***Commentary***

***USP 39–NF 34***

November 2, 2015

In accordance with USP's Rules and Procedures of the 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 Notices and Requirements

**General Chapters:**

- <129> *Analytical Procedures for Recombinant Therapeutic Monoclonal Antibodies*
- <661> *Containers—Plastics*
- <661.1> *Plastic Materials of Construction*
- <661.2> *Plastic Packaging Systems for Pharmaceutical Use*
- <670> *Containers—Auxiliary Components*
- <711> *Dissolution*
- <730> *Plasma Spectrochemistry*
- <790> *Visible Particulates in Injections*
- <855> *Nephelometry, Turbidimetry, and Visual Comparison*
- <914> *Viscosity-Pressure Driven Methods*
- <1059> *Excipient Performance*
- <1251> *Weighing on an Analytical Balance*
- <1661> *Evaluation of Plastic Packaging Systems and their Materials of Construction with Respect to their User Safety Impact*
- <1730> *Plasma Spectrochemistry—Theory and Practice*
- <1735> *X-Ray Fluorescence Spectrometry—Theory and Practice*
- <2040> *Disintegration and Dissolution of Dietary Supplements*

**Monographs:**

- *Abiraterone Acetate*
- *Abiraterone Acetate Tablets*
- *Aprepitant*
- *Aprepitant Capsules*
- *Aripiprazole Orally Disintegrating Tablets*
- *Aripiprazole Tablets*
- *Ascorbic Acid Tablets*
- *Bacitracin*
- *Bacitracin Zinc*
- *Budesonide*
- *Butylated Hydroxyanisole*
- *Calcipotriene*
- *Calcipotriene Ointment*
- *Calcium Gluconate*
- *Candesartan Cilexetil and Hydrochlorothiazide Tablets*
- *Ciprofloxacin Ophthalmic Ointment*
- *Clotrimazole Lozenges*
- *Clotrimazole Topical Solution*
- *Clotrimazole Vaginal Inserts*
- *Cyclobenzaprine Hydrochloride Extended-Release Capsules*
- *Dalteparin Sodium*
- *Diclofenac Potassium Tablets*
- *Diclofenac Sodium Delayed-Release Tablets*
- *Diphenhydramine and Phenylephrine Hydrochlorides Tablets*
- *Diphenhydramine Hydrochloride Capsules*
- *Diphenhydramine Hydrochloride Injection*
- *Diphenhydramine Hydrochloride Oral Solution*
- *Entecavir*

- *Epitetracycline Hydrochloride*
- *Erythromycin Ophthalmic Ointment*
- *Eszopiclone*
- *Eszopiclone Tablets*
- *Ethylparaben Sodium*
- *Fluconazole in Sodium Chloride Injection*
- *Fluconazole Injection*
- *Fluticasone Propionate and Salmeterol Inhalation Aerosol*
- *Fluticasone Propionate and Salmeterol Inhalation Powder*
- *Glyceryl Monocaprylate*
- *Iodixanol*
- *Ketorolac Tromethamine Injection*
- *Lidocaine Hydrochloride*
- *Meloxicam*
- *Memantine Hydrochloride*
- *Mesalamine*
- *Methocarbamol Injection*
- *Montelukast Sodium Chewable Tablets*
- *Montelukast Sodium Oral Granules*
- *Montelukast Sodium Tablets*
- *Mycophenolate Sodium*
- *Mycophenolic Acid Delayed-Release Tablets*
- *Orphenadrine Citrate Injection*
- *Oxacillin Sodium*
- *Paliperidone*
- *Phenylephrine Hydrochloride Tablets*
- *Pyridostigmine Bromide Tablets*
- *Simvastatin Tablets*
- *Sitagliptin Phosphate*
- *Sitagliptin Tablets*
- *Sodium Salicylate*
- *Teriparatide*
- *Tetracycline*
- *Tetracycline Hydrochloride*
- *Tetracycline Hydrochloride Capsules*
- *Tolcapone*
- *Valine*

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

***General Chapters***

- <21> Thermometers
- <162> Diphtheria Antitoxin Potency Testing For Human Immune Globulin
- <411> Folic Acid Assay
- <503> Acetic Acid in Peptides
- <503.1> Trifluoroacetic Acid (TFA) In Peptides
- <580> Vitamin C Assay
- <751> Metal Particles in Ophthalmic Ointments
- <771> Ophthalmic Ointments
- <851> Spectrophotometry and Light-Scattering
- <1045> Biotechnology-Derived Articles
- <1771> Ophthalmic Products—Performance Tests

**Monographs:**

- 5-Hydroxy-L-Tryptophan
- Aminolevulinic Acid Hydrochloride
- Antazoline Phosphate
- Astragalus Root
- Astragalus Root Dry Extract
- Astragalus Root Powder
- Atropine Sulfate Ophthalmic Ointment
- Bacitracin Ophthalmic Ointment
- Bacitracin Zinc and Polymyxin B Sulfate Ophthalmic Ointment
- Benzocaine and Menthol Topical Aerosol
- Benzocaine Lozenges
- Benzocaine Otic Solution
- Bland Lubricating Ophthalmic Ointment
- Borage Seed Oil
- Chloramphenicol and Polymyxin B Sulfate Ophthalmic Ointment
- Chloramphenicol Ophthalmic Ointment
- Chlortetracycline Hydrochloride Ophthalmic Ointment
- Cholesterol
- Chondroitin Sulfate Sodium, Shark
- Cloxacillin Sodium
- Dexamethasone Sodium Phosphate Ophthalmic Ointment
- Diclofenac Sodium Extended-Release Tablets
- Dicloxacillin Sodium
- Enalapril Maleate Tablets
- Entecavir Tablets
- Ephedrine Sulfate Injection
- Evening Primrose Oil
- Flax Seed Oil
- Fluorescein Sodium
- Gentamicin and Prednisolone Acetate Ophthalmic Ointment
- Gentamicin Sulfate Ophthalmic Ointment
- Glyceryl Monocaprylocaprate
- Halcinonide
- Halcinonide Cream
- Halcinonide Ointment
- Hydrocortisone Acetate Ophthalmic Ointment
- Idoxuridine Ophthalmic Ointment
- Iohexol
- Ketorolac Tromethamine Tablets
- Loratadine Tablets
- Neomycin and Polymyxin B Sulfates and Bacitracin Ophthalmic Ointment

- Neomycin and Polymyxin B Sulfates and Bacitracin Zinc Ophthalmic Ointment
- Neomycin and Polymyxin B Sulfates and Dexamethasone Ophthalmic Ointment
- Neomycin and Polymyxin B Sulfates Ophthalmic Ointment
- Neomycin and Polymyxin B Sulfates, Bacitracin Zinc, and Hydrocortisone Ophthalmic Ointment
- Neomycin and Polymyxin B Sulfates, Bacitracin Zinc, and Hydrocortisone Acetate Ophthalmic Ointment
- Neomycin and Polymyxin B Sulfates, Bacitracin, and Hydrocortisone Acetate Ophthalmic Ointment
- Neomycin Sulfate and Dexamethasone Sodium Phosphate Ophthalmic Ointment
- Neomycin Sulfate Ophthalmic Ointment
- Oil- and Water-Soluble Vitamins Capsules
- Oil- and Water-Soluble Vitamins Oral Solution
- Oil- and Water-Soluble Vitamins Tablets
- Oil- and Water-Soluble Vitamins with Minerals Capsules
- Oil- and Water-Soluble Vitamins with Minerals Oral Solution
- Oil- and Water-Soluble Vitamins with Minerals Tablets
- Orphenadrine Citrate Extended-Release Tablets
- Oxytetracycline Hydrochloride and Polymyxin B Sulfate Ophthalmic Ointment
- Pancuronium Bromide Injection
- Pharmaceutical Glaze
- Propoxyphene Hydrochloride
- Propoxyphene Hydrochloride and Acetaminophen Tablets
- Propoxyphene Hydrochloride Capsules
- Propoxyphene Hydrochloride, Aspirin, and Caffeine Capsules
- Propoxyphene Napsylate
- Propoxyphene Napsylate and Acetaminophen Tablets
- Propoxyphene Napsylate and Aspirin Tablets
- Propoxyphene Napsylate Oral Suspension
- Propoxyphene Napsylate Tablets
- Salycylamide
- Sesame Oil
- Sodium Chloride Ophthalmic Ointment
- Sodium Salicylate Tablets
- Sulfacetamide Sodium and Prednisolone Acetate Ophthalmic Ointment
- Sulfacetamide Sodium Ophthalmic Ointment
- Tetracycline Hydrochloride Ophthalmic Ointment
- Thyroid
- Thyroid Tablets
- Tobramycin and Dexamethasone Ophthalmic Ointment
- Tobramycin Ophthalmic Ointment
- Tolcapone Tablets
- Trihexyphenidyl Hydrochloride
- Water-Soluble Vitamins Capsules
- Water-Soluble Vitamins Tablets
- Water-Soluble Vitamins with Minerals Capsules
- Water-Soluble Vitamins with Minerals Tablets
- Zaleplon

**General Notices Sections:** General Notices & Requirements/Multiple Sections
**Expert Committee:** Council of Experts
**No. of Commenters:** 4

***2.10 Official Text***
**Comment Summary #1:** The commenter suggested adding language to the *General Notices* to make clear that general chapters numbered below 1000, which are not referenced in a monograph, another general chapter, or the *General Notices* are for stakeholder use, but are not mandatory.
**Response:** Comment incorporated. The Council of Experts agreed there is a need to clarify the applicability of general chapters. This text was revised and moved to a more appropriate section, 3.10 *Applicability of Standards*. See Expert Committee-initiated Change #1, below, for further revisions to this text.

***2.20 Official Articles***
**Comment Summary #2:** The commenter suggested revising the *General Notices* such that all terms are consistent with those defined in Section 2.20 (i.e. drug substances, drug products, excipients, etc.) and in cases where a deviation is necessary, adding the definition of the term.
**Response:** Comment not incorporated. The Council of Experts may consider this suggestion in a future *General Notices* revision.

***3.10 Applicability of Standards***
**Comment Summary #3:** The commenter indicated that manufacturing specifications and practices are not limited by the compendium and are developed with the goals being patient safety and quality.
**Response:** Comment incorporated. The text “developed and” was removed.
**Comment Summary #4:** The commenter indicated that Section 3.10 does not clarify how industry should understand and use USP tests. The frequency of testing and sampling are left to the user, which creates a range of possible standards, rather than one standard. Additionally, the removal of the sentence, “[t]he similarity to statistical procedures may seem to suggest an intent to make inference to some larger group of units, but in all cases, statements about whether the compendial standard is met apply only to the units tested” makes the meaning of a sample failure unclear.
**Response:** Comment partially incorporated. The sentence addressing the similarity of compendial tests to statistical procedures was added back to Section 3.10. The Council of Experts will consider further revisions on this section.
**Comment Summary #5:** The commenter suggested revising the sentence, “[t]hese tests, albeit using a number of dosage units, are in fact one determination” to replace the word “determination” with “a single reportable value.” This change would bring consistency to the use of the term “determination,” which is used in Sections 5.70 and 7.10 to refer to a measurement on an individual dosage unit.
**Response:** Comment not incorporated. The Council of Experts agreed that the use of “determination” is appropriate in all cases.

***5.80 USP Reference Standards***
**Comment Summary #6:** The commenter indicated that because alternative methods are allowed per *General Notices,* the use of alternative reference standards should also be permitted and suggested adding the following text to the first paragraph, "Alternative reference standards may be used with data showing comparability to the official USP reference standard*.*"
**Response:** Comment not incorporated. The establishment of a reference material and its suitability for compendial uses requires qualification that goes beyond the establishment of comparability in the hands of the user for a given test, including establishment of traceability chains and value assignment.

***6.30. Alternative and Harmonized Methods and Procedures***
**Comment Summary #7:** The commenter indicated that because there is flexibility in the *General Notices* for methods and specifications, there should also be flexibility for validation criteria and suggested adding the following text to the first paragraph, "When specific requirements for validation criteria are presented in monographs and/or general chapter, the criteria represent general guidance on the given analysis. Where justified, alternative criteria can be applied. The addition or revisions to validation criteria does not impact established methods*.*"
**Response:** Comment not incorporated. Validation criteria in general chapters for specific procedures or analytical techniques represent the relevant Expert Committee's understanding of the minimum method capability for those procedures used in compendial testing.

***7.20. Rounding Rules***
**Comment Summary #8:** The commenter suggested revising the examples in the *Illustration of Rounding Numerical Values for Comparison with Requirements* table to make clear that unrounded values can contain more than one additional decimal place than the rounded value. This change would keep users from double-rounding.
**Response:** Comment not incorporated. The Council of Experts determined the table is sufficiently clear.

***9.10 Use of Metric Units Tests***
**Comment Summary #9:** The commenter noted that the section did not make clear whether all types of units could not be abbreviated or the word "units" could not be abbreviated.
**Response:** Comment incorporated. The sentence was changed from "[a]bbreviations for units or International Units shall not be used for labeling or prescribing purposes" to "[a]bbreviations for the terms "Units" or "International Units" shall not be used for labeling or prescribing purposes."

***10. Preservation, Packaging, Storage, and Labeling***
**Comment Summary #10:** The commenter suggested deleting the note that points users to the omission of much of *General Notices* Section 10.10 *Packaging and Storage*. The commenter noted that the note is redundant to the text in Section 10.10.
**Response:** Comment incorporated.

**Council of Experts-initiated Change #1:** The Council of Experts revised the policy that made applicable any general chapter numbered between 1000 and 1999 that is referenced by the *General Notices*, a monograph, or a general chapter numbered under 1000 so that general chapters numbered 1000-1999 are now for informational purposes only, regardless of citation.

Applicability of general chapter text was moved from Section 2.10 *Official Text* to Section 3.10 *Applicability of Standards*.

| | |
|---|---|
| **General Chapter/Sections:** | <129> Analytical Procedures for Recombinant Therapeutic Monoclonal Antibodies |
| **Expert Committee:** | General Chapters—Biological Analysis |
| **No. of Commenters:** | 7 |

***General Comments***

**Comment Summary #1:** The commenter indicated that the General Chapter provides very specific information and the specified parameters do not offer opportunity for optimization of the assay as potentially required for particular antibodies.

**Response:** Comment not incorporated. The option of using alternative methods and/or procedures is always open to stakeholders and is covered under *General Notices 6.30. Alternative and Harmonized Methods and Procedures*.

**Comment Summary #2:** The commenter questioned the suitability of a non-product specific standard for system suitability. The size exclusion chromatography and CE-SDS methods call for the use of a USP Monoclonal IgG System Suitability Reference Standard (RS). The commenter stated that it is general analytical practice to use a standard that is composed of the specific analyte to establish system suitability and a non-specific standard does not provide product-specific detail and consequently presents a suboptimal strategy for establishment of system suitability.

**Response:** Comment not incorporated. The proposed standard is aimed at providing means to independently control the analytical test procedure itself. These test procedures are designed as more or less “generic” for typical monoclonal antibodies. Thus it seems to be reasonable to provide also a “one for most purposes” standard. Depending on the specific product, a product specific reference standard may also be necessary.

**Comment Summary #3:** The commenter questioned the suitability of non-product specific methods. The commenter stated that the methods listed are general, non-product specific methods which may limit the use of more advanced methods that are currently in place or in development.

**Response:** Comment not incorporated. See *General Notices* 6.30 for using alternative methods.

***1. Size-Exclusion Chromatography***

**Comment Summary #4:** The commenter requested clarification regarding the applicability of size-exclusion chromatography method to all monoclonal antibodies.

**Response:** Comment incorporated. In the introduction, a statement was added that the suitability of the method will need to be confirmed for each molecule.

**Comment Summary #5:** The commenter stated that while Size-Exclusion Chromatography (SE-HPLC) is robust for measuring monomer and HMW species (aggregates), but the quantitation of LMW species (fragments) can be highly variable depending on the mAb studied the measurement of LMW species is better quantitated by CE-SDS.

**Response:** Comment incorporated. A clarification regarding the limited value of SE-HPLC for detecting LMW species was added.

**Comment Summary #6:** The commenter requested the definition of underlined terms in the following statement, “*The chromatogram of the System Suitability solution is <u>consistent</u> with the <u>typical</u> chromatogram as illustrated in the USP Certificate for USP Monoclonal IgG System*

*Suitability RS*." The commenter requested that these underlined terms be defined in the document and should be based on actual performance characteristics of the chromatography.
**Response:** Comment incorporated. The number and elution order of the peaks in the reference standard were added.
**Comment Summary #7:** The commenter suggested subtracting the blank rather than excluding peaks which may change in intensity due to co-elution of impurities and buffer contaminants.
**Response:** Comment not incorporated. Subtraction of the blank is not a common practice and has the potential to introduce artifacts as well as significantly increasing data processing time.
**Comment Summary #8:** The commenter suggested providing additional information on the statement *"bracketed with injections of the system suitability solution*."
**Response:** Comment incorporated. Text was revised to state, *"bracketed minimally with single injections of the system suitability solution".*

***2. Capillary SDS Electrophoresis (Reduced and Nonreduced)***
**Comment Summary #9:** The commenter suggested removing less than 1% impurity limit from the Acceptance criteria.
**Response:** Comment incorporated.
**Comment Summary #10:** The commenter indicated that USP IgG Monoclonal System Suitability RS has only 1% nonglycosylated heavy chain (NGHC) and would like USP to consider replacing it with IgG control standard provided by Beckman which has 10% NGHC content.
**Response:** Comment not incorporated. A typical monoclonal antibody product contains approximately 1% NGHC; therefore, USP IgG Monoclonal System Suitability RS is representative of typical commercial products, and it is clearly resolved allowing reliable quantitation.
**Comment Summary #11:** The commenter indicated that the following NOTE only accounts for the degradation of the antibody, "[NOTE—Slight variations in sample preparation may be necessary depending on the stability of the individual antibody. If 15 min incubation at 70 degrees leads to fragmentation or cleavage of disulfide bonds for a particular antibody sample, adjust the incubation time accordingly.] If the sample preparation is modified, the commenter requests clarification if that invalidates the performance of the rest of the method with respect to system suitability.
**Response:** Comment not incorporated. Most monoclonal antibodies are stable under these conditions and are sufficiently loaded with SDS to provide good analytical results
There are, however, some antibodies which are not as stable. In that case, use more gentle conditions, but also use these modified conditions for the preparation of the system suitability standard.
**Comment Summary #12:** The commenter requested flexible concentration of iodoacetamide concentration.
**Response:** Comment not incorporated. The stated concentration works for all monoclonal antibodies tested and it is in large molar excess.
**Comment Summary #13:** The commenter requested removing the usage of an internal 10 kDa marker as it is not needed for a relative purity testing by CE-SDS.
**Response:** Comment not incorporated. Using an internal marker with sharp signal intensity assures consistent results.

**Comment Summary #14:** The commenter requested removing the requirement on the total length as an effective length is described in the same sentence. The total length is too precise.
**Response:** Comment incorporated. Total length is important for electric conditions; however, the exact total length of capillary has been changed from 30.2 cm to 30 cm.
**Comment Summary #15:** The commenter requested replacing electrokinetic injection with hydrodynamic injection. The commenter noted that an electrokinetic injection is dependent on the protein concentration as well as the ionic strength of the sample buffer (product specific formulation buffer).
**Response:** Comment not incorporated. While this is theoretically correct, no large differences in signal heights for different formulations have been observed for all monoclonal antibodies tested.
**Comment Summary #16:** The commenter requested defining acceptance criteria for S/N or total peak area to ensure that each injection is within the working range of the method.
**Response:** Comment not incorporated. The exact values depend largely on the equipment.
**Comment Summary #17:** The commenter requested clarification on the purity of USP Monoclonal IgG System Suitability RS. The commenter questioned how a sample with 0.4 to 0.6% aggregate and 99.1 to 99.5% main peak in SEC method yields only 70-80% main peak in a CE purity method.
**Response:** Comment not incorporated. HP-SEC and CE-SDS are not directly comparable. Resolution in HP-SEC is relatively poor compared to CE-SDS. HP-SEC usually resolves between aggregates, dimers and monomers. HP-SEC is only of limited value for the quantitative determination of fragments if the molecular weight is relative close to the main component. HP-SEC separates according to the hydrodynamic radius of intact proteins. Even under non-reducing conditions CE-SDS completely unfolds the protein revealing even smaller differences between protein species.

