COMMENTARY– *First Supplement to the USP 33-NF 28 Reissue*

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 were received for the following proposals*:**

General Chapters
<1024> Bovine Serum
<1225> Validation of Compendial Methods
<525> Sulfur Dioxide
<729> Globule Size Distribution in Lipid Injectable Emulsions

Monographs
Alpha-Lactalbumin
Atenolol
Diclofenac Sodium Delayed-Release Tablets
Dolasetron Mesylate
Dronabinol Capsules
Egg Phospholipids
Esomeprazole Magnesium
Ethylene Glycol and Vinyl Alcohol Graft Copolymer
Fenofibrate
Fumaric Acid
Levothyroxine Sodium
Meloxicam
Morphine Sulfate Extended-Release Capsules
Nateglinide Tablets
Olopatadine Hydrochloride Ophthalmic Solution
Oxazepam Capsules
Oxybutynin Chloride Extended-Release Tablets

Pectin
Pentamidine Isethionate
Praziquantel Tablets
Primidone
Primidone Tablets
Propoxyphene Hydrochloride Capsules
Propylene Glycol Dilaurate
Psyllium Husk
Salmeterol Xinafoate
Sucrose Palmitate
Sucrose Stearate
Sulfadiazine Tablets
Sulfinpyrazone
Tamsulosin Hydrochloride
Tizanidine Tablets
Topiramate Tablets
Tranylcypromine Tablets
Valproic Acid Capsules
Vitamin A Oral Liquid Preparation
Zinc Gluconate Tablets
Zonisamide

General Chapters

General Chapter/Section: <1> Injections/Foreign and Particulate Matter
Expert Committee(s): Parenteral Products—Industrial
No. of Commenters: 8
Comment Summary #1: The commenters indicated that the new requirement for subcutaneous and intramuscular injection should be deleted because there is no scientific or patient safety reason to require testing. Higher limits may be appropriate for subcutaneous and intramuscular products; and the standard does not address the issues related to biologic materials.
Response: The Parenteral Products—Industrial Expert Committee decided not to delete the new requirement since they considered the limits in General Chapter <788> minimum requirements for any formulation for which the test is applicable. Realizing the need, in some cases, to establish testing and collect product data, USP will delay implementation for one year and, through the appropriate Expert committee, reach out to stakeholders to more completely dimension the potential impact of this change.

General Chapter/Section: <381> Elastomeric Closures for Injections/Introduction
Expert Committee(s): Parenteral Products—Industrial
No. of Commenters: 1
Comment Summary #1: The commenter requested that the seventh paragraph be revised because it asserts that only type I closure can be used for aqueous preparation, which is incorrect.
Response: Comment incorporated by revising the second sentence to “Type I closures are those typically used for aqueous preparations.”

General Chapter/Section: <467> Residual Solvents/Water-Soluble Articles, Procedure A
Expert Committee(s): General Chapters
No. of Commenters: 1

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Comment Summary: A commenter indicated that the solubility of the solvents is affected by ambient conditions. Therefore, the stirring conditions (time and method of agitation) proposed under Class 1 Standard Stock Solution may not be appropriate in all the circumstances.
Response: Comment incorporated.

General Chapter/Section(s): <921> Water Determination/Multiple Sections
Expert Committee(s): General Chapters
No. of Commenters: 1
Comment Summary #1: The commenter suggested changing the *Procedure* in *Method Ia* and *Method Ib* from "transfer 30 to 40 mL of methanol" to "transfer enough methanol … (approximately 30 to 40 mL)" because the goal is to ensure that sufficient solvent is added to cover the electrodes.
Response: Comment incorporated.

General Chapter/Section(s): <788> Particulate Matter in Injections/Introduction
Expert Committee(s): Parenteral Products—Industrial
No. of Commenters: 8
Comment Summary #1: The commenters indicated that the new requirement for subcutaneous and intramuscular injection should be deleted because there is no scientific or patient safety reason to require testing. Higher limits may be appropriate for subcutaneous and intramuscular products; and the standard does not address the issues related to biologic materials.
Response: The Parenteral Products—Industrial Expert Committee decided not to delete the new requirement since they considered the limits in <788> minimum requirements for any formulation for which the test is applicable. Realizing the need, in some cases, to establish testing and collect product data, USP will delay implementation for one year and, through the appropriate Expert Committee, reach out to stakeholders to more completely dimension the potential impact of this change.

