



## ***Commentary***

### ***USP 38–NF 33***

November 3, 2014

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

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

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

**General Chapters:**

- <1> [Injections](#)
- <4> [Mucosal Drug Products-Product Quality Tests](#)
- <7> [Labeling](#)
- <51> [Antimicrobial Effectiveness Testing](#)
- <89> [Enzymes Used As Ancillary Materials in Pharmaceutical Manufacturing](#)
- <209> [Low Molecular Weight Heparin Molecular Weight Determinations](#)
- <231> [Heavy Metals](#)
- <660> [Containers -- Glass](#)
- <852> [Atomic Absorption Spectroscopy](#)
- <853> [Fluorescence Spectroscopy](#)
- <854> [Mid-Infrared Spectroscopy](#)
- <857> [UltravioletVisibleSpectroscopy](#)
- <911> [Viscosity - Capillary Viscometer Methods](#)
- <912> [Rotational Rheometer Methods](#)
- <1152> [Animal Drugs for Use in Animal Feeds](#)
- <1787> [Measurement of Subvisible Particulate Matter](#)
- <1852> [Atomic Absorption Spectroscopy - Theory and Practice](#)
- <1853> [Fluorescence Spectroscopy - Theory and Practice](#)
- <1854> [Middle Infrared Spectroscopy - Theory and Practice](#)

**Monographs:**

- |   |   |
|---|---|
| <a href="#">Azithromycin</a>                          | <a href="#">Methocarbamol</a>                       |
| <a href="#">Azithromycin Tablets</a>                  | <a href="#">Metoprolol Tartrate</a>                 |
| <a href="#">Cisatracurium Besylate</a>                | <a href="#">Nicardipine Hydrochloride Injection</a> |
| <a href="#">Cisatracurium Besylate Injection</a>      | <a href="#">Prochlorperazine Maleate Tablets</a>    |
| <a href="#">Clarithromycin Tablets</a>                | <a href="#">Protamine Sulfate</a>                   |
| <a href="#">Cosyntropin</a>                           | <a href="#">Pyrantel Tartrate</a>                   |
| <a href="#">Cyclobenzaprine Hydrochloride Tablets</a> | <a href="#">Quetiapine Fumarate</a>                 |
| <a href="#">Desipramine Hydrochloride</a>             | <a href="#">Quetiapine Tablets</a>                  |
| <a href="#">Diethyltoluamide</a>                      | <a href="#">Repaglinide Tablets</a>                 |
| <a href="#">Diethyltoluamide Topical Solution</a>     | <a href="#">Salicylic Acid</a>                      |
| <a href="#">Duloxetine Delayed-Release Capsules</a>   | <a href="#">Sodium Bicarbonate</a>                  |
| <a href="#">Dutasteride</a>                           | <a href="#">Sulbactam Sodium</a>                    |
| <a href="#">Fondaparinux Sodium</a>                   | <a href="#">Tigecycline</a>                         |
| <a href="#">Fondaparinux Sodium Injection</a>         | <a href="#">Tigecycline for Injection</a>           |
| <a href="#">Hydrogenated Lanolin</a>                  | <a href="#">Venlafaxine Tablets</a>                 |
| <a href="#">Idarubicin Hydrochloride Injection</a>    | <a href="#">Vigabatrin for Oral Solution</a>        |
| <a href="#">Insulin Glargine</a>                      | <a href="#">Vinorelbine Injection</a>               |
| <a href="#">Insulin Glargine Injection</a>            | <a href="#">Zinc Carbonate</a>                      |
| <a href="#">Magnesium Oxide</a>                       | <a href="#">Zinc Sulfate</a>                        |

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

**General Chapters**

- <251> Lead
- <659> Packaging and Storage Requirements
- <697> Container Content for Injection
- <913> Viscosity—Rolling Ball Method
- <1857> Ultraviolet-Visible Spectroscopy -Theory and Practice

**Monographs:**

Alfentanil Hydrochloride	Lithium Carbonate
Ascorbyl Palmitate	Magnesium Aluminum Silicate
Azathioprine	Methacrylic Acid and Ethyl Acrylate Copolymer
Azithromycin for Oral Suspension	Methacrylic Acid and Methyl Methacrylate Copolymer
Banaba Leaf	Methacrylic Acid Copolymer
Banaba Leaf Dry Extract	Methacrylic Acid Copolymer Dispersion
Banana Leaf Powder	Methimazole Tablets
Bentonite	Methocarbamol Tablets
Betaxolol Ophthalmic Solution	Misoprostol Dispersion
Biotin	Olanzapine Tablets
Brinzolamide	Oleovitamin A and D
Brinzolamide Ophthalmic Suspension	Oxaprozin Tablets
Calcium Propionate	Phenytoin Oral Suspension
Chlorobutanol	Pimozide
Citalopram Hydrobromide	Powdered Rosemary
Cloprostenol Sodium	Prednisone
Corn Syrup	Prilocaine
Corn Syrup Solids	Prilocaine Hydrochloride
Desipramine Hydrochloride Tablets	Prochlorperazine Maleate Tablets
Desonide	Protamine Sulfate for Injection
Desoxycholic Acid	Protamine Sulfate Injection
Dexchlorpheniramine Maleate Tablets	Purified Bentonite
Dyphylline and Guaifenesin Oral Solution	Rosemary
Ergotamine Tartrate and Caffeine Tablets	Rosemary Leaf Dry Aqueous Extract
Erythritol	Squalane
Fluocinolone Acetonide	Stannous Chloride
Flurbiprofen Tablets	Tamsulosin Hydrochloride
High Fructose Corn Syrup	Thiopental Sodium for Injection
Hydrophobic Colloidal Silica	Venlafaxine Hydrochloride
Hydroxyzine Hydrochloride Injection	Vigabatrin Tablets
pratopium Bromide	Zinc Chloride
Latanoprost	Zinc Sulfate Tablets
Levodopa	Ziprasidone Hydrochloride
Lindane Cream	

**General Chapter/Section(s):** <1>Injections/Multiple Sections  
**Expert Committee(s):** General Chapters—Dosage Forms  
**No. of Commenters:** 4

### ***General***

**Comment Summary #1:** The commenter suggested adding clarity to the General Chapter and an explanation on how it will be used in current existing monographs.

**Response:** Comment incorporated.

**Comment Summary #2:** The commenter recommended adding language to the General Chapter on its structure and how it is to be used.

**Response:** Comment incorporated.

### ***Introduction***

**Comment Summary #3:** The commenter recommended adding language to the introduction on how the General Chapter applies to biologics.

**Response:** Comment incorporated.

### ***Product Quality Tests Common to Parenteral Dosage Forms—Universal Tests***

**Comment Summary #4:** The commenter recommended deleting the section on “Description,” because it is not a test.

**Response:** Comment not incorporated. Description is an important qualitative descriptor.

**Comment Summary #5:** The commenter recommended revising the “Leachables and Extractables” section to make it less restrictive.

**Response:** Comment incorporated.

### ***Product Quality Tests Common to Parenteral Dosage Forms—Specific Tests***

**Comment Summary #6:** The commenter recommended revising vehicles and added substances section so as to include other vehicles.

**Response:** Comment incorporated.

### ***Product Quality Tests for Specific Parenteral Dosage Forms***

**Comment Summary #7:** The commenter recommended deleting all of the tests included in the General Chapter for which there is no official compendial test.

**Response:** Comment not incorporated. The Expert Committee finds it necessary to list other non-compendial tests that are important in determining product quality.

### ***Product Quality Tests For Specific Parenteral Dosage Forms—Sterile Powders for Solution***

**Comment Summary #8:** The commenter recommended deleting other dosage forms, such as suspensions, because they should not be associated with this section.

**Response:** Comment incorporated.

**Comment Summary #9:** The commenter suggested deleting the section on completeness and clarity of solution, because it also appears in *Specific Test* section.

**Response:** Comment incorporated.

### **Product Quality Tests For Specific Parenteral Dosage Forms—Emulsions**

**Comment Summary #10:** The commenter recommended referencing General Chapter <729> *Globule Size Distribution in Lipid Injectable Emulsions* and deleting the “Lipid Droplet Test.”

**Response:** Comment incorporated.

**Comment Summary #11:** The commenter suggested deleting Zeta potential from the list of tests, because it is not a quality test.

**Response:** Comment incorporated.

**General Chapter/Section(s):** <4> Mucosal Drug Products—Product Quality Tests/Multiple Sections

**Expert Committee(s):** General Chapters—Dosage Forms

**No. of Commenters:** 3

**Comment Summary #1:** The commenter requested changing the *Duration of foam expansion* test title to *Volume of foam expansion* under both the vaginal as well as the rectal routes.

**Response:** Comment incorporated.

**Comment Summary #2:** The commenter requested the addition of General Chapter *Rotating Rheometer Methods* <912> under the lists of tests for ophthalmic solutions and suspensions.

**Response:** Comment incorporated.

**Comment Summary #3:** The commenter requested the addition of a reference to ICH Q3B *Impurities in New Drug Products* to the *Impurities* section under *Generally Necessary Tests*.

**Response:** Comment incorporated.

**Comment Summary #4:** The commenter requested changing the wording, “push button,” to “dose actuating device” in the *Duration of foam expansion* test under both the vaginal and rectal routes.

**Response:** Comment incorporated.

**Comment Summary #5:** The commenter requested removal of the relative foam density test from the list of specific tests for ointments under the rectal route.

**Response:** Comment incorporated.

**Expert Committee-initiated Change #1:** The General Chapter *Rolling Ball Viscometer Methods* <913> was added for solutions and suspensions and General Chapter *Rotating Rheometer Methods* <912> was added for emulsions, under the list of specific tests for the ophthalmic route section.

**General Chapter/Section(s):** <7> Labeling/Multiple Sections

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

**No. of Commenters:** 3

### **Labels and Labeling for Injectable Products**

**Comment Summary #1:** The commenter suggested consolidating dry preparation requirements.

**Response:** Comment incorporated.

**Comment Summary #2:** Multiple commenters suggested making the storage conditions requirement a separate bullet.

**Response:** Comment incorporated.

**Comment Summary #3:** The commenter suggesting deleting the statement “large volume injection,” because the statement also applies to small volume injections.

**Response:** Comment not incorporated. This section is specific to salt- and sugar-water products.

**Comment Summary #4:** The commenters indicated discrepancies between the examples expressed and currently marketed products.

**Response:** Comment incorporated. The examples were revised to reflect currently marketed products.

**Comment Summary #5:** The commenter questioned the applicability of labeling requirements for smaller volumes.

**Response:** Comment incorporated. The section was clarified and additional information about smaller volume containers was added.

**Comment Summary #6:** Multiple commenters recommended clarity in the language regarding veterinary products.

**Response:** Comment incorporated. The text has been revised to provide better clarity.

**Comment Summary #7:** The commenter indicated several concerns regarding the labeling requirements for ingredients added to adjust pH.

**Response:** Comment incorporated. The language has been revised to match that in 21 *CFR 201.100*.

**Comment Summary #8:** The commenter raised several concerns regarding the ability to include information on exceptionally small labels.

**Response:** Comment incorporated. A reference to the *CFR* guidance for space limitations has been added.

**Comment Summary #9:** The commenter suggested labeling for vaccines.

**Response:** Comment not incorporated. Vaccines are outside the scope of this General Chapter.

**Comment Summary #10:** Multiple commenters suggested relocating a paragraph pertaining to non-injectable products packaged in containers for injections.

**Response:** Comment incorporated.

**Comment Summary #11:** The commenter suggested revising the lidocaine example to include strength per mL.

**Response:** Comment incorporated.

**Comment #12:** The commenter suggested consolidating all information related to ratios in a single section.

**Response:** Comment incorporated.

**Comment #13:** The commenter suggested several revisions to the ratio expressions subsection regarding the expression of strength and the examples used.

**Response:** Comments not incorporated. The subsection title was changed, an epinephrine example now included and single entity products are separate from combination products.

**Comment #14:** The commenter indicated that the term “total parenteral nutrition” is preferred to “parenteral nutrition” and noted several places where it should be replaced.

**Response:** Comment incorporated.

**Comment #15:** The commenter suggested indenting the warning paragraphs to clarify that both are to appear on the label.

**Response:** Comment incorporated.

### ***Labeling for Products and other Categories***

**Comment #16:** Multiple commenters noted that the injectable information was misplaced in the “Injectable and Topical” subsection.

**Response:** Comment incorporated. The General Chapter was reformatted to clearly delineate injectable information from non-injectable information.

**Comment #17:** Multiple commenters indicated that the text regarding the amount of ingredient per dosage unit was confusing.

**Response:** Comments incorporated. The text has been revised for clarity. Per USP’s salt naming policy, legacy products can continue to be named as they have been, but the requirements will apply going forward.

**Comment #18:** The commenter suggested several changes regarding the labeling on multiple unit containers.

**Response:** Comments incorporated. The beyond-use-date and expiration date will be included.

**Comment #19:** The commenter made suggestions for clarity and precision in the Compounded preparations subsection.

**Response:** Comment incorporated. The first sentence was clarified to refer to the names and strengths of compounded preparation. The word “Compounded” was added to the veterinary example.

**Comment #20:** The commenter suggested revising the “Electrolytes” subsection to read “sodium chloride” and “potassium chloride.”

