Commentary

USP 37–NF 32

November 1, 2013

In accordance with USP's Rules and Procedures of the 2010-2015 Council of Experts ("Rules") and except as provided in Section 7.02 Accelerated Revision Processes, USP publishes proposed revisions to the *United States Pharmacopeia and the National Formulary* (*USP–NF*) for public review and comment in the *Pharmacopeial Forum (PF),* USP's free bimonthly journal for public notice and comment. After comments are considered and incorporated as the Expert Committee deems appropriate, the proposal may advance to official status or be republished in *PF* for further notice and comment, in accordance with the Rules. In cases when proposals advance to official status without republication in *PF,* a summary of comments received and the appropriate Expert Committee's responses are published in the Revisions and Commentary section of the USP Web site at the time the official revision is published.

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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General Notices Revision

The Council of Experts Executive Committee (Council of Experts), composed of the chairs of USP's Expert Committees, is responsible for determining and approving content of the General Notices in USP's compendia. The following chart summarizes the sections of USP-NF General Notices for which changes were proposed, and the decisions of the Council of Experts on each section. These decisions occurred in June 2013 through balloting following the consideration of the public comments received. The commentary appears below the chart.

Section Proposed for Revision	Council of Experts Executive Committee Decision
1. Title and Revision	Approve with edits
2.10: Official Text	Cancel
2.30: Legal Recognition	Cancel
3.10: Applicability of Standards	Approve with edits
3.10.10: Applicability of Standards	Approve (no comments received)
3.20: Indicating Conformance	Cancel
4.10.11: Dissolution, Disintegration and Drug Release Tests	Approve with edits
5.60: Impurities and Foreign Substances	Approve (no comments received)
5.60.10: Other Impurities in USP and NF Articles	Cancel
5.60.30 Elemental Impurities	Defer
5.80 Reference Standards	Approve with edits
6.50.20: Solutions	Approve (no comments received)
6.50.20.1: Adjustments to Solutions	Approve with edits
6.80.10.1: Pipet/Pipette	Approve (no comments received)
6.80.30: Temperature Reading Devices	Approve (no comments received)
8.20: About	Approve (no comments received)
8.240: Weights and Measures	Approve with edits
10.10/20/30/50: Packaging and Storage	Approve with edits

General Notices Section: 1. Title and Revision
No. of Commenters: 1
Comment Summary #1: The commenter requested inclusion of an Internet address where Interim Revision Announcements, Revision Bulletins, Errata, and Stage 6 Harmonization are published and specific instructions on how to locate these revisions.
Response: Comment not incorporated. USP prefers to avoid inclusion of web addresses in official text when possible, as they may change. Additional information on accessing this information is included in the Mission and Preface that is incorporated in each official print publication.
Expert Committee-initiated Change #1: The Council of Experts deleted the sentence, "Errata are effective upon publication." from Section 1.0 Title and Revision. This statement was in conflict with current practice, which conforms to the USP Guideline on Use of Accelerated Processes for Revisions to the USP-NF that states that Errata become official on the first day of the month following publication.

General Notices Section: 2.10 Official Text
No. of Commenters: 1
Comment Summary #2: The commenter suggests possible confusion regarding 1) whether two versions can simultaneously be official and 2) the definition of "other electronic version."
Comment Summary #3: The commenter suggests that the text be revised to indicate that Accelerated Revisions supersede other standards in the online publication and in the USP-NF or its Supplements, and to note that revisions "become official on the date specified."
Response: Based on these comments, the Council canceled the revision to allow further consideration.

General Notices Section: 2.30 Legal Recognition
No. of Commenters: 3
Comment Summary #4: A commenter suggests revision to more accurately reflect the text of the status and regulations.
Comment Summary #5: Several commenters suggest identification of Accelerated Revisions in this section as official text.
Comment Summary #6: A commenter noted the omission of medical devices from this section.
Response: Based on these comments, the Council canceled the revision to allow further consideration.

General Notices Section: 3.10 Applicability of Standards
No. of Commenters: 2
Comment Summary #7: A commenter requested a revision to the language related to early adoption of compendial standards.

Response: Comment not incorporated. The suggestion was beyond the scope of the proposed revisions and will be considered as a request for future revision.
Comment Summary #8: A commenter requested a revision clarifying the priority of compendial standards, including monographs, general chapters, and General Notices.
Response: Comment not incorporated. The suggestion was beyond the scope of the proposed revisions and will be considered as a request for future revision.

General Notices Section: 3.10.10 Applicability of Standards to Drug Products, Drug Substances, and Excipients
No. of Commenters: 0

General Notices Section: 3.20 Indicating Conformance
No. of Commenters: 4
Comment Summary #9: A commenter suggested that the text be clarified to specify that compliance is necessary whether or not an article is labeled as USP or NF, similar to Section 3.10.10.
Comment Summary #10: Several commenters suggested that manufacturers should be required to comply with all monograph requirements in order to label their article as USP or NF.
Comment Summary #11: A commenter indicated that the requirement to include on an article's label any differences from the monograph criteria might be interpreted to require inclusion of alternative methods performed under Section 6.30 Alternative and Harmonized Methods and Procedures.
Response: Based on these comments, the Council canceled the revision to allow further consideration.

General Notices Section: 4.10 Monographs
No. of Commenters: 1
Comment Summary #12: The commenter requested replacing the term "interchangeability" with the term "substitutability" or similar.
Response: Comment not incorporated. The suggestion was beyond the scope of the proposed revisions and will be considered as a request for future revision.

General Notices Section: 4.10.11 Dissolution, Disintegration and Drug Release Tests
No. of Commenters: 2
Comment Summary #13: A commenter requested a change to the proposed language so that it does not suggest that FDA provides information to USP about FDA-approved tests.
Response: Comment incorporated.

