



Commentary

USP 38–NF 33, First Supplement

February 1, 2015

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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Comments were received for the following, when they were proposed in Pharmacopeial Forum

General Chapters:

[<202> Identification of Fixed Oils by Thin-Layer Chromatography](#)

[<203> High Performance Thin-Layer Chromatography Procedure for Identification of Articles of Botanical Origin](#)

[<1010> Analytical Data—Interpretation and Treatment](#)

[<1066> Physical Environments that Promote Safe Medication Use](#)

[<1092> The Dissolution Procedure—Development and Validation](#)

[<1106.1> Immunogenicity Assays-- Design and Validation of Assays to Detect Anti-Drug Neutralizing Antibody](#)

[<1229.11> Vapor Phase Sterilization](#)

[<1663> Extractables Associated with Pharmaceutical Packaging Systems](#)

[<1664> Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery Systems](#)

Monographs:

[Acebutolol Hydrochloride](#)

[Adenine](#)

[Alanine](#)

[Almotriptan Malate](#)

[Almotriptan Tablets](#)

[Amlodipine, Valsartan and Hydrochlorothiazide Tablets](#)

[Anastrozole Tablets](#)

[Bacillus subtilis subsp. subtilis Menoquinone-7 Extract](#)

[Benzocaine Cream](#)

[Benzocain Gel](#)

[Borage Seed Oil Capsules](#)

[Butabarbital Sodium Tablets](#)

[Dipivefrin Hydrochloride](#)

[Dipivefrin Hydrochloride Ophthalmic Solution](#)

[Donepezil Hydrochloride](#)

[Doxazosin Mesylate](#)

[Epirubicin Hydrochloride Injection](#)

[Flax Seed Oil Capsules](#)

[Flumazenil Injection](#)

[Formoterol Fumarate](#)

[Galantamine ER Capsules](#)

[Galantamine Oral Solution](#)

[Hydroxocobalamin](#)

[Hydroxyzine Pamoate](#)

[Imiquimod Cream](#)

[Levetiracetam Injection](#)

[Levocetirizine Dihydrochloride](#)

[Lidocaine Hydrochloride Oral Topical Solution](#)

[Lidocaine Hydrochloride Topical Solution](#)

[Menoquinone-7](#)

[Menoquinone-7 Preparation](#)

[Metaxalone](#)

[Metronidazole Tablets](#)

[Minocycline Hydrochloride ER Tablets](#)

[Naproxen Sodium Tablets](#)

[Naproxen Tablets](#)

[Niacin](#)

[Norelgestromin](#)

[Norfloxacin](#)

[Phenytoin Sodium](#)

[Repaglinide](#)

[Tetracaine](#)

[Tienchi Ginseng Root and Rhizome](#)

[Tienchi Ginseng Root and Rhizome Dry Extract](#)

[Tienchi Ginseng Root and Rhizome Powder](#)

**No comments received for the following, when they were proposed in
Pharmacopeial Forum**

General Chapters

<161> Transfusion and Infusion Assemblies and Similar Medical Devices
<361> Barbiturate Assay
<789> Particulate Matter in Ophthalmic Solutions
<1064> Identification of Articles of Botanical Origin using HPLC Procedure
<1160> Pharmaceutical Calculations in Prescription Compounding
<1664.1> Orally Inhaled and Nasal Drug Products

Monographs:

Amlodipine Besylate Tablets	Levocarnitine Injection
Amobarbital Sodium for Injection	Menaquinone-7 Capsules
Antipyrine	Menaquinone-7 Tablets
Benzocaine	Metaxalone Tablets
Buprenorphine Compounded Buccal Solution, Veterinary	Methylcobalamin
Butabarbital Sodium Oral Solution	Metronidazole Injection
Cefotaxime Sodium	Milrinone
Cromolyn Sodium Inhalation Solution	Potassium Metaphosphate
Cromolyn Sodium Nasal Solution	Safflower Oil
Diclofenac Sodium and Misoprostol DR Tablets	Sunflower Oil
Dinoprostone	Selegiline Compounded Topical Gel
Diphenoxylate Hydrochloride	Tadalafil Compounded Oral Suspension
Esmolol Hydrochloride	Temazepam
Estradiol Cypionate	Tetracaine Hydrochloride
Ethyl Acetate	Ticarcillin Disodium
Flumazenil	Ticarcillin Monosodium
Ibutilide Fumarate	Tramadol Hydrochloride Compounded Oral Suspension, Veterinary
Indomethacin	Tropicamide
Indomethacin Suppositories	Urea C13 for Oral Solution
Isoniazid	Voriconazole Compounded Ophthalmic Solution, Veterinary
Levalbuterol Hydrochloride	Zonisamide Compounded Oral Suspension

General Chapter/Section(s): <202> Identification of Fixed Oils by Thin-Layer Chromatography/Identification
Expert Committee(s): General Chapters—Chemical Analysis
Expert Committee-Initiated Change #1: The Expert Committee changed the plate information from “10 cm × 20 cm” to “20 cm × 10 cm” in *Method I*.

Monograph/Section(s): <203> High Performance Thin-Layer Chromatography Procedure for Identification of Articles of Botanical Origin/Procedure

Expert Committee: General Chapters—Chemical Analysis

No. of Commenters: 1

Comment Summary: The commenter requested that the application volume be specified for improved clarity and to provide for the integrity of the samples applied during the plate drying.

Response: Comment incorporated. The requirements for the sample application and development of the plate were modified to provide clarity.

General Chapter/Section(s): <1010> Analytical Data—Interpretation and Treatment/Multiple Sections

Expert Committee(s): General Chapters—Statistics

No. of Commenters: 2

Introduction

Comment Summary # 1: The commenter indicated that the usage of the definition “Equivalence testing” may be misleading and should not be mixed with the definition of an equivalent analytical procedure.

Response: Comment not incorporated. Equivalence testing is an appropriate statistical test we propose for comparison of two analytical procedures or the same analytical procedure before and after transfer. The General Chapter states, “The goal of a method procedure comparison experiment is to generate adequate data to evaluate the equivalency of the two procedures over a range of concentrations.”

Comment Summary # 2: The commenter suggested modifying the reference to final-product testing, because it appears to exclude real time or parametric release.

Response: Comment not incorporated. The Expert Committee determined that a reference to final-product testing does not exclude real time or parametric release.

Use of Reference Standards

Comment Summary # 3: The commenter suggested deleting the second sentence, because it is redundant with the information in *General Notices* 5.80.

Response: Comment not incorporated. While the sentence is similar to what is stated in *General Notices* 5.80, the concept is important and worth reiterating here. From USP’s perspective, conformance can only be assured with the use of USP procedures and reference standards.

Comment Summary # 4: The commenters recommended clarifying the use of secondary reference standard.

Response: Comment not incorporated. USP clarified both here and in *General Notices* 5.80, that from USP's perspective, conformance can only be conclusively demonstrated using a USP reference standard. It is up to the user to decide whether they are comfortable using secondary standards or other approaches to achieve compliance.

Outlying Results

Comment Summary # 5: The commenter suggested indicating that not all investigations will require a process or manufacturing review or investigation.

Response: Comment incorporated.

Comparison of Analytical Procedures

Comment Summary # 7: The commenter suggested replacing the phrase "over a range of concentrations" with "over a range of responses (or values)," because the current phrase is too restrictive for the General Chapter considerations.

Response: Comment incorporated

Appendix F: Equivalence Testing and TOST

Comment Summary # 6: A commenter suggested including an example of calculations for Equivalence Testing and TOST.

Response: Comment not incorporated; however, the Expert Committee may incorporate this information in a future revision.

General Chapter/Section(s):	<1066> Physical Environments that Promote Safe Medication Use/Multiple Sections
Expert Committee(s):	Nomenclature, Safety, and Labeling
No. of Commenters:	2

Framework

Comment Summary #1: The commenter suggested that a framework/figure be added to organize and focus reader thoughts.

Response: Comment not incorporated. The Expert Committee found that a graphic would not add value to the content.

Comment Summary #2: The commenter suggested adding adverse event information in the General Chapter to provide the reader with a sense of the enormous issue of medication safety.

Response: Comment not incorporated. This topic is currently being addressed by the National Coordinating Council for Medication Error Reporting and Prevention.

Medication Safety Zone

Comment Summary #3: The commenter requested that sharps disposal containers be included in the General Chapter and raised several concerns regarding the ability to include information on exceptionally small labels.

Response: Comment partially incorporated. A reference to *Code of Federal Regulations* guidance for space limitations has been added.

Tools and Technology in the Physical Environment

Comment Summary #4: The commenter suggested relocating evidence-based sections that pertain to the physical environment in the *Tools and Technology in the Physical Environment* section.

Response: Comment not incorporated. *Principles from Human-Factors Research* are a justification and framework for the whole report, and should not be its own section.

Comment Summary #5: A commenter suggested that a link to the Center for Health Design be included as a reference.

Response: Comment incorporated.

Evidence-Based Design

Comment Summary #6: The commenter suggested a different definition for evidence-based design.

Response: Comment not incorporated. The Expert Committee found that the definition for evidence based design provided in the General Chapter is more robust than the one proposed by the commenter.

Challenges in the Physical Environment

Comment Summary #7: A commenter requested that a figure depicting each phase of the medication use cycle be added to aid non-practitioners.

Response: Comment not incorporated. The Expert Committee determined that this information would not be appropriate for this General Chapter.

Physical Environmental Factors

Comment Summary #8: A commenter requested new references for illumination, noise, and sound.

Response: Comment not incorporated. The references in the General Chapter were removed according the USP Style Guide.

Sound and Noise

Comment Summary #9: The commenter requested that the standard for sound levels in medication safety zones be set at 45 decibels.

Response: Comment incorporated.

General Chapter/Section(s): <1092> The Dissolution Procedure—Development and Validation/Multiple Sections

Expert Committee(s): General Chapters—Dosage Forms

No. of Commenters: 12

Scope

Expert Committee-initiated Change #1: A statement was added which indicates that recommendations are given with the understanding that modifications of apparatus or procedures in USP general chapters need to be justified.

Expert Committee-initiated Change #2: The procedure for determining in-vitro performance of the dosage form will be termed the “dissolution procedure” replacing the term, “dissolution method.”

1. Preliminary Assessment (For Early Stages of Product Development/Dissolution Method Development)

Comment Summary #1: The commenter suggested reordering the information in this section based on the relationship of filter compatibility to the selection of apparatus and medium.

Response: Comment not incorporated. The operations discussed in this section are interrelated and the order given in this section is not intended to dictate a specific approach.

1.1 Performing Filter Compatibility

Comment Summary #2: The commenter requested giving consideration to concentration range in filter compatibility studies and acknowledgment to the fact that interference is not necessarily dependent on drug concentration.

Response: Comment incorporated.

Comment Summary #3: The commenter indicated that filtration removes undissolved material that may otherwise interfere with the measurement rather than the procedure.

Response: Comment incorporated. The measurement is part of the analytical finish.

Comment Summary #4: The commenter suggested replacing the phrase “should be evaluated” with “should be considered” with respect to adsorptive interference by the filter.

Response: Comment not incorporated. Consideration of adsorptive interference implies that it is evaluated at some level.

Comment Summary #5: The commenter suggested replacing the words “filter size” with the word “size” as a characteristic used in selecting filters.

Response: Comment incorporated.

Comment Summary #6: The commenter requested reducing the upper pore size for filters from 70 µm to 5 µm.

Response: Comment not incorporated. Change of the upper pore size limit may be considered in a future revision upon receipt of the necessary supporting data.