***3. Oligosaccharide Analysis –Analysis of N-Linked Oligosaccharides of Monoclonal Antibodies***
**Comment Summary #18:** The commenter suggested providing a set of glycan standards.
**Response:** Comment not incorporated. The addition of glycan standards may be considered at a later date.
**Comment Summary #19:** The commenter suggested adding wording about properly validating the sample preparation steps as part of the method.
**Response:** Comment incorporated.

***3.1 Oligosaccharide Analysis—Analysis of N-Linked Oligosaccharides of Monoclonal Antibodies, Method A: Capillary Electrophoresis with Laser-Induced Fluorescence Detection***
**Comment Summary #20:** The commenter recommended that the digestion efficiency of the PNGase F and the labeling efficiency of the fluorophore must be optimized for all methods and not just for method B.
**Response:** Comment incorporated.
**Comment Summary #21:** The commenter suggested adding an internal standard for checking matrix effects and electrokinetic injections between each injection.
**Response:** Comment partially incorporated. Electrokinetic injection was replaced with hydrodynamic injection.

**Comment Summary #22:** The commenter recommended adding appropriate system suitability requirements.
**Response:** Comment not incorporated. The system suitability requirements may be added at a later date.

***3.2 Oligosaccharide Analysis—Analysis of N-Linked Oligosaccharides of Monoclonal Antibodies, Method B: Liquid Chromatography with Fluorescence Detection***
**Comment Summary #23:** The commenter recommended adding appropriate system suitability requirements.
**Response:** Comment not incorporated. The addition of system suitability requirements may be considered at a later date.

***3.3 Oligosaccharide Analysis—Sialic Acid Analysis***
**Comment Summary #24:** The commenter recommended adding appropriate system suitability requirements.
**Response:** Comment not incorporated. The addition of system suitability requirements may be considered at a later date.
**Comment Summary #25:** The commenter requested adding a provision to this procedure that if the sialic acid content is extremely low, it may not be a required test for that antibody. The commenter recommended offering provision of alternatives (i.e., HPLC-FLD on DMB derivitized sialic acid).
**Response:** Comment not incorporated. Including information on situations when a test should or should not be included is outside the scope for this General Chapter.

| | |
|---|---|
| **General Chapter/Sections:** | <661> Plastic Packaging Systems and Their Materials of Construction |
| **Expert Committees:** | General Chapters—Packaging, Storage and Distribution |
| **No. of Commenters:** | 14 |

***General***
**Comment Summary #1:** The commenter suggested that not all materials of construction need to be tested and that testing should be based on product risk and route of administration.
**Response:** Comment not incorporated. The Expert Committee's position is that there is a minimum quality standard (set of tests and specifications) for all materials and systems regardless of their application and the implied risk. Considering materials, as covered in <661.1> *Plastic Materials of Construction*, this minimum set of tests and specifications are: 1) their composition must be known; 2) their biocompatibility must be established; 2) their ability to leach relevant metals and metallic substances must be established, and; 3) general properties of extracted substances are known. Also, in <661.1> there is reduced testing allowed for low risk dosage forms. Considering systems and/or components, as covered in <661.2> *Containers – Plastics*, the ability of the component or system is required to be properly assessed by performing studies that consider the conditions of use. This is where the concept of risk management is properly applied. If the conditions of use are less risky, then the study design will reflect this lessened risk. If the conditions of use are more risky, then the study design will reflect this.

The Expert Committee does not agree with the assertion that a risk-based approach would conclude that no testing is necessary in certain low risk circumstances, as because no testing is only appropriate, if there is truly no risk.

**Comment Summary #2:** The commenter suggested referencing <1661> *Evaluation of Plastic Packaging Systems and their Materials of Construction with Respect to their User Safety Impact* in the General Chapter.

**Response:** Comment incorporated. The Expert Committee agreed to not place explanatory text in <661>, <661.1> or <661.2>, but rather to include the test and specification in the General Chapters. General Chapter <1661> was developed to give more background and explanation regarding the content and application of these General Chapters.

**Comment Summary #3:** The commenter suggested having an overview in the General Chapter that discusses the extent of testing needed for different dosage forms.

**Response:** Comment not incorporated. This information is provided in both <661.1> and <661.2>and therefore it is not necessary to include it in <661>.

**Comment Summary #4:** The commenter recommended adding reference to General Chapter(s) dealing with labels, inks, and adhesives which can also contribute leachables.

**Response:** Comment not incorporated. Labels, inks, and adhesives are parts of packaging per <659> *Packaging and Storage Requirements* and <1663> *Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems*; therefore, reference to General Chapters <659> and <1663> fulfills the commenter's recommendation.

**Comment Summary #5:** The commenter recommended adding a discussion on packaging performance testing.

**Response:** Comment not incorporated. The Expert Committee determined that packaging performance is outside the scope of the General Chapter. Performance requirements for packaging systems are typically done on a case-by-case basis and thus are very difficult to standardize.

***Introduction***

**Comment Summary #6:** The commenter suggested that the <659> definition for packaging systems does not include specificity for plastics and therefore the term should be removed from the introduction or modified to align with General Chapter <659>.

**Response:** Comment incorporated. The Introduction was revised to remove the definition.

***Scope***

**Comment Summary #7:** The commenter recommended using the term "potential leachables," which is a term that has been used within the industry for many years.

**Response:** Comment incorporated.

**Comment Summary 8:** The commenter suggested that the second bullet appears to be equating simulation studies with controlled extraction studies; however, they are not equivalent and should not be suggested to be so.

**Response:** Comment not incorporated. Controlled extraction studies do not require aggressive extraction. The term implies that the extraction conditions be controlled (specified) and that they be consistent with the intended use of the controlled extraction study. If the purpose of the controlled extraction study is to deformulate the test article, then aggressive conditions might be appropriate.

**Comment Summary #9:** The commenter recommended clarifying that leachables assessment should be performed by the pharmaceutical applicant using the therapeutic product in the pharmaceutical packaging/delivery system intended for the commercial market.
**Response:** Comment incorporated.
**Comment Summary #10:** The commenter suggested clarifying the definition of the phrase "materials of construction"
**Response:** Comment incorporated.
**Comment Summary #11:** The commenter recommended adding specifics around materials and packaging systems for API's and excipients.
**Response:** Comment not incorporated. The Expert Committee determined that this information is outside the scope of the General Chapter.
**Comment Summary #12:** The commenter requested that it be stated that extractable profiles can be used to establish extractable and leachable correlations.
**Response:** Comment incorporated.
**Comment Summary #13:** The commenter suggested that in some cases it may not be feasible to experimentally test the entire packaging system. Testing of individual components may be necessary and in some cases beneficial to understand where the highest chemical risk may occur. Component testing should not be omitted as an option.
**Response:** Comment incorporated. The option of component testing is discussed in <1661> *Evaluation of Plastic Packaging Systems and Their Materials of Construction with Respect to Their User Safety Impact*.

| | |
|---|---|
| **General Chapter/Section:** | <661.1> Plastic Packaging Systems for Pharmaceutical Use |
| **Expert Committee:** | General Chapters—Packaging, Storage and Distribution |
| **No. of Commenters:** | 14 |

***General***
**Comment Summary #1:** The commenter suggested that the physicochemical tests do not provide more helpful information than what can be provided from suppliers/manufacturers and should not be included in the chapter.
**Response:** Comment not incorporated. The value that the physiochemical tests are as follows:

- Acidity/alkalinity: One of the more significant issues with drug product stability (both chemical and physical) is pH. Drugs degrade faster or precipitate when they are out of the ph range. Thus knowing the material's acidity or alkalinity provides insight into the potential for this problem. Additionally, these alert one to look for acidic or basic extractables.
- UV absorbance: Provides an indication of the amount of organic extractables and their general chemical nature, which is useful.
- TOC: Provides an estimate of the total amount of organic extractables.

**Comment Summary #2:** The commenter indicated that the connection of <661.1> to the reference to 21 *CFR Indirect Food Additives* in <661.2> is not clear.
**Response:** Comment incorporated. Table 1 has been revised to provide greater clarity and to indicate when reference to *CFR Indirect Food Additives* is relevant and adequate.

***Introduction***

**Comment Summary #3:** The commenter suggested that polyvinyl chloride and vinyl chloride content should be evaluated separately from additives and extractable metals, as an additional measure of Composition.

**Response:** Comment incorporated. Appropriate text was added to the *Additives* section

**Comment Summary #4:** The commenter recommended that the minimum for well characterized materials be identity, and that using a risk-based approach should determine subsequent testing.

**Response:** Comment incorporated. Table 1 was revised to include such a risk-based approach. The approach allows reference to food additives to replace plastic additives for low risk dosage forms; however, this requirement is retained because reference to food additives does not address extractable metals.

***Scope***

**Comment Summary #5:** The commenter recommended that the General Chapter's scope be expanded to include requirements on stability testing of the product in the final packaging system.

**Response:** Comment not incorporated. The requirement to perform stability testing in the product stored in packaging is outside the scope <661.1>.

**Comment Summary #6:** The commenter recommended input regarding the handling of multiple layer materials or a statement that such materials are not within scope.

**Response:** Comment not incorporated. The new General Chapter <1661> establishes that a multi-layer structure is a component made up of individual materials of construction. Thus, <661.1> is not intended to apply to the film, but rather the resins that go into making the film. Component testing is addressed in <661.2>.

**Comment Summary #7:** The commenter suggested that clarification is needed in the General Chapter that science can drive the conclusion that data can be extended from one packaging system to another.

**Response:** Comment not incorporated. The General Chapter does not say suitability "must be established by testing," therefore, if suitability for use can be established based on sound science, it would fulfill the intent of the chapter.

**Comment Summary #8:** The commenter suggested clarifying which regulatory authorities would be considered acceptable in determining the appropriateness of a given packaging system.

**Response:** Comment not incorporated. Any regulatory authority is considered acceptable in determining the appropriateness of a packaging system within the region for which it has jurisdiction.

**Comment Summary #9:** The commenter suggested that alternate reference materials as well as test methods and procedures be allowed.

**Response:** Comment not incorporated. See *General Notices* 6.30 for using alternative methods.

***Table 1. Guidelines for Application of Tests***

**Comment Summary #10:** The commenter recommended that USP adopt ISO: 10993 as a standard as this would give a common standard across all markets.

**Response:** Comment not incorporated. The proper place for USP to consider ISO*:* 10993 is in General Chapters <87> and <88>, not in <661.1>.

**Comment Summary #11:** The commenter indicated that not all plastics need to be tested to meet USP Class VI.

**Response:** Comment not incorporated. General Chapter <661.1> does not indicate that all plastics have to be Class VI; it states that all plastics should be classified based on their intended use.

**Comment Summary #13:** The commenter suggested that the heavy metals and nonvolatile residue testing should not be omitted from the General Chapter

**Response:** Comment not incorporated. The Expert Committee deemed that these two tests do not add value in the new testing paradigm.

***Specifications. Polyethylene, Identification, Differential Scanning Calorimetry***

**Comment Summary #14:** The commenter suggested there is no benefit of doing Differential scanning calorimetry testing and comparing their thermograms. Many plastics have an overlapping Tg and Tm. The thermogram might be very different, especially for a semi-crystalline thermoplastic, depending on how the sample is prepared and processed (thermal history).

**Response:** Comment not incorporated. The Expert Committee understands that there is a certain amount of objectivity in these requirements; however, if a spectrum does not match the standard, but the sponsor believes that the sample is the material that it is claimed to be, the effort can be made to explain the differences, test spectrum versus reference spectrum. In this way, the testing is not likely to produce false positives (i.e., ID a material as PVC when in fact it is PP) and false negatives (PP is tested and does not meet the PP specs) can be managed by explanation.

***Specifications. Polypropylene, Extractable Metals***

**Comment Summary #15:** The commenter suggested that clarification is required regarding which metals should be addressed, based on the information provided in Table 2.

**Response:** Comment incorporated.

**Specifications. Polyethylene Terephthalate and Polyethylene Terephthalate G, Extractable Metals**

**Comment Summary #16:** The commenter indicated that the test for barium is not consistent with Table 2, which does not list this element as a required extractable metal.

**Response:** Comment incorporated.

**Comment Summary #17:** The commenter suggested the test for cobalt is not consistent with Table 2, which does not list this element as a required extractable metal.

**Response:** Comment incorporated.

**Comment Summary #18:** The commenter suggested the test for manganese is not consistent with Table 2, which does not list this element as a required extractable metal.

**Response:** Comment incorporated.

***Specifications. Polyvinyl Chloride, Identification, Differential scanning calorimetry***
**Comment Summary #19:** The commenter indicated that there are different types of PVC, e.g. plasticized and non-plasticized resulting in different properties and specifications and the General Chapter should reflect this.
**Response:** Comment incorporated.

***Specifications. Polyvinyl Chloride, Extractable Metals***
**Comment Summary #20:** The commenter suggested the test for barium is not consistent with Table 2, which does not list this element as a required extractable metal.
**Response:** Comment incorporated.
**Comment Summary #21:** The commenter suggested the test for cadmium is not consistent with Table 2, which does not list this element as a required extractable metal.
**Response:** Comment incorporated.
**Comment Summary #22:** The commenter suggested the test for calcium is not consistent with Table 2, which does not list this element as a required extractable metal.
**Response:** Comment incorporated.
**Comment Summary #23:** The commenter suggested the test for tin is not consistent with Table 2, which does not list this element as a required extractable metal.
**Response:** Comment incorporated.

***Specifications. Polyvinyl Chloride, Plastic Additives***
**Comment Summary #24:** The commenter indicated that a specific test procedure for di(2-ethylhexyl)phthalate should be provided as part of this General Chapter.
**Response:** Comment not incorporated. The test procedure for DEHP, TLC, is listed under the Section Test Methods, Plastic Additives, Polyvinyl Chloride and Vinyl Chloride
**Comment Summary #25:** The commenter indicated that VCM is not an additive, and the "additives" described for VCM are not typically added to VCM. While testing for these additives in PVC compound may be useful, testing for these additives in VCM (or in the PVC base polymer) would be of no value.
**Response:** Comment incorporated. A statement in the appropriate sections was added in the General Chapter to clarify that while VCM is not a plastic additive per say, it is an important residue that must be tested for. The test method and specification for VCM will be captured in the section on Plastic Additives.

***Test Methods. Identification***
**Comment Summary #26:** The commenter recommended using the term “melt index” instead of “melt temperature. “
**Response:** Comment incorporated.

***Physicochemical Test. Extractions***
**Comment Summary #27:** The commenter suggested the possibility that during the extraction and cooling the solution may lose some volume and adding a step for dilution to the original volume should loss occur.
**Response:** Comment incorporated.

**General Chapter/Section(s):** <661.2> Plastic Packaging Systems for Pharmaceutical Use
**Expert Committee:** General Chapters—Packaging, Storage and Distribution
**No. of Commenters:** 14

***General***

**Comment Summary #1:** The commenter suggested that not all materials of construction need to be tested and that testing should be based on product risk and route of administration.
**Response:** Comment not incorporated. The Expert Committee's position is determined that there is a minimum quality standard (set of tests and specifications) for all materials and systems regardless of their application and the implied risk. Considering materials, as covered in <661.1>, this minimum set of tests and specifications are: 1) their composition must be known; 2) their biocompatibility must be established; 2) their ability to leach relevant metals and metallic substances must be established, and; 3) general properties of extracted substances are known. Also, in <661.1> there is reduced testing allowed for low risk dosage forms.

Considering systems and/or components, as covered in <661.2>, the ability of the component or system is required to be properly assessed by performing studies that consider the conditions of use. This is where the concept of risk management is properly applied. If the conditions of use are less risky, then the study design will reflect this lessened risk. If the conditions of use are more risky, then the study design will reflect this.

The Expert Committee does not agree with the assertion that a risk-based approach would conclude that no testing is necessary in certain low risk circumstances because no testing is only appropriate if there is truly no risk.

**Comment Summary #2:** The commenter recommended that the first paragraph of the Introduction to <1661> clearly communicate the scope of the General Chapter.
**Response:** Comment incorporated.
**Comment Summary #3:** The commenter suggested that component testing should be a part of the scope of the General Chapter
**Response:** Comment incorporated.

***Scope***

**Comment Summary #4:** The commenter suggested deleting dry powder inhalers, metered dose inhalers and nebulizers and prefilled syringes from this list.
**Response:** Comment not incorporated. The paragraph was revised to clarify the Expert Committee's intent.
**Comment Summary #5:** The commenter indicated that because the General Chapter is applicable to plastic packaging systems the term "plastic" should be incorporated to accurately reflect the scope of the General Chapter.
**Response:** Comment incorporated.

***Test Methods—Biological Reactivity***

**Comment Summary #6:** The commenter recommended deleting testing for Topical Delivery Systems, Topical Solutions and Suspensions, and Topical and Lingual Aerosols, Oral Solutions

and Suspensions and Topical Powders, Oral Powders Oral Tablets and Oral (Hard and Soft Gelatin) Capsules.
**Response:** Comment not incorporated. The Expert Committee determined that the requirement is applicable and appropriate to all dosage forms.
**Comment Summary #7:** The commenter suggested that Class VI plastics are meant for use in implants and there is no reason to meet this requirement for inhalation or parenterals.
**Response:** Comment not incorporated. The current General Chapter does not indicate that all plastics have to be Class VI. It states that all plastics should be classified based on their intended use.

***Test Methods—Physiochemical Tests: Water Extraction***
**Comment Summary #8:** The commenter recommended allowing flexibility in using other inert materials in sealing glass flask for blank.
**Response:** Comment incorporated.
**Comment Summary #9:** The commenter indicated that under the subsection of acidity or alkalinity, there is not sufficient volume to achieve the desired results of the test.
**Response:** Comment incorporated.

***Test Methods—Physiochemical Tests: Total Terephthaloyl Moieties in Polyethylene Terephthalate and Polyethylene Terephthalate G Packaging Systems, preparations***
**Comment Summary #10:** The commenter suggested that the target temperature 49º for the incubation of the test article should include an allowable range of variation.(±) over a 10 day period and include the required temperature scale, i.e. Celsius.
**Response:** Comment not incorporated. This is consistent with USP usage for Celsius and range and is also consistent with current practice.
**Comment Summary #11:** The commenter requested clarification on whether the extracting media is prepared with hexane or n-heptane.
**Response:** Comment incorporated.

***Test Methods—Physiochemical Tests: Total Terephthaloyl Moieties in Polyethylene Terephthalate and Polyethylene Terephthalate G Packaging Systems, procedure***
**Comment Summary #12:** The commenter suggested clarification on whether the extracting media is prepared with hexane or n-heptane
**Response:** Comment incorporated.
***Specifications****—Physicochemical Tests*
**Comment Summary #13:** The commenter requested clarification on whether the extracting media is prepared with hexane or n-heptane.
**Response:** Comment incorporated.

***Specifications—Chemical Safety Assessment***
**Comment Summary #14:** The commenter indicated that in some cases it may not be feasible to experimentally test the entire packaging system. Testing of individual components may be necessary and in some cases beneficial to understand where is the highest chemical risk may occur. Component testing should not be omitted as an option.

**Response:** Comment incorporated. The option of component testing is discussed in <1661> *Evaluation of Plastic Packaging Systems and Their Materials of Construction with Respect to Their User Safety Impact*.

**General Chapter/Section:** <670> Containers—Auxiliary Components
**Expert Committee** General Chapters—Packaging, Storage and Distribution
**No. of Commenters:** 9

***General***

**Comment Summary #1:** The commenter suggested that the proposed changes to add standards for the various desiccant materials appear overly prescriptive and would like USP to consider General Chapter language that offers greater flexibility for alternate and newer methods
**Response:** Comment not incorporated. The *USP–NF* provides for the use of alternate methods in *General Notices* 6.30.
**Comment Summary #2:** The commenter recommended placing instructions on when to apply the General Chapter, as users cannot be expected to review every single chapter to determine whether it applies to their product or material.
**Response:** Comment not incorporated. The General Chapter does not mandate the use of a desiccant in any individual official article but provides standards for the most commonly used desiccants.
**Comment Summary #3:** The commenter indicated that the proposal is redundant or in conflict with other *USP–NF* text. Three of these desiccants have monographs already in other USP compendia: bentonite, calcium chloride, silica gel.
**Response:** Comment not incorporated. The specifications and tests for the desiccants listed in the General Chapter are based on the monographs listed in the *Food and Chemical Codex* (*FCC*) that without addition or modifications, are not appropriate for the testing of desiccants used as part of a packaging system.
**Comment Summary #4:** The commenter stated that no requirement or test method is provided to instruct manufacturers to test desiccant types other than those specifically listed and suggested that a general requirement be added.
**Response:** Comment incorporated.
**Comment Summary #5:** The commenter requested that the purpose of the required testing be described.
**Response:** Comment incorporated.
**Comment Summary #6:** The commenter recommended adding language on who should preform testing.
**Response:** Comment not incorporated. USP does not mandate in its General Chapters who is responsible for conducting testing.
**Comment Summary #7:** The commenter suggested adding a section on desiccants that contain carbon.
**Response:** Comment not incorporated. The Expert Committee may consider including desiccants that contain carbon in a future revision upon submission of supporting data.
**Comment Summary #8:** The commenter recommended clarifying what conditions are needed to ignite a sample using a Meker burner.
**Response:** Comment incorporated.

