



## Commentary – USP 36-NF 31

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

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### ***No comments were received for the following proposals:***

#### **General Chapters**

- <681> Repackaging into Single-Unit Containers and Unit-Dose Containers for Nonsterile Solids and Liquid Dosage Form
- <788> Particulate Matter in Injections
- <1051> Cleaning Glass Apparatus
- <1136> Packaging—Unit-of-Use
- <1146> Packaging Practice—Repackaging a Single Solid Oral Drug Product into a Unit-Dose Container
- <2040> Disintegration and Dissolution of Dietary Supplements

## **Monographs**

Abacavir Tablets  
Amitriptyline Hydrochloride Injection  
Amodiaquine Hydrochloride Tablets  
Betaxolol Hydrochloride  
Calcium Pantothenate Tablets  
Caprylocaproyl Polyoxylglycerides  
Clarithromycin  
Clarithromycin for Oral Suspension  
Clarithromycin Extended-Release Tablets  
Didanosine Delayed-Release Capsules  
Diethyl Sebacate  
Doxycycline Tablets  
Estradiol Injectable Suspension  
Glyceryl Tristearate  
Iron, carbonyl/Multiple Sections  
Ketorolac Tromethamine Tablets  
Levocarnitine Tablets  
Levodopa Capsules  
Levodopa Tablets  
Levothyroxine Sodium  
Lithium Oral Solution  
Lopinavir  
Melatonin Tablets  
Meso-Zeaxanthin  
Meso-Zeaxanthin Preparation  
Mirtazapine  
Oil-Soluble Vitamins with Minerals Capsules  
Oil-Soluble Vitamins with Minerals Oral Solution  
Oil-Soluble Vitamins with Minerals Tablets  
Oil-Soluble Vitamins Oral Solution  
Oleic Acid  
Potassium Iodide Delayed-Release Tablets  
Potassium Iodide Oral Solution  
Potassium Iodide Tablets  
Rufinamide Tablets  
Trospium Chloride Tablets  
Vitamin E Capsules  
Vitamin E Preparation/Multiple Sections

## General Chapters

**General Chapter/Sections:** <1> *Injections*  
**Expert Committee(s):** General Chapters–Dosage Forms  
**No. of Commenters:** 1

**Comment Summary #1:** The commenter recommended revising the Foreign and Particulate Matter section to state that some parenteral preparations are not amenable to General Chapter <788> *Particulate Matter in Injections* testing.

**Response:** Comment Incorporated.

**General Chapter/Section(s):** General Chapter <17> *Prescription Container Labeling*  
**Expert Committee(s):** Nomenclature, Safety and Labeling  
**No. of Commenters:** 193

### Introduction and General Comments

**Comment Summary #1:** Several commenters suggested that responsibility and oversight be assigned for creation and maintenance of standardized formats, dictionaries, and glossaries.

**Response:** Comment not incorporated. The jurisdiction of prescription container labeling is state by state and thus may vary.

**Comment Summary #2:** Several commenters indicated that compressed gas is exempted from prescription container labeling according to 21CFR and should also be exempt from the standard.

**Response:** Comment incorporated.

**Comment Summary #3:** Several commenters suggested that specific technologies be applied to manage the patient centered label.

**Response:** Comment not incorporated. The Expert Committee does not endorse any particular type of technology to allow for flexibility and cost considerations to accomplish compliance with the standards.

**Comment Summary #4:** Several commenters suggested that the General Chapter emphasize that the standards pertain to prescription containers that are directly dispensed to patients.

**Response:** Comment incorporated.

**Comment Summary #5:** Several commenters suggested that the label specifications in the standards be compliant with federal and state laws.

**Response:** Comment incorporated.

**Comment Summary #6:** Several commenters suggested the patient has the right to know the country of origin of the drug.

**Response:** Comment not incorporated. This is a supply chain issue and will be considered for incorporation in the General Chapter related to supply chain management.

**Comment Summary #7:** Several commenters suggested that the brand name and the generic name be included on the prescription container label.

**Response:** Comment incorporated.

**Comment Summary #8:** A commenter suggested that the written medication description and picture be required on the prescription container label.

**Response:** Comment not incorporated. The General Chapter allows for flexibility in the manner in which a patient centered label can be accomplished but does not require a written medication description or picture.

**Comment Summary #9:** A commenter suggested that the use of standardized color and shape be required on the patient centered label to identify medication.

**Response:** Comment not incorporated. The General Chapter allows for flexibility in the manner in which a patient centered label can be accomplished but does not require the use of color or shape.

**Comment Summary #10:** A commenter suggested that the General Chapter be numbered over 1000 to be considered as a voluntary guideline rather than an enforceable chapter (numbered below 1000).

**Response:** Comment not incorporated. The root cause for patient misunderstanding, non-adherence, and medication errors is a lack of universal standards for labeling on dispensed prescription containers. The standard will be more readily adopted by state regulatory agencies if the chapter is numbered below 1000.

**Comment Summary #11:** A commenter suggested that the gluten status of the medication be included on the prescription container label.

**Response:** Comment not incorporated. There are currently no standards related to gluten content in drugs.

**Comment Summary #12:** Several commenters suggested that the General Chapter be eliminated due to unjust financial impact to vendors, pharmacies, and patients.

**Response:** Comment not incorporated. The prescription container labeling standards were developed to promote patient understanding and prevent medication misuse, nonadherence, and medication errors.

### **Organize Prescription Label in Patient Centered Manner**

**Comment Summary #1:** A commenter suggested that the organization of the label not be specified.

**Response:** Comment not incorporated. Information shall be organized in a way that best reflects how most patients seek out and understand medication instructions.

**Comment Summary #2:** One commenter suggested that the patient centered label be field tested.

**Response:** Comment not incorporated. Two states have adopted patient centered labels that were reviewed by the Expert Committee.

**Comment Summary #3:** Several commenters suggested that examples of patient centered labels be incorporated in the General Chapter.

**Response:** Comment not incorporated. The General Chapter allows flexibility in the manner in which the patient center label can be accomplished.

### **Emphasize Instructions to Patients**

**Comment Summary #1:** Several commenters suggested prescriber contact information be included as critically important information.

**Response:** Comment not incorporated. The Expert Committee acknowledges the importance of prescriber contact information but this should not supersede information critical to the patient's safe and effective use of the medicine.

**Comment Summary #2:** A commenter suggested that the medication picture be required on the patient centered label.

**Response:** Comment not incorporated. The General Chapter allows for flexibility in the manner in which a patient centered label can be accomplished.

### **Simplify Language**

**Comment Summary #1:** Several commenters suggested that "SIG" be defined.

**Response:** Comment incorporated.

**Comment Summary #2:** Several commenters suggested that the SIGs (signature, directions) be standardized.

**Response:** Comment not incorporated. The Expert Committee agrees standard directions should be used whenever possible but standardizing the SIG did not fall within the scope of this revision. The Expert Committee will review further studies.

### **Give Explicit Instructions**

**Comment Summary #1:** A commenter suggested that the principles of Doak, Doak be defined.

**Response:** Comment not incorporated. Doak, Doak and Root reference were removed and replaced with other health literacy references that are more accessible.

**Comment Summary #2:** A commenter suggested that a direction schema be developed and incorporated into the prescription container label standards.

**Response:** Comment not incorporated. There is continuing research in this area. Best practices will be considered for future revisions as evidence becomes available.

**Comment Summary #3:** Several commenters suggested that the instructions should take into account a patient's lifestyle, e.g., different shift work hours.

**Response:** Comment incorporated. The Expert Committee acknowledges that dosing by precise hours may present greater adherence issues due to individual lifestyle patterns and general time frames such as in the morning may be more easily understood.