Monographs

Monograph /Section(s): Articaine Hydrochloride/Multiple Sections
Expert Committee(s): Monograph Development—Pulmonary and Steroids
No. of Commenters: 2
Comment Summary #1: The commenter requested replacing USP Articaine RS in *Identification Test A* with USP Articaine Hydrochloride RS because the free base is not available.
Response: Comment not incorporated. USP Articaine RS is available.
Comment Summary #2: The commenter requested revising the total impurities criterion in the *Organic Impurities* test to be consistent with the corresponding *European Pharmacopoeia* monograph limit which does not include Articaine related compound A.
Response: Comment incorporated.

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Comment Summary #3: The commenter requested revising the limits for a*ny other impurity* in the *Organic Impurities* test from 0.1% to 0.10% to make the criterion consistent with the corresponding *European Pharmacopeia* monograph.
Response: Comment incorporated.
Comment Summary #4: The commenter requested deleting the *System suitability solution* in the *Organic Impurities* test because the *Standard solution*, which contains Articaine related compound A and Articaine related compound E, can be used to establish the system suitability.
Response: Comment incorporated.
Comment Summary #5: The commenter requested removing Articaine related compound E from the *Standard solution* for the *Organic Impurities* test because this compound is not used in the calculation formula.
Response: Comment not incorporated. The *Standard solution* will be used to evaluate system suitability and Articaine related compound E is required to establish the resolution.
Comment Summary #6: The commenter requested adding a *Note* to the *Assay* to clarify how the volume of titrant is determined.
Response: Comment incorporated. The analysis section was changed to make it consistent with *Titrimetry* <541>.
Comment Summary #7: The commenter indicated that the *Description and solubility* entry has not been published.
Response: The *Description and solubility* entry was published in *Pharmacopeial Forum* 35(3) [May-June 2009], p. 651.
Expert Committee-initiated Change #1: "On the dried basis" was added to the *Acceptance criteria* under *Assay* to make the section consistent with current USP format.
Expert Committee-initiated Change #2: The definition of C_S in the *Organic Impurities* test was corrected from concentration of Articaine Related Compound A in the *Standard solution* (mg/mL) to concentration of USP Articaine Related Compound A RS in the *Standard solution* (mg/mL).

Monograph/Section(s): Atorvastatin Calcium/Multiple Sections
Expert Committee(s): Monograph Development—Gastrointestinal, Renal and Endocrine
No. of Commenters: 8
Comment Summary #1: Three commenters reported poor peak shape (fronting) of atorvastatin related compound B and atorvastatin peaks under the *Assay* and *Organic Impurities*, and were unable to meet the resolution requirement of NLT 1.5. The commenters indicated that the problem is caused by the use of the "strong" solvent (*N*,*N*-Dimethylformamide) as a *Diluent*, and suggested using alternative diluents to achieve a good peak shape.
Response: Comment incorporated. A *Note* is included to allow using an alternative *Diluent* when significant fronting of the atorvastatin related compound B and atorvastatin peaks is observed.

Comment Summary #2: The commenter requested to add a *Note* that the composition of the Mobile phase under the Assay and Organic impurities may be adjusted to achieve a retention time of 26-34 minutes for atorvastatin peak
Response: Comment incorporated.
Comment Summary #3: Two commenters reported that related compound D may undergo transformation equilibrium in the solution, forming a cyclic hemiketal which elutes about 1-2 minutes before atorvastatin related compound D. The commenters suggested reporting the content of atorvastatin related compound D in the test for *Organic Impurities* as the sum of these two peaks.
Response: Comment incorporated.
Comment Summary #4: The commenter requested to change the name of atorvastatin related compound D from "Oxirane Impurity" to "Epoxide Impurity".
Response: Comment incorporated.
Comment Summary #5: The commenter indicated that the proposal published in *PharmEuropa* 21.3 includes an updated method for *Heavy metals*, and requested to incorporate it in the USP monograph.
Response: Comment incorporated.
Comment Summary #6: Two commenters reported difficulties in performing the test for *Content of Calcium*. Commenters indicated that USP monographs usually include only an identification test for a counter ion, and suggested to delete the quantitative test and to replace it with an Identification test for calcium.
Response: Comment incorporated.
Comment summary #7: Four commenters requested that other hydrated and amorphous forms of atorvastatin calcium be included in the monograph, and different *Water* limits be established for them.
Response: Comment not incorporated because the commenters' products have not yet received full FDA approval. The Expert Committee will consider addressing this comment via a Pending revision to the monograph as part of the USP Pending Monographs initiative.

