Commentary

USP 40–NF 35, First Supplement

February 1, 2017

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 re-published in *PF* for further notice and comment, in accordance with the Rules. In cases when proposals advance to official status without re-publication 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.org at the time the official revision is published.

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

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

General Chapters:

- <1058> Analytical Instrument Qualification
- <621> Chromatography
- <232> Elemental Impurities–Limits
- <210> Monosaccharide Analysis
- <1225> Validation of Compendial Procedures
- <1790> Visual Inspection of Injections

Monographs:

- Betamethasone Valerate Lotion
- Buprenorphine Hydrochloride
- Cabergoline Tablets
- Carisoprodol Tablets
- Carnauba Wax
- Ceftiofur Hydrochloride
- Ceftiofur Sodium
- Cefuroxime Axetil
- Cefuroxime Axetil Tablets
- Chocolate
- Cinnamomum Cassia Twig
- Cinnamomum Cassia Twig Powder
- Ciprofloxacin for Oral Suspension
- Ciprofloxacin Tablets
- Dalfampridine
- Desogestrel
- Desoxycholic Acid
- Doxycycline for Injection
- Doxycycline Tablets
- Echinacea Species Dry Extract Capsules
- Echinacea Species Dry Extract Tablets
- Etomidate
- Etomidate Injection
- Fluticasone Propionate Lotion
- Goserelin Implants
- Hydroxyzine Hydrochloride Oral Solution
- Imipramine Hydrochloride Tablets
- Indomethacin for Injection
- Krill Oil Capsules
- Krill Oil Delayed-Release Capsules
- Leuprolide Acetate
- Methionine
- Miconazole Compounded Ophthalmic Solution

- Neotame
- Olive Leaf
- Paricalcitol Capsules
- Phenazopyridine Hydrochloride Tablets
- Plant Stanol Esters
- Potassium Chloride Extended-Release Tablets
- Pregabalin
- Timolol Maleate
- Tizanidine Tablets
- Vanilla
- Venlafaxine Tablets
- Zolpidem Tartrate

No comments were received for the following proposals:

General Chapters:

- <126> Somatropin Bioidentity Tests
- <371> Cobalamin Radiotracer Assay
- <1171> Phase-Solubility Analysis

Monographs:

- Acetaminophen and Codeine Phosphate Capsules
- Acetaminophen and Codeine Phosphate Tablets
- Acetohexamide
- Acetohexamide Tablets
- Aloe
- Aminohippurate Sodium Injection
- Belladonna Leaf
- Benzocaine, Butamben, and Tetracaine Hydrochloride Gel
- Benzocaine, Butamben, and Tetracaine Hydrochloride Topical Aerosol
- Benzocaine, Butamben, and Tetracaine Hydrochloride Topical Solution
- *Bifidobacterium Animalis* ssp. *Lactis*
- Butamben
- Caraway
- Cardamom Seed
- Cascara Sagrada
- Clavulanate Potassium
- Cyproheptadine Hydrochloride
- Desoximetasone Cream
- Desoximetasone Gel
- Desoximetasone Ointment
- Dexamethasone Gel
- Dexamethasone Topical Aerosol
- Digitalis
- Esmolol Hydrochloride

- Ethambutol Hydrochloride Compounded Oral Suspension
- Etidronate Disodium
- Etidronate Disodium Tablets
- Ezetimibe Tablets
- Flumazenil Injection
- Gluconolactone
- Idarubicin Hydrochloride Injection
- Indomethacin Oral Suspension
- Indomethacin Sodium
- Ipecac
- Iron Sucrose Injection
- *Lactobacillus acidophilus* LA-14
- *Lactobacillus acidophilus* NCFM
- *Lactobacillus Rhamnosus* HN001
- Loratadine Oral Solution
- Loratadine Tablets
- Lorazepam Oral Concentrate
- Methyldopa
- Myrrh
- Naloxone Hydrochloride Injection
- Olive Leaf Dry Extract
- Olive Leaf Powder
- Ondansetron Orally Disintegrating Tablets
- Phenazopyridine Hydrochloride
- Pimobendan
- Plantago Seed
- Podophyllum
- Potassium Citrate Extended-Release Tablets
- Ramipril Tablets
- *Rauwolfia Serpentina*
- Salmeterol Xinafoate
- Senna Leaf
- Senna Pods
- Storax
- Theophylline Extended-Release Capsules
- Theophylline in Dextrose Injection
- Tobamycin
- Tripelennamine Hydrochloride
- Witch Hazel
- Zaleplon Capsules

General Chapters

General Chapter/Sections: <210> Monosaccharide Analysis/Multiple Sections
Expert Committee: General Chapters–Biological Analysis
No. of Commenters: 2

General
Comment Summary #1: The commenter indicated that the document appears to be very prescriptive and the content may be better suited for an informational general chapter numbered above 1000.
Response: Comment not incorporated. This General Chapter was designed as a prescriptive to complement General Chapter <1084> *Glycoprotein and Glycan Analysis—General Considerations*.
Comment Summary #2: The commenter requested adding a note to clarify that other columns and detection modes can be used if proven equivalent.
Response: Comment not incorporated. The Expert Committee determined that *General Notices* (*GN*) 6.30 *Alternative and Harmonized Methods and Procedures* provides sufficient clarification about alternative procedures.
Comment Summary #3: The commenter requested adding a note to clarify that alternative columns and chromatographic systems are possible and that retention times for NeuAc and NeuGc may vary accordingly.
Response: Comment partially incorporated. A note was added to indicate the retention times are for the system described.
Comment Summary #4: The commenter requested adding a statement to clarify that other reference standards can be used if validated as equivalent to USP Reference Standards (RS).
Response: Comment not incorporated. The Expert Committee determined that *GN* 5.80 *USP Reference Standards* provides sufficient clarification.

Title
Comment Summary #5: The commenter indicated that the title should be modified because the General Chapter is dedicated to the quantification of the sialic acids, a specific family of monosaccharides.
Response: Comment not incorporated. The initial scope of the General Chapter was prioritized to address sialic acid quantification. It is envisioned to expand to cover other monosaccharides.

Sample Handling Prior to Monosaccharide Analysis
Comment Summary #6: The commenter suggested changing “free of salts” to “absence of interfering salts” to allow flexibility within the method.
Response: Comment not incorporated. The General Chapters—Biological Analysis Expert Committee determined that the existing text is sufficient.

Sialic Acid Quantification
Comment Summary #7 The commenter requested specifying the volume of the sample in the procedure of typical de-O-acetylation.
Response: Comment incorporated.

Procedure 1: Enzymatic Release and Analysis by HPAEC-PAD of Unlabeled Sialic Acids
Comment Summary #8: The commenter requested modification to the *Note* to highlight the need to verify this step for each product tested.
Response: Comment not incorporated. The Expert Committee determined that the existing note is sufficient.
Comment Summary #9: The commenter requested adding: "For the system described, typical retention times are…" because the retention times of Neu5AC and Neu5GC applies only to the specific condition described.
Response: Comment incorporated.
Comment Summary #10: The commenter requested adding a paragraph in the HPAEC analysis section to indicate that the waveform provided in Table 10 may be used, and moved the table into *Procedure 1*.
Response: Comment incorporated.
Comment Summary #11: The commenter requested listing the resin composition for all three columns.
Response: Comment partially incorporated. The resin composition for the column in *Chromatographic system* 2 is added as a footnote.

Procedure 2: Acid Hydrolysis and Analysis by HPAEC-PAD of Unlabeled Sialic Acids
Comment Summary #12: The commenter suggested flexibility of using a validated method that limits the standard's exposure to hydrolysis conditions.
Response: Comment incorporated.
Comment Summary #13: The commenter requested adding a note to allow flexibility regarding the drying method.
Response: Comment incorporated.
Comment Summary #14: The commenter requested adding a note to allow that the standards and samples may not be dried before hydrolysis.
Response: Comment not incorporated. The Expert Committee determined that drying standard and sample before hydrolysis can ensure the accuracy of the test.
Comment Summary #15: The commenter requested changing "Add desalted protein" to "Add protein, desalted if necessary."
Response: Comment not incorporated. The Expert Committee determined that this is covered by the text under *Sample Handling Prior to Monosaccharide Release*.

Procedure 3: Enzymatic Hydrolysis and Analysis by RP-HPLC of DMB-labeled Sialic Acids
Comment Summary #16: The commenter requested indicating *Chromatographic systems* 3 and 4 are isocratic to distinguish them from *Chromatographic systems* 1 and 2.
Response: Comment incorporated.

General Chapter/Sections: <232> Elemental Impurities–Limits/Multiple Sections
Expert Committee: General Chapters–Chemical Analysis
No. of Commenters: 3

Introduction

Comment Summary #1: The commenter requested including clinical trial material in General Chapter <232> for closer alignment with ICH Q3D.
Response: Comment not incorporated. Clinical trial materials are not marketed drug products and therefore not subject to General Chapter <232>.
Comment Summary #2: The commenter suggested replacing the duplicated text from the last paragraph of the *Introduction* section with a reference to the *Drug Substance and Excipients* section.
Response: Comment not incorporated. The Expert Committee determined that the text is significant enough to warrant duplication.