### **Include Purpose for Use**

**Comment Summary #1:** Several commenters suggested that Include Purpose for Use not be required in the standard.

**Response:** Comment not incorporated. The Expert Committee decided that if the purpose of the medication is included on the prescription, then it should be included on the prescription container label.

**Comment Summary #2:** Several commenters suggested that the prescriber be required to write the purpose for use on the prescription.

**Response:** Comment not incorporated. The General Chapter does not address how a prescription should be written.

**Comment Summary #3:** Several commenters suggested that patient preference for inclusion of the purpose for use be excluded.

**Response:** Comment not incorporated. The label is meant to be patient-centered to allow for patient preference.

**Comment Summary #4:** A commenter suggested that prescription container labeling should include contraindications, side effects, interactions with other medications, directions for use and the drug's purpose for use as approved by the Food and Drug Administration (FDA).

**Response:** Comment not incorporated. The Expert Committee decided that if the FDA-approved purpose of the medication is included on the prescription, then it should be included on the prescription container label. The prescription container label should feature only the most important patient information needed for safe and effective understanding and use. Less critical but important content should be placed away from dosing instructions because it distracts patients, and this can impair patients' recognition and understanding. Medication guides that accompany the prescription are still appropriate for elements such as FDA approved use, contraindications, side effects, and drug interactions.

### **Limit Auxiliary Information**

**Comment Summary #1:** A commenter suggested getting patient feedback (which is important to the patient) should be included on the auxiliary information.

**Response:** Comment not incorporated. The General Chapter recommends getting patient feedback on simplified language on the patient-centered label. If the auxiliary information is printed on the label, the standard would apply.

**Comment Summary #2:** One commenter suggested adding pregnancy and lactation status of the drug product with accompanying side effects, contraindications and interactions.

**Response:** Comment not incorporated. The items requested are beyond the scope of the prescription container label and would be listed in the medication guide given with the prescription at time of dispensing.

**Comment Summary #3:** Several commenters suggested that a clear statement referring the patient to supplemental instructions be stated on the label.

**Response:** Comment not incorporated. The General Chapter allows flexibility in the manner in which a patient centered label can be accomplished.

### **Address Limited English Proficiency**

**Comment Summary #1:** Several commenters suggested that the label specifications address patients with low English proficiency.

**Response:** Comment incorporated.

**Comment Summary #2:** Several commenters suggested that the label be produced in a language that the patient understands.

**Response:** Comment not incorporated. Whenever possible, the directions for use should be provided in the patient's preferred language.

### **Improve Readability**

**Comment Summary #1:** A commenter suggested that a minimum font size be included for "non-critical information."

**Response:** Comment incorporated.

**Comment Summary #2:** Several commenters suggested that the font on the entire label be 12 pt.

**Response:** Comment not incorporated. 12 pt font size (New Times Roman) or 11 pt Arial are to be used for critical information.

**Comment Summary #3:** Several commenters suggested that the use of 12 pt font would result in the use of larger labels and containers.

**Response:** Comment not incorporated. The General Chapter allows flexibility in the manner in which a patient centered label can be accomplished.

**Comment Summary #4:** A commenter suggested that a statement be included to provide adequate space between words and numerals.

**Response:** Comment not incorporated. The typography of the label shall be optimized to include white space to distinguish sections on the label, but does not require a statement to provide adequate space between words and numerals.

**Comment Summary #5:** A commenter suggested the use of two labels on prescription containers.

**Response:** Comment not incorporated. The General Chapter allows for flexibility in the manner in which a patient centered label can be accomplished.

**Comment Summary #6:** A commenter suggested a standardized location on the prescription label for prescription date and beyond use date.

**Response:** Comment not incorporated. The General Chapter allows for flexibility in the manner in which a patient centered label can be accomplished.

**Comment Summary #7:** Several commenters suggested that the prescription container labeling address access for the visually impaired.

**Response:** Comment incorporated.

**Comment Summary #8:** A commenter suggested that the lot number and or expiration date be standard information on the label.

**Response:** Comment not incorporated. The General Chapter allows flexibility in the manner in which a patient centered label can be accomplished.

**Comment Summary #9:** A commenter suggested that the barcode be required as standard information on the label.

**Response:** Comment not incorporated. The General Chapter allows flexibility in the manner in which a patient centered label can be accomplished. Barcode technology currently is not universally available in all practice settings.

**Comment Summary #10:** A commenter suggested that while the specific hour for dosing emphasizes patient understanding, it is not within the realm of pharmacy practice to convert or interpret the prescription.

**Response:** Comment not incorporated. The General Chapter states, "whenever available, use standardized directions" and recognizes that regulations and authoritative bodies will determine how the standards will be adopted

**Comment Summary #11:** A commenter suggested the General Chapter highlight further research being done to test proposed changes.

**Response:** Comment not incorporated. The General Chapter is dynamic and will incorporate evidence based information in future revisions if warranted.

**General Chapter/Section(s):** <761> *Nuclear Magnetic Resonance Spectroscopy*

**Expert Committee(s):** General Chapters—Chemical Analysis

**No. of Commenters:** 6

Editorial changes suggested by commenters have been reviewed by the Expert Committee. Some of these changes were approved by the Expert Committee and have been incorporated in the General Chapter. Where they have not been incorporated, the Expert Committee's response is indicated below.

**Comment Summary #1:** The commenter suggested describing some principles and fundamentals of NMR spectroscopy in an introduction to this General Chapter.

**Response:** Comment not incorporated. This information is included in General Chapter <1761> *Applications of Nuclear Magnetic Resonance Spectroscopy*.

**Comment Summary #2:** The commenter recommended moving the information on validation and quantitation to an above 1000 chapter, i.e., <1761> *Applications of NMR Spectroscopy*.

**Response:** Comment not incorporated. The new USP chapter format incorporates this information in the below 1000 General Chapter.

**Comment Summary #3:** The commenter indicated that the performance qualification (PQ) is a very elaborate and thorough procedure. It usually is performed rarely, e.g., once in an instrument's lifetime. Daily or time of use is a reasonable interval for a System Suitability Test that is fairly simple and less time consuming. Therefore, the interval and the extent of testing ought to be decided by the instrument operator, based on previous instrument qualifications and method validations.

**Response:** Comment not incorporated. System suitability tests verify that a system will perform in accordance with specific performance criteria established in a specific analytical procedure. A performance qualification is performed to demonstrate that a system consistently performs according to specifications appropriate for the intended application. In this General Chapter, the Operational Qualification and PQ criteria are included to establish minimum requirements for instrument performance. Ultimately, the use of a qualified instrument contributes to confidence in the validity of analytical data used to guarantee patient safety. The General Chapter does not mandate PQ testing intervals and states that other tests and samples may be used by the user to establish specifications. The Chapter states that system suitability tests, if available, may be used in lieu of PQ requirements for official procedures.

**Comment Summary #4:** The commenter noted that the use of larger weights in the quantitative NMR method is only one way to reduce the source error introduced by weighing. Another equally valid way is the use of a balance with the lowest possible minimum weight and the best readability.

**Response:** Comment not incorporated. Even with the balance suggested, the use of larger weights results in a smaller weighing error than the use of smaller weights.

**Comment Summary #5:** The commenter indicated that the use of three samples seems excessive. The number of samples should be decided based upon the experiences during method validation, in particular the determined accuracy and precision. Currently, the use of only two samples seems to be the industry standard and has been shown to be absolutely sufficient.

**Response:** Comment not incorporated. Fewer than three replicates require calculating an estimate of the standard deviation of the analysis. The Expert Committee believes

that providing a minimally sufficient number of replicates to determine the precision of the measurement is a requirement. If justified, the monograph provides a route for incorporation of an NMR procedure with fewer required replicates.

