indicate conformance with USP-NF standards in the event of such early adoption – unless in a specific instance USP deems a revision inappropriate for early adoption (revised in response to comments to clarify the exception). This allowance for early adoption regarding USP-NF standards is also intended to assist manufacturers in obtaining timely changes from FDA where necessary or appropriate (e.g., NDA supplements and related GMPs).

<p>Current</p> <p>3. CONFORMANCE TO STANDARDS</p> <p>3.10. Applicability of Standards</p> <p>Standards for an article recognized in a USP compendium are expressed in the article's monograph, applicable general chapters, and these <i>General Notices</i>. Unless specifically exempted elsewhere in a compendium, the identity, strength, quality, and purity of an article are determined by the official tests, procedures, and acceptance criteria, whether incorporated in the monograph itself, in the <i>General Notices</i>, or in the applicable general chapters.</p>	<p>Proposed</p> <p>3. CONFORMANCE TO STANDARDS</p> <p>3.10. Applicability of Standards</p> <p>Standards for an article recognized in a USP compendium are expressed in the article's monograph, applicable general chapters, and these <i>General Notices</i>. Unless specifically exempted elsewhere in a compendium, the identity, strength, quality, and purity of an article are determined by the official tests, procedures, and acceptance criteria, whether incorporated in the monograph itself, in the <i>General Notices</i>, or in the applicable general chapters. Early adoption of revised standards is allowed. Where revised standards for an existing article have been published but are not yet official, compliance with the revised standard shall not preclude a finding or indication of conformance with USP official standards, unless USP deems a revision inappropriate for early adoption.</p>
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3.10 Concept of “Will Pass If Tested”

During the last revision process, changes were made to clarify key points about the applicability of compendial standards, including that they apply at all times (“any time”) in the life of an article. Specific mention was also made to the role of manufacturer’s specifications, and GMPs, in helping to ensure compliance with compendial requirements. These changes were made, in part, in response to input from various stakeholders. A related issue that was also raised during the last revision process concerned the notion of recognizing that while an article must pass compendial standards if and/or when tested, routine testing is not the only means of ensuring compliance. In part, this reflects not only the role of USP standards, but also the collateral and supporting role of manufacturer’s specifications and GMPs. Stakeholders continue to have keen interest in this issue. Additional revisions are proposed to further clarify that: (1) USP standards apply at any and all times in the life of an article; (2) that when tested, articles must pass to demonstrate compliance; and (3) that USP does not set the frequency of, or specify circumstances for, testing. Frequency of testing is left to the preferences and direction of those performing compliance testing, and (as suggested by a commenter) other users of USP-NF, including manufacturers, buyers, or regulatory authorities. With regard to batch testing from the perspective of compliance with USP compendial standards, for example, it is each company’s responsibility to decide whether to batch test or not, and with regard to any batch testing that is undertaken to set any batch release specifications to control the risk that a product might fail to meet USP specifications, including content uniformity, if tested.

Current

3. CONFORMANCE TO STANDARDS

3.10. Applicability of Standards

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

The standards in the relevant monograph, general chapter(s), and *General Notices* apply at any time in the life of the article from production to expiration. The manufacturer's specifications, and good manufacturing practices generally, are developed and followed to ensure that the article will comply with compendial standards until its expiration date, when stored as directed. Thus, any official article tested as directed in the relevant monograph shall comply.

At times, compendial standards take on the character of statistical procedures, The similarity to statistical procedures may seem to suggest an intent to make inference to some larger group of units, but in all cases, statements about whether the compendial standard is met apply only to the units tested. Repeats, replicates . . . as well as the necessity and appropriate frequency of batch testing, are neither specified nor proscribed by the compendia. First-party (manufacturer), second-party (buyer), or third-party (regulator) compliance testing may or may not require examination of additional specimens, in accordance with predetermined guidelines or

Proposed

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

At times, compendial standards take on the character of statistical procedures, The similarity to statistical procedures may seem to suggest an intent to make inference to some larger group of units, but in all cases, statements about whether the compendial standard is met apply only to the units tested. Repeats, replicates . . . as well as the necessity and appropriate frequency of batch testing, are neither specified nor proscribed by the compendia. **Frequency of testing and sampling are left to the preferences or direction of those performing compliance testing, and other users of USP-NF, including manufacturers, buyers, or regulatory authorities.**

Official products other than dietary supplements are prepared”

<p>sampling strategies. Official products other than dietary supplements are prepared”</p>	
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3.10 Good Manufacturing Practices

During the last *General Notices* revision, there were requests to retain, and strengthen, the reference to GMPs. This request was largely adopted, following input from the CoE EC to the effect that the included 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. It has been suggested that good manufacturing practices also be referenced in the paragraph pertaining to official products, as they currently are with regard to official substances.