Monograph/Section(s): Carmustine/Multiple Sections
Expert Committee(s): Monograph Development—Ophthalmology, Oncology, and Dermatology
No. of Commenters: 3
Comment Summary #1: The commenter requested changing the column designation in *Organic Impurities Procedure 4* from G14 to G16 to be consistent with the validation.
Response: Comment incorporated.
Comment Summary #2: The commenter requested elimination of the run time in *Organic Impurities Procedure 4* because it is already listed in the temperature program table.
Response: Comment incorporated.
Comment Summary #3: The commenter indicated the limits for any unspecified impurity in *Organic Impurities Procedure 4* and *Procedure 5* should be deleted because these tests employ gas chromatographic procedures with column temperatures up to 200ºC and 210ºC. Carmustine is known to decompose at these conditions and therefore it is not appropriate to include the limits for any unspecified impurity in these procedures.

Response: Comment incorporated.
Comment Summary #4: The commenter suggested including a test of appearance because the changes in appearance may indicate decomposition of the drug substance.
Response: Comment not incorporated because this test is not in the approved application.
Expert Committee-initiated Change: The term “disposable latex surgical gloves” in the *Definition* was replaced with “appropriate surgical gloves” because alternate material is acceptable.

Monograph/Section(s): Carmustine for Injection/Multiple Sections
Expert Committee(s): Monograph Development—Ophthalmology, Oncology, and Dermatology
No. of Commenters: 2
Comment Summary #1: The commenter requested making minor changes in the mobile phase gradient table in *Assay* based on the recent re-validation.
Response: Comment incorporated.
Comment Summary #2: The commenter requested changing the limit of carmustine related compound A in *Organic Impurities* from NMT 0.5% to NMT 1.0% to be consistent with the acceptance criterion for their FDA approved product.
Response: Comment incorporated.
Comment Summary #3: The commenter suggested including a test of appearance because the changes in appearance may indicate decomposition of the drug substance.
Response: Comment not incorporated because this test is not in the approved application.
Expert Committee-initiated Change: The term “disposable latex surgical gloves” in the *Definition* was replaced.

Monograph/Section(s): Epirubicin/Multiple/Sections
Expert Committee(s): Monograph Development—Antibiotics
No. of Commenters: 3
Comment Summary #1: The commenter requested replacing the *Assay* and *Organic Impurities* tests with a single validated procedure.
Response: Comment not incorporated as the commenter’s procedure does not offer significant advantages over the one proposed in PF 35(2) [Mar-Apr 2009].
Comment Summary #2: The commenter requested revising the limit for doxorubicinone in *Organic Impurities*, *Procedure 1* from 1.0% to 0.50%.
Response: Comment not incorporated as the monograph sponsor has approval for the less stringent limit.
Comment Summary #3: The commenter requested revising the limit for doxorubicin in *Organic Impurities*, *Procedure 1* from 1.0% to 0.50%.
Response: Comment not incorporated as the monograph sponsor has approval for the less stringent limit.
Comment Summary #4: The commenter requested revising the limit for any individual unspecified impurity in *Organic Impurities, Procedure 1* from 0.5% to 0.10%.
Response: Comment not incorporated as the monograph sponsor has approval for the less stringent limit.

Comment Summary #5: The commenter requested revising the limit for total impurities in *Organic Impurities, Procedure 1* from 3.0% to 1.0%.
Response: Comment not incorporated as the monograph sponsor has approval for the less stringent limit.
Comment Summary #6: The commenter requested revising the limit for acetone in *Organic impurities, Procedure 2* from 1.5% to 0.2%.
Response: Comment not incorporated as the monograph sponsor has approval for the less stringent limit.
Comment Summary #7: The commenter submitted an 'Intent to Comment' letter.
Response: The Expert Committee is willing to consider future changes to the monograph upon receipt of supporting data.
Comment Summary #8: The commenter requested adding a specific rotation test.
Response: Comment not incorporated. The Expert Committee is willing to consider future changes to the monograph upon receipt of supporting data.