**Comment Summary #9:** The commenter recommended including special cases, such as a desiccant embedded into a carrier resin or bounded by a carrier.
**Response:** Comment incorporated.

***Bentonite. Inorganic impurities***
**Comment Summary #10:** The commenter indicated that the specification for Arsenic, NMT 100 mg/kg, is not correct and should be 10 mg/kg
**Response:** Comment incorporated.
**Comment Summary #11:** The commenter indicated that the specification for Lead, NMT 100 mg/kg, is not correct and should be 15 mg/kg
**Response:** Comment incorporated.

***Bentonite. Specific Tests, Moisture Adsorption Capacity***
**Comment Summary #12:** The commenter indicated that the acceptance criteria for Moisture Adsorption Capacity should be NLT 21%.
**Response:** Comment incorporated.
**Comment Summary #13:** The commenter suggested making a note that all references to moisture adsorption capacity and loss on drying/loss on ignition herein is currently related to standard "dry" desiccants.
**Response:** Comment incorporated.

***Bentonite. Specific Tests, Loss on Drying <731>***
**Comment Summary #14:** The commenter recommended adding that <670> testing should be done immediately after the first opening of the original packaging of the samples.
**Response:** Comment incorporated.

***Bentonite. Specific Tests, Moisture Adsorption Capacity***
**Comment Summary #15:** The commenter recommended changing the intermediate data point from 50% RH to 40% RH. 40% RH is a control point required by other standards and it is already common in the industry to conduct testing at this humidity level.
**Response:** Comment incorporated.
**Comment Summary #16:** The commenter recommended testing at only 40%RH and 80%RH to reduce the burden of control.
**Response:** Comment incorporated.
**Comment Summary #17:** The commenter recommended adding that <670> testing should be done immediately after the first opening of the original packaging of the samples.
**Response:** Comment incorporated.

***Calcium Oxide. Specific Tests***
**Comment Summary #18:** The commenter recommended including a specification for adsorption capacity for Calcium Oxide
**Response:** Comment incorporated.

***Molecular Sieves. Specific Tests, pH <791>***
**Comment Summary #19:** The commenter suggested that the upper specification limit for pH value appears to be challenging and recommended changing the specification upper limit from NMT 11 to NMT 12.0.
**Response:** Comment incorporated.

***Molecular Sieves. Specific Tests, Loss on Drying <731>***
**Comment Summary #20:** The commenter recommended adding that <670> testing should be done immediately after the first opening of the original packaging of the samples.
**Response:** Comment incorporated.

***Molecular Sieves. Specific Tests, Moisture Adsorption Capacity***
**Comment Summary #21:** In order to be consistent with the test conditions for silica gel and bentonite, the commenter recommended changing the intermediate data point from 50% RH to 40% RH.
**Response:** Comment incorporated.
**Comment Summary #22:** The commenter recommended adding that <670> testing should be done immediately after the first opening of the original packaging of the samples.
**Response:** Comment incorporated.

***Test Methods, Identification test B: Aluminum***
**Comment Summary #19:** The commenter indicated that Identification B needs to be done on two separate samples of the filtrate obtained from A and recommended rephrasing this section because the instructions have been misinterpreted.
**Response:** Comment incorporated.

***Silica Gel. Identification A***
**Comment Summary #24:** The commenter suggested changing the text to specify ammonium molybdate as the reactant, with addition of a sufficient amount of nitric acid, because the current reagent is not readily available.
**Response:** Comment incorporated. Instructions have been added as a footnote although USP also provides instructions in *Reagents: Test Solutions* (TS) on how to prepare this reactant.

***Silica Gel. Assay***
**Comment Summary #25:** The commenter recommended revising the instruction for better clarification.
**Response:** Comment incorporated.

**Silica Gel*. Inorganic impurities. Soluble Ionizable Salts*** (as $NaSO_3$)
**Comment Summary #26:** The commenter recommended specifying the type of the mixer to be used as well as the test temperature when determining Soluble Ionizable salts in Silica Gel.
**Response:** Comment not incorporated. The method stipulates a “high-speed mixer.” The Sample is measured against a control solution at the same temperature.

***Silica Gel. Specific Tests. pH <791>***

**Comment Summary #27:** The commenter recommended implementing a dedicated specification for Orange silica gels: 2 < pH < 8.

**Response:** Comment incorporated. The Reference to all moisture-indicating silica gels has been deleted; however, the specification for Orange silica remains unchanged.

***Silica Gel. Specific Tests. Loss on Drying <731>***

**Comment Summary #28:** The commenter recommended a drying time of 3hr at 145C and a 3.0% limit.

**Response:** Comment incorporated. Lab data confirms that 145°C for 3 hours of drying time with a specification of NMT 3.0% provides reproducible data.

**Comment Summary #29:** The commenter recommended adding in the USP <670> standard that testing has to be done immediately after the first opening of the original packaging of the samples

**Response:** Comment incorporated.

***Silica Gel. Specific Tests. Moisture Adsorption Capacity***

**Comment Summary #30:** The commenter recommended changing the intermediate data point from 50% RH to 40% RH. 40% RH is a control point required by other standards and it is already common in the industry to conduct testing at this humidity level.

**Response:** Comment incorporated.

**Comment Summary #31:** The commenter recommended adding that <670> testing should be done immediately after the first opening of the original packaging of the samples.

**Response:** Comment incorporated.

| | |
|---|---|
| **General Chapter/Section:** | <711> Dissolution/For Dosage Forms Containing or Coated with Gelatin |
| **Expert Committee:** | General Chapters—Dosage Forms |
| **No. of Commenters:** | 29 |

**Comment Summary #1:** The commenter suggested that <1094> Capsules - Dissolution Testing and Related Quality Attributes could propose alternate techniques to evaluate cross-linking such as NIR.

**Response:** Comment not incorporated. A revision will be made to <1094> to add more details on the possible ways of demonstrating the presence of cross-linking in gelatin capsules.

**Comment Summary #2:** The commenter suggested including that enzymes can be added to the dissolution medium, if there is interaction between ingredients in the capsule or ingredient and gelatin.

**Response:** Comment not incorporated. The text of <711> addresses only cross-linking. A revision will be made to <1094> to address potential interactions of the formulation with the gelatin capsule.

**Comment Summary #3:** The commenter suggested adding a more descriptive wording explaining how to confirm/observe cross-linking as it is currently described in the Stimuli article or new section in <1094>. This additional information in <711> would guide the analysts to decide when to stop current dissolution testing of cross linked drug product and change to an enzyme system.

**Response:** Comment not incorporated. A revision will be made to <1094> to add more details on the possible ways of demonstrating the presence of cross-linking in gelatin capsules.
**Comment Summary #4:** The commenter suggested adding the text “in the capsule material” in the sentence **“**For hard or soft gelatin capsules and gelatin-coated tablets that do not conform to the dissolution specification because of the presence of cross-linking, the dissolution procedure should be repeated with the addition of enzymes to the medium, as described below."
**Response:** Comment not incorporated. The procedure in <711> is applicable for both gelatin capsules and for gelatin coated tablets.
**Comment Summary #5:** The commenter suggested adding text explaining how to identify the presence of cross-linking.
**Response:** Comment not incorporated. A revision will be made to <1094> to add more details on the possible ways of demonstrating the presence of cross-linking in gelatin capsules.
**Comment Summary #6:** The commenter suggested standardizing the expression of the enzymes activities using Units/volume.
**Response:** Comment not incorporated. For pepsin, papain and pancreatin the activity is expressed as U/L. For bromelain the activity has to be expressed as gelatin digesting units (GDU)/L.
**Comment Summary #7:** The commenter suggested changing the statement, “750,000 Units/L or less” to “No more than 750,000 units/L” or adding a range, because the first statement is not clear and could result in the addition not enough pepsin.
**Response:** Comment not incorporated. The enzymes activities are already expressed as not more than (NMT).
**Comment Summary #8:** The commenter suggested providing more details on how to select the amount of enzymes to be added to the dissolution medium. The current text allows the interpretation that any amount up to the limit can be used.
**Response:** Comment not incorporated. Using the limit amount is the usual way to interpret NMT. A revision will be made to <1094> to provide more details on how to select the amount of enzymes.
**Comment Summary #9:** The commenter indicated that in some particular cases, such as aqueous microencapsulation, gelatin coating can intentionally be treated to get cross-linking. The required enzymatic activity to get full dissolution of the cross-linked coating may be higher that the concentrations described in the revision and it should be tailored on a case-by-case basis.
**Response:** Comment not incorporated. A revision will be made to <1094> to address special cases.
**Comment Summary #10:** The commenter suggested adding a statement that the activity from the label can be accepted. If the lab does not routinely run enzyme activity assays then it would not be recommended to perform for any of the enzymes and using the activity on the label is the preferred method.
**Response:** Comment not incorporated. The activity on the label is for informational purposes only and does not represent the actual activity of the enzyme.
**Comment Summary #11:** The commenter suggested the deletion of recommended typical pretreatment time.
**Response:** Comment not incorporated. The text is written in such a way to allow flexibility by the user.

**Comment Summary #12:** The commenter suggested the exclusion of the pre-treatment time from the total time of the test.
**Response:** Comment not incorporated. The text is written in such a way to allow flexibility by the user.
**Comment Summary #13:** The commenter stated that as the pretreatment time has to be included in the total dissolution time, for many products it needs a trial and error approach to minimize the time for disintegration in the presence of enzyme and the time needed for dissolving in the presence of the surfactant to still meet the specification. During the pretreatment time a poorly soluble compound coming out of the capsule requiring a surfactant will not be able to start dissolving while without crosslinking and without the pretreatment the release active can already dissolve. Therefore, considering the same spec, it can be an unfair comparison and still lead to false OOS results. As a result, including the pretreatment time in the total dissolution time in some cases can still be an overly conservative approach.
**Response:** Comment not incorporated. The text is written in such a way to allow flexibility by the user. A revision will be made to <1094> to give some recommendations on pre-treatment step development.
**Comment Summary #14:** The commenter recommended including the text “or interact with gelatin" in the pretreatment procedure to be used when the dissolution medium contains a surfactant or other ingredients known to denature the enzyme being used.
**Response:** Comment not included. The pre-treatment step is to avoid denaturation of the enzyme by any component of the dissolution medium.
**Comment Summary #15:** The commenter suggested including more details on how to run the pre-treatment step.
**Response:** Comment not incorporated. A revision will be made to <1094> to include more details on the pre-treatment step.
**Comment Summary #16:** The commenter indicated that information should be provided on what could be done if an ingredient present in the formulation denatures the enzyme and there is also evidence of cross-linking. The commenter also inquired whether there is any opportunity to empty the contents of the gelatin capsule into the dissolution vessel in response to this issue. One example is capsules containing bismuth subcitrate potassium that denatures pepsin in acidic conditions.
**Response:** Comment not incorporated. Enzyme inhibitors in the formulation would contact the enzyme only after the capsule ruptures. The enzyme is not needed when this occurs.
**Comment Summary #17:** The commenter indicated that the pre-treatment time should not be included in the total time, because it would be needed for breaking the capsule shell and expose the content to the medium. The dissolution of the capsules content starts when the capsule shell breaks. Usually capsule shell dissolution time is negligible towards the overall dissolution time; normal capsule shell dissolves in a few minutes. This is not the case when they are cross-linked therefore the dissolution time becomes more relevant.
**Response:** Comment not incorporated. Technically, dissolution of capsules should include the following steps: breaking of the capsule shell, content disintegration/disaggregation (or erosion), and dissolution. Breaking of the capsule shell is part of the dissolution and is the first step to make the drug available.
**Comment Summary #18:** The commenter indicated that enzymes are proteins, many of which are surface active and, depending upon the amount used, can affect the surface tension of water. Therefore, the addition of enzymes to dissolution media may contribute to an

improvement in the dissolution, which is partly related to a reduction in the surface tension of the medium (i.e. a surfactant effect) rather than just the activity of the enzyme on the gelatin capsule. The Commenter also suggested that for completeness, it would be useful to include a discussion of this and any suggested method of assessing the contribution of the surfactant effect, e.g. using un-aged capsules with/without enzymes or using aged capsules with denatured/non-denatured enzymes. Many enzymes can be denatured by heating above about 45°C. The effect of pepsin on surface tension is illustrated in the article, "Simulation of fasting gastric conditions and its importance for the in vivo dissolution of lipophilic compounds," Vertzoni et al, *European Journal Pharmaceutics and Biopharmaceutics*, Vol 60, 3, August 2005, p413-417.

**Response:** Comment not incorporated. Figures 6 and 7 in the *Stimuli* article published in *PF* 40(6) indicate the dissolution profile of non-cross-linked capsules with and without enzymes.

**Comment Summary #19:** The commenter indicated that based on the pH, proteolytic activity relationship diagram in the referred *Stimuli* article (Figure 3 and 5), the pH cut-off pH values in the proposed new monograph <711> are overly conservative. The commenter noted that pepsin works well in a buffer pH 4.5. As such for this buffer, the user can have the choice between pepsin and papain/bromelain. For pancreatin, the same applies for a buffer pH 6.5. The *Stimuli* article in Figure 12 (pH 4.5) and 16 (pH 6.5) should have added respectively pepsin and pancreatin to compare with the new enzymes to be convincing towards the proposed ranges. The commenter proposes to change the cut-off limits to:

Dissolution medium with pH <= 4.5: pepsin

Dissolution medium with pH > 4 and < 6.8: papain/bromelain

Dissolution medium with pH >= 6.5: pancreatin

**Response:** Comment not incorporated. Additional studies and data are needed to verify these proposed ranges.

**Comment Summary #20:** The commenter recommended justifying the rationality for increasing the pancreatin from 1750 USP Units/L of protease activity to 2000 USP Units/L of protease.

**Response:** Comment not incorporated. See the *Stimuli* article published in PF 40(6), which explains this rationale. It is the amount that gives a dissolution profile similar to the one obtained with pepsin at 750000 units/L.

**Comment Summary #21:** The commenter suggested including information on the evaluation of the stability of the API especially for the substances that have amide bond. The enzyme will increase the risk of hydrolysis of those substances.

**Response:** Comment not incorporated. A revision will be made to <1094> to address special cases.

**Comment Summary #22:** The commenter requested information on whether an in vitro in vivo correlation has been established previously without adding enzymes or increasing the pancreatin or without pretreatment and if it will be necessary to re-establish an in vitro in vivo correlation for the revised dissolution.

**Response:** Comment not incorporated. The revisions to the General Chapter are not retroactive. They will apply only for methods developed after the revision becomes official.

**General Chapter/Sections:** <730> Plasma Spectrochemistry/Multiple Sections
**Expert Committee:** General Chapters—Chemical analysis
**No. of Commenters:** 4

***Qualification Of Plasma Spectrophotometers – Performance Qualification* subsection**
**Comment Summary #1:** The commenter recommended revising the third sentence to state: "Appropriate solutions within the linear calibration range and similar in composition to the standard solutions used to prepare the initial calibration curve should be prepared and re-assayed as check standards at appropriate, pre-established intervals throughout the analysis of the samples," because there is no need for these to be the same as the calibration solutions, and some protocols explicitly exclude the standards from being used. These are often referred to as low level continuing calibration verification solution (LLCCV), typically at a concentration approximately equal to the second lowest standard concentration, the continuing calibration verification solution (CCV), typically at a concentration at the middle of the standard range, and the continuing calibration blank (CCB).
**Response:** Comment not incorporated. It is a common practice in the field of atomic spectroscopy to use calibration standard solutions as check standards at pre-established intervals throughout the analysis of samples. The intent of this General Chapter is to follow established practice in this field.
**Comment summary #2:** The commenter suggested revising the first sentence in the second paragraph to state, "For single-element ICP-OES analyses, when analytical wavelengths are between 200 and 500 nm, or concentrations are >1 ug/mL, the continuing calibration verification solutions should agree with its expected value to within±10%, or as specified in an individual monograph."
**Response:** Comment not incorporated. Please see response in Comment Summary #1.
**Comment Summary #3:** The commenter proposed revising the second sentence in the second paragraph state, "For multi-element ICP-OES analyses, when analytical wavelengths are <200 nm or >500 nm, or at concentrations of <1g/mL, the continuing calibration verification solutions should agree with its theoretical value to within ±20%, or as specified in an individual monograph."
**Response:** Comment not incorporated. Please see response in Comment Summary #1.

***Procedure. Standard Solution***
**Comment Summary #4:** The commenter suggested clarifying the following statement, "For these reasons, standard solutions with concentrations<10 ppm (w/v) should be retained for NMT 24 h, unless stability is demonstrated experimentally," because 10 ppm standards are common stock solutions for ICPMS, and are generally supplied with a certificate of analysis (COA) and an expiration date, which is typically 12-18 months after purchase. If the COA is accepted as evidence of stability, then the statement is acceptable.
**Response:** Comment not incorporated. While stock standards may be stable for extended periods of time, diluted stock standards may not exhibit the same level of stability.
**Comment Summary #5:** The commenter suggested correcting the error in the following sentence, "This method involves adding a known concentration of the analyte element to the sample at NMT two concentration levels against an unspiked sample preparation**,"** because it should read "NLT" instead of "NMT.

**Response:** Comment incorporated.
**Comment Summary #6:** The commenter indicated that the purpose of the second paragraph is not clear. It is typically acceptable to use the standard addition method with any instrumental method and it is not clear why this is specified here. The commenter proposes that it would be more useful to discuss the use of internal standards in ICPMS and ICPOES, as this is almost always required for these methods.
**Response:** Comment not incorporated. This section is provided so analysts are aware that they may use standard additions, if desired. Additional information regarding standard additions is also found within the General Chapter.

***Validation and Verification***
**Comment Summary #7:** The commenter requested a clarification on the need for numerical and specific validation criteria. The validation criteria should be established to demonstrate that the method is fit for purpose. It was further noted that the numerical values provided in this General Chapter are inconsistent with the USP's recent *Stimuli* article on lifecycle management of analytical methods.
**Response:** Comment not incorporated. The validation criteria are aligned with those in the General Chapter<233> *Elemental Impurities-—Procedures.*
**Comment Summary #8:** The commenter indicated that the validation criteria is stated as follows: "Validation criteria: 95.0%-105.0% mean recovery for the drug substance assay and the drug product assay, and 70.0%- 150.0% mean recovery for the impurity analysis. These criteria apply throughout the intended range."
ICP is a destructive technique and an organic drug substance will not generally survive; consequently, it will be rare to have drug substance assayed by a plasma spectroscopic method, unless it is composed of a single element.
**Response:** Comment incorporated. The sentence was revised to state**. "…**95.0%-105.0% mean recovery for assay and 70.0%-150.0% mean recovery for the impurity analysis."
**Comment Summary #9:** The commenter indicated that the validation criteria for Precision is almost exclusively used for analysis of metals and elemental impurities, and it is not clear if there are any drug substances that will be analyzed by plasma spectroscopy.
**Response:** Comment not incorporated. Although it is rare to perform assays using ICP-OES or ICP-MS, it is not out of the realm of published literature**.**

***Performance Characterization***
**Comment Summary # 10:** The commenter indicated that the proposed chapter claims different criteria for single-and multi-element analysis, which makes sense, but could be confusing, as not all possible concentration and wavelength ranges are covered therefore a table should be included to provide an overview for the operator.
**Response:** Comment not incorporated. Different instruments and different samples may require the use of different wavelengths for the same element. Because there are many experiment-specific parameters, it would be imprudent to restrict or limit wavelengths available for analyses by virtue of trying to establish a fully comprehensive table.