**Comment Summary #6:** The commenter suggested to either remove the whole section on spectral overlap or to more precisely specify the method used, as the use of an external standard does not *per se* avoid the risk of potential signal overlap. This is only true for the sequential measurement of the analyte and the external standard in two separate NMR tubes. This method, however, introduces numerous possibilities for errors, as the exact same conditions usually are difficult to reproduce. Also, the risk of overlap when using internal standards is reduced by the required specificity test.

**Response:** Comment not incorporated. The Definition section of External reference standard (II.B.2.a of Quantitative Applications) clarifies that, "The classical external reference standard method consists of a reference standard and analyte that are each in separate NMR tubes. One variation of an external reference standard is the standard test solution contained in a coaxial tube and is inserted into an analyte test solution contained in an NMR tube..." This section addresses the use of an external reference in the classical sense."

**Comment Summary #7:** The commenter expressed concern over the last sentence of the Operational Qualification section indicating that the operational qualification should be targeted to specifications for the application instead of instrument specifications. It is not possible to know every application that may be run on the instrument at the time that initial operational qualification data are documented.

**Response:** Comment incorporated

**Comment Summary #8:** The commenter indicated that the statement, "Once an NMR response is calibrated with external reference standard solutions, the calibration may be applied to any other sample in the same solvent..." in the Quantitative Applications section, under calibration, is incorrect if the samples are in coaxial NMR tubes. The resonances of the reference standard will occur in the spectrum and just because they are in separate containers does not guarantee that they will not overlap the analyte. This is only correct if two separate spectra are acquired and then the absolute integrals are compared.

**Response:** Comment incorporated

**Comment Summary #9:** The commenter suggested changing the sentence under S/N MEASUREMENTS -<sup>1</sup>H NMR with a spinning sample, (see FIGURE 2) as follows: "With a spinning sample, the S/N value that is measured should be only about 10% higher than that obtained with a non-spinning sample." The word "non" was missing. Also, the end of the statement is not needed as it is redundant because it is explained in the next sentence.

**Response:** Comment incorporated. However, the last phrase of that sentence was not deleted because it leads to the following sentence.

**Comment Summary #10:** The commenter suggested modifying the sentence, "Slow processes (on an NMR time scale) result in more than one signal; fast processes average these signals to one line; and intermediate processes produce broad signals" under Qualitative Applications, by adding, "which sometimes cannot be easily found in

the spectra " to point out on the possible "absence" of some exchangeable signals in the spectra.

**Response:** Comment incorporated.

**Comment Summary #11:** The commenter suggested revising the definition of internal standard under "Glossary" to "One should select an IS with a minimum possible number of NMR resonances." The IS NMR signals should not overlap with those of the analyte as in some cases it may not be possible to find appropriate standard with just a single NMR peak.

**Response:** Comment incorporated.

**Comment Summary #12:** The commenter suggested revising the definition of "NMR Reference" under Glossary to "Common examples for proton and carbon NMR analyses are tetramethylsilane (TMS) for use in organic solvents and the sodium salt of 2,2-dimethyl-2-silapentane-S- sulfonic acid (DSS) for use in structures of both NMR references sulfonic acid for use in aqueous media. DSS is a common abbreviation for the sodium salt of 2,2-dimethyl-2- silopentane-5-sulfonic acid. It is also suggested to include structures of both NMR references.

**Response:** Comment incorporated

**Comment Summary #13:** The commenter suggested adding guidance for validating an NMR procedure for use in Identity testing (Category IV).

**Response:** Comment incorporated.

**Comment Summary #14:** The commenter indicated that the accuracy requirements given in the chapter are acceptable for small molecule DS (drug substance) but for a biologic DS these may be unattainable. Therefore, please add a footnote to clarify that for biologic entities, requirements should be based on development data and agreed upon with the local regulatory authority. Comment not incorporated.

**Response:** The Expert Panel and Expert Committee recognize that in some instances the specified accuracy criteria cannot be met, and this would preclude the use of NMR as a suitable technique. In addition, it should be noted that accuracy specifications for a biologic DS published in an official monograph supersede those specified in this General Chapter.

**General Chapter/Section(s):** <921> *Water Determination/Multiple Sections*

**Expert Committee(s):** General Chapters—Chemical Analysis

**No. of Commenters:** 3

***Method 1a (Direct Titration) – Principle***

**Expert Committee-initiated Change #1:** The Expert Committee revised this section based on queries received and decided to incorporate the following statement: "In some cases, other suitable solvent may be used for special or unusual test specimens. In these cases, the addition of at least 20% of methanol or other primary alcohol is recommended," because methanol is not only a solvent but a necessary component in the Karl Fischer reaction, even when other methanol-free systems are used (e.g., aldehydes and ketones).

### ***Method Ia (Direct Titration) – Reagent***

**Comment Summary #1:** The commenter suggested replacing the proposal “(less than 1%)” with “(specification limit less than 1%)” in the following sentence: “For determination of trace amounts of water (less than 1%), it is preferable to use a *Reagent* with a water equivalency factor of not more than 2.0, which will lead to the consumption of a more significant volume of titrant.”

**Response:** Comment not incorporated. It is more accurate to choose reagent titer based on content instead of the specification. When water is less than 1% it is better to use a diluted reagent in order to get more accurate results, regardless of whether there is a specification for the limit of water.

**Comment Summary #2:** The commenter suggested the addition of the following statement wherever automated systems are used: “For automated systems, the reagents with the water equivalency factor of not more than 2.0 may not be required considering the fact that automated systems have very small least count of the burette, e.g. 10 µL.”

**Response:** Comment not incorporated. This comment results more from miniaturization of the burette dispensing capabilities than from automation. Based on information provided from suppliers, a very slow rate for the titrant addition throughout the complete titration should be used and the analysis time may be impractical. Also, other parameters such as sample weight, equilibration time, total volume and others may be critical. If a user has demonstrated through instrument qualification that its titration apparatus is capable of achieving acceptable performance with small titration volumes, the USP General Notices allow its usage under 6.30 (Alternative and Harmonized Methods and Procedures).

### ***Method Ia (Direct Titration) – Test Preparation***

**Comment Summary #1:** The commenter suggested replacing the current expression of estimated content of water in the specimen under test from “2-250 mg” to “2 to 250 mg” in order to clarify that the intent is 2 to 250 mg instead of 200 to 250 mg of water.

**Response:** Comment not incorporated. The current expression is correct and in concordance with the USP style.

### ***Method II (Azeotropic-Toluene Distillation) – Apparatus***

**Expert Committee-initiated Change #1:** The Expert Committee decided to replace the reference to “chromic acid cleansing mixture” (no longer used due to environmental concerns) by “suitable cleanser.”

**General Chapter/Section(s):** General Chapter <1197> *Good Distribution Practices for Bulk Pharmaceutical Excipients*

**Expert Committee(s):** General Chapters–Physical analysis

**No. of Commenters:** 2

**Comment Summary #1:** The commenter recommended modifying text in Section 1.4 Pharmaceutical-Grade Excipients to allow the use of materials from other pharmacopeias before considering food grade.

**Response:** Comment incorporated.

**Comment Summary #2:** The commenter recommended adding text to clarify Section 2.7 Audits: Internal, External and Third-Party where it states that a response to a questionnaire is not a substitute for an audit.

**Response:** Comment incorporated.

**Comment Summary #3:** The commenter recommended adding text to Section 4.8.2 Traceability Related Documents to allow the use of copies of the original Certificate of Analysis (COA).

**Response:** Comment not incorporated. Section 3.4.5 already includes additional information regarding the original COA when the excipient supply chain includes "additional links" beyond the original maker.