Comment Summary #7: The commenter requested deletion of the reference to centrifuged solution as a comparator for filter interference purposes.

Response: Comment not incorporated. Centrifugation can promote additional dissolution of the drug causing disparity with the filtered solution concentration. Within the same section the sample solution is described as having the drug load dissolved completely.

Comment Summary #8: The commenter requested removing the statement which indicates that the filter cannot adsorb the drug.

Response: Comment incorporated.

1.2 Determining Solubility and Stability of Drug Substance in Various Media

Comment Summary #9: The commenter requested examples of the cases when drug solubility must be performed at room temperature.

Response: Comment partially incorporated. The wording was changed to indicate that solubility of the drug may be necessary at temperatures other than 37°.

Comment Summary #10: The commenter requested definition for the phrase “poorly soluble drug.”

Response: Comment partially incorporated. The phrase was removed in recognition that the use of surfactants is intended to enhance the solubility of the drug in the dissolution medium.

Comment Summary #11: The commenter requested a definition of the term “critical micelle concentration (CMC).”

Response: Comment not incorporated. The concept is beyond the scope of this General Chapter and that information is readily available elsewhere.

Comment Summary #12: The commenter requested additional information on the purity of the surfactant used.

Response: Comment not incorporated. A paragraph is provided that warns of possible issues related to the purity or grade of the surfactant used. This information serves to alert the laboratory to possible concerns in the use of surfactants.

Comment Summary #13: The commenter requested modification of the description of solubility determination to include kinetic solubility after 3 hours.

Response: Comment not incorporated. Equilibrium solubility is the measure of the physical chemical limit to dissolution. Specifying other time frames or approaches would be overly prescriptive and burdensome.

Comment Summary #14: The commenter requested inclusion of the procedure used in determining the reported values of surfactant CMC.

Response: Comment partially included. The observed CMC of a surfactant is affected by experimental conditions. References are included in Table 1 to provide access to the experimental conditions. The text has been changed to note that the CMC values given are approximate.

Comment Summary #15: The commenter requested that the entry, “Polysorbate 80 (Polyoxyethylene (80) sorbitan monooleate, Tween 80,” should be “Polysorbate 80 (Polyoxyethylene (20) sorbitan monooleate, Tween 80).”

Response: Comment incorporated.

Comment Summary #16: The commenter indicated that room temperature should be 25° and not 20°.

Response: Comment incorporated.

Comment Summary #17: The commenter requested inclusion of information on the rationale for the use of physiological surfactants.

Response: Comment partially included. This information can be found in paragraph 3 of *Section 1.3 Choosing a Medium and Volume*.

Comment Summary #18: The commenter requested the addition of Triton X to *Table 1*.

Response: Comment incorporated.

Comment Summary #19: The commenter suggested that solubility studies should be carried out for not less than 24 hours unless equilibrium is observed sooner.

Response: Comment not incorporated. Equilibrium solubility is the measure used for determining solubility and specific time limits may be too restrictive.

Expert Committee-initiated Change #3: The text was modified to indicate that alternative approaches for solubility determination may be used.

Expert Committee-initiated Change #4: The statement on the time requirements under the conditions of the test was revised to specifically indicate that this is related to the stability of the drug substance.

1.3 Choosing a Medium and Volume.

Comment Summary #20: The commenter requested more information on the determination of sink conditions.

Response: Comment not included. The definition of sink conditions is provided in Section 1.3 *Choosing a Medium and Volume*.

Comment Summary #21: The commenter suggested that the final concentration of the surfactant used in the dissolution medium should be supported by experimental results using varying concentrations.

Response: Comment incorporated.

Comment Summary #22: The commenter indicated that the units, C, should be included whenever a temperature is given.

Response: Comment not incorporated. *General Notices, Section 8.180 Temperatures* makes clear that temperatures are expressed in centigrade (C) degrees.

Comment Summary #23: The commenter indicated that the characterization of the physical and chemical properties of the drug substance happens as part of the selection of the proper dissolution medium and not before.

Response: Comment incorporated.

Comment Summary #24: The commenter requested including reasons that would justify violating sink conditions.

Response: Comment partially incorporated. *Section 2.6 Dissolution Procedure Assessment* provides the objectives of the dissolution procedure and justification for medium selection where sink conditions may be violated.

Comment Summary #25: The commenter requested inclusion of the solubility limits that would justify the use of surfactants.

Response: Comment partially included. The solubility data and dissolution profiles are used to justify the use of a particular surfactant and the concentration employed.

Comment Summary #26: The commenter indicated that discriminatory power is coupled with solubility and stability as an attribute of dissolution medium composition and volume.

Response: Comment not incorporated. While the medium volume and composition contribute to discriminatory power, discriminatory power is an attribute of the dissolution procedure as a whole.

Comment Summary #27: The commenter requested the removal of 900 mL mentioned as the most common volume used.

Response: Comment incorporated.

Comment Summary #28: The commenter requested the use of a more inclusive term than HPLC in recognition of the development of UPLC.

Response: Comment partially incorporated. A statement was added indicating that HPLC can be considered for the purposes of this General Chapter to include UPLC and other liquid chromatographic approaches.

Expert Committee-initiated Change #5: The text was modified to indicate that where enzymes are used in the dissolution medium, validation should be performed according to Section 5. *Validation*.

Expert Committee-initiated Change #6: The usefulness of an acid stage test for the detection of enteric-coating failure is compromised when the solubility of the drug in acid media is less than 10% of label claim or when the drug degrades in acid media.

1.4 Choosing an Apparatus

Comment Summary #29: The commenter indicated that Apparatus 3 is not used for rapidly disintegrating formulations.

Response: Comment not incorporated. This use for Apparatus 3 is not described for rapidly disintegrating formulations.

Comment Summary #30: The commenter requested the addition of pediatric granules to the list of dosage forms for which Apparatus 4 is useful.

Response: Comment incorporated.

Comment Summary #31: The commenter requested the addition of stents and implants to the list of dosage forms tested by Apparatus 4.

Response: Comment partially incorporated. The list begins with the phrase “such as” to indicate that the dosage forms listed are only examples from a larger set.

Comment Summary #32: The commenter suggested that elimination of coning should be removed as the reason to resort to peak vessels.

Response: Comment incorporated.

2. Method Development

Comment Summary #33: The commenter requested the removal of the sentence “One guidance defines dissolution results as highly variable if the relative standard deviation (RSD) is more than 20% at time points of 10 min or less and more than 10% at later time points for a sample size of 12.”

Response: Comment not incorporated. The reference is accurate.

2.2 Sinkers

Comment Summary #34: The commenter indicated that the text should state that the sinker “should not be too tight” rather than “wound too tightly” and that the reason is not that it will restrict a disintegrating release mechanism, but that it will “restrict interaction with the medium.”

Response: Comment incorporated.

2.3 Agitation

Comment Summary #35: The commenter requested clarification of the statement that elements should conform with the requirements and specifications of General Chapter <711> when appropriately calibrated.

Response: Comment incorporated. The sentence was removed as it was seen not to add value to the General Chapter.

Comment Summary #36: The commenter requested changing the statement on flow rates for Apparatus 4 to state the flow rates given in <711> and to mention the capability of the pump to conform to the requirements in <711> as a limitation for other flow rates.

Response: Comment incorporated.

Comment Summary #37: The commenter requested revision of the discussion of the flow patterns in Apparatus 4.

Response: Comment incorporated. Reference to the scientific literature is given for the flow characteristics. The descriptive terms for the flow-through cell with and without glass beads replaced the more detailed discussion of flow characteristics.

Comment Summary #38: The commenter suggested that the lower limit of 50 rpm should be deleted.

Response: Comment partially included. The phrase “used most commonly” was changed to “used commonly” in connection with rotation speeds for Apparatus 1 and 2.

2.4 Study Design

Comment Summary #39: The commenter indicated that f2 similarity factor is used for profiles with mean percent dissolved (n=12) below 85% for at least two time points.

Response: Comment incorporated.

Comment Summary #40: The commenter requested clarification of the BCS classes for which the use of dissolution profile comparisons by the f2 similarity factor is not necessary for rapidly dissolving products.

Response: Comment partially included. A general statement was included that the f2 similarity factor may not be useful where 85% is dissolved in less than 15 minutes.

Comment Summary #41: The commenter recommended clarification that the percentages released discussed in this section are not in terms of Q.

Response: Comment not incorporated. Q is discussed in Section 6. *Acceptance Criteria*.

Comment Summary #42: The commenter recommended that the phrase “very rapidly dissolving” be used for products that dissolve more than 85% in not more than 15 minutes.

Response: Comment incorporated.

Comment Summary #43: The commenter recommended that f2 can be used where at least two time points with not more than 85% is dissolved and only one time point where more than 85% is dissolved for either test or reference. This would conform with the European Medicines Agency’s requirements.

Response: Comment not incorporated. The reference given for the statement conforms to FDA guidance.

Expert Committee-initiated Change #7: The text was modified to indicate that the selection of the agitation rate or other study design element should conform to the requirements and specifications in <711>.

Expert Committee-initiated Change #8: The phrase “is not necessary” was changed to “may not be useful” in the discussion of the use of the f2 similarity factor when more than 85% is dissolved in 15 minutes or less.

2.4.3 Sampling

Comment Summary #44: The commenter requested giving an additional allowance for sampling devices and their materials of construction.

Response: Comment incorporated. A revision was made to include allowance of chemically inert sampling devices and cannulas. Materials of construction include polymers.

Comment Summary #45: The commenter recommended that the sampling site for Apparatus 1 and 2 should focus on consistent sampling instead of reliance on specifications in <711>.

Response: Comment partially incorporated. The section on *Scope* was modified to indicate that general recommendations are given in the General Chapter with the understanding that modifications of the apparatus and procedures in <711> or other general chapters need to be justified.

2.4.4 Cleaning

Comment Summary #46: The commenter requested including guidance on an appropriate cleaning solution.

Response: Comment not incorporated. Cleaning solutions should be matched to the conditions. Providing a specific product or formula could be restrictive.

2.5 Data Handling

Comment Summary #47: The commenter recommended changing the statement that for the purposes of in vivo correlation, “dissolution data may need a fit to mathematical models” to “may need to fit mathematical models.”

Response: Comment partially incorporated. The section was revised to state, “parameters of mathematical models are obtained by fitting to dissolution data.”

Comment Summary #48: The commenter recommended the addition of a qualifying statement that the amount of drug removed at earlier time points is accounted in calculation only if significant.

Response: Comment partially incorporated. A statement was added that states: “the total amount removed at earlier time points should be assessed and may be part of the calculation of the amount dissolved, if considered important.”

Comment Summary #49: The commenter indicated that the plots shown in Figures 1 and 2 are only observed if sampling intervals are very small.

Response: Comment partially incorporated. The figure captions are revised to indicate that the plots presented are examples.

Comment Summary #50: The commenter indicated that the y-axis label for Figure 2 should be dC/dt .

Response: Comment partially incorporated. The caption is revised to indicate that the concentration is proportional to the instantaneous dissolution rate.

Comment Summary #51: The commenter recommended that the term “LC,” meaning label claim, should be spelled out to avoid confusion with the term “liquid chromatography.”

Response: Comment incorporated.

2.6 Dissolution Procedure Assessment

Comment Summary #52: The commenter suggested that stressed samples can be used to challenge the discriminatory power of the dissolution procedure.

Response: Comment incorporated.

Comment Summary #53: The commenter recommended that “discrimination” be clarified to mean adequate to assess product quality.