Comment Summary #14: A commenter requested that the text be expanded to indicate that labeling need not prescribe which dissolution test is performed when monographs contain multiple dissolution tests.
Response: Comment not incorporated. The suggestion was beyond the scope of the proposed revisions and will be considered as a request for future revision.

General Notices Section: 5.60 Impurities and Foreign Substances
No. of Commenters: 0

General Notices Section: 5.60.10 Other Impurities in USP and NF Articles
No. of Commenters: 7
Comment Summary #15: A commenter suggested revision to the text so that excipients, dietary supplements, etc. are not excluded from impurity standards, but to clarify that certificates of analysis (CoAs) apply only to drug substances.
Comment Summary #16: Several commenters indicated that the limit of 0.1% should apply only to drug substances in alignment with ICH guidelines.
Comment Summary #17: A commenter suggested that the text should not specify the section of a CoA under which the amount and identity of impurities are listed, as the CoA may have been submitted to and approved by a regulatory authority.
Response: The proposal was canceled by the Council of Experts to allow further consideration. USP has established an Expert Panel on Impurities in Drug Products to make recommendations to the General Chapters-Physical Analysis Expert Committee regarding General Chapter <1086> Impurities in Drug Substances and Drug Products. This Expert Panel also will make recommendations to the Council of Experts on this General Notices section.

General Notices Section: 5.60.30 Elemental Impurities in USP and NF Articles
No. of Commenters: 32
Comment Summary #18: Several commenters suggested, in addition to commenting on other aspects, delaying the implementation of General Chapters <232> Elemental Impurities – Limits and <233> Elemental Impurities – Methods for varying periods to provide manufacturers more time to implement the standards and/or to enable further alignment with the output of the ICH Q3D Expert Working Group.
Response: The proposal was deferred by the Council of Experts to allow further consideration. USP has established an Advisory Group to consider implementation recommendations to USP. Additional information can be found at http://www.usp.org/usp-nf/key-issues/elemental-impurities.

General Notices Section: 5.80 Reference Standards
No. of Commenters: 22
Comment Summary #19: A commenter requested that the first sentence of section 5.80 be revised to indicate who approves USP reference standards as suitable for use.

Response: Comment not incorporated. The suggestion was beyond the scope of the proposed revisions and will be considered as a request for future revision.
Comment Summary #20: Several commenters requested that the language be modified so that use of suitably qualified secondary or other reference materials are not prohibited.
Response: Comment incorporated. The Council of Experts noted that, while only those results obtained using the specified USP Reference Standard are conclusive, USP has no intention to prohibit use of suitably qualified reference materials.

General Notices Section: 6.50.20 Solutions
No. of Commenters: 0

General Notices Section: 6.50.20.1 Adjustment to Solutions
No. of Commenters: 5
Comment Summary #21: Several commenters requested that Normality be retained, as it is commonly used.
Response: Comment incorporated.
Comment Summary #22: A commenter requested the following revision to the proposed second sentence of the first paragraph of the section to improve clarity: "…provided the measurement is made with at least equivalent accuracy and provided that any subsequent steps, such as dilutions, are adjusted accordingly to ~~yield concentrations equivalent to those specified and are made in such manner as to provide at least equivalent accuracy~~."
Response: Comment incorporated. The text was further truncated to, "…provided the measurement is made with at least equivalent accuracy."

Comment Summary #23: A commenter requested deletion of the term "special" from the second sentence of the second paragraph of the section.
Response: Comment not incorporated. The suggestion was beyond the scope of the proposed revisions and will be considered as a request for future revision.

General Notices Section: 6.80.10.1 Pipet/Pipette
No. of Commenters: 0

General Notices Section: 6.80.30 Temperature Reading Devices
No. of Commenters: 0

General Notices Section: 8.20 About
No. of Commenters: 0

General Notices Section: 8.240 Weights and Measures
No. of Commenters: 4
Comment Summary #24: The commenter requested retention of the abbreviation "MeV," which currently is used elsewhere in the USP-NF.
Response: Comment incorporated.
Comment Summary #25: Several commenters indicated that the symbol for "gamma" was missing from the table, and that typographical errors were included for the terms "centimeter" and "millimeter."
Response: Comment incorporated.
Comment Summary #26: The commenter requested inclusion of text indicating that the degrees symbol without a unit of measure means the temperature is in degrees Celcius.
Response: Comment not incorporated. The suggestion was beyond the scope of the proposed revisions and will be considered as a request for future revision.

General Notices Section: 10. Preservation, Packaging, Storage, and Labeling
No. of Commenters: 1
Comment Summary #27: A commenter separately requested changes to General Chapter <659> Packaging and Storage Requirements, which was published for revision in PF 38(6) and includes the concepts proposed for deletion from Section 10 of General Notices.
Response: These comments will be addressed during the finalization of revisions to General Chapter <659>.

General Chapters:

General Chapter/Section(s): <735> X-ray Fluorescence Spectrometry
Expert Committee(s): General Chapters—Chemical Analysis
No. of Commenters: 4
Comment Summary #1: The commenter requested that the scope of General Chapter <735> be clarified by including the following text in the "Introduction" section: "This general test chapter is being proposed to support the new general chapter Elemental Impurities—Procedures 233."
Response: Not incorporated. This general chapter may not be used only for elemental impurities analysis.
Comment Summary #2: The commenter requested that the implementation date of this General Chapter be aligned with the implementation of General Chapters <232> and <233> because XRF spectrometry currently is being used for elemental impurities analysis.
Response: Not incorporated. See response to comment #1.
Comment Summary #3: The commenter requested to replace the text under Installation Qualification with the following: See also USP general information chapter Analytical Instrument Qualification <1058>.
Response: Comment incorporated.
Comment Summary #4: The commenter requested that the text under the Operational Qualification (OQ) section be revised to read, "The OQ tests and specifications in the

