COMMENTARY– *USP 32-NF 27 Second Supplement*

Revision proposals published in *Pharmacopeial Forum* often elicit public comments that are forwarded to the appropriate Expert Committee for review and response. In accordance with the Rules and Procedures of the 2005-2010 Council of Experts, revision proposals can advance to official status with minor modifications, as needed, without requiring further public review. In such cases a summary of comments received and the appropriate Expert Committee's responses are published in the *Commentary* section of the USP website at the time the revision becomes official. For those proposals that require further revision and republication in *Pharmacopeial Forum*, a summary of the comments and the Expert Committee's responses will be included in the briefing that accompanies each article.

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

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***No comments received for the following proposals*:**

General Chapters

<711> Dissolution
<905> Uniformity of Dosage Units

Monographs

Acetaminophen
Alpha Lipoic Acid
Amifostine
Amlodipine Besylate
Amphetamine Sulfate
Amphetamine Sulfate Tablets
Anhydrous Citric Acid
Aspirin
Atovaquone Oral Suspension
Atracurium Besylate Injection
Aurothioglucose Injectable Suspension
Aztreonam for Injection
Benzalkonium Chloride
Benzocaine
Benzoic Acid
Bicalutamide Tablets
Bleomycin for Injection
Caffeine
Caprylocaproyl Polyoxylglycerides
Carvedilol Tablets

No comments received for the following proposals, continued

Ceftazidime Injection
Chloral Hydrate
Citric Acid Monohydrate
Cocaine
Cocaine Hydrochloride
Codeine
Codeine Sulfate
Corn Oil
Dantrolene Sodium Capsules
Desmopressin Acetate Nasal Spray
Dextroamphetamine Sulfate
Dicyclomine Hydrochloride
Dopamine Hydrochloride
Doxazosin Mesylate
Erythromycin Pledgets
Ethyl Acetate
Ethyl Maltol
Famotidine for Oral Suspension
Fexofenadine Hydrochloride Tablets
Fish Oil Containing Omega-3 Acids
Fluconazole Tablets
Gabapentin Tablets
Glimepiride Tablets
Glutamic Acid
Glyburide and Metformin Hydrochloride Tablets
Granisetron Hydrochloride Tablets
Ground Limestone
Guggul
Guggul Tablets
Human Insulin Isophane Suspension and Human Insulin Injection
Hydrogenated Polydecene
Hydroxychloroquine Sulfate Tablets
Ibuprofen
Ibuprofen Tablets
Imipramine Hydrochloride
Irbesartan
Ivermectin Tablets
Lactic Acid
Lanolin Alcohols
Lauroyl Macrogolglycerides
Levalbuterol Inhalation Solution
Levothyroxine Sodium Tablets
Lindane
Linoleoyl Macrogolglycerides
Liothyronine Sodium Tablets
Liotrix Tablets
Lisinopril and Hydrochlorothiazide Tablets
Lisinopril Tablets
Methyl Alcohol
Midazolam Injection
Minocycline Periodontal System
Moxifloxacin Hydrochloride
Native Guggul Extract
Niacinamide
Oleoyl Macrogolglycerides
Pamidronate Disodium
Physostigmine
Physostigmine Salicylate
Physostigmine Sulfate
Pilocarpine Hydrochloride
Pilocarpine Nitrate
Potassium Bitartrate
Pralidoxime Chloride for Injection
Pravastatin Sodium Tablets
Purified Guggul Extract
Quinapril Tablets
Risedronate Sodium Tablets
Secobarbital Sodium
Sodium Sulfate
Spectinomycin for Injectable Suspension
Stearoyl Macrogolglycerides
Sterile Erythromycin Ethylsuccinate
Streptomycin Injection
Sulfadoxine
Thimerosal
Thioguanine
Tylosin Injection
Vancomycin Hydrochloride
Vancomycin Hydrochloride for Injection
Vasopressin
Vasopressin Injection
Vinblastine Sulfate for Injection
Xylose
Zein

General Chapters

General Chapter/Section(s): <1> Injections/Ingredients
Expert Committee(s): Excipient Monographs 2/General Chapters–Parenteral Products Industrial
No. of Commenters: 3
Comment Summary #1: The commenters suggested three changes to *Aqueous vehicles:* 1) use the *Coulometric Karl Fisher titration* method, which is more suitable for determination of low water contents, 2) allow the use of commercial *Karl Fisher Reagents*, and 3) remove chloroform due to its toxicity.
Response: Comments incorporated. The Expert Committee revised the *Water* method from *Method Ia* to *Method Ic* (*Coulometric Karl Fisher titration*) and deleted a proposed solvent.
Comment Summary #2: In the *Limit of copper, iron, lead, and nickel* test, a commenter indicated that metal catalysts are not used in unhydrogenated oils manufacturing and therefore nickel is not likely to be an impurity.
Response: Comment incorporated. The Expert Committee clarified the impurities requirements by adding a *Note* to the *Limit of copper, iron, lead and nickel* test.

General Chapter/Section(s): <207> Test for 1,6-Anhydro Derivative for Enoxaparin Sodium/Multiple Sections
Expert Committee(s): Biologics and Biotechnology–Blood and Blood Products
No. of Commenters: 3
Comment Summary #1: The commenters indicated that the equation provided to calculate the mole percent of components containing a 1,6-anhydro structure is not correct.
Response: Correction incorporated.
Comment Summary #2: The commenter indicated the assumption is not accurate that all species observed in the chromatogram have an equivalent response factor.
Response: Comment not incorporated because the assumption is based on an equivalent molar response factor.
Comment Summary #3: The commenters suggested adding a chromatogram with annotation.
Response: Comment incorporated. A reference chromatogram will be provided with the instructions for use of the relevant USP Reference Standards.
Comment Summary #4: The commenters suggested adding the following additional Reference Standards: 1) a control Enoxaparin Reference Standard that can be digested and chromatographed as part of system suitability, and 2) a disaccharide solution containing the ΔIS 1,6-anhydro and the ΔIS-IS 1,6-anhydro compounds.
Response: Comment incorporated to include the control Enoxaparin Sodium Reference Standard (RS). The disaccharide compounds are commercially available as reagents.
Comment Summary #5: The commenter suggested that the depolymerization suitability specification was not met.
Response: Comment not incorporated because submitted results were obtained on the formulated drug product. The results clearly indicate an incomplete depolymerization. It