Options for Demonstrating Compliance

Comment Summary #3: The commenter suggested introducing the ICH Q3D option 2a, "Common permitted concentration limits across drug product components for a product with a specified daily intake."
Response: Comment not incorporated. The Expert Committee determined that considerable effort was extended to provide clear information; therefore, the current text is sufficient.
Comment Summary #4: The commenter recommended adding text about including manufacturing process and container closure system contributions into the calculations of elemental impurities.
Response: Comment not incorporated. This information is provided under summation and individual component option.
Comment Summary #5: The commenter suggested adding the ICH Q3D option number, e.g., "*drug product analysis option (option 3)*"
Response: Comment not incorporated. USP believes that the current text is sufficient in the chapter.
Comment Summary #6: The commenter suggested revising the final paragraph under the subsection *Summation Option* to clarify that the manufacturer must ensure that the additional contributions are included in the summation.
Response: Comment not incorporated. This information is already included in the *Summation Option* subsection.
Comment Summary #7: The commenter suggested revising the final sentence in the *Individual Component Option* to clarify that the individual component option can be used as long as the contributions from these sources are addressed.
Response: Comment not incorporated. This information is already included under individual component option.
Comment Summary #8: The commenter suggested adding text about sources of elemental impurities other than drug substances and excipients to the *Drug Substance and Excipients* section to further harmonize the General Chapter with ICH Q3D.
Response: Comment not incorporated. This information is already included in the *Summation Option* and *Individual Component Option* sections.

Comment Summary #9: The commenter suggested revising the final sentence in the *Routes of Administration* section to include the phrase major routes of administration of drug products.
Response: Comment not incorporated. This General Chapter does not indicate that it includes all possible routes of administrations.
Comment Summary #10: The commenter recommended adding clear definitions to explain the meaning of the different Classes in *Table* 1, 2, and 3.
Response: Comment not incorporated. The Expert Committee determined that the current text is sufficient; however, this may be considered for future revisions to the General Chapter upon the receipt of the necessary supporting data.

General Chapter/Section(s): <621> Chromatography
Expert Committee: General Chapters–Chemical Analysis
No. of Commenters: 4

System Suitability
Comment Summary #1: The commenter suggested rephrasing the sentence related to the allowable linear velocity to provide more clarity.
Response: Comment incorporated.
Comment Summary #2: The commenter suggested adding additional guidance on factors that could be considered and how they might indicate a certain particle size over another.
Response: Comment not incorporated. The intention is to provide flexibility to the users in terms of what particle size can be used initially. That was the approach in General Chapter <621> *Chromatography* before the possibility of particle size adjustment was introduced in the *USP–NF*.
Comment Summary #3: The commenter suggested modifying the definition of *B* in the *%RSD* formula under *System Suitability* A to state, "*B* is the difference between the upper limit given in the definition of the individual monograph and 100%."
Response: Comment not incorporated. This section of the General Chapter was not subjected to revisions in the *PF* proposal. The EC will consider the comment for a future revision of the General Chapter.
Comment Summary #4: The commenter suggested modifying *Figure* 5 under *System suitability* A to add illustrations of $W_{h/2}$ (the peak width at its half-height) and of five times $W_{h/2}$ around the baseline.
Response: Comment not incorporated. This section of the General Chapter was not subjected to revisions in the *PF* proposal. The Expert Committee will consider the comment for a future revision of the General Chapter.

General Chapter/Sections: <1058> Analytical Instrument Qualification/Multiple Sections
Expert Committees: General Chapters—Chemical Analysis
No. of Commenters: 7

General
Comment Summary #1: The commenter indicated that the General Chapter should specifically consider instrument configuration, which can be a critical control point for instruments.

Response: Comment not incorporated. The General Chapter already contains a section with “Practices for Performance qualification, change control, and periodic review” addressing instrument configuration.
Comment Summary #2: The commenter suggested using the phrase “fitness for its intended use” rather than “suitability for its intended use” or “appropriate for the intended use,” to be consistent with the statement used in U.S. Food and Drug Administration (FDA) guidance.
Response: Comment partially incorporated. The text was revised depending on the context and consistency with other sections in the General Chapter.

Introduction
Comment Summary #3: The commenter requested correction of a grammatical error from “is” to “are” in the sentence about the range of analytical instruments used in the pharmaceutical industry.
Response: Comment incorporated.
Expert Committee-initiated Change #1: The sentence defining “instrument” was changed to include any apparatus, equipment, instrument, or instrument system used in “pharmacopeial analyses”.
Expert Committee-initiated Change #2: A sentence was revised to indicate that this informational General Chapter provides general guidance in a scientific risk-based approach.
Expert Committee-initiated Change #3: A sentence was revised to indicate that detailed instrument operating parameters to be qualified are found in the respective general chapters for specific instrument types.
Expert Committee-initiated Change #4: A sentence was revised to indicate that instrument owners/users and their management are responsible for assuring their instruments are suitably qualified.
Comment Summary #4: The commenter requested correction of a typographical error in the sentence about the principles and framework.
Response: Comment incorporated. The paragraph was completely replaced.
Comment Summary #5: The commenter requested modifications to the sentence about risk assessment to clarify and align it with other sections of the introduction.
Response: Comment incorporated.
Comment Summary #6: The commenter requested modifying a sentence to clarify that risk assessment does not classify the instrument and that guidance from regulatory is needed to determine the amount of qualification work for the instrument.
Response: Comment incorporated.
Comment Summary #7: The commenter recommended deleting the sentence, “Therefore, no specific examples are provided.” because each classification provides examples.
Response: Comment incorporated.
Comment Summary #8: The commenter suggested revising the wording under *Group* B because it is generally recognized that compliance for certain types of instruments is ensured through documented calibration or performance checks, and the extend of activities may depend on the criticality of the application.
Response: Comment incorporated.
Expert Committee-initiated Change #5: A sentence was modified to indicate that Group C comprises analytical instruments with “a significant degree of…”

Comment Summary #9: The commenter suggested modifying a sentence to include FTIR spectrometers in the group C of instruments.
Response: Comment not incorporated because there are already two examples.

Components of Data Quality
Comment Summary #10: The commenter suggested adding one more layers to *Figure* 1, under the triangle "Calibration Standards," because they form the basis of accuracy and precision for Analytical Instrument Qualification (AIQ).
Response: Comment not incorporated. The Expert Committee will consider this change in a future revision to this General Chapter to align the terminology and content with the upcoming General Chapter <1220> *The Analytical* Procedure *Lifecycle* upon the receipt of the necessary supporting data.

Components of Data Quality/Analytical Method Validation
Comment Summary #11: The commenter indicated that it is only partly correct to state that the criteria "will generate test data of acceptable quality" because correct metadata must also be generated for a complete record of testing.
Response: Comment not incorporated. All data generated by a validated procedure with qualified analytical instruments must be reliable.

Components of Data Quality/Quality Control Check Samples
Comment Summary #12: The commenter indicated that the section is not directly relevant to AIQ, as check samples primarily assess the method rather than suitability of the instrument.
Response: Comment not incorporated. Quality control check samples are considered ongoing procedure verification.

Components of Data Quality/System Suitability Tests
Expert Committee-initiated Change #6: A sentence was revised to state that General Chapter <621> Chromatography presents a more detailed discussion of system suitability tests (SST) related to chromatographic systems.

Analytical Instrument Qualification Process/Qualification Phases
Comment Summary #13: The commenter indicated that the use of Design Qualification is not accurate for URS (User Requirement Specification); and the term DQ does not match the acknowledged V-model.
Response: Comment incorporated. This section was completely replaced.
Comment Summary #14: The commenter requested deleting the clause "as documented in the DQ" in a sentence pertaining to Operational Qualification (OQ) tests specifically designed to verify the instrument's operation.
Response: Comment incorporated. This section was completely replaced.

***Analytical Instrument Qualification Process/Qualification Phases/Design* Qualification**
Comment Summary #15: The commenter recommended modifying a sentence to state that DQ is the documented collection of activities necessary to demonstrate that design and functions of instrument is suitable for intended purpose.
Response: Comment incorporated. Clarifying wording was added under the section *Qualification Phases*.

Comment Summary #16: The commenter suggested clarifying that the expectation of DQ requirements for commercial, off-the-shell instruments should be based on system complexity and configuration.
Response: Comment not incorporated. It is stated that the functional and operational specifications are based on the intended purpose of the instrument.

Analytical Instrument Qualification Process/Qualification Phases/Operational Qualification
Comment Summary #17: The commenter suggested that: OQ should be specified as "verification of manufacturer's specification at customer's site" (instead of "operational specification testing"); and that testing "according to its operational specification testing" does not describe how the OQ script is to be written. The commenter suggested that USP describe how to write the script and commented that fitness for purpose of user's way of working is PQ.
Response: Comment partially incorporated by deleting the "fitness for purpose of user's way of working". How the OQ script is to be written is out of the scope of the General Chapter.
Comment Summary #18: The commenter suggested modifying a sentence to include the phrase "fitness for purpose for the selected environment" instead of "OQ demonstrates fitness for purpose for the user's ways of working."
Response: Comment partially incorporated. The sentence was revised to read: "OQ demonstrates fitness for the selected use."
Comment Summary #19: The commenter suggested modifying a sentence to state that OQ demonstrates fitness for purpose for the user's ways of working, and should reflect user's requirements and specifications (URS) instead of the "DQ document".
Response: Comment incorporated. A revision to the text was included in the *Errata* table on January 27, 2017.