**General Chapter/Section(s):** <1761> *Applications of Nuclear Magnetic Resonance Spectroscopy*

**Expert Committee(s):** General Chapters—Chemical Analysis

**No. of Commenters:** 6

Editorial changes suggested by commenters have been reviewed by the Expert Committee. Some of these changes as approved by the Expert Committee have been incorporated in the General Chapter. Where they have not been incorporated, the Expert Committee's response is indicated below.

**Comment Summary #1:** The commenter suggested modifying the sentence "...where  $g$  is the magnetogyric ratio and is a constant for all nuclei of a given isotope..." in the PRINCIPLES OF NMR Section, to "...magnetogyric ratio whose numerical value is a characteristic of the nucleus in question and is the same regardless of the position of the nucleus in the molecule" for improved clarity.

**Response:** Comment not incorporated. The definition of magnetogyric ratio in the chapter is felt to be sufficient and additional clarification is not required.

**Comment Summary #2:** The commenter suggested quoting energies in Joules rather than in calories and field strength in Tesla rather than in Kilogauss.

**Response:** Comment incorporated

**Comment Summary #3:** The commenter recommended modifying the sentence, "Therefore, zero filling until each peak is represented by at least 7-10 data points results in a more accurate integration," in the POST ACQUISITION DATA PROCESSING Section, Zero Filing subsection, to "To obtain reliable peak representation and quantitative peak integration there should be at least 4 to 5 data points above the full width at half height of a peak."

**Response:** Comment incorporated

**Comment Summary #4:** The commenter suggested using values for Table 5 from Gottlieb et al. "NMR Chemical Shifts of Common Laboratory Solvents as Trace Impurities," *J Org. Chem.* 1997, 62, 7512-7515.

**Response:** Comment not incorporated. Erroneous values were corrected. The values included in the table are acceptable for general use.

**Comment Summary #5:** The commenter suggested that in the SOLID-STATE NMR Section, the field strength of the instrument used for the data should be provided.

**Response:** Comment not incorporated. The point illustrated by the data presented is independent of spectrometer field strength.

**Comment Summary #6:** The commenter suggested modifying the following statement in the Principle section with respect to internal references DSS-d6 and TMSP-d4: "The resonance frequency of the TMSP or DSS methyl groups closely approximates that of the TMS signal, but DSS has the disadvantage of showing a number of methylene multiplets that may interfere with signals from the test substance."

**Response:** Comment incorporated.

**Comment Summary #7:** The commenter suggested adding a note in Table 5 to provide information on temperature of analysis as for some solvents, chemical shifts = f(T).

**Response:** Comment incorporated. The temperature at which the chemicals shifts were measured was added.

**Comment Summary #8:** The commenter suggested adjusting digits in Table 5 to the same level of significance.

**Response:** Comment incorporated. In some cases, the additional significant figure was not available.

**Comment Summary #9:** The commenter suggested adding the following two statements at the end of the subsection on "Increasing the Resolution."

1) Numerous other window functions have been proposed though not always widely used.

2) It should be also noted quantitative experiments increasing the resolution should be used with caution because they may change the accuracy of signal integration in the spectrum.

**Response:** Comment incorporated.

**Comment Summary #10:** The commenter suggested modifying the section on "General Procedure for Structure Identification" by adding the additional wording as follows: "A positive identification can be concluded when the chemical shifts multiplicities, and coupling constants of the spectrum of the test sample match those of the reference standard acquired in the same solvent and at the same temperature or, in the case of a USP monograph, the values listed in the monograph."

**Response:** Comment incorporated.

## Monographs

**Monograph/Section(s):** Adenosine/Multiple Sections

**Expert Committee(s):** Monographs–Small Molecules 4

**No. of Commenters:** 1

**Comment Summary #1:** The commenter requested retaining the wet chemistry procedures for *Limit of chloride* and *Limit of sulfate*.

**Response:** Comment not incorporated. The wet chemistry procedures are not consistent with USP's modernization efforts. The Expert Committee will consider future changes to the monograph upon receipt of modern procedures and supporting data.

**Content Summary #2:** The commenter requested retaining the test for *Melting Range or Temperature* as an additional means to ensure the purity of the material.

**Response:** Comment incorporated.

**Monograph/Section(s):** Adenosine Injection/Multiple Sections

**Expert Committee(s):** Monographs–Small Molecules 4

**No. of Commenters:** 1

**Comment Summary #1:** The commenter recommended tightening the currently official acceptance criteria for the Assay to be consistent with the specifications approved by the FDA.

**Response:** Comment not incorporated. The currently official acceptance criteria are consistent with the FDA-approved specifications.

**Content Summary #2:** The commenter recommended adding a table of specified, unspecified, and total impurities with corresponding relative retention times and limits similar to those in the Adenosine monograph.

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

**Monograph/ Section(s):** Alfuzosin Hydrochloride Extended-Release Tablets/  
Dissolution

**Expert Committee(s):** Monographs–Small Molecules 4

**No. of Commenters:** 3

**Comment Summary #1:** The commenters requested including additional *Dissolution* tests to accommodate their FDA-approved specifications.

**Response:** Comments not incorporated. The Expert Committee will consider addressing these comments in a future revision upon the receipt of the necessary supporting data.

**Comment Summary #2:** The commenter requested including additional *Dissolution* test to the monograph.

**Response:** Comment not incorporated. The Expert Committee will consider future changes to the monograph when the commenter's product receives full FDA approval.

**Monograph/Section(s):** Amiodarone Hydrochloride Oral Suspension/  
Multiple Sections

**Expert Committee(s):** Compounding

**No. of Commenters:** 1

**Comment Summary #1:** Commenter requested the rationale for pH adjustment with sodium bicarbonate in the Definition section.

**Response:** Comment not incorporated. The published peer-reviewed stability data was based on the preparation compounded with Ora-Sweet and Ora-Plus vehicle adjusted to pH between 6 and 7.

**Expert Committee-initiated Change #1:** The compounding table under Definition was revised to reflect the specific components used to compound the formulation in the published peer-reviewed stability study.

**Expert Committee-initiated Change #2:** The Assay was revised to remove the requirement to conduct a linear regression analysis. The published peer-reviewed stability study validated the assay and found it to be linear. The standard solution and sample solution preparation were revised to increase sampling size to improve accuracy.

**Monograph/Section(s):** Amitriptyline Hydrochloride/Multiple Sections

**Expert Committee(s):** Monographs—Small Molecules 4

**No. of Commenters:** 1

**Comment Summary #1:** The commenter requested shortening the run time for the Assay from “40 min” to “1.5 times the retention time of the main peak.”

**Response:** Comment incorporated.

**Comment Summary #2:** The commenter requested retaining the run time for *Organic Impurities* as 40 min instead of cross-referencing the Assay.

**Response:** Comment not incorporated. Based on supporting data, the run time specified in the Assay is suitable for use in the *Organic Impurities* procedure.

**Monograph/Section(s):** Amlodipine Oral Suspension/ Multiple Sections

**Expert Committee(s):** Compounding

**No. of Commenters:** 1

**Comment Summary #1:** Commenter indicated an error in the desipramine hydrochloride concentration in the standard solution preparation under the Assay.

**Response:** Comment not incorporated. The Expert Committee recognized the error in the monograph but has revised the Assay to remove the use of an internal standard since the assay was shown to be linear.

**Expert Committee-initiated Change #1:** The compounding table under Definition was revised to reflect the specific components used to compound the formulation in the published peer-reviewed stability study.

**Expert Committee-initiated Change #2:** A note to recommend homogenization was added in Definition to ensure uniformity of the preparation due to its high viscosity and propensity to form lumps.