following sections…," because tests and specifications are dependent on the use of the spectrometer and are set to have methods which comply with the planned validation criteria.
Response: Comment incorporated.
Comment Summary #5: The commenter indicated that the acceptance criteria for "Detector Resolution "(row 2, column 3 of Table 1) should be deleted because the change of resolution from IQ to OQ is not relevant. What would be relevant is resolution during IQ, OQ, PQ and especially during daily operations (the latter is ensured by system suitability). The combination of equipment and analytical methodology i.e., sample prep in conjunction with the intended use determines performance. Different equipment suppliers may choose different technical realizations and such a requirement might grant an unfair advantage to one or a few suppliers.
Response: Comment not incorporated. Manufacturers strive to keep detector resolution constant over time. The different realizations will not lead to unfair advantages of one or more suppliers.
Comment Summary #6: The commenter requested modification of the language for Count Rate acceptance criteria in Table 1 (Row 3, column 3) to read: "Loss of count rate from value of instrument calibration NMT 10% for Assay and NMT 20% for Impurities Tests" instead of "<10% change…each peak" because the accuracy of the instrument should be adapted to the intended use of the spectrometer.
Response: Comment not incorporated. This test is done on two intense peaks. The OQ is a general test on equipment operation, not checking the intended use (i.e., the particular analytical problem).
Comment Summary #7: The commenter recommended revising the text in the *Procedure* section as follows: "Analyst should check the suitability of all reagents and materials for contamination depending on the method used before using them in an analysis," because this section should only provide general recommendations.
Response: Comment incorporated.
Comment Summary #8: The commenter requested a change in the Procedure section for powder samples as follows because a micro powder does not need grinding, "…then dried, ground if necessary, and thoroughly mixed before analysis."
Response: Comment incorporated.
Comment Summary #9: The commenter requested revising the text in the "Analysis" subsection under Procedure as follows because the XRF spectrometry can be used for assay, quantitative impurity test, limit impurity test, and identification tests: "…standardized for the ~~quantification~~ intended use."
Response: Comment incorporated.
Comment Summary #10: The commenter suggested the addition of the following sentence in the section on "Samples, Powders" to allow direct measurement of loose powders as it is the easiest form of sample preparation and it is widely used: "Prepared powders may be measured directly in a liquid sample holder. Alternatively they may be pressed into pellets."
Response: Comment incorporated.
Comment Summary #11: The commenter recommended revising the section on "Analysis" as follows: "To demonstrate the stability of the system's initial standardization, at appropriate intervals throughout their tests on the sample set analysts must re-assay the calibration standard used in the initial standard curve as a check standard. The use of an independently prepared standard or a suitable long-lasting solid material such as a glass which is physically and chemically stable under prolonged exposure to X-ray radiation also is acceptable."

Response: Comment not incorporated. To provide relevant system stability information for the analytical method, it is recommended to measure standards prepared using the calibration standard matrix as opposed to reference materials in matrices unrelated to the method.

Comment Summary #12: The commenter indicated that it is a normal practice in the determination of "Linearity" to automatically employ corrective procedures to produce useful net count spectra. Examples include background, matrix and line-over-lap procedures. Therefore, the "Linearity" section should be revised as follows: "Analysts should demonstrate a linear relationship between the analyte concentration and corrected XRF response by preparing no fewer than five standard solutions at concentration that encompass the anticipated concentration of the test solution."

Response: Comment incorporated.

Comment Summary #*13:* The commenter suggested clarifying the third sentence in the section on Quantitation Limit by revising as follows: "A measurement of a test sample prepared from a representative sample matrix without measurable content of the analyte and spiked at the estimated LOQ concentration must be performed to confirm accuracy."

Response: Comment incorporated.

Comment Summary #14: The commenter indicated that the X-Ray Fluorescence technique is not limited to measurement of solutions. Solid samples such as powders are measured using XRF. Therefore, the term "Standard solution" should be replaced with "Standard sample" in the Precision and Linearity subsection.

Response: Comment incorporated.

Comment Summary #15: The commenter requested modifying the following sentence in the repeatability section as follows: "…concentration range. ~~If this is done,~~ In the latter case the repeatability at the three concentrations is pooled…"

Response: Comment incorporated.

Comment Summary #16: The commenter requested deleting the text: "These acceptance criteria should be met throughout the validated range" in the section on Precision because this is in contradiction to current ICH Q2A guideline. The ICH precision test with n=6 at 100% cannot give an indication about the precision throughout the validated range.

Response: Comment incorporated.

Comment Summary #17: The commenter suggested addition of the following text at the end of the chapter (after the text, "The samples for validation should be independent of the calibration set"): "Methods for which no validation specifications and tests are described (elsewhere) in a monograph or in a general method, e.g. Elemental Impurities-Procedures <233> have to be validated according to the following characteristics and criteria."

Response: Comment not incorporated. The issue is addressed in USP General Notices section 6.30. Alternative and Harmonized Methods and Procedures. Adding this statement to this General Chapter would be redundant.

General Chapter/Section(s): General Chapter <1197> Good Manufacturing
Expert Committee(s) Practices for Bulk Pharmaceutical Excipients
General Chapters—Physical Analysis
No. of Commenters: 1

4.2.2 Transportation
Comment Summary #1: The commenter suggested including a risk-based approach for defining the need of temperature-controlled transport as well as for the monitoring strategy. This approach should be based on the products' stability, the distribution route, the mode of transportation and the potential risk to compromise the quality of the product.
Response: Comment incorporated.
Comment Summary #2: The commenter stated that the packaging label represents only storage conditions, which are derived from sound stability studies as outlined in section 3.2 of the General Chapter. A differentiation should be made concerning the distribution conditions which might differ from storage conditions for short terms during transportation which must then be based and justified depending on additional stability studies e.g., cycling studies.
Response: Comment incorporated.

4.3 Tampering or Damaged Materials
Comment Summary #3: In addition to the current statement in the General Chapter regarding the return procedure of materials if tampering or damage is suspected or confirmed, the commenter proposed including an alternative procedure according to which the investigation and potential destruction of the tampered excipient could be performed and documented at the receiving site in cooperation with the supplier.
Response: Comment incorporated.