is recommended that this test be performed on the Active Pharmaceutical Ingredient (API) rather than drug product.
Comment Summary #6: The commenters indicated that the column specified in the procedure should be removed from the General Chapter because the column is no longer manufactured.
Response: Comment not incorporated because the appropriate column is commercially available.
Comment Summary #7: The commenters indicated that the quality of the heparinases is one of the major uncontrolled variables and therefore suggested that USP could either qualify such materials or provide them as Reference Standards.
Response: Comment not incorporated because the quality of heparinases is controlled by the system suitability requirements described in the procedure.
Comment Summary #8: The commenter suggested including High Performance Liquid Chromatography (HPLC) system parameters in order to ensure reproducible results between laboratories.
Response: Comment not incorporated because the USP Enoxaparin Sodium Reference Standard and the associated reference chromatogram provide the appropriate controls for reproducible results between laboratories.
Comment Summary #9: The commenter indicated that the concentration of acetic acid used in the method is not specified.
Response: Comment incorporated to specify glacial acetic acid.
Comment Summary #10: The commenter indicated that the storage conditions for material after depolymerization are not specified.
Response: Comment incorporated to specify storage conditions.
Comment Summary #11: The commenter indicated that the volume specified for exposure to sodium borohydride is difficult to transfer to an HPLC vial because foaming occurs upon mixing; therefore, the sample requires centrifuging before transferring to the HPLC vial.
Response: Comment not incorporated because gentle mixing minimizes foaming.
Comment Summary #12: The commenter suggested including requirements for expiration dates and storage conditions for mobile phases, buffers, and enzyme cocktail.
Response: Comment not incorporated because expiration dates and storage conditions are manufacturing documentation and labeling requirements for regulated products.

General Chapter/Section(s): <467> Residual Solvents/Other Analytical Procedures
Expert Committee(s): General Chapters
No. of Commenters: 1
Comment Summary #1: The commenter indicated retaining *Methods I, IV, V, and VI* because the *Methods* are used to quantitate residual solvents in approved marketed products.
Response: Comment not incorporated because no supporting data was provided, indicating that these methods provide the necessary specificity and sensitivity for quantitation of the solvents listed in the current version of General Chapter <467> Residual Solvents.

General Chapter/Section(s): <621> Chromatography/System Suitability
Expert Committee(s): General Chapters
No. of Commenters: 1
Comment Summary #1: The commenter indicated that the proposed flow rate adjustments in High Performance Liquid Chromatography (HPLC) implies the flow rate can be adjusted an additional ±50% after changing to a column with a different internal diameter, regardless of the linear velocity.
Response: Comment not incorporated. The proposed change was intended to allow more latitude in the adjustment of flow rate after an ID column change.

General Chapter/Section(s): <643> Total Organic Carbon/Multiple Sections
Expert Committee(s): General Chapters–Pharmaceutical Waters
No. of Commenters: 2
Comment Summary #1: The commenter suggested removing the following sentence from the *Introduction* because no supporting documentation was provided: "In addition to other requirements listed below, the *System suitability test* is the challenge to the total organic carbon instrument."
Response: Comment incorporated.
Comment Summary #2: The commenter suggested removing the proposed sentence, "For both on line and off line measurements, the appropriateness of the instrument for quality control purposes is also dependant on the sampling location(s) in the water system" (under *Apparatus requirement*) because the requirement is redundant and is not within the scope of the *Total organic carbon* procedure.
Response: Comment incorporated with changes to provide clarity and guidance for both on line and off line sampling and release.
Comment Summary #3: The commenter suggested revising *Apparatus requirements* from "sampling instrument" to instead state "water sampling." The final revision would read as follows: "The selected sampling instrument location(s) must reflect the quality of the water used."
Response: Comment incorporated with additional changes to provide clarity and guidance for both on line and off line sampling and release.
Comment Summary #4: The commenter suggested removing the proposed sentence, "The nature of the water production and use should be considered when selecting either off line or on line measurement" (under *Apparatus requirement*) because the nature of the water production and use is outside the scope of the chapter.
Response: Comment incorporated with changes to provide clarity and guidance for both on line and off line sampling and release.
Comment Summary #5: The commenter suggested replacing *Other control solutions* "if necessary" to read "as necessary" because the sentence is too subjective. If incorporated, the text would read: "Prepare appropriate reagent blank solutions or other specified solutions needed for establishing the apparatus baseline or for calibration adjustments following the manufacturer's instructions, and run the appropriate blanks to zero the instrument, as necessary."
Response: Comment not incorporated because no supporting data was provided.
Comment Summary #6: The commenter indicated replacing the *System suitability* formula to calculate *Percent Recovery* instead of *Percent Response Efficiency* because

Percent Response Efficiency will not detect a significant calibration change for an on line total organic carbon instrument.
Response: Comment not incorporated because no supporting data was provided.
Comment Summary #7: The commenter suggested simplifying the *System suitability* mathematical form of the calculation to read as follows: "The *Test solution* meets the requirements if r_u is not more than 0.50 mg as carbon/liter."
Response: Comment not incorporated because no supporting data was provided.
Comment Summary #8: The commenter suggested including commercially available total organic carbon standards as alternatives to the USP Sucrose Reference Standard.
Response: Comment not incorporated because no supporting data was provided. The Expert Committee determined that the USP Reference Standard best meets the current chapter requirements.
Comment Summary #9: The commenter suggested retaining the *Test solution* off line and on line testing because the procedures minimize or detect artifact contamination of total organic carbon samples.
Response: Comment not incorporated because no supporting data was provided. The Expert Committee further clarified off line and on line testing in *Apparatus requirements*.
Expert Committee-initiated Change #1: The Expert Committee clarified the *Introduction* to read as follows: "(total carbon is the sum of organic carbon and inorganic carbon)."
Expert Committee-initiated Change #2: The Expert Committee revised the *Introduction* from "oxidization" to read "oxidation."