***Validation. Quantitation Limit***
**Comment Summary # 11:** The commenter indicated that the criteria for the recovery rate for spiked sample solution are missing.

**Response:** Comment not incorporated. Please refer to spike recovery requirements in <233>.

***Sample Preparation***

**Comment Summary #12:** The commenter recommended retaining the sentence, "The use of lab-ware that is certified to meet Class A tolerances for volumetric flasks is acceptable if the linearity,… have been experimentally demonstrated to be suitable for the purpose at hand," into the new General Chapter, because background metal levels coming from commercial Class A flasks may not always be suitable for the intended purpose of the testing therefore some flexibility is needed.

**Response:** Comment not incorporated. A reference is made to this potential issue in the *Procedure* section.

**Comment Summary #13:** The commenter requested including text to address the suitability of the one point standardization for limit tests and identification.

**Response:** Comment incorporated.

***Validation and Verification***

**Comment Summary # 14:** The commenter indicated that the General Chapter should also include the validation requirements for limit test, since limit tests are included in <233> as one of the valid analytical testing strategies.

**Response:** Comment not incorporated. Please refer to <233> for validation criteria for limit tests.

**General Chapter/Section:** <790> Visible Particulates in Injections/General
**Expert Committee:** General Chapters—Dosage Forms
**No. of Commenters:** 2

***Introduction***

**Comment Summary #1:** The commenter recommended adding additional information on the inspection of lyophilized and frozen products.

**Response:** Comment not incorporated. Due to the broad scope of this comment the Expert Committee requests additional information as to the specific information on the inspection of lyophilized and frozen products that should be added.

***Inspection Procedure***

**Comment Summary #2:** The commenter suggested that there should be an option to whether or not the label has to be removed before inspecting.

**Response:** Comment not incorporated. The USP provides for the use of alternate methods in General Notices 6.30.

**General Chapter/Section:** <855> Nephelometry, Turbidimetry, and Visual Comparison/Multiple Sections
**Expert Committee(s):** General Chapters—Chemical Analysis
**No. of Commenters:** 6

**Comment Summary #1:** Several commenters noted that the equation given for the relationship between turbidity and weight-average molecular weight is only formally correct for particles that are small relative to the wavelength of the incident light and which therefore scatter isotropically. If this condition is not met, then the infinite dilution value of the MW obtained at 90° scattering

angle will not be correct. The commenters suggest clarification on the valid range for the equation.
**Response:** Comment not incorporated. Additional text on this issue may be added in a future revision upon receipt of supporting data.
**Comment Summary #2:** The commenter noted that the equation [(n x $n_0$)/c] does not match the equivalent equation in <851>, which reads [(n - $n_0$)/c].
**Response:** Comment incorporated.
**Comment Summary #3:** The commenter indicated that color and turbidity assessments should be independently addressed. Additionally, viewing conditions should be tailored to intent/type of testing.
**Response:** Comment incorporated
**Comment Summary #4:** The commenter indicated that an additional 'Visual Assessment' section should be added for color/clarity testing. The section needs to review vessel parameters (should not require tube usage) and viewing conditions (aligning with verbiage in above comment) for non-comparison situations, when a determination of acceptability is against a text based requirement. This allows for alignment in the general practice of clarity and color testing.
**Response:** Comment not incorporated. The inclusion of assessment of color/turbidity in non-standardized conditions is outside the scope of this General Chapter.
**Comment Summary #5:** The commenter suggested that monographs (for example Copovidone) where color/clarity testing exists should reference the newly proposed *Visual Assessment* section of the General Chapter to ensure testing alignment.
**Response:** Comment not incorporated. References to the *Visual Assessment* General Chapter will be incorporated after it is approved by the Expert Committee.
**Comment Summary #6:** The commenter indicated that information on the *Qualification of Nephelometers* equipment is missing and suggested that some guidance should be given on this important technique.
**Response:** Comment not incorporated. Additional text providing guidance will be added in a future revision.
**Comment Summary #7:** The commenter indicated that the General Chapter should include the description of preparation of standard solutions (e.g. Formazin standards) to determine the NTU.
**Response**: Comment not incorporated. Additional text providing a description will be added in a future revision.
**Comment Summary #8:** The commenter indicated that the General Chapter should include a reference to/or of information from the detailed section *Appearance of Solution Turbidity/Opalescence and Color* in the General Chapter <381> *Elastomeric Closures for Injections*.
**Response:** Comment not incorporated. The references to the new General Chapter <381> will be incorporated in <855> after <381> is approved by the Expert Committee.
**Comment Summary #9:** The commenter suggested including a *System Suitability* test and requirements prior to performing the test.
**Response:** Comment not incorporated. Additional text regarding system suitability will be added in a future revision.

**General Chapter/Section:** <914> Viscosity—Pressure Driven Method/Method I. Slit Viscometers/Rheometers
**Expert Committee:** General Chapters—Physical Analysis
**No. of Commenters:** 1
**Comment Summary #1:** The commenter recommended replacing the word "Calculate" with "Calibrate" in the sentence, "Calculate individual pressure sensors by following the recommendations from the manufacturer" under the section *Calculation and Calibration*.
**Response:** Comment incorporated.

**General Chapter/Sections:** <1059> Excipients Performance/Multiple Sections
**Expert Committee:** General Chapters—Physical Analysis
**Expert Committee-initiated Change #1:** For the references to General Chapters <232> Elemental Impurities—Limits, <233> Elemental Impurities—Procedures, and <231> Heavy Metals the official date for implementation of <232> and <233> and omission of <231> was changed from "*USP 39–NF 34"* to "January 1, 2018" to align the change with the implementation date of *General Notices* Section 5.60.30: *Elemental Impurities in USP Drug Products and Dietary Supplements*.

**General Chapter/Sections:** <1251> Weighing on an Analytical Balance/Multiple Sections
**Expert Committee:** General Chapters—Physical Analysis
**No. of Commenters:** 4

***Introduction***
**Comment Summary #1:** The commenter requested the removal of the reference to *ASTM* E898, because it is in conflict with the recommendations in <1251> and represents outdated terminology.
**Response:** Comment incorporated.
**Expert Committee-initiated Change #1:** The reference to National Physical Laboratory's *Good Practice Guide No. 70, Weighing in the Pharmaceutical Industry*, 2004 was removed. The continued reference to this document would imply that tests outside of the recommendations in <1251> would need to be applied. The content of the General Chapter represents the current and complete recommendation of the Expert Committee.

***Qualification***
**Comment Summary #2:** The commenter requested clarification on the phrase change in weight value and the process to calculate the sensitivity of the balance as found in Table 1 *Suggested Performance Tests and Acceptance Criteria*.
**Response:** Comment incorporated. The revised definition of sensitivity adds additional information on this property.
**Comment Summary #3:** The commenter requested clarification of the 0.05% deviation given as the acceptance criteria for sensitivity given in Table 1.
**Response:** Comment incorporated. Additional information on the required ratio is provided in the revised Table 1 entry for acceptance criteria under *Sensitivity* in Table 1.
**Comment Summary #4:** The commenter requested clarification that the minimum weight as discussed in the section, *Minimum Weight*, is the individual weight observed and not the difference of weights that may be part of an analytical procedure.

**Response:** Comment incorporated.
**Comment Summary #5:** The commenter recommended the removal of the symbol, >, from the statement, "i.e., > the desired smallest net weight that the users plan to use…"
**Response:** Comment incorporated.
**Comment Summary #6:** The commenter recommended that weighing should be made at values equal to or larger than the minimum weight in contrast to the chapter text indicating only values larger than the minimum weight.
**Response:** Comment not incorporated. The minimum weight is determined at a point in time and is subject to fluctuation over time being based on an experimentally observed standard deviation. Weighing above the minimum weight reduces the chance of non-compliance when a subsequent observation finds the minimum weight above the value previously found.
**Comment Summary #7:** The commenter recommended that the General Chapter clarify that weighing by difference is an acceptable practice and that the calculated difference between two weights can be outside the range determined for minimum balance weight. Weighing by difference is a procedure used in General Chapters <281> Residue on Ignition, and <731> Loss on Drying and wording is needed in <1251> to specify that this practice is permitted.
**Response:** Comment not incorporated. The subsection, *Minimum Weight*, already defines weighing as consisting of two readings, without the sample and with the sample placed on the balance pan. The net sample weight is the difference between those two balance indications. Weighing by difference as described in <281> and <731> is therefore the calculated difference of two such net sample weights.

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|---|---|
| **General Chapter/Sections:** | <1661> Evaluation of Plastic Packaging Systems and Their Materials of Construction with Respect to Their User Safety Impact/Multiple Sections |
| **Expert Committee:** | General Chapters—Packaging, Storage and Distribution |
| **No. of Commenters:** | 5 |

***General Principles. The Overall Assessment Process***
**Comment Summary #1:** The commenter indicated that the section implies that <661.1> and <661.2> (including extractables and leachables) must be performed for all packaging systems. It is not clear in <661.2> if all three stages or only two of the three stages need to be performed
**Response:** Comment incorporated. <1661> and <661.2> were edited to provide clarification.

***General Principles. Materials Assessment: Characterization, Screening, and Selection, USP <661.1>***
**Comment Summary #2:** The commenter suggested that the requirement for biocompatibility is not justified for all dosage forms and routes of administration and recommended a risk-based approach.
**Response:** Comment incorporated. General Chapter <661.1> has been modified with respect to using a risk-based approach for biocompatibility requirements and General Chapter <1661> is modified to also reflect those changes.

***General Principles. Packaging System Assessment and Qualification, USP <661.2>***
**Comment Summary #3:** The commenter suggested that the requirement for biocompatibility is not justified for all dosage forms and routes of administration and recommended a risk-based approach.
**Response:** Comment incorporated. General Chapter <661.1> has been modified with respect to using a risk-based approach for biocompatibility requirements and <1661> is modified to also reflect those changes.
**Comment Summary #4:** The commenter recommended adding language from the EMEA *Guideline on Plastic Immediate Packaging Materials* that states, leachables studies may be omitted if data from extraction studies justify it.
**Response:** Comment incorporated.

***Applicability and Application of <661.1>. Applicability***
**Comment Summary #4:** The commenter suggested giving examples of "non-interacting material of construction" and "no direct contact material of construction."
**Response:** Comment incorporated.
**Comment Summary #5:** The commenter suggested that the section is not clear. Non-interacting materials are not discussed in <661.1>. If this section is included in <1661>, then non-interacting materials should be described/included in <661.1>.
**Response:** Comment not incorporated. The purpose of this section is to limit the scope of <661.1> to potentially interacting materials. As the concept of non-interacting materials is too complex to address in <661.1> it is properly addressed in sufficient detail in <1661>.
**Comment Summary 6:** The commenter indicated that the Reference Standards included in <661.1> are inadequate for the wide ranges of materials supported by <661.1>.
**Response:** Comment not incorporated. The flexibility in <661.1> concerning the test methods and the concept of “substantial equivalency” will be adequate for the purpose of identification.
**Comment Summary #7:** The commenter suggested that the ability to claim compliance based on having been accepted by the appropriate regulatory authority is unclear.
**Response:** Comment incorporated. The General Chapter was revised for clarification.
**Comment Summary #8:** The commenter suggested that the way the word “component” is being defined is inconsistent with the usage of this term by the FDA.
**Response:** Comment incorporated. The text was modified to address this issue.
**Comment Summary #10:** The commenter suggested that the list of plastic additives is not complete.
**Response:** Comment not incorporated. While the tests may be such that their purpose is not fully achieved, the purpose of the tests is properly stated. Future revisions of <661.1> will include additional tests for additional additives as necessary and appropriate.
**Comment Summary #11:** The commenter requested the addition of text stating that substitutions for specifications that exist in <661.1> are not allowed unless justified and subject to approval by an appropriate regulatory authority.
**Response:** Comment incorporated.

***Applicability and Application of <661.1>. Application***
**Comment Summary #12:** The commenter recommended that a risk-based approach be used.
**Response:** Comment incorporated. A risk based approach has been adopted for <661.1> and the text of <1661> has been modified to include the change to <661.1>.

***Description of Polymers Contained in <661.1>***
**Comment Summary #13:** The commenter suggested adding the material definition to <661.1>.
**Response:** Comment not incorporated. The exact location of these descriptions was dictated by the desire to keep <661.1> concise and focused on tests methods and specifications.
**Comment Summary #14:** The commenter recommended adding a section on Linear Low Density Polyethylene.
**Response:** Comment incorporated

***Description of Polymers Contained in <661.1>. Polyolefins***
**Comment Summary #15:** The commenter suggested that the polyolefin section is not accurate and needs to be revised.
**Response:** Comment incorporated. The entire section was modified to be specific for Cyclic Olefins.

**General Chapter/Section(s):** <1730> Plasma Spectrochemistry—Theory and Practice
**Expert Committee(s):** General Chapters—Chemical analysis
**No. of Commenters:** 1
**Comment Summary #1:** The commenter indicated that the internal standards were not discussed in the associated General Chapter <730> Plasma Spectrochemistry but discussed in the *Sample Preparation* section, where it states*, "*The use of an internal standard should be considered the rule, rather than the exception, in the case of ICP-MS analyses."
**Response:** Comment not incorporated. There is more information provided in <1730> than in <730>, because it is an informational chapter. The intent in <730> is to do not mandate the use of internal standards if they are not required.
**Comment Summary #2:** The commenter indicated that the following sentence in *Standard Preparation* section is correct:
"The method of standard additions involves adding a known concentration of the analyte element to the sample at no (fewer than two concentration levels plus an unspiked sample preparation" but General Chapter <730> Plasma Spectrochemistry erroneously states that it should be not more than 2 concentrations. Therefore the error in <730> should be corrected.
**Response:** Comment incorporated. The correction was made in General Chapter <730>.

**General Chapter/Section:** <1735> X-Ray Fluorescence Spectrometry.
**Expert Committee:** General Chapters—Chemical Analysis
**No. of Commenters:** 1
**Comment Summary #1:** The commenter suggested changing the term "lower limit of detection" in section 3.8 to "detection limit" which is the correct term according to *General Chapter <1125> Validation of Compendial Procedures*.
**Response:** Comment incorporated.
**Comment Summary #2:** The commenter indicated that the subtraction of background is an optional step as the algorithm for peak search can remove the background automatically therefore, the following statement in section 6.2 Qualitative Analysis should be modified, "*After the spectra have been collected, the background is subtracted."*
**Response:** Comment incorporated.

**Comment Summary #3:** The commenter requested addressing the interference between elements in the General Chapter as it is an important problem with qualitative analysis.
**Response:** Comment incorporated.

**General Chapter/Sections:** <2040> Disintegration and Dissolution of Dietary Supplements/Multiple Sections
**Expert Committee:** General Chapters—Dosage Forms
**No. of Commenters:** 7
**Comment Summary #1:** The commenter commented that not enough supporting data are provided to show that papain with activity of NMT 550,000 U/L or bromelain with activity of 30 GDU/L are appropriate to use for dissolution testing of cross-linked capsules.
**Response:** Comment not incorporated. The supporting data were presented in 2014 Dissolution Workshop and in the *Stimuli* article "Use of Enzymes in the Dissolution Testing of Gelatin Capsules and Gelatin-Coated Tablets" published in *Pharmacopeial Forum* 40(6).
**Comment Summary #2:** The commenter suggested clarifying if the use of enzymes is applicable to dietary supplements that have ingredients that are gelatin coated within the dosage form or in which gelatin is an ingredient in the dosage form.
**Response:** Comment not incorporated. A revision was made to <1094> Capsules-Dissolution Testing and Related Quality Attributes to address special cases.
**Comment Summary #3:** The commenter commented that dietary supplement gelatin capsules (soft-gelatin capsules) cannot meet <2040> Disintegration and Dissolution of Dietary Supplements acceptance criteria due to issues related to gelatin cross-linking during accelerated stability studies.
**Response:** Comment not incorporated. The relevant monograph(s), general chapter(s), and *General Notices* apply at all times in the life of the article from production to expiration when stored as directed.
**Comment Summary #4:** The commenter indicated that for specific types of dietary supplements the *Rupture test for soft shell capsules* is too stringent.
**Response:** Comment not incorporated. The Expert Committee concluded that there is no adequate justification to consider the additional changes of the revised *Rupture Test for Soft Shell Capsules*. Failure to comply with the requirements of the *Rupture test* may be due to a multitude of factors, including incompatible excipients, dietary ingredient interactions with the gelatin shell, or formulation issues.
**Comment Summary #5:** The commenter indicated that the *Rupture* test does not include accommodations for suspension filled products, as soft shell capsule rupture is very difficult to detect by operators and leads to QC failures, investigations, etc.
**Response:** Comment not incorporated. The *Rupture* test provides a fixed time (15 min); therefore, it is unnecessary to monitor the exact time when the rupture occurs. The capsules can be observed at the end of the test time.
**Comment Summary #6:** The commenter indicated that <2040> *Rupture Test for Soft Shell Capsules* is only for USP monographed dosage forms however other countries utilize General Chapter <2040> for all soft shell products. Typically other regulatory authorities require stability data to conform to General Chapter <2040>.
**Response:** Comment not incorporated. USP standards should be used considering the multiple interlaced parts of the compendia and not as separate independent pieces. General chapters, *General Notices*, and monographs are written to work together. Blanket regulatory enforcement

of <2040> by other countries to products without a monograph is outside the scope of the general chapter.

**Comment Summary #7:** The commenter suggested adding specific recommendations for testing of veggie softgel capsules. The veggie softgels are composed of starch, carrageenan, glycerin, and water. The starch is easy to dissolve in the low pH; therefore the use of simulated gastric fluid could be more appropriate for veggie softgels composed of starch and carrageenan.

**Response:** Comment not incorporated. The suggestion is outside the scope of the proposed revisions and will be considered as a request for future revision.

**Comment Summary #8:** The commenter recommended revising the *Disintegration* methods given in <701> and <2040> to allow, in the absence of monographs for probiotic capsules, the use of the disk, not only when prescribed, but when the capsule floats.

**Response:** Comment not incorporated. The wording in the General Chapters <2040> and <701> "if prescribed" indicates that the use of the disk is permitted if it is so stated in the individual monograph.

**Comment Summary #9:** The commenter indicated that all dietary supplements capsules and tablets are immediate release formulations; therefore, it would be worthwhile testing them through a disintegration test only, instead of a dissolution test.

**Response:** Comment not incorporated. GC <2040> applies to USP monograph dosage forms. It is not mandatory for a vast majority of dietary supplement products on the U.S. market today.

**Comment Summary #10:** The commenter recommended, in response to the proposed removal of the exception from compliance with the *Dissolution* requirements for chewable tablets, that compliance with *Disintegration* requirements for uncoated chewable products would be acceptable and that there would be no need to verify the release of the dietary ingredients via Dissolution from an uncoated dosage form that is labeled as a chewable product.

**Response:** Comment not incorporated. FDA guidance recommends that chewable tablets (as a whole) be subject to in vitro dissolution testing, because they might be swallowed by a user without proper chewing. In general, FDA guidance recommends that in vitro dissolution test conditions for chewable tablets be the same as for non-chewable tablets of the same active ingredient or moiety.

**Comment Summary #11:** The commenter indicated that further refinement of GC <2040>, perhaps finding ways to harmonize more effectively with both Health Canada Natural Health Products Directorate's Quality of Natural Health Products Guide options under their DO-25 method would be a service to the industry, allow more U.S. and multi-national companies to use, rely, and espouse USP's general chapters and monographs in their global markets, and drive a more interactive and mutually-reliable relationship between USP and this growing industry.

**Response:** Comment not incorporated. Disintegration apparatus in the DO-25 method is not comparable with USP compendial disintegration Apparatus A or Apparatus B, which are harmonized with *European Pharmacopoeia*. Also DO-25method is not intended to be applied to soft gelatin capsules. It was designed to measure the disintegration time of uncoated, plain coated and enteric coated tablets. The Quality of Natural Health Products Guide recommends "other pharmacopoeial methods", including USP, for testing hard and soft shell capsules disintegration times.

**Comment Summary #12:** The commenter provided suggestions for editorial revisions to strengthen the language of the General Chapter.

**Response:** Comment incorporated.

**Expert Committee-initiated Change #1:** The Expert Committee proposed to fix a typographical error and change the proposed activity of papain from NMT 555,000 U/L to NMT 550,000 U/L.