4.4 Packaging: Tamper Evident Seals
Comment Summary #4: The commenter recommended considering the option of tamper-evident sealing of transportation system (e.g., ocean freight containers, air freight container) instead of sealing every single secondary container closure system.
Response: Comment incorporated.

General Chapter/Section(s): <1911> Rheometry/Multiple Sections
Expert Committee(s): General Chapters—Physical Analysis
No. of Commenters: 1
Comment Summary #1: In the section on Newtonian Viscosity, the commenter recommended that the proposed equation (6) should be replaced with $\nu = k \times t - (E/t_2)$, such that the proposed b term definition should be replaced with an E term definition. Correspondingly, the commenter suggested changing the text, "This complete calibration

of a viscometer requires the measurement of the viscosities (at a given temperature) of two reference standards of different viscosities to determine values for both constants." to "The viscometer constant, k, and kinetic factor, E, are determined from flow times measured for a set of stable, clean, Newtonian fluids of known kinematic viscosity (viscosity standard reference materials)."
Response: Comment incorporated.

Expert Committee-initiated Change #1: In the section on Non-Newtonian Rheology, the Expert Committee introduced the two sections entitled “Calculation of shear rate, shear stress, and viscosity using a concentric (coaxial) cylinder rheometer” and “Calculation of shear rate, shear stress, and viscosity using a cone-and-plate rheometer” which are included in the newly official general chapter <912> Rotational Rheometer Methods. Subsequently, the Expert Committee is going to delete these two sections from the general chapter <912> Rotational Rheometer Methods through a future revision of the chapter <912>.
Expert Committee-initiated Change #2: The Expert Committee replaced “Viscosity” with “Rheological Properties,” in the section of Non-Newtonian Rheology, for one of the subtitles, “Measurement of Viscosity Using a Nonrotational Rheometer.”

Monographs:

Monograph/Section(s): Alfuzosin Hydrochloride/Assay
Expert Committee(s): Monographs—Small Molecules 4
No. of Commenters: 1
Comment Summary #1: The commenter requested replacing the procedure with the HPLC method from the test for Organic impurities.
Response: Comment not incorporated. The Expert Committee concluded that the procedure was validated and shown to be suitable for its intended use.

Monograph/Section(s): Anastrozole/Organic Impurities
Expert Committee(s): Monographs—–Small Molecules 3
Expert Committee-initiated Change #1: Anastrozole related compound D was revised to 5-Bromomethyl anastrozole in Table 2 to be consistent with the naming convention for specified impurities.

Monograph/Section(s): Carbidopa and Levodopa Extended-Release Tablets/Multiple Sections
Expert Committee(s): Monographs—Small Molecules 4
No. of Commenters: 1
Comment Summary #1: The commenter requested replacing Identification test A by IR with a TLC procedure for consistency with their FDA-approved specifications.
Response: Comment not incorporated. The replacement of ID by IR procedures with TLC procedures is not consistent with current USP initiatives. Additionally, the requested TLC procedure requires the use of chloroform.
Comment Summary #2: The commenter requested replacing the HPLC procedures for the Assay, Organic Impurities, and Uniformity of Dosage Units with their procedures.

Response: Comment not incorporated. The Expert Committee will consider further revisions to the monograph upon the receipt of the necessary supporting data.
Comment Summary #3: The commenter requested adding a dissolution test to the monograph. The new test (Dissolution Test 5) was validated using a Nucleodur 100 C8 brand of L7 column. The typical retention times for levodopa and carbidopa are about 2.5 min and 4 min, respectively.
Response: Comment incorporated.

Monograph/Section(s): Clonidine Hydrochloride/Multiple Sections
Expert Committee(s): Monographs—Small Molecules 2
No. of Commenters: 3
Comment Summary #1: The commenter suggested revising the chemical name of Clonidine Related Compound A from 1-acetyl-2-(2,6-dichlorophenylamino)-2-(4,5-dihydroimidazole) to 1-acetyl-2-(2,6-dichlorophenylimino) imidazolidine.
Response: Comment incorporated**.**
Comment Summary #2: The commenter suggested revising the proposed methods for Assay and Organic Impurities to use a different type of column.
Response: Comment not incorporated**.** The Expert Committee will consider further revisions to the monograph upon the receipt of the necessary supporting data.
Comment Summary #3: The commenter indicated that the clonidine peak is not symmetrical under the Assay conditions and splits under the Organic Impurities test conditions.
Response: Comment not incorporated**.** The Expert Committee will consider further revisions to the monograph upon the receipt of the necessary supporting data.

Monograph/ Section(s): Clopidogrel Bisulfate/Multiple Sections
Expert Committee(s): Monographs—Small Molecules 2
No. of Commenters: 4
Comment Summary #1: The commenter suggested using a single procedure for monitoring chiral and achiral impurities.
Response: Comment not incorporated**.** The Expert Committee will consider further revisions to the monograph upon the receipt of the necessary supporting data.
Comment Summary #2: The commenters suggested replacing the Organic Impurities procedure because the Blank peaks interfere with the clopidogrel related compound B peak.
Response: Comment not incorporated**.** The Expert Committee will consider further revisions to the monograph upon the receipt of the necessary supporting data.
Comment Summary #3: The commenter suggested increasing the specification limit for Clopidogrel related compound C from NMT 0.5% to NMT 1.0%.
Response: Comment not incorporated**.** The Expert Committee will consider further revisions to the monograph upon the receipt of the necessary supporting data.
Comment Summary #4: The commenter suggested including the USP Clopidogrel Related Compound A RS in the System suitability solution within the Organic Impurities procedure for peak identification.
Response: Comment incorporated**.**
Expert Committee Initiated Change #1: The molecular weights for USP Clopidogrel Related Compound A RS and USP Clopidogrel Related Compound B RS in the <11> Reference Standard section are revised from 307.8 and 419.90 to 344.26 and 358.28 to reflect the chemical composition of the reference standards.