Analytical Instrument Qualification Process/Qualification Phases/Operational Qualification/Instrument Function Tests
Comment Summary #20: The commenter suggested modifying a sentence to state that holistic tests involving the entire system demonstrate compliance with users' requirements and specifications (URS) instead of "user specifications in the DQ".
Response: Comment incorporated. A revision to the text was included in the *Errata* table on January 27, 2017.

Analytical Instrument Qualification Process/Qualification Phases/Operational Qualification/Software Configuration /or Customization
Comment Summary #21: The commenter recommended placing text about configuration or customization of instrument software in the Instrument Qualification (IQ) section.
Response: Comment partially incorporated. Clarifying text was added under the section *Qualification Phases* enabling language IQ and OQ can overlap.
Comment Summary #22: The commenter suggested reconsidering revising the text of section as follows: "Any configuration or customization of instrument software should occur before the OQ and be documented in the IQ."
Response: Comment partially incorporated. Clarifying text was added under the section *Qualification Phases* enabling language IQ and OQ can overlap.

Comment Summary #23: The commenter requested modifications because OQ is performed by the supplier when the users start their testing, and suppliers will typically only perform their testing in the environment in which they are trained.
Response: Comment incorporated. Clarifying text was added under the section *Qualification Phases*.

Analytical Instrument Qualification Process/Qualification Phases/Performance Qualification
Comment Summary #24: The commenter indicated that the description of "continued PQ" vs SST needs to be revised.
Response: Comment partially incorporated. Clarification was added that SST is element of continued Performance Qualification (PQ), not the PQ itself.

Analytical Instrument Qualification Process/Qualification Phases/Performance Qualification/Practices for Performance Qualification, Change Control, and Periodic Review
Comment Summary #25: The commenter suggested that the General Chapter define criteria for determining if an instrument is critical and provide examples of critical instruments.
Response: Comment not incorporated. Specific requirements are described in the particular instrumental General Chapters.
Comment Summary #26: The commenter indicated that the "instrument owner/user and their management" group is too large to be responsible for the qualified state of the equipment, and that the GxP responsible roles are "Process Owner" and "System Owner."
Response: Comment not incorporated. The user needs to define each term and proper responsibility.
Comment Summary #27: The commenter indicated that instrument owners/users need to be trained to be responsible for assuring their instruments are suitably qualified, and "organization management" is part of user group.
Response: Comment partially incorporated. The user needs to define "organization management." Clarifying text was added to the *Introduction*.

Roles and Responsibilities/Quality Unit
Expert Committee-initiated Change #7: The sentence: "Quality personnel are responsible for ensuring that the AIQ process meets compliance requirements, that processes are being followed, and that the intended use of the equipment is supported by valid and documented data." was deleted.

Software Validation
Comment Summary #28: The commenter suggested removing the specific reference to a GAMP to avoid unneeded revision when the Good Automated Manufacturing Practice (GAMP) 5 is changed to GAMP 6.
Response: Comment incorporated.

Software Validation/Firmware

Comment Summary #29: The commenter suggested modifying a sentence to read, "Planned changes made to firmware versions should be tracked through the change control of the instrument."
Response: Comment not incorporated. The current language matches the proposal.
Comment Summary #30: The commenter indicated that in most cases firmware capability is not visible to users, and therefore it would not be possible to comply with the requirement of calculations defined by users.
Response: Comment incorporated.
Comment Summary #31: The commenter recommended defining and verifying fixed calculations performed by firmware used to acquire data, and recommended that USP provide examples.
Response: Comment partially incorporated. The sentence was revised to “These calculations need to be verified by the user.”

Software Validation/Instrument Control, Data Acquisition, and Processing Software
Comment Summary #32: The commenter suggested changing the first type of software classification from “non-configurable software” to “commercial off the shelf (COTS).”
Response: Comment not incorporated. There are configurable COTS.

Change Control
Comment Summary #33: The commenter recommended modifying a sentence to state that if implementation of the changes is needed, install the changes to the system before IQ.
Response: Comment incorporated. The section was completely replaced.

Glossary
Comment Summary #34: The commenter indicated that the definition of Software (SW) validation as part of qualification process is inaccurate because SW validation for COTS can only be performed by manufacturer having access to the source code.
Response: Comment not incorporated. Software validation can be performed without the source code.
Comment Summary #35: The commenter suggested adding a definition for “User” to the *Glossary*.
Response: Comment not incorporated. The term “user” is already described in the body of the General Chapter.

General Chapter/Section: <1225> Validation of Compendial Procedures
Expert Committee: General Chapters–Chemical Analysis
No. of Commenters: 1
Comment Summary #1: A commenter suggested adding the characteristic “Ruggedness” to *Table* 1 *Typical Analytical Characteristics Used in Method Validation*.
Response: Comment not incorporated. Ruggedness is already considered under the *Precision* section

General Chapter/Sections: <1790> Visual Inspection of Injections/Multiple Sections
Expert Committee: General Chapters–Dosage Form

No. of Commenters: 11

General
Comment Summary #1: The commenter recommended that the General Chapter should more broadly address “visual inspection“ of parenteral dosage forms.
Response: Comment not incorporated. The General Chapter was written to be broad in its discussion around visual inspection.
Comment Summary #2: The commenter suggested that the failure rate in 100% testing (“yield”) should not require limits for clinical trial drug products.
Response: Comment not incorporated. There is an obligation to set some type of limit to ensure the process is in control, even for clinical trial drug products.
Comment Summary #3: The commenters recommended adding specifics on how to deal with cell therapy products.
Response: Comment not incorporated. The goal of <1790> was to capture 80–90% of situations; alternative inspection scheme are needed for special case situations.
Comment Summary #4: The commenter recommended working to align concepts of <1790> with other major pharmacopoeias such as *European Pharmacopoeia* (*EP*) and *Japanese Pharmacopoeia* (*JP*) prior to publication.
Response: Comment incorporated. Collaboration already occurs with the *EP* and *JP* around particulate matter nomenclature.

Scope
Comment Summary 5: The commenter suggested distinguishing particles as visible versus sub-visible.
Response: Comment incorporated.

Defect Prevention
Comment Summary #6: The commenter recommended adding text that secondary packaging components of the container closure system should also be part of the life-cycle approach
Response: Comment incorporated.
Comment Summary #7: The commenter recommended adding text about the life cycle of defect samples and that they should be characterized, qualified, and maintained.
Response: Comment incorporated.
Comment Summary #8: The commenter suggested discussing the partnership between the component manufacturer and the buyer of containers to optimize a particle control strategy, alignment of detection methods, and defect definitions.
Response: Comment incorporated. Topic was added to the appropriate section

Introduction
Comment Summary #9: The commenter recommends changing this title to “*Background*,” because the heading for Section 1.1 is also “*Introduction*” and thus may cause confusion.
Response: Comment incorporated.

2.1 Inspection Process Capability
Comment Summary #10: The commenter recommended discussing the importance of particle number in detection.
Response: Comment incorporated.

Comment Summary #11: The commenter suggested including strategy of when to use visual and when to use instrumental analysis.
Response: Comment not incorporated. The Expert Committee determined that this was out of scope for this General Chapter.

2.2 Patient Risk
Comment Summary #12: The commenter recommended deleting the text that suggests that only extraneous particles are of possible safety concern and "inherent" are not.
Response: Comment incorporated.
Comment Summary #13: The commenter recommends referencing the Compendial fragmentation test.
Response: Comment not incorporated. The Expert Committee determined that this is out of scope for this General Chapter because it is a unique phenomenon, not part of the manufacturing process.
Comment Summary #14: The commenter recommended a discussion on coring.
Response: Comment not incorporated. The Expert Committee determined that this is out of scope for this General Chapter because it is not primary hazards and not something addressed in a visual inspection program.

3.1 100% Inspection
Comment Summary #15: The commenter suggested providing information on what constitutes a defect.
Response: Comment incorporated.
Comment Summary #16: The commenter suggested including the concept of ejected units versus rejected units
Response: Comment incorporated. Reference and text that points to section that discusses two stage testing were added.
Comment Summary #17: The commenter suggested that the General Chapter should include an additional paragraph on the current 100% visual inspection process.
Response: Comment not incorporated. There is a section already in the General Chapter that addresses this topic.

3.2 Acceptance Sampling and Testing
Comment Summary #18: The commenter recommends removing specific approaches prescribed in the General Chapter to allow other approaches.
Response: Comment not incorporated. The objective was to provide a way to implement General Chapter <790> *Visual Particles in Injections*. *GN* 6.30 allows for alternative approaches.

3.2 Acceptance Sampling and Testing. Table 1
Comment Summary #19: The commenter requested adding definitions or reference to definitions, for defect categories (critical, major, and minor) in the table.
Response: Comment incorporated.
Comment Summary #20: The commenter suggested clarifying which Unacceptable Quality Level (UQL) values should be considered.
Response: Comment incorporated.
Comment Summary #21: The commenter suggested explanation how to do trending for UQL.