**Monograph/Sections:** Abiraterone Acetate/Multiple sections
**Expert Committee:** Monographs—Small Molecules 3
**No. of Commenters:** 8
**Comment Summary #1:** The commenter requested revising the storage condition from "Store at room temperature" to "Store at controlled room temperature," under *Packaging and Storage,* to be consistent with FDA approved requirements.
**Response:** Comment incorporated.
**Comment Summary #2:** The commenter requested adding 7-Ketoabiraterone acetate as a specified impurity in *Table 3* in the test for *Organic Impurities*.
**Response:** Comment not incorporated. The impurities listed *Table 3* reflect FDA requirements. The Expert Committee will consider revising the monograph upon receipt of supporting data.
**Comment Summary #3:** The commenter requested using lower UV wavelength than 254 nm for the detection of α-Epoxyabiraterone acetate and β-Epoxyabiraterone acetate in the test for *Organic Impurities* because of their better responses.
**Response:** Comment not incorporated. The Expert Committee determined that the test procedure is consistent with the validation data and suitable for its intended use.
**Comment Summary #4:** The commenter requested tightening the limits for specified impurities in the test for *Organic impurities* to be consistent with ICH guideline.
**Response:** Comment not incorporated. The acceptance criteria in the monograph reflect FDA approved requirements. The public standard is intended to address all approved drug products.
**Comment Summary #5:** The commenter requested replacing the L1 column used in the *Assay* and the test for *Organic Impurities* with an L11 phenyl column because high back pressure was observed with L1 column.
**Response:** Comment not incorporated. The procedure was evaluated in USP laboratory and no problems were reported.
**Comment Summary #6:** The commenter requested adding the specific optical rotation procedure to control the stereoisomeric purity.
**Response:** Comment not incorporated. The Expert Committee determined that the stereoisomeric control is not necessary for abiraterone acetate.
**Comment Summary #7:** The commenter requested revising the concentration of the *Sensitivity solution* to the level of disregard limit and the requirement for *signal to noise ratio* from NLT 5 to NLT 10 in the test for *Organic Impurities.*
**Response:** Comment incorporated.
**Comment Summary #8:** The commenter requested revising the test for *Organic Impurities* procedure with their in-house procedure to be capable of quantitating the impurities in their product.
**Response:** Comment not incorporated. The Expert Committee will consider revising the monograph upon receipt of supporting data.
**Comment Summary #9:** The commenter requested reducing the concentration for *Standard solution* in the test for *Organic Impurities.*
**Response:** Comment not incorporated. The Expert Committee determined that the procedure is suitable for its intended use.

**Comment Summary #10:** The commenter requested revising the molecular weight of 3-Deoxy-3-acetyl abiraterone-3-ene in *USP Reference Standards <11>* from 405.54 to 373.53.
**Response**: Comment incorporated.
**Comment Summary #11:** The commenter requested revising the *Assay procedure* to shorten the run time.
**Response:** Comment not incorporated. The Expert Committee determined that there are some operational advantages to use the same HPLC procedure for *Assay* and *Organic Impurities*.
**Comment Summary #12:** The commenter indicated the pH of *Solution A* in *Assay* is outside of the buffer capacity of the ammonium acetate buffer.
**Response:** Comment not incorporated. The ammonium acetate is intended to function as a salt in the *Mobile phase*.
**Comment Summary #13:** The commenter requested reducing the concentrations of *Standard solution* and *Sample solution* in *Assay*, because the abiraterone peak responses exceed 1 AU and can result in inaccurate assay determination.
**Response:** Comment not incorporated. The concentration in the monograph reflects the validated procedure. The Expert Committee determined that the validation adequately demonstrates the good accuracy and precision at the concentration of *Standard solution*.
**Comment Summary #14:** The commenter requested replacing the resolution requirement using unspecified impurities in the test for *Organic Impurities* with the resolution between specified impurities of α-epoxyabiraterone acetate and ß-epoxyabiraterone acetate, and ß-epoxyabiraterone acetate and abiraterone.
**Response:** Comment not incorporated. The Expert Committee determined that the resolution requirement in the monograph is suitable as proposed.

**Monograph/Sections:** Abiraterone Acetate Tablets/Multiple sections.
**Expert Committee:** Monographs—Small Molecules 3
**No. of Commenters:** 4
**Comment Summary #1:** The commenter requested replacing the HPLC procedure with an UV procedure in *Dissolution,* because of their concern with the abiraterone peak shape.
**Response:** Comment not incorporated. The dissolution procedure reflects FDA requirements. The Expert Committee will consider revising the monograph upon receipt of supporting data.
**Comment Summary #2:** The commenter requested revising the *Assay procedure* to shorten the run time.
**Response:** Comment not incorporated. The Expert Committee determined that there are some operational advantages to use the same HPLC procedure for *Assay* and *Organic Impurities*.
**Comment Summary #3:** The commenter indicated the pH of *Solution A* in *Assay* is outside of the buffer capacity of the ammonium acetate buffer.
**Response**: Comment not incorporated. The ammonium acetate is intended to function as a salt in the *Mobile phase*.
**Comment Summary #4:** The commenter requested reducing the concentrations of *Standard solution* and *Sample solution* in the *Assay* because the abiraterone peak responses exceed 1 AU and they can result in inaccurate assay determination.
**Response:** Comment not incorporated. The concentration in the monograph reflects the validated procedure. The Expert Committee determined that the validation adequately demonstrates the good accuracy and precision at the concentration of *Standard solution*.

**Comment Summary #5:** The commenter requested replacing the resolution requirement using unspecified impurities in *Organic Impurities* with the resolution between specified impurities of α-epoxyabiraterone acetate and ß-epoxyabiraterone acetate, and ß-epoxyabiraterone acetate and abiraterone.
**Response:** Comment not incorporated The Expert Committee determined that the resolution requirement in the monograph is suitable as proposed.
**Comment Summary #6:** The commenter requested revising the concentration of the *Sensitivity solution* to the level of disregard limit and the requirement for *signal to noise ratio* from NLT 5 to NLT 10.
**Response:** Comment incorporated.
**Comment Summary #7:** The commenter requested tightening the limits for α-epoxyabiraterone acetate and β-epoxyabiraterone acetate in *Organic Impurities* to be consistent with the ICH guideline.
**Response:** Comment not incorporated. The acceptance criteria in the monograph reflect FDA requirements. The public standard is intended to address all approved drug products.
**Comment Summary #8:** The commenter requested replacing L1 column used in the *Assay* and the test for *Organic impurities* with L11 phenyl column, because high back pressure was observed with L1 column.
**Response:** Comment not incorporated. The procedure was evaluated in USP laboratory and no problems were reported.
**Comment Summary #9:** The commenter requested revising the *Sample solution* preparation in *Assay* and *Organic Impurities* using whole tablets because of a safety concern.
**Response**: Comment not incorporated. The Expert Committee will consider revising the monograph upon receipt of supporting data.
**Comment Summary #10:** The commenter requested increasing the concentration of the *Sample solution* in order to detect some unspecified impurities.
**Response:** Comment not incorporated. The Expert Committee determined that the procedure is suitable for its intended use.
**Comment Summary #11:** The commenter requested reducing the concentration for *Standard solution* in the test for *Organic Impurities.*
**Response:** Comment not incorporated. The Expert Committee determined that the procedure is suitable for its intended use.
**Comment Summary #12:** The commenter requested including the degradation product N-oxide impurity in the test for *Organic Impurities*.
**Response:** Comment not incorporated. The impurities listed *Table 3* are in accordance with FDA requirements. The Expert Committee will consider revising the monograph upon receipt of supporting data.
**Comment Summary #13:** The commenter requested revising the test for *Organic Impurities* with their in-house procedure.
**Response:** Comment not incorporated. The Expert Committee will consider revising the monograph upon the receipt of supporting data.
**Comment Summary #14:** The commenter requested to verify the relative response factors listed in *Table 3* of *Organic Impurities* because these values are different from their internal procedure.
**Response:** Comment not incorporated. The Expert Committee determined that the relative response factors listed in *Table 3* are consistent with FDA requirements.

**Monograph/Sections:** Aprepitant/Multiple Sections
**Expert Committee:** Monographs—Small Molecules 3
**No. of Commenters:** 3
**Comment Summary #1:** The commenter recommended tightening the acceptance criteria for the total impurities under *Organic Impurities*.
**Response:** Comment not incorporated. The acceptance criteria in the proposal are consistent with FDA requirements. The public standard is intended to address all approved drug products.
**Comment Summary #2:** The commenter recommended revising the structure of Aprepitant following the IUPAC recommendations to include hashed lines instead of dashed lines for the bonds "beyond-the-plane."
**Response:** Comment incorporated.
**Comment Summary #3:** The commenter indicated that the test for *Organic Impurities* was not adequately selective for their product.
**Response:** Comment not incorporated. The Expert Committee determined that the procedure is adequately selective. The Expert Committee will consider revising the monograph upon the receipt of supporting data.
**Comment Summary #4: T**he commenter indicated that desfluoroaprepitant, coelutes with aprepitant peak in the test for *Enantiomeric purity* and -the proposed method may not have the selectivity to quantify the S, R, S enantiomer by area percent method.
**Response:** Comment not incorporated. The limit of desfluoroaprepitant is NMT 0.15%. Even if this impurity coelutes with the main peak, the effect on the percentage of S,R,S-enantiomer will be negligible.
**Comment Summary #5:** The commenter requested including their procedures for *Assay* and the test for *Organic Impurities* in the monograph using a flexible monograph approach.
**Response:** Comment not incorporated. The procedure in the monograph is suitable for separating all impurities listed in the commenter's supporting documentation.
**Comment Summary #6:** The commenter requested revising the test for *Water Determination* to provide flexibility to use either <921> *Method 1a* or <921> *Method* 1c.
**Response:** Comment incorporated.
**Comment Summary #7:** The commenter requested indicating that the test for *Enantiomeric purity* should be performed only when this impurity is possible from the manufacturing process.
**Response:** Comment incorporated. The name of the test is changed from "*Enantiomeric purity*" to "*Limit of S,R,S-enantiomer* (if present)," and a note is added to indicate that this test should be performed if this impurity is possible from the manufacturing process.

**Monograph/Sections:** Aprepitant Capsules/Multiple Sections
**Expert Committee:** Monographs—Small Molecules 3
**No. of Commenters:** 2
**Comment Summary #1:** The commenter requested including their procedures for Assay and the test for Organic Impurities, using a flexible monograph approach.
**Response:** Comment not incorporated. The procedure in the monograph is suitable for separating all impurities listed in the commenter's supporting documentation.
**Comment Summary #2:** The commenter requested to provide flexibility regarding the type of sinker used in *Dissolution* Test 2, by indicating that other suitable sinkers may be used.
**Response:** Comment incorporated.

**Monograph/Section:** Aripiprazole Orally-Disintegrating Tablets/Organic impurities
**Expert Committee:** Monographs—Small Molecules 4
**Expert Committee-initiated Change #1:** The definition of $r_T$ in the second equation in the test for *Organic Impurities* is revised to clarify that the result from the first equation should be used.

**Monograph/Sections:** Aripiprazole Tablets/Multiple sections
**Expert Committee:** Monographs—Small Molecules 4
**No. of Commenters:** 2
**Comment Summary #1:** The commenter requested widening the limits for aripiprazole related compound G and aripiprazole related compound F from NMT 0.20% to NMT 0.5% and for any unspecified degradation product from NMT 0.10% to NMT 0.2% in the test for *Organic Impurities*.
**Response:** Comment not incorporated. The limits are consistent with FDA requirements. The Expert Committee will consider revising the monograph upon receipt of supporting data.
**Comment Summary #2:** The commenter requested revising the acceptance criteria for tolerances from NLT 75% (Q) to NLT 80% (*Q*) in the *Dissolution* test.
**Response:** Comment not incorporated. The acceptance criteria for tolerances are consistent with the FDA requirements. The Expert Committee will consider revising the monograph upon receipt of supporting data.

**Monograph/Sections:** Ascorbic Acid Tablets/Multiple Sections
**Expert Committee** Monographs—Dietary Supplements and Herbal Medicines
**No. of Commenters:** 1
**Comment Summary #1:** The commenter indicated that the following phrase in the labeling section, “The Label also states whether it is to be disintegrated in the mouth” is not clear enough as to intention.
**Response:** Comment incorporated. The statement was revised to state, “Tablets that are intended to be disintegrated in the mouth before swallowing are so labeled.”
**Comment Summary #2:** The commenter indicated that the term “disintegrated” is not easily understandable by lay people and therefore is not friendly to a dietary supplement label.
**Response:** Comment not incorporated.

**Monograph/Section:** Bacitracin/Composition of Bacitracin
**Expert Committee:** Monographs—Small Molecules 1
**No. of Commenters:** 2
**Comment Summary #1:** The commenter requested replacing the procedure with the commenter’s validated procedure to align with the *Pharmeuropa* 26.4 revision proposal.
**Response:** Comment not incorporated. The Expert Committee will consider revising the monograph upon receipt of supporting data.
**Comment Summary #2:** The commenter requested replacing references to *retention time* in the *System suitability* subsection with *relative retention time*.
**Response:** Comment incorporated.

**Expert Committee-initiated Change #1:** A statement was added to the *Analysis* subsection to indicate that quantitative analysis is based on peak responses at 254 nm.

**Monograph/Section:** Bacitracin Zinc/Composition of Bacitracin
**Expert Committee:** Monographs—Small Molecules 1
**No. of Commenters:** 2
**Comment Summary #1:** The commenter requested replacing the procedure with the commenter's validated procedure to align with the *Pharmeuropa* 26.4 revision proposal.
**Response:** Comment not incorporated. The Expert Committee considers revising monographs based on supporting data.
**Comment Summary #2:** The commenter requested replacing references to *retention time* in the *System suitability* subsection with *relative retention time*.
**Response:** Comment incorporated.
**Expert Committee-initiated Change #1:** A statement was added to the *Analysis* subsection to indicate that quantitative analysis is based on peak responses at 254 nm.

**Monograph/Section:** Budesonide/Organic Impurities
**Expert Committee:** Monographs—Small Molecules 4
**No. of Commenters:** 1
**Comment Summary #1:** The commenter indicated that the wavelength change from 254 nm to 240 nm could result in the overestimation of some of the specified impurities unless appropriate relative response factors are applied.
**Response:** Comment not incorporated. Based on the supporting data, the Expert Committee determined that the validated procedure is suitable for the intended purpose.
**Comment Summary #2:** The commenter recommended the addition of a *Sensitivity solution* at the disregard limit of 0.05% with a signal to noise requirement of NLT 10 to ensure method robustness.
**Response:** Comment incorporated.

**Monograph/Section:** Butylated Hydroxyanisole/*Identification* test *B*
**Expert Committee:** Monographs—Excipients
**No. of Commenters:** 2
**Comment Summary #1:** The commenter recommended that the *Assay* test chromatographic conditions be changed to those proposed for *Identification* test *B* to minimize the burden for a lab to conduct two HPLC procedures for testing the material. The commenter questioned whether the *Assay* test chromatographic system has any advantage with the ability to separate the two isomers present in butylated hydroxyanisole (BHA).
**Response:** Comment not incorporated. Because BHA is a mixture of two isomers and these isomers have different response factors, it is not possible to recommend the exact content of each isomer in the standard solution in the *Assay* to match the sample composition. Under the proposed method conditions for *Identification* test *B,* the two isomers elute as a single peak. If this method is to be used for *Assay,* manufacturers and users may run into a situation where a perfectly good material will fail the *Assay* acceptance criteria. Although the butylated hydroxyanisole monograph does not have a requirement for the content of each isomer, the information obtained by the current *Assay* may be very important for drug formulators and excipient manufactures that produce butylated hydroxyanisole for the global market.

**Comment Summary #2:** The commenter indicated that the acceptance criteria in the proposed *Identification* test *B* are not clear.
**Response:** Comment not incorporated. The Expert Committee determined that the requirement "The chromatographic profile of the Sample solution should be similar to that of the Standard solution and exhibit only one major peak corresponding to butylated hydroxyanisole" in the acceptance criteria in the identification (ID) test, covers different aspects of the test such as identification of the target compound, which is the major (the biggest) butylated hydroxyanisole peak, and the sample impurity profile. If the sample profile does not match the standard profile, for example, butylated hydroxytoluene (BNT) is present then the sample fails the ID test.

**Comment Summary #3:** The commenter suggested including the BHA and the BHT retention time information from the *PF* briefing in the acceptance criteria of the *Identification* test *B.*
**Response:** Comment not incorporated. The Expert Committee concluded that specifying the BHT retention time may focus the users' attention on BHT only and other compounds in BHA samples may be overlooked.

**Monograph/Sections:** Calcipotriene/Multiple sections
**Expert Committee:** Monographs—Small Molecules 3
**No. of Commenters:** 3
**Comment Summary #1:** The commenter requested adding the acceptance criteria for total impurities in the test for *Organic Impurities*.
**Response:** Comment not incorporated. The test for *Organic Impurities by* HPLC has acceptance criteria for total impurities. The acceptance criteria in the monograph reflect FDA requirements.
**Comment Summary #2:** The commenter requested adding calcipotriene impurity B based on *European Pharmacopoeia,* in *Table 2* of the test for *Organic Impurities*, because it is a reversible isomerism of calcipotriene and a known degradation product.
**Response:** Comment not incorporated. The acceptance criteria reflect FDA requirements. The Expert Committee considers revising monographs based on supporting data.
**Comment Summary #3:** The commenter requested adding the flexible storage condition, "store at -20° or below" based on supporting data.
**Response:** Comment incorporated.

**Monograph/Sections:** Calcipotriene Ointment/Multiple sections
**Expert Committee:** Monographs—Small Molecules 3
**No. of Commenters:** 2
**Comment Summary #1:** The commenter requested adding the test for viscosity in the monograph.
**Response:** Comment not incorporated. The Expert Committee determined that viscosity is product dependent and the test for viscosity is not needed in the public standard.
**Comment Summary #2**: The commenter requested deleting the relative response factors in *Table 1* of the test for *Organic Impurities* to be consistent with the procedure in *Calcipotriene* monograph.
**Response:** Comment incorporated. The Expert Committee determined that the relative response factor for Calcipotriene related compound C calculated based on the linearity data is in the range of 0.8-1.2.

**Monograph/Sections:** Calcium Gluconate/Multiple Sections
**Expert Committee:** Monographs—Dietary Supplements
**No. of Commenters:** 1
**Comment Summary #1:** The commenter recommended the titration procedure in the Assay be replaced with a suitable HPLC procedure.
**Response:** Comment not incorporated. The Expert Committee will consider future revisions to this monograph upon the receipt of supporting data for a suitable HPLC procedure.
**Comment Summary #2:** The commenter recommended that a quantitative test for calcium content be included in the monograph, to be consistent with FDA requirements.
**Response:** Comment not incorporated. The current titration procedure in the Assay is a quantitative method suitable for determining the calcium content. The Expert Committee will consider using this titration as a specific test for calcium content determination in future revisions to this monograph upon receipt of supporting data.

**Monograph/Sections:** Candesartan Cilexetil and Hydrochlorothiazide Tablets/Multiple Sections
**Expert Committee:** Monographs—Small Molecules 2
**No. of Commenters:** 1
**Comment Summary #1:** The commenter requested revising the chemical names for candesartan cilexetil related compounds B, D, and F to be consistent with the current *USP* naming convention.
**Response:** Comment incorporated.
**Expert Committee-initiated change #1:** The wavelength range for the detector for *Identification* test *B* under *Assay* is revised to include the UV range 200 - 400 nm.

**Monograph/Section:** Ciprofloxacin Ophthalmic Ointment/Assay
**Expert Committee:** Monographs—Small Molecules 1
**No. of Commenters:** 1
**Comment summary #1:** The commenter requested correcting the concentration of tetrabutylammonium phosphate in the preparation of *Buffer* in the *Assay* from 0.17g/L to 1.7 g/L.
**Response:** Comment incorporated.

**Monograph/Section:** Clotrimazole Lozenges/Organic impurities
**Expert Committee:** Monographs—Small Molecules 1
**Expert Committee-initiated Change #1:** Widen the individual impurity limit in the test for *Organic Impurities* from NMT0.1% to NMT 0.2% to be consistent with ICH limits.