Monograph/Section(s): Compressible Sugar/Specific Rotation
Expert Committee(s): Monographs—Excipients
No. of Commenters: 1
Comment Summary #1: In the section of Acceptance criteria for the *Specific Rotation* test, based on the supporting data the commenter requested changing the proposed specification for the specific rotation determined from the *Uninverted solution* from “62.6°–67.0°” to “62.6°–73.4°,” and changing the proposed specification for the specific

rotation determined from the *Acid-inverted solution* from "−24.0° to −17.0°" to "levorotatory."
Response: Comment incorporated.

Monograph/ Section(s): Dexmedetomidine Hydrochloride/Organic Impurities
Expert Committee(s): Monographs—Small Molecules 2
No. of Commenters: 1
Comment Summary #1: The commenter indicated that the run time is too long for the Organic impurities test procedure.
Response: Comment not incorporated. The Expert Committee will consider further revisions to the monograph upon the receipt of the necessary supporting data.
Comment Summary #2: The commenter requested revising the test for Organic Impurities to remove the specific references to the impurities listed in Table 1, and replacing these references with the acceptance criteria of NMT 0.10% for Individual impurities and NMT 0.3% for Total impurities, to be consistent with the FDA approved specifications.
Response: Comment incorporated.
Expert Committee Initiated Change #1: Table 1 was moved from the Acceptance Criteria section to the Analysis section.

Monograph/Sections: Doxycycline Extended-Release Capsules/Multiple Sections
Expert Committee(s): Monographs—Small Molecules 1
Expert Committee Initiated Change #1: Standard solutions 1 and 2 in the test for Organic Impurities were revised to remove references to USP Methacycline Hydrochloride RS, which is not used for system suitability or quantitative evaluations.
Expert Committee Initiated Change #2: The USP Reference Standards section was revised to remove references to USP Doxycycline Related Compound A RS and USP Methacycline Hydrochloride RS, which are not used in the monograph.

Monograph/Sections: Famotidine/Organic Impurities
Expert Committee(s): Monographs—Small Molecules 3
No. of Commenters: 1
Comment Summary #1: The commenter indicated that the flow rate gradient adds variability which may affect the relative response factors for the impurities and that one of their unspecified impurities is coeluting with the peak of famotidine related compound B. The commenter requested replacing the procedure with the commenter's procedure that uses a constant flow rate and is specific for all impurities present in the commenter's material.
Response: Comment not incorporated. The Expert Committee indicated that the current procedure is harmonized with the procedure in the corresponding European Pharmacopoeia monograph, and that the harmonization approach is supported by pharmaceutical industry. To address the coelution of impurities, the Expert Committee may consider adding the commenter's procedure using a flexible monograph approach upon the receipt of the necessary supporting data.

Monograph/Sections: Heparin Sodium/Multiple sections
Expert Committee(s): Monographs—Biologics & Biotechnology 1

Definition
No. of Commenters: 2
Comment Summary #1: The commenter requested that USP should consider removing the statement about the clearance of lipids unless they are willing to provide a suitable method by which to demonstrate this.
Response: Comment not incorporated. If a process can be validated to show removal of lipids to levels acceptable to regulatory authorities, then a company should not have to run a lipid analysis with every batch just to conform to the USP monograph.

Heparin Sodium/Identification/^{1}H NMR Spectrum
No. of Commenters: 3
Comment Summary #2: The commenter indicated that the change of the residual solvent range from 0.10-3.00 to 0.10 to 3.75 imply that a signal greater than 200% in the range of 3.35-3.75 ppm would be identified as residual solvent peak, and therefore constitute an ID A failure. The commenter requested that the acceptance criteria range of 'no signals greater than 200%' should be changed from 3.35-4.55 to 3.75-4.55.
Response: Comment incorporated.
Comment Summary #3: The commenter requested keeping the current value of 0.02% deuterated trimethylsilylproprionic (TSP) acid sodium salt and not change it to 0.002% TSP.
Response: Comment not incorporated. TSP is present to ensure accurate chemical shift and the proposed lower concentration lessens risks of excess peaks due to TSP.
Comment Summary #4: The commenter requested removing the sentence "In the event that EDTA is added to the Sample solution, spectra should be recorded and compared both with and without addition of EDTA". Alternately, the commenter also requested the use of EDTA for all analyses as this procedure is appropriate for any heparin sample.
Response: Comment not incorporated. The necessity for EDTA is unusual. Therefore, it is not necessary to mandate the addition of EDTA for all analyses.

Heparin Sodium/Identification/Chromatographic Identity
No. of Commenters: 8
Comment Summary #5: The commenters requested adding a flat step at 90% for 3 min at 30 min to accommodate for a potential shift in the retention time or another oversulfated impurity.
Response: Comment not incorporated. The Expert Committee will consider future revisions to the monograph when appropriate and upon receipt of the necessary supporting data.
Comment Summary #6: The commenter requested adding a specific requirement to the window in which the retention time may vary between the sample solution and the standard solution.
Response: Comment not incorporated. The validation data does not support a specific window. The Expert Committee will consider future revisions to the monograph when appropriate and upon the receipt of the necessary supporting data.
Comment Summary #7: The commenters requested that the system suitability criteria for precision be based on heparin retention time rather than heparin peak area.