Response: Comment incorporated. In addition, the words “discriminating” and “discriminatory” were replaced with the words “sensitive” and “sensitivity.”

Comment Summary #54: The commenter recommended additional clarification of the phrase “unacceptable degree of variability.”

Response: Comment not incorporated. Variability is discussed under Section 2. *Method Development* with a reference to FDA guidance.

3.4 Analytical Procedures

Comment Summary #55: The commenter requested clarification of the statement, “Modern HPLC systems employ autosamplers than may reduce speed and simplicity advantages of spectrophotometric analysis.”

Response: Comment incorporated. The sentence was revised to indicate that HPLC systems employ autosamplers that provide speed and simplicity advantages comparable to spectrophotometric analysis.

3.5 Spectrophotometric Analysis

Comment Summary #56: The commenter requested that less prescriptive wording be used to describe the sequence of standard, sample, and blank measurements for spectrophotometric analysis.

Response: Comment not incorporated. The sentence is given as a recommendation using the wording, “may be analyzed in a sequence.”

Comment Summary #57: The commenter recommended reorganization of the sentence speaking to the use of the isosbestic point in spectrophotometric analysis so that the example, aspirin, is associated with the substance that may degrade in the medium and not a particular isosbestic point.

Response: Comment incorporated.

Comment Summary #58: The commenter suggested clarification of the statement that in spectrophotometric analysis, standard solutions are used at a single concentration, while in analysis of dissolution profiles or of products of differing strength, multiple concentrations of the standard may be required.

Response: Comment incorporated. A single concentration of the standard solution may be used where the linearity of the analytical finish has been established. However, prior to validation for profile analysis or for analysis of multiple strengths of product, multiple standard solutions covering the expected range of concentrations are used.

Expert Committee-initiated Change #9: Recognition that fiber optic instruments can be used for the analysis during dissolution testing was added.

3.6 HPLC

Comment Summary #59: The commenter indicated that for HPLC analysis no necessity exists for the organic content of the standard solution solvent to match that of the sample.

Response: Comment incorporated. The wording “small amounts of an organic solvent” was changed to “organic solvent.”

4. Automation

Comment Summary #60: The commenter requested clarification of the deviations from the standard procedure described in <711>.

Response: Comment partially incorporated. A statement was added under *Scope* indicating that the General Chapter provides recommendations with the understanding that modifications of the apparatus and procedures given in other USP general chapters need to be justified.

Comment Summary #61: The commenter requested removing the reference to open or closed loop in connection with the discussion of the complexity for automation.

Response: Comment not incorporated. All of the factors listed effect the complexity of the automation.

Comment Summary #62: The commenter suggested that elements that apply generally, as well as to automated systems, should be moved from special placement in the Section 4. *Automation*.

Response: Comment incorporated. Several sentences and paragraphs were moved from Section 4. *Automation* to other places in the General Chapter.

4.1 Medium Preparation

Comment Summary #63: The commenter indicated that the evaluation of the chemical and physical stability of dissolution medium concentrates is not part of method validation.

Response: Comment incorporated.

Comment Summary #64: The commenter indicated that medium deaeration is not a special concern for automated systems.

Response: Comment partially incorporated. If deaeration of the medium is required, the level should be specified.

Comment Summary #65: The commenter suggested that automated media preparation systems dispense media monitoring by volume as well as by weight.

Response: Comment incorporated.

4.2 Sample Introduction and Timing

Comment Summary #66: The commenter requested eliminating the reference to the 2% pharmacopeial timing tolerance.

Response: Comment not incorporated. The statement is accurate. No other timing tolerance is given in <711>.

4.3 Sampling and Filtration

Comment Summary #67: The commenter requested clarification of the relative inertness of glass and polymeric sampling devices and whether cross validation is necessary.

Response: Comment partially incorporated. No preference of material for equipment construction is given, but glass and polymeric materials are mentioned as examples. More considerations for automation is given under Section 5. *Validation*.

Comment Summary #68: The commenter recommended that metal contamination is not only a concern for automated systems.

Response: Comment incorporated. Some of this information was moved to the more general section *Method Development*.

Comment Summary #69: The commenter requested removing the statement that contamination by leachables may affect complex media containing organic solvents.

Response: Comment incorporated.

Comment Summary #70: The commenter suggested that the discussion of the need to compensate in calculations for the volume change due to sampling should be deleted.

Response: Comment not incorporated. A reference was added to Section 2.5 *Data Handling* in which the subject is discussed with new detail.

Comment Summary #71: The commenter recommended removal of the statement that hollow shaft sampling apertures should have adjustable inlet depth.

Response: Comment not incorporated. The overarching statement under *Scope* indicates that a modification of the apparatus in USP general chapters needs to be justified.

4.4 Cleaning

Comment Summary #72: The commenter requested clarifying that cleaning is not an issue for automation alone.

Response: Comment incorporated. A new sub-section 2.4.4 *Cleaning* under *Method Development* discusses cleaning as a general concern.

5. Validation:

Comment Summary #73: The commenter indicated that validation studies address variations associated with different profile time points.

Response: Comment incorporated.

Comment Summary #74: The commenter recommended that the text be revised to indicate that the validation of assessments of filter suitability and potential for glass adsorption “may occur” during spiked recovery experiments, rather than being necessary.

Response: Comment incorporated.

Expert-Committee-initiated Change #10: The dissolution step was differentiated from the analytical finish as separate components of the dissolution procedure requiring consideration during validation.

Expert-Committee-initiated Change #11: The section was modified to indicate that validation of the analytical finish will evaluate linearity and range, precision, specificity, accuracy/recovery, robustness, and stability of the sample and standard solutions. Validation of the dissolution step will involve precision and robustness of the sample preparation.

Expert-Committee-Initiated Change #12: The text was revised to indicate that a standard solution, spiked placebo, or the method of standard addition is used in validation of the analytical finish. A well-characterized dosage form is used for the validation of the dissolution step.

5.1 Specificity/Placebo Interference

Comment Summary #75: The commenter suggested clarifying that placebo interference should not exceed 2% of label claim.

Response: Comment not incorporated. The formula given for placebo interference gives the result in percentage of label claim.

Comment Summary #76: The commenter suggested for UV analysis, and if the sample and standard are dissolved in dissolution medium, the blank absorbance will not be significant. If this is not the case, as with multi-stage dissolution tests, the blank absorbance will need to be understood.

Response: Comment not incorporated. The section notes the possibility that the blank will contribute to the absorbance of the sample or standard solution and provides limits.

Comment Summary #77: The commenter requested the inclusion of additional types of data transformations when approaching issues with interference to spectrophotometric analysis from suspended particulates in sample solutions.

Response: Comment incorporated.

Comment Summary #78: The commenter indicated that the information on specificity and placebo interference is focused on spectrophotometric analysis.

Response: Comment incorporated. Other analytical techniques have been added as examples.

Comment Summary #79: The commenter requested recognition of the influence of the dissolution process on concentration of dissolved placebo components.

Response: Comment incorporated.

5.2 Linearity and Range

Comment Summary #80: The commenter requested replacing the word “significantly” with “importantly” when describing the difference of the y-intercept from zero.

Response: Comment not incorporated. The word “significantly” implies a statistical inference that may misrepresent the importance of a difference especially in the case of precise data.

Comment Summary #81: The commenter indicated that the discussion of linearity limits only mentions the limitations associated with high concentrations.

Response: Comment incorporated. The wording now mentions a concentration range limited by the linearity of the method including instrumentation.

5.3 Accuracy/Recovery

Comment Summary #82: The commenter requested specifics in connection with the lowest concentration range where the limit of NMT 10% in the Acid Stage testing in <711> is effective.

Response: Comment partially incorporated. The wording was revised to acknowledge the need to address case-by-case recovery experiments, such as for acid stage testing where the drug has low solubility.

Comment Summary #83: The commenter recommended removing the mention of the use of organic solvents to enhance drug solubility for accuracy/recovery experiments.

Response: Comment partially incorporated. The text was revised to state that solutions may be directly prepared in dissolution medium and alternatively from less than 5% organic solvent.

Comment Summary #84: The commenter requested an example of an accuracy/recovery experiment for acid stage testing of a delayed-release product where the drug is poorly soluble.

Response: Comment partially incorporated. The text was revised to indicate that such situations may need to be addressed case-by-case. Providing a specific example is outside the scope of the General Chapter and may be misinterpreted as a restrictive recommendation.

Comment Summary #85: The commenter requested a recommendation on the conditions of the recovery experiments. Are they conducted in the dissolution vessel with a stirring element turning?

Response: Comment incorporated. Like the linearity experiments, accuracy/recovery is evaluated using spiked placebo or the method of standard addition.

Comment Summary #86: The commenter suggested that a range of recovery greater than from 95% to 105% of the amount added may be appropriate for low concentrations.

Response: Comment partially incorporated. The range given is longstanding in the General Chapter. The added case-by-case recommendation for drugs poorly soluble in acid stage media can subsume other situations where concentrations are low.

5.4 Precision

Comment Summary #87: The commenter recommended updating the repeatability criteria for UV and HPLC analysis.

Response: Comment incorporated.

Comment Summary #88: The commenter requested a statement that the use of a finished drug product in repeatability studies is due to the added error from inherent product variability.

Response: Comment partially incorporated. The first sentence was reworded to state, "For the analytical finish, repeatability is evaluated by obtaining replicate measurements of standard and/or spiked placebo/standard addition solution." In addition, a sentence was added that states, "The demonstration of the repeatability for the dissolution step is conducted by performing the dissolution step on separate units of a well-characterized dosage form or equivalent composite."

Comment Summary #89: The commenter recommended adding a statement that the design of experiments approach during investigation of intermediate precision may help to identify interaction effects not observed in single variable experiments.

Response: Comment incorporated.

Comment Summary #90: The commenter suggested mentioning that a well-characterized lot of product will result in uniform dissolution performance, in addition to having tight content uniformity.

Response: Comment incorporated.

Comment Summary #91: The commenter requested a literature citation for the ruggedness criteria that the difference of the means is not more than 10% for results less than 85% and not more than 5% for results greater than 85%.

Response: Comment not incorporated. These criteria have been part of the General Chapter since its original adoption.

Expert-Committee-initiated Change #13: The text was revised to indicate that the dissolution step is assumed to be the major contributor to variability of the results and therefore may be part of the study of the effect of random events on the results of the dissolution procedure.

Expert-Committee-initiated Change #14: The text was revised to indicate that the use of a spiked placebo could be used in the assessment of the contribution of the analytical finish on the variability observed for the results.

5.5 Robustness

Comment Summary #92: The commenter recommended criteria for robustness.

Response: Comment not incorporated. The addition of such criteria would require publication for comment in *Pharmacopeial Forum* and may be considered for a future revision.

Comment Summary #93: The commenter requested clarification of the term “well-characterized lot of drug product.”

Response: Comment incorporated. In addition to having tight content uniformity, a well-characterized lot will have uniform in-vitro performance.

5.6 Stability of Standard and Sample Solutions

Comment Summary #94: The commenter requested details on the range of dissolution medium temperature that might be employed as a robustness parameter.

Response: Comment not incorporated. While a range of 36.5° to 37.5° is typical for such studies, presenting this range would require concomitant ranges for the other possible robustness parameters and be misinterpreted to be prescriptive.

Comment Summary #95: The commenter suggested that physical stability is a concern and that modifiers can be added to increase stability of the standard or sample.

Response: Comment not incorporated. Physical stability is addressed under Section 2. *Method Development*.