**Monograph/Section:** Clotrimazole Vaginal Inserts/Organic impurities
**Expert Committee:** Monographs—Small Molecules 1
**Expert Committee-initiated Change #1:** Widen the individual impurity limit in the test for *Organic Impurities* from NMT0.1% to NMT 0.2% to be consistent with ICH limits.

**Monograph/Section:** Clotrimazole Topical Solution/Organic impurities
**Expert Committee:** Monographs—Small Molecules 1
**Expert Committee-initiated Change #1:** Widen the individual impurity limit in the test for *Organic Impurities* from NMT0.1% to NMT 0.2% to be consistent with ICH limits.

**Monograph/Sections:** Cyclobenzaprine Hydrochloride Extended-Release Capsules/Multiple Sections
**Expert Committee:** Monographs—Small Molecules 4
**No. of Commenters:** 1
**Comment Summary #1:** The commenter requested adding an optional step in *Identification* test *A* to analyze the placebo and adding a statement in the corresponding acceptance criteria to exclude any absorption bands that may be attributable to excipients or placebo effects.
**Response:** Comment not incorporated. The Expert Committee determined that the acceptance criteria for *Identification* test *A* are appropriate as written.
**Comment Summary #2:** The commenter indicated that the *Assay* procedure is not suitable, because the separation between the peaks from cyclobenzaprine and cyclobenzaprine related compound B is not adequate.
**Response:** Comment not incorporated. The Expert Committee determined that the procedure is suitable as written
**Comment Summary #3:** The commenter requested removal of amitriptyline as degradation product from Table 2 and its associated system suitability requirements in the test for Organic impurities because it is not a degradation product.
**Response:** Comment incorporated.

**Monograph/Section:** Dalteparin Sodium/Identification
**Expert Committee:** Monographs—Biologics and Biotechnology 1
**No. of Commenters:** 2
**Comment Summary #1:** The commenter requested defining the concentration of deuterated trimethylsilylpriopionic acid (TSP) sodium salt to 0.002% (w/v) as was done in the Heparin Sodium monograph.

**Response:** Comment not incorporated. The TSP concentration in unfractionated heparin was to ensure that TSP signals do not interfere with accurate quantitation of oversulfated chondroitin sulfate (OSCS). Unfractionated heparin is used as raw material to produce dalteparin sodium. Because the current monograph specifies that the starting material has to comply with the quality requirements in the USP Heparin Sodium monograph, potential contamination of dalterparin sodium is not an issue. It was therefore proposed to retain the less prescriptive procedure, if it does not give rise to laboratory issues.
**Comment Summary #2:** The commenter stated that chemical shifts for system suitability are not exact and some are not correct.
**Response:** Comment incorporated. Correct chemical shifts were added.
**Comment Summary #3:** The commenter requested removing the freeze-drying step in the preparation of Standard solution and Sample solution.
**Response:** Comment incorporated. A NOTE states, “Depending on the field strength it may be beneficial to remove the water from the Standard solution and Sample solution.”

***Dalteparin Sodium/Boron***
**Comment Summary #4:** The commenter requested replacing the current Boron ICP method with ICP-MS.

**Response:** Comment not incorporated. The current boron method will be updated with ICP-MS method in a future revision.

***Dalteparin Sodium/Sulfate to Carboxylate Molar Ratio***
**Comment Summary #5:** The commenter requested including an upper limit of Sulfate to Carboxylate Molar Ratio.
**Response:** Comment not incorporated. The upper limit will be proposed in a future revision to allow stakeholders an opportunity to evaluate and comment.

***Dalteparin Sodium/Nitrite***
**Comment Summary #6:** The commenter requested changing the word "nitrate" to "nitrite" in the sentence "NLT 4000 theoretical plates for the nitrate peak for all calibration and sample solution runs" under Impurities, Limit of Nitrites, Suitability requirements, Column efficiency.
**Response:** Comment incorporated.

**Monograph/Section:** Diclofenac Potassium Tablets /Identification
**Expert Committee:** Monographs—Small Molecules 2
**No. of Commenters:** 1
**Comment Summary #1:** The Commenter recommended not deleting the *Potassium* identification test in order to identify the salt form.
**Response:** Comment not incorporated. The counter-ion is controlled in the drug substance monograph, which is consistent with USP practices.

**Monograph/Sections:** Diclofenac Sodium Delayed Release Tablets/Multiple
**Expert Committee:** Monographs—Small Molecules 2
**No. of Commenters:** 3
**Comment Summary #1:** The Commenter recommended modification of the gradient procedure in the test for *Organic Impurities* to mitigate potential interference from product matrix.
**Response:** Comment not incorporated. The Expert Committee determined that the test procedure is suitable for its intended use based on the validation data.
**Comment Summary #2:** The Commenter recommended tightening the limit for *Any Unspecified Impurities* to be consistent with the approved limits.
**Response:** Comment not incorporated. The proposed limit is consistent with FDA requirements. The public standard is intended to address all approved drug products.
**Comment Summary #3:** The Commenter recommended not removing the *Sodium* identification test in order to identify the salt form.
**Response:** Comment not incorporated**.** The counter-ion is controlled in the drug substance monograph, which is consistent with USP practices.

**Monograph/Sections:** Diphenhydramine and Phenylephrine Hydrochloride Tablets/Multiple Sections
**Expert Committee:** Monographs—Small Molecules 2
**No. of Commenters:** 1

**Comment Summary #1:** The commenter requested clarifying why plastic vials are required in the *Assay* and the tests for *Dissolution* when all standard and sample preparations do not state the use of plastic volumetric flasks.
**Response:** Comment incorporated. Based on the supporting information the statement, “Use plastic vials for analysis” was revised to “It is suggested to use plastic vials for analysis” in both tests.
**Comment Summary #2:** The commenter requested changing the wavelength range for the detector for *Identification test* A from UV 200-400 nm to UV 200-350 nm as phenylephrine does not absorb above 350 nm.
**Response:** Comment incorporated.
**Comment Summary #3:** The commenter requested changing the Tailing factor requirement from 0.5-3.0 to NMT 3.0 in the *Assay*.
**Response:** Comment not incorporated. The requirement for the Tailing factor is based on the validation data and the lower limit of 0.5 is used to control the fronting of both API peaks.
**Comment Summary #4:** The commenter requested the clarification of “non-activated” vials in the test for *Organic Impurities*.
**Response:** Comment incorporated. The term “non-activated” was replaced with “silanized” for clarification.
**Comment Summary #5:** The commenter requested clarification in designating impurity names, i.e., as acronyms or related compounds, and recommended designating impurity names as related compounds.
**Response:** Comment not incorporated. The Expert Committee determined that the impurity names are appropriate based on the current USP naming convention. Impurities are named as acronyms if they are not available as USP reference standards. Otherwise, they are named as USP related compounds
**Comment Summary #6:** The commenter recommended a general approach to address specifications for organic impurities in the USP OTC monographs.
**Response:** Comment not incorporated. USP is continuously working with the FDA and stakeholders to develop appropriate approaches to create/update OTC monographs. The Expert Committee will consider a revision to the monograph upon the receipt of supporting data.

**Monograph/Section(s):** Diphenhydramine Hydrochloride Capsules/Multiple Sections
**Expert Committee:** Monographs—Small Molecules 4
**No. of Commenters:** 2
**Comment Summary #1:** The commenter requested replacing the *Organic Nitrogenous Bases* <181> test for *Identification A* with a spectral match by PDA.
**Response:** Comment not incorporated. The Expert Committee will consider future revisions to this monograph upon the receipt of supporting data.
**Comment Summary #2:** The commenter requested removing benzophenone (diphenhydramine related **compound A?)** as specified impurities and individual unspecified impurity from Table 2 as a potential general approach for USP OTC monograph.
**Response:** Comment not incorporated. The Expert Committee will consider future revisions to the monograph upon the receipt of supporting data.
**Comment Summary #4:** The commenter requested removal of resolution from the system suitability requirements in the Assay.

**Response:** Comment not incorporated. The Expert Committee determined the system suitability requirements are appropriate based on the supporting data.
**Comment Summary #5:** The commenter requested the clarification of the acceptance criteria of each specified impurity and the associated qualification data.
**Response:** Comment not incorporated. The specifications for Organic impurities are consistent with FDA requirements.
**Comment Summary #6:** The commenter suggested that the acceptance criteria for unspecified impurities exceed the ICH Q3B identification threshold.
**Response:** Comment not incorporated. The specifications for Organic impurities are consistent with FDA requirements.

**Monograph/Section:** Diphenhydramine Hydrochloride Injection/Organic Impurities
**Expert Committee:** Monographs—Small Molecules 4
**No. of Commenters:** 1
**Comment Summary #1:** The commenter requested changing the impurity profile and tightening the limit of total impurities to be consistent with FDA requirements.
**Response:** Comment not incorporated. The specifications for *Organic Impurities* are consistent with FDA requirements. The public standard is intended to address all approved drug products.

**Monograph/Sections:** Diphenhydramine Hydrochloride Oral Solution/Multiple Sections
**Expert Committee:** Monographs—Small Molecules 4
**No. of Commenters:** 2
**Comment Summary #1:** The commenter suggested removing the acceptance criteria for benzophenone from *Table 2* in the test for *Organic Impurities* to reduce the complexity of modernizing diphenhydramine containing monographs stating that although the limit is acceptable, the likelihood that it will form is very small.
**Response:** Comment not incorporated**.** The tolerances in the monograph reflect FDA requirements.
**Comment Summary #2:** The commenter requested the removal of diphenhydramine related compound B from *Table 2* in the test for *Organic Impurities* because it is a formulation specific degradation product which should not be included in a public standard given the number of products from different producers.
**Response:** Comment not incorporated**.** The tolerances in the monograph reflect t FDA requirements. A footnote was added to *Table 2* to indicate monitoring of this degradation product in liquid formulations that contain glycerin.
**Comment Summary #3:** The commenter requested the removal of diphenhydramine related compound A from *Table 2* in the test for *Organic Impurities*, because it is a process related impurity and should only be used for resolution of system suitability purposes and not quantified, which would reduce the complexity of modernizing diphenhydramine containing monographs.
**Response:** Comment not incorporated**.** The tolerances in the monograph reflect FDA requirements. This degradation product has been observed in stability samples and is monitored under unspecified impurities.
**Comment Summary #4:** The commenter requested the removal of the acceptance criteria for “individual unspecified degradation products” and “total degradation products” in the test for

*Organic Impurities* to reduce the complexity of modernizing diphenhydramine containing monographs.
**Response:** Comment not incorporated**.** The tolerances in the monograph reflect FDA requirements.
**Comment Summary #5:** The commenter requested the removal of the impurities from the *Standard solution* and the use of relative response factors to quantify specified and unspecified impurities in the test for *Organic Impurities*.
**Response:** Comment not incorporated**.** The use of external standards for quantification of impurities is more accurate than using relative response factors.
**Comment Summary #6:** The commenter suggested that the limits shown in *Table 2* in the test for *Organic Impurities* should be dosage dependent.
**Response:** Comment not incorporated**.** The tolerances in the monograph reflect FDA requirements. No information is available to incorporate dosage dependent limits.
**Comment Summary #7:** The commenter requested clarification on using 272 nm up until 8.5 min in the test for *Organic Impurities*. The commenter also requested clarification of how unspecified impurities are quantified.
**Response:** A wavelength of 272 nm is used for optimal quantitation of sodium benzoate, which elutes prior to 8.5 min. All unspecified impurities are quantitated against diphenhydramine as specified in the monograph.
**Comment Summary #8:** The commenter requested increasing the disregard level from 0.05% to 0.1% in the test for *Organic Impurities* to be consistent with the ICH reporting threshold.
**Response:** Comment incorporated.
**Comment Summary #9:** The commenter suggested adding the chemical names for diphenhydramine related compound A and diphenhydramine related compound B to *Table 2* in the test for *Organic Impurities*.
**Response:** Comment not incorporated. Chemical information for the impurities is provided in the *Reference Standards <11>* section.
**Comment Summary #10:** The commenter used the *System suitability solution* in the test for *Organic Impurities* for determination of % RSD and had difficulty achieving typical method validation requirements for % RSD.
**Response:** Comment not incorporated. The *System suitability solution* in the method is used to determine resolution between several critical pairs of impurities. The % RSD is determined from the *Standard solution*.
**Comment Summary #11:** The commenter states that the approach to setting limits for impurities in this monograph is not focused on using the key degradant concept, as was used in the acetaminophen family of monographs
**Response:** Comment not incorporated. This is a topic for discussion by the Expert Committee on the need to form a future OTC Expert Panel to address this concern.
**Comment Summary #12:** The commenter requested the relocation of the test for A*lcohol Determination* from under *Other Components* to *Specific Tests* and the addition of “if present,” as not all Diphenhydramine Hydrochloride Oral solutions contain alcohol.
**Response:** Comment incorporated. This test is located under the appropriate heading, but “if present” was added.
**Comment Summary #13:** The commenter requested the removal of sodium perchlorate from the mobile phase in the *Assay,* because it is explosive.

**Response:** Comment not incorporated. The Expert Committee will consider revising the monograph upon the receipt of supporting data.
**Comment Summary #14:** The commenter requested the removal of the *System suitability solution* in the *Assay,* because resolution can be determined on each sample injection.
**Response:** Comment not incorporated. The *System suitability solution* contains diphenhydramine hydrochloride and diphenhydramine related compound A. The *Sample solution* contains diphenhydramine hydrochloride. Two components are required to determine resolution.
**Comment Summary #15:** The commenter requested revising the *Sample solution* in the *Assay* to allow for testing of oral solutions containing various label claims of diphenhydramine hydrochloride.
**Response:** Comment incorporated.
**Comment Summary #16:** The commenter requested revising the tailing factor requirement in the *Assay* from" 0.5- 2.0" to "NMT 2.0" for consistency with other monographs.
**Response:** Comment not incorporated. A tailing factor of "0.5- 2.0" is consistent with validation data supporting the Expert Committee's decision.
**Expert Committee-initiated Change #1:** The chemical name for diphenhydramine *N*-oxide was corrected in the *Reference Standards <11>* section.

**Monograph/Sections:** Entecavir/Multiple Sections
**Expert Committee:** Monographs—Small Molecules 1
**No. of Commenters:** 2
**Comment summary #1:** The commenter requested revising the calculation in the test for *Organic Impurities* to quantitate impurities against the Standard solution instead of by peak area normalization.
**Response:** Comment incorporated.
**Comment summary #2:** The commenter requested widening the acceptance criteria in the *Water Determination* from 5.5–7.0% to 5–7 %.
**Response:** Comment not incorporated. The acceptance criteria in the monograph reflect FDA requirements. The Expert Committee will consider revising the monograph upon receipt of supporting data.

**Monograph/Sections** Epitetracycline Hydrochloride/Multiple Sections
**Expert Committee:** Monographs—Small Molecules 1
**No. of Commenters:** 2
**Comment Summary #1:** The commenter requested correcting the spelling of the word "tetracycline" in the Assay and the test for Organic Impurities.
**Response:** Comment incorporated.
**Comment Summary #2:** The commenter requested updating the chemical name, formula, and molecular weight for USP Anhydrotetracycline Hydrochloride RS and USP 4-Epianhydrotetracycline Hydrochloride RS to indicate that these are hydrochloride salts.
**Response:** Comment incorporated.
**Expert Committee-initiated Change #1:** The *Solution A* preparation in the *Assay* was updated for clarification.

**Expert Committee-initiated Change #2:** A note for chromatographic column in the *Assay* and the test for *Organic Impurities* was added to indicate that both L1 and L60 columns are suitable for the procedures.
**Expert Committee-initiated Change #3:** The autosampler temperature in the *Assay* and the test for *Organic Impurities* was revised from 4° to 10° based on supporting data.
**Expert Committee-initiated Change #4:** The calculation formulas in the *Assay* and the test for *Organic Impurities* were revised to factor in the potency of the reference standards.

**Monograph/Section:** Erythromycin Ophthalmic Ointment/USP Reference Standards
**Expert Committee:** Monographs—Small Molecules 1
**Expert Committee-initiated Change #1:** The USP Reference Standards section is revised to include reference standards that are used in the Assay.

**Monograph/Section:** Ethylparaben Sodium/Assay
**Expert Committee:** Monographs—Excipients
**No. of Commenters:** 1
**Comment Summary #1:** The commenter suggested specifying column temperature and auto sampler temperatures in the *Assay.*
**Response:** Comment not incorporated. Temperatures for measurements are covered by General Notices under section 8.180 Temperatures.
**Comment Summary #2:** The commenter recommended clarifying the calculation method for System Suitability, whether the relative standard deviation (RSD) is calculated based on total area of the all components, or area of individual components, or area of the main component.
**Response:** Comment not incorporated. The *Assay* System Suitability section contains all necessary information to conduct the test.

**Monograph/Section(s):** Eszopiclone/Multiple Sections
**Expert Committee:** Monographs—Small Molecules 4
**No. of Commenters:** 2
**Comment Summary #1:** The commenter requested revising the procedure to improve the peak shape of eszopiclone in the *Assay*.
**Response:** Comment not incorporated. The Expert Committee determined that the procedure is suitable for the intended purpose, but will consider future revisions upon receipt of supporting data.
**Comment Summary #2:** The commenter reported observing different retention times and relative retention times in the test for *Organic Impurities*.
**Response:** Comment not incorporated. There are no monograph requirements associated with retention times or relative retention times. The Expert Committee determined that the procedure is suitable as written.
**Comment Summary #3:** The commenter requested replacing the *Organic Impurities* test with their in-house procedure, because the *Organic Impurities* test does not completely separate a potential degradation impurity from eszopiclone related compound A or eszopiclone and does not result in consistent retention times for eszopiclone related compound A.

**Response:** Comment not incorporated. The Expert Committee determined that the procedure is suitable for the intended purpose and will consider future revisions upon receipt of supporting data.
**Comment Summary #4:** The commenter requested replacing alcohol with absolute alcohol in *Mobile phase* in the test for the Limit of *R*-isomer.
**Response:** Comment incorporated.

**Monograph/Section:** Eszopiclone Tablets/Organic Impurities
**Expert Committee:** Monographs–Small Molecules 4
**No. of Commenters:** 2
**Comment Summary #1:** The commenter requested correcting the typographical error in the *Dissolution* test by revising the pH of the *Mobile phase* from 6.5 ± 0.5 to 6.5 ± 0.05.
**Response:** Comment incorporated.
**Comment Summary #2:** The commenter requested adding in-situ generation of eszopiclone related compound A in the *System suitability solution* in the test for *Organic Impurities* by heating the eszopiclone in 30% hydrogen peroxide at 90° for 1 h as an alternative solution preparation in case USP Eszopiclone Related Compound A RS is not available.
**Response:** Comment not incorporated. The use of the available USP Eszopiclone Related Compound A RS avoids the need to heat solutions of 30% hydrogen peroxide.
**Comment Summary #3:** The commenter requested revising the relative response factor for zopiclone alcohol from 1.6 to 1.7 in the test for *Organic Impurities* to be consistent with the validated procedure.
**Response:** Comment incorporated.
**Comment Summary #4:** The commenter requested increasing the disregard limit from 0.04% to 0.1% in the test for *Organic impurities* for consistency with the ICH reporting threshold for drug products with a maximum daily of dose NMT 1 g.
**Response:** Comment not incorporated. The Expert Committee will consider revising the monograph upon receipt of supporting data.
**Comment Summary #5:** The commenter requested adding 1-methylpiperizine as a degradation product in Table 1.
**Response:** Comment not incorporated. The Expert Committee will consider revising the monograph upon receipt of supporting data.

**Monograph/Section(s):** Fluconazole Injection/Assay
**Expert Committee:** Monographs—Small Molecules 1
**Expert Committee-initiated Change #1:** *Buffer* in the *Assay* is revised to indicate that anhydrous form of sodium acetate is used.

**Monograph/Section:** Fluconazole in Sodium Chloride Injection/Assay
**Expert Committee:** Monographs—Small Molecules 1
**Expert Committee-initiated Change #1:** *Buffer* in the *Assay* is revised to indicate that anhydrous form of sodium acetate is used.
**Expert Committee-initiated Change #2:** The calculation in the test for *Organic Impurities, procedure 4* is revised to include relative response factor.