**Expert Committee-initiated Change #3:** The Assay was revised to increase sample size for standard solution and sample solution preparation to improve accuracy in preparing viscous samples. The standard stock solution and equation were revised to account for the besylate content of the amlodipine tablets. System suitability requirements for column efficiency and tailing factor were included and retention time revised based on validation of the assay with a Phenomenex Luna CN brand of 3.0-mm x 15.0-cm column containing 5- $\mu$ m packing L10.

**Monograph/Section(s):** Ammonium Alum/Multiple Sections

**Expert Committee(s):** Monographs—Small Molecules 3

**Expert Committee-initiated Change #1:** The odor test in *Identification-A* is deleted from the monograph because of the safety concern.

**Expert Committee-initiated Change #2:** Under the Assay, the Analysis section is clarified to state “titrate the excess edetate disodium with 0.05M zinc sulfate VS” instead of “titrate with 0.05M zinc sulfate VS.”

**Monograph/Section(s):** Benzaldehyde/Limit of Ethylbenzene, Cyclohexylmethanol, Benzyl Alcohol, and Benzoic Acid

**Expert Committee(s):** Monographs—Excipients

**No. of Commenters:** 1

**Comment Summary #1:** The commenter recommended changing “0.1% of USP Ethylbenzene RS, 0.1% of USP Cyclohexylmethanol RS, 0.2% of USP Benzoic Acid RS, and 0.2% of USP Benzyl Alcohol RS in the Sample solution” to “0.1% of USP Ethylbenzene RS, 0.1% of USP Cyclohexylmethanol RS, 0.2% of USP Benzoic Acid RS, and 0.2% of USP Benzaldehyde RS in USP Benzyl Alcohol RS” for preparation of Standard solution based on the lab data.

**Response:** Comments incorporated.

**Monograph/Section(s):** Black Pepper

**Expert Committee(s):** Nomenclature Safety and Labeling

**Expert Committee-initiated Change #1:** Changed the title of the monograph from Pepper to Black Pepper.

**Monograph/Section(s):** Bupropion Hydrochloride/Multiple Sections

**Expert Committee(s):** Monographs—Small Molecules 4

**No. of Commenters:** 3

**Comment Summary #1:** The commenters indicated that a specified impurity in their drug substance coelutes with the *m*-chlorobenzoic acid peak in the test for the *Limit of m-Chlorobenzoic Acid*.

**Response:** Comment not incorporated. A revised procedure will be published in a future issue of PF.

**Expert Committee-initiated Change #1:** The trivial names and chemical names of impurities listed in Table 1 under *Organic Impurities* have been updated.

**Monograph/Section(s):** Caprylic Acid/Limit of Related Linear and Branched Alkyl Carboxylic Acids, Related Esters, Cyclic Esters and Ketone

**Expert Committee(s):** Monographs—Excipients

**No. of Commenters:** 1

**Expert Committee-initiated Change #1:** The Expert Committee changed “Disregard limit: 0.5 times the area of the major peak from the System suitability solution, corresponding to 0.05%” to “Disregard any peak with an area less than 0.5 times the area of the major peak from the System suitability solution” because the term for “Disregard limit” is not defined.

**Monograph/Section(s):** Chloroquine Phosphate Oral Suspension/ Multiple Sections

**Expert Committee(s):** Compounding

**Expert Committee-initiated Change #1:** The compounding table under Definition was revised to reflect the specific components used to compound the formulation in the published peer-reviewed stability study.

**Expert Committee-initiated Change #2:** The sample solution preparation in the Assay was changed to remove storage in a freezer, which is not required when analysis is preceded immediately. The detector wavelength was corrected based on the published peer-reviewed stability study. The relative standard deviation under system suitability was widened to 2%.

**Monograph/Section(s):** Codeine Phosphate Oral Solution/ Multiple Sections

**Expert Committee(s):** Compounding

**No. of Commenters:** 1

**Comment Summary #1:** The commenter requested the basis and rationale for using codeine powder in the compounding of this preparation.

**Response:** Comment not incorporated. The selection of ingredients used in the preparation is based on a published peer-reviewed stability study.

**Comment Summary #2:** The commenter indicated the control of the supply chain for the ingredients used in the monograph.

**Response:** Comment not incorporated. The monograph references General Chapter <795> *Pharmaceutical Compounding-Nonsterile Preparations*, which has a section that addresses the selection, handling, and storage of components in compounded preparations. Issues regarding control of the supply chain are outside the scope of this monograph and may be addressed elsewhere in the *USP-NF*.

**Comment Summary #3:** The commenter requested the basis of the Beyond-Use Date at the specific storage temperature.

**Response:** Comment not incorporated. The beyond-use date stated in the monograph is based on the published peer-reviewed stability study for the preparation stored at controlled room temperature.

**Comment Summary #4:** The commenter requested grouping all compounding monographs together.

**Response:** Comment not incorporated. The Expert Committee will consider revising the name of the monograph in the future to include “compounded” in the title to identify that the monograph is for a compounded preparation versus a manufactured product.

**Expert Committee-initiated Change #1:** The compounding table under Definition was revised to reflect the specific components used to compound the formulation in the published peer-reviewed stability study.

**Expert Committee-initiated Change #2:** Gravimetric measurement step in the sample solution preparation in the Assay was removed because the Expert Committee felt that volumetric measurement would not affect the accuracy of the assay.

**Monograph/Section(s):** Dapsone Oral Suspension/ Multiple Sections

**Expert Committee(s):** Compounding

**Expert Committee-initiated Change #1:** The compounding table under Definition was revised to reflect the specific components used to compound the formulation in the published peer-reviewed stability study.

**Expert Committee-initiated Change #2:** The sample size used to prepare the standard solution and sample solution in the Assay was increased to improve accuracy for studying suspensions.

**Monograph/Section(s):** Enalapril Maleate Oral Suspension/ Multiple Sections

**Expert Committee(s):** Compounding

**No. of Commenters:** 1

**Comment Summary #1:** The commenter indicated the basis and rationale for using enalapril tablets in the compounding of this preparation.

**Response:** Comment not incorporated. The selection of ingredients used in the preparation is based on a published peer-reviewed stability study.

**Comment Summary #2:** The commenter indicated the control of the supply chain for the ingredients used in the monograph.

**Response:** Comment not incorporated. The monograph references General Chapter <795>, which contains a section that addresses the selection, handling, and storage of components in compounded preparations. Issues regarding control of supply chain are outside the scope of this monograph and may be addressed elsewhere in *USP-NF*.

**Comment Summary #3:** The commenter indicated the basis of the Beyond-Use Date at the specific storage temperature.

**Response:** Comment not incorporated. The beyond-use date stated in the monograph is based on the published peer-reviewed stability study for the preparation stored at controlled cold temperature and controlled room temperature.

**Comment Summary #4:** Commenter requested grouping all compounding monographs together.

**Response:** Comment not incorporated. The Expert Committee will consider revising the name of the monograph in the future to include “compounded” in the Title to identify that the monograph is for a compounded preparation versus product.

**Expert Committee-initiated Change #1:** The compounding table under Definition was revised to reflect the specific components used to compound the formulation in the published peer-reviewed stability study.

**Expert Committee-initiated Change #2:** The sample solution preparation in the Assay was changed to remove storage in a freezer which is not required when analysis is preceded immediately.

**Expert Committee-initiated Change #2:** The acceptable pH range was expanded.

**Monograph/Section(s):** Escitalopram Oxalate/Multiple Sections

**Expert Committee(s):** Monographs–Small Molecules 4

**No. of Commenters:** 1

**Comment Summary #1:** The commenter requested including an additional Identification test for the counter-ion (oxalic acid) by retention time agreement.

**Response:** Comment not incorporated. The Expert Committee will consider this change to the monograph as part of a future revision.