Monograph/Section(s): Fluconazole Injection/Organic Impurities
Expert Committee (s): Monograph Development—Antivirals and Antimicrobials
No. of Commenters: 1
Comment Summary #1: The commenter requested changing the acceptance criteria for the largest unknown non-polar impurity and largest unknown polar impurity to reflect the acceptance criteria for multiple approved products.
Response: Comment not incorporated. The Expert Committee is willing to consider future changes to the monograph upon receipt of supporting data.

Monograph/Section(s): Lamivudine and Zidovudine Tablets/Multiple Sections
Expert Committee (s): Monograph Development—Antivirals and Antimicrobials
No. of Commenters: 3
Comment Summary # 1: The commenter suggested deleting the statement "Pass a portion of the solution through a 0.45 um filter, discarding the first 2-3 mL. Accurately transfer 5.0 mL of the filtrate into a 50-mL volumetric flask, and dilute with *Diluent* to volume" in *Sample stock solution* in the *Assay* because this information is included in the preparation of the *Sample solution*.
Response: Comment incorporated.
Comment Summary # 2: The commenter requested revising the common name of an impurity in *Organic Impurities* test from "Lamivudine-trans" to "Lamivudine diastereomer" to be consistent with the name used for the same impurity in the drug substance (Lamivudine) monograph.
Response: Comment incorporated.
Comment Summary # 3: The commenter requested revising the chemical name of an impurity in the *Organic Impurities* test from "6-Aminopyrimidin-2(1H)-one" to "4-Aminopyrimidin-2(1H)-one" for simpler name (lower locants).
Response: Comment incorporated.

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Monograph/Section(s): Misoprostol/Multiple Sections
Expert Committee(s): Monograph Development—Gastrointestinal, Renal and Endocrine
No. of Commenters: 2
Comment Summary #1: Commenters reported difficulties in obtaining resolution of NLT 1.4 in the HPLC method for *Assay* and *Organic impurities, Procedure 1*. Commenters suggested changing the requirement to NLT 1.2, to be consistent with the requirement in the currently official *European Pharmacopoeia* monograph for Misoprostol.
Response: Comment incorporated.
Comment Summary #2: The commenter recommended adding a diluted solution containing 5 µg/mL of Misoprostol (equivalent to 0.1%) for quantitation of impurities under *Organic impurities, Procedure 1*.
Response: Comment not incorporated. The Expert Committee will consider addressing this comment and revising the monograph in a future PF proposal.
Comment Summary #3: The commenter suggested revising the acceptance criteria for the fraction of the first Diastereomer in the *Organic impurities, Procedure 2: Content of Diastereomers* from "0.51-0.56" to "0.45-0.55", to be consistent with the requirement in the currently official *European Pharmacopoeia* monograph for Misoprostol.
Response: Comment not incorporated. The acceptance criteria included in the monograph are consistent with the sponsor's FDA-approved regulatory filing.

Monograph/Section(s): Olanzapine Tablets/Mulitple Sections
Expert Committee(s): Monograph Development—Psychiatrics and Psychoactives
No. of Commenters: 2
Comment #1: The commenter requested the addition of the word "about" in the *Assay* to avoid misinterpretation of the RRT as a requirement.
Response: Comment not incorporated because the *Chromatography* <621> states that RRT values are for informational purpose only. Redesign addresses this by appropriate placement.
Comment #2: The commenter requested the addition of the section title Analysis in *Dissolution.*
Response: Comment incorporated.
Comment #3: The commenter requested concentration of *Sensitivity solution* in the *Organic Impurities* to be changed from 0.2 µg/mL to 0.4 µg/mL.
Response: Comment not incorporated because the validation data supports the use of 0.2 µg/mL.
Comment #4: The commenter requested an increase in olanzapine related compound B limit from 0.20% to 0.3%.
Response: Comment not incorporated because the commenter's ANDA is not yet approved by the FDA.
Comment #5: The commenter indicated that the *Sample solution* preparation *Assay and Organic Impurities* is difficult due to the use of high concentration of sodium dodecyl sulfate which causes severe foaming. No suggestions for reducing the foaming were offered.
Response: Comment not incorporated. The Expert Committee is willing to consider improvements to the procedure with appropriate supporting data.