Response: Comment not incorporated. Since the method is also used to demonstrate absence of oversulfated chondroitin sulfate (OSCS), it is important to demonstrate good replicate performance of peak area, not just retention time.
Comment Summary #8: The commenter requested to include a Sensitivity solution containing only OSCS, which will allow for a larger segment of baseline where the noise window requirements specified in General Chapter <621> could be met.
Response: Comment not incorporated. There is enough space around the OSCS peak to calculate a signal-to-noise ratio.
Comment Summary #9: The commenter requested that the concentration of OSCS and dermatan sulfate remain unchanged. This will allow analysts to correctly integrate and identify peaks.
Response: Comment not incorporated. The validation data supports the proposed concentration of OSCS and dermatan sulfate.
Comment Summary #10: The commenter requested updating the column definition for the L61 packing to include the range of particle sizes that are currently available for High Capacity IonPac AS-11 and AG-11 columns.
Response: Comment incorporated. Current L61 definition is indeed specific to AS11 non-high capacity, but includes High Capacity AG-11. USP will assign L81 to High Capacity IonPac AS-11 column.

Heparin Sodium/Identification/Molecular Weight Determinations
The commenter requested including Calibration solution to the list of samples for System suitability.
Response: Comment incorporated.
Comment Summary #11: The commenter requested deleting $\%M_{8000}$ from the Acceptance criteria because it is calculated but not used.
Response: Comment incorporated.
Comment Summary #12: The commenter requested to modifying the Acceptance criteria to include values of 20,000 Da for the upper limit of M_w, changing M_w from 'between 15,000 and 19,000' to '14,000 and 19,000' and NMT 25% for $\%M_{24000}$.
Response: Comment not incorporated. The proposed acceptance criteria were based on the batch data derived from extensive USP led collaborative studies performed by 30 participating laboratories.
Comment Summary #13: The commenter indicated that additional time should be allowed for manufacturers to evaluate and comment on the Molecular Weight Determinations analysis since the reference standard needed for the analysis is not availble.
Response: Comment not incorporated. USP Heparin Sodium Molecular Weight Calibrant RS was released on January 4, 2013 and USP extended the public comment period to accommodate for the RS availability.
Comment Summary #14: The commenter recommended the use of size exclusion chromatography, coupled to multi-angle light scattering (SEC-MALLS) since SEC-MALLS is an absolute measurement. Absolute measurements are made without reference to molar mass standards, column calibration or molecular conformation.
Response: Comment not incorporated. The proposed monograph method is technically simpler than SEC-MALLS and yields improved inter-laboratory reproducibility.

Heparin Sodium/Organic Impurities/Nucleotidic Impurities
No. of Commenters: 8
Comment Summary #15: The commenters requested addressing the integration range used in the method.
Response: Comment not incorporated. Any peaks present in the Blank chromatogram, including a void peak, should be disregarded in the sample. Any unidentified peaks not corresponding to the Blank preparation should be integrated and included.
Comment Summary #16: The commenter requested specifying the integration range used in the method.
Response: Comment not incorporated. Any peaks present in the Blank chromatogram, including a void peak, should be disregarded in the sample. Any unidentified peaks not corresponding to the Blank preparation should be integrated and included.
Comment Summary #17: The commenters requested a widening of the temperature range to 23± 3°C.
Response: Comment not incorporated. The Expert Committee will consider future revisions to the monograph upon the receipt of the necessary supporting data.
Comment Summary #18: The commenter requested keeping the current nucleotidic impurities method, as the new proposed method brings complexity with no additional sensitivity value. Because the current test is not specific, it can monitor other non-nucleotidic impurities absorbing at 260 nm. The new specification is set at 0.1% which is equivalent to 4 times the current specification.
Response: Comment not incorporated. The current test corresponds to a limit of 0.25% and the proposed limit of 0.1% represents a significant decrease when compared to the current limit. The proposed method is precise, specific, accurate, and has a very low detection limit for the determination of DNA in sample solution.
Comment Summary #19: The commenter requested a clarification of why a MW_{ratio} for adenosine must be used during the calculation of the percentage of adenosine. Because the adenosine is already present in the standard solution, a correction does not seem to be necessary.
Response: Comment not incorporated. Because adenosine is used as the reference standard in the Standard solution, the relative response factor (RRF) for adenosine is 1.00. However, a MWratio for adenosine is necessary because adenosine monophophate species is present in DNA.
Comment Summary #20: The commenter requested a lowering of the resolution system suitability requirement for 2'-deoxycytidine and uridine peaks from NLT 1.3 to NLT1.0.
Response: Comment not incorporated. The resolution system suitability requirement was set based on the data from USP led collaborative studies performed by more than 10 participating laboratories.
Comment Summary #21: The commenter requested specifying the final concentration of phosphodiesterase 1 in Units per mL.
Response: Comment incorporated.
Comment Summary #22: The commenters requested that USP provide enzymes as standards and include system suitability requirements to assess enzymatic activity.
Response: Comment not incorporated. The enzymes required for the method are readily available commercially from various vendors.

Heparin Sodium/Organic Impurities/Protein Impurities
No. of Commenters: 8
Comment Summary #23 The commenters requested clarification on when the interfering substance treatment (IST) should be performed on the standard curve and the system suitability standard as well as the samples and spiked samples.
Response: Comment not incorporated. If the IST is used, the treatment must be performed on the standard curve and the system suitability standard as well as the samples and spiked samples.
Comment Summary #24: The commenter recommended rearranging the Analysis section to place the IST procedure at the beginning to more accurately reflect the order of steps in the assay.
Response: Comment not incorporated. The order assumes that the IST is not needed, and only invokes the IST if it is needed.
Comment Summary #25: The commenter requested that a spiked sample for IST system suitability be prepared in water instead of a sample. If a heparin sample contains large amount of protein to begin with, the prepared spiked sample using this heparin sample may cause the system suitability criteria to fail.
Response: Comment not incorporated. Matrix effects from the sample cannot be evaluated by spiking into water for the IST system suitability sample.
Comment Summary #26: The commenter requested revising the procedure to dissolve the protein 'pellet' created by centrifuging the IST sample in water instead of Lowry reagent C.
Response: Comment not incorporated. Dissolving the protein pellet in Lowry reagent C gives the most consistent results.
Comment Summary #27: The commenter indicated that few, if any, manufacturers' products would meet the proposed specifications of 0.1% (w/w) without the removal of interfering substance. Therefore, the commenter requested to keep the current procedure until a method with greater sensitivity and less interference from heparin can be used to assess residual protein contamination.
Response: Comment not incorporated. An assessment was made whether heparin products on the market could meet the lowered 0.1% (w/w) residual protein specification in the proposed Heparin Sodium monograph. That assessment showed that a 0.1% (w/w) residual protein specification was reasonable. The IST is a standard technique that has been used in the area of protein content determination for many years. The IST has been shown to render heparin samples containing interfering substances suitable for assay using the proposed procedure.