**Monograph/Section(s):** Hydrochloric Acid Injection/ Multiple Sections

**Expert Committee(s):** Compounding

**No. of Commenters:** 1

**Comment Summary #1:** Commenter indicated that NF grade Hydrochloric Acid should be used in the compounding of this preparation and stated in the Definition section.

**Response:** Comment incorporated.

**Expert Committee-initiated Change #1:** The Assay was revised to fit the redesign format. Preparation of carbon dioxide free water, potassium biphthalate solution and test solutions were removed since they are described elsewhere in the USP-NF. The equations were modified based on General Chapter <541> Titrimetry.

**Expert Committee-initiated Change #2:** A Bacterial Endotoxin Test limit was added.

**Expert Committee-initiated Change #3:** Labeling was revised to remove a statement that does not pertain to the label of the preparation.

**Expert Committee-initiated Change #4:** The Beyond-Use Date was revised to indicate that the preparation may be used for not more than 120 days after passing sterility and endotoxin testing. Otherwise, the conditions set forth in High-Risk Level compounded sterile preparations (CSPs) in General Chapter <797> *Pharmaceutical Compounding—Sterile Preparations* apply.

**Monograph/Section(s):** Isradipine Oral Suspension/ Definition

**Expert Committee(s):** Compounding

**Expert Committee-initiated Change #1:** The compounding table under Definition was revised to reflect the specific components used to compound the formulation in the published peer-reviewed stability study.

**Monograph/Section(s):** Levodopa/Organic Impurities

**Expert Committee(s):** Monographs—Small Molecules 4

**No. of Commenters:** 1

**Comment Summary #1:** The commenter requested updating the relative response value for *L*-tyrosine.

**Response:** Comment not incorporated. The Expert Committee will consider a future revision to the monograph to use USP *L*-Tyrosine RS as a quantitative standard.

**Monograph/Section(s):** Lisinopril Oral Suspension/ Multiple Sections

**Expert Committee(s):** Compounding

**No. of Commenters:** 1

**Comment Summary #1:** Commenter indicated the basis and rationale for using lisinopril tablets in the compounding of this preparation.

**Response:** Comment not incorporated. The selection of ingredients used in the preparation is based on a published peer-reviewed stability study.

**Comment Summary #2:** Commenter indicated the control of supply chain for the ingredients used in the monograph.

**Response:** Comment not incorporated. The monograph references General Chapter <795>, which contains a section that addresses the selection, handling, and storage of components in compounded preparations. Issues regarding control of supply chain are outside the scope of this monograph and may be addressed elsewhere in the *USP-NF*.

**Comment Summary #3:** Commenter indicated the basis of the Beyond-Use Date at the specific storage temperature.

**Response:** Comment not incorporated. The beyond-use date stated in the monograph is based on the published peer-reviewed stability study for the preparation stored at controlled cold temperature and controlled room temperature.

**Comment Summary #4:** Commenter suggested grouping all compounding monographs together.

**Response:** Comment not incorporated. The Expert Committee will consider revising the name of the monograph in the future to include “compounded” in the Title to identify that the monograph is for a compounded preparation versus product.

**Expert Committee-initiated Change #1:** The compounding table under Definition was revised to reflect the specific components used to compound the formulation in the published peer-reviewed stability study.

**Expert Committee-initiated Change #2:** The Assay was revised after validation using a Phenomenex Luna brand of 4.6-mm x 25.0-cm column containing 5- $\mu$ m packing L7. Suitability requirements were revised to include column efficiency and tailing factor and to decrease the relative standard deviation to 2.0%.

**Monograph/ Section(s):** Minoxidil Tablets/Dissolution

**Expert Committee:** Monographs–Small Molecules 2

**Expert Committee-initiated change #1:** The subsection header “Chromatographic system” is replaced with “Spectrometric conditions” to reflect the analytical procedure based on the UV absorption.

**Monograph/Section(s):** Mycophenolate Mofetil/Assay

**Expert Committee:** Monographs–Small Molecules 3

**Expert Committee-initiated Change #1:** The requirement for column efficiency under *System suitability* is deleted. The remaining criteria are sufficient to establish suitability of the chromatographic system.

**Monograph/Section(s):** Myristic Acid/Identification

**Expert Committee(s):** Monographs—Excipients

**No. of Commenters:** 1

**Comment Summary #1:** The commenter recommended changing “<197F>” to “<197K> or <197D>” based on the data

**Response:** Comment incorporated.

**Monograph/Section(s):** Olanzapine/Organic Impurities

**Expert Committee(s):** Monographs–Small Molecules 4

**No. of Commenters:** 1

**Comment Summary #1:** The commenter indicated that the relative response factor for olanzapine related compound A is not consistent with the value approved by the FDA.

**Response:** Comment not incorporated because the value of relative response factor is based upon the supporting information provided by the sponsor.

**Monograph/Section(s):** Olanzapine Tablets/Multiple Sections

**Expert Committee(s):** Monographs–Small Molecules 4

**No. of Commenters:** 3

**Comment Summary #1:** The commenters reported difficulties performing the *Identification–A* test by IR, and suggested modifying the procedure for the sample preparation.

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

**Comment Summary #2:** Commenter indicated that the Assay employs an ion-pairing HPLC procedure which requires a long equilibration time, and suggested replacing it with a procedure that does not use ion-pairing reagent.

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

**Comment Summary #3:** The commenter requested widening the limit of olanzapine related compound B from NMT 0.20% to NMT 0.5%.

**Response:** Comment incorporated via a Revision Bulletin, posted at the USP website on June 29, 2012 and official on July 1, 2012.

**Comment Summary #4:** Commenter reported the coelution of olanzapine lactam and olanzapine related compound B in the test for *Organic impurities*, and requested to incorporate the commenter's procedure which is able to separate these impurities.

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

**Comment Summary #5:** The commenter indicated that the HPLC column with L10 packing used in the currently official *Dissolution* test requires frequent replacement, and requested to incorporate the commenter's procedure which uses an HPLC column with L1 packing.

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

**Monograph/Section(s):** Omeprazole Oral Suspension/ Multiple Sections

**Expert Committee(s):** Compounding

**No. of Commenters:** 1

**Comment Summary #1:** Commenter indicated the basis and rationale for using omeprazole and sodium bicarbonate for oral suspension in the compounding of this preparation.

**Response:** Comment not incorporated. The selection of ingredients used in the preparation is based on a published peer-reviewed stability study.

**Comment Summary #2:** Commenter requested that control of the supply chain for the ingredients be used in the monograph.

**Response:** Comment not incorporated. The monograph references General Chapter <795>, which has a section that addresses the selection, handling, and storage of components in compounded preparations. Issues regarding control of the supply chain are outside the scope of this monograph and may be addressed elsewhere in the *USP-NF*.

**Comment Summary #3:** Commenter indicated the basis of the Beyond-Use Date at the specific storage temperature.

**Response:** Comment not incorporated. The beyond-use date stated in the monograph is based on the published peer-reviewed stability study for the preparation stored at controlled cold temperature.

**Comment Summary #4:** Commenter requested grouping all compounding monographs together.

**Response:** Comment not incorporated. The Expert Committee will consider revising the name of the monograph in the future to include "compounded" in the Title to identify that the monograph is for a compounded preparation versus product.

**Expert Committee-initiated Change #1:** The compounding table under Definition was revised to reflect the specific components used to compound the formulation in the published peer-reviewed stability study.

**Expert Committee-initiated Change #2:** Assay was revised based on a method validated in a published peer-reviewed stability study.

**Monograph/Section(s):** Paricalcitol/Multiple Sections

**Expert Committee(s):** Monographs–Small Molecules 3

**Expert Committee-initiated Change #1:** The *Note* under the *Assay* and *Organic Impurities* is revised from “Use low-actinic glassware to prepare solutions of paricalcitol” to “Protect paricalcitol solutions from light” to provide more flexibility for the users.