Response: Comment not incorporated. Goal is to not do UQL trending.
Comment Summary #22: The commenter suggested adding information on UQL and typical values.
Response: Comment incorporated.
Comment Summary #23: The commenter suggested stating that the effectiveness of an automated system should be equivalence to the manual inspection effectiveness without changing the definition of what size is visible.
Response: Comment not incorporated. The goal is to not use automated inspection for Acceptable Quality Level (AQL).
Comment Summary #24: The commenter suggested extending the particle testing requirement to the raw materials.
Response: Comment not incorporated. The Expert Committee determined that this was out of scope for this General Chapter.

3.3 Reinspection
Comment Summary #25: The commenter suggested clarifying that re-inspection refers to repeated 100% and sampling plan inspections.
Response: Comment incorporated.
Comment Summary #26: The commenter recommended clarifying what is meant by “approved procedure.”
Response: Comment incorporated.

3.3. Two Stage Inspection
Comment Summary #27: The commenter recommended describing the concept of “ejects” and “rejects” because it is pertinent to automated stage one of two-stage inspection.
Response: Comment incorporated.
Comment Summary #28: The commenter recommended defining the conditions in which a two pass inspection can be justified.
Response: Comment incorporated.
Comment Summary #29: The commenter requested an option for using automated inspection of ejects from automated inspection.
Response: Comment incorporated.

4.1 Extrinsic, Intrinsic or Inherent Particles
Comment Summary #30: The commenter recommended acknowledging that particles may be introduced into the process/product via raw material.
Response: Comment not incorporated. The Expert Committee determined that this was out of scope for this General Chapter.
Comment Summary #31: The commenter suggested removing the new category "inherent particles.”
Response: Comment not incorporated. The term is used widely within the pharmaceutical industry.
Comment Summary #32: The commenter suggested clarifying that biological products are not included in the scope of the General Chapter.
Response: Comment not incorporated. The Expert Committee determined that biological products are included in the scope of the General Chapter.

4.2 Prevention of Particulates

Comment Summary #33: The commenter suggested deleting this section because it varies from the General Chapter's description of the best practice for the visual inspection process.
Response: Comment not incorporated. The Expert Committee determined that the section has value and should be retained.

4.2 Common Sources of Intrinsic Particulates
Comment Summary #34: The commenter suggested clarifying the threshold levels for the formation of visible change for certain products.
Response: Comment incorporated.

4.2 Formulation Components
Comment Summary #35: The commenter suggested correcting text to state the stopper or piston moves not the barrel.
Response: Comment incorporated.

4.3 Particle Removal by Component Washing
Comment Summary #36: The commenter recommended deleting the entire section as it deviates from the scope of the chapter.
Response: Comment not incorporated. The Expert Committee determined that there is value in keeping section.

4.4 Trending
Comment Summary #37: The commenter suggested emphasizing the importance of the information from the 100% inspection.
Response: Comment incorporated.

5.1 Defect Classification
Comment Summary #38: The commenter indicated that the definition of critical, major, minor defect is provided, but this section does not provide typical examples of each category of defects.
Response: Comment not incorporated. The Expert Committee determined that adding examples to the General Chapter would only create confusion.
Comment Summary #39: The commenter suggested removing the reference to "Knapp's methodology."
Response: Comment not incorporated. The goal was to use terminology that is widely used within the industry.
Comment Summary #40: The commenter suggested adding a discussion on the detection level for fibers.
Response: Comment incorporated.
Comment Summary #41: The commenter suggested removing very specific approaches prescribed in the section.
Response: Comment not incorporated. General Chapter <790> discusses the ability to use alternative sampling plans.
Comment Summary #42: The commenter recommends adding fill volume to this list of dependents, because smaller fill volume is more strenuous to inspect.
Response: Comment incorporated.

5.2 Unique Product and Container Considerations: Lyophilized Products

Comment Summary #43: The commenter requested that a statement be added that larger sample sizes are necessary for lot size greater than 150,000.
Response: Comment incorporated.
Comment Summary #44: The commenter recommends adding a statement that at stage two, you would have to work through your batch size.
Response: Comment incorporated.

5.2 Unique Product and Container Considerations: Translucent Plastic Containers
Comment Summary #45: The commenter suggested that there are now plastic resins available that are optically as clear as glass and this point should be reflected in the General Chapter.
Response: Comment incorporated.

6.1 Critical Process Parameters in MVI—Light Intensity
Comment Summary #46: The commenter suggested stating that lux levels >~8000 cause glare and a Tyndall effect that mask particles and lead to inspector fatigue.
Response: Comment incorporated.
Comment Summary #47: The commenter suggested adding a warning of photo-sensitivity at U/V spectrum.
Response: Comment not incorporated. The Expert Committee determined that this was out of scope for this General Chapter.

6*.1 Critical Process Parameters in MVI—Background and Contrast*
Comment Summary #48: The commenter suggested it would be useful if this section specified that the background (white/black) should have mat finish/non glossy/non glary finish.
Response: Comment incorporated.

6.1 *Critical Process Parameters in MVI—Container handling and movement*
Comment Summary #49: The commenter suggested indicating the approximate distance between eye and container during visual inspection.
Response: Comment not incorporated. The Expert Committee determined that the distance will depend on the individual's visual acuity and specify a distance range would add unnecessary complexities to the General Chapter.

6.2 Critical Process Parameters from Semi-automated Inspection
Comment Summary #50: The commenter suggested adding the control of wavelength range to the section.
Response: Comment not incorporated. The Expert Committee determined that the edits are too specific.

6.3 Light Obscuration Methods
Comment Summary #51: The commenter suggested that "Light obscuration" is incorrect terminology for automated inspection.
Response: Comment not incorporated. Light obscuration is used for visible and subvisible detection.
Comment Summary #52: The commenter suggested that detection of smaller particles can greatly improve when more than one particle is present.
Response: Comment incorporated.

6.3 Other Technologies
Comment Summary #53: The commenter suggested that the reference to container closure integrity is unnecessary.
Response: Comment incorporated.

7.2 Preparing Defect Standards
Comment Summary #54: The commenter recommended adding discussion about the number of defects in a defect kit.
Response: Comment not incorporated. This topic is discussed in section 7.5 *Test Sets*.
Comment Summary #55: The commenter recommended adding intrinsic product-specific particle defects identified during pharmaceutical development as potential defect standards.
Response: Comment not incorporated. The Expert Committee determined that this was out of scope for this General Chapter.

7.4 Rejection Probability Determination
Comment Summary #56: The commenter suggested removing specific approaches prescribed in the General Chapter; e.g. specified AQL procedure, probability of detection (POD), Knapp testing, etc.
Response: Comment not incorporated. This is an informational general chapter numbered above 1000 and the Expert Committee determined there was value in providing some guidance on the specific approaches.

7.5 Test Sets
Comment Summary #57: The commenter suggested removing specific approaches prescribed in the General Chapter; e.g., specified AQL procedure, POD, Knapp testing, etc.
Response: Comment not incorporated. This is an informational chapter numbered above 1000 and the Expert Committee determined there was value in providing some guidance on the specific approaches.
Comment Summary #58: The commenter suggested that a limit should be set for each individual defect to be limited to approximately 10%, and, a maximum number of total defects in a test set to approximately 30%.
Response: Comment not incorporated. The Expert Committee needs more data to support such a conclusion.
Comment Summary #59: The commenter requested removing the grey zone from the application of a test set.
Response: Comment not incorporated. The text it states “may” be used and this is an informational chapter numbered above 1000, use of the grey zone is not required.

7.6 Types of Test Sets
Comment Summary #60: The commenter suggested adding that that there is a regulatory expectation of 95% detection and that the size threshold is 250–300 micron.
Response: Comment not incorporated. This is not a current regulatory expectation.

7.7 Training and Qualification of Human Inspectors
Comment Summary #61: The commenter recommended adding acceptance criteria for near vision, e.g., “N6.”

Response: Comment not incorporated. The most common way to represent near vision is included in the General Chapter.
Comment Summary #62: The commenter recommended adding a statement that eyesight correction is allowed.
Response: Comment incorporated.
Comment Summary #63: The commenter suggested that a 100% pass on much larger size particles that is defined by 70% POD should be set.
Response: Comment not incorporated. This will lead to increased failures.

8.0 Product in Distribution
Comment Summary #64: The commenter recommended revising the text to clarify the factors that determine the potential for coincidence counting.
Response: Comment not incorporated. The Expert Committee determined that this is out of scope for this General Chapter.

Monographs

Monograph/Section: Betamethasone Valerate Lotion/Organic Impurities
Expert Committee: Chemical Medicines Monographs 5
No. of Commenters: 2
Comment Summary #1: The commenter requested that the acceptance criterion for betamethasone valerate related compound A be revised from NMT 1.0% to NMT 10.0%, and the acceptance criterion for total degradation products be revised from NMT 2.0% to NMT 12.0% to match the commenter's approved specifications.
Response: Comment incorporated.
Comment Summary #2: The commenter noted that the impurities profile differs from what has been approved by the FDA.
Response: Comment incorporated, as described in Comment Summary #1.