5.7 Considerations for Automation

Comment Summary #96: The commenter suggested that the interaction between excipients, dissolution media, and the apparatus, as well as the issue of carryover are not only a concern for automated systems.

Response: Comment not incorporated. The statements made are true with respect to automated systems.

6. Acceptance Criteria

Comment Summary #97: The commenter requested clarification on the inclusion of stability study data or data from aged samples within the context of historical data.

Response: Comment incorporated.

6.4 Multiple Dissolution Tests

Comment Summary #98: The commenter recommended clarification that if multiple dissolution tests appear in a monograph, product meeting Test 1 is not required to state this in its labeling.

Response: Comment incorporated. Although incorporated in this section, the information is also found in *General Notices*, section 4.10.11.

6.5 Interpretation of Dissolution Results

Comment Summary #99: The commenter recommended removal of this section, because this information is already found in <711>.

Response: Comment not incorporated. The commenter did not identify specific errors. USP receives a number of queries that evidence the lacking understanding of the information in the dissolution General Chapter. Although the *Interpretation* section in <711> is clear to many readers, the additional detailed treatment in General Chapter <1092> is intended to explain the approach and provide clarity to others.

Comment Summary #100: The commenter indicated that a disparity occurs in Section 6.5.1 *Immediate-Release Dosage Forms* among the presentation of criteria as equivalent percentage of label claim and total mg released.

Response: Comment incorporated.

Comment Summary #101: The commenter recommended clarification that the staged approach using three levels in the dissolution test is applied later in product development.

Response: Comment incorporated.

General Chapter/Section(s):	<1106.1> Immunogenicity Assays—Design and Validation of Assays to Detect Anti-Drug Neutralizing Antibody/Multiple Sections
Expert Committee(s):	General Chapters—Biological Analysis
No. of Commenters:	3

Introduction and Scope

Comment Summary #1: The commenter requested that reference(s) be added to support the sentence mentioning anti-drug antibodies (ADA's) that affect drug clearance.

Response: Comment incorporated. Two references were added to the *Appendix* and noted in the *Introduction and Scope* section (see book chapter by M. Subramanyam and paper by Zhou et al.).

Comment Summary #2: The commenter requested the following text revision, "Another important consideration in selecting the assay format is the degree of risk to patient safety that NAb formation would pose; thus, for therapeutics where Ab pose a high risk to patients, the assay format should be sufficiently sensitive for detecting clinically relevant NAbs."

Response: Comment incorporated.

Factors that Influence the Development of Neutralizing Antibodies

Comment Summary #3: The commenter requested the following text revision, "As the immune response matures, more epitopes of the therapeutic protein may be recognized by ADAs leading to an increased possibility of NAbs, as epitopes within the active region of the therapeutic protein may be recognized."

Response: Comment incorporated.

Determination of Preclinical and Clinical Immunogenicity

Comment Summary #4: The commenter asked for deletion of the second paragraph, because ICH S6 (R1) states that characterization of neutralizing potential is only warranted in the absence of a pharmacodynamic (PD) marker.

Response: Comment partially incorporated. The paragraph was not deleted, because the suggestions are stated as "should" and are not requirements; however, a qualifier was added as shown by the underlined text, "If confirmation that the PD marker is due to the presence of NAb is desired then this can be confirmed with a NAb assay as a surrogate..."

Risk-based Approach to Assessing Neutralizing Antibodies and Their Consequences

Comment Summary #5: The commenter requested modifying the sentence with the underlined text, " Potential assay formats are selected based on MoA on a case-by-case basis with proper consultation with regulatory agencies when needed, while the analytical (or immunogenicity assessment) strategy is driven by the risk of immunogenicity for the specific therapeutic."

Response: Comment incorporated.

Comment Summary #6: Three commenters requested consolidating almost identical statements in the fourth paragraph regarding therapeutics against humoral targets.

Response: Comments incorporated. The first sentence was modified to state, " For antagonistic therapeutics (e.g., anti-IgE or anti-coagulation factors), some regulatory agencies have accepted non-cell-based competitive ligand binding assays for detection of NAb that are directed against therapeutics with humoral targets." The last sentence of the paragraph was also deleted.

Design of NAb Test Methods

Comment Summary #7: The commenter requested that the "b" in the title *Design of NAb Test Methods* be lower case.

Response: Comment incorporated.

Comment Summary #8: The commenter requested that Table 1 be reformatted, because they could not see the entire last column.

Response: Comment not incorporated. The compendial file shows all the columns and is suitable for viewing; therefore, no change was needed.

Comment Summary #9: The commenter requested that the sentences, "Cell-based NAb assays can be technically challenging because of the need to optimize the cell line, culture conditions, and sample matrix components. Lack of optimization can compromise assay precision, robustness, and sensitivity." currently found in the *Non-cell Based Methods for NAb Assessment* subsection need to be moved to the *Cell-based Methods for NAb Assessment* subsection.

Response: Comment incorporated. In addition, after moving the text, the following sentence was added to the *Non-Cell-Based* subsection to improve the language after the removal, "However, in comparison to the technical challenges of cell-based assays described above, non-cell-based immunoassays are capable of overcoming some of the technical limitations inherent to the cell-based bioassays, and have therefore become another useful technology platform for NAb evaluation."

Validation of NAb Assays

Comment Summary #10: The commenter requested that the "b" in the title *Validation of NAb Assays* be lower case.

Response: Comment incorporated.

Comment Summary #11: The commenter requested clarifying that the second sentence in the *Assay Cut-Points* subsection does not apply to the direct format for non-cell based NAb assays.

Response: Comment incorporated. The sentence was modified with the underlined text: "All individual drug-naive subject samples and NC samples used for the cut-point evaluation should be spiked with a fixed concentration of drug determined prior to validation; however, this would not apply to the direct format for non-cell based NAb assays."

Comment Summary #12: The commenter requested that "independent runs" (in the second paragraph of the *Assay Cut-Points* subsection) be clarified.

Response: Comment incorporated. The statement "(e.g., days, analysts)" was added after the term in the sentence.

Comment Summary #13: The commenter requested that the Shapiro-Wilk test be called the "Shapiro-Wilk *W*" test.

Response: Comment not incorporated. The test is commonly called the Shapiro-Wilk test. The *W* is the test variable, but is not usually included in the test title.

Comment Summary #14: Two commenters requested deleting the suggestions to include a non-neutralizing antibody as a negative control in the *System Suitability Criteria* and again in the *Assay Specificity* subsections, because it does not add value.

Response: Comment not incorporated. The first sentence starts by saying "In some circumstances..." because it can be helpful, but it is not a requirement. In the second section, it is also shown as a helpful option.

Comment Summary #15: The commenter requested that values be added to the Figure 3 axes.

Response: Comment incorporated.

Comment Summary #16: The commenter requested that the second paragraph of the *Selectivity and Interference* subsection regarding the PC concentration be clarified to align with the ranges proposed for drug tolerance assessment.

Response: Comment incorporated. The paragraph was edited as follows, "To ensure that the assay method is sensitive enough to detect NAb in the presence of circulating drug, the positive NAb control could be titrated in undiluted pooled matrix sample (e.g., at 250 ng/mL or 500 ng/mL for clinical studies or 1000 ng/mL for nonclinical studies) to assess drug tolerance level for the assay method. Thus, based on the sensitivity of the NAb assay, the PC should be diluted to that level when trying to detect NAb in the presence of circulating drug."

Comment Summary #17: The commenter requested that the "b" in the subsection title *Quasi-Quantitative NAb Assays* be lower case.

Response: Comment incorporated.

Comment Summary #17: The commenter requested adding an option to dilute the HPC in the MRD matrix pool as long as future samples are diluted in the same manner to the first paragraph of the subsection *Quasi-Quantitative NAb Assays*.

Response: Comment incorporated.

Appendix

Comment Summary #18: The commenter suggested adding the *2013 FDA Guidance for Industry: Immunogenicity Assessment of Therapeutic Protein Products* to the *Appendix*.

Response: Comment incorporated.

Expert Committee-initiated Change #1: The publication year of the Wadhwa and Thorpe reference in the *Appendix* was corrected to 2009.

General Chapter/Sections: General Chapter <1229.11> Vapor Phase Sterilization/Multiple Sections

Expert Committee: General Chapters—Microbiology

No. of Commenters: 3

Comment Summary #1: The commenter suggested adding the term “chamber” as an alternative to vessel for the introduction of vaporized sterilizing agents.

Response: Comment incorporated.

Comment Summary #2: The commenter suggested adding a sentence to indicate that the selection of the appropriate Biological Indicator and resistance should be based on experimentation within the users own decontamination system.

Response: Comment partially incorporated. The following sentence was added, “Selection of the appropriate biological indicator (BI) and resistance should be based on experimentation within the user's system.” This is not a General Chapter that deals with decontamination.

Comment Summary #3: The commenter suggested clarifying the term “safe levels” in the section on Hydrogen Peroxide as to whether it refers to a safe level for operators or for the product.

Response: Comment incorporated.

Comment Summary #4: The commenter suggested clarifying that standard sterilizing conditions have not been defined due to the varying phase and multi-phase nature of the sterilant during sterilization processes; therefore, no standardized biological indicators (BIs), having D-values that may be used for conventional predictive analysis of kill rates, have been established.

Response: Comment incorporated.

Comment Summary #5: The commenter suggested that without a defined range of resistance for the BIs, the statement, "Sterilization process parameters (usually time) that do not kill the BIs may be adjusted until a complete kill is achieved" could result excessively and unnecessarily long cycles to be developed.

Response: Comment not incorporated. The Expert Committee determined that while this may be true, in the absence of a D-value there is no real alternative. It is not

possible to suggest that the lab results can predict the operational results due to large differences in scale that make any estimate highly suspect.

Comment Summary #6: The commenter suggested that apart from “half cycle” approach, the more general “overkill approach” should be clearly stated as acceptable.

Response: Comment not incorporated. General Chapter <1229> already includes overkill, bioburden-biological indicator, and bioburden approaches all of which can be used.

Comment Summary #7: The commenter suggested adding a reference to <1229.7> *Gaseous Sterilization* as a reference to validation approaches used.

Response: Comment incorporated.

Comment Summary #8: The commenter indicated that the reference to a probability of non-sterile unit (PNSU) for this particular application is inappropriate and should be removed.

Response: Comment incorporated.

Comment Summary #9: The commenter indicated that temperature should also be considered as a process condition that needs to be adjusted, because temperature has a greater effect on this process than relative humidity.

Response: Comment incorporated.

General Chapter/Sections: <1663> Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems

Expert Committee(s): General Chapters—Dosage Form

No. of Commenters: 4

General

Comment Summary #1: The commenter suggested using a word beside “stoichiometry” in the General Chapter.

Response: Comment not incorporated. The Expert Committee determined that “stoichiometry” was the best word based on all other options.

Comment Summary #2: The commenter recommended adding a risk based table to the General Chapter.

Response: Comment not incorporated. The General Chapter does not discuss when testing is to be performed.

Comment Summary #3: The commenter recommended adding a discussion on the Analytical Evaluation Threshold (AET) concept.

Response: Comment incorporated.

Introduction

Comment Summary #4: The commenter recommended adding language on how to set safety threshold.

Response: Comment not incorporated. Setting safety threshold is not within the scope of the General Chapter.

Comment Summary #5: The commenter recommended referencing General Chapters <232> and <233>.

Response: Comment not incorporated. General Chapters <232> and <233> apply to finished drug products.