**Expert Committee-initiated Change #2:** Under *Organic Impurities*, the *Control solution* and the system suitability requirement for the *Area Ratio* are deleted. The remaining criteria are sufficient to establish suitability of the chromatographic system.

**Monograph/Section(s):** Pentoxifylline Oral Suspension/ Multiple Sections

**Expert Committee(s):** Compounding

**No. of Commenters:** 1

**Comment Summary #1:** The commenter indicated that the immediate-release nature of the oral suspension was probably causing an increase of adverse reactions compared to the extended-release tablet products.

**Response:** Comment not incorporated. The Expert Committee has reviewed published peer-reviewed literature to support the use of the oral suspension formulation to aid in dosage adjustment in special populations where the oral tablets present challenges to administration. The extended-release tablet provides improved gastrointestinal tolerance. Gastrointestinal intolerance with the oral suspension can be addressed individually by healthcare professionals based on the patient’s presentation.

**Expert Committee-initiated Change #1:** The compounding table under *Definition* was revised to reflect the specific components used to compound the formulation in the published peer-reviewed stability study.

**Expert Committee-initiated Change #2:** The standard solution preparation in the *Assay* was changed to match the sample solution preparation. The retention time was corrected to relative retention time. Suitability requirements revised to include resolution, column efficiency, and tailing factor based on validation of the method using a Partisil 5 ODS3 brand of 4.6-mm x 25.0-cm column containing 5-µm packing L1. The relative standard deviation decreased to 2.0%.

**Expert Committee-initiated Change #3:** Expanded acceptable pH range.

**Monograph/Section(s):** Phenobarbital Oral Suspension/ Multiple Sections

**Expert Committee(s):** Compounding

**Expert Committee-initiated Change #1:** The compounding table under *Definition* was revised to reflect the specific components used to compound the formulation in the published peer-reviewed stability study.

**Expert Committee-initiated Change #2:** Expert committee corrected the beyond-use date to storage at controlled room temperature based on the published peer-reviewed stability study.

**Monograph/Section(s):** Powdered Black Pepper

**Expert Committee(s):** Nomenclature Safety and Labeling

**Expert Committee-initiated Change #1:** Changed the title of the monograph from Powdered Pepper to Powdered Black Pepper

**Monograph/Section(s):** Powdered Black Pepper Extract  
**Expert Committee(s):** Nomenclature Safety and Labeling  
**Expert Committee-initiated Change #1:** Changed the title of the monograph from Powdered Pepper Extract to Powdered Black Pepper Extract

**Monograph/Section(s):** Propylthiouracil Oral Suspension/ Multiple Sections  
**Expert Committee(s):** Compounding  
**Expert Committee-initiated Change #1:** The compounding table under Definition was revised to reflect the specific components used to compound the formulation in the published peer-reviewed stability study.  
**Expert Committee-initiated Change #2:** The Assay was revised to change the diluent for preparing the internal standard solution, 6-methyl-2-thiouracil, to methanol because of solubility problems with mobile phase. Suitability requirement revised to include resolution, column efficiency, and tailing factor and relative retention time revised based on re-validation using a Zorbax ODS brand of 3.0-mm x 15.0-cm column containing 5- $\mu$ m packing L1. The relative standard deviation decreased to 2.0%.

**Monograph/Section(s):** Pyrazinamide Oral Suspension/ Multiple Sections  
**Expert Committee(s):** Compounding  
**Comment Summary #1:** The commenter requested the basis and rationale for using pyrazinamide tablets in the compounding of this preparation.  
**Response:** Comment not incorporated. The selection of ingredients used in the preparation is based on a published peer-reviewed stability study.  
**Comment Summary #2:** Commenter requested the control of the supply chain for the ingredients used in the monograph.  
**Response:** Comment not incorporated. The monograph references General Chapter <795>, which contains a section that addresses the selection, handling, and storage of components in compounded preparations. Issues regarding control of the supply chain are outside the scope of this monograph and may be addressed elsewhere in *USP-NF*.  
**Comment Summary #3:** The commenter requested the basis of the Beyond-Use Date at the specific storage temperature.  
**Response:** Comment not incorporated. The beyond-use date stated in the monograph is based on the published peer-reviewed stability study for the preparation stored at controlled cold temperature and controlled room temperature.  
**Comment Summary #4:** The commenter requested grouping all compounding monographs together.  
**Response:** Comment not incorporated. The Expert Committee will consider revising the name of the monograph in the future to include “compounded” in the Title to identify that the monograph is for a compounded preparation versus product.  
**Expert Committee-initiated Change #1:** The compounding table under Definition was revised to reflect the specific components used to compound the formulation in the published peer-reviewed stability study.  
**Expert Committee-initiated Change #2:** The sample solution preparation in the Assay was changed to remove storage in a freezer which is not required when analysis is preceded immediately. The sample size used in the standard solution and sample

solution preparation was increased to improve accuracy. Suitability requirement revised to include column efficiency and tailing factor based on validation using a LiChrospher RP-8 brand of 4.6-mm x 25.0-cm column containing 5-µm packing L7.

**Expert Committee-initiated Change #3:** The acceptable pH range was expanded.

**Monograph/Section(s):** Pyrimethamine Oral Suspension/ Multiple Sections

**Expert Committee(s):** Compounding

**Expert Committee-initiated Change #1:** The compounding table under Definition was revised to reflect the specific components used in the method development/validation and stability study. Procedures for compounding were revised for clarity and consistency between compounded preparation monographs.

**Expert Committee-initiated Change #1:** The sample solution preparation in the Assay was revised to add a step to ensure homogeneity prior to sampling. The retention time was corrected for pyrimethamine and the suitability requirements were revised based on the validation information received.

**Monograph/Section(s):** Raloxifene Hydrochloride/Organic Impurities

**Expert Committee(s):** Monographs–Small Molecules 4

**No. of Commenters:** 1

**Comment Summary #1:** The commenter requested that the *in situ* degradation procedure to form the raloxifene *N*-oxide impurity be maintained as an alternate preparation for the *System suitability solution*.

**Response:** Comment not incorporated. USP Raloxifene Related Compound C RS is now available to prepare the solution. The revised preparation eliminates a lengthy degradation procedure and results in a solution containing a known concentration of raloxifene *N*-oxide.

**Monograph/Section(s):** Raloxifene Hydrochloride Tablets/Organic Impurities

**Expert Committee(s):** Monographs–Small Molecules 4

**No. of Commenters:** 1

**Comment Summary #1:** The commenter requested that the *in situ* degradation procedure to form the raloxifene *N*-oxide impurity be maintained as an alternate preparation for the *System suitability solution*.

**Response:** Comment not incorporated. USP Raloxifene Related Compound C RS is now available to prepare the solution. The revised preparation eliminates a lengthy degradation procedure and results in a solution containing a known concentration of raloxifene *N*-oxide.

**Monograph/Section(s):** Rifabutin Oral Suspension/ Multiple Sections

**Expert Committee(s):** Compounding

**Expert Committee-initiated Change #1:** The compounding table under Definition was revised to reflect the specific components used to compound the formulation in the published peer-reviewed stability study.

**Expert Committee-initiated Change #2:** The standard solution preparation in the Assay was modified to use the same diluent as the sample solution preparation. The suitability requirement was revised to include column efficiency and tailing factor and

the retention time was revised based on validation using a Hypersil MOS brand of 4.6-mm x 15.0-cm column containing 5-µm packing L7.

**Expert Committee-initiated Change #3:** The acceptable pH range was revised based on the published peer-reviewed stability study and validation study.