<p>Current 3. CONFORMANCE TO STANDARDS 3.10 Applicability of Standards Standards for an article recognized The standards in the relevant monograph, The manufacturer’s specifications, and good manufacturing practices generally, are developed and followed to ensure that the article will comply with compendial standards until its expiration date, At times, compendial standards take on the character of Official products other than dietary supplements are prepared from ingredients that meet USP or NF standards, where standards for such ingredients exist. Official substances are prepared according to recognized principles of good manufacturing practice and from ingredients complying with specifications designed to ensure that the resultant substances meet the requirements of the compendial monographs.</p>	<p>Current 3. CONFORMANCE TO STANDARDS 3.10 Applicability of Standards Standards for an article recognized The standards in the relevant monograph, The manufacturer’s specifications, and good manufacturing practices generally, are developed and followed to ensure that the article will comply with compendial standards until its expiration date, At times, compendial standards take on the character of Official products other than dietary supplements are prepared according to recognized principles of good manufacturing practice and from ingredients that meet USP or NF standards, where standards for such ingredients exist. Official substances are prepared according to recognized principles of good manufacturing practice and from ingredients complying with specifications designed to ensure that the resultant substances meet the requirements of the compendial monographs.</p>
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3.10.10 Applicability to Articles Recognized in Compendium; Synonymously Named Compounded Drugs

As previously noted with regard to the role of USP in Federal law (General Notices Section 2.30), a drug with a name recognized in *USP* or *NF* must comply with compendial identity standards, or be deemed adulterated, mislabeled, or both. To avoid being deemed adulterated, such drugs must also comply with compendial standards for strength, quality, and purity, or be truthfully labeled to show any difference. Due to the nature of compounding practices, labeled

drug names may vary from the precise names in the compendium. Compounding preparations that vary from USP identity standards require use of a distinguishing name. These and related compounding issues entail much broader issues of concern to FDA and various stakeholders that are beyond the scope of these General Notices. However, it is USP's intent to clarify that USP standards apply where synonyms are used "with the intent or effect of suggesting a significant degree of identity with the official name or title."

<p>Current 3.10.10. Applicability of Standards to Drug Products, Drug Substances, and Excipients The applicable <i>USP</i> or <i>NF</i> standard applies to any article marketed in the United States that (1) is recognized in the compendium and (2) is intended or labeled for use as a drug or as an ingredient in a drug. The applicable standard applies to such articles whether or not the added designation "<i>USP</i>" or "<i>NF</i>" is used. The standards apply equally to articles bearing the official titles or names derived by transposition of the definitive words of official titles or transposition in the order of the names of two or more active ingredients in official titles.</p>	<p>Proposed 3.10.10. Applicability of Standards to Drug Products, Drug Substances, and Excipients The applicable <i>USP</i> or <i>NF</i> standard applies to any article marketed in the United States that (1) is recognized in the compendium and (2) is intended or labeled for use as a drug or as an ingredient in a drug. The applicable standard applies to such articles whether or not the added designation "<i>USP</i>" or "<i>NF</i>" is used. The standards apply equally to articles bearing the official titles or names derived by transposition of the definitive words of official titles or transposition in the order of the names of two or more active ingredients in official titles, or where there is use of synonyms with the intent or effect of suggesting a significant degree of identity with the official title or name.</p>
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4.10.10 Appropriate Test Procedure

Product monographs may have multiple test procedures specified. Although most stakeholders including FDA understand, for example with regard to dissolution test procedures, that only that dissolution test indicated as being appropriate for a particular product is to be applied, some confusion on this point has persisted. The proposed language would clarify generally (and, as suggested by some commenters citing the now-completed monograph redesign, not just with regard to dissolution) that where a particular monograph has multiple tests, only the test appropriate for the product (e.g., as is required to be specified on the product labeling, unless "Test 1" is used) need be used.

<p>Current 4.10.10. Applicability of Test Procedures A single monograph may include several different tests, procedures, and/or acceptance criteria that reflect attributes of different manufacturers' articles. Such alternatives may be presented for different polymorphic forms, impurities, hydrates, and dissolution cases. Monographs indicate the tests, procedures,</p>	<p>Proposed 4.10.10. Applicability of Test Procedures A single monograph may include several different tests, procedures, and/or acceptance criteria that reflect attributes of different manufacturers' articles. Such alternatives may be presented for different polymorphic forms, impurities, hydrates, and dissolution cases. Monographs indicate the tests, procedures, and/or acceptance criteria to be used and the required labeling. A test in a monograph may contain and require multiple procedures. However, multiple procedures may be included in particular monographs specifically</p>
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and/or acceptance criteria to be used and the required labeling.	for the purpose of assuring the availability of an appropriate procedure for a particular product. In such cases, a labeling statement to indicate the appropriate application of the procedure(s) will be included in the monograph. A labeling statement is not required if Test 1 is used.
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5.20 Added Substances - Eliminate Double-Negative Wording