Monograph/Sections: Buprenorphine Hydrochloride/Multiple Sections
Expert Committee: Chemical Medicines Monographs 2
No. of Commenters: 2

Comment Summary #1: The commenter indicated the concentration of USP Buprenorphine Hydrochloride RS in the *Standard solution* under *Organic impurities* was too low to show a visible peak.
Response: Comment not incorporated. The Expert Committee determined that the proposed concentration is suitable for the intended use based on validation and other supporting data.
Comment Summary #2: The commenter indicated they did not support the addition of *Identification* B, because they did not support the proposed high-performance liquid chromatography (HPLC) *Assay* procedure.
Response: Comment not incorporated. The Expert Committee determined that the addition of an orthogonal identification test strengthened the standard.

Comment Summary #3: The commenter indicated that the proposed changes in *Identification* C do not provide significant improvements to the test procedure.
Response: Comment not incorporated. The Expert Committee determined that the proposed changes are adequate for a public standard.
Comment Summary #4: The commenter indicated the proposed HPLC procedures for *Assay* and *Organic impurities* are unsuitable for their product.
Response: Comment not incorporated. The Expert Committee will consider future revisions to the monograph upon receipt of necessary supporting data.
Comment Summary #5: The commenter indicated that the proposed changes in *pH/Acidity* or *Alkalinity* do not provide significant improvements to the test procedure.
Response: Comment not incorporated. The Expert Committee determined that the proposed changes are adequate for a public standard.
Expert Committee-initiated Change #1: The statement **"**Disregard any peaks below 0.05%" was replaced with "The reporting threshold is 0.05%" in *Organic impurities* to be consistent with the ICH terminology.
Expert Committee-initiated Change #2: It was clarified that the chemical name under USP Buprenorphine System Suitability Mixture RS in the section of General Chapter <11> *USP Reference Standards* is for ethenobuprenorphine only.
Expert Committee-initiated Change #3: The description for USP Buprenorphine System Suitability Mixture RS in the *USP Reference Standards* <11> section was revised to remove "hydrochloride" from buprenorphine hydrochloride, because the drug substance is present in the base form not in the hydrochloride salt form in the system suitability mixture.

Monograph/Section: Cabergoline Tablets/Dissolution
Expert Committee: Chemical Medicines Monographs 4
Expert Committee-initiated Change #1: The solution description for the *Standard solution* in the test for *Dissolution* was revised for consistency with the calculation section.

Monograph/Section: Carisoprodol Tablets/Organic Impurities
Expert Committee: Chemical Medicines Monographs 4
Expert Committee-initiated change #1: The solution description for the *Standard solution* in the test for *Organic Impurities* was revised for consistency with the calculation section.

Monograph/Section: Carnauba Wax/Identification A
Expert Committee: Excipient Monographs 2
No. of Commenters: 4
Comment Summary #1: The commenter indicated that the addition of an infrared identification (IR ID) test is a positive development, because the monograph had no ID test. The commenter requested that USP consider including additional ID tests for the types of fatty acid present and any other tests that would be helpful in preventing industrial grades from meeting the monograph specification, because the proposed test might not provide adequate specificity.
Response: Comment not incorporated. The Expert committee agreed that it is a significant improvement to add an ID test in the monograph. The request to include

additional ID tests will be considered by the committee in the future revisions to this monograph upon the receipt of the necessary supporting data.
Comment Summary #2: The commenter indicated that there may be sample-to-sample variability and issues matching peaks between standards and samples because Carnauba wax is a natural product (extracted from leaves of the *Copernicia cerifera* plant), and recommended a requirement only for distinctive IR peaks.
Response: Comment not incorporated. The sample variability was considered already by testing IR for available Carnauba Wax *NF* grade samples produced by different manufacturers. The results demonstrated that the IR spectra were consistent for all Carnauba wax samples. In addition, the Carnauba Wax can be distinguished from other waxes, such as Emulsifying wax, Microcrystalline wax, White wax and Yellow wax, by comparison of IR spectra. The Expert Committee decided to adopt requirements from General Chapters <197A> or <197F> rather than distinctive Carnauba wax absorbance peaks only as acceptance criteria, based on the IR results.
Comment Summary #3: The commenter commented that there should be a USP RS available for the IR test.
Response: Comment incorporated. USP Carnauba Wax RS was added to the monograph and USP had qualified Carnauba Wax RS available prior to the implementation of the method.
Comment Summary #4: The commenter asked whether the sample preparation should be neat or a melt.
Response: Comment not incorporated. The response is that neat sample is added to the ATR accessory if using <197A>; and the sample should be melted first and then spread onto KBr plates if using <197F>.

Monograph/Section: Ceftiofur Hydrochloride/Organic Impurities
Expert Committee: Chemical Medicines Monographs 3
No. of Commenters: 1
Comment Summary #1: The commenter indicated that USP Ceftiofur System Suitability Mixture RS is not fully soluble in Diluent at the proposed concentration and requested revision of the concentration of USP Ceftiofur System Suitability Mixture RS in the System suitability solution from 0.3 mg/mL to 0.1 mg/mL.
Response: Comment incorporated.
Expert Committee-initiated Change #1: In the test for *Organic impurities, Table 2*, the impurity at RRT 0.03 was revised from Ceftiofur oxime ethyl ester to Aminothiazolyl oxime ethyl ester to be consistent with the nomenclature style used in the Ceftiofur Sodium monograph.

Monograph/Sections: Ceftiofur Sodium /Multiple Sections
Expert Committee: Chemical Medicines Monographs 3
No. of Commenters: 4
Comment Summary #1: The commenter requested that the ceftiofur hydrochloride be used as the RS for this monograph.
Response: Comment not incorporated. The Expert Committee determined that the use of ceftiofur sodium as the RS was appropriate.
Comment Summary #2: The commenter requested to include their procedure to evaluate the impurities in their product.
Response: Comment incorporated. The monograph is capable of evaluating the commenter's impurity profile as well as the profiles of additional stakeholders. The

Expert Committee added language to the monograph to indicate specific impurities in the low molecular weight procedure that are to be evaluated only if possible from the manufacturing process. In addition, a statement was added to the high molecular weight impurities procedure indicating the test is to be performed only if the impurities are possible from the manufacturing process.
Comment Summary #3: The commenter requested adding a resolution requirement for the peaks due to N-Deacyl ceftiofur and cefotaxime in the test for *Organic impurities*.
Response: Comment not incorporated. The Expert Committee determined that the proposed system suitability requirements are suitable for the public standard.
Comment Summary #4: The commenter indicated that the limit for unspecified impurities in the test for *Organic impurities* is too high.
Response: Comment not incorporated. The limit for unspecified impurities is consistent for an FDA-approved product.

Monograph/Sections: Cefuroxime Axetil/Multiple Sections
Expert Committee: Chemical Medicines Monographs 1
No. of Commenters: 4
Comment Summary #1: The commenter requested that the Zorbax TMS-250 x 4.6 mm be incorporated into the test for *Organic Impurities*.
Response: Comment not incorporated. The Zorbax TMS-250 x 4.6 mm is stated in the *Pharmacopeial Forum* 41(2) [Mar.–Apr. 2015] briefing, and can be found in the *USP Chromatographic Columns* and at http://www.uspchromcolumns.com/.
Comment Summary #2: The commenter requested revising the acceptance criteria for organic impurities to be consistent with the approved requirements.
Response: Comment incorporated. The acceptance criteria are changed as follows based on FDA-approved limits: Methoxyiminofuranyl acetic acid, NMT 0.30%; Cefuroxime lactone, NMT 0.30%; Cefuroxime axetil delta-3 isomers, NMT 1.20%; Cefuroxime axetil E-isomers, 1.0%; any other individual impurity, NMT 0.30%; Total impurities, NMT 3.0%.
Comment Summary #3: The commenter requested that the proposed procedures for *Assay* and *Organic impurities* be replaced with their procedures.
Response: Comment not incorporated. The Expert Committee determined that the proposed procedures are suitable for public standard and resolves the impurities in the commenter's impurity profile.
Comment Summary #4: The commenter indicated that the retention time for cefuroxime axetil diastereoisomer A in the procedure for *Organic impurities* could only be achieved with modification of the stated mobile phase.
Response: Comment not incorporated. The retention time provided in the briefing is consistent with the USP lab procedure evaluation.
Comment Summary #5: The commenter requested canceling the revision for the *Assay* limits. The commenter indicated that it is not possible to achieve proposed *Assay* limit of 90% based on the theoretical content of cefuroxime in cefuroxime axetil on anhydrous basis.
Response: Comment incorporated.
Comment Summary #6: The commenter indicated the poor peak shape obtained for the Peak identification solution when using 100% methanol in the solution preparation. The chromatography is much improved using mobile phase as diluent.
Response: Comment incorporated.

Comment Summary #7: The commenter indicated that the relative retention times in the test for *Organic impurities* did not agree with those published in *Table* 1 in their evaluation. The commenter also noted some late eluting impurities may interfere with subsequent injections.
Response: Comment not incorporated. The Expert Committee determined that the test for *Organic Impurities* is suitable for its intended purpose. The relative retention times in the *Table* 1 are provided for informational purpose.

