COMMENTARY– *USP 33-NF 28 Reissue*

Revision proposals published in *Pharmacopeial Forum* (*PF*) 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 *PF*, 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.

For further information, contact:
USP Executive Secretariat
United States Pharmacopeia
12601 Twinbrook Parkway
Rockville, MD 20852-1790 USA
execsec@usp.org

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

Monographs
Ampicillin Sodium
Benzoin
Cefixime for Oral Suspension
Clavulanate Potassium
Clindamycin Palmitate Hydrochloride
Diclazuril
Didanosine for Oral Solution
Enzymatically-Hydrolyzed
Carboxymethylcellulose Sodium
Ethyl Acrylate and Methyl

***No comments received for the following proposals (continued)*:**

Monographs

Methacrylate Copolymer Dispersion
Liquefied Phenol
Methacrylic Acid Copolymer Dipsersion
Mometasone Furoate Cream
Mometasone