**Response:** Comment not incorporated. The breaking out of sodium, potassium, and chloride was deliberate to reflect milliequivalents separately for each electrolyte (sodium, potassium and chloride) and the surrounding text was revised for clarity.

**Comment #21:** The commenter suggested clarifying the note in the Electrolytes subsection.

**Response:** Comment incorporated. The note has been revised to provide better clarity.

**Comment #22:** The commenter made several corrections for precision in the “Light-resistant” container subsection.

**Response:** Comments incorporated.

**Comment #23:** The commenter noted that the information in the *Repackaged single-unit container* section was inconsistent with that in General Chapter <659> *Packaging and Storage Requirements*.

**Response:** Comment incorporated. This information has been brought into alignment with General Chapter <659>.

**Comment #24:** The commenter indicated that the information in the Repackaged single-unit container subsection duplicates much of the information in General Chapter <1136> *Packaging and Repackaging-Single-Unit Containers* and questioned having such information in both a mandatory and informational chapter.

**Response:** Comment incorporated. This information was removed from <7> *Labeling*.

**Comment #25:** The commenter indicated that FDA labeling requirements for single-unit containers may change.

**Response:** Comment not incorporated. If appropriate a change in this labeling requirement can be addressed in future revisions.

**Comment #26:** The commenter indicated discrepancies between the “unit-of-use subsection” and USP *General Notices*.

**Response:** Comment incorporated. The text was revised to be consistent with USP *General Notices*.

**Comment #27:** The commenter recommended the clarification on the language Protection from freezing subsection.

**Response:** Comment incorporated. The text has been revised to provide better clarity.

### ***Definitions***

**Comment #28:** The commenter requested adding information to provide guidance regarding the difference between the USP standard and national governmental regulatory bodies which establish labeling requirements.

**Response:** Comment not incorporated. References to governmental labeling requirements were deleted.

### ***Labels and Labeling for Drug Products as Expressed as Active Moiety in Name and Strength***

**Comment #29:** The commenter recommended deleting “on the label” from the end of the sentence on exceptions as it is inconsistent with other parts of USP.

**Response:** Comment incorporated.

### ***General Comments***

**Comment Summary #30:** The commenter indicated that the phrase “drug substance” should be replaced with “active moiety and/or drug substance.”

**Response:** Comment incorporated.

**Comment Summary #31:** The commenter suggested replacing “labeling” with “labels and labeling.”

**Response:** Comment incorporated.

**Comment Summary #32:** The commenter asked for clarification of the preferred use of  $\mu\text{L}$  or mL.

**Response:** Comment not incorporated as this is not part of USP *General Notices*.

**General Chapter/Section(s):** General Chapter <51> Antimicrobial Effectiveness Testing/Multiple Sections

**Expert Committee(s):** General Chapters—Microbiology

**No. of Commenters:** 7

**Comment Summary #1:** The commenter suggested clarifying the text that indicates the intent of addition of antimicrobial preservatives.

**Response:** Comment incorporated. The text has been revised to provide better clarity.

**Comment Summary #2:** The commenter suggested revising the definition of aqueous as an Aw of greater than 0.6 since the reference chapter being called out to support this definition is <1112> *Application of Water Activity Determination to Nonsterile Pharmaceutical Products*. This General Chapter calls out aqueous products as having an Aw of greater than 0.6 and not 0.5.

**Response:** Comment incorporated.

**Comment Summary #3:** The commenter suggested revising the statement on the panel of challenge organisms to emphasize that this prescribed panel need not prevent the inclusion of other organisms to the test panel in addition to those indicated where appropriate or useful.

**Response:** Comment incorporated.



**Comment Summary #4:** The commenter suggested revising the statement that refers to the applicability of the procedures and requirements of the General Chapter concerning the container, by replacing “unopened” with “sealed.”

**Response:** Comment incorporated.

**Comment Summary #5:** The commenter suggested revising the text indicating conditions for reconfirmation of method suitability to indicate that any change in the composition of the direct product contact materials of the container closure should also be considered as part of the reconfirmation.

**Response:** Comment incorporated.

**Comment Summary #6:** The commenter suggested revising the paragraph on harvesting and preparation of cultures in the section on *Preparation of Test Strains* to make it more general with respect to the procedures employed.

**Response:** Comment incorporated.

**Comment Summary #7:** The commenter suggested revising the section on *Growth Promotion of the Media* to harmonize it with the requirements of General Chapter <61> *Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests*, that specify testing every batch of media and an acceptance criteria for recovery of challenge organisms as 50%.

**Response:** Comment incorporated.

**Comment Summary #8:** The commenter suggested revising the section on *Suitability of the Counting Method in the Presence of Product* to harmonize it with the requirements of General Chapter <61>, regarding the number of replicate plating and also allow use of higher levels of initial inoculum, where no suitable neutralization conditions are found and higher levels of dilution are needed to demonstrate or measure a 3 log unit reduction.

**Response:** Comment incorporated.

**Comment Summary #9:** The commenter suggested revising Table 2 to correct the name of the strain *A.niger* (ATCC 16404) to *A.brasiliensis* (ATCC 16404).

**Response:** Comment incorporated.

**General Chapter/Section(s):** <89> Enzymes Used As Ancillary Material in Pharmaceutical Manufacturing – Recombinant Trypsin /Multiple Sections

**Expert Committee(s):** Monographs—Biologics and Biotechnology 1

**No. of Commenters:** 4

**Comment Summary #1:** The commenter suggested adding a clarification on the status of requirement for this General Chapter, to specify that because no monographs reference General Chapter <89>, the specifications for individual materials would not be considered mandatory. Manufacturers would be able to cite the specifications in General Chapter <89> in their product registrations, which would then make them mandatory for those specific products.

**Response:** Comment not incorporated. The status requirement for General Chapters is explained in Section 3.10 of the USP *General Notices*, which states, “Standards for an article recognized in the compendia (*USP–NF*) are expressed in the article’s monograph, **applicable general chapters**, and *General Notices*.” Moreover, Section 2.10 of the *General Notices* states as follows, “General Chapters numbered from 1000 to 1999 are considered interpretive and are intended to provide information on, give definition to, or describe a particular subject. They contain no mandatory requirements

applicable to any official article unless specifically referenced in *General Notices*, a monograph, or general chapter numbered below 1000.”

### **Definition**

**Comment Summary #2:** The commenter suggested revising the specification of specific activity of NLT 3,800 Units/mg to 2,500 Units/mg as described in *Crystallized Trypsin* monograph and to clarify that the specification only applies to the recombinant trypsin.

**Response:** Comment partially incorporated. USP will retain the specification of NLT 3,800 Units/mg of protein as it applies only to recombinant trypsin. A clarification was made by removing the statement, “specific activity of NLT 3,800 Units/mg” to a *NOTE* section.

**Comment Summary #3:** The commenter suggested providing cross-reference or assay procedure for the specific activity of recombinant trypsin determined using *N*-benzoyl-L-arginine ethyl ester hydrochloride as the substrate.

**Response:** Comment incorporated.

**Comment Summary #4:** The commenter suggested adding a clarification to state that this General Chapter only applies to recombinant porcine sequence trypsin from yeast.

**Response:** Comment incorporated.

### **Assay**

**Comment Summary #5:** The commenter suggested including the acceptance criteria of NLT 3800 USP Trypsin Units/mg of protein using *N*-benzoyl-L-arginine ethyl ester hydrochloride as the substrate.

**Response:** Comment not incorporated. The Assay only uses carbobenzoxy-valyl-glycylarginine-4-nitril-anilide acetate as the substrate.

**Comment Summary #6:** The commenter suggested clarifying that the substrate used in the test should reflect the use of the material. The Assay, as written, can easily be interpreted as requiring use of the specified substrate, or demonstration of equivalency per the *General Notices*.

**Response:** Comment incorporated. The definition was revised to reflect that the Assay is based only on using carbobenzoxy-valyl-glycyl-arginine-4-nitril-anilide acetate as the substrate.

### **Purity**

**Comment Summary #7:** The commenter recommended revising the system suitability requirement for Resolution from NLT 1.0 to NLT 1 between the peaks of  $\alpha$ -trypsin and  $\beta$ -trypsin.

**Response:** Comment incorporated.

**Comment Summary #8:** The commenter suggested allowing using different flow rate.

**Response:** Comment not incorporated. Requirements for change in flow rate are addressed in <621> *Chromatography, System Suitability*.

**Comment Summary #9:** The commenter requested increasing injection volume from 1  $\mu$ L to 5  $\mu$ L, 10  $\mu$ L, or 20  $\mu$ L.

**Response:** Comment not incorporated. Requirements for change in injection volume are addressed in <621> *Chromatography, System Suitability* and under the provisions in USP *General Notices*.

**Comment Summary #10:** The commenter suggested removing the requirement of autosampler.

**Response:** Comment incorporated.

**Comment Summary #11:** The commenter suggested for a clarification on the integration time of 25 min. when the retention time for recombinant trypsin is 12–17 min.

**Response:** Comment not incorporated. The integration time of 25 min. allows integrating the impurity peaks.

### ***Specific Tests***

**Comment Summary #12:** The commenter suggested including a test and a limit for allowable level of host cell protein. The host cell protein can be introduced into a pharmaceutical manufacturing process.

**Response:** Comment not incorporated. Recombinant Trypsin, used as ancillary material, will be removed in subsequent processing steps within the preparation process of active pharmaceutical ingredients (APIs).

### ***Protein Content***

**Comment Summary #13:** The commenter suggested including other common tests, such as BCA, Kjeldahl, Lowry and Bradford, for determination of protein content.

**Response:** Comment not incorporated. Alternative methods can be used if following the *General Notices 6.30 Alternative and Harmonized Methods and Procedures*.

### ***Additional Requirements, Labeling***

**Comment Summary #14:** The commenter suggested including product number in the labeling.

**Response:** Comment incorporated.

### ***Reference Standard***

**Expert Committee-initiated Change #1:** The name of reference standard was revised to USP Trypsin Recombinant Porcine RS.

**General Chapter/Section(s):** <209> Low Molecular Weight Heparin Molecular Weight Determinations/Multiple Sections

**Expert Committee(s):** Monographs—Biologics & Biotechnology 1

**No. of Commenters:** 1

**Comment Summary #1:** The commenter indicated that the rationale for using Dalteparin Sodium to make the system suitability solution is not clear when the Low Molecular Weight Heparin Molecular Weight RS chemical structure seems to be consistent with that of Enoxaparin Sodium.

**Response:** Comment not incorporated. The procedure is intended for all low molecular weight heparins, it makes little difference which low molecular weight heparin molecule is used for system suitability requirement testing. Additionally, it is noted that the general formula referred to is not unique to enoxaparin and the low molecular weight heparin molecular weight RS is not made from enoxaparin.

**Comment Summary #2:** The commenter requested that USP perform a comparison of the General Chapter <209> method and the current Enoxaparin Sodium gel permeation chromatography method. If they give the same results with an appropriate level of confidence, then the method proposed in General Chapter <209> would be acceptable.

**Response:** Comment not incorporated. The comparison was carried out during method validation and results are equivalent.

**Comment Summary #3:** The commenter indicated that the proposed formula for calculation of a, b, c, and d is incorrect.

**Response:** Comment incorporated. The formula was corrected and revised.

**General Chapter/Section(s):** <231> Heavy Metals/Multiple Sections

**Expert Committee(s):** General Chapters—Dosage Forms

**No. of Commenters:** 7

**Comment #1:** The commenter recommended that USP retain General Chapter <231> or, at a minimum, maintain the General Chapter for the full implementation period recommended under General Notices, because of its significant impact. Deleting General Chapter <231> will not only impact animal health materials currently exempt from <232> *Elemental Impurities—Limits*, but also impact non-monographed human health materials in which General Chapter <231> is referenced in approved US and international registrations.

**Response:** Comment not incorporated. USP has had representation regarding animal health materials on the Elemental Impurities Advisory Panel for quite some time. USP also worked with Center for Veterinary Medicine (CVM) at FDA to resolve issues related to veterinary products resulting from the deletion of General Chapter <231>. The concern raised by this comment has been taken under consideration by CVM. Please contact CVM for any additional information or questions.

**Comment Summary #2:** Commenter proposed to keep Heavy Metals <231> as an information chapter only, after <232> and <233> *Elemental Impurities—Procedures* are implemented, so as to make cross reference to <231> testing conditions easier when they are applied on articles out of the scope of <232> and <233> e.g. raw materials and chemical intermediates of API manufacturing processes, and cross-referencing in the relevant regulatory documentation.

**Response:** Comment not incorporated. The limitations of General Chapter <231> have been the subject of growing attention for many years; therefore, it is prudent to implement more modern and workable testing.

**Comment Summary #3:** Commenter suggested maintaining temporary applicability of General Chapter<231> to elastomeric closures until more data are available on the level of 'elemental impurities' in General Chapter<381> *Elastomeric Closures for Injections*, extracts and, based on these data, either more appropriate limit values for 'elemental impurities' from elastomeric closures can be formulated or other actions can be undertaken. This can be done by the inclusion of the relevant parts of text of General Chapter <231>directly into General Chapter<381>. General Chapter <231> *Heavy Metals* is also referenced in General Chapter <381>.