Monograph/Section: Cefuroxime Axetil Tablets/Organic Impurities
Expert Committee: Chemical Medicines Monographs 1
No. of Commenters: 2
Comment Summary #1: The commenter requested that the Zorbax TMS-250 x 4.6 mm be incorporated into the test for *Organic Impurities*.
Response: Comment not incorporated. Monographs do not specify specific column manufacturers or brands. The Zorbax TMS-250 x 4.6 mm is suitable and will be added to the USP *Chromatographic Columns* and at http://www.uspchromcolumns.com/.
Comment Summary #2: The commenter requested that the proposed procedures for *Assay* and *Organic impurities* be replaced with their procedures.
Response: Comment not incorporated. The Expert Committee determined that the proposed procedures are suitable for public standard and resolves the impurities in the commenter's impurity profile.
Comment Summary #3: The commenter requested revising the acceptance criteria for organic impurities to be consistent with the approved requirements.
Response: Comment incorporated. The acceptance criteria are changed as follows: Cefuroxime lactone, NMT 0.30%; Cefuroxime axetil delta-3 isomers, NMT 1.20%; any other individual impurity, NMT 0.30%.

Monograph/Section: Chocolate
Expert Committee: Botanical Dietary Supplements and Herbal Medicines
No. of Commenters: 1
Comment Summary #1: The commenter recommended addition of an identification test
Response: Comment not incorporated. An identification test will be proposed in a later revision with inputs from sponsors.

Monograph/Sections: Cinnamomum Cassia Twig/Multiple Sections
Expert Committee: Botanical Dietary Supplements and Herbal Medicines
No. of Commenters: 1
Comment Summary #1: The commenter indicated that the *Definition* section should include cassia's common Latin binomial synonym of *Cinnamomum aromaticum* Nees.
Response: Comment incorporated.
Expert Committee-initiate Change #1: USP Lab project test results indicated the time established (2 minutes) for heating the High Performance Thin-Layer Chromatography (HPTLC) plate after the derivatization process was insufficient to obtain the yellow color for the band immediately below the cinnamaldehyde band, after 4 minutes the yellow color was developed. The monograph revised from 2 to 4 minutes.

Expert Committee-initiate Change #2: USP Lab project test results indicated that after derivatization of the HPTLC plate, under UV light at 366 nm, cinnamaldehyde band did not display a light-blue but seems a gray band. To avoid color description confusion, the sentences were deleted.

Monograph/Sections: Cinnamomum Cassia Twig Powder/Multiple Sections
Expert Committee: Botanical Dietary Supplements and Herbal Medicines
No. of Commenters: 1
Comment Summary #1: The commenter indicated that the Definition section should include cassia's common Latin binomial synonym of *Cinnamomum aromaticum* Nees.
Response: Comment incorporated.
Expert Committee-initiate Change #1: USP Lab project test results indicated the time established (2 minutes) for heating the HPTLC plate after the derivatization process was insufficient to obtain the yellow color for the band immediately below the cinnamaldehyde band, after 4 minutes the yellow color was developed. The monograph revised from 2 to 4 minutes.
Expert Committee-initiate Change #2: USP Lab project test results indicated that after derivatization of the HPTLC plate, under UV light at 366 nm, cinnamaldehyde band did not display a light-blue but seems a gray band. To avoid color description confusion, the sentences were deleted.

Monograph/Sections: Ciprofloxacin for Oral Suspension/Multiple Sections
Expert Committee: Chemical Medicines Monographs 1
No. of Commenters: 2
Comment Summary #1: The commenter indicated that the limits for ciprofloxacin ethylenediamine analog and any individual unspecified impurity are not consistent with approved requirements.
Response: Comment incorporated. The limit for ciprofloxacin ethylenediamine analog is revised form NMT 0.20% to NMT 0.3%, and the limit for any individual unspecified impurity is revised from NMT 0.13% to NMT 0.2% based on FDA-approved limits.
Comment Summary #2: The commenter suggested adding “store upright” in the *Packaging and Storage* section.
Response: Comment not incorporated. The Expert Committee determined that the storage condition in the monograph is adequate.
Comment Summary #3: The commenter requested the inclusion of their approved dissolution tolerances.
Response: Comment incorporated. The *Dissolution Test 2* is added to reflect the approved dissolution conditions.

Monograph/Section: Ciprofloxacin Tablets/Organic Impurities
Expert Committee: Chemical Medicines Monographs 1
No. of Commenters: 2
Comment Summary #1: The commenter requested to revise the acceptance criterion for ciprofloxacin ethylenediamine analog from NMT 0.3% to NMT 0.5% to be consistent with approved requirement.
Response: Comment incorporated.

Comment Summary #2: The commenter requested to not include the process impurities in *Table* 1 in the test for *Organic Impurities*.
Response: Comment incorporated.
Comment Summary #3: The commenter indicated that the impurity limits are not consistent with approved requirements.
Response: Comment incorporated. The acceptance criterion for the ciprofloxacin ethylenediamine analog is revised form NMT 0.3% to NMT 0.5% based on the FDA-approved limit.
Comment Summary #4: The commenter indicated that process impurity 6-hydroxy compound partially coelutes with decarboxyciprofloxacin.
Response: Comment not incorporated. The Expert Committee will consider future revision to the monograph upon receipt of necessary supporting data.

Monograph/Sections: Dalfampridine/Multiple Sections
Expert Committee: Chemical Medicines Monographs 4
No. of Commenters: 3
Comment Summary #1: The commenters requested revising the acceptance criteria for dalfampridine related compound A in the test for *Organic Impurities* and for dalfampridine related compound B and dalfampridine related compound C in the *Limit of Dalfampridine Related Compound B and Dalfampridine Related Compound C.*
Response: Comment not incorporated. Additional investigation established that the proposed acceptance criteria are consistent with FDA-approved specifications.
Comment Summary #2: The commenter requested including a different analytical procedure in the test for *Organic Impurities*.
Response: Comment not incorporated. The Expert Committee will consider future revisions to the monograph upon the receipt of the necessary supporting data.
Expert Committee-initiated Change #1: The reference to “Chromatographic acetonitrile” in the *Assay* was replaced with a reference to “acetonitrile,” because the proposal to add an entry to the reagent section for “Chromatographic acetonitrile” has been cancelled.
Expert Committee-initiated Change #2: The duplicate reference to General Chapter <621> *Chromatograph*y and the resolution requirement within the test for the *Limit of Dalfampridine Related Compound B and Dalfampridine Related Compound C* were removed.
Expert Committee-initiated Change #3: The chemical name for dalfampridine related compound B was updated from 3,5-dibromopyridine-4-amine to 3,5-dibromopyridin-4-amine in the *USP Reference Standards* <11> section.

Monograph/Section: Desogestrel/Organic Impurities
Expert Committee: Chemical Medicines Monographs 5
No. of Commenters: 2
Comment Summary #1: The commenter suggested using 100% acetonitrile to prepare the *Standard stock solution* to ensure complete dissolution of the RS.
Response: Comment not incorporated. The potential solubility issue is resolved by decreasing by 10 fold the concentration of the *Standard stock solution*.
Comment Summary #2: The commenter requested the deadline for public comments be extended due to the lack of availability of RS.
Response: Comment not incorporated. All RS are available.

Monograph/Sections: Desoxycholic Acid/ Multiple Sections
Expert Committee: Excipient Monographs 1
No. of Commenters: 1

Comment Summary #1: The commenter recommended the addition of an origin distinguishing/verifying test to the *Identification* section of the monograph because the monograph states that desoxycholic acid of animal origin is to be used as an excipient only and not as an active ingredient.

Response: Comment not incorporated. The commenter reevaluated the request and withdrew the original comment. However, to make cholic acid, which is typically present in animal-derived Desoxycholic Acid, easily identifiable in samples of Desoxycholic Acid, the Expert Committee decided to add *Cholic acid solution* to the *Organic Impurities* test and add the USP Cholic Acid RS to the *USP Reference Standard*s <11> section.

Comment Summary #2: The commenter recommended that the Desoxycholic Acid monograph clearly lists the sources that are acceptable for the material to be used as a drug substance, because animal-origin Desoxycholic Acid is to be excluded from use as a drug substance.

Response: Comment incorporated. The statement, “FDA has not approved the use of animal-derived Desoxycholic Acid as a drug substance” was added to the *Definition.*

Expert Committee-initiated Change #1: The chemical names and molecular weight were updated.

Expert Committee-initiated Change #2: On the basis of the IR data, <197K > was added as an option to the *Identification* section of the monograph.

Expert Committee-initiated Change #3: On the basis of the solution stability data, the requirement for “Autosampler temperature: 5°” was removed from the *Assay* and *Organic Impurities* tests.

Monograph/Sections: Doxycycline for Injection/Multiple Sections
Expert Committee: Chemical Medicines Monographs 1
No. of Commenters: 1

Comment summary #1: The commenter recommended retaining the *Loss on Drying* test in the monograph to provide a mechanism for monitoring moisture for a lyophilized drug product.

Response: Comment incorporated.

Comment summary #2: The commenter recommended adding the molecular structures for all specified impurities in the test for *Organic impurities*.

Response: Comment not incorporated. The Expert Committee will take this recommendation into consideration in the future upon the receipt of the necessary supporting data.

Expert Committee-initiated Change #1: The chemical information for USP Doxycycline Related Compound A RS was revised to include information for the hydrochloride salt. The free base and the hydrochloride salt can be used interchangeably.

Monograph/Sections: Doxycycline Tablets/Multiple Sections
Expert Committee: Chemical Medicines Monographs 1
Expert Committee-initiated Change #1: The chemical information for USP Doxycycline Related Compound A RS was revised to include information for the hydrochloride salt. The free base and the hydrochloride salt can be used interchangeably.
Expert Committee-initiated Change #2: The relative retention times in the test for *Organic Impurities* are changed to be consistent across the family of monographs.