Monograph/Section(s): Lumefantrine/Assay
Expert Committee(s): Monographs—Small Molecules 1
No. of Commenters: 1
Comment Summary #1: The commenter requested replacing the temperature gradient across the column with a constant column temperature of 40^{o}.
Response: Comment not incorporated. The Expert Committee will consider further revisions to the monograph upon the receipt of the necessary supporting data**.**

Monograph/Section(s): Memantine Hydrochloride/Multiple Sections
Expert Committee(s): Monographs—Small Molecules 4
No. of Commenters: 5
Comment Summary #1: The commenter requested revising the test for Organic Impurities to include the commenter's procedure.

Response: Comment not incorporated. The Expert Committee will consider further revisions to the monograph upon the receipt of the necessary supporting information.
Comment Summary #2: The commenter requested specifying a new impurity and corresponding limit within the test for Organic Impurities.
Response: Comment not incorporated. The Expert Committee will consider further revisions to the monograph upon the receipt of the necessary supporting information.
Comment Summary #3: The commenter indicated that the impurity profile in the test for Organic Impurities is inconsistent with what has been approved by the FDA.
Response: Comment not incorporated. The impurities and limits are consistent with those of an FDA-approved drug product. The Expert Committee will consider further revisions to the monograph upon the receipt of the necessary supporting data.
Comment Summary #4: The commenter indicated that the test for Organic Impurities lacks adequate selectivity to separate and quantify some process impurities in their manufacturing process.
Response: Comment not incorporated. The Expert Committee will consider further revisions to the monograph upon the receipt of the necessary supporting data.
Comment Summary #5: The commenter requested widening the limit of water content.
Response: Comment not incorporated. The Expert Committee will consider further revisions to the monograph upon the receipt of the necessary supporting data.
Comment Summary #6: The commenter requested adding tests for pH and Color and Clarity.
Response: Comment not incorporated. The Expert Committee will consider further revisions to the monograph upon the receipt of the necessary supporting data.

Monograph/Section(s): Memantine Hydrochloride Tablets/Multiple Sections
Expert Committee(s): Monographs—Small Molecules 4
No. of Commenters: 2
Comment Summary #1: The commenter requested adding a Dissolution test to the monograph.
Response: Comment not incorporated. The Expert Committee will consider further revisions to the monograph upon the receipt of the necessary supporting information.
Comment summary #2: The commenter requested replacing the Assay procedure based on GC with an Assay procedure based on HPLC.
Response: Comment not incorporated. The Expert Committee will consider further revisions to the monograph upon the receipt of the necessary supporting data.
Comment summary #3: The commenter requested revising the preparation of Standard stock solution B to clarify that the use of a volumetric flask is not required within the test for Organic impurities.
Response: Comment incorporated. Additionally, Standard stock solution A and Standard stock solution B were renamed System suitability stock solution A and System suitability stock solution B, respectively, to reflect how these solutions are used in the monograph.

Monograph/ Section(s): Moexipril Hydrochloride/Multiple Sections
Expert Committee(s): Monographs—Small Molecules 2
No. of Commenters: 2
Comment Summary #1: The commenter requested specifying the Sample solution preparation (0.11 g/mL of Moexipril Hydrochloride in alcohol) in the test for Optical Rotation.
Response: Comment incorporated.

Comment Summary #2: The commenter requested revising footnote [b] in Table 2, from 2-methyl-2-propylpropane-1,3-diyl dicarbamate to (3s)-2-{(2s)-n-[(1s)-1-carboxy-3-phenylpropyl]alanyl}-1,2,3,4-tetrahydro-6,7-dimethoxy-3-isoquinolinecarboxylic acid to be consistent with the correct structure.
Response: Comment incorporated

Monograph/ Section(s): Moexipril Hydrochloride Tablets/Organic Impurities
Expert Committee(s): Monographs—Small Molecules 2
No. of Commenters: 1
Comment Summary #1: The commenter requested revising the concentration of Solution A in the test for Organic Impurities from 0.25% trifluoroacetic acid to 0.025% trifluoroacetic acid to be consistent with the validation data.
Response: Comment incorporated.

Monograph/ Section(s): Moexipril Hydrochloride and Hydrochlorothiazide Tablets/Multiple Sections
Expert Committee(s): Monographs—Small Molecules 2
No. of Commenters: 1
Comment Summary #1: The commenter requested revising the nominal concentration of hydrochlorothiazide from 2 mg/mL to 1.5 mg/mL for the 15/12.5 mg tablet strength in the Sample solution within the test for Organic Impurities to be consistent with the validation data.
Response: Comment incorporated.
Comment Summary #2: The commenter requested revising the concentrations of moexipril hydrochloride from 0.006 to 0.06 mg/mL for all tablet strengths and hydrochlorothiaze from 0.01 mg/mL to 0.1 mg/mL for the 7.5 /12.5 and 15/25 mg tablet strengths in the Standard solution within the Assay to be consistent with the validation data.
Response: Comment incorporated.

Monograph/ Section(s): Nimodipine/Assay
Expert Committee(s): Monographs—Small Molecules 2
Expert Committee-initiated change #1: The system suitability requirement for relative standard deviation under Assay is revised from 0.7% to 0.73% to be consistent with the requirements described in General Chapter <621>.