Comment Summary 6: The commenter indicated that the current tone of the General Chapter is geared towards plastic materials; however, glass, metal, and elastomer materials can be major contributors to drug product leachables.

Response: Comment incorporated.

Comment Summary #7: The commenter recommended using the term “target leachables” instead of “potential leachables.”

Response: Comment incorporated. A statement was added to clarify that all extractables have the potential to be leachables.

Title

Comment Summary #8: The commenter recommended defining the term “Delivery Systems.”

Response: Comment incorporated.

Scope

Comment Summary #9: The commenter suggested that a statement be added that describes who is responsible for testing.

Response: Comment not incorporated. The focus of the General Chapter is the scientific principles for conducting an extractable study, not who is responsible for performing the testing.

Comment Summary #10: The commenter recommended not using the word “sponsor” to note the pharmaceutical manufacturer.

Response: Comment incorporated. The term “Holder of the NDA (applicant holder)” will be used.

Comment Summary #11: The commenter requested that it be stated that extractable profiles can be used to establish extractable and leachable correlations.

Response: Comment incorporated.

Background Information

Comment Summary #12: The commenter suggested clarifying the meaning of the phrase “critical secondary packaging component.”

Response: Comment incorporated.

Generating the Extract—General Concepts and Critical Experimental Design

Comment Summary #13: The commenter recommended removing the word “contaminate,” because it will create confusion.

Response: Comment incorporated.

Comment Summary #14: The commenter recommended adding pressure as an extraction parameter.

Response: Comment incorporated.

Comment Summary #15: The commenter suggested that it is not desirable to disrupt or dissolve the component or material during an extraction study, and this concept should be reflected in the text.

Response: Comment not incorporated. There are multiple reasons for doing an extraction study. Depending on the study dissolving the material may be appropriate.

Generating the Extract—Extraction Time and Temperature

Comment Summary #16: The commenter suggested deleting the reference to modeling studies.

Response: Comment not incorporated. The sentence adds value and gives insight into what should be known about modeling.

Comment Summary #17: The commenter suggested that language in the General Chapter states that asymptotic levels should be reached during an extractable study.

Response: Comment not incorporated. The General Chapter states that extractables should be monitored for equilibrium.

Comment Summary #18: The commenter suggested adding a cautionary statement on the impact of cutting or sizing of materials and how it impacts extractables profile.

Response: Comment incorporated.

Comment Summary #19: The commenter suggested adding a reference to General Chapter <1664>.

Response: Comment incorporated.

Characterizing the Extract—Table 3

Comment Summary #20: The commenter suggested adding NMR and FTIR to the list of spectroscopic techniques.

Response: Comment incorporated.

General Chapter/Sections:	<1664> Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery Systems
Expert Committee(s):	General Chapters—Packaging, Storage and Distribution
No. of Commenters:	4

Key Terms

Comment Summary #1: The commenter suggested that delivery systems should be mentioned in this section, because it is in the General Chapter title.

Response: Comment incorporated.

Comment Summary #2: The commenter recommended clarifying that secondary packaging is not and will not be in contact with drug product.

Response: Comment incorporated.

Scope

Comment Summary #3: The commenter suggested that the scope should discuss relevant application, not history.

Response: Comment incorporated. The scope was changed to emphasize background not history.

Concepts—General Concepts for Leachables Assessment

Comment Summary #4: The commenter recommended deleting this section and just referencing <1663>.

Response: Comment not incorporated. General Chapter <1663> does not cover topics discussed in section.

Comment Summary #5: The commenter recommended using a term beside “safety qualification,” because it was being used incorrectly.

Response: Comment not incorporated. The Expert Committee determined that the term is used correctly.

Comment Summary #6: The commenter suggested defining the terms “combination drug product” and “medical devices.”

Response: Comment not incorporated. Those products are not within the scope of this General Chapter.

Concepts—Safety Thresholds

Comment Summary #7: The commenter recommended adding a summarized list of threshold values consistent with risk levels.

Response: Comment not incorporated. The Expert Committee determined that it was not practical to develop such a list at this time.

Comment Summary #8: The commenter recommended moving the PQRI decision tree to General Chapter <1664.1>.

Response: Comment incorporated.

Comment Summary #9: The commenter suggested that the discussion on special case compounds should be moved to General Chapter <1664.1>.

Response: Comment not incorporated. The information surrounding special case compounds is correct and is currently being applied across all dosage forms.

Concepts—Information Sharing

Comment Summary #10: The commenter recommended adding delivery system engineers as a stakeholder.

Response: Comment not incorporated. “Delivery system engineer” is not a term commonly used within the pharmaceutical industry.

Leachables Study Design

Comment Summary #11: The commenter suggested that there are cases in which it is not necessary to include real-time leachables assessments and text should reflect this point.

Response: Comment incorporated.

Comment Summary #12: The commenter suggested that there are specific reasons for doing post-market leachables assessments and that these reasons should be provided.

Response: Comment not incorporated. The General Chapter already discusses change control.

Comment Summary #13: The commenter suggested that it is not necessary to do leachables study on every batch in early development, because the choice of packaging components is done with knowledge of extractables provided by vendor.

Response: Comment not incorporated. The Expert Committee does not agree with this comment, but will consider future revisions to the General Chapter upon the receipt of the necessary supporting data.

Comment Summary #14: The commenter suggested all discussion on Orally Inhaled Nasal Drug Products (OINDP) be moved to General Chapter <1664.1>.

Response: Comment not incorporated. In context, the discussion of OINDP is used to support text.

Comment Summary #15: The commenter suggested that the use of the word “semi-permeable” is not appropriate and that “permeable” is a better word choice.

Response: Comment not incorporated. The term “semi-permeable” is well defined and is well referenced in the regulatory literature.

Comment Summary #16: The commenter suggested that tertiary packaging cannot be included in E&L testing as standard practice. The storage and testing for these substances would exceed practical or reasonable monitoring.

Response: Comment incorporated. The text was revised to clarify what the impact of tertiary packaging can have on drug product leachables.

Leachables Characterization—Analytical Thresholds

Comment Summary #17: The commenter suggested there is no acknowledgement of inorganics as leachables and should be addressed.

Response: Comment not incorporated. Inorganic leachables are discussed later in the document.

Comment Summary #18: The commenter suggested making the *Analytical Evaluation Threshold* (AET) formula general.

Response: Comment incorporated.

Leachable Characterization--Preparing the Drug Product for Analysis—Sample Preparation

Comment Summary #19: The commenter recommended adding more information related to therapeutic products.

Response: Comment not incorporated. The General Chapter does list sample preparation for the various dosage forms. A new General Chapter, <1664.2>, will be developed to address this topic.

Comment Summary #20: The commenter suggested highlighting that it is risky to take organic extract to dryness, as some compounds may not redissolve.

Response: Comment incorporated.

Leachables Characterization—Analytical Techniques

Comment Summary #21: The commenter recommends adding a discussion on determination of silicon and SiO₂.

Response: Comment not incorporated. This is addressed in the *Inorganic (Elemental) Leachables* section.

Leachables Characterization-- Quantitative Methods—Validation Considerations

Comment Summary #22: The commenter recommended adding references to General Chapter <1225>.

Response: Comment incorporated.

Comment Summary #23: The commenter recommended allowing other approaches in creating a robust evaluation protocol (e.g., serial change of critical parameters).

Response: Comment incorporated.

Considerations in Developing Leachables Specification and Acceptance Criteria

Comment Summary #24: The commenter recommended adding an example of when a specification and acceptance criteria would be applicable.

Response: Comment incorporated.

Comment Summary #25: The commenter suggested that typically two packaging/delivery system batches are adequate for developing specification and acceptance criteria.

Response: Comment not incorporated. The comment was directed to a statement that was about drug product batches, not packaging.

Additional Consideration—Simulation Studies

Comment Summary #26: The commenter recommended deleting this section and placing information in General Chapter <1663>.

Response: Comment not incorporated. Simulation studies can be used to augment leachables studies when they cannot be done.

Monograph/Section: Acebutolol Hydrochloride/Organic Impurities

Expert Committee: Monographs—Small Molecules 2

No. of Commenters: 1

Comment Summary #1: The commenter recommended widening the relative standard deviation requirement in the test for *Organic Impurities* from NMT 0.5% to NMT 2.0%, which is more suitable for an impurities procedure.

Response: Comment incorporated.

Monograph/Section(s): Adenine/Impurities

Expert Committee: Monographs—Dietary Supplements and Herbal Medicines

No. of Commenters: 1

Comment Summary #1: The commenter requested replacing the proposed Related Compounds method with their in-house method, which they said better characterizes adenine and its related compounds.

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

Monograph/Section(s): Alanine

Expert Committee: Monographs—Dietary Supplements and Herbal Medicines

No. of Commenters: 3

Comment Summary #1: The commenter requested removing the Alanine standard solution in the proposed Related Compound test, because this solution is not appropriate for the determination of organic acid impurities. Fumaric standard solution should replace the Alanine standard solution for the determination of the unspecified impurities.

Response: Comment incorporated.

Comment Summary #2: The commenter suggested tightening the relative standard deviation requirement for the three acid impurities in the System suitability requirement of the Related Compounds test, because it is too large (NMT 10.0%).

Response: Comment incorporated. The relative standard deviation was changed from NMT 10.0% to NMT 5.0%.

Comment Summary #3: The commenter suggested replacing the proposed HPLC Related Compounds method using underivatized samples with a method using derivatized samples in combination with an amino acid analyzer (AAA).

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

Monograph/Sections: Almotriptan Malate/Multiple Sections

Expert Committee: Monographs—Small Molecules 4

No. of Commenters: 2

Comment Summary #1: The commenters requested revising *Table 1* to update the trivial name of the impurity with a relative migration time of 0.71 from “almotriptan dimer derivative” to “almotriptan *N*-dimer” and revising the chemical name of this impurity to 2-{1-({3-[2-(dimethylamino)ethyl]-1*H*-indol-5-yl)methyl]-5-[(pyrrolidin-1-ylsulfonyl)methyl]-1*H*-indol-3-yl)-*N,N*-dimethylethan-1-amine.

Response: Comment incorporated.

Monograph/Section: Almotriptan Tablets/Specific Tests

Expert Committee: Monographs—Small Molecules 4

No. of Commenters: 1

Comment Summary #1: The commenter requested adding a test for *Water Determination* with appropriate acceptance criteria.

Response: Comment not incorporated. The Expert Committee has determined that water content requirements for drug products should remain as agreements between individual manufacturers and regulatory agencies. These requirements should not be included in the public standard, because of the inherent variability arising from differences in formulation.

Monograph/ Sections: Amlodipine, Valsartan and Hydrochlorothiazide
Tablets/Multiple Sections

Expert Committee: Monographs—Small Molecules 2

No. of Commenters: 5

Comment Summary #1: The commenter requested revising the test for *Organic Impurities* to specify which *Sample solution* is used to evaluate the disregard limit.

Response: Comment not incorporated. The Expert Committee determined that the monograph adequately describes the disregard limit as 0.1%, which applies to all three *Sample solutions*.

Comment Summary #2: The commenter requested including a note in the test for *Dissolution* to indicate that the paddles should be covered with Teflon or be made of any inert material other than steel because amlodipine degrades when exposed to stainless steel.

Response: Comment not incorporated. The changes do not reflect approved procedures. The Expert Committee will consider future revisions to the monograph upon receipt of the necessary supporting data.

Comment Summary #3: The commenter requested widening the acceptance criteria in the Assay from 95.0–105.0% to 90–110%.