Monograph/Section: Echinacea Species Dry Extract Capsules
Expert Committee: Botanical Dietary Supplements and Herbal Medicines
No. of Commenters: 1
Comment Summary #1: The commenter proposed to use a suitable grade of cynarin (1,3-di-*O*-caffeoylquinic acid) instead of USP Cynarin RS, which had not been developed yet.
Response: Comment incorporated.

Monograph/Section: Echinacea Species Dry Extract Tablets
Expert Committee: Botanical Dietary Supplements and Herbal Medicines
No. of Commenters: 1
Comment Summary #1: The commenter proposed to use a suitable grade of cynarin (1,3-di-*O*-caffeoylquinic acid) instead of USP Cynarin RS, which had not been developed yet.
Response: Comment incorporated.

Monograph/Section: Etomidate/Organic Impurities
Expert Committee: Chemical Medicines Monographs 4
Expert Committee-initiated Change #1: The solution description for the *Standard solution* in the test for *Organic Impurities* was revised for consistency with the calculation section.

Monograph/Sections: Etomidate Injection/Multiple Sections
Expert Committee: Chemical Medicines Monographs 4
Expert Committee-initiated change #1: The solution descriptions for the *Standard solution* in the test for *Organic Impurities, Procedure 1*, and *Organic Impurities, Procedure 2* were revised for consistency with the corresponding calculation sections.

Monograph/Section: Fluticasone Propionate Lotion/Impurities
Expert Committee: Chemical Medicines Monographs 5
No. of Commenters: 2

Comment Summary #1: The commenter indicated that the acceptance criteria within the test for *Organic Impurities* are too stringent and suggested widening the specification for any individual impurity.
Response: Comment not incorporated. The Expert Committee will consider further revisions to the monograph upon receipt of the necessary supporting data.
Comment Summary #2: The commenter requested revising the acceptance criteria for fluticasone propionate related compound C, any unspecified degradation product, and total impurities in the test for *Organic Impurities* to match the specifications approved by the FDA and to be consistent with ICH Q3B guidelines.
Response: Comment not incorporated. The commenter has no objections to the proposed acceptance criteria within the test for *Organic* Impurities after additional investigation established that they are consistent with FDA-approved specifications.

Monograph/Section: Goserelin Implants/Other Components, Acetic Acid
Expert Committee: Biologics Monographs 1–Peptides
No. of Commenter: 1
Comment Summary #1: The commenter requested correcting the chemical name of the internal standard. The chemical name should be hexadecane not hexane.
Response: Comment incorporated. Details are also added to the system suitability criteria to be more specific.

Monograph/Section: Hydroxyzine Hydrochloride Oral Solution/Organic Impurities
Expert Committee: Chemical Medicines Monographs 4
No. of Commenters: 1
Comment Summary #1: The commenter requested revising the acceptance criteria for 4-chlorobenzophenone, any individual unspecified degradation product and Total degradation products.
Response: Comment not incorporated. Additional investigation established that the proposed acceptance criteria are consistent with FDA-approved specifications.
Expert Committee-initiated Change #1: The references to “Chromatographic acetonitrile” in the *Assay* were replaced with references to “acetonitrile” because the proposal to add an entry to the reagent section for “Chromatographic acetonitrile” has been cancelled.

Monograph/Sections: Indomethacin for Injection/Multiple Sections
Expert Committee: Chemical Medicines Monographs 2
No. of Commenters: 1
Comment Summary #1: The commenter recommended tightening the acceptance criterion for indomethacin related compound B.
Response: Comment not incorporated. The acceptance criterion for indomethacin related compound B was not a part of revisions proposed in *PF* 42(2) [Mar.–Apr. 2016]. The Expert Committee will consider future revisions to the monograph upon receipt of necessary supporting data.
Comment Summary #2: The commenter recommended revising the acceptance criteria for pH to be consistent with what has been approved by the FDA.

Response: Comment not incorporated. The acceptance criteria for the pH were not included in the *PF* 42(2) [Mar.–Apr. 2016] revisions. The Expert Committee will consider future revisions to the monograph upon receipt of necessary supporting data.

Monograph/Sections: Imipramine Hydrochloride Tablets/Multiple Sections
Expert Committee: Chemical Medicines Monographs 4
No. of Commenters: 4
Comment Summary #1: The commenter requested the inclusion of a different test for *Organic Impurities*.
Response: Comment not incorporated. The test for *Organic Impurities* is suitable for use as a public standard.
Comment Summary #2: The commenters requested revising the acceptance criteria for desipramine, depramine, iminodibenzyl, and any individual unspecified degradation product in the test for *Organic Impurities*.
Response: Comment incorporated. The acceptance criteria for desipramine, depramine, iminodibenzyl, and any individual unspecified degradation product were widened for consistency with approved drug product specifications. The acceptance criterion for depramine was removed from the monograph.
Expert Committee-initiated Change #1: The concentration of the *Sample solution* in the *Assay* was revised to reference imipramine hydrochloride instead of imipramine for consistency with the remainder of the monograph.
Expert Committee-initiated Change #2: The reference to General Chapter <851> *Spectrophotometry and Light-Scattering* in the test for the *Uniformity of Dosage Units* is removed.
Expert Committee-initiated Change #3: The note in the *System suitability* section and one of the calculations in the test for *Organic Impurities* were revised to support the removal of depramine from *Table* 2 and from the relative standard deviation requirement.

Monograph/Section: Krill Oil Capsules
Expert Committee: Non-Botanical Dietary Supplements
No. of Commenters: 2
Comment Summary #1: The commenter proposed that the upper limit of total phospholipids be increased from NMT 55% to NMT 59% due to new data recently obtained.
Response: Comment incorporated.
Comment Summary #2: The commenter proposed the following changes to the fatty acid profile in the *Identification* test: 1) removal of alpha-linolenic acid and moroctic acid; and 2) changes to the range limits for eicosenic acid, erucic acid, and linoleic acid. The commenter proposed the changes to reflect the relatively large variability of these fatty acids based on the source (krill catch) season-to-season and year-to-year basis.
Response: Comment incorporated.

Comment Summary #3: The commenter proposed that the sentence "Phosphatidylcholine: 60%-96% (w/w) of the *total phospholipids content*" be changed to, "Phosphatidylcholine (sum of PC + 1-LPC + 2-LPC): 60%-96% (w/w) of the *total phospholipids content*" for clarification purposes.
Response: Comment incorporated.
Comment Summary #4: The commenter suggested revising the *Sample solution* procedure for content of total phospholipids using whole capsules instead of inner filling due to possible interaction of Krill oil inner filling phospholipids with the soft gel material.
Response: Comment not incorporated. The Expert Committee concluded that there is no adequate justification to consider the replacement of the existing sample preparation procedure. Additional clarifications to the *Sample solution* procedure and determination of the phospholipids content were provided instead.

Monograph/Section: Krill Oil Delayed-Release Capsules
Expert Committee: Non-Botanical Dietary Supplements
No. of Commenters: 2
Comment Summary #1: The commenter proposed that the upper limit of total phospholipids be increased from NMT 55% to NMT 59% due to new data recently obtained.
Response: Comment incorporated.
Comment Summary #2: The commenter proposed the following changes to the fatty acid profile in the *Identification* test: 1) removal of alpha-linolenic acid and moroctic acid; and 2) changes to the range limits for eicosenic acid, erucic acid, and linoleic acid. The commenter proposed the changes to reflect the relatively large variability of these fatty acids based on the source (krill catch) season-to-season and year-to-year basis.
Response: Comment incorporated.
Comment Summary #3: The commenter proposed that the sentence "Phosphatidylcholine: 60%-96% (w/w) of the *total phospholipids content*" be changed to, "Phosphatidylcholine (sum of PC + 1-LPC + 2-LPC): 60%-96% (w/w) of the *total phospholipids content*" for clarification purposes.
Response: Comment incorporated.
Comment Summary #4: The commenter suggested revising the *Sample solution* procedure for content of total phospholipids using whole capsules instead of inner filling due to possible interaction of Krill oil inner filling phospholipids with the soft gel material.
Response: Comment not incorporated. The Expert Committee concluded that there is no adequate justification to consider the replacement of the existing sample preparation procedure. Additional clarifications to the *Sample solution* procedure and determination of the phospholipids content were provided instead.

Monograph/Sections: Leuprolide Acetate/Multiple Sections
Expert Committee: Biologics Monographs 1–Peptides
No. of Commenters: 2

Chemical Information
Comment Summary #1: The commenter requested noting that the CAS # [74381-53-6] refers to the leuprolide acetate salt.
Response: Comment incorporated. The CAS # for Leuprolide free base is also added.

Assay

Comment Summary #2: The commenter requested information on why the calculation equation changed.
Response: Comment not incorporated**.** The change was made to update the monograph to current USP style. The assigned value of the USP RS is given on the individual RS label/certificate.