**Monograph/Section(s):** Fluticasone Propionate and Salmeterol Inhalation Aerosol/Multiple Sections
**Expert Committee:** Monographs—Small Molecules 4
**No. of Commenters:** 3
**Comment Summary #1:** The commenter indicated that the diluent may not be suitable for dissolving the standards and samples.
**Response:** Comment not incorporated. The diluent has been successfully verified in USP labs. The Expert Committee will consider revising the monograph upon the receipt of the necessary supporting data
**Comment Summary #2:** The commenter indicated that the apparatus used in Particle Size Distribution is non-standard. Using the standard apparatus in <601> does not allow the proposed particle size distribution to be met. The commenter requested that the specifications should be based on the use of standard apparatus listed in <601>.
**Response:** Comment not incorporated. The particle size distribution is a performance test and is dependent on the sampling apparatus. The proposal in *PF* is based on FDA requirements. The Expert committee will consider revising the monograph upon receipt of supporting data.
**Comment Summary #3:** The commenter requested lowering the run time in the *Assay* from NLT 2 times the retention time of salmeterol to NLT 1.5 times as this will lower the run time by 25%.
**Response:** Comment incorporated.

**Monograph/Sections :** Fluticasone Propionate and Salmeterol Inhalation Powder/Multiple
**Expert Committee:** Monographs—Small Molecules 4
**No. of Commenters:** 5
**Comment Summary #1:** The commenter indicated that the elution order for fluticasone propionate and salmeterol are reversed in the *Assay*, *Aerodynamic Size Distribution*, and *Delivered Dose Uniformity* tests.
**Response:** Comment incorporated. The elution order was corrected.
**Comment Summary #2:** The commenter indicated that only fluticasone propionate is included while salmeterol is missing in Tier 2 acceptance criteria for *Delivered Dose Uniformity*
**Response:** Comment incorporated.
**Comment Summary #3:** The commenter requested the deletion of the phrase, “with metered valves fitted with a dose counter and provided with oral inhalation actuators” from the *Packaging and Storage* section as the dosage form does not have metering valves and actuators
**Response:** Comment incorporated.
**Comment Summary #4:** The commenter requested that the acceptance criteria in the test for *Aerodynamic Size Distribution* and *Delivered Dose Uniformity* should be based on the use of standard apparatus listed in <601> instead of the non-standard apparatus included in the proposal.
**Response:** Comment not incorporated. The aerodynamic size distribution and delivered dose uniformity are performance tests and are dependent on the sampling apparatus. The acceptance criteria in *PF* proposal are based on what has been approved by the FDA. The Expert Committee will consider revising the monograph upon receipt of supporting data.

**Comment Summary #5:** The commenter indicated that the specifications in *Microbial Enumeration Tests* are not consistent with <1111> *Microbiological examination of nonsterile* Ramipril Tablets *products: acceptance criteria for pharmaceutical preparations and substances for pharmaceutical use*.
**Response:** Comment not incorporated. The specifications are consistent with FDA requirements.
**Comment Summary #6:** The commenters indicated that the concentrations of the standard solutions in *Organic Impurities* do not match the expected concentrations of the sample solutions.
**Response:** Comment not incorporated. The procedure is consistent with FDA requirements.
**Comment Summary #7:** The commenter requested the quantification of each salmeterol related degradation product using salmeterol as opposed the salmeterol related compound H.
**Response:** Comment not incorporated. The quantification of each salmeterol related degradation product is consistent with FDA requirements.
**Comment Summary #8:** The commenter indicated that a relative response factor of 0.62 of salmeterol related compound H should be included in the calculation of impurities.
**Response:** Comment not incorporated. The procedure is consistent with the validation data supporting the Expert Committee's decision.
**Comment Summary #9:** The commenters indicated that lactose adduct of the active drug substances as well as photodegradation products are potential degradation products and the procedure is not specific enough to monitor all the possible degradation products.
**Response:** Comment not incorporated. The proposal is consistent with FDA requirements. The Expert Committee will consider inclusion of other degradation products upon receipt of supporting data.
**Comment Summary 10:** The commenter requested the use of diode array detector for identification.
**Response:** Comment not incorporated. The Expert Committee will consider revising the monograph upon receipt of supporting data.
**Comment Summary #11:** The commenter requested the replacement of the phrase "delivered dose" with the phrase "emitted dose."
**Response:** Comment not incorporated. The Expert Committee determined that the existing wording was sufficient.
**Expert Committee-initiated change:** The run time of NLT 1.5 times the retention time of salmeterol was introduced in the Assay to be consistent with the *Fluticasone Propionate and Salmeterol Inhalation Aerosol* monograph.
**Response:** Comment incorporated.

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|---|---|
| **Monograph/Section:** | Glyceryl Monocaprylate/Fats and Fixed Oils, Saponification Value <401> |
| **Expert Committee:** | Monographs—Excipients |
| **No. of Commenters:** | 1 |

**Comment Summary #1:** The commenter recommended revising the proposed acceptance criteria for saponification value of Glyceryl Monocaprylate Type I from "275–300" to "266–300, and revising the proposed acceptance criteria for saponification value of Glyceryl Monocaprylate Type II from "245–265" to "245–272."

**Response:** Comment incorporated. The Expert Committee revised the acceptance criteria based on supporting data.

**Monograph/Sections:** Iodixanol/Multiple Sections
**Expert Committee:** Monographs—Small Molecules 4
**No. of Commenters:** 1
**Comment Summary #1:** The commenter requested the inclusion of Limit of Total Unspecified impurities
**Response:** Comment not incorporated. ICH guidelines do not require a limit for total unspecified impurities.
**Comment Summary #2:** The commenter requested the inclusion of %RSD as a system suitability criterion
**Response:** Comment not incorporated. The Expert Committee has determined that the system suitability requirements in the *PF* proposal are sufficient for the intended purpose of the test.
**Comment Summary #3:** The commenter requested the correction of the chemical name of USP related compound B from 5-Amino-*N*,*N*′-bis(2,3-dihydroxypropyl)-2,4,6-triiodo-1,3-benzenedicarboxamide to 5-Acetylamino-*N*,*N*′-bis(2,3-dihydroxypropyl)-2,4,6-triiodo-1,3-benzenedicarboxamide
**Response:** Comment not incorporated. The proposal requires the use of USP Iohexol Related Compound B RS whose correct chemical name is in the proposal.
**Comment Summary #4:** The commenter requested the storage conditions to specify “store at controlled room temperature.”
**Response:** Comment not incorporated. The stability data does not support the need to control the storage temperature.

**Monograph/Section:** Ketorolac Tromethamine Injection/Organic Impurities
**Expert Committee:** Monographs—Small Molecules 2
**No. of Commenters:** 1
**Comment Summary #1:** The commenter requested widening the specifications for ketorolac related compound B and ketorolac related compound C from 0.20% to 0.5%.
**Response:** Comment incorporated.

**Monograph/Section:** Lidocaine Hydrochloride/Packaging and Storage
**Expert Committee:** Monographs—Small Molecules 4
**No. of Commenters:** 1
**Comment Summary #1:** The commenter requested updating the storage condition from room temperature to controlled room temperature.
**Response:** Comment incorporated.

**Monograph/Section(s):** Meloxicam/Multiple Sections
**Expert Committee:** Monographs—Small Molecules 2
**No. of Commenters:** 1
**Comment Summary #1**: The commenter suggests revising the temperature for *Package and Storage* from room temperature to controlled room temperature.
**Response:** Comment not incorporated. The Expert Committee will consider revising the monograph upon receipt of supporting data.

**Monograph/Section(s):** Memantine Hydrochloride/Multiple Sections
**Expert Committee:** Monographs—Small Molecules 4
**No. of Commenters:** 1
**Comment Summary #1:** The commenter requested the revision of the %RSD to reflect the ratio of the analyte to internal standard
**Response:** Comment incorporated.

**Monograph/Section(s):** Mesalamine/Multiple Sections
**Expert Committee:** Monographs—Small Molecules 2
**No. of Commenters:** 2
**Comment Summary #1:** The commenters recommended retaining the limits in the *Definition* and the *Acceptance Criteria* in the *Assay* to be consistent with FDA requirements.
**Response:** Comment incorporated.
**Comment Summary #2:** The commenter recommended retaining the test for *Hydrogen Sulfide and Sulfur Dioxide*, because both components cannot be detected by the test for *Chloride and Sulfate, Sulfate* <221>.
**Response:** Comment incorporated.
**Comment Summary #3:** The commenter recommended harmonizing the *Assay*, the tests for *Chloride and Sulfate, Chloride* <221>, *Heavy Metal, Method II* <231>, *Hydrogen Sulfide and Sulfur Dioxide*, *Content of Aniline*, *2-aminophenol*, *4-aminophenol*, *Clarity of Solution,* and *Loss on Drying* with those in the corresponding *EP* monograph.
**Response:** Comment not incorporated. The Expert Committee will consider revising the monograph upon receipt of supporting data.
**Comment Summary #4:** The commenter indicated that the test for *Clarity of Solution* is needed to detect dimerization/polymerization degradation products and should be retained in the monograph.
**Response:** Comment incorporated.

**Monograph/Section:** Methocarbamol Injection/Limit of Aldehydes
**Expert Committee:** Monographs—Small Molecules 4
**No. of Commenters:** 1
**Comment summary 1:** The commenter indicated that the proposal limit is not consistent with FDA requirements.
**Response:** Comment not incorporated. The Expert Committee will consider revising the monograph via Revision Bulletin.

**Monograph/Section(s):** Montelukast Sodium Tablets/Multiple Sections
**Expert Committee:** Monographs—Small Molecules 4
**No. of Commenters:** 5
**Comment Summary #1:** The commenters requested widening of the *Assay* acceptance criteria from 94.0–105.0% to the commenter's approved criteria.
**Response:** Comment incorporated. The *Assay* acceptance criteria were widened to 92.5–107.5% based on FDA requirements.

**Comment Summary #2:** The commenter requested revising the *Note* to allow for a more generic way of protecting the samples from light, instead of specifying the use of low actinic glassware.
**Response:** Comment incorporated.
**Comment Summary #3:** The commenter recommended the approach used in the montelukast sodium monograph for inclusion of the cis-isomer of montelukast in the *System suitability solution* in the *Assay* by using the Impurity solution (USP Montelukast for Peak Identification RS).
**Response:** Comment not incorporated. USP Montelukast for Peak Identification RS contains montelukast and 5 impurities, including the cis-isomer of montelukast. In this monograph proposal, the cis isomer of montelukast was generated *in situ* from a portion of the *Standard solution*, consisting of USP Montelukast Dicyclohexylamine RS, by treatment with hydrogen peroxide and light. The approach used is the same in all three drug products (Tablets, Chewable Tablets, and Oral Granules) monographs.
**Comment Summary #4:** The commenter requested the inclusion of their approved dissolution tolerances.
**Response:** Comment not incorporated. The Expert Committee will consider adding *Dissolution Test 2* and *Test* 3 to the monograph via Revision Bulletin.
**Comment Summary #5:** The commenter requested the addition of "for 5 injections" to the %RSD requirement in the test for *Dissolution*.
**Response:** Comment not incorporated. The number of injections is specified in *Chromatography* <621>*, System Suitability,* as referenced in the monograph.
**Comment Summary #6:** The commenter requested the inclusion of a temperature of 37 ºC ± 0.5 for the medium in the test for *Dissolution*.
**Response:** Comment not incorporated. Dissolution <711> specifies a default temperature of 37 ºC ± 0.5 for the medium.
**Comment Summary #7:** The commenter requested a change of dissolution time from 20 min. to 30 min. in the test for *Dissolution* to align with the value in the Office of Generic Drugs Database.
**Response:** Comment not incorporated. The *Dissolution* time of 20 min. is consistent with FDA requirements.
**Comment Summary #8:** The commenter requested the addition of a molecular weight correction factor to the equation for calculating the amount of montelukast dissolved in the test for *Dissolution*.
**Response:** Comment not incorporated. A molecular weight correction factor is not needed because the concentration of both the *Standard solution* and *Sample solution* are given in amount of montelukast.
**Comment Summary #9:** The commenter recommended inclusion of methylstyrene impurity as degradation product in *Table 2* in the test for *Organic Impurities*.
**Response:** Comment not incorporated. The supporting data reviewed by the Expert Committee indicates that the methylstyrene impurity should be considered an API process impurity, not a degradant. It is limited through appropriate drug substance specifications and is not included in the calculation of total degradation products.
**Comment Summary #10:** The commenter requested changing "any other individual degradation product" to "largest unspecified" in *Table 2* in the test for *Organic Impurities* to align with ICH guidelines.

**Response:** Comment not incorporated. "Any other individual degradation product" is standard USP terminology and is used for consistency in drug product monograph proposals.

**Monograph/Section(s)** Montelukast Sodium Chewable Tablets/Multiple Sections
**Expert Committee:** Monographs—Small Molecules 4
**No. of Commenters:** 5
**Comment Summary #1:** The commenter requested widening of the *Assay* acceptance criteria from 93.5–105.0% to the commenters' approved criteria.
**Response:** Comment incorporated. The *Assay* acceptance criteria were widened to 92.5–107.5% based on FDA requirements.
**Comment Summary #2:** The commenter requested the inclusion of their approved dissolution tolerances.
**Response:** Comment not incorporated. *Dissolution Test 2* will be added to the monograph at a later date via a Revision Bulletin.
**Comment Summary #3:** The commenter requested the addition of "for 5 injections" to the %RSD requirement in the test for *Dissolution*.
**Response:** Comment not incorporated. The number of injections is specified in *Chromatography* <621>*, System Suitability,* as referenced in the monograph.
**Comment Summary #4:** The commenter requested the inclusion of a temperature of 37 ºC ± 0.5 for the medium in the test for *Dissolution*.
**Response:** Comment not incorporated. *Dissolution* <711> specifies a default temperature of 37 ºC ± 0.5 for the medium.
**Comment Summary #5:** The commenter indicated that the shape of the montelukast peak appeared to be distorted.
**Response:** Comment not incorporated. The method was extensively evaluated in USP laboratories and distorted peak shapes were not observed.
**Expert Committee-initiated Change #1:** The *Note* was revised for consistency among montelukast drug product monographs to allow for a more generic way of protecting the samples from light, instead of specifying the use of low actinic glassware.

**Monograph/Section(s):** Montelukast Sodium Oral Granules/Multiple Sections
**Expert Committee:** Monographs—Small Molecules 4
**No. of Commenters:** 2
**Comment Summary #1:** The commenter requested the inclusion of their approved dissolution tolerances.
**Response:** Comment not incorporated. The Expert Committee will consider adding *Dissolution Test* 2 to the monograph upon the receipt of supporting data.
**Comment Summary #2:** The commenter requested the addition of "for 5 injections" to the %RSD requirement in the test for *Dissolution*.
**Response:** Comment not incorporated. The number of injections is specified in *Chromatography* <621>*, System Suitability,* as referenced in the monograph.
**Comment Summary #3:** The commenter requested the inclusion of a temperature of 37 ºC ± 0.5 for the medium in the test for *Dissolution*.
**Response:** Comment not incorporated. *Dissolution* <711> specifies a default temperature of 37 ºC ± 0.5 for the medium.

**Expert Committee-initiated Change #1:** The *Note* was revised for consistency among montelukast drug product monographs to allow for a more generic way of protecting the samples from light instead of specifying the use of low actinic glassware.

**Monograph/Sections:** Mycophenolate Sodium/Multiple Sections
**Expert Committee:** Monographs—Small Molecules 3
**No. of Commenters:** 1
**Comment Summary #1:** The commenter indicated that the z-isomer coelutes with the mycophenolate peak in the test for *Organic Impurities* and requested revising the test procedure to be capable of quantifying this impurity.
**Response:** Comment not incorporated. The Expert Committee determined that the test procedure is suitable for its intended use. The Expert Committee will consider revising the monograph upon receipt of supporting data.
**Comment Summary #2:** The commenter requested widening the acceptance criteria in the test for *Water Determination* from NMT 1.5% to NMT 2.0%.
**Response:** Comment not incorporated. The acceptance criteria in the monograph reflect FDA requirements. The Expert Committee will consider revising the monograph upon receipt of supporting data.

**Monograph/Section:** Mycophenolic Acid Delayed-Release Tablets/Organic Impurities
**Expert Committee:** Monographs—Small Molecules 3
**No. of Commenters:** 1
**Comment Summary #1:** The commenter requested revising the acceptance criteria of any individual unspecified impurity from NMT 0.1% to NMT 0.139% based on the ICH Q3B Guideline.
**Response**: Comment not incorporated. The acceptance criteria in the monograph reflect FDA requirements.

**Monograph/Section:** Oxacillin Sodium/Organic Impurities
**Expert Committee:** Monographs—Small Molecules 1
**No. of Commenters:** 1
**Comment Summary #1:** The commenter requested revising the limit for unspecified impurities to reflect FDA approved acceptance criteria.
**Response:** Comment not incorporated. The acceptance criteria in the proposal are consistent with FDA requirements. This public standard is intended to address all approved drug products.

**Monograph/Section(s):** Orphenadrine Citrate Injection/Organic Impurities
**Expert Committee:** Monographs—Small Molecules 4
**No. of Commenters:** 1
**Comment summary 1:** The commenter indicated that the proposal limits are not consistent with what has been approved by FDA.
**Response:** Comment not incorporated. The Expert Committee will consider revising the monograph upon receipt of supporting data.

**Monograph/Section:** Paliperidone/Organic Impurities
**Expert Committee:** Monographs—Small Molecules 4
**No. of Commenters:** 2
**Comment summary 1:** The commenter indicated that the procedure is not specific enough to separate other known process impurities.
**Response:** Comment not incorporated. The Expert Committee will consider revising the monograph upon receipt of supporting data.
**Comment summary 2:** The commenter suggested omitting the limit for paliperidone related compound C as their manufacturing process ensures the impurity is eliminated because it could be a potential genotoxic impurity.
**Response:** Comment not incorporated. The Expert Committee will address the limit of paliperidone related compound C in a future revision when supporting data is available regarding its genotoxic nature.

**Monograph/Section(s):** Phenylephrine Hydrochloride Tablets/Multiple Sections
**Expert Committee:** Monographs—Small Molecules 2
**No. of Commenters:** 1
**Comment Summary #1:** The commenter requested clarification on why plastic vials are required in the *Assay* and the test for *Dissolution* when all standard and sample preparations do not state the use of plastic volumetric flasks.
**Response:** Comment incorporated. Based on the supporting information, the statement, “Use plastic vials for analysis” was revised to, “It is suggested to use plastic vials for analysis” in both tests.
**Comment Summary #2:** The commenter requested changing the wavelength range for the detector for *Identification test A* from UV 200–400 nm to UV 200–350 nm as phenylephrine does not absorb above 350 nm.
**Response:** Comment incorporated.
**Comment Summary #3:** The commenter requested changing the Tailing factor requirement from 0.5–3.0 to NMT 3.0 in the *Assay*.
**Response:** Comment not incorporated. The requirement for the Tailing factor is based on the validation data and the lower limit of 0.5 is used to control the fronting of both API peaks.
**Comment Summary #4:** The commenter requested removing phenylephrine related compound F from the *System suitability solution* in the test for *Organic Impurities* as there is no system suitability requirement for this impurity.
**Response:** Comment not incorporated. Phenylephrine related compound F is provided as a retention time marker in the *System suitability solution* to differentiate phenylephrine related compound F from phenylephrine related compound G which elutes closely with phenylephrine related compound F.
**Comment Summary #5:** The commenter requested clarification in designating impurity names as acronyms or related compounds, and recommended designating impurity names as related compounds.
**Response:** Comment not incorporated. The Expert Committee determined that the impurity names are appropriate based on the current USP’s naming convention. Impurities are named as acronyms if they are not available as USP reference standards. Otherwise, they are named as USP related compounds.

**Comment Summary #6:** The commenter recommended a general approach to address specifications for organic impurities in the USP OTC monographs.
**Response:** Comment not incorporated. USP is continuously working with the FDA and stakeholders to develop appropriate approaches to create/update OTC monographs. The Expert Committee will consider a revision to the monograph upon receipt of supporting data.

**Monograph/Section:** Pyridostigmine Bromide Tablets/Organic Impurities
**Expert Committee:** Monographs—Small Molecules 4
**No. of Commenters:** 1
**Comment Summary #1:** The commenter requested tightening the impurity specifications to be consistent with FDA requirements.
**Response:** Comment not incorporated. The Expert Committee determined that it is reasonable to set the impurity specifications based on the British Pharmacopoeia monograph and will consider revising the monograph upon the receipt of supporting data.