Monograph/Sections: Olanzapine and Fluoxetine Capsules/Organic Impurities
Expert Committee(s): Monographs—Small Molecules 4
No. of Commenters: 1
Comment Summary #1: The commenter requested identifying the degradation products as being related to fluoxetine or olanzapine in Table 1.
Response: Comment incorporated.

Monograph/Section(s): Oxybenzone/Assay
Expert Committee(s): Monographs—Small Molecules 3
Expert Committee-initiated Change #1: The Standard solution and Sample solution within the Assay are prepared using Mobile phase instead of methanol to be consistent with the validation report.
Expert Committee-initiated Change #2: The HPLC column diameter is changed from 4.7 mm to 4.6 mm to be consistent with the validation report.

Monograph/Section(s): Oxygen/Limit of Carbon Dioxide
Expert Committee(s): Monographs—Small Molecules 4
No. of Commenters: 1
Comment Summary #1: The commenter requested retaining a Limit of Carbon dioxide test with an acceptance criterion that is consistent with *USP 36-NF 21*.
Response: Comment incorporated.

Monograph/Section(s): Ropinirole Hydrochloride/Definition
Expert Committee(s): Monographs—Small Molecules 4
No. of Commenters: 1
Comment Summary #1: The commenter requested adding the phrase "solvent-free basis."
Response: Comment not incorporated. The Expert Committee will consider further revisions to the monograph upon the receipt of the necessary supporting data.

Monograph/Section(s): Ropinirole Tablets/USP Reference Standards
Expert Committee(s): Monographs—Small Molecules 4
Expert Committee-initiated Change #1: The chemical name of USP Ropinirole Related compound B RC is revised to include the salt form.

Monograph/Section(s): Selegiline Hydrochloride Capsules/Multiple sections
Expert Committee(S): Monographs—Small Molecules 4
No. of Commenters: 1
Comment Summary #1: The commenter requested revising the Identification test to be based on a chiral HPLC procedure and adding a second Identification test using a different procedure such as FTIR.
Response: Comment not incorporated. The Identification test in the monograph is consistent with an FDA-approved drug product.
Comment Summary #2: The commenter requested including a chiral HPLC procedure and the use of a chiral reference standard.
Response: Comment not incorporated. The procedures in the monograph are consistent with those of an FDA-approved drug product.
Comment Summary #3: The commenter requested tightening the limits within the test for Organic Impurities.
Response: Comment not incorporated. The limits in the monograph are consistent with those of an FDA-approved drug product.

Monograph/Section(s): Sugar Spheres/Assay
Expert Committee(s): Monographs—Excipients
No. of Commenters: 1
Comment Summary #1: The commenter requested the Expert Committee retain the Specific Rotation test as the assay and if an additional identification test is required, that the Ph. Eur. TLC method be considered.
Response: Comments not incorporated. The Expert Committee determined that the validated LC method is an appropriate assay, specifically identifies sucrose from any other carbohydrates, and accurately provides content of sucrose. Furthermore, the proposed LC method is being applied in Compressible Sugar, Confectioner's Sugar, and Sugar Spheres monographs. Incorporating the LC test makes the TLC method unnecessary.

Monograph/Section(s): Temozolomide Oral Suspension/ Multiple Sections
Expert Committee(s): Compounding
No. of Commenters: 1
Comment Summary #1: The commenter suggested including the basis and rationale for using temozolomide capsules 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 suggested including further information regarding control of supply chain for the ingredients used in the monograph preparation.
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 supply chain are outside the scope of this monograph and may be addressed elsewhere in *USP-NF.*
Comment Summary #3: The commenter suggested including drug-specific stability studies and/or general stability documentation used to establish 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 when stored at controlled cold temperature.
Comment Summary #4: The 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 upon the receipt of the necessary supporting data.
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. Procedures under *Definition* were revised to include a note to specify that povidone is required for physical stability of the preparation. Procedures were also added to emphasize the importance of using personal protective equipment while compounding because temozolomide is cytotoxic.
Expert Committee-initiated Change #2: The *Assay* was revised to improve clarity and to fit the redesigned *USP-NF* monograph format. The sample size used for preparing the sample solution was increased to improve accuracy. Suitability requirement revised to include tailing factor of not more than 2.0.

Monograph/Section(s): Thioguanine Tablets/Organic Impurities
Expert Committee(s): Monographs—Small Molecules 3
No. of Commenters: 1
Comment Summary #1: The commenter suggested revising the limits to be consistent with FDA-approved specifications.
Response: Comment not incorporated. FDA-approved specifications do not include limits for organic impurities. The limits are consistent with those in the corresponding British Pharmacopoeia monograph.

Monograph/Section(s): Topiramate Capsules/Dissolution Test 1
Expert Committee(s): Monographs—Small Molecules 4
No. of Commenters: 1
Comment Summary #1: The commenter requested correcting the dimensions of the column used in the HPLC analysis from 25 cm to 15 cm to be consistent the procedure for an FDA-approved drug product.
Response: Comment incorporated.

Monograph/Section(s): Trospium Chloride/Limit of Trospium Chloride Related Compound C
Expert Committee(s): Monographs—–Small Molecules 3
No. of Commenters: 2
Comment Summary #1: The commenter suggested changing the Diluent from water to Mobile phase and increasing the injection volume from 10 µL to 20 µL.
Response: Comment not incorporated. The current procedure is supported by the validation data and is suitable for the analysis.
Comment Summary #2: The commenter requested specifying the sensitivity of the refractive index detector under the description of chromatographic system.
Response: Comment not incorporated. The settings for sensitivity (also known as attenuation) are different for different brands of refractive index detectors and should be optimized by the user.

Monograph/ Section(s): Verapamil Hydrochloride/Assay
Expert Committee(s): Monographs–Small Molecules 2
Expert Committee-initiated change #1: The system suitability requirement for relative standard deviation in the Assay is revised from 0.7% to 0.73% to be consistent with the requirements in General Chapter <621>.