***Other Components*, Acetic Acid**
Comment Summary #3: The commenter requested correcting the chemical name of internal standard. The chemical name should be hexadecane not hexane.
Response: Comment incorporated. Details are also added to the system suitability criteria to be more specific.**Monograph/Section:** Methionine/Impurities
Expert Committee: Non-Botanical Dietary Supplements
No. of Commenters: 1
Comment Summary #1: The commenter recommended that the relative response factor for the methionine sulfoxide impurity should be taken into account in order to measure it accurately. The commenter proposed a relative response factor of 0.53 for methionine sulfoxide based on their submitted data.
Response: Comment incorporated.

Monograph/Sections: Miconazole Compounded Ophthalmic Solution/Multiple Sections
Expert Committee: Compounding
No. of Commenters: 2
Comment Summary #1: The commenter suggested restricting the packaging requirement to single-use ophthalmic dropper bottles for a single patient because the compounded preparation does not contain an antimicrobial preservative.
Response: Comment incorporated.
Comment Summary #2: The commenter recommended that that the Expert Committee review and consider the concentration of polyoxyl 40 hydrogenated castor oil in ophthalmic solution.
Response: Comment not incorporated. The monograph formulation was based on a previously commercially available intravenous product that was administered ophthalmically for fungal keratitis. Stability testing was performed based on the formula in the monograph. While the concentration of the polyoxyl 40 hydrogenated castor oil may be a concern, the monograph formulation is a needed treatment, because there is no commercially available alternative.

Monograph/Section: Neotame/Water Determination
Expert Committee: Excipient Monographs 1
No. of Commenters: 1
Comment Summary #1: The commenter indicated that due to the nature of the apparatus and technique “weight by difference” used to obtain the actual sample weight it was difficult to meet the requirement for the sample weight (0.50g ± 10%) specified in the *Water Determination* test of the monograph. The commenter recommended adding the word “approximate” to the sample size to allow a bigger than 10% variance in the sample weight measurement.
Response: Comment not incorporated. The commenter reevaluated the changes to the test and withdrew the original comment.

Monograph/Sections: Olive Leaf/Multiple Sections
Expert Committee: Botanical Dietary Supplements and Herbal Medicines
Expert Committee-initiated Change #1: The description of leaf margins was changed to indicate that they are “slightly resolute.”
Expert Committee-initiated Change #2: In parentheses, the qualifier “in some species” was replaced with the more definitive “in Asian material of subsp. *cuspidata*.”

Monograph/Sections: Olmesartan Medoxomil Tablets/Multiple Sections
Expert Committee: Chemical Medicines Monographs 2
No. of Commenters: 4
Comment Summary #1: The commenter requested deleting the olefinic impurity listed in the table under *Organic impurities*, because it is a process related impurity.
Response: Comment not incorporated. The Expert Committee determined that the listed impurity is both process related and a degradation product based on the supporting data.
Comment Summary #2: The commenters requested clarifying the Sample solution preparation in the *Assay* and *Organic Impurities* and including the details regarding the number of tablets and the filter used.
Response: Comment incorporated.
Comment Summary #3: The commenter requested revising the signal to noise ratio from NLT 30.0 to NLT 10 under *Organic Impurities*, in accordance with the ICH guidelines.
Response: Comment not incorporated. The Expert Committee will consider future revisions to the monograph upon receipt of necessary supporting data.
Comment Summary #4: The commenter requested revising the pH in the *Dissolution* test procedure from pH 6.8 to pH 6.80 +/-0.05% because the procedure is too sensitive to pH.
Response: Comment not incorporated. The Expert Committee will consider future revisions to the monograph upon receipt of necessary supporting data.
Comment Summary #5: The commenter indicated that a UHPLC procedure is too expensive for assay test and adds to the manufacturing cost of the drug product.
Response: Comment not incorporated. The Expert Committee determined that the proposed procedure is consistent with the procedures used in the FDA-approved drug products.
Comment Summary #6: The commenter indicated that under *Organic Impurities*, the olmesartan peak comes at void volume and unspecified impurities co elute with the main peak.
Response: Comment not incorporated. The Expert Committee will consider future revisions to the monograph upon receipt of necessary supporting data.
Expert Committee-Initiated Change #1: The requirement for signal to noise ratio under the Organic Impurities section was revised from NLT 30.0 to NLT 30.
Expert Committee-Initiated Change #2: The term total impurities under the Organic Impurities section was revised to total degradation products to be consistent with the ICH terminology**.**

Monograph/Section: Paricalcitol Capsules/Identification
Expert Committee: Chemical Medicines Monographs 3
No. of Commenters: 1
Comment Summary #1: The commenter suggested adding a second identification test.
Response: Comment not incorporated. The Expert Committee will consider future revisions to the monograph upon the receipt of supporting data.

Monograph/Section: Phenazopyridine Hydrochloride Tablets/Identification
Expert Committee: Chemical Medicines Monographs 2
Expert Committee-Initiated Change #1: The inadvertently added text "Infrared Absorption <197K>" was deleted from *Identification A.*

Monograph/Section: Plant Stanol Esters/Identification
Expert Committee: Non-Botanical Dietary Supplements
No. of Commenters: 1
Comment Summary #1: The commenter suggested changing the name of the derivatized analytes in the test for *Identification B* from "campestanol methyl ester" to "campestanol trimethylsilyl (TMS)," and from "sitostanol methyl ester" to "sitostanol TMS," to reflect the type of derivatization reagent used.
Response: Comment incorporated.
Comment Summary #2: The commenter commented that the acceptance criteria for the percentage of campestanol in the test for *Content of Total Plant Stanols* should be "NMT" 32%, not "NTL" 32% as stated in the proposed monograph.
Response: Comment incorporated.
Comment Summary #3: The commenter suggested a replacement formula for the calculation of the percentage of unesterified stanols in the test for *Content of Unesterified Stanols*.
Response: Comment not incorporated. USP's formula and the commenter's formula use different defined terms in their formula but both formulas produce the same results.
Expert Committee-initiated Change #1: A statement was added to the *Definition* section that the plant stanols esters are obtained from esterification of plant stanols with fatty acids from rapeseed oil, sunflower oil, corn oil, soybean oil, and their blends.

Monograph/Sections: Potassium Chloride Extended-Release Tablets/Multiple Sections
Expert Committee: Chemical Medicines Monographs 5
No. of Commenter: 1
Comment Summary #1: The commenter requested to retain the reference to <191> *Identification Tests* instead of using the flame test.
Response: Comment incorporated.
Comment Summary #2: The commenter suggested revising the *Assay* to use ion-exchange chromatography.
Response: Comment not incorporated. The Expert Committee will consider future revisions to the monograph upon the receipt of supporting data.

Monograph/Section: Pregabalin/Organic Impurities
Expert Committee: Chemical Medicines Monographs 2

No. of Commenters: 2
Comment Summary #1: The commenter requested adding two specified impurities not referenced in any FDA-approved products.
Response: Comment not incorporated. The Expert Committee will consider future revisions to the monograph upon receipt of necessary supporting data.
Comment Summary #2: The commenter indicated that the proposed HPLC procedure is not suitable to monitor a known process specific impurity controlled as an unspecified impurity.
Response: Comment not incorporated. The Expert Committee determined the proposed HPLC procedure is suitable for the intended purpose and will consider future revisions, if needed, upon the receipt of the necessary supporting data.

Monograph/Section: Timolol Maleate/Enantiomeric Purity
Expert Committee: Chemical Medicines Monographs 2
No. of Commenters: 1
Comment Summary #1: The commenter requested deleting the autosampler temperature requirement of 4°C, because it is not required to perform the test.
Response: Comment incorporated.
Comment Summary #2: The commenter requested increasing the acceptance criterion for relative standard deviation for system suitability.
Response: Comment incorporated. The Expert Committee widened the acceptance criteria for the relative standard deviation from NMT 1.0% to NMT 1.5% based on the supporting data.
Expert Committee-initiated Change #1: The term total impurity under the Organic Impurities section was revised to total degradation products to be consistent with the ICH terminology**.**

Monograph/Section: Tizanidine Tablets/Organic Impurities
Expert Committee: Chemical Medicines Monographs 4
No. of Commenters: 1
Comment Summary #1: The commenter indicated that the *Acceptance criterion for Any unspecified degradation product is* different from what has been approved by FDA.
Response: Comment not incorporated. Additional investigation established that the proposed acceptance criteria are consistent with FDA-approved specifications.

Monograph/Section: Vanilla/Identification
Expert Committee: Botanical Dietary Supplements and Herbal Medicines
No. of Commenters: 1
Comment Summary #1: The commenter recommended addition of an identification test
Response: Comment not incorporated. The Expert Committee will consider future revisions to add an identification test with input from sponsors upon the receipt of the necessary supporting data.

Monograph/Section: Venlafaxine Tablets/Assay
Expert Committee: Chemical Medicines Monographs 4
No. of Commenters: 1

Comment Summary #1: The commenter requested that the Detector in the *Assay* be revised from: “For Identification B, …” to “For Identification A, …” to reflect that the UV spectrum is used for *Identification* A.
Response: Comment incorporated.

Monograph/Section: Zolpidem Tartrate/Impurities
Expert Committee: Chemical Medicines Monographs 4
No. of Commenters: 1
Comment Summary #1: The commenter indicated that the acceptance criterion of *Zolpidem related compound A* is different from what has been approved by the FDA.
Response: Comment not incorporated. Additional investigation established that the proposed acceptance criteria are consistent with FDA-approved specifications.