**Monograph/Section(s):** Simvastatin Tablets/Multiple Sections
**Expert Committee:** Monographs—Small Molecules 2
**No. of Commenters:** 2
**Comment Summary #1:** The commenter requested replacing the UV-Vis diode array based procedure for *Identification test B* with a TLC or IR based procedure.
**Response:** Comment not incorporated. The Expert Committee determined that the UV-Diode array based identification procedure is suitable for a public standard.
**Comment Summary #2:** The commenter requested widening the acceptance criteria for tenivastatin from NMT 0.80% to NMT 1.0% and for any individual unspecified impurity from NMT 0.2% to NMT 0.5% to be consistent with the FDA requirements.
**Response:** Comment incorporated.
**Comment Summary #3:** The commenter requested replacing the *Organic Impurities* procedure with their in-house procedure that can also be used for *Assay* and *Uniformity of Dosage Units.*
**Response:** Comment not incorporated. The Expert Committee demonstrated that the current procedure is specific and can adequately quantitate all impurities.
**Comment Summary #4:** The commenter requested keeping the nomenclature of Tenivastatin and Tenivastatin methyl ester the same in both API and dosage form monographs.
**Response:** Comment incorporated.

**Monograph/Sections:** Sitagliptin Phosphate/Multiple Sections
**Expert Committee:** Monographs—Small Molecules 3
**No. of Commenters:** 12
**Comment Summary #1:** The commenter requested adding a statement to indicate that this monograph has been prepared in close cooperation with the *European Pharmacopoeia* and the corresponding monographs are considered harmonized.
**Response:** Comment not incorporated. The development of this monograph was undertaken as an informal exercise with the aim of achieving the maximum possible consistency in the specifications, taking into accounts each pharmacopoeia's policies and constraints.
**Comment Summary #2:** The commenter requested specifying the concentration of the analyte under the Identification test for phosphate.
**Response:** Comment incorporated.

**Comment Summary #3:** The commenters requested deleting the test for *Residue on ignition,* because the results may be inconsistent due to possible formation of $P_2O_5$ which is not volatile at the ignition temperature for this phosphate salt.
**Response:** Comment incorporated.
**Comment Summary #4:** The commenters indicated that the main degradation product sitagliptin amine (3-(Trifluoromethyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine) elutes at the void volume and cannot be controlled by the proposed procedure, and requested including their in-house procedure in the test for *Organic Impurities*.
**Response:** Comment not incorporated. The Expert Committee will consider revising the monograph upon receipt of supporting data.
**Comment Summary #5:** The commenters indicated that several other known impurities are not detected or separated by the proposed procedure in the test for *Organic Impurities*, and requested including their in-house procedure with suitable impurity limits.
**Response:** Comment not incorporated. The Expert Committee will consider revising the monograph upon receipt of supporting data.
**Comment Summary #6:** The commenter suggested establishing a USP Sitagliptin System Suitability Mixture RS containing known impurities and using it to establish system suitability requirements, instead of currently used fumarate adduct of sitagliptin prepared *in situ*.
**Response**: Comment not incorporated. The Expert Committee will consider revising the monograph upon the receipt of supporting data.
**Comment Summary #7:** The commenter suggested simplifying the description of the preparation of the *System suitability solution* in the test for *Organic Impurities*.
**Response:** Comment incorporated. The description for the preparation of *System suitability solution* is updated for clarity.
**Comment Summary #8:** The commenters reported difficulties in meeting the *signal-to-noise ratio* requirement under the test for *Organic Impurities*.
**Response:** Comment incorporated. The *signal-to-noise ratio* requirement is deleted from the monograph. The Expert Committee will consider revising the monograph upon receipt of supporting data.
**Comment Summary #9:** The commenter requested revising the test for *Organic Impurities* to quantitate the impurities against the *Standard solution* which has the same concentration as the *Sample solution*.
**Response:** Comment not incorporated. The quantitation is performed against the Standard solution having a concentration similar to the expected concentration of the impurities.
**Comment Summary #10:** The commenter requested replacing the term “any individual impurities” with “any unspecified impurity” under *Organic Impurities*.
**Response:** Comment not incorporated. All impurities in the current proposal are treated as unspecified. The Expert Committee may consider this approach in a future revision when adding a procedure suitable for a different impurity profile.
**Comment Summary #11:** The commenter indicated that the phrase, “reporting level for impurities” is based on the maximum daily dose and is determined by the FDA.
**Response:** Comment incorporated. The statement, “reporting level for impurities is 0.05%” was replaced with, “disregard any peak below 0.05%,” which is consistent with the current USP style.
**Comment Summary #12*:*** The commenters requested including anhydrous and amorphous forms of sitagliptin phosphate with the corresponding limits of *Water Determination*, in addition to the monohydrate form.

**Response:** Comment not incorporated. The Expert Committee will consider revising the monograph upon receipt of supporting data.
**Comment Summary #13:** The commenters requested widening the acceptance criteria for *Water Determination* for the monohydrate form from 3.3–3.7% to 3.1–3.9%.
**Response:** Comment not incorporated. The Expert Committee will consider revising the monograph upon receipt of supporting data.

**Monograph/Section(s):** Sitagliptin Tablets/Multiple Sections
**Expert Committee:** Monographs—Small Molecules 3
**No. of Commenters:** 4
**Comment Summary #1**: The commenter requested adding a statement to indicate that this monograph has been prepared in close cooperation with the *European Pharmacopoeia* and the corresponding monographs are considered harmonized.
**Response:** Comment not incorporated. The development of this monograph was undertaken as an informal exercise with the aim of achieving the maximum possible consistency in the specifications, taking into accounts each pharmacopoeia's policies and constraints.
**Comment Summary #2:** The commenter requested adding the following statement, "Alternate tests may be performed to support release when the product is developed using Quality by Design (QbD) principles and a Real Time Release Testing (RTRT) strategy that has been approved by a regulatory health authority. There must be assurance that the product will meet the requirements, if tested according to this monograph."
**Response:** Comment not incorporated. This issue is outside of the scope of this specific monograph.
**Comment Summary #3:** The commenter requested revising the test for *Organic Impurities* to quantitate the impurities against the *Standard solution* which has the same concentration as the *Sample solution*.
**Response:** Comment not incorporated. The quantitation is performed against the *Standard solution* having a concentration similar to the expected concentration of the impurities.
**Comment Summary #4:** The commenter recommended tightening the acceptance criteria for the total impurities under the test for *Organic Impurities* from NMT 0.6% to NMT 0.2%, to be consistent with *European Pharmacopoeia's* proposal.
**Response:** Comment not incorporated. The acceptance criteria in the proposal are consistent with FDA requirements. The public standard is intended to address all approved drug products.
**Comment Summary #5:** The commenter suggested simplifying the description of the preparation of the *System suitability solution* in the test for *Organic Impurities*.
**Response:** Comment incorporated. The description for the preparation of *System suitability solution* is updated for clarity.
**Comment Summary #6:** The commenters indicated that several other known impurities and degradation products are not detected or separated by the test for *Organic Impurities*, and requested including their in-house procedure with suitable impurity limits.
**Response:** Comment not incorporated. The Expert Committee will consider revising the monograph upon receipt of supporting data.
**Comment Summary #7:** The commenters requested adding a *Dissolution* test to the monograph.
**Response:** Comment not incorporated. The proposed test for *Disintegration* is consistent with FDA requirements.

**Monograph/Section(s):** Sodium Salicylate/Assay and Organic Impurities
**Expert Committee:** Monographs—Small Molecules 2
**No. of Commenters:** 2
**Comment Summary #1:** The commenter requested replacing the proposed UHPLC method with conventional HPLC method.
**Response:** Comments not incorporated. UHPLC has been commonly accepted by the industry as the current analytical trend and method of testing.

**Monograph/Section(s):** Teriparatide/Multiple Sections
**Expert Committees:** Monographs—Biologics and Biotechnology 1
**No. of Commenters:** 5

***Title***
**Comment Summary #1:** The commenter recommended changing the monograph title from *Teriparatide Acetate* to *Teriparatide*. *Teriparatide* seems to be an appropriate monograph title for this drug substance, because it is a legitimate USAN nomenclature and the monograph defines the strength in terms of the free base described in the *Assay*.
**Response:** Comment incorporated. In addition, the name of RS is changed from USP Teriparatide Acetate RS to USP Teriparatide RS.

***Definition***
**Comment Summary #2:** The commenter suggested the monograph also refers to synthetic teriparatide by including synthetic teriparatide in the definition section.
**Response:** Comment not incorporated. The only FDA approved product in the US is recombinantly produced Teriparatide. The Expert Committee will consider revising the monograph upon receipt of supporting data.
***Identification. Peptide Mapping***
**Comment #3:** The commenter suggested allowing the flexibility of using different buffers to dilute *Staphylococcus aureus V8 protease* because the conditions for reconstitution and storage of this enzyme are based on the manufacturer's instructions.
**Response:** Comment not incorporated. The Expert Committee will consider revising the monograph upon receipt of supporting data.
**Comment Summary #4:** The commenter suggested omitting the initial step of preparing 1.5 mg/mL of Teriparatide in *Standard solution* and *Sample solution* because the final concentration is 0.25 mg/mL.
**Response:** Comment not incorporated. The Expert Committee will consider revising the monograph upon receipt of supporting data.
**Comment Summary #5:** The commenter recommended providing a clarification on the ratio of Teriparatide to *Staphylococcus aureus V8 protease* in *Standard solution* and *Sample solution*.
**Response:** Comment incorporated. The ratio of Teriparatide to *Staphylococcus aureus V8 protease* was revised as 10:1 (w/w).
**Comment Summary #6:** The commenter recommended revising the requirement of tailing factor < 2.3 to NMT 2.3 for the peak indicated as fragment IV.
**Response:** Comment incorporated.

**Comment Summary #7:** The commenter suggested including a typical chromatogram prepared from USP Teriparatide RS digested with *Staphylococcus aureus V8 protease* for the test of *Peptide Mapping*.
**Response:** Comment not incorporated. The typical chromatogram is provided in the USP Certificate for USP Teriparatide RS.

***Assay***
**Comment Summary #8:** The commenter suggested changing the recommendations for the equilibration and weighting to allow alternative approaches for handling of teriparatide, because it is a hygroscopic material, e.g. saturation of USP Teriparatide RS and the teriparatide sample with water under humid conditions prior to weighing. The described *Assay* method requires performing equilibration and weighting of a sample in a controlled humidity chamber. Controlled humidity chambers are not widely available in QC labs.
**Response:** Comment not incorporated. The Expert Committee will consider revising the monograph upon receipt of supporting data.
**Comment Summary #9:** The commenter suggested reporting data from five injections of a single solution when perform the system suitability, because it was difficult to meet the requirement of %RSD from injections of three separate *Standard solutions*.
**Response:** Comment not incorporated. The Expert Committee will consider revising the monograph upon receipt of supporting data.
**Comment Summary #10:** The commenter suggested clarifying whether the *Mobile phase* volume or the *Diluent* volume is used for the calculation of concentration of teriparatide.
**Response:** Comment incorporated. The volume of the diluent should be used for the calculation.
**Comment Summary #11:** The commenter suggested adding different basis of assay calculation for synthetic teriparatide. The production of synthetic teriparatide does not involve chloride at any stage therefore the calculation of assay for synthetic teriparatide is on an anhydrous, acetic acid free basis.
**Response:** Comment not incorporated. The Expert Committee will consider revising the monograph upon receipt of supporting data.

***Other Components. Acetate Content***
**Comment Summary #12:** The commenter suggested washing the column with an eluent containing an organic solvent (up to 50% acetonitrile or methanol) to elute the teriparatide.
**Response:** Comment not incorporated. It is suitable to wash the column using the mobile phase described in the monograph.
**Comment Summary #13:** The commenter recommended revising the formula from "$\{[(r_S - b)/a]C_S\} \times 100$" to "$\{[(r_S - b)/a]/C_S\} \times 100$".
**Response:** Comment incorporated.

***Chloride Content***
**Comment Summary #14:** The commenter suggested excluding requirement for chloride content for synthetic teriparatide. Chloride is not involved in the synthetic process of teriparatide acetate, which is produced as acetate salt. Trifluoroacetic acid (TFA) is involved in the process therefore, TFA content is controlled.

**Response:** Comment not incorporated. The Expert Committee will consider revising the monograph upon receipt of supporting data.
**Comment Summary #15:** The commenter suggested replacing IonPac AS4A and AG4A with IonPac AS4A-SC and AG4A-SC, which are designated as L12.
**Response:** Comment not incorporated. The column equivalency study between the two columns needs to be performed.
**Comment Summary #16:** The commenter recommended adding the requirement of relative standard deviation of standard curve <3.0% for system suitability.
**Response:** Comment incorporated.

***Product-Related Substances and Impurities. Product-Related Impurities***
**Comment Summary #17:** The commenter suggested correcting the percentage of *Solution A* and *Solution B* corresponding the time at 35 min. in *Mobile phase* described in the *Table* 2.
**Response:** Comment incorporated. The percent of *Solution B* is corrected from 45% to 40%.
**Comment Summary #18:** The commenter recommended revising title, “Resolution” for the system suitability requirement to “Peak to valley ratio,” because this is determined by the ratio of the height of the first post-main peak to the valley between the teriparatide peak and the first post-main peak.
**Response:** Comment incorporated.
**Comment Summary #19:** The commenter suggested widening the range for the first post-main peak percentage, or allowing modification of degradation conditions. The percentage of generated first post-main peak following the condition described in the monograph was much higher than the monograph suggested value, 0.8%.
**Response:** Comment incorporated. The condition for generating the first post-main peak is revised.
**Comment Summary #20:** The commenter recommended providing the storage conditions for *System suitability solution*.
**Response:** Comment incorporated.
**Comment Summary #21:** The commenter suggested using a forced oxidized sample for system suitability evaluation. Post peak impurity is considered as a part of system suitability however, pre-peaks (oxidized forms) are part of specification/limit but are not evaluated for resolution during system suitability. Also, post peak generation takes nine days.
**Response:** Comment not incorporated. The Expert Committee will consider revising the monograph upon receipt of supporting data.
**Comment Summary #22:** The commenter recommended removing the requirement of relative standard deviation from system suitability. General Chapter <*621*> *Chromatography* does not require the repeatability test for related substances with a normalization procedure, and actually the determination of the impurities percentage is a ratio of the areas of the same injection.
**Response:** Comment incorporated.
**Comment Summary #23:** The commenter recommended adding the information of relative retention times for the oxidized impurities.
**Response:** Comment incorporated. The information of the relative retention times for these oxidized impurities provided by the sponsor was added to the monograph.

***Specific Tests. Bacterial Endotoxins Test <85>***
**Comment Summary #24:** The commenter suggested changing the specification from 50 USP Endotoxin Units/mg of Teriparatide to 17,500 USP Endotoxin Units/mg. According to General Chapter *<85> Bacterial EndotoxinsTest*, the limit for bacterial endotoxin is 350 Endotoxin Units (for 70 kg body weight). The recommended dose for RLD is 20 μg once a day. Based on that, the specification should be 17.5 EU/μg (equivalent to 17,500 USP Endotoxin Units/mg).
**Response:** Comment not incorporated. The specification aligns with FDA requirements. The Expert Committee will consider revising the monograph upon receipt of supporting data.

***Additional Requirements. Labeling***
**Comment Summary #25:** The commenter suggested adding a labeling description for synthetic teriparatide.
**Response:** Comment not incorporated. The only approved product in US is recombinantly produced teriparatide. The Expert Committee will consider revising the monograph upon receipt of supporting data.

**Monograph/Section(s):** Tetracycline/Multiple Sections
**Expert Committee:** Monographs—Small Molecules 1
**Expert Committee-initiated Change #1:** *Identification* test *C*, which is based on thin-layer chromatography was deleted. The Expert Committee determined that the remaining tests, which are based on the ultraviolet absorption spectrum and chromatographic retention time, are adequate for identification.
**Expert Committee-initiated Change #2:** The chromatographic column information in the *Assay* and the test for *Organic Impurities* was revised to indicate that both L1 and L60 columns are suitable for the procedures.
**Expert Committee-initiated Change #3:** The autosampler temperature in the *Assay* and the test for *Organic Impurities* was revised from 4° to 10° based on supporting data.
**Expert Committee-initiated Change #4:** To align with the monograph for *Tetracycline Hydrochloride*, the limit for unspecified impurities was deleted from the test for *Organic Impurities*.

**Monograph/Section(s):** Tetracycline Hydrochloride/Multiple Sections
**Expert Committee:** Monographs—Small Molecules 1
**No. of Commenters:** 2
**Comment Summary #1:** The commenters requested revising the autosampler temperature in the *Assay* and the test for *Organic Impurities* from 4° to 10° based on supporting data.
**Response**: Comment incorporated.
**Comment Summary #2:** The commenters requested revising the test for *Organic Impurities* to include a limit for a specified impurity in their impurity profiles.
**Response:** Comment not incorporated. The Expert Committee will consider a future revision to add the limit for the specified impurity upon receipt of supporting data. However, to prevent compliance concerns for FDA approved manufacturers, the limit for unspecified impurities was deleted from the test for *Organic Impurities*.
**Comment Summary #3**: The commenters requested revising the relative standard deviation in *Assay* from 0.73% to 2.0% based on the acceptance criteria for the test.
**Response:** Comment incorporated.

**Comment Summary #4:** The commenter requested revising the chromatographic column in the *Assay* to address concerns about limited column lifetimes.
**Response**: Comment incorporated. The chromatographic column information in the *Assay* and the test for *Organic Impurities* was revised to indicate that both L1 and L60 columns are suitable for the procedures.
**Expert Committee-initiated Change #1:** *Identification* test *B* based on ultraviolet absorption, and Identification test E, which is based on thin-layer chromatography were deleted. The Expert Committee determined that the remaining tests, which are based on infrared absorption and chromatographic retention time, are adequate for identification.
**Expert Committee-initiated Change #2:** The section of *Other Requirements* was deleted, because the requirements are captured in other sections of the monograph.
**Expert Committee-initiated Change #3:** The labeling statement was revised to include the intended use.

**Monograph/Section(s):** Tetracycline Hydrochloride Capsules/Loss on Drying
**Expert Committee:** Monographs—Small Molecules 1
**Expert Committee-initiated Change #1:** The test for *Loss on Drying* was deleted because the limit is formulation-specific and hence not appropriate for a public standard.
**Expert Committee-initiated Change #2:** The chromatographic column information in the *Assay* and the test for *Organic Impurities* was revised to indicate that both L1 and L60 columns are suitable for the procedures.
**Expert Committee-initiated Change #3:** The autosampler temperature in the *Assay* and the test for *Organic Impurities* was revised from 4° to 10° based on supporting data.

**Monograph/Section(s):** Tolcapone/USP Reference Standards
**Expert Committee(s):** Monographs—Small Molecules 4
**No. of Commenters:** 1
**Comment Summary #1**: The commenter requested revising the incorrect chemical name of Tolcapone Related Compound A from 4N-Methyl-3,4-dihydroxybenzophenone to 4'-Methyl-3,4-dihydroxybenzophenone
**Response:** Comment incorporated.

**Monograph/Section(s):** Valine/Multiple Sections
**Expert Committee:** Monographs—Dietary Supplements and Herbal Medicines
**No. of Commenters:** 2
**Comment Summary #1:** The commenter recommended that the *Sample solution* and the *Standard solution* in the test for *Related Compounds* be prepared in acetonitrile and a buffer mixture (1:1, v/v) instead of water in order to improve the peak shape and resolution of the analytes.
**Response:** Comment incorporated.
**Comment Summary #2:** The commenter recommended that the relative retention times of the compounds listed in Table 1 in the test for *Related Compounds* be changed as a result of using acetonitrile and water mixture to prepare solutions recommended in Comment Summary #1.
**Response:** Comment incorporated.

**Comment Summary #3:** The commenter recommended that the limit of total amino acid impurities be changed from NMT 2.6% to NMT 2.0%, to be consistent with the previous limit set by the TLC *Related Compounds* test.
**Response:** Comment not incorporated. With the replacement of the TLC procedure with an HPLC procedure in the test for the *Related Compounds*, more amino acids impurities can be detected and characterized. As a result, the total amino acid impurities detected by the new method can exceed the limit of NMT 2.0%, previously set for the TLC procedure.