During the last round of revisions there were requests to clarify the Added Substances and Ingredients provision to eliminate the awkward double negative terminology. It had been suggested that the negative wording (“Substances are unsuitable unless”) be made positive (“Substances are suitable if . . .). The Expert Committee decided to continue to use the negative form “because it encourages users to consider added substances carefully before use.” The awkward terminology remains of concern, and it appears possible to eliminate it while retaining the current negative (“substances are unsuitable”) language that may be favored by the EC. As suggested by commenters, it also appears appropriate to eliminate the reference to “excipients, and ingredients” in the title. This would be accomplished with the following proposed changes.

<p>Current</p> <p>5. MONOGRAPH COMPONENTS</p> <p>5.20 Added Substances, Excipients, and Ingredients</p> <p>Substances are regarded as unsuitable for inclusion in an official article and therefore prohibited unless: (1) they do not exceed the minimum quantity required for providing their intended effect; (2) their presence does not impair the bioavailability, therapeutic efficacy, or safety of the official article; and (3) they do not interfere with the assays and tests prescribed for determining compliance with the compendial standards.</p> <p>The air in a container of an official article may, where appropriate, be evacuated or be replaced by carbon dioxide, helium, argon, or nitrogen, or by a mixture of these gases. The use of such gas need not be declared in the labeling.</p>	<p>Proposed</p> <p>5. MONOGRAPH COMPONENTS</p> <p>5.20 Added Substances, Excipients, and Ingredients</p> <p>Added substances are presumed to be regarded as unsuitable for inclusion in an official article, and therefore prohibited, unless if: (1) they do not exceed the minimum quantity required for providing their intended effect; (2) their presence does not impairs the bioavailability, therapeutic efficacy, or safety of the official article; and or (3) they do not interfere with the assays and tests prescribed for determining compliance with the compendial standards.</p> <p>The air in a container of an official article may, where appropriate, be evacuated or be replaced by carbon dioxide, helium, argon, or nitrogen, or by a mixture of these gases. The use of such gas need not be declared in the labeling.</p>
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5.40 Clarify Role of “Identification” and “Identity” Tests

The General Notices currently are unclear about the role of Identity tests. Current 5.40, for example (one of the Monograph Components), is titled “Identification Test” (in the singular), but refers in the body of the provision to multiple “tests.” The current provision also indicates that while such tests may be used to assist in establishing “identity,” they are not necessarily

sufficient for that purpose. Under Federal law, however, FDA has equated legal compliance with “identity” with whether an article satisfies prescribed compendial identity (see, e.g., the addition at the request of FDA of an Identity test for DEG adulteration in the USP monograph for Propylene Glycol). The preamble to FDA’s initial GMP regulations also makes clear that the intent of requiring verification of identity “is to assure that some identification procedure is used for each component and that it is as specific as possible.” 43 Fed. Reg. 45046 (September 29, 1978). See, e.g., 21 CFR §211.84, which requires each lot of drug components to be sampled before use, and in particular that “At least one test shall be conducted to verify the identity of each component of a drug product. Specific identity tests, if they exist, shall be used.” 21 CFR 211.84(d)(1). Accordingly, the *General Notices* should be clarified with regard to “Identity” tests, to avoid ambiguity about USP standards (a “test” for Identity may consist of one or more procedures, all of which must be performed to satisfy the requirements of the test; see, e.g., the multiple procedures required for the identification of Heparin Sodium). Clarification of “Identity” can also help satisfy the expectation in federal law and regulations that USP compendial standards provide an “identity” test that can be used to determine whether or not an article named in USP-NF is what it purports to be.

<p>Current</p> <p>5.40. Identification Test</p> <p>The compendial test titled <i>Identification</i> is provided as an aid in verifying the identity of articles as they are purported to be, e.g., those taken from labeled containers. Tests presented in the <i>Identification</i> section shall be used to assist in establishing the identity of the substance but are not necessarily sufficient to establish proof of identity. Other tests and specifications in the monograph often are necessary to establish or confirm the identity of an article. Failure of an article to meet the requirements of a prescribed <i>Identification</i> test may indicate that the article is mislabeled.</p>	<p>Proposed</p> <p>5.40. Identity Test</p> <p>A compendial test titled <i>Identity or Identification</i> is provided to establish the identity of an article as it is purported to be, i.e., to establish whether it is the article named in <i>USP-NF</i>. The <i>Identity or Identification</i> test for a particular article may consist of one or more procedures. When a compendial test for Identity or Identification is undertaken, all requirements of all specified procedures in the test must be met to satisfy the requirements of the test. Failure of an article to meet all the requirements of a prescribed <i>Identity or Identification</i> test (i.e. failure to meet the requirements of all of the specified procedures that are components of that test) indicates that the article is mislabeled and/or adulterated.</p>
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5.60.30 Clarify Scope of Control of Elemental Impurities (Metals)