General Chapter/Section(s): <785 > Osmolality and Osmolarity/ Measurement of Osmolality
Expert Committee(s): General Chapters
No. of Commenters: 1
Comment Summary #1: The commenter indicated that permitting commercially-available standard solutions allows greater flexibility while maintaining adequate calibration.
Response: Comment incorporated.

General Chapter/Section(s): <891> Thermal Analysis/Multiple Sections
Expert Committee(s): General Chapters
No. of Commenters: 2
Comment Summary #1: The commenter suggested removing the *Boiling method* from *Table 1* because boiling is not common practice for converting liquid to gas.
Response: Comment incorporated.
Comment Summary #2: The commenter suggested removing the direction of the temperature change requirement because the requirement is addressed when the initial temperature, heating rate and final temperature are set into the instrument before operation.
Response: Comment not incorporated because the direction of the temperature change requirement indicates either a heating rate or a cooling rate.

Comment Summary #3: The commenter suggested clarifying and standardizing the direction of exotherms between *Figure 1 Thermogram* and *Figure 2 Superimposed thermograms illustrating the effect of impurities on DSC melting peak shape*.
Response: Comment incorporated with changes. *Figure 2* was revised with the endotherm down to match *Figure 1*.
Comment Summary #4: The commenter indicated revising the *Eutectic impurity analysis* to provide units in the modified *van't Hoff* equation and in *Equation 3*. The units should be: J/mol for melting range (ΔH_f), J/mol × kelvins for gas constant (R) and kelvins for absolute temperature (T).
Response: Comment incorporated.
Comment Summary #5: The commenter indicated the *Eutectic impurity analysis* should additionally include the pre-existing conditions to determine which materials can use the *van't Hoff* calculations to determine impurities.
Response: Comment incorporated with changes for further clarification.
Comment Summary #6: The commenter indicated *Transition and melting point temperature* should retain the paragraph beginning with the sentence: "A complete description of the conditions employed …"
Response: Comment incorporated with changes. The text was reinserted under *Reporting results of instrumental methods*.
Comment Summary #7: The commenter suggested incorporating an additional column to the *Table 1* that indicates whether the event is endothermic or exothermic.
Response: Comment incorporated with changes. *Table 1* was revised with a new column indicating the heating cycle.
Comment Summary #8: The commenter suggested standardizing the heating rates required in the *Determination of transition temperature* test and the *Melting point temperature* test.
Response: Comment incorporated.
Comment Summary #9: The commenter suggested standardizing the terms "peak" and "vertex" rather than using the terms interchangeably.
Response: Comment not incorporated because the terms in the chapter were defined to accommodate both peak and vertex, as appropriate.

General Chapter/Section(s): <1090> Assessment of Drug Product Performance–Bioavailability, Bioequivalence, and Dissolution/Multiple Sections
Expert Committee(s): Biopharmaceutics
No. of Commenters: 1
Comment Summary #1: The commenter suggested including pharmaceutical alternatives as possible interchangeable pharmaceutical product as described in the World Health Organization (WHO) guidelines.
Response: Comment not incorporated because the U.S. Food and Drug Administration (FDA) requires pharmaceutical equivalence as an element of therapeutic equivalence, in contrast to the WHO guidelines.
Comment Summary #2: The commenter indicated that *Bioequivalence* study sample size should be based on statistical analysis and a lower limit should be defined.
Response: Comment incorporated.

Comment Summary #3: The commenter suggested in *Immediate-release drug products* revising a sampling truncation at 72 hours for drugs with long elimination half-life.
Response: Comment incorporated.
Comment Summary #4: The commenter suggested removing mention under *Immediate-release drug products* of a requirement for bioequivalence and bioavailability in food effect studies if the marketing label discloses that concomitant food administration does not influence the bioavailability of the drug product.
Response: Comment not incorporated because a claim of no food effect implies a demonstration.
Comment Summary #5: The commenter indicated *Orally administered drug products, not for systemic effect* should clarify when systemic monitoring may be needed.
Response: Comment incorporated.
Comment Summary #6: The commenter indicated under *Bioequivalence studies,* the subject's data can be used in all pharmacokinetic measurements and calculations if the pre-dose drug substance concentration is less than or equal to 5 percent of the maximum drug concentration (C_{max}) value.
Response: Comment incorporated.
Comment Summary #7: The commenter suggested expanding *Bioequivalence studies* to include description of food effect study conditions (e.g., high fat, high calorie meals).
Response: Comment incorporated.
Comment Summary #8: The commenter suggested adding a requirement in *Bioequivalence studies* that study subjects consume identical meals within a pre-specified time.
Response: Comment incorporated.
Comment Summary #9: The commenter suggested revising the *Statistical Analysis* requirement for testing the sequence effect because the test is not current practice.
Response: Comment not incorporated because no supporting data was provided.
Comment Summary #10: The commenter suggested revising *Statistical analysis*: "In other words, data from BE studies should have a normal distribution."
Response: Comment not incorporated and the sentence was deleted.
Comment Summary #11: The commenter suggested in the *Two one-sided tests procedure* revising the term "significant difference" to read "important difference."
Response: Comment incorporated.
Comment Summary #12: The commenter suggested clarifying the comparison for area under the cureve (AUC) and maximum concentration (Cmax) by adding "of the T product."
Response: Comment incorporated.
Comment Summary #13: The commenter indicated *Dissolution profile comparison* should calculate the similarity factor (f_2) using no more than one data point that exceeds 85% dissolved.
Response: Comment incorporated.
Comment Summary #14: The commenter suggested clarifying in *Biowaver* the in vitro dissolution (equivalence) test is considered more stringent and reliable than the in vivo bioequivalence test.
Response: Comment was incorporated by deleting the sentence.