**Response:** Comment not incorporated. General Chapter <381> is a stand-alone General Chapter. General Chapter <231> includes procedures that have been demonstrated to be largely ineffective. Continuing to use General Chapter <231> is not analytically sound. The *Heavy Metals* section in General Chapter <381> will be omitted, while the Expert Committee works to modernize this General Chapter. The modernized General Chapter will include specific testing requirements for elastomeric materials of construction and elastomeric materials used in packaging systems. As part of this modernization effort, the elemental impurities tests for elastomeric materials and materials used in final packaging systems will also be updated.

**General Chapter/Section(s):** <660> Containers—Glass/Multiple Sections  
**Expert Committee(s):** General Chapters—Packaging, Storage and Distribution  
**No. of Commenters:** 2

### ***General Comments***

**Comment Summary #1:** The commenter suggested changing the ramping up and cool down procedure to fit an off-the-shelf autoclave, not ones designed to fit the parameters of the test.

**Response:** Comment not incorporated. The European Glass Commission has studied this issue and issued a detailed report. The ramping up and cooling down speeds are critical to obtaining an accurate result.

### ***Description***

**Comment Summary #2:** The commenter suggested changing the phrase “glass network” to “glass lattice structure.”

**Response:** Comment Incorporated.

**Comment Summary #3:** The commenter requested a clarification of what is meant by “arsenic release.”

**Response:** Comment incorporated. The sentence was deleted, because it is repeated under *Specific Tests* and is more appropriate in this section.

### ***Specific Tests—Glass***

**Comment Summary #4:** The commenter suggested changing the phrase “test liquid” to “test solution.”

**Response:** Comment incorporated.

### ***Specific Tests—Glass Grains***

**Comment Summary #5:** The commenter suggested revising the sentence so that a standard reference material is not required for each glass batch, which would increase the workload and the costs of analysis.

**Response:** Comment incorporated.

### ***Specific Tests—Glass Grains: Method***

**Comment Summary #6:** The commenter requests the option of using an internal thermocouple of the autoclave chamber, because not every autoclave uses a thermocouple as described in the proposal.

**Response:** Comment incorporated.

**Comment Summary #7:** The commenter suggested clarification that for autoclaves using a steam generator it is not necessary to maintain the temperature for 10 min. at 100°.

**Response:** Comment incorporated.

**Comment Summary #8:** The commenter requested rewriting the section to ensure that the autoclave is vented in order to purge “atmospheric air” without a specific reference to vent-cocks and visible steam emission.

**Response:** Comment incorporated.

**Comment Summary #9:** The commenter recommended that the autoclave should not be opened until it has cooled to 95° to avoid opening chamber while solution is still boiling.

**Response:** Comment incorporated.

**Comment Summary #10:** The commenter suggested that some glass containers may remain unused in customer inventory for several years and asked if customers would be required to re-test inventories to new standard.

**Response:** Comment not incorporated. All revisions to the *USP–NF* have a date which indicates when the General Chapter becomes effective. Once official, compliance is regulated by the U.S. Food and Drug Administration.

**Comment Summary #11:** The commenter suggested specifying that the cool down time is essential to obtaining a correct result since a slower cool down will give higher values.

**Response:** Comment incorporated.

**Comment Summary #12:** The commenter requested clarification of the cleaning procedure. It is currently interpreted that the containers are rinsed twice and then filled, left to stand and then immediately before testing emptied and rinsed.

**Response:** Comment incorporated. The cleaning procedure was revised to clarify the intent of the Expert Committee.

#### ***Specific Tests—Glass Grains: Method (Table 3)***

**Comment Summary #13:** The commenter suggested that the units of measure should be mL/g, rather than mg/g to match Table 4.

**Response:** Comment incorporated.

**Comment Summary #14:** The commenter requested clarification regarding the unit applied in Table 3. The amount of 0.02 M HCl is listed as “mg/g”. It is expected that the units should be mL/g or just mL.

**Response:** Comment incorporated.

<b>General Chapter/Section(s)</b>	<852> Atomic Absorption Spectroscopy
<b>Expert Committee(s):</b>	General Chapters—Chemical analysis
<b>No. of Commenters:</b>	3

#### ***Qualification of Atomic Absorption Spectrophotometers***

**Comment Summary #1:** Under Precision, the commenter indicates that replicates of the 0.10-µg/mL Zn standard and calculation against the same standard curve will generate the same result if the absorbance values are used directly.

**Response:** Comment not incorporated. The intent of this test is to make certain that the standard reads back correctly as a sample.

**Comment Summary #2:** Under Precision, the commenter suggested that the specification should be lower than repeatability from method validation where matrix effects and other sources of variation may influence the measurements.

**Response:** Comment incorporated.

#### ***Procedure***

**Comment Summary #3:** Under Analysis, the commenter suggested modifying the requirement for reassayed value to make it consistent with the acceptance criteria suggested for “repeatability” in OQ section and typical vendor specifications.

**Response:** Comment incorporated.

### ***Validation and Verification***

**Comment Summary #4:** Under validation, the commenter suggested modifying the text to indicate that not all the performance characteristics listed are necessarily required for validation.

**Response:** Comment incorporated.

**Comment Summary #5:** The commenter suggested adding Linearity to the list of performance characteristics to be studied during the verification of quantitative procedures.

**Response:** Comment incorporated.

**Comment Summary #6:** The commenter suggested that, in a standard additions analysis, if a sample contains any of the analyte in question, each spike level will be biased high; therefore, the accuracy assessment must be based on the final sample concentration, instead of the solution concentration (implied by the use of “final intercept concentration”).

**Response:** Comment not incorporated. This is standard for working with the method of standard additions. Experienced analysts will be able to perform standard additions analysis.

**Comment Summary #7:** The commenter indicated that calculating the precision from the experimental results will produce falsely high standard deviations, especially for samples with background levels.

**Response:** Comment not incorporated. This is standard for working with the method of standard additions. Experienced analysts will be able to perform the analysis.

**Comment Summary #8:** The commenter suggested a reduction in the number of experiments requested for Intermediate Precision.

**Response:** Comment incorporated.

**Comment Summary #9:** The commenter indicates that the experiment described under Quantitation Limit subsection may not be practical if a sample has a background level of analyte. It is recommended that the QL spiked matrix sample level should be no less than the instrument estimated QL concentration and not more than 50% of the specification.

**Response:** Comment not incorporated. The General Chapter allows the use of other suitable approaches.

**Comment Summary #10:** The commenter indicated that when spiking weighed samples, variation in the effective spike level will occur due to the sample weight which may cause the validation criteria to be too tight, under the subsection Range.

**Response:** Comment not incorporated. The stated ranges indicate the minimum range for validation, not the exact values.

**General Chapter/Section(s):** <853> Fluorescence Spectroscopy/Multiple Sections  
**Expert Committee(s):** General Chapters—Chemical analysis  
**No. of Commenters:** 6

### ***Qualification of Fluorescence Instruments***

**Comment Summary #1:** A commenter requested adding more flexibility regarding the source of tests and standards for OQ.

**Response:** Comment incorporated.

**Comment Summary #2:** The commenter indicated that bandwidth control needs to be addressed as wavelength accuracy/precision may be dependent to bandwidth.

**Response:** Comment not incorporated. The effect of bandwidth on wavelength precision is negligible when compared to the allowed tolerance.

**Comment Summary #3:** The commenter suggested aligning the values for holmium oxide and didymium standards with those in General Chapter <857> *Ultraviolet-Visible Spectroscopy*.

**Response:** Comment incorporated.

**Comment Summary #4:** Several commenters suggested incorporating uncertainties requirements for the standards.

**Response:** Comment not incorporated. USP is not addressing standards uncertainty at this time, but will consider future revisions to the General Chapter upon receipt of the necessary data but will consider future revisions to the General Chapter upon receipt of the necessary supporting data.

**Comment Summary #5:** The commenter suggested including instrument effects such as a deteriorating light source (constancy at multiple wavelengths and intensity) that could affect fluorimeter results.

**Response:** Comment incorporated.

#### ***Qualitative and Quantitative Fluorescence Measurements***

**Comment Summary #6:** The commenter suggested incorporating a phrase to indicate that the minimum amount of analyte should be considered to ensure that the method is appropriate for the particular application.

**Response:** Comment incorporated.

#### ***Good Spectroscopic Practice***

**Comment Summary #7:** Under Use of Reference Standards subsection, the commenter recommended to use the word “study” instead of “test.”

**Response:** Comment not incorporated. The term test was deemed to be appropriate.

**Comment Summary #8:** Under Sample Solution Preparation subsection, the commenter suggested revising sentence eight to read, "Solvents that do not have an interfering fluorescence signature at the wavelength(s) of interest should be used."

**Response:** Comment incorporated

#### ***Validation and Verification***

**Comment Summary #9:** The commenter suggested using S/N ratio >3 instead of 3.3 for the detection limit.

**Response** Comment not incorporated. The 3.3 comes from the fact that the alpha and beta errors are equal at 5%. Three is used as an approximation.

**Comment Summary #10:** The commenter recommended replacing the term “absorbance” used in the *Linearity* section with “fluorescence signal.”

**Response:** Comment incorporated.

**Comment Summary #11:** Under Linearity subsection, the commenter suggested revising the first sentence to read "A linear response curve between the analyte concentration ... solution."

**Response:** Comment incorporated.

**Comment Summary #12:** The commenter suggested incorporating validation criteria under the subsection Robustness.



**Response:** Comment not incorporated. Robustness studies are the final stage of method development, rather than a validation experiment, and the acceptable variations of method parameters needs to be defined on a case by case basis.

**General Chapter(s):** <854> Mid-Infrared spectroscopy/Multiple Sections  
**Expert Committee(s):** General Chapters—Chemical analysis  
**No. of Commenters:** 7

### ***Introduction***

**Comment Summary #1:** A commenter suggested to specifically mention FTIR instruments in the title of the document.

**Response:** Comment not incorporated. The General Chapter is concerned with the process of mid-IR spectroscopy rather than the nature of the measuring instrument and the title should be consistent with all the other spectroscopy chapters for which the same principle is applied.

**Comment Summary #2:** A commenter suggested clarifying the use of wavelength and wavenumbers.

**Response:** Comment incorporated

**Comment Summary #3:** A commenter suggested deleting the word “certain” in the following sentence in the introduction, “The absorption of certain photons causes the promotion... excited vibrational state.”

**Response:** Comment incorporated.

**Comment Summary #4:** A commenter suggested incorporating a discussion about selection rules in the introduction.

**Response:** Comment not incorporated. The Expert Committee considered that information on selection rules may be a good addition to General Chapter <1854> *Mid-Infrared Spectroscopy—Theory and Practice* instead of General Chapter <854>. This will be proposed in a future revision.

### ***Qualification of IR Spectrophotometers***

**Comment Summary #5:** The commenters indicated that the General Chapter should address alternate forms of materials and procedures for the measurement of wavenumber accuracy.

**Response:** Comment not incorporated. This section allows the use of alternatives.

**Comment Summary #6:** The commenter indicated that the traceability of transmittance needs to be identified.

**Response:** Comment not incorporated. Information on photometric accuracy was moved to General Chapter <1854>.

**Comment Summary #7:** The commenter pointed out that polystyrene bands identified by various organizations as important for calibration purposes may have differences including film thickness and degree of matte finish. These differences will affect the measured location of the bands.

**Response:** Comment not incorporated. The Expert Committee acknowledges the differences between existing standards; however, the General Chapter allows the use of any suitable standard.

### ***Procedure***

**Comment Summary #8:** The commenter suggested clarifying under the section *Attenuated Total Reflection* that if the sample is a liquid or paste, pressure is not required.

**Response:** Comment incorporated.

### ***Validation and Verification***

**Comment Summary #9:** The commenter suggested modifying the text to indicate that not all the performance characteristics listed are necessarily required for validation.

**Response:** Comment incorporated.

**Comment Summary #10:** The commenter suggested providing details on how to demonstrate specificity for Category IV tests.

**Response:** Comment incorporated.

**General Chapter/Section(s):** <857> Ultraviolet-Visible Spectroscopy/Multiple Sections

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

**No. of Commenters:** 15

### ***Qualification of UV-VIS Spectrophotometers***

**Comment Summary #1:** The commenter requested adding more flexibility regarding the source of tests and standards for OQ.

**Response:** Comment incorporated.

**Comment Summary #2:** The commenter indicated that the General Chapter does not address how to verify the measurements when fixed bandpass filters are used or there is no temperature control.

**Response:** Comment not incorporated. This is covered by the existing statement, “Instrument vendors often have samples and test parameters available as part of the IQ/OQ package.”

**Comment Summary #3:** The commenter suggested eliminating the need for replicate measurements for diode array instruments, under Control of Wavelengths.

**Response:** Comment incorporated.

**Comment Summary #4:** The commenter indicates that peaks at 241, 278, and 287 nm of the Holmium Oxide Glass are difficult or not able to be resolved.

**Response:** Comment not incorporated. This General Chapter clearly states the requirement to use CRM that are appropriate for the intended use of the instrumentation.

**Comment Summary #5:** The commenter suggested mentioning “precision” in the introductory paragraph under the section “Control of Absorbance.”

**Response:** Comment incorporated.

**Comment Summary #6:** The commenter indicates that the potassium dichromate powder (SRM 935) cannot be used, because the values on the certificate do not correspond to stated requirements later in document: “The acceptance criteria are  $\pm 0.5\%A$  or  $\pm 0.005A$ , whichever is larger.”

**Response:** Comment not incorporated. The expanded uncertainty budget quoted for SRM 935a detailed the allowance, if correctly prepared; therefore, the  $\pm 0.010A$  allows for an acceptable contribution to be made from the spectrophotometer under test.