General Chapters numbered below 1000 are mandatory and have official status. This includes General Chapters that are pertinent to a particular monograph, even where not specifically referenced in a monograph. This is exemplified, for example, in current GN §5.60.20, which provides that all *USP* and *NF* articles are subject to relevant control of residual solvents, as specified in <467>. Similarly, proposed new GN § 5.60.30 (below) anticipates two new General Chapters that are in development, that will address both limits (<232>) and procedures (<233>) for elemental impurities (metals). GN § 5.60.30 is included with proposed GN revisions for purposes of illustrating how these new broadly-applicable General Chapters would apply, once they become applicable on a date expected to be deferred to allow for reasonable opportunity for implementation.

<p>Current No provision.</p>	<p>Proposed 5.60.30 Elemental Impurities in USP and NF Articles All <i>USP</i> and <i>NF</i> articles are subject to control of inorganic impurities, even when no test is specified in the individual monograph. Elemental impurities are a special class of inorganic impurities. These elemental impurities shall be limited in drug products according to the principles defined and the requirements specified in <i>Elemental Impurities—Limits</i> (232) using the procedures specified in <i>Elemental Impurities – Procedures</i> (233). Appropriate limits and procedures for the control of elemental impurities and <i>organometallic</i> impurities in dietary supplements are indicated in <i>Elemental Contaminants in Dietary Supplements</i> (2232). [Note – Official September 1, 2013]</p>
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5.80 Monograph Components – Reference Standards

Starting with the next cycle, it is contemplated that RS will be reviewed and approved by the same Expert Committee that approves the entire standard package (i.e. monograph); the change below accommodates this change (e.g., RS will no longer be approved by the RS Expert Committee). In addition, the current *General Notices* provides that no new standard will be official until the specified RS is available. Amended language makes clear that it is only the test, etc. requiring the RS that is held in abeyance; the remainder of the standard can still be considered official.

<p>Current 5.80. USP Reference Standards USP Reference Standards are authentic specimens that have been approved by the USP Reference Standards Expert Committee as suitable for use as comparison standards in <i>USP</i> or <i>NF</i> tests and assays. (See USP Reference Standards (11).) Current official lots of USP Reference Standards are published in the <i>USP Reference Standards Catalog</i>. Where a procedure calls for the use of a compendial article rather than for a USP Reference Standard as a material standard of reference, a substance meeting all of the compendial monograph requirements for that article shall be used. No new <i>USP</i> or <i>NF</i> standard or procedure requiring the use of a new USP Reference Standard shall be official until the specified USP Reference Standard is available. Unless a reference standard label bears a specific potency or</p>	<p>Proposed 5.80. USP Reference Standards USP Reference Standards are authentic specimens that have been approved by the USP Reference Standards Expert Committee as suitable for use as comparison standards in <i>USP</i> or <i>NF</i> tests and assays. (See USP Reference Standards (11).) Current official lots of USP Reference Standards are published in the <i>USP Reference Standards Catalog</i>. Where a procedure calls for the use of a compendial article rather than for a USP Reference Standard as a material standard of reference, a substance meeting all of the compendial monograph requirements for that article shall be used. If any new <i>USP</i> or <i>NF</i> standard requires the use of a new USP Reference Standard that is not yet available, that portion of the standard containing the requirement shall be held in abeyance not be official until the specified USP reference material is available. Unless a reference standard label bears a specific potency or content, assume the reference standard is 100.0% pure in the official application. Unless otherwise directed in the procedure in the individual monograph or in a general chapter, USP Reference Standards are to be used in accordance with the instructions on the label of the Reference Standard.</p>
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<p>content, assume the reference standard is 100.0% pure in the official application. Unless otherwise directed in the procedure in the individual monograph or in a general chapter, USP Reference Standards are to be used in accordance with the instructions on the label of the Reference Standard.</p>	
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7.10.05 Add definition for “nominal” in Test Results section

It has been suggested in the course of the monograph redesign project that it would be helpful to add a definition of “nominal” to address recurring stakeholder and customer inquiries involving the “nominal concentration” issue. Such a definition is proposed, below.

<p>Current No provision</p>	<p>Proposed 7. TEST RESULTS 7.10.05 Nominal Concentrations in Equations Where a “nominal concentration” is specified, calculate the concentration based on the label claim. In Assay procedures, water correction is typically stated in the definition and on the label of the USP Reference Standard. For other procedures, correction for Assayed content, Potency or both is made prior to using the concentration in the equation provided in the monograph.</p>
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