Comment Summary #15: The commenter suggested that *Biowaiver based on the pharmaceutical dosage form* should waive in vivo comparative bioavailability or bioequivalence testing if the reference product is a solid oral immediate-release product and the test product is a solution.
Response: Comment not incorporated because the sentence was deleted.
Comment Summary #16: The commenter suggested *Biowaiver based on dosage form proportionality* should require both the lower and higher strengths in the linear pharmacokinetic range.
Response: Comment incorporated.
Comment Summary #17: The commenter suggested deleting in vitro dissolution study information from *Biowaver based on the biopharmaceutics classification system* because dissolution is not described as one of the three major factors that govern the rate and extent of drug absorption from immediate-release dosage forms.
Response: Comment not incorporated because the dissolution characteristics of a dosage form needs to be evaluated when a biowaver is being considered.
Expert Committee-initiated Change #1: The Expert Committee removed the "distribution" and "clearance profile" of the systemic drug exposure in *Bioavailability, bioequivalence, and dissolution*.
Expert Committee-initiated Change #2: The Expert Committee clarified the *Bioequivalence* example methods for pharmacokinetic studies in humans and for other pharmacokinetic method types.

Monographs

Monograph/Section(s): Azithromycin for Injection/Multiple Sections
Expert Committee(s): Monograph Development–Antibiotics
No. of Commenters: 4
Comment Summary #1: The commenter suggested revising the *Bacterial endotoxins limit* from "0.35 EU per mg" to "0.7 EU per mg" based on the maximum daily drug substance dose.
Response: Comment incorporated.
Comment Summary #2: The commenter suggested revising the *pH* range from "between 6.4 and 6.8, as determined in a solution reconstituted in the labeling" to read as follows: "between 6.0 and 7.0, after reconstitution in sterile water for injection to yield an approximately 50 mg per mL solution."
Response: Comment not incorporated because the current pH range reflects approved marketed product.
Comment Summary #3: The commenter suggested replacing the *Assay*, *related compounds* test and the *Limit of azithromycin N-oxide* test with methods based on *European Pharmacopoeia* tests for azithromycin.
Response: Comment not incorporated because no supporting data was provided. The Expert Committee is willing to consider future changes upon receipt of supporting data.
Comment Summary #4: The commenter suggested revising the *Related compound*s test solution and the *Assay preparation* test solution to use 10 vials instead of 3 vials.
Response: Comment incorporated.

Comment Summary #5: The commenter suggested deleting the specifications for specifically-identified synthetic process impurities because the synthetic process impurities are controlled in the drug substance.
Response: Comment incorporated.
Comment Summary #6: The commenter suggested revising the acceptance criteria for the impurities in the *Related compounds* test to the limits specified in the drug substance monograph.
Response: Comment not incorporated because the current acceptance criteria reflect approved marketed product.
Comment Summary #7: The commenter suggested revising the *Related compounds limit* for Desosaminylazithromycin from “0.3%” to “0.7%.”
Response: Comment not incorporated because the current test limit reflects the acceptance criteria for the approved marketed product.
Comment Summary #8: The commenter suggested revising the limit for N-demethylazithromycin in the *Related compounds* test from “0.7%” to “1.0%.”
Response: Comment incorporated.
Comment Summary #9: The commenter suggested revising the limit for *Total impurities* in the *Related compounds* test from “3.0%” to “4.0%.”
Response: Comment not incorporated because current limit reflects the acceptance criteria for the approved marketed product.
Comment Summary #10: The commenter suggested adding the chemical name for *Azaerythromycin A* as a footnote to *Related compounds* test, *Table 1.*
Response: Comment incorporated.
Comment Summary #11: The commenter suggested replacing the *Limit of azithromycin N-oxide* and *Related compounds* tests with a different validated test for *Related compounds*.
Response: Comment not incorporated because no supporting data was provided. The Expert Committee is willing to consider future changes upon receipt of supporting data.
Expert Committee initiated change #1: The Expert Committee updated the *Related compounds* test and *Assay* chromatographic column type to L67, which is the new number assigned to the column.
Expert Committee initiated change #2: The Expert Committee revised the limit for N-Demethylazithromycin in the *Related compounds* test from “0.7%” to “1.0%.”

Monograph/Section(s): Azithromycin Tablets/Multiple Sections
Expert Committee(s): Monograph Development–Antibiotics
No. of Commenters: 2
Comment Summary #1: The commenter suggested including a pH adjustment for *Solution A* in the *Related compounds* test.
Response: Comment not incorporated because no supporting data was provided. The Expert Committee is willing to consider future changes upon receipt of supporting data.
Comment Summary #2: The commenter suggested revising the relative response factors in the *Related compounds* test since they differ from those provided in the drug substance monograph that was published in *Pharmacopeial Forum* 34(3) [May-June 2008].

Response: Comment not incorporated. The relative response factors are different between the drug substance monograph and the drug product monograph because the methods are different between the two monographs.
Comment Summary #3: The commenter suggested adding a Reference Standard containing a mixture of related compounds for peak identification to the *Related compounds* test.
Response: Comment not incorporated because no supporting data was provided. The Expert Committee is willing to consider future changes upon receipt of supporting data.
Comment Summary #4: The commenter indicated providing a relative response factor for 3'-*N*-{[4-(Acetylamino)phenyl]sulfonyl}-3'-demethylazithromycin to prevent the overestimation of this impurity in the *Related compounds* test.
Response: Comment not incorporated because the current requirements reflect the approved marketed product.
Comment Summary #5: The commenter suggested providing a combined specification for 14-demethyl-14-(hydroxymethyl) azithromycin and desosaminylazithromycin in the *Related compounds* test.
Response: Comment not incorporated the current *Related compounds* test reflect the approved marketed product.
Comment Summary #6: The commenter suggested revising the acceptance criteria in the *Related compounds* test to harmonize this monograph with the limits stated in the *European Pharmacopoeia* monograph for this drug.
Response: Comment not incorporated because the current limits reflect the acceptance criteria in the approved marketed product.
Comment Summary #7: The commenter submitted an 'Intent to Comment' letter.
Response: Comment not incorporated because no supporting data was provided. The Expert Committee is willing to consider future changes upon receipt of supporting data.