**Comment Summary #7:** The commenter indicated that the precision acceptance criteria for the control of absorbance is unclear as written and needs to be clarified.

**Response:** Comment incorporated.

**Comment Summary #8:** The commenter requested modifying the text to indicate that only one replicate be required to Control of Absorbance using Acidic Potassium Dichromate Solutions.

**Response:** Comment not incorporated. A minimum number of measurements is needed to obtain a reliable result for the test.

**Comment Summary #9:** The commenter indicated that certified neutral density glasses with sufficient low uncertainty are not available.

**Response:** Comment not incorporated. There are multiple commercially available vendors of neutral density filters with the required uncertainty.

**Comment Summary #10:** The commenter suggested including a criteria for maximum expanded uncertainty for the certified Neutral-Density Glass Filter.

**Response:** Comment not incorporated. The application and use of such decision rules with regards to uncertainty is outside the scope of the revision of General Chapter <857>. It is currently under discussion by the USP Validation and Verification Expert Panel.

**Comment Summary #11:** The commenter indicated that the wavelengths for precision under control of absorbance test needs to be stated in the text.

**Response:** Comment not incorporated. Wavelength(s) should be appropriate to the operating range.

**Comment Summary #12:** The commenter suggested incorporating alternatives to the *NIST SRM 930, SRM 1930, SRM 2930* standards, because they are discontinued.

**Response:** Comment not incorporated. The General Chapter indicates that standards from any recognized accredited source are acceptable.

**Comment Summary #13:** The commenter indicates that the current text on “control of absorbance” section does not allow the use of metal on quartz filters for verification of absorbance accuracy.

**Response:** Comment not incorporated. The General Chapter states that “other certified standard solutions or optical filters can be used, if they are traceable to a national or international standard.”

**Comment Summary #14:** The proposed General Chapter specifies pre-defined accuracy limits rather than allowing the user to define the measurement accuracy needed. These pre-defined limits do not take into account the total measurement uncertainty of the traceability chain.

**Response:** Comment not incorporated. The application and use of limits based on total measurement uncertainty of the traceability chain and method requirements are consistent with the requirements of accreditation to *ISO/IEC 17025* and are therefore perfectly valid. However, the acceptance of such a protocol is outside the scope of the revision to <857>. It is currently under discussed by the USP Validation and Verification Expert Panel of the USP.

**Comment Summary #15:** The commenter indicates that the stray light measurement is too complicated and not clear for routine use. The proposed procedure requires a 10 mm cell to be referenced against a 5 mm cell. If the instrument only has the standard 10mm cell holder this is not possible.

**Response:** Comment not incorporated. The document allows for use of an alternative procedure: “Alternatively, analysts can measure the absorbance of the filters specified

in [Table 3](#) against the appropriate reference, and record the maximum absorbance value.” In many instances, instrument cell holders can accommodate 5mm cell easily, and in those that are ‘fixed’ at 10 mm, a 5 mm cell can be accommodated by the simple use of a readily available spacer.

**Comment Summary #16:** The commenter suggested avoiding the use of toluene due to its carcinogenicity for the resolution check.

**Response** Comment not incorporated. There is no conclusive evidence of toluene’s carcinogenicity. The Expert Committee will consider future revisions to the General Chapter upon the receipt of supporting data.

### **Procedure**

**Comment Summary #17:** A commenter indicated that the equation shown in which  $39.9\%T = 0.399A$  can mislead a reader of the article to assume that absorbance and transmittance are linearly proportional to each other in which case they are not.

**Response** Comment not incorporated. The Beer-Lambert law logarithmic relationship between Absorbance and Transmittance is clearly stated in the *Introduction*.

### **Validation and Verification**

**Comment Summary #18:** The commenter suggested expanding the intermediate precision acceptance criteria for drug substances to 1.5% to include contribution from other sources of variation.

**Response** Comment incorporated.

**Comment Summary #19:** The commenter suggested including a definition for category III procedures under Accuracy.

**Response:** Comment not incorporated. Reference to <1225> *Validation of Compendial Procedures* is included.

**Comment Summary #20:** The commenter suggested using S/N ratio >3 instead of 3.3 for the detection limit.

**Response:** Comment not incorporated. The 3.3 comes from the fact that the alpha and beta errors are equal at 5%. Three is used as an approximation.

**General Chapter/Section(s):** <911> Viscosity-Capillary Viscometer Methods

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

**Expert Committee-Initiated Change #1:** The Expert Committee defined the variables and line numbers in *Figure 2* in *Method II*.

**General Chapter/Section(s):** <912> Rotational Rheometer Methods

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

**Expert Committee-Initiated Change #1:** The Expert Committee defined all variables in *Figures 3–7*.

**General Chapter/Section(s):** <1152> Animal Drugs for Use in Animal Feeds

**Expert Committee(s):** General Chapters—Dosage Forms

**No. of Commenters:** 1

**Comment Summary #1:** The commenter requested the incorporation of the terminology, “premix,” in acknowledgement of its use in other regions for Type A Medicated Articles and Type B Medicated Feeds.

**Response:** Comment not incorporated. The Expert Committee will consider future revisions of the chapter to include mention that premix is an alternative term not preferred in the United States, but used in other places.

**General Chapter/Section(s):** <1787> Measurement of Subvisible Particulate Matter in Therapeutic Protein Injections/Multiple Sections  
**Expert Committee(s):** General Chapters—Dosage Form  
**No. of Commenters:** 7

### ***General***

**Comment Summary #1:** The commenter suggested specifying the methods to use and how to apply them including the provision of specific examples and guidelines.

**Response:** Comment not incorporated. The revision proposed by the commenter is outside the scope of this General Chapter.

**Comment Summary #2:** The commenter recommended changing the lower limit to 2 µm, which is based on current technology.

**Response:** Comment incorporated.

### ***Introduction***

**Comment Summary #3:** The commenters recommended clarifying that enumeration, characterization, and identification may not be necessary and/or achievable.

**Response:** Comment incorporated.

**Comment Summary #4:** The commenter recommended adding a clarifying explanation of extrinsic, intrinsic, and inherent particles.

**Response:** Comment incorporated.

### ***Extrinsic Definition***

**Comment Summary 5:** The commenter suggested that the potential effect on sterility and bioburden is more relevant to microbiological tests than to particulate matter; therefore, reference to bioburden should be deleted.

**Response:** Comment incorporated.

**Comment Summary #6:** The commenter suggested that the classification of extrinsic, intrinsic, and inherent should be edited for clarity.

**Response:** Comment incorporated.

### ***Intrinsic Definition***

**Comment Summary #7:** The commenter requested that a statement be added to indicate the possibility that intrinsic particles may trigger aggregation of the therapeutic protein.

**Response:** Comment incorporated.

### ***Inherent Definition***

**Comment Summary #8:** The commenter suggested that the distinction between the “inherent” and “intrinsic” is vague and unclear and recommend deleting “inherent.”

**Response:** Comment not incorporated. The inherent definition is meant to identify that some particles are a part of the product formulation.

**Comment Summary #9:** The commenter recommends mentioning the importance of assessing the presence of protein aggregates (i.e., that a primary concern is that these aggregates can generate an immunogenic response).

**Response:** Comment incorporated.

### ***Objective***

**Comment Summary #10:** The commenter recommended adding a clarification on how small and large volume parenterals are to be handled.

**Response:** Comment not incorporated.

### ***Background***

**Comment Summary #11:** The commenter suggested mentioning the concern about the limitation of analytical methods when it comes to characterizing the ability of the protein aggregates to dissociate.

**Response:** Comment not incorporated. The revision proposed by the commenter is outside the scope of the General Chapter

**Comment Summary #12:** The commenter recommends clarifying that inherent particles should also be minimized during development and production.

**Response:** Comment incorporated.

**Comment Summary #13:** The commenter recommended mentioning that intrinsic or extrinsic particles may also form dissociable aggregates.

**Response:** Comment incorporated.

**Comment Summary #14:** The commenter recommended elaborating on all the factors that can impact an instrument's ability to measure particle size and number.

**Response:** Comment not incorporated. The revision proposed by the commenter is outside the scope of the General Chapter.

### ***Table 1***

**Comment Summary #15:** The commenter indicated that the distinction between "Reversible" and "Dissociable" is unclear. These terms have been used synonymously. It should be clarified that inherent particles should also be minimized during development and production.

**Response:** Comment incorporated. Clarifying text was added to address this concern.

**Comment Summary #16:** The commenter suggested that the absence of an exact definition for the term "ordered" opens a number of possibilities for interpretations elaborating on all the factors that can impact technologies ability to measure particle size and number and requests clarification.

**Response:** Comment incorporated.

### ***Silicone Oil***

**Comment Summary #17:** The commenter requested additional information on the handling/characterizing of silicone oil droplets.

**Response:** Comment not incorporated. This topic is outside the scope of the General Chapter.

**Comment Summary #18:** The commenter recommended adding a paragraph dedicated to the interaction of Tungsten in pre-filled syringes potentiating aggregate/particle formation.

**Response:** Comment not incorporated. This specific topic has been substantially discussed in the literature.

**Comment Summary #19:** The commenter requested additional information on the handling/characterizing of silicone oil droplets surrounded by proteins.

**Response:** Comment not incorporated. This topic is outside the scope of the General Chapter.

**Comment Summary #20:** The commenter indicated that there is no consensus that excess or free silicone can migrate from the product–contact surface into the fill over time and requested clarification on this topic.

**Response:** Comment incorporated. Clarifying text was added to address this concern.

### ***Particle Standards***

**Comment Summary #21:** The commenter suggested that there are standards available, but they may differ from proteinaceous particles.

**Response:** Comment incorporated. Clarifying text was added to address this concern.

**Comment Summary #22:** The commenter requested that proteinaceous particles which are still under development should be reflected in the text.

**Response:** Comment incorporated.

### ***Subvisible Particle Measurement and Characterization Technologies (Table)***

**Comment Summary #23:** The commenter recommended that focused beam reflection measurement (FBRM), light obscuration time, size exclusion chromatography-multi angle laser light scattering, field flow fractionation, nanoparticle tracking and resonant mass sensors techniques be added to the General Chapter.

**Response:** Comment not incorporated. The techniques selected were based on their wide industry use.

**Comment Summary #24:** The commenter suggested deleting the section on turbidimetry and nephelometry, because measurements cannot provide information about particle distribution.

**Response:** Comment incorporated.

**Comment Summary #25:** The commenter indicated that for electrical sensing zone, measurement down to 0.4  $\mu\text{m}$  is possible and text should reflect this.

**Response:** Comment incorporated.

**Comment Summary #26:** The commenter recommended adding the time of flight secondary ion mass spectrometer (TOF-SIMS) technique to the General Chapter, because it is a widely used characterization technique.

**Response:** Comment incorporated.

### ***Size and Count Distribution— Light Obscuration***

**Comment Summary #27:** The commenter recommended changing the working range to 2-100  $\mu\text{m}$ .

**Response:** Comment not incorporated. The technique has a working range of 1-300  $\mu\text{m}$ .

**Comment Summary #28:** The commenter recommended stating that for maximum sensitivity, the user may need different orifices to accommodate multiple particle size ranges.

**Response:** Comment incorporated.

**Comment Summary #29:** The commenter recommended revising the text to clarify the factors that determine the potential for coincidence counting.

**Response:** Comment not incorporated. Expanding the topic of coincidence counting is not within the scope of this General Chapter.

#### ***Size and Morphology—Flow Image Analysis***

**Comment Summary #30:** The commenter recommended clarifying whether the intent was to compare the method to other methods.

**Response:** Comment incorporated. The bullet point in question was deleted.

**Comment Summary #31:** The commenter suggested that all methods are dependent on an algorithm for selecting and classifying particle size and this should be reflected in the General Chapter whether the intent was to compare this method to other methods.

**Response:** Comment not incorporated. Not all methods listed in the General Chapter use algorithms.

#### ***Size and Morphology—Electron Microscopy***

**Comment Summary #32:** The commenter suggested that the working range is in the low  $\mu\text{m}$  size-range and should be reflected in the General Chapter.

**Response:** Comment not incorporated. The Expert Committee believes that the current working range is correct.

**Comment Summary #33:** The commenter suggested adding information about the high cost of the electron microscope and training.

**Response:** Comment not incorporated. A discussion on the cost of a technology is not within the scope of the General Chapter

#### ***Characterization—Fourier Transform Infrared (FTIR) Microspectroscopy***

**Comment Summary #34:** The commenter suggested deleting or elaborating on the specific limitations that are common between light microscopy and microspectroscopy.

**Response:** Comment incorporated.

**Comment Summary #35:** The commenter suggested that FTIR is not sensitive to other molecules that do not possess or can be induced to a dipole moment and this point should be reflected in the General Chapter.

**Response:** Comment incorporated.

#### ***Strategy***

**Comment Summary #36:** The commenter requested an explanation on how comprehensive characterization can be used and in which cases it would be appropriate to apply.

**Response:** Comment incorporated.

**Comment Summary #37:** The commenter indicated that it is not generally accepted that particle data are useful for candidate selection and suggested that the General Chapter be revised to reflect this.

**Response:** Comment incorporated.

#### ***Early Development***

**Comment Summary #38:** The commenter suggested that the General Chapter specify that particle count and size be monitored on representative batches.