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Monograph/Section(s): Olopatadine Hydrochloride/Organic Impurities and Loss on Drying
Expert Committee(s): Monograph Development—Ophthalmology, Oncology, and Dermatology
No. of Commenters: 1
Comment Summary #1: The commenter requested changing the limit for total impurities in *Organic Impurities* from NMT 0.25% to NMT 0.50%.
Response: Comment not incorporated because the proposal reflects the specification in the FDA-approved product and the commenter's regulatory filing has not yet received approval by the FDA.
Comment Summary **#2:** The commenter suggested replacing the *Loss on Drying* by the test for *Water.*
Response: Comment not incorporated because the proposal reflects the specification in the FDA-approved product and the commenter's regulatory filing has not yet received approval by the FDA.

Monograph/Section: Oxaliplatin Injection/Multiple Sections
Expert Committee: Monograph Development—Ophthalmology, Oncology, and Dermatology
No. of Commenters: 3
Comment Summary #1: The commenter requested changing the definition of the *Assay* range from "95.0-105.0%" to "90.0-110.0%" to reflect the specification in approved product.
Response: Comment incorporated.
Comment Summary #2: The commenter suggested including a *Sensitivity solution* and *Signal to Noise Ratio* requirement in the *Organic Impurities Procedure 1*.
Response: Comment incorporated.
Comment Summary #3: The commenter requested changing the limit for oxalic acid in *Organic Impurities* from 0.30% to 0.60% to reflect the specification in the FDA-approved product.
Response: Comment incorporated.
Comment Summary #4: The commenter requested adding "Do not freeze" in the *Packaging and Storage* to reflect the storage condition for the FDA-approved product.
Response: Comment incorporated.
Comment Summary #5: The commenter requested the water for injection as a possible diluent be deleted in the *Labeling* to reflect the labeling requirement for the FDA-approved product.
Response: Comment incorporated.
Comment Summary #6: The commenter recommended adding the test for appearance of solution.
Response: Comment not incorporated because this test is not normally included in the USP monographs. The Expert Committee is willing to consider this proposal in the future if there is a quality-related concern.
Expert Committee-initiated Change: The limit for total unspecified impurities was deleted from *Impurity Table 1* to be consistent with ICH guideline.

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Monograph/Section(s): Pentamidine Isethionate/Identification
Expert Committee (s): Monograph Development—Antivirals and Antimicrobials
No. of Commenters: 1
Comment Summary # 1: The commenter suggested replacing *Identification Test B* (Oxygen-Flask Combustion) with a less complex wet chemistry test based on *Identification Test B* in the corresponding *European Pharmacopoeia* monograph.
Response: Comment not incorporated because this is a major revision and is not processed through the commentary process. The Expert Committee will consider this request through the regular revision process with via publication in *Pharmacopeial Forum* in the future.

Monograph/Section(s): Purified Water/Multiple Sections
Expert Committee(s): General Chapters—Pharmaceutical Waters
No. of Commenters: 1
Comment Summary #1: The commenter suggested changes to help clarify the definitions of bulk and packaged waters in the *Introduction*.
Response: Comment incorporated with changes to the following sentences: "Purified Water is intended…" to "Purified water, whether it is available in bulk or packaged forms, is intended…" and "Purified Water packaged in bulk for commercial use elsewhere…" to "In addition to the Specific Tests, Purified Water that is packaged for commercial use elsewhere…" In addition, two notes will be added: 1) After SPECIFIC TESTS: "[NOTE-Required for bulk and packaged forms of *Purified Water*]" and 2) After ADDITIONAL TEST: "[NOTE-Required for packaged forms of *Purified Water*]" for better clarification.
Comment Summary #2: The commenter suggested the inclusion of a rationale for the replacement of the test for *Oxidizable Substances* with the one for *Total Organic Carbon* (*TOC*). The commenter agreed with the replacement.
Response: Comment not incorporated. There is widespread agreement on the superiority of TOC methodology compared to the *Oxidizable Substances* test. Also, the rationale for the TOC was in the Briefing in *PF*.
Comment Summary #3: The commenter suggested changing the storage conditions in *Sterile Purified Water* to those for *Purified Water* for consistency between the monographs.
Response: Comment not incorporated because the storage requirements for the two official articles are different.