Monograph/Section(s): Behenoyl Polyoxylglycerides/Water
Expert Committee(s): Excipient Monographs 2
No. of Commenters: 1
Comment Summary #1: The commenter indicated the *Water* should be increased from "0.5%" to "1.0%" for all the polyoxylglyceride monographs because polyoxyglycerides are highly hydroscopic.
Response: Comment incorporated.

Monograph/Section(s): Citalopram Hydrobromide/Related Compounds Test 2
Expert Committee(s): Monograph Development–Psychiatrics and Psychoactives
No. of Commenters: 2
Comment Summary #1: The commenter suggested including a *Note* to indicate the location of the bromide peak and the clear instructions to disregard this peak.
Response: Comment incorporated.
Comment Summary #2: The commenter suggested three revisions: 1) increase the limit of *Citalopram Related Compounds A, C, D, G,* and *H* from "0.10%" each to "0.15%" each, 2) revise the limit of any individual unspecified impurity from "0.10%" to "0.1%," and 3) increase the limit for total specified and unspecified impurities from "0.50%" to "0.75%."

Response: Comment incorporated.

Monograph/Section(s): Cloprostenol Injection/Multiple Sections
Expert Committee(s): Veterinary Drugs
No. of Commenters: 1
Comment Summary #1: The commenter indicated that under *Related compounds* test, the proposed limit of "NMT 0.1% of any individual impurity" is too restrictive and does not reflect the quality of the product available on the market. The commenter requested increasing the limit of any individual impurity to "NMT 1.0%."
Response: Comment incorporated.
Comment Summary #2: The commenter requested adding a *Standard solution* containing 0.1mg/mL of cloprostenol sodium to the *Related compounds* test, and to rename the solution containing cloprostenol sodium and hydrocortisone acetate as "system suitability solution," to be used for both the *Related compounds* and *Assay* tests.
Response: Comment incorporated.
Summary #3: The commenter requested a correction to the calculations under *Related compounds* test, to take the concentrations of the *Standard solution* and *Test solution* into account.
Response: Comment incorporated.
Summary #4: The commenter requested a correction to the calculation under *Assay*, to take into account different molecular weights of the cloprostenol and its sodium salt.
Response: Comment incorporated.

Monograph/Section(s): Cloprostenol Sodium/Multiple Sections
Expert Committee(s): Veterinary Drugs
No. of Commenters: 4
Comment Summary #1: The commenters indicated that under *Chromatographic purity* test, the proposed limit of "not more than 0.1% of any individual impurity" is too restrictive and does not reflect the quality of the material available on the market. The commenters requested increasing the limit of any individual impurity to "not more than 1.0%," and also requested adding a note to disregard any peak below 0.05%.
Response: Comment incorporated.
Comment Summary #2: The commenter suggested to correct the packaging included in the *Packaging and storage* section to indicate that the material needs to be stored in tight and light-resistant containers.
Response: Comment incorporated.

Monograph/Section(s): Cottonseed Oil/Multiple Sections
Expert Committee(s): Excipient Monographs 2
No. of Commenters: 4
Comment Summary #1: The commenters indicated revising Fatty Acid Composition specification ranges for the following: myristic acid (C14:0), palmitic acid (C16:0), oleic acid (C18:1), linolenic acid (C18:3), arachidic acid (C20:0), erucic acid (C22:1), and lignoceric acid (C24:0).
Response: Comment incorporated.

Expert Committee-initiated Change #1: The Expert Committee made two changes to the *Water* method: 1) revise "*Method Ia"* to "*Method Ic"* (C*oulometric Karl Fisher titration*), and 2) delete a proposed solvent.
Expert Committee-initiated Change #2: The Expert Committee clarified *Other requirements* to now read "injectable dosage forms," which are specified in *Labeling*.

Monograph/Section(s): Ecamsule Solution/Multiple Sections
Expert Committee(s): Monograph Development–Ophthamology, Oncology and Dermatology
No. of Commenters: 2
Comment Summary #1: The commenter suggested changing *Identification test B* "maxima" to "maximum" because the multiple maxima in a range of 4 nm for ultraviolet bands are not likely.
Response: Comment incorporated.
Comment Summary #2: The commenter suggested changing the concentration of silver nitrate from "0.1 N" to "0.01 N" for the *Limit of chloride* test in order to be consistent with General Chapter <541> Titrimetry.
Response: Comment incorporated.
Expert Committee-initiated Change #1: The Expert Committee revised *Related compounds*, *Table 1* relative retention times to use average values.

Monograph/Section(s): Enrofloxacin/Related Compounds Test 1
Expert Committee(s): Veterinary Drugs
No. of Commenters: 1
Comment Summary #1: The commenter suggested correcting the mixing order under the *Developing solvent mixture*. The commenter observed that when the components of the *Developing solvent mixture* were mixed in the order listed in *Pharmacopeial Forum* 34(4) [July-Aug. 2008], the mixture did not form two layers. However, if the mixing order was "butyl acetate, n-butanol, water, and glacial acetic acid," two distinct layers were observed.
Response: Comment incorporated and a *Note* was added to emphasize that the mixing order should be carefully followed.

Monograph/Section(s): Fexofenadine Hydrochloride and Pseudoephedrine Hydrochloride Extended/Multiple Sections
Expert Committee(s): Monograph Development–Pulmonary and Steroids
Expert Committee-initiated Change #1: The Expert Committee made two changes to the *Assay stock preparation*: 1) add a *Note* to consider centrifuging the stock solution if the excipients cannot be filtered, and 2) indicate the specific supernatant.

Monograph/Section(s): Fludarabine Phosphate for Injection/Related Compounds
Expert Committee(s): Monograph Development–Ophthamology, Oncology and Dermatology
Expert Committee-initiated Change: The Expert Committee corrected *Test B (Late-eluting impurities)* injection volume from "10 mL" to "10 µL."