**Response:** Comment not incorporated. It is up to the individual user to determine a monitoring strategy.

### ***Late Development—Post-Market and Life Cycle***

**Comment Summary #39:** The commenter suggested changing the section title to *Post Marketing*.

**Response:** Comment incorporated.

### ***Sample Consideration***

**Comment Summary #40:** The commenter suggested developing a section on statistical consideration related to particle characterization.

**Response:** Comment not incorporated. This topic is not within the scope of the General Chapter.

**General Chapter/Section(s):** <1852> Atomic Absorption Spectroscopy—Theory and Practice/Multiple Sections

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

**No. of Commenters:** 1

**Comment Summary #1:** The commenter suggested that the second sentence of the first paragraph under the subsection, Sample Cell Designs, Flame Atomic Absorption Spectrometry, would read better as, “Via the nebulizer, the sample is converted to a mist that is composed of uniform droplets that are easily introduced into the flame.”

**Response:** Comment incorporated.

**Comment Summary #2:** The commenter proposed to remove the word “heated” as the furnace is generally at room temperature when the sample is introduced, under the subsection, Electrothermal Vaporization – Graphite Furnace Atomic Absorption Spectrometry.

**Response:** Comment incorporated.

**Comment Summary #3:** The commenter requested inverting the use of ppb and ppt in the last sentence, under the subsection, Cold Vapor and Hydride Generation Atomic Absorption Spectrometry to match the earlier use of these terms in this section.

**Response:** Comment incorporated.

**Comment Summary #4:** The commenter suggested inverting the terms “hollow cathode lamps (HCL)” and “continuum electrodeless discharge lamps (EDL)” in the second sentence under the subsection, Line Sources, because the HCL is much more commonly used.

**Response:** Comment incorporated.

**Comment Summary #5:** The commenter suggested to replace “sprayed” with “aspirated” in the sentence beginning “Absorption of radiation from . . .” because these are more accurate descriptions of the nebulization process.

**Response:** Comment incorporated.

**Comment Summary #6:** The commenter suggested removing the sentences, “A common line source for AAS is the HCL.” and “Another type of line source is EDL.” The first sentences in each of the paragraphs immediately following each of these sentences adequately introduce the reader to each of those paragraphs.

**Response:** Comment incorporated.

**Comment Summary #7:** The commenter suggested revising the first sentence under the subsection, Wavelength Selector to read, “Because atomic resonance lines are

narrow, spectrophotometers frequently utilize monochromators of moderate resolution, such as Ebert and Czerny-Turner systems.”

**Response:** Comment incorporated.

**Comment Summary #8:** The commenter suggested revising the last sentence under Detection Systems.

**Response:** Comment incorporated.

**Comment Summary #9:** The commenter indicated that Dr. Hieftje’s name is spelled incorrectly.

**Response:** Comment incorporated

**Comment Summary #10:** The commenter suggested including “slurries” in the last sentence of the first paragraph under the subsection, Sample Preparation, to make it consistent with the first sentence.

**Response:** Comment incorporated.

**Comment Summary #11:** The commenter suggested deleting the sentence, “Spike and recovery studies are to be routinely carried out for digestions,” because this is not required except during validation.

**Response:** Comment incorporated.

**Comment Summary #12:** The commenter indicates that the end of the first bullet statement under the subsection, Matrix Modification, Releasing Agents, and Ionization Suppressants, should include the statement, “removed during the ashing or pyrolysis step” instead of “burned off”.

**Response:** Comment incorporated.

**Comment Summary #13:** The commenter suggested adding “ashing or” to the second bullet statement just before “pyrolysis” to make it consistent with the earlier ETV subsection.

**Response:** Comment incorporated.

**Comment Summary #14:** The commenter suggested adding the sentence “Volatile compounds transported to the cell with the hydride can also interfere non-selectively” in the last paragraph of this section.

**Response:** Comment incorporated.

**General Chapter/Section(s)** <1853> Fluorescence Spectroscopy-Theory and Practice/Multiple Sections

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

**No. of Commenters:** 1

**Comment Summary #1:** The commenter recommended making reference to Rayleigh scattering under Excitation wavelength selector.

**Response:** Comment incorporated.

**Comment Summary #2:** Under the subsection, Analyte Concentration-Calibration curves, paragraph 2, the commenter recommended revising sentence 1 to read, "In some cases, calibration samples that are made from reference materials and that have known concentrations are not available."

**Response:** Comment incorporated.

**Comment Summary #3:** The commenter recommend deleting sentence 4 under the subsection, Reference Signal Level (Relative Excitation), paragraph 3, in order to avoid confusion to the users of this General Chapter.

**Response:** Comment incorporated.

**Comment Summary #4:** The commenter recommend adding the following sentence, "Fluorescence quantum yield values range from 0 (i.e. no molecules fluoresce) to 1 (theoretical maximum in which all molecules fluoresce that had absorbed radiation)" in the *APPENDIX: Definitions* section, under Fluorescence quantum yield (F),  
**Response:** Comment incorporated.

**General Chapter/Section(s):** <1854> Middle-Infrared Spectroscopy—Theory and Practice/Multiple Sections  
**Expert Committee(s):** General Chapters—Chemical Analysis  
**No. of Commenters:** 2

**Comment Summary #1:** The commenter requested a clarification that the numbers in "2.5 and 25  $\mu\text{m}$ " and "(2.6 to 15  $\mu\text{m}$ )" corresponds to wavelength range.  
**Response** Comment incorporated.

**Comment Summary # 2:** The commenter indicated that, under *Sensitivity* the description of the conditions for measurement conditions may be prescriptive for certain instrument manufacturers.  
**Response:** Comment incorporated.

**Monograph/Section(s):** Azithromycin/Multiple Sections  
**Expert Committee(s):** Monographs—Small Molecules 1  
**No. of Commenters:** 4

**Comment Summary #1:** The commenter requested correcting the salt used to prepare the buffer for the *Mobile phase* and *Diluent* from potassium phosphate monobasic to potassium phosphate dibasic.  
**Response:** Comment incorporated.

**Comment Summary #2:** The commenter requested revising *Organic Impurities Procedure 2* to include a limit of 0.15% for 3'-N-[[4-(Acetylamino)phenyl]sulfonyl]-3',3'-didemethylazithromycin to reflect FDA-approved requirements.  
**Response:** Comment incorporated.

**Comment Summary #3:** The commenter requested revising the relative standard deviation requirement for the Assay from 0.85% to 1.10% for consistency with the Assay acceptance criteria.  
**Response:** Comment incorporated.

**Comment Summary #4:** The commenter requested including a footnote in *Table 2* in *Organic Impurities Procedure 2* to indicate that azithromycin related compound F (3'-N-demethyl-3'-N-formylazithromycin) has two rotamers and that the limit is for the sum of these rotamers.  
**Response:** Comment incorporated.

**Monograph/Section(s):** Azithromycin Tablets/Organic Impurities  
**Expert Committee(s):** Monographs—Small Molecules 1  
**No. of Commenters:** 1

**Comment Summary #1:** The commenter requested revising the chromatographic conditions in the test for *Organic Impurities* to improve selectivity.  
**Response:** Comment not incorporated. The supporting validation data indicate that the procedure is adequately selective. The Expert Committee will consider a future revision upon receipt of supporting data.

**Expert Committee-Initiated Change #1:** The test for *Organic Impurities* was revised to remove the requirement for low-actinic glassware, leaving it up to the analytical laboratory to determine the appropriate technique to protect solutions from light.

**Monograph/Section(s):** Cisatracurium Besylate/Multiple Sections

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

**No. of Commenters:** 6

**Comment Summary #1:** The commenter requested replacing all of the procedures in the proposal with the procedures from the *Atracurium Besylate* monograph and including one additional isomer test.

**Response:** Comment not incorporated. The monograph reflects FDA approved specifications and procedures.

**Comment Summary #2:** The commenters requested widening the acceptance criteria in the *Assay* and *Definition* from 97.0–101.0% to 97.0–102.0% to reflect FDA approved limits.

**Response:** Comment incorporated.

**Comment Summary #3:** The commenters requested tightening the acceptance criteria in the *Assay* and *Definition*.

**Response:** Comment not incorporated. The monograph reflects FDA approved limits.

**Comment Summary #4:** The commenters requested tightening the acceptance criteria in the *Limit of Methyl Benzenesulfonate* test from NMT 10 ppm to NMT 1 ppm.

**Response:** Comment not incorporated. The monograph reflects FDA approved limits.

**Comment Summary #5:** The commenters requested increasing the concentration of the *Sample solution* from 0.7 mg/mL to 1.5 mg/mL or 2 mg/mL to increase the sensitivity of 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.

**Comment Summary #6:** The commenter requested revising the test for *Organic Impurities* to add an autosampler temperature of 5°.

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

**Comment Summary #7:** The commenter requested removing the system suitability requirements for tailing factor and relative standard deviation from the test for *Organic Impurities*.

**Response:** Comment not incorporated. The system suitability requirements are needed to establish that the system is suitable for its intended use.

**Comment Summary #8:** The commenters requested using relative response factors in the test for *Organic Impurities* to quantitate the impurities present and revising the acceptance criteria accordingly.

**Response:** Comment not incorporated. Relative response factors are not used in the validated procedure. The Expert Committee will consider future revisions to the monograph upon the receipt of the necessary supporting data.

**Comment Summary #9:** The commenter requested adding the relative retention time of the besylate counter ion peak to *Table 1* in the *Organic Impurities* test along with a statement clarifying that this peak is a counter ion and not an impurity.

**Response:** Comment incorporated.

**Comment Summary #10:** The commenter requested revising the disregard limit in the test for *Organic Impurities* to harmonize with the ICH Q3A value of 0.05%, because the disregard limit is too close to the acceptance criteria for any unspecified impurity.

**Response:** Comment not incorporated. The current disregard limit reflects the FDA approved validated procedure.

**Comment Summary #11:** The commenters requested tightening the acceptance criteria for several impurities in the test for *Organic Impurities*.

**Response:** Comment not incorporated. The acceptance criteria reflect the FDA approved limits.

**Comment Summary #12:** The commenters requested replacing the test for *Organic Impurities* with their in-house procedure, because the test for *Organic Impurities* is not suitable for their impurity profile.

**Response:** Comment not incorporated. The Expert Committee determined that the procedure is adequate for the public standard but will consider a future revision upon receipt of the necessary supporting data.

**Comment Summary #13:** The commenter requested replacing the test for *Specific Rotation* with their in-house chiral HPLC procedure.

**Response:** Comment not incorporated. The Expert Committee determined that the test for *Specific Rotation* is sufficient.

**Comment Summary #14:** The commenters requested widening the acceptance criteria in the test for *pH* to accommodate different manufacturing processes.

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

**Comment Summary #15:** The commenters requested widening the acceptance criteria in the test for *Water Determination* from NMT 2.0% to NMT 5.0% to reflect FDA approved limits.

**Response:** Comment incorporated.

**Comment Summary #16:** The commenter requested adding tests for enantiomeric purity and besylate counter ion content.

**Response:** Comment not incorporated. The Expert Committee determined that the tests and acceptance criteria are sufficient.

**Comment Summary #17:** The commenter requested adding tests for bacterial endotoxins, and microbial limits.

**Response:** Comment not incorporated. Tests for bacterial endotoxins and microbial limits are included in the relevant drug product monograph.

**Expert Committee-initiated Change #1:** The trivial name for the impurity with a relative retention time of 0.16 in *Table 1* was corrected from (*R*)-*N*-Methylaudanosine to (*R*)-*N*-Methylaudanosine.

**Expert Committee-initiated Change #2:** The USP Reference Standards section of the monograph was revised to add cisatracurium besylate to the list of components of USP Cisatracurium Besylate System Suitability Mixture RS.

**Monograph/Section(s):** Cisatracurium Besylate Injection/Multiple Sections  
**Expert Committee(s):** Monographs—Small Molecules 4  
**No. of Commenters:** 6

**Comment Summary #1:** The commenter requested replacing all of the procedures in the proposal with the procedures from the *Atracurium Besylate Injection* monograph and including one additional isomer test.

**Response:** Comment not incorporated. The monograph reflects the FDA approved specifications and procedures.

**Comment Summary #2:** The commenter requested widening the acceptance criteria for the *Assay* and the *Definition* from 90.0%–110.0% to 90.0%–115.0% for consistency with the *Atracurium Besylate Injection* monograph.

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

**Comment Summary #3:** The commenter requested revising *Identification* test A to provide additional details for clarity.

**Response:** Comment incorporated.

**Comment Summary #4:** The commenter requested using ultraviolet absorption instead of infrared absorption in *Identification* test A to eliminate interference from benzyl alcohol.

**Response:** Comment not incorporated. *Identification* test A provides sample handling instructions for injections to eliminate interference from benzyl alcohol.

**Comment Summary #5:** The commenter requested revising the calculation in the *Assay* and the test for *Organic Impurities* to address the purity of USP Cisatracurium Besylate RS.

**Response:** Comment not incorporated. The analyst should follow the directions on the USP Cisatracurium Besylate RS label when using the reference standard.

**Comment Summary #6:** The commenter requested widening the acceptance criteria for the test for *Benzyl Alcohol Content* from 90.0%–110.0% to 80.0%–110.0%.

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

**Comment Summary #7:** The commenters requested using relative response factors in the test for *Organic Impurities* to quantify the impurities present and revising the acceptance criteria accordingly.