Response: Comment not incorporated. The acceptance criteria in the monograph reflect FDA approved requirements. The Expert Committee will consider future revisions to the monograph upon receipt of the necessary supporting data.

Comment Summary #4: The commenter requested widening the acceptance criteria for amlodipine related compound A in the test for *Organic Impurities* from NMT 0.5% to 1.0% for consistency with other amlodipine drug product monographs.

Response: Comment not incorporated. The acceptance criteria in the monograph reflect FDA approved requirements. The Expert Committee will consider future revisions to the monograph upon receipt of the necessary supporting data..

Comment Summary #5: The commenter requested widening the acceptance criteria for total degradation products in the test for *Organic Impurities* from NMT 1.5% to NMT 2.0% and to exclude amlodipine related compound A and D-valsartan from this limit.

Response: Comment not incorporated. The acceptance criteria in the monograph reflect FDA approved requirements. The Expert Committee will consider future revisions to the monograph upon receipt of the necessary supporting data.

Monograph/Sections: Anastrozole Tablets/Multiple Sections

Expert Committee: Monographs—Small Molecules 3

No. of Commenters: 2

Comment Summary #1: The commenter requested adding an alternative *Organic impurities* procedure to accommodate a different impurity profile.

Response: Comment not incorporated. The organic impurities in the specification provided by the commenter are process impurities. Upon receipt of supporting data, the Expert Committee will consider revising the drug substance monograph in the future to include limits for these impurities.

Comment Summary #2: The commenter requested correcting the column used in *Dissolution Test 2* from L1 to L42.

Response: Comment incorporated.

Monograph/Section(s): Bacillus subtilis subsp. subtilis Menaquinone-7 Extract
Expert Committee: Monographs—Dietary Supplements and Herbal Medicines

No. of Commenters: 1

Comment Summary #1: The commenter suggested reducing the amount of USP Menaquinone-7 RS used to prepare the Standard solution in the test for *Content of Menaquinone-7*, from 25 mg to 12.5 mg, to conserve the RS for multiple uses.

Response: Comment incorporated.

Monograph/Sections: Benzocaine Cream/Multiple Sections

Expert Committee: Monographs—Small Molecules 4

Expert Committee-initiated Change #1: The order of identification tests is revised for consistency with the Benzocaine Gel monograph.

Expert Committee-initiated Change #2: The Assay was revised to change the relative standard deviation requirement from NMT 0.73% to NMT 1.0%, which is more suitable for a drug product monograph.

Monograph/Sections: Benzocaine Gel/Multiple sections

Expert Committee: Monographs—Small Molecules 4

No. of Commenters: 1

Comment Summary #1: The commenter requested revising the order of the identification tests for consistency with the Benzocaine Cream monograph.

Response: Comment not incorporated. The order of the tests in the Benzocaine Cream monograph was revised to align with this revision.

Comment Summary #2: The commenter requested revising the *System suitability solution* in the Assay to be consistent with the Benzocaine Cream monograph.

Response: Comment not incorporated. The *System suitability solution* reflects the one used during method validation.

Comment Summary #3: The commenter requested revising the *Relative Standard Deviation* requirement in the Assay from NMT 0.73% to NMT 1.0% based on available data.

Response: Comment incorporated.

Comment Summary #4: The commenter requested revising the *Standard solution* in the test for *Organic Impurities* to be consistent with the Benzocaine Cream monograph.

Response: Comment not incorporated. The *Standard solution* reflects the one used during method validation.

Monograph/Section(s): Borage Seed Oil Capsules/Definition

Expert Committee: Monographs—Dietary Supplements and Herbal Medicines

No. of Commenters: 1

Comment Summary: The commenter requested that the requirement “NLT 90.0% and NMT 110.0% for the sum of the labeled amounts of gamma-linolenic, linoleic, and oleic acids” in monograph *Definition* be revised to accommodate the inherent variability of constituents in formulations containing natural products, such as borage seeds, and due to the need to add sufficient overages to guarantee fulfillment of label claim through the end of the product shelf life.

Response: Comment incorporated. The requirements for the fatty acids content were modified as “NLT 95.0% of the labeled amounts of gamma-linolenic, linoleic, and oleic acids” based on the supporting data received.

Monograph/Section: Butabarbital Sodium Tablets/Identification

Expert Committee: Monographs—Small Molecules 4

No. of Commenters: 1

Comment Summary #1: The commenter requested adding an orthogonal identification test to be consistent with ICH Q6A.

Response: Comment not incorporated. The Expert Committee will consider a future revision upon receipt of supporting data.

Monograph/Sections: Dipivefrin Hydrochloride/Multiple Sections

Expert Committee: Monographs—Small Molecules 3

Expert Committee-initiated Change #1: The *USP Reference Standards* section was revised to replace the name USP Dipivefrin Related Compound B RS with USP Adrenalone Hydrochloride RS, because this reference material is used in multiple monographs.

Expert Committee-initiated Change #2: The test for *Limits of Epinephrine and Dipivefrin Related Compound B* was revised to change the name to *Limits of Epinephrine and Adrenalone* and to indicate that water is used as the solvent to prepare *Solution A*.

Expert Committee-initiated Change #3: *Table 2* in the test for *Limits of Epinephrine and Adrenalone* was revised to add a footnote indicating that epinephrine is a racemate also known as racepinephrine or (\pm) adrenaline.

Expert Committee-initiated Change #4: The test for *Organic Impurities* was revised to include USP Dipivefrin Related Compound E RS in the *Standard solution* to provide a more accurate way of determining this impurity.

Expert Committee-initiated Change #5: The test for *Organic Impurities* was revised to delete the relative standard deviation requirement for dipivefrine related compound E. The Expert Committee determined that the relative standard deviation of the dipivefrin peak is adequate to evaluate system suitability.

Expert Committee-initiated Change #6: The chemical name of USP Dipivefrin Related Compound E RS in the *USP Reference Standards <11>* was changed to be consistent with the reference standard labeling.

Monograph/Sections: Dipivefrin Hydrochloride Ophthalmic Solution/Multiple Sections

Expert Committee: Monographs—Small Molecules 3

No. of Commenters: 1

Comment Summary #1: The commenter recommended tightening the limit for individual unspecified impurities.

Response: Comment not incorporated. The limit in the monograph is consistent with that in the corresponding *British Pharmacopoeia* monograph. The Expert Committee will consider a future revision upon receipt of supporting data.

Expert Committee-initiated Change #1: The test for *Organic impurities* was revised to specify that the relative standard deviation requirement applies to the dipivefrin peak. The Expert Committee determined that the relative standard deviation of this peak is adequate to evaluate system precision.

Expert Committee-initiated Change #2: The limit of dipivefrin related compound E in the test for *Organic Impurities* was revised from NMT 1.0% to NMT 1% to be consistent with the limit in the corresponding *British Pharmacopoeia* monograph.

Expert Committee-initiated Change #3: The chemical name of USP Dipivefrin Related Compound E RS in the *USP Reference Standards* section was changed to be consistent with the reference standard labeling.

Monograph/Section: Donepezil Hydrochloride/Organic Impurities
Expert Committee: Monographs—Small Molecules 4
No. of Commenters: 1
Comment Summary #1: The commenter requested retaining the existing *Organic Impurities, Procedure 1*, because the procedure better addresses the commenter's impurity profile.
Response: Comment incorporated. The existing *Organic Impurities Procedure 1* was retained, the proposed *Organic Impurities* procedure was renamed *Organic Impurities, Procedure 2*, and the *Labeling* section was retained.
Expert Committee-initiated Change #1: *Table 3* was corrected to include a limit of 0.1% for donepezil *N*-oxide.

Monograph/ Section: Doxazosin Mesylate/Multiple Sections
Expert Committee: Monographs—Small Molecules 2
No. of Commenters: 2
Comment Summary #1: The commenter recommended revising the requirement for resolution between doxazosin related compounds A and B in the test for *Organic Impurities* from NLT 4 to NLT 2, which is a more suitable limit based on available data.
Response: Comment incorporated.
Comment Summary #2: The commenter recommended revising the column packing under *Assay* from L1 to L7 to be consistent with the currently official monograph.
Response: Comment incorporated.

Monograph/Section: Epirubicin Hydrochloride/Packaging and Storage
Expert Committee: Monographs—Small Molecules 1
No. of Commenters: 1
Comment Summary #1: The commenter requested revising the *Packaging and Storage* section to provide flexibility in the storage conditions and to accommodate a different polymorphic form.
Response: Comment incorporated.

Monograph/Sections: Epirubicin Hydrochloride Injection/Multiple Sections
Expert Committee: Monographs—Small Molecules 1
No. of Commenters: 2
Comment Summary #1: The commenter requested revising the concentration of the *Sample solution* in the *Assay*, which is too viscous to be injected directly into the HPLC instrument.
Response: Comment incorporated.
Comment Summary #2: The commenter requested revising the *Packaging and Storage* section to delete the requirement for tight containers as this requirement is not appropriate for an injectable product.
Response: Comment incorporated.

Monograph/Section(s): Flax Seed Oil Capsules/Definition
Expert Committee: Monographs—Dietary Supplements and Herbal Medicines

No. of Commenters: 1

Comment Summary: The commenter requested that requirement “NLT 90.0% and NMT 110.0% for the sum of the labeled amounts of alpha-linolenic, linoleic, and oleic acids” in monograph *Definition* be revised to accommodate the inherent variability of constituents in formulations containing natural products, such as flax seeds, and due to the need to add sufficient overages to guarantee fulfillment of label claim through the end of the product shelf life.

Response: Comment incorporated. The requirements for the fatty acids content were modified as “NLT 95.0% of the labeled amounts of alpha-linolenic, linoleic, and oleic acids” based on the supporting data received.

Monograph/Section: Flumazenil Injection/Packaging and Storage
Expert Committee: Monographs—Small Molecules 4

No. of Commenters: 1

Comment Summary #1: The commenter requested revising the *Packaging and Storage* section to delete the requirement for tight containers as this requirement is not appropriate for an injectable product.

Response: Comment incorporated.

Monograph/Sections: Formoterol Fumarate/Multiple Sections
Expert Committee: Monographs—Small Molecules 4

Expert Committee-initiated Change #1: The incorrect CAS number of Formoterol Fumarate was corrected. The currently official monograph contains the chemical name, molecular formula, molecular weight and structure of the hydrate, but the CAS number for the anhydrous form.

Expert Committee-initiated Change #2: The relative response factors in *Table 2* in the test for *Organic Impurities* were changed from 1.00 to 1.0 for consistency with current USP format.

Monograph/Sections: Galantamine Extended-Release Capsules/Multiple Sections

Expert Committee: Monographs—Small Molecules 4

No. of Commenters: 3

Comment Summary #1: The commenter requested replacing the isocratic Assay with the gradient HPLC procedure from the test for *Organic Impurities*.

Response: Comment not incorporated. The Expert Committee determined that the Assay is appropriate for inclusion in the public standard.

Comment Summary #2: The commenter requested widening the relative standard deviation requirement in the Assay from NMT 1.0% to NMT 2.0%.

Response: Comment not incorporated. The Expert Committee determined that the relative standard deviation requirement is appropriate for the public standard.

Comment Summary #3: The commenter requested renumbering *Dissolution Test 2* as *Dissolution Test 1*.

Response: Comment not incorporated. Dissolution tests are generally listed in the order in which USP receives complete submission packages (request for revision, supporting data, and notification of full FDA approval).