Monograph/Section(s): Granisetron Hydrochloride Injection/Multiple Sections
Expert Committee(s): Monograph Development–Gastrointestinal, Renal and Endocrine
No. of Commenters: 1
Comment Summary #1: At the time of the comment (August 2008), USP Granisetron Related compound C RS was not available, and the Commenter suggested generating this impurity in the solution by exposure to sunlight or ultraviolet radiation.
Response: Comment not incorporated. The USP Reference Standards for all granisetron related compounds are now available.
Comment Summary #2: The commenter requested to revise the concentration of the *Standard* and *Assay preparations* under *Assay* from "(1.1 x L)" to "(0.11 x L)" to achieve a better peak shape. The same change is also proposed for the *Standard solution* under *Related compounds*.
Response: Comment incorporated.
Committee-initiated Change #1: The Expert Committee noticed that the monographs for Granisetron Hydrochloride Injection and Granisetron Hydrochloride Tablets utilize similar chromatographic systems but the requirement for column efficiency is more stringent in the proposed *Granisetron Hydrochloride Injection* Monograph. Based on this, the Expert Committee agreed to delete the requirement for column efficiency under the *Assay*.

Monograph/Section(s): Itraconazole/Related Compounds
Expert Committee(s): Monograph Development–Antivirals and Antimicrobials
No. of Commenters: 1
Comment Summary #1: The commenter indicated impurities should be identified as either "specified" or "unspecified."
Response: Comment incorporated.
Comment Summary #2: The commenter suggested adding the specified impurities with their corresponding limit of 0.5% each: 4-methoxy derivative, 4-triazolyl isomer, propyl analog, isopropyl analog, epimer, *n*-butyl isomer and didioxolanyl analog.
Response: Comment incorporated.

Monograph/Section(s): Losartan Potassium Tablets/Multiple Sections
Expert Committee(s): Monograph Development–Cardiovascular
No. of Commenters: 2
Comment Summary #1: The commenter suggested deleting the *Uniformity of dosage units* test procedure.
Response: Comment not incorporated because the current *Uniformity of dosage units* procedure reflects approved marketed product. General Chapter <905> Uniformity of Dosage Units defaults to the *Assay* procedure.
Comment Summary #2: The commenter suggested neutralizing the pH of *Stock system suitability solution* using 0.1 N hydrochloride or 0.1 N sodium hydroxide.
Response: Comment incorporated.
Comment Summary #3: The commenter indicated adding acetonitrile to the *Stock system suitability solution* after the neutralization step should improve the solubility of losartan potassium. The current procedure results in a cloudy solution.

Response: Comment not incorporated because the stock system suitability solution will become clear during the system suitability solution preparation. The Expert Committee added a *Note* to the *Stock system suitability solution* explaining the solution may be cloudy during preparation.
Comment Summary #4: The commenter suggested revising the *System suitability preparation* from "Add 7 mL of *Stock system suitability preparation* to 3 mL of acetonitrile" to read as follows: "Add 3 mL of acetonitrile to 7 mL of *Stock system suitability preparation* to clear the cloudy solution."
Response: Comment incorporated.

Monograph/Section(s): Mesna/Mulitple Sections
Expert Committee(s): Monograph Development–Cough, Cold and Analgesics
No. of Commenters: 0
Expert Committee-initiated Change #1: The Expert Committee deleted the *Limit of sulfate* and *Related compounds* sections. The sections will be replaced after the *Standard solution* is revised and the *Related compounds* test corrects for response factors for the three respective impurities.

Monograph/Section(s): Midazolam/Chromatographic Purity
Expert Committee(s): Monograph Development–Pulmonary and Steroids
No. of Commenters: 1
Comment Summary #1: The commenter requested changing the relative response factor for desfluoromidazolam from "0.5" to "1.0."
Response: Comment incorporated.
Comment Summary #2: The commenter suggested replacing the L60 column with an L1 column.
Response: Comment not incorporated because no supporting data was provided. The Expert Committee is willing to consider future changes upon receipt of supporting data.
Expert Committee-initiated Change #1: The Expert Committee made two changes: 1) corrected the *Table 1* chemical name of the 6*H*-isomer impurity and 2) corrected the chemical names of Midazolam and other impurities.

Monograph/Section(s): Mirtazapine/Related Compounds
Expert Committee(s): Monograph Development–Psychiatrics and Psychoactives
No. of Commenters: 1
Comment Summary#1: The commenter suggested the use of relative response factor instead of relative retention time in the calculation.
Response: Comment incorporated.

Monograph/ Section(s): Moxifloxacin Ophthalmic Solution/Related Compounds
Expert Committee (s): Monograph Development–Antivirals and Antimicrobials
No. of Commenters: 1
Comment Summary #1: The commenter suggested revising the relative response factor for decarboxy compound from "0.1" to "0.13" to ensure the required two decimal places in the Moxifloxacin Ophthalmic Solution Monograph are consistent with other

USP Monographs with relative response factor requirements, which indicate two decimal places if the value is less than 1.0.
Response: Comment incorporated.

Monograph/Section(s): Mupirocin Nasal Ointment/Related compounds test
Expert Committee(s): Monograph Development–Antibiotics
No. of Commenters: 1
Comment Summary #1: The commenter indicated that the related compounds chemical names listed in the footnotes should be revised to match *Related compounds*, *Table 1.*
Response: Comment incorporated.

Monograph/Section(s): Norethindrone Acetate/Chromatographic Purity
Expert Committee(s): Monograph Development–Pulmonary and Steroids
No. of Commenters: 0
Expert Committee-initiated Change #1: The Expert Committee clarified the *Test 1* requirement for the total impurities in thin-layer chromatography (TLC). The requirement was changed from "The sum of the intensities of all of the secondary spots is not more intense than the spot in the chromatogram obtained from Standard solution A: not more than 1.5% of total impurities is found" to read as follows: "Any individual secondary spot is not more intense than the spot in the chromatogram obtained from Standard solution B: not more than 0.5% of any individual impurity is found, and the total of impurities found is not more than 1.5%."