**Response:** Comment not incorporated. Relative response factors are not used in the validated procedure. The Expert Committee will consider future revisions to the monograph upon the receipt of the necessary supporting data.

**Comment Summary #8:** The commenter requested adding the relative retention time of the besylate counter ion peak to *Table 1* along with a statement clarifying that this peak is a counter ion and not an impurity.

**Response:** Comment incorporated.

**Comment Summary #9:** The commenters requested widening the acceptance criteria for *cis*-quaternary alcohol from NMT 4.1% to NMT 5.0% to reflect FDA approved limits.

**Response:** Comment incorporated.

**Comment Summary #10:** The commenter requested widening the acceptance criteria for *cis*-quaternary acid for consistency with the *Atracurium Besylate Injection* monograph and with the limit in other pharmacopeias.

**Response:** Comment not incorporated. The acceptance criteria reflect FDA approved limits.

**Comment Summary #11:** The commenter requested tightening the acceptance criteria for total impurities and adding a limit for other known synthetic impurities.

**Response:** Comment not incorporated. The acceptance criteria reflect the FDA approved limits.

**Comment Summary #12:** The commenter requested adding a test for benzaldehyde with acceptance criteria of NMT 0.05% for consistency with the *Benzyl Alcohol NF* monograph intended for parenteral applications.

**Response:** Comment not incorporated. The Expert Committee determined that the tests and acceptance criteria are sufficient, but will consider a future revision upon receipt of supporting data to indicate that benzaldehyde is a degradation product in this drug product.

**Comment Summary #13:** The commenters requested tightening the acceptance criteria in the test for *pH*.

**Response:** Comment not incorporated. The acceptance criteria reflect the FDA approved limits.

**Comment Summary #14:** The commenter requested adding tests for isomeric purity and color of solution.

**Response:** Comment not incorporated. The Expert Committee determined that the tests and acceptance criteria are sufficient.

**Expert Committee-initiated change #1:** The trivial name for the impurity with a relative retention time of 0.16 in *Table 1* was corrected from (*R*)-*N*-Methylaudanosine to (*R*)-*N*-Methylaudanosine.

**Expert Committee-initiated change #2:** The USP Reference Standards section of the monograph was revised to add cisatracurium besylate to the list of components of USP Cisatracurium Besylate System Suitability Mixture RS.

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

**Expert Committee(s):** Monographs—Small Molecules 1

**No. of Commenters:** 1

**Comment Summary #1:** The commenter requested revising the *Sample solution* in the test for *Organic Impurities* to be similar to the *Standard solution* because clarithromycin does not readily dissolve in water.

**Response:** Comment incorporated.

**Comment Summary #2:** The commenter requested revising the chromatographic conditions to improve selectivity.

**Response:** Comment not incorporated. Laboratory data indicates that the procedure is adequately selective. The procedure in the *Clarithromycin Tablets* is the same as the one in the *Clarithromycin* drug substance monograph, which has been official for several years.

**Expert Committee-initiated Change #1:** The *USP Reference Standards* section was revised to correct the molecular weight of clarithromycin related compound A.

**Monograph/Section(s):** Cosyntropin/Multiple Sections  
**Expert Committee(s):** Monographs—Biologics and Biotechnology 1  
**No. of Commenters:** 3

#### ***Identification***

**Comment Summary #1:** The commenter recommended the addition of Appearance/Description to the monograph.

**Response:** Comment not incorporated. Appearance/Description is not consistent with Therapeutic Peptide Expert Panel recommendations on Quality Attributes for peptides' monographs.

#### ***Identification***

**Comment Summary #2:** The commenter recommended the addition of *Identification by Mass Spectrometry* to the monograph, because chromatography is not a specific identity test for the relatively long peptide.

**Response:** Comment not incorporated. Chromatography combined with amino acid analysis provides an orthogonal approach to Identification, consistent with the Therapeutic Peptide Expert Panel recommendations on Quality Attributes (AAA+HPLC or AAA+MS).

**Comment Summary #3:** The commenter recommended the addition of a Bioassay to the monograph to confirm the biological activity of the relatively long peptide.

**Response:** Comment not incorporated. Biological activity is demonstrated as part of CMC characterization of API and not be part of routine lot release.

#### ***Amino Acid Analysis***

**Comment Summary #4:** The commenter recommended changing the acceptance criteria to “not more than trace amounts of other amino acids are present, with the exception of Tryptophan,” because acceptance criteria for “any other amino acids” is too tight and “NMT 1 pmol of any other amino acid” cannot be consistently quantified due to baseline oscillation. The commenter noted the presence of tryptophan in cosyntropin, and poor recovery of tryptophan would result in greater than trace amounts.

**Response:** Comment incorporated. Both the Expert Committee and Expert Panel recommended removal of “NMT 1 pmol of any other amino acid” as this is an identity test and not a limit test. The presence of other amino acids would be captured under the Organic Impurities, Related Peptides test.

#### ***Assay, Procedure***

**Comment Summary #5:** The commenter provided chromatogram sample using an in-house method demonstrating that their chromatographic test method will provide higher resolution of impurities than that of the published monograph.

**Response:** Comment not incorporated. USP will consider this higher resolution chromatographic method when a complete submission package is available, including method and associated validation data.

#### ***Impurities***

##### ***Organic Impurities, Related Peptides***

**Comment Summary #6:** The commenter recommended removal of the “Relative standard deviation: NMT 2.0% for the cosyntropin peak from three replicate injections of



the Standard solution” system suitability requirement, because it does not apply to the *Impurities* test.

**Response:** Comment not incorporated. USP will retain the current system suitability criteria as it applies to both the *Impurities* and *Assay*.

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

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

**Expert Committee-initiated Change #1:** The *Samples* subsection is revised to add a reference to the *Standard solution*.

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

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

**No. of Commenters:** 1

**Comment Summary #1:** The commenter requested revising the *Assay* to widen the tailing factor for Desipramine from NLT 1.5 to NLT 2.

**Response:** Comment incorporated.

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

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

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

**Expert Committee(s):** Monographs—Small Molecules 1

**Expert Committee-initiated Change #1:** The details for *Solution A* in the *Assay* were revised for clarity.

**Expert Committee-initiated Change #2:** The *Assay* was revised to update the name of a related compound from diethyltoluamide *p*-isomer to USP Diethyltoluamide Related Compound A RS, because the related compound was developed as a reference material.

**Expert Committee-initiated Change #3:** The *USP Reference Standards <11>* section was updated to include the newly developed USP Diethyltoluamide Related Compound A RS.

**Monograph/Section(s):** Diethyltoluamide Topical Solution/Multiple Sections

**Expert Committee:** Monographs—Small Molecules 1

**Expert Committee-initiated Change #1:** The details for *Solution A* in the *Assay* were revised for clarity.

**Expert Committee-initiated Change #2:** Revised the *Assay* to update the name of a related compound from diethyltoluamide *p*-isomer to USP Diethyltoluamide Related Compound A RS, because the related compound was developed as a reference material.

**Expert Committee-initiated Change #3:** The *USP Reference Standards <11>* section was updated to include the newly developed USP Diethyltoluamide Related Compound A RS.

**Monograph/Section(s):** Duloxetine Delayed-Release Capsules/Multiple Sections

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

**No. of Commenters:** 3

**Comment Summary #1:** The commenter requested revising *Identification* test A to include a description of how to prepare the buffer.

**Response:** Comment incorporated.

**Comment Summary #2:** The commenter requested revising the acceptance criteria in *Identification* test A by adding a statement to disregard peaks arising from excipients.

**Response:** Comment not incorporated. The acceptance criteria for *Identification* test A are appropriate as written.

**Comment Summary #3:** The commenter requested adding *Dissolution Test 2* with different conditions and tolerances to support their approved drug product. *Dissolution Test 2* was validated using the Inertsil ODS-3 brand of L1 column.

**Response:** Comment incorporated.

**Comment Summary #4:** The commenter requested including the relative retention times for duloxetine and 1-naphthol in *Dissolution Test 1*.

**Response:** Comment incorporated.

**Comment Summary #5:** The commenter requested revising *Dissolution Test 1* to add a limit for the resolution between the duloxetine and 1-naphthol peaks.

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

**Comment Summary #6:** The commenter requested including an additional degradation product, duloxetine related compound C, as part of the calculation in order to more accurately account for the percentage of duloxetine released in the Acid stage medium in *Dissolution Test 1*.

**Response:** Comment not incorporated. The current procedure is consistent with the FDA-approved conditions, procedures, and acceptance criteria.

**Comment Summary #7:** The commenter requested adding another test for *Organic Impurities* to address a different impurity profile.

**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:** A footnote was added to *Table 1* in the test for Organic Impurities to clarify that duloxetine related compound F is a process impurity that is included in the table for identification purposes only. It is controlled in the drug substance and is not to be reported or included in the *Total impurities*.

**Expert Committee-initiated Change #2:** The *Dissolution test* was renamed *Dissolution Test 1* and a *Labeling* section is added to the monograph to support the addition of *Dissolution Test 2*.

**Expert Committee-initiated Change #3:** The chemical name for USP Duloxetine Related Compound H RS was updated.

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

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

**No. of Commenters:** 3

**Comment Summary #1:** The commenter requested revising the test for *Limit of Platinum* to add the note, "Perform this test only if platinum is a known inorganic impurity of the manufacturing process."

**Response:** Comment incorporated.

**Comment Summary #2:** The commenter requested adding a limit of NMT 0.15% for the specified impurity, dihydrodutasteride, based on FDA approved limits.

**Response:** Comment incorporated.

**Comment Summary #3:** The commenter requested revising the test for Organic Impurities to change the relative response factor for chlorodutasteride from 1.0 to 0.33 to match the value in the *European Pharmacopoeia*.

**Response:** Comment incorporated.

**Comment Summary #4:** The commenter requested adding a limit of NMT 0.15% for the specified impurity, methyl-3-oxo-4-aza androst-1-ene-17-beta carboxylate, based on FDA approved limits.

**Response:** Comment incorporated.

**Comment Summary #5:** The commenter requested adding a note to *Organic Impurities Procedure 2* to disregard peaks that are detected by *Organic Impurities Procedure 1*.

**Response:** Comment not incorporated. *Organic Impurities Procedure 2* already contains a note to exclude the impurities detected by *Procedure 1*.

**Comment Summary #6:** The commenter requested revising the test for Water Determination to widen the limits from NMT 0.2% to NMT 0.50% to reflect FDA approved limits.

**Response:** Comment incorporated.

**Comment Summary #7:** The commenter requested revising the *Standard stock solution* to correct the dilution scheme from "1:10" to "1:100".

**Response:** Comment incorporated.

**Comment Summary #8:** The commenter requested removing the relative standard deviation requirement in the test for *Organic Impurities Procedure 1*, because the impurity calculation is based on area normalization.

**Response:** Comment incorporated.

**Comment Summary #9:** The commenter requested revising *Organic Impurities Procedure 1* to address the commenter's impurity profile.

**Response:** Comment not incorporated. The commenter's impurity profile will be addressed in a future revision upon receipt of the necessary supporting data.

**Comment Summary #10:** The commenter requested adding temperature, heating time, and sample size to the test for *Water Determination*.

**Response:** Comment incorporated.

**Comment Summary #11:** The commenter requested widening the limits in the test for Water Determination from NMT 0.2% to NMT 2.0% to reflect the water content of a different polymorphic form.

**Response:** Comment not incorporated. The water limit will be widened in a future revision upon receipt of necessary supporting data.

**Monograph/Section(s):** Fondaparinux Sodium  
**Expert Committee(s):** Monographs—Biologics & Biotechnology 1  
**No. of Commenters:** 7

### ***Identification***

**Comment Summary #1:** The commenter requested revising the proposed  $^{13}\text{C}$  NMR procedure to include line broadening parameter to process the data and to achieve signal-to-noise ratio of 20:1.

**Response:** Comment incorporated.

**Comment Summary #2:** The commenter requested investigating the correct concentration for the internal standard Trimethylsilyl propionate (TSP). Following the proposed procedure, the commenter was not able to see the TSP methyl signal.

**Response:** Comment incorporated. The method innovator uses external calibrant, but it is also possible to use an internal TSP standard at an increased concentration of 0.05%.

### ***Ethanol and Pyridine***

**Comment Summary #3:** The commenter requested revising the *Ethanol and Pyridine Impurities* section to include methods for methanol, acetonitrile, toluene, and dimethyl formamide. It was noted that the solvents methanol and toluene co-elute with each other in the current Ethanol and Pyridine method.

**Response:** Comment not incorporated. Per USP *General Notices* section 5.60.20 *Residual Solvents in USP and NF Articles*, all USP–NF articles should comply with the requirements stated in USP *Residual Solvents* <467>.

### ***Free Sulfate and Residual Chloride Determination***

**Comment Summary #4:** The commenter requested revising the *Free Sulfate and Residual Chloride* method to improve column robustness. The commenter observed that the retention time for the sulfate is at 5.327 min instead of 14.1 min and the column needs to be regenerated frequently for every two injections.

**Response:** Comment not incorporated. Users are expected to regenerate the column after each injection of fondaparinux sample as the fondaparinux sodium binds to the column. An emphasis on column cleaning will be added to the NOTE.

**Comment Summary #2:** The commenter requested replacing the proposed *Free Sulfate and Residual Chloride* method with a method that avoids such regeneration requirements.