Comment Summary #4: The commenter requested changing the style of the calculation formula for time point 3 in *Dissolution Test 1* and *Dissolution Test 2*.

Response: Comment not incorporated. The format of the calculation formula is consistent with current USP format.

Comment Summary #5: The commenter requested adding *Dissolution Test 3* to support the FDA approved drug product.

Response: Comment incorporated.

Comment Summary #6: The commenter requested adding a dissolution test to support a different formulation.

Response: Comment not incorporated. The Expert Committee determined that such test is not necessary but will consider future revisions to the monograph upon receipt of the necessary supporting data.

Comment Summary #7: The commenter requested including a specific analytical procedure in the test for *Uniformity of Dosage Units*.

Response: Comment not incorporated. The Expert Committee determined that a specific procedure did not need to be included in the public standard.

Comment Summary #8: The commenter requested replacing the test for *Organic Impurities* with their in-house procedure, which contains a limit for epigalantamine.

Response: Comment not incorporated. The test for *Organic Impurities* contains a limit for epigalantamine, which is listed in the test for *Organic Impurities* as 6S-galantamine.

Comment Summary #9: The commenter requested revising the column temperature units in the test for *Organic Impurities* to clarify that these reflect degrees Celsius.

Response: Comment not incorporated. *General Notices 8.180. Temperatures*, defines temperature units used in USP as degrees centigrade (Celsius). The monograph is consistent with current USP format.

Comment Summary #10: The commenter requested adding a footnote in *Table 5* in the test for *Organic Impurities* to indicate that *N*-desmethyl galantamine is only present in the drug substance obtained from natural sources. This impurity is not present in the purely synthetic drug substance.

Response: Comment incorporated.

Comment Summary #11: The commenter requested widening the limits for galantamine *N*-oxide from NMT 0.5% to NMT 0.75% with appropriate changes to the limit of total degradation products.

Response: Comment not incorporated. The acceptance criteria in the monograph reflect FDA approved requirements. The Expert Committee will consider future revisions to the monograph upon receipt of the necessary supporting data.

Comment Summary #12: The commenter requested removing *N*-desmethyl galantamine and 6S-galantamine from *Table 5* in the test for *Organic Impurities*, because these impurities are not part of the commenter's impurity profile.

Response: Comment not incorporated. The acceptance criteria in the monograph reflect FDA approved requirements. The Expert Committee will consider future revisions to the monograph upon receipt of the necessary supporting data.

Comment Summary #13: The commenter requested removing the limit for 6S-galantamine in the test for *Organic Impurities*, because it is a process impurity.

Response: Comment not incorporated. 6S-galantamine has been identified as a degradation product by a monograph sponsor.

Comment Summary #14: The commenter indicated that the limit for *N*-desmethyl galantamine is tighter than the corresponding limit in the drug substance monograph.

Response: Comment not incorporated. The acceptance criteria are not tighter, because the two monographs use different relative response factors to quantitate the same impurity.

Monograph/Sections: Galantamine Oral Solution/Multiple Sections

Expert Committee: Monographs—Small Molecules 4

No. of Commenters: 3

Comment Summary #1: The commenter requested revising the *Definition* to indicate that the product could contain one or more suitable preservatives.

Response: Comment incorporated.

Comment Summary #2: The commenter requested adding an orthogonal identification test to be consistent with ICH Q6A.

Response: Comment not incorporated. The Expert Committee will consider a future revision upon receipt of the necessary supporting data.

Comment Summary #3: The commenter requested tightening the acceptance criteria for *N*-desmethyl galantamine in the test for *Organic Impurities*.

Response: Comment not incorporated. The limit is consistent with the acceptance criteria in the official drug substance monograph and other galantamine-containing drug product monographs.

Comment Summary #4: The commenter requested revising the impurity profile in the test for *Organic Impurities*.

Response: Comment not incorporated. The acceptance criteria are aligned with the limits in the drug substance monograph and other drug product monographs that contain galantamine hydrobromide.

Comment Summary #5: The commenter requested adding a footnote to *Table 2* in the test for *Organic Impurities* to indicate that *N*-desmethyl galantamine and narwedine are only possible in the drug substance when it is obtained from natural sources. These impurities are not present in the purely synthetic drug substance.

Response: Comment incorporated. Narwedine was deleted from *Table 2*. A footnote is added to the entry for *N*-desmethyl galantamine stating, "This degradation product may be found if the drug substance is isolated from a natural source."

Comment Summary #6: The commenter requested revising the format of *Table 2* in the test for *Organic Impurities*.

Response: Comment not incorporated. The Expert Committee determined that the format of the table is appropriate for presenting process impurities and degradation products.

Comment Summary #7: The commenter requested widening the acceptance criteria for total yeasts and mold counts from NMT 10^1 cfu/mL to NMT 5×10^1 cfu/mL, to reflect FDA-approved limits.

Response: Comment incorporated.

Comment Summary #8: The commenter requested widening the acceptance criteria in the test for pH from 4.0–6.0 to 3.9–6.2 to reflect FDA approved limits.

Response: Comment incorporated.

Monograph/Section(s): Hydroxocobalamin/Multiple Sections
Expert Committee: Monographs—Dietary Supplements and Herbal Medicines

No. of Commenters: 4

Comment Summary #1: The commenter requested the loss on drying (LOD) test be replaced with the *Water Determination* <921> test which measures the moisture more accurately.

Response: Comment incorporated.

Comment Summary #2: The commenter requested adding the *Residual Solvent* <467> test for acetone.

Response: Comment incorporated.

Comment Summary #3: The commenter requested adding the requirement “store in dry place. Do not freeze” to the *Packaging and Storage* section.

Response: Comment incorporated.

Expert Committee-initiated Change #1: The acceptance criteria in the Assay was changed from 94.0%–102.0% to 95%–102.0% to better reflect the data submitted by the sponsor.

Monograph/Sections: Hydroxyzine Pamoate/Multiple Sections
Expert Committee: Monographs—Small Molecules 4
No. of Commenters: 2

Comment Summary #1: The commenter requested correcting the composition of the *Mobile phase* in the Assay from “Acetonitrile and *Solution A* (55:45)” to “Acetonitrile and *Solution A* (45:55)” to reflect the validated procedure.

Response: Comment incorporated.

Comment Summary #2: The commenter requested including an impurities test with appropriate acceptance criteria.

Response: Comment not incorporated. The Expert Committee will consider a future revision upon receipt of the necessary supporting data.

Expert Committee-initiated Change #1: *Solution A* in the Assay was revised to indicate that the anhydrous form of sodium 1-octanesulfonate is used.

Expert Committee-initiated Change #2: The reference to USP Pamoic Acid RS was removed from the *USP Reference Standards* section, because it is not required in the monograph.

Monograph/Sections: Imiquimod Cream/Multiple Sections
Expert Committee: Monographs—Small Molecules 1
No. of Commenters: 1

Comment Summary #1: The commenter requested widening the limit for individual unspecified impurities in the test for *Organic impurities* from 0.2% to 0.5%, to be consistent with FDA-approved acceptance criteria.

Response: Comment incorporated.

Comment Summary #2: The commenter requested tightening the limits in the test for pH from 4.5–7.0 to 5.0–7.0.

Response: Comment not incorporated. The acceptance criteria in the monograph are consistent with FDA approved limits.

Monograph/Sections: Levetiracetam Injection/Organic Impurities

Expert Committee: Monographs—Small Molecules 4

No. of Commenters: 1

Comment Summary #1: The commenter requested tightening the limit of levetiracetam acid in the test for *Organic Impurities*.

Response: Comment not incorporated. The proposed limit reflects FDA-approved acceptance criteria and is consistent with the acceptance criteria in the drug substance monograph.

Comment Summary #2: The commenter requested including a test for levetiracetam *R*-enantiomer with appropriate limits.

Response: Comment not incorporated. Levetiracetam *R*-enantiomer is a process impurity, which is controlled in the drug substance. The Expert Committee will consider this request upon receipt of stability data supporting that racemization occurs in the drug product.

Monograph/Sections: Levocetirizine Dihydrochloride/Multiple Sections

Expert Committee: Monographs—Small Molecules 4

No. of Commenters: 2

Comment Summary #1: The commenter requested replacing the retention time match based on the Assay with one based on the test for *Enantiomeric Purity*, because it is important to identify the correct isomer.

Response: Comment incorporated.

Comment Summary #2: The commenter requested replacing the test for *Organic Impurities* with their in-house procedure to address a process impurity in the commenter's impurity profile.

Response: Comment not incorporated. The Expert Committee determined that the resolution obtained in the test for *Organic Impurities* is sufficient.

Comment Summary #3: The commenter requested replacing the test for *Enantiomeric Purity* with their in-house procedure to address the commenter's impurity profile.

Response: Comment not incorporated. The Expert Committee will consider a future revision upon receipt of supporting data.

Monograph/Sections: Lidocaine Hydrochloride Oral Topical Solution/Multiple Sections

Expert Committee: Monographs—Small Molecules 4

No. of Commenters: 2

Comment Summary #1: The commenter requested revising the pH (8.00) of *Solution A* to prevent peak splitting, because the pH is close to the pKa (7.9) of lidocaine.

Response: Comment not incorporated. Peak splitting is not observed in available data. The Expert Committee determined that the procedure is adequate for the public standard, but will consider a future revision upon receipt of supporting data.

Comment Summary #2: The commenter requested revising the test for *Organic Impurities* to improve the resolution of 2,6-dimethylaniline from an unspecified impurity and to minimize tailing.

Response: Comment not incorporated. Based on available validation data, the procedure is sufficiently selective and peak shape is adequate. The Expert Committee determined that the procedure is adequate, but will consider a future revision upon receipt of the necessary supporting data.

Comment Summary #3: The commenter recommended tightening the acceptance criteria for lidocaine related compound H.

Response: Comment not incorporated. The limits are consistent with ICH guidelines. The Expert Committee will consider a future revision upon receipt of supporting data.

Comment Summary #4: The commenter recommended changing the name of ropivacaine related compound A to reflect that the impurity is related to lidocaine.

Response: Comment not incorporated. The impurity name is inconsistent with current USP naming policy for reference materials.

Comment Summary #5: The commenter recommended including a molecular weight correction in the calculation for related compound A in the test for *Organic Impurities*.

Response: Comment incorporated.

Comment Summary #6: The commenter recommended including a test for microbial enumeration.

Response: Comment not incorporated. The Expert Committee will consider a future revision upon receipt of the necessary supporting data.

Monograph/Sections: Lidocaine Hydrochloride Topical Solution/Multiple Sections

Expert Committee: Monographs—Small Molecules 4

No. of Commenters: 2

Comment Summary #1: The commenter requested revising the concentration of the sodium hydroxide solution used to adjust the pH of *Solution A* in the *Assay*.

Response: Comment not incorporated. Laboratory data to support such a revision is not currently available. The Expert Committee will consider a future revision upon receipt of the necessary supporting data.

Comment Summary #2: The commenter recommended tightening the acceptance criteria for lidocaine related compound H.

Response: Comment not incorporated. The limits are consistent with ICH guidelines. The Expert Committee will consider a future revision upon receipt of the necessary supporting data.

Comment Summary #3: The commenter recommended changing the name of ropivacaine related compound A to reflect that the impurity is related to lidocaine.

Response: Comment not incorporated. The impurity name is inconsistent with current USP naming policy for reference materials.

Comment Summary #4: The commenter recommended including a molecular weight correction in the calculation for related compound A in the test for *Organic Impurities*.

Response: Comment incorporated.