Monograph/Section(s): Octisalate/Assay
Expert Committee(s): Monograph Development–Ophthamology, Oncology and Dermatology
No. of Commenters: 1
Comment Summary #1: The commenter indicated the column phase designation in the *Chromatographic Reagent Database* should be changed from "G2" to "G1" to be consistent with the Monograph.
Response: Comment incorporated.

Monograph/Section(s): Ondansetron Tablets/Definition
Expert Committee(s): Monograph Development–Psychiatrics and Psychoactives
No. of Commenters: 1
Comment Summary #1: The commenter suggested revising the *Definition* to clarify hydrochloride salt is the active ingredient.
Response: Comment incorporated.

Monograph/Section(s): Oxaliplatin/Multiple Sections
Expert Committee(s): Monograph Development–Ophthamology, Oncology and Dermatology
No. of Commenters: 3
Comment Summary #1: The commenter suggested changing the *Limits* of Oxalic acid, (SP-4-2)-Diaqua[(1R,2R)-cyclohexane-1,2-diamine-N,N']platinum, Oxaliplatin related compound C, Oxaliplatin related compound D and unspecified impurity.
Response: Comment not incorporated because the limits in the monograph reflect the approved specifications for the marketed approved product.

Monograph/Section(s): Palm Oil/Multiple Sections
Expert Committee(s): Excipient Monographs 2
Expert Committee-initiated Change #1: The Expert Committee revised the *Introduction* by adding "and" between *Test A and Test B* to clarify that both tests are required to identify this oil.
Expert Committee-initiated Change #2: The Expert Committee made two changes to the *Water* method: 1) revise "*Method Ia"* to "*Method Ic"* (*Coulometric Karl Fisher titration*), and 2) delete a proposed solvent system.
Expert Committee-initiated Change #3: The Expert Committee deleted the requirement for "freshly distilled" acetone because acetone is commercially available in suitable grades.

Monograph/Section(s): Piperacillin and Tazobactam for Injection/Multiple Sections
Expert Committee(s): Monograph Development–Antibiotics
No. of Commenters: 2
Comment Summary #1: The commenter suggested revising the *pH* range from "5.5 to 6.8 (200 mg/mL solution)" to the range of "5.0 – 7.0 (40 mg/mL solution)" originally proposed in *Pharmacopeial Forum* 31(2) [Mar.-Apr. 2005].
Response: Comment not incorporated because the current pH range reflects the approved marketed product.
Comment Summary #2: The commenter suggested implementing the *Particulate matter* procedures that were proposed in *Pharmacopeial Forum* 31(2) [Mar.-Apr. 2005] instead of the procedures that were proposed in *Pharmacopeial Forum* 34(4) [July-Aug. 2008].
Response: Comment not incorporated because the current particulate matter acceptance criteria reflect the approved marketed product.
Comment Summary #3: The commenters suggested different validated procedures for the *Related compounds* method.
Response: Comments not incorporated because no supporting data was provided. The Expert Committee is willing to consider future changes upon receipt of supporting data.
Comment Summary #4: The commenter suggested revising the acceptance criteria for the *Related compounds* test to match the International Conference Harmonization (ICH) guidelines and also based on data from production-scale batches.
Response: Comment not incorporated because the current *Related compounds* acceptance criteria reflect approved marketed product.

Comment Summary #5: The commenter suggested implementing the *Assay* method proposed in *Pharmacopeial Forum* 31(2) [Mar.-Apr. 2005] instead of the *Assay* method that was proposed in *Pharmacopeial Forum* 34(4) [July-Aug. 2008].
Response: Comment not incorporated because no supporting data was provided. The Expert Committee is willing to consider future changes upon receipt of supporting data.

Monograph/Section(s): Risedronate Sodium/Multiple Sections.
Expert Committee(s): Monograph Development–Gastrointestinal, Renal and Endocrine
No. of Commenters: 4
Comment Summary #1: The commenter suggested updating the Chemical Abstracts Service (CAS) number for the hemi-pentahydrate form.
Response: Comment incorporated.
Comment Summary #2: Commenter suggested tightening the *Heavy metals* limit.
Response: Comment not incorporated. The limit included in the Monograph (NMT 20 ppm) is consistent with the specifications currently approved by the U.S. Food and Drug Administration.
Comment Summary #3: The commenters suggested using *Volumetric Karl Fisher titration* rather than *Coulometric Karl Fisher titration* when testing for drug substances which that contain 11.9-13.9% of water.
Response: Comment not incorporated. The Expert Committee noted that bisphosphonates are potent drugs, and the use of the *Coulometric Karl Fisher titration* allows a reduction in the sample size, thereby minimizing exposure to these drugs.

Monograph/Section(s): Silicified Microcrystalline Cellulose/Particle Size Distribution
Expert Committee(s): Excipient Monographs 2
No. of Commenters: 1
Comment Summary #1: The commenter suggested a *Note* that would indicate when tests would need performed for functional or product performance purposes.
Response: Comment not incorporated because the test only needs performed if indicated in the Certificate of Analysis, which is consistent with the *Labeling* requirement.

Monograph/Section(s): Soybean Oil/Multiple Sections
Expert Committee(s): Excipient Monographs 2
No. of Commenters: 4
Comment Summary #1: The commenters indicated revising *Fatty Acid Composition* specification ranges for the following: stearic acid (C18:0), oleic acid (C18:1), behenic acid (C22:0), erucic acid (C22:1), and lingnoceric acid (C24:0).
Response: Comment incorporated. The Expert Committee made two types of revisions to the respective fatty acids: 1) revise the following specification ranges to harmonize with current *European Pharmacopoeia* specification ranges: stearic acid (C18:0), oleic acid (C18:1), and behenic acid (C22:0), and 2) revise the following specification ranges to align with the *Codex Alimentarius*: erucic acid (C22:1) and lingnoceric acid (C24:0).
Comment Summary #2: A commenter suggested deleting the specifications for erucic acid (C22:1) and lingnoceric acid (C24:0).