Monograph/Section(s): Repaglinide Tablets/Dissolution
Expert Committee(s): Monograph Development—Gastrointestinal, Renal and Endocrine
No. of Commenters: 1
Comment Summary #1: The commenter requested to revise the system suitability requirements in the *Dissolution* section and to delete the requirement for the capacity factor to be "about 1.8" as unnecessary restrictive.
Response: Comment incorporated.

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Monograph/Section(s): Telmisartan/Multiple Sections
Expert Committee(s): Monograph Development—Cardiovascular
No. of Commenters: 6

Comment Summary #1: Commenters suggested revising the text under *Identification B* procedure, from "the chromatogram of the sample solution corresponds to that of the standard solution, as obtained in the *Assay"* to "the chromatogram of the sample solution corresponds to that of the standard solution, as obtained in the *Organic Impurities"* as the *Assay* does not use a chromatographic procedure.
Response: Comment incorporated.
Comment Summary #2: The commenter suggested either to revise the concentration of USP Telmisartan RS in *System suitability solution* under *Organic Impurities* procedure, from 2.5 mg/mL to 0.125 mg/mL as given in the corresponding *European Pharmacopeia* monograph or to revise the resolution criterion to NLT 2.0.
Response: Comment not incorporated. The concentration of USP Telmisartan RS included in the PF proposal, 2.5 mg/mL, is consistent with the sponsor's validation data.
Comment Summary #3: The commenter suggested revising the Injection volume under *Organic Impurities* procedure from 10 µL to 2 µL, to be consistent with the sponsor's validation data.
Response: Comment incorporated.
Comment Summary #4: Commenters requested that the relative retention time for telmisartan diacid impurity given in Table1 be revised from1.1 to 0.67 to be consistent with the sponsor's validation data.
Response: Comment incorporated.
Comment Summary #5: The commenter requested that the chemical name for telmisartan diacid Impurity be changed from 1-[(2'-carboxybiphenyl-4-yl)methyl-4-methyl-2-propyl]-1H -benzimidazole-6-carboxylic acid to 1-[(2'-carboxybiphenyl-4-yl)methyl]-4-methyl-2-propyl-1H -benzimidazole-6-carboxylic acid in the footnote to the Table 1.
Response: Comment incorporated.
Comment Summary #6: Commenters requested to include a column temperature of 40º under the procedure for *Organic Impurities* to improve peak resolution.
Response: Comment incorporated.
Comment Summary #7: Commenters requested that the reference to the general chapter number stated under *Inorganic Impurities- Residue on Ignition,* be corrected from 231 to 281 to be consistent with the corresponding general chapter number given in *USP-NF.*
Response: Comment incorporated.
Comment Summary #8: The commenter indicated that their product as filed in their ANDA has different specifications for the *Assay, Heavy metals, Residue on Ignition, Water and Organic Impurities* than the corresponding procedures and specifications proposed in PF, and suggested USP to revise the procedures for moisture content and *Organic Impurities*.
Response: Comment not incorporated because the commenter's product has not yet received full FDA approval. The Expert Committee will consider addressing this comment as part of the USP Pending Monographs initiative.

Comment Summary #9: The commenter suggested adding a storage statement, "protect from light." under Additional Requirements - Packaging and Storage, to be consistent with the sponsor's regulatory filing.
Response: Comment incorporated.

Monograph/Section(s): Telmisartan Tablets/Assay
Expert Committee(s): Monograph Development—Cardiovascular
No. of Commenters: 1
Comment Summary #1: The commenter requested to revise the preparation of *Standard solution* for clarity and to indicate that the final dilution is done in *Mobile phase* and not *Diluent*.
Response: Comment incorporated.