Comment Summary #5: The commenter recommended including a test for microbial enumeration.

Response: Comment not incorporated. The Expert Committee will consider a future revision upon receipt of supporting data.

Monograph/Section(s): Menoquinone-7/Impurities
Expert Committee: Monographs—Dietary Supplements and Herbal Medicines

No. of Commenters: 1

Comment Summary #1: The commenter suggested the name “enantiomeric impurity” test be changed to “isomeric” test.

Response: Comment incorporated.

Monograph/Section(s): Menoquinone-7 Preparation/Multiple Sections
Expert Committee: Monographs—Dietary Supplements and Herbal Medicines

No. of Commenters: 3

Comment Summary #1: The commenter suggested the name “enantiomeric impurity” test be changed to “isomeric” test.

Response: Comment incorporated.

Comment Summary #2: The commenter requested the test for *Residue on Ignition* be removed from the monograph, because this test is not appropriate for the dosage form.

Response: Comment incorporated.

Comment Summary #3: The commenter requested the loss on drying (LOD) value be incorporated into the result equation in the test for *Content of Menaquinone-7* and Menaquinone-6.

Response: Comment not incorporated. Per *General Notices*, Section 7.10.5, the LOD value is not part of the result equation. LOD correction for assayed content is made prior to using the concentration in the equation provided in the monograph.

Monograph/Section: Metaxalone/Organic Impurities
Expert Committee: Monographs—Small Molecules 4
No. of Commenters: 2

Comment Summary #1: The commenters requested including additional process impurities from different manufacturing processes.

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

Monograph/Sections: Metronidazole Tablets/Multiple Sections
Expert Committee: Monographs—Small Molecules 1
Expert Committee-initiated Change #1: The calculation formula in the *Dissolution* test was updated to include a dilution factor.
Expert Committee-initiated Change #2: The *Packaging and Storage* section was revised to add storage conditions.

Monograph/Sections: Minocycline Hydrochloride Extended-Release Tablets/Multiple Sections
Expert Committee: Monographs—Small Molecules 1

No. of Commenters: 2

Comment Summary #1: The commenter requested revising *Dissolution Test 2* to indicate the solutions containing minocycline should be protected from light.

Response: Comment incorporated.

Comment Summary #2: The commenter requested revising *Dissolution Test 2* to correct the calculation formulas.

Response: Comment incorporated.

Comment Summary #3: The commenter requested including an identification test based on thin-layer chromatography.

Response: Comment not incorporated. The monograph contains two orthogonal identification tests. Thin-layer chromatographic procedures are not consistent with USP's monograph modernization initiative. The Expert Committee will consider a future revision upon receipt of the necessary supporting data for additional orthogonal test procedures that use modern technology.

Comment Summary #4: The commenter requested widening the limit for 4-epiminocycline in the test for *Organic Impurities* from 2.0% to 4.0% to reflect FDA-approved acceptance criteria.

Response: Comment incorporated.

Comment Summary #4: The commenter requested including *Dissolution Test 3* to conform to the FDA-approved product.

Response: Comment incorporated.

Comment Summary #5: The commenter requested including *Dissolution Test 4* to conform to the FDA-approved product.

Response: Comment not incorporated at this time. The Expert Committee will consider a future revision upon receipt of the necessary supporting data.

Monograph/Sections: Naproxen Sodium Tablets/Multiple Sections

Expert Committee: Monographs—Small Molecules 2

No. of Commenters: 5

Comment Summary #1: The commenter recommended including a limit for 1-(6-methoxy-2-naphthyl)-ethanol in the test for *Organic Impurities*.

Response: Comment not incorporated. The monograph reflects FDA approved limits. The Expert Committee will consider a future revision upon receipt of supporting data.

Comment Summary #2: The commenters requested widening the limits for individual impurities and total impurities in the test for *Organic Impurities*.

Response: Comment incorporated. The limits for individual impurities were widened from 0.10% to 0.2%, and for total impurities from 0.50% to 1.5%. The revised limits reflect FDA-approved acceptance criteria.

Comment Summary #3: The commenter requested revising the test for *Organic Impurities* to include limits of 0.20% each for (1*RS*)-1-(6-methoxynaphthalen-2-yl)-ethanol and 2-ethyl-6-methoxynaphthalene.

Response: Comment not incorporated. The Expert Committee will consider a future revision upon receipt of the necessary supporting data.

Comment Summary #4: The commenter requested revising the disregard limit from the limit of quantitation to 0.05% to be consistent with ICH Q3B guidelines.

Response: Comment not incorporated. The limits in the proposal reflect FDA-approved specifications.

Comment Summary #6: The commenter requested revising the *Sample stock solution* in the *Assay* to remove the requirement for finely powdered tablets; the tablets are allowed to disperse in the *Mobile phase* and do not need to be finely powdered before they are added to the volumetric flask.

Response: Comment incorporated.

Comment Summary #7: The commenter requested adding a statement indicating that naproxen methyl ester is identified by the relative retention time.

Response: Comment not incorporated. The Expert Committee determined that it was adequate to provide the relative retention time of the impurity without explicitly stating that it is identified by relative retention time.

Expert Committee-initiated change #1: *Table 2* in the test for *Organic Impurities* was revised to delete the limit for naproxen which was erroneously included in the revision proposal.

Monograph/Sections: Naproxen Tablets/Multiple Sections

Expert Committee: Monographs—Small Molecules 2

No. of Commenters: 3

Comment Summary #1: The commenter recommended including a limit for 1-(6-methoxy-2-naphthyl)-ethanol to the test for *Organic impurities*.

Response: Comment not incorporated. The monograph reflects FDA approved limits. The Expert Committee will consider a future revision upon receipt of the necessary supporting data.

Comment Summary #2: The commenter requested revising *Table 2* in the test for *Organic Impurities* to delete the limit for naproxen which was erroneously included in the revision proposal.

Response: Comment incorporated.

Comment Summary #3: The commenter requested revising the test for *Organic Impurities* to add limits of 0.20% for (1RS)-1-(6-methoxynaphthalen-2-yl)-ethanol and 2-ethyl-6-methoxynaphthalene; widening the limit for naproxen related compound L from 0.10% to 0.20%; for any other individual impurity from 0.10% to 0.15%; and for total impurities from 0.50% to 1.0%.

Response: Comment not incorporated. The Expert Committee will consider a future revision upon receipt of the necessary supporting data.

Comment Summary #4: The commenter requested revising limits for all specified impurities to be from 0.10% to 0.20%, unspecified impurity from 0.10% to 0.16%, and the disregard limit from the limit of quantitation to 0.05% to be consistent with ICH Q3B guidelines.

Response: Comment not incorporated. The Expert Committee will consider a future revision upon receipt of the necessary supporting data.

Monograph/Section(s): Niacin/Multiple Section

Expert Committee: Monographs—Dietary Supplements and Herbal Medicines

No. of Commenters: 2

Comment Summary #1: The commenter requested that the Resolution solution be incorporated into the *System suitability solution* in the *Related Compounds test*, and the USP Niacin RS be removed from the *System suitability solution*, because it is not relevant to the system suitability requirements.

Response: Comment incorporated.

Comment Summary #2: The commenter requested adding the limits for the unspecified impurity (NMT 0.05%) and total unspecified impurities (NMT 0.2%) to the Table 2 of Related Compounds test.

Response: Comment incorporated.

Monograph/Section: Norelgestromin/Organic Impurities

Expert Committee: Monographs—Small Molecules 4

No. of Commenters: 1

Comment Summary #1: The commenter requested replacing the test for *Organic Impurities* with their in-house procedure, which offers improved chromatographic characteristics for the late eluting peaks.

Response: Comment not incorporated. The Expert Committee will consider a future revision upon receipt of the necessary supporting data.

Monograph/Section: Norfloxacin/Organic impurities

Expert Committee: Monographs—Small Molecules 1

No. of Commenters: 1

Comment Summary #1: The commenter requested revising *Table 2* in the test for *Organic Impurities* to correct the limit for total impurities from 0.10% to 0.5%.

Response: Comment incorporated.

Monograph/Sections: Phenytoin Sodium/Multiple Sections

Expert Committee: Monographs—Small Molecules 4

No. of Commenters: 1

Comment Summary #1: The commenter requested revising the *Definition* to indicate the salt form of the drug substance.

Response: Comment incorporated.

Comment Summary #2: The commenter requested revising the *Assay* to correct the units for concentration of the *Sample solution* in the calculation variable definition from mg/mL to µg/mL.

Response: Comment incorporated.

Monograph/Sections: Repaglinide/Multiple Sections

Expert Committee: Monographs—Small Molecules 3

No. of Commenters: 5

Comment Summary #1: The commenters indicated that the *Buffer* prepared as described in the test for *Enantiomeric purity* has a pH of about 4.7, and may require only minor pH adjustment. The commenters requested to specify that the pH should be adjusted to 4.7 only if needed, using either 2N sodium hydroxide or diluted phosphoric acid.

Response: Comment incorporated.

Comment Summary #2: The commenter requested widening the requirement for relative standard deviation in the test for *Enantiomeric purity* from NMT 2.0% to NMT 5.0%, to be consistent with the sponsor's validated procedure.

Response: Comment incorporated.

Comment Summary #3: The commenters evaluated the test for *Organic Impurities* using the USP reference standards for repaglinide related compounds A, B and C and reported discrepancies between the relative response factors obtained and the values proposed.

Response: Comment not incorporated. USP reference standards for repaglinide related compounds A, B and C are not labeled as quantitative standards and may not be suitable for the determination of relative response factors.

Comment Summary #4: The commenter requested changing the chemical name for USP Repaglinide Related Compound E RS from "2-Ethoxy-4-[2-[(1R)-3-methyl-1-[2-(piperidin-1-yl)phenyl]butyl]amino]-2-oxoethyl]benzoic acid" to "(R)-2-Ethoxy-4-[2-({3-methyl-1-[2-(piperidin-1-yl)phenyl]butyl}amino)-2-oxoethyl] benzoic acid" to be consistent with the reference standard labeling.

Response: Comment incorporated.

Monograph/Section: Tetracaine/USP Reference Standards

Expert Committee: Monographs—Small Molecules 4

Expert Committee-Initiated Change #1: The *USP Reference Standards* section of the monograph was revised to add USP Tetracaine RS, which is used in *Identification A*.

Monograph/Section(s): Tienchi Ginseng Root and Rhizome/Labeling

Expert Committee: Monographs—Dietary Supplements and Herbal Medicines

No. of Commenters: 1

Comment Summary #1: The commenter indicated that the labelling as written repeats the information provided in the monograph titles.

Response: Comment not incorporated. The current format is utilized in all dietary supplement monographs. The Expert Committee may consider future revisions to this format.

Monograph/Section(s): Tienchi Ginseng Root and Rhizome Dry Extract/Labeling

Expert Committee: Monographs—Dietary Supplements and Herbal Medicines

No. of Commenters: 1

Comment Summary #1: The commenter indicated that the labelling as written repeats the information provided in the monograph titles.

Response: Comment not incorporated. The current format is utilized in all dietary supplement monographs. The Expert Committee may consider future revisions to this format.

Monograph/Section(s): Tienchi Ginseng Root and Rhizome Powder/Labeling
Expert Committee: Monographs—Dietary Supplements and Herbal Medicines

No. of Commenters: 1

Comment Summary #1: The commenter indicated that the labelling as written repeats the information provided in the monograph titles.

Response: Comment not incorporated. The current format is utilized in all dietary supplement monographs. The Expert Committee may consider future revisions to this format.