Response: Comment not incorporated because the specifications are used as safety controls during the manufacturing process.
Comment Summary #3: The commenters suggested increasing the higher *Unsaponifiable matter limit* to "not more than 1.5%" because the higher limit would match the current *European Pharmacopoeia* specification and would also align the limit with the proposed in General Chapter <1> Injections.
Response: Comment incorporated.
Comment Summary #4: The commenter suggested the Monograph should defer to the *Peroxide value* specifications stated in General Chapter <401> Fats and Fixed Oils.
Response: Comment incorporated.
Comment Summary #5: The commenters indicated two revisions: 1) the *Coulometric Karl Fisher titration* method is more suitable for determination of low water contents, and 2) commercial *Karl Fisher Reagents* should be included in the Monograph.
Response: Comments incorporated. The Expert Committee made two changes to the *Water* method: revise "*Method Ia"* to "*Method Ic"* (*Coulometric Karl Fisher titration*), and 2) delete a proposed solvent.
Comment Summary #6: The commenter indicated "freshly distilled" acetone should be deleted because acetone is commercially available in suitable grades.
Response: Comment incorporated.

Monograph/Section(s): Sterile Water for Injection/Multiple Sections
Expert Committee(s): General Chapters–Pharmaceutical Waters
No. of Commenters: 0
Expert Committee-initiated Change #1: The Expert Committee incorporated a *Conductivity* test as a measure of ionic control for this sterile water with limits that harmonize with the *European Pharmacopoeia*.
Expert Committee-initiated Change #2: The Expert Committee deleted the "wet chemistry" procedures from the *Ammonia*, *Calcium*, *Carbon dioxide*, *Chloride*, and *Sulfate* tests because the *Conductivity* test is current best practice.
Expert Committee-initiated Change #3: The Expert Committee deleted the requirement for a pH standard because a sample cannot pass the *Conductivity* test and fail the *pH* test.
Expert Committee-initiated Change #4: The Expert Committee retained the test for *Oxidizable substances* with a reduction in the potassium permanganate solution concentration to harmonize with the *European Pharmacopoeia*.

Monograph/Section(s): Tamsulosin Hydrochloride Capsules/Multiple Sections.
Expert Committee(s): Monograph Development–Gastrointestinal, Renal and Endocrine
No. of Commenters: 2
Comment Summary #1: The commenter suggested adding "shake for 1 hour" under *Identification test A* to ensure the analyte is completely extracted.
Response: Comment incorporated.
Comment Summary #2: The commenter suggested adding a filtering step to the *Dissolution* procedure.

Response: Comment not incorporated because the drug is being released from the granules, and is also freely soluble in water.
Comment Summary #3: The commenter suggested a modification in the preparations under the *Dissolution*, to address the aliquot withdrawn for testing at the buffer stage.
Response: Comment not incorporated because the method's internal standard compensates for the aliquot.
Comment Summary #4: The commenter suggested modifying the volumes and compositions of the solutions under *Uniformity of dosage units* and *Assay*.
Response: Comment not incorporated. The Expert Committee noted that the validation data show the acceptable accuracy of the method.
Comment Summary #5: The commenter suggested adding the test for *Related compounds* to the Monograph.
Response: Comment not incorporated. The Expert Committee will consider addressing this comment and revising the Monograph in the future if the necessary supporting data are submitted by the interested parties.

Monograph/Section(s): Terconazole/Multiple Sections
Expert Committee(s): Monograph Development–Antivirals and Antimicrobials
No. of Commenters: 1
Comment Summary #1: The commenter suggested revising the *Assay* acceptance criteria from "98.5%-101.5%" to "98.0%-102.0%" to be consistent with their approved specification.
Response: Comment incorporated.
Comment Summary #2: The commenter suggested revising the *Loss on drying* acceptance criteria from "0.5%" to "0.75%" to be consistent with their approved specification.
Response: Comment incorporated.

Monograph/Section(s): Tramadol Hydrochloride/Multiple Sections
Expert Committee(s): Monograph Development–Cough, Cold and Analgesic
No. of Commenters: 1
Comment Summary #1: The commenter suggested the *Assay* specification retain the original limits of "99.0 to 101.0%" rather than revise to the proposed limits of "98.0 to 102.0."
Response: Comment not incorporated because no supporting data was provided.
Comment Summary #2: The commenter suggested the reintroduction of the *pH* test as an alternative option or replacement to the *Acidity test*.
Response: Comment not incorporated because the *Acidity* test is best current practice.
Comment Summary #3: The commenter suggested retaining the *Assay* titration procedure and not approving the High Performance Liquid Chromatography (HPLC) procedure.
Response: Comment not incorporated because the HPLC procedure is best current practice.
Comment Summary #4: The commenter indicated the *Tramadol Related Compound* B limit should not be increased from "0.1%" to "0.2%."
Response: Comment incorporated.

Expert Committee-initiated Change #1: The Expert Committee removed the test for the *Limit of Tramadol Related Compound B* due to ongoing consideration regarding the acceptance criterion of 0.2%.

Monograph/Section(s): Trehalose/Multiple Sections
Expert Committee(s): Excipient Monographs 1
No. of Commenters: 2
Comment Summary #1: The commenter suggested revising the current assay specification from "NLT 99.0% to include a range of NLT 97.0%" to read "NMT 102.0%" because the NMT 102.0% reflects approved marketed product and would harmonize with the assay specification proposed in the *European Pharmacopoeia*.
Response*:* Comment incorporated.
Comment Summary #2*:* The commenter suggested removing the *Color and clarity of solution* requirement to confirm the concentration of the solution.
Response: Comment incorporated.
Comment Summary #3: The commenter indicated *Heavy metals* should correct the sample amount from "5.0 g" to "4.0 g" to reflect the limit expressed in the acceptance criterion.
Response: Comment incorporated.

Monograph/ Section(s): Valganciclovir Tablets/Multiple Sections
Expert Committee(s): Monograph Development–Antivirals and Antimicrobials
No. of Commenters: 3
Comment Summary #1: The commenter indicated *Assay*, *Related compounds* and *Uniformity of dosage units* should require USP Reference Standard instead of the reagent *Ganciclovir mono-N-Methyl Valinate* because the reagent is not commercially available.
Response: Comment incorporated.