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

### ***Organic Impurities***

**Comment Summary #3:** The commenter requested replacing the proposed *Organic Impurities* method with a better method that enables the conformance to ICH guidelines. The proposed USP method has an LOQ of 0.200% for all impurities except Compound B and G, rendering it incapable of meeting ICH guidelines for reporting threshold of 0.1%.

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

**Comment Summary #4:** The commenter requested naming the structure of the impurity with RRT of approximately 0.93. This impurity is identified as Impurity B in the Glaxo/Sanofi patent US2005/0020536.

**Response:** Comment incorporated. This impurity is referred to as Compound A in the proposed monograph. There are two impurities closely co-eluting and their structures will be named in the revised monograph.

**Comment Summary #5:** The commenter requested investigating the poor sensitivity of the proposed Organic Impurities method. The commenter consistently obtained a signal-to-noise ratio of around 3 (less than 10) for fondaparinux peak in the injection of sensitivity check solution which fails to meet the suitability requirement set in the monograph.

**Response:** Comment not incorporated. The chromatographic column is sensitive to dissolved gases. It is critical that the mobile phase and samples are degassed properly to obtain suitable signal-to-noise ratio, stable baseline and a better resolution of impurities. Following the proper degassing procedure, signal-to-noise ratio of 12-20 can be routinely obtained.

### **Specific Tests**

**Comment Summary #6:** The commenter requested revising the proposed specification for *Water Determination, pH, Bacterial Endotoxins Test, and Microbial Enumeration Tests* to include other FDA approved limits.

**Response:** Comment incorporated. The *Water Determination* specification will be revised from NMT 15.0% to NMT 20.0%. The *pH* specification will be revised from 6.0-8.0 to 5.5 to 8.0. The *Bacterial Endotoxins Test* specification will be revised from NMT 3.3 EU/mg to NMT 25 EU/mg. The *Microbial Enumeration Tests* specification will be revised from NMT 100 CFU/g to NMT 350 CFU/g.

**Monograph/Section(s):** Fondaparinux Sodium Injection/Organic Impurities  
**Expert Committee(s):** Monographs—Biologics & Biotechnology 1

**Comment Summary #1:** The commenter requested revising the proposed formula for determination of the content of impurities B, C and G.

**Response:** Comment incorporated

**Monograph/Section:** Hydrogenated Lanolin/Assay

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

**No. of Commenters:** 1

**Comment Summary #1:** In the test for *Chromatographic Profile of Fatty Alcohols, Hydrocarbons, and Sterols* under the Assay, the commenter recommended preparing the standard solutions for cetyl alcohol and stearyl alcohol separately. Correspondingly, the *Standard solution C* using USP Cetyl Alcohol RS and *Standard solution D* using USP Stearyl Alcohol RS will be used in the system suitability test and subsequent sample analysis.

**Response:** Comment incorporated.

**Monograph/Sections:** Idarubicin Hydrochloride Injection/Multiple Sections  
**Expert Committee:** Monographs—Small Molecules 1  
**No. of Commenters:** 1

**Comment Summary #1:** The commenter requested deleting the requirement for *Osmolality and Osmolarity*, because the product is diluted with saline or dextrose solution before it is administered as an infusion.

**Response:** Comment incorporated.

**Comment Summary #2:** The commenter requested widening the limits for the specified, unspecified and total impurities in the *Organic Impurities* procedure to reflect FDA approved limits.

**Response:** Comment incorporated.

**Comment Summary #3:** The commenter requested revising the *Organic Impurities* test to correct the chemical names of the related compounds.

**Response:** Comment incorporated. The trivial and chemical names of the impurities were updated.

**Comment Summary #4:** The commenter requested removing the need to evaluate the organic impurities at two different wavelengths.

**Response:** Comment incorporated.

**Monograph/Section(s):** Insulin Glargine/Multiple Sections  
**Expert Committee(s):** Monographs—Biologics and Biotechnology 1  
**No. of Commenters:** 3

### ***Impurities***

**Comment Summary #1:** The commenter recommended revising the acceptance criteria for *Related Compounds* and *Limit of High Molecular Weight Proteins* to be consistent with other approved insulin monographs.

**Response:** Comment not incorporated. The acceptance criteria for *Related Compounds* and *Limit of High Molecular Weight Proteins* for each Insulin analogue (such as insulin human, insulin aspart, insulin lispro and insulin glargine) are different because these insulin analogues are different structure variants. Due to the differences in their molecular structures the insulins exhibit different levels of susceptibility with respect to degradation (such as deamidation) and formation of high molecular weight proteins. Additionally, the synthetic pathways for insulins can be different; they can be produced from natural insulins by enzymatic conversion or recombinant expression by microbiological fermentation using bacteria or yeast. The monographs were prepared based on the information available for the marketed insulin products; therefore, the specifications reflect the qualities available on the market: These products are approved by the competent authorities and each has an adequate safety profile.

### ***Related Compounds***

**Comment Summary #2:** The commenter recommended changing *Related Compounds* to *Related Proteins*.

**Response:** Comment incorporated.

**Comment Summary #3:** The commenter recommended changing the specifications for *Related Compounds*.

**Response:** Comment incorporated. The specification for any individual insulin glargine related compound was revised from 0.4% to 0.5 %, and the specification for total insulin

glargine related compounds from 1.0% to 1.5 %. These revisions align with FDA approved specifications.

#### ***Limit of High Molecular Weight Proteins***

**Comment Summary #4:** The commenter suggested adding this statement “if splitting of the principal peak is observed, the injection volume may be decreased according to the permitted adjustments in <621> *Chromatography*.” The injection volume of 100 µL (greater than 60 µL) can produce peak splitting due to total injection volume rather than total protein concentration.

**Response:** Comment not incorporated. Reduced injection volume is permitted and addressed in <621> *Chromatography, System Suitability, Injection Volume (HPLC)*: The injection volume can be reduced as far as is consistent with accepted precision and detection limits; no increase is permitted.

#### ***Specific Tests, Insulin assays: <121> Bioidentity Test***

**Comment Summary #5:** The commenter suggested removal of <121> *Bioidentity Test* <121>. Should it be necessary to include the *Bioidentity Test*, the commenter recommended including a NOTE stated that “the *Bioidentity Test* may be performed either on the *Insulin Glargine* bulk drug substance or on the finished pharmaceutical product.”

**Response:** Comment not incorporated. The procedure and specification align with FDA approved specifications, and are included in the drug substance monograph because the bulk drug substance can be prepared into different drug products.

#### ***Water Determination***

**Comment Summary #6:** The commenter suggested aligning the loss on drying specification with other insulin analog drug substance monographs, NMT 10.0%, because the volatile content depends on the manufacturing platform used.

**Response:** Comment not incorporated. The Expert Committee found the current *Water determination* test with the specification of NMT 8.0% to be sufficient. The Expert Committee will consider further revisions to the monograph upon receipt of supporting data based on approval of other insulin glargine drug products.

#### ***Additional Requirements***

##### ***Labeling***

**Comment Summary #7:** The commenter recommended removing the microbial synthesis from labeling requirement, or adding a qualifier that this requirement is only necessary if Insulin Glargine is obtained from microbial synthesis because Insulin Glargine can be produced in other systems.

**Response:** Comment incorporated.

**Monograph/Section(s):** Insulin Glargine Injection/Multiple Sections  
**Expert Committee(s):** Monographs—Biologics and Biotechnology 1  
**No. of Commenters:** 3

**Comment Summary #1:** The commenter suggested that a possible path forward for Insulin Glargine Injection monograph would be to publish the drug substance monograph first and wait for FDA approval of other drug products.

**Response:** Comment not incorporated. The Expert Committee will consider further revisions to the monograph upon receipt of supporting data based on approval of other insulin glargine drug products.

### ***Impurities***

**Comment Summary #2:** The commenter recommended that the acceptance criteria for *Related Compounds*, and *Limit of High Molecular Weight Proteins* to be revised to be consistent with other approved insulin monographs.

**Response:** Comment not incorporated. The acceptance criteria for *Related Compounds* and *Limit of High Molecular Weight Proteins* for each Insulin analogue (such as insulin human, insulin aspart, insulin lispro and insulin glargine) are different because these insulin analogues are different structure variants. Due to the differences in their molecular structures the insulins exhibit different levels of susceptibility with respect to degradation (such as deamidation) and formation of high molecular weight proteins. Additionally, the synthetic pathways for insulins can be different; they can be produced from natural insulins by enzymatic conversion or recombinant expression by microbiological fermentation using bacteria or yeast. The monographs were prepared based on the information available for the marketed insulin products; therefore, the specifications reflect the qualities available on the market: These products are approved by the competent authorities and each has an adequate safety profile.

### ***Other Components, Zinc Determination***

**Comment Summary #3:** The commenter suggested considering a limit of zinc aligned with *Insulin Human Injection* monograph or with a wider limit around product target. Other compendial drug products have wider specifications and more allowance should be made for analytical variability.

**Response:** Comment not incorporated. The limit of zinc in of an injection monograph should align with that of the drug substance, because the formulation should not have impact on zinc quantity. The Expert Committee will consider further revisions to the monograph upon receipt of supporting data based on approval of other insulin glargine drug products.

### ***Impurities, Related Compounds***

**Comment Summary #4:** The commenter suggested having a wider specification, like NMT 3.0%, to allow companies to use methods that are able to monitor changes in their process and more modern HPLC column technology. The specification for total impurities (NMT 2.0%) seems to not take all degradation products into account.

**Response:** Comment not incorporated. The specifications in Injection should align with those for the drug substance because the formulation should not have impact on the product-related impurities. The Expert Committee will consider further revisions to the monograph upon receipt of supporting data based on approval of other insulin glargine drug products.

### ***Limit of High Molecular Weight Proteins***

**Comment Summary #5:** The commenter suggested revising the specification from NMT 0.3% to NMT 0.5% and to add the procedure from <121.1> *Physical analytical Procedures for Insulins, Limit of High Molecular Weight Proteins*



**Response:** Comment not incorporated. The Expert Committee will consider further revisions to the monograph upon receipt of supporting data based on approval of other insulin glargine drug products.

***Additional Requirements, Labeling***

**Comment Summary #6:** The commenter recommended removing the microbial synthesis from labeling requirement, or adding a qualifier that this requirement is only necessary if Insulin Glargine is obtained from microbial synthesis because Insulin Glargine can be produced in other systems.

**Response:** Comment incorporated. The statement of “microbial synthesis” was removed from the labeling requirement.

**Monograph/Section(s):** Magnesium Oxide/Assay  
**Expert Committee(s):** Monographs—Small Molecules 3  
**No. of Commenters:** 1

**Comment Summary #1:** The commenter requested creating a new Volumetric Solution for 0.1 M edetate disodium VS.

**Response:** Comment incorporated.

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

**Comment Summary #1:** The commenter requested increasing the concentration of the *Standard solution*.

**Response:** Comment not incorporated. The concentration is consistent with the validation data and suitable for its intended purpose.

**Monograph/ Section(s):** Metoprolol Tartrate/Multiple Sections  
**Expert Committee(s):** Monographs—Small Molecules 2  
**No. of Commenters:** 2

**Comment Summary #1:** The commenter suggested widening the limits for metoprolol related compound D from NMT 0.10% to NMT 0.20% and for total impurities from NMT 0.30% to NMT 0.50% in the test for *Organic Impurities*.

**Response:** Comment partially incorporated. The limit for total impurities was widened to NMT 0.50%. The limit for metoprolol related compound D reflects FDA approved acceptance criteria. The Expert Committee will consider a future revision to revise the limit for metoprolol related compound D upon receipt of supporting data.

**Comment Summary #2:** The commenter requested revising the test for *Organic Impurities* to correct the reference standard names in the *Standard solution* to match those in the *USP Reference Standards* section.

**Response:** Comment incorporated.

**Expert Committee-initiated Change #1:** The relative standard deviation requirement in the Assay was revised from 0.7% to 0.73% to be consistent with the General Chapter <621> requirement.

**Monograph/ Section(s):** Nicardipine Hydrochloride Injection/Multiple Sections  
**Expert Committee:** Monographs—Small Molecules 2  
**No. of Commenters:** 1

**Comment Summary #1:** The commenter requested including a second *Identification* test.

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

**Expert Committee-initiated Change #1:** The column efficiency requirements in the tests for *Limit of N-Benzyl-N-methyl-ethanolamine* and *Organic Impurities* were deleted as the remaining system suitability parameters are adequate to evaluate system suitability.

**Expert Committee-initiated Change #2:** The sensitivity requirement in the test for *Content of Sorbitol* was deleted, because this requirement is not appropriate for a public standard.

**Monograph/Section(s):** Prochlorperazine Maleate/Organic impurities  
**Expert Committee(s):** Monographs—Small Molecules 3  
**No. of Commenters:** 1

**Comment Summary #1:** The commenter requested replacing the test for *Organic Impurities* with their in-house procedure because the test for *Organic Impurities* is not suitable for their impurity profile.

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

**Comment Summary #2:** The commenter requested revising *Table 2* in the *Organic Impurities* test to add chemical names for the specified unknown impurities.

**Response:** Comment not incorporated. No additional information is available at this time. The Expert Committee will consider future revisions to the monograph upon the receipt of the necessary supporting data.

**Monograph/Section(s):** Protamine Sulfate/Multiple Sections  
**Expert Committee(s):** Monographs—Biologics & Biotechnology 1  
**No of Commenters:** 5

### ***Identification***

**Comment Summary #1:** The commenter requested deleting the *Bioidentity* as a further identification test is not likely to be necessary.

**Response:** Comment not incorporated. The old Assay has been replaced by an HPLC analytical method in the new monograph, the clotting assay will remain as the *Bioidentity* test pursuant to a request from FDA.

**Comment Summary #2:** The commenter requested deleting the requirement that the retention times of the four peaks are within +/- 5% to those of standards solution. The molecular weight and ionic properties of peptides in USP standard solution may differ from protamine sulfate batches produced by individual companies, resulting in different retention times.

**Response:** Comment incorporated.

## **Assay**

**Comment Summary #3:** The commenter requested revising the proposed suitability requirement to remove the specific retention time for peptide #4. Companies observed that the retention time for the peptide #4 varies significantly depending on a column used.

**Response:** Comment incorporated.

**Comment Summary #4:** The commenter requested revising the proposed Assay to consider a different column for this application and sent in a description of an alternative method. The commenter reported that the columns required replacement after less than 100 injections due to degradation of the column material under high temperature and low pH requirement of the proposed test method.

**Response:** Comment not incorporated. 100-150 injections per column are consistent with what the innovator reported for column lifetime. The Expert Committee will consider future revisions to the monograph upon the receipt of the necessary supporting data.

## **Chromatographic Purity**

**Comment Summary #5:** The commenter requested removing the *Chromatographic purity* specification from the monograph until a suitable alternative, capable of providing an appropriate level of resolution to minor and major peptides has been evaluated and can be incorporated with corresponding limits. Alternatively, the commenter suggested that the USP consider revising the purity specification to “not less than 88%” to allow for the use of a column that can provide improved resolution.

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

**Comment Summary #6:** The commenter requested revising the proposed *Chromatographic purity* method to include acceptance criterion for smaller peaks separately from the four major peaks. This is critical to maintaining consistent quality of protamine sulfate.

**Response:** Comment not incorporated. The proposed method and associated acceptance criteria are validated only for the major 4 peaks, not for smaller peaks.

**Comment Summary #7:** The commenter requested revising the proposed chromatographic method to include integration parameters in the monograph. Peaks derived from protamine sulfate do not result in baseline separation; therefore, HPLC data processing method drastically affects the percent area of the peaks.

**Response:** Comment incorporated. The monograph will be revised to include vertical drop down integration. Detailed integration parameters will be included in the Certificate of the USP Protamine Sulfate RS.

## **Other Sections**

**Comment Summary #8:** The commenter requested either removing the pH or broadening the pH limit to cover protamine sulfate used as an excipient. A commenter proposed 6.5–8 as an acceptable criterion of pH instead of 4–7, based on their product record for the past eight years. Also, the *Japanese Pharmacopeia* Protamine Sulfate monograph contains an acceptance criterion of pH 6.5–7.5. Another commenter stated testing of pH is not important for protamine used as an excipient, but for only protamine sulfate API used in injectables.

**Response:** Comment incorporated. The pH specification was deleted from the drug substance monograph and a specification of pH 6.0–7.0 was added to the drug product monograph.

**Comment Summary #9:** The commenter requested revising the specification for *Methylmercury* to include the following sentence: “Analysis is not necessary when the content for total mercury is less than the limit for methylmercury,” as stated in General Chapter <2232>.

**Response:** Comment incorporated.

**Comment Summary #10:** The commenter requested including a suitable method to ensure adequate removal of non-protamine like proteins and residual DNA from the salmon tissue from which protamine is isolated.

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

**Comment Summary #11:** The commenter requested revising the packaging and storage requirement to include cold storage (2–8°).

**Response:** Comment incorporated.

**Monograph/Section(s):** Pyrantel Tartrate/Organic Impurities

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

**Expert Committee-initiated Change #1:** The *Diluted sample solution* is replaced with a *Standard solution* containing USP Pyrantel Tartrate RS at the same concentration.

**Monograph/Section(s):** Quetiapine Fumarate/Multiple Sections

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

**No. of Commenters:** 6

**Comment Summary #1:** The commenter requested revising the *Standard solution* and *Sample solution* in the Assay for clarity.

**Response:** Comment incorporated.

**Comment Summary #2:** The commenter requested the test for *Organic Impurities* to change the relative response factor for quetiapine quaternary salt from 0.62 to 0.76 based on the commenter’s data.

**Response:** Comment not incorporated. Lower relative response factors allow a more conservative estimate of the impurity

**Comment Summary #3:** The commenters indicated that the relative retention time for quetiapine tetraethylene glycol analog in the test for *Organic Impurities* is the same as quetiapine.

**Response:** Comment incorporated. The relative retention time for quetiapine tetraethylene glycol analog was changed from 1.0 to 1.2 based on supporting data.

**Comment Summary #4:** The commenter requested the inclusion of a gas chromatographic procedure for monitoring one of the process intermediates.

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

**Comment Summary #5:** The commenter requested tightening the limits in the test for *Organic Impurities* to be consistent with ICH Q3A guidelines.

**Response:** Comment not incorporated. The limits reflect FDA approved acceptance criteria.

**Comment Summary #6:** The commenter requested revising the test for *Organic Impurities* to delete the limits for impurities that are specific to a particular manufacturing process.

**Response:** Comment not incorporated. The drug substance synthesized by the relevant manufacturing process is used in several approved applications.

**Comment Summary #7:** The commenter requested harmonizing the monograph with *European Pharmacopoeia*.

**Response:** Comment not incorporated. The procedure in *European Pharmacopoeia* does not offer significant advantages over the proposed procedure.

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

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

**No. of Commenters:** 3

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

**Response:** Comment incorporated.

**Comment Summary #2:** The commenter requested replacing the *Assay* procedure with a different chromatographic procedure.

**Response:** Comment not incorporated. The alternative procedure provided by the commenter does not offer significant advantages over the proposed procedure.

**Comment Summary #3:** The commenter indicated that the molecular weight correction in the calculation of the test for *Dissolution* is incorrect.

**Response:** Comment not incorporated. The molecular weight correction used in the dissolution calculation is consistent with the product definition.

**Comment Summary #4:** The commenter requested deleting the limit for quetiapine related compound B in the test for *Organic Impurities* as this is a process impurity that is controlled in the drug substance.

**Response:** Comment not incorporated. There is evidence to show that quetiapine related compound B is both a process impurity and degradation product.

**Comment Summary #5:** The commenter requested tightening the limit for unspecified degradation products from NMT 0.2 % to NMT 0.20%.

**Response:** Comment not incorporated. The acceptance criteria are consistent with FDA approved limits.

**Comment Summary #6:** The commenter requested adding *Dissolution Test 3* with different conditions and tolerances to support their approved drug product. *Dissolution Test 3* was validated using the Waters Symmetry C18 brand of L1 column.

**Response:** Comment incorporated.

**Mono graph/Section(s):** Repaglinide Tablets/Multiple Sections

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

**No. of Commenters:** 1

**Comment Summary #1:** The commenter requested specifying that a variable wavelength UV detector may be used in the *Assay*, and that a photodiode array detector should be used to perform *Identification C*.

**Response:** Comment incorporated.

**Comment Summary #2:** The commenter requested providing the relative retention time of repaglinide related compound A as 0.4, instead of 0.37, under the *System suitability* in the *Assay* and *Organic impurities*.

**Response:** Comment incorporated.

**Monograph/Section(s):** Salicylic Acid/Multiple Sections  
**Expert Committee(s):** Monographs—Small Molecules 3  
**No. of Commenters:** 1

**Comment Summary #1:** The commenter suggested removing second *Identification* test.

**Response:** Comment not incorporated. At least two orthogonal identification tests is the preferred approach.

**Comment Summary #2:** The commenter indicated the tailing factor is too tight.

**Response:** Comment incorporated. The tailing factor was widened from NMT 2.0 to NMT 2.5 based on supporting data.

**Comment Summary #3:** The commenter requested canceling the revision to the Assay procedure and retaining the original titration procedure.

**Response:** Comment not incorporated. Replacement of a nonspecific titration procedure with a more specific chromatographic procedure is consistent with current USP modernization initiative.

**Comment Summary #4:** The commenter indicated that the test for *Sulfate* underestimates the sulfate content.

**Response:** Comment not incorporated. The Expert Committee determined that the test is adequately accurate but will consider a future revision upon receipt of supporting data.

**Monograph/Section(s):** Sodium Bicarbonate/Limit of Ammonia  
**Expert Committee(s):** Monographs—Small Molecules 3  
**No. of Commenters:** 3

**Comment Summary #1:** The commenter expressed a support of the proposal and indicated that the ability to report quantitative results is a significant benefit both to the commenter's company as well as to their customers.

**Response:** The Expert Committee takes note of the commenter's view of the impact of the revision.

**Comment Summary #2:** The commenter requested canceling the proposal and replacing it with the titration procedure which is currently official in *European Pharmacopoeia* monograph for *Sodium hydrogen carbonate*.

**Response:** Comment not incorporated. The procedure in *European Pharmacopoeia* employs mercury-containing Nessler Reagent which is a safety hazard.

**Comment Summary #3:** The commenter indicated that they had no false positive results while performing the currently official test, and requested canceling the proposal.

**Response:** Comment not incorporated. Replacement of a wet chemistry pass-fail test with a quantitative chromatographic procedure is consistent with current USP modernization initiative.

**Monograph/Section(s):** Sulbactam Sodium/Organic Impurities  
**Expert Committee(s):** Monographs—Small Molecules 1

**Expert Committee-initiated Change #1:** The test for *Organic Impurities* and the *USP Reference Standards* section were revised to delete references to USP Sulbactam Related Compound C RS. This material is not available at a quality required to develop a reference standard.

**Expert Committee-initiated Change #2:** Based on laboratory data, the *System suitability solution* in the test for *Organic Impurities* was updated to indicate that it should be protected from light.

**Monograph/Section(s):** Tigecycline/Multiple Sections  
**Expert Committee(s):** Monographs—Small Molecules 1  
**No. of Commenters:** 3

**Comment Summary #1:** The commenter requested revising the *Packaging and Storage* conditions to address different polymorphs.

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

**Comment Summary #2:** The commenter requested widening the pH range.

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

**Comment Summary #3:** The commenter requested revising the *Assay* procedure with the commenter's validated procedure.

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

**Comment Summary #4:** The commenter requested revising the *Organic Impurities* test to correct the chemical names one related compound and to provide more information about the specified impurities.

**Response:** Comment incorporated. The trivial and chemical names of the impurities were updated where the information is available.

**Comment Summary #5:** The commenter requested tightening the limit for tigecycline open ring in the test for *Organic Impurities*.

**Response:** Comment not incorporated. The acceptance criteria are consistent with the FDA approved limit.

**Comment Summary #6:** The commenter requested revising the *Organic Impurities* procedure with the commenter's validated procedure.

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

**Comment Summary #7:** The commenter requested widening the limit for *Residue on Ignition*.

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

**Comment Summary #8:** The commenter requested widening the limits in the test for *Water Determination*.

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

**Monograph/Section(s):** Tigecycline for Injection/Multiple Sections  
**Expert Committee(s):** Monographs—Small Molecules 1  
**No. of Commenters:** 1

**Comment Summary #1:** The commenter requested revising the test for *Identification* based on infrared absorption, because there was significant interference from excipients.

**Response:** Comment partially incorporated. The test for *Identification* based on infrared absorption was deleted. The Expert Committee will consider future revisions to the monograph upon the receipt of the necessary supporting data.

**Expert Committee-initiated Change #1:** The *Labeling* requirements were deleted because this information is not required in the monograph.

**Monograph/Section(s):** Venlafaxine Tablets/Definition  
**Expert Committee(s):** Monographs—Small Molecules 4  
**No. of Commenters:** 1

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

**Response:** Comment incorporated.

**Monograph/Section(s):** Vigabatrin for Oral Solution/Organic Impurities  
**Expert Committee(s):** Monographs—Small Molecules 4  
**No. of Commenters:** 1

**Comment Summary #1:** The commenter requested deleting N-Carboxymethylvinylpyrrolidinone and N-3-Oxocarboxypentylvinylpyrrolidinone from *Table 1* as these degradation products are not found in this dosage form.

**Response:** Comment incorporated.

**Monograph/Section(s):** Vinorelbine Injection/Organic Impurities  
**Expert Committee(s):** Monographs—Small Molecules 3  
**No. of Commenters:** 1

**Comment Summary #1:** The commenter requested not widening the disregard limit from 0.02% to 0.1% because the limit of quantitation of the *Organic impurities* procedure is lower than 0.02%.

**Response:** Comment not incorporated. The disregard limit is consistent with ICH Q3B guidelines.

**Monograph/Section(s):** Zinc Carbonate/Definition  
**Expert Committee:** Monographs—Small Molecules 3  
**No. of Commenters:** 1

**Comment Summary #1:** The commenter requested correcting the CAS number for zinc subcarbonate.

**Response:** Comment incorporated.

**Monograph/Section(s):** Zinc Sulfate/Alkalies and Alkaline Earths  
**Expert Committee(s):** Monographs—Small Molecules 3  
**No. of Commenters:** 1

**Comment Summary #1:** The commenter suggested revising “ignite” to “ignite to constant weight” for clarification.

**Response:** Comment incorporated.