Monograph/Section(s): Ticlopidine Hydrochloride/Organic Impurities
Expert Committee(s): Monograph Development—Cardiovascular
No. of Commenters: 1
Comment Summary #1: The commenter requested that the chemical names for ticlopidine related compound A and ticlopidine related compound B in Procedure 1 be changed from 4-methyl-6-(1-methyl-1H -benzimidazol-2-yl)-2-propyl-1H –benzimidazole and 4′-[[7-methyl-5-(1-methyl-1H -enzimidazol-2-yl)-2-propyl-1H-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid to (4-oxo-4,5,6,7-tetrahydrothieno-[3,2-*c*]pyridine and 5-(2-chlorobenzyl)-4-oxo-4,5,6,7-tetrahydrothieno-[3,2-*c*]pyridine) respectively.
Response: Comment incorporated.

Monograph/Section(s): Ticlopidine Hydrochloride Tablets/Assay
Expert Committee(s): Monograph Development—Cardiovascular
No. of Commenters: 1
Comment Summary #1: The commenter requested revising the column dimensions from 3.9-mm x 3-cm column to 3.9-mm x 30-cm length to be consistent with the column used in the validation.
Response: Comment incorporated.

Monograph/Section(s): Tranylcypromine Sulfate/*Organic Impurities*
Expert Committee(s): Monograph Development—Psychiatrics and Psychoactive
No. of Commenters: 1
Comment#1: The commenter indicated that relative response factor for related compound A is incorrect.
Response: Comment incorporated by changing the RRF value from 0.84 to 0.74 based on validation data.

Monograph/Section(s): Trenbolone Acetate/Organic Impurities
Expert Committee(s): Veterinary Drugs
No. of Commenters: 2

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Comment Summary #1: The sponsor reevaluated the relative response factor of conjugated dihydrotrenbolone acetate and requested it to be changed to 1.0.
Response: Comment incorporated.
Comment Summary #2: The commenter requested to add a note to clarify that the conjugated dihydrotrenbolone acetate is 11,12-dihydrotrenbolone acetate.
Response: Comment incorporated.
Comment Summary #3: The commenter indicated that the reporting level for impurities is inconsistent with the VICH GL 10 Guideline, and requested to revise it from 0.05% to 0.10%.
Response: Comment incorporated.

Monograph/ Section(s): Valacyclovir Hydrochloride/Multiple Sections
Expert Committee (s): Monograph Development—Antivirals and Antimicrobials
No. of Commenters: 4
Comment Summary #1: The commenter suggested replacing the *Content of Chloride* test with a qualitative Identification test for the chloride counter ion.
Response: Comment incorporated.
Comment Summary #2: The commenter suggested removing the redundant Rf values from *Impurity Table 1* because the Relative Rf values are already included in this Table.
Response: Comment incorporated.
Comment Summary #3: The commenter suggested using another submitted procedure as part of flexible monograph approach because of the difficulty in resolving the TLC spots for valacyclovir, valacyclovir related compound D and valacyclovir related compound E using *Procedure 1.*
Response: Comment not incorporated because several other laboratories were able to resolve the three above compounds using this procedure. Furthermore, the flexible monograph approach is not used as a mechanism for publishing multiple procedures that provide equivalent results for the same test.
Comment Summary #4: The commenter suggested increasing the acceptance criterion for valacyclovir related compound F in *Procedure* 1 from “NMT 0.1%” to “NMT 0.3%” to be consistent with the limit for this impurity published in the corresponding *Pharmeuropa monograph.*
Response: Comment not incorporated because the acceptance criterion for this impurity reflects the FDA-approved limit.
Comment Summary #5: The commenter suggested modifying the resolution requirement for valacyclovir related compound C and acyclovir related compound A in *Procedure 2* because of the difficulty in achieving this resolution.
Response: Comment not incorporated because several other laboratories successfully met this resolution requirement using this procedure.
Comment Summary #6: The commenter suggested removing the *Sensitivity solution* and the signal-to-noise ratio requirement in *Procedure 2* because adequate system suitability requirements are included using the *System suitability solution.*
Response: Comment incorporated.
Comment Summary #7: The commenter requested clarifying the relative response factors (RRFs) in *Impurity Table 2* by specifying their corresponding values of 1.0.
Response: Comment incorporated.

Comment Summary #8: The commenter suggested modifying *Procedure 3* because of the co-elution of peaks for guanine and acyclovir.
Response: Comment not incorporated because these two impurities do not need to be resolved and the acceptance criterion is for the sum of these two impurities.
Comment Summary #9: The commenter suggested using another submitted procedure as part of Flexible Monograph approach because of the difficulty in resolving the TLC spots for valacyclovir, valacyclovir related compound D and valacyclovir related compound E using *Procedure 3.*
Response: Comment not incorporated because multiple other laboratories were able to separate these compounds using this procedure. Furthermore, the flexible monograph approach is not used as a mechanism for publishing multiple procedures that provide equivalent results for the same test.
Comment Summary #10: The commenter suggested replacing the term "hydrate" with "hydrous" in the labeling requirement because the amount of water is not stoichiometrically defined.
Response: Comment incorporated.
Comment Summary #11: The commenter suggested increasing the acceptance criterion for Palladium from NMT 10 ppm to NMT 25 ppm to be more consistent with the European Medicine Agency (EMEA) Guideline on Specification Limits for Residues of Metal Catalysts or Metal Reagents.
Response: Comment not incorporated because the acceptance criterion for palladium is consistent with the FDA-approved product.
Comment Summary # 12: The commenter requested that brand names of the sources for *Palladium stock solution* be moved from the monograph to the footnotes because this information is not considered as part of the requirement for the public standard.
Response: Comment incorporated.
Comment Summary #13: The commenter suggested removing the term "Hydrochloride" from the names of USP Related Compound Reference Standards to be consistent with the naming convention used for such compounds.
Response: Comment incorporated.

Monograph/Section(s): Ziprasidone Hydrochloride/Assay and *Organic Impurities*
Expert Committee(s): Monograph Development—Psychiatrics and Psychoactives
No. of Commenters: 3
Comment #1: Commenters requested clarifying the acceptable pH range for the Buffer used in the *Assay*. The pH should be changed from 3.0 to 3.0 $\pm$ 0.1, which is consistent with validation data.
Response: Comment incorporated.
Comment #2: The commenter requested the deletion of the use of a refrigerated autosampler in the *Assay* and *Organic Impurities* procedures based on supporting data.
Response: Comment incorporated.
Comment #3: The commenter requested the addition of theoretical plates as a system suitability requirement.
Response: Comment not incorporated because the procedure includes adequate system suitability parameters and the addition of theoretical plates does not significantly improve the procedure.

Comment #4: The commenter requested correcting the formula in the *Organic Impurities* procedure because the molecular weights of salt and free base are inverted.
Response: Comment incorporated.
Comment #5: The commenter indicated lowering the concentration of related compound B used for RSD determination in *Organic Impurities* from 0.8 μg/mL to 0.2 μg/mL.
Response: Comment not incorporated because higher concentration will not compromise the utility of the monograph.
Comment #6: The commenter indicated that the pH of the buffer in the *Late Eluting Impurities* procedure is inconsistent with the validation data. The pH should be changed from 6.0 to 3.0.
Response: Comment incorporated.
Comment #5: The commenter indicated clarifying the definition of unspecified impurities in both the *Early Eluting Impurities* and the *Late Eluting Impurities* procedures. Impurities with a relative retention time (RRT) less than 1.0 are considered the "early eluting impurities" (Procedure 1) and those impurities with RRT greater than 1.0 are the "late eluting impurities" (Procedure 2).
Response: Comment incorporated.

Monograph/Section(s): Zolpidem Tartrate Extended Release Tablets/Organic Impurities and Dissolution
Expert Committee(s): Monograph Development—Psychiatrics and Psychoactive
No. of Commenters: 2
Comment #1: The commenter indicated that the *Organic Impurities* procedure does not describe the *Sample solution* preparation. A *Sample solution* preparation needs to be added to the monograph.
Response: Comment incorporated.
Comment #2: The commenter requested the inclusion of their *Dissolution* procedure.
Response: Comment not incorporated because of the commenter has not yet received FDA approval of their ANDA.

Monograph/Section(s): Zolpidem Tartrate Extended-Release Tablets
Expert Committee(s): Biopharmaceutics
Expert Committee-initiated Change #1: Dissolution test, the cell length is being added
Expert Committee-initiated Change #2: Dissolution test, Tolerances, Acceptance Table 1 is being replaced by Acceptance Table 2.