**Monograph/Section(s):** Rufinamide/Organic Impurities

**Expert Committee(s):** Monographs–Small Molecules 4

**No. of Commenters:** 4

**Comment Summary #1:** The commenters requested that additional *Organic impurities* procedures be added to the monograph to accommodate the impurity profiles generated by their manufacturing processes.

**Response:** Comment not incorporated. The Expert Committee will consider future changes to the monograph when the commenters' products receive full FDA approval.

**Monograph/Section(s):** Sertraline Hydrochloride Oral Solution/Multiple Sections

**Expert Committee(s):** Monographs–Small Molecules 4

**No. of Commenters:** 2

**Comment Summary #1:** The commenter indicated that the limit of total impurities in the Organic Impurities procedure is not consistent with the FDA-approved specifications.

**Response:** Comment not incorporated. The proposed limit is consistent with the FDA-approved specifications.

**Comment Summary #2:** The commenter requested widening the limit for any individual unspecified degradation product from NMT 0.1% to NMT 0.2%.

**Response:** Comment not incorporated. The Expert Committee will consider future changes to the monograph when the commenter's product receives full FDA approval.

**Comment Summary #3:** The commenter requested widening the acceptance criteria for *Microbial limits*.

**Response:** Comment not incorporated. The Expert Committee will consider future changes to the monograph when the commenter's product receives full FDA approval.

**Monograph/Section(s):** Sildenafil Citrate Oral Suspension/ Multiple Sections

**Expert Committee(s):** Compounding

**No. of Commenters:** 1

**Comment Summary #1:** The commenter indicated that the title of the preparation does not identify that the monograph is for a compounded preparation.

**Response:** Comment not incorporated. The Expert Committee will consider revising the monograph title in the future to include "compounded" in the name to denote that that the monograph is for a compounded preparation versus manufactured product.

**Expert Committee-initiated Change #1:** The compounding table under Definition was revised to reflect the specific components used to compound the formulation in the published peer-reviewed stability study.

**Expert Committee-initiated Change #2:** Standard stock solution, standard solution, and sample solution preparation was changed to use mobile phase as the diluent.

Sildenafil is slightly soluble in methanol. The expert committee has found supporting evidence to use mobile phase as the diluent.

**Monograph/Section(s):** Sodium Phenylbutyrate Oral Suspension/ Multiple Sections

**Expert Committee(s):** Compounding

**Expert Committee-initiated Change #1:** The compounding table under Definition was revised to reflect the specific components used to compound the formulation in the published peer-reviewed stability study.

**Expert Committee-initiated Change #2:** The Assay was revised to place a note in the standard solution preparation to use appropriate reference material until a USP reference standard is available.

**Monograph/Section(s):** Sotalol Hydrochloride Oral Suspension/ Multiple Sections

**Expert Committee(s):** Compounding

**Expert Committee-initiated Change #1:** The compounding table under Definition was revised to reflect the specific components used to compound the formulation in the published peer-reviewed stability study.

**Expert Committee-initiated Change #1:** Removed filtration step from the sample solution preparation in the Assay since a filter study has not been performed.

**Monograph/Section(s):** Spironolactone Oral Suspension/ Multiple Sections

**Expert Committee(s):** Compounding

**Expert Committee-initiated Change #1:** The compounding table under Definition was revised to reflect the specific components used to compound the formulation in the published peer-reviewed stability study.

**Expert Committee-initiated Change #2:** The sample solution preparation under Assay was changed to remove storage in a freezer which is not required when analysis is performed immediately.

**Expert Committee-initiated Change #3:** Revised retention time and included column efficiency and tailing factor in suitability requirement based on results from a validation study using a Partisil 5 ODS3 brand of 4.6-mm x 25.0-cm column containing 5- $\mu$ m packing L1.

**Expert Committee-initiated Change #4:** Expanded pH range based on the published peer-reviewed stability study and validation study.

**Monograph/Section(s):** Spironolactone and Hydrochlorothiazide Oral Suspension/  
Multiple Sections

**Expert Committee(s):** Compounding

**Expert Committee-initiated Change #1:** The compounding table under Definition was revised to reflect the specific components used to compound the formulation in the published peer-reviewed stability study.

**Expert Committee-initiated Change #2:** The sample solution preparation under Assay was changed to remove storage in a freezer which is not required when analysis is performed immediately. The retention time for spironolactone and hydrochlorothiazide was revised based on a published peer-reviewed stability study.

**Monograph/Section(s):** Tacrolimus Oral Suspension/ Multiple Sections

**Expert Committee(s):** Compounding

**Expert Committee-initiated Change #1:** The compounding table under Definition was revised to reflect the specific components used to compound the formulation in the published peer-reviewed stability study.

**Expert Committee-initiated Change #2:** Note added to the standard solution and standard solution preparation under Assay to proceed with assay immediately after preparation due to degradation of tacrolimus. Verification study showed about 10% loss in about 3 hours.

**Expert Committee-initiated Change #3:** Suitability requirement revised to include column efficiency and tailing factor based on validation using a Spheri-5 ODS brand of 4.6-mm x 25.0-cm column containing 5- $\mu$ m packing L1.

**Monograph/Section(s):** Tadalafil/Organic Impurities  
**Expert Committee:** Monographs–Small Molecules 4  
**No. of Commenters:** 1

**Comment Summary #1:** Commenter requested widening acceptance criteria for individual impurities from 0.1% to 0.15%, and total impurities from 0.3% to 0.50%.

**Response:** Comment not incorporated. The proposed limits for individual and total impurities are consistent with the specifications approved by the FDA.

**Monograph/Section(s):** Tadalafil Tablets/Assay  
**Expert Committee(s):** Monographs–Small Molecules 4  
**No. of Commenters:** 1

**Comment Summary #1:** Commenter requested that the *Sample solution* description be corrected to state “Centrifuge or filter the solution” instead of “Centrifuge and filter the supernatant solution.”

**Response:** Comment incorporated.

**Monograph/Section(s):** Tramadol Hydrochloride Oral Suspension/ Definition  
**Expert Committee(s):** Compounding

**Expert Committee-initiated Change #1:** The compounding table under Definition was revised to reflect the specific components used to compound the formulation in the published peer-reviewed stability study.

**Monograph/Section(s):** Tramadol Hydrochloride and Acetaminophen Oral Suspension/ Multiple Sections

**Expert Committee(s):** Compounding

**Expert Committee-initiated Change #1:** The compounding table under Definition was revised to reflect the specific components used to compound the formulation in the published peer-reviewed stability study.

**Monograph/Section(s):** Ursodiol Oral Suspension/ Multiple Sections

**Expert Committee(s):** Compounding

**Expert Committee-initiated Change #1:** The compounding table under Definition was revised to reflect the specific components used to compound the formulation in the published peer-reviewed stability study.

**Expert Committee-initiated Change #2:** Sample solution preparation under Assay was revised to use methanol as the diluent based on the method validated in a published peer-reviewed stability study.

**Monograph/Section(s):** Valacyclovir Oral Suspension/ Multiple Sections

**Expert Committee(s):** Compounding

**No. of Commenters:** 2

**Comment Summary #1:** The commenters recommended revising the monograph Definition to prepare a 25 mg/mL or 50 mg/mL suspension with cherry flavor and Suspension Structured Vehicle.

**Response:** Comments not incorporated. Flavoring can affect the stability of a preparation. The suggested formula does not specify the cherry flavoring to be used and substitution with different manufacturers of cherry flavorings may adversely affect the stability of the preparation. The expert committee will consider an alternative formulation in future proposed revisions if supporting stability data is received.

**Expert Committee-initiated Change #1:** The components in the compounding table under Definition was changed to reflect those used in the published peer-reviewed stability study.

**Expert Committee-initiated Change #2:** Revised the standard solution preparation and equation under Assay to account for the hydrochloride salt since valacyclovir is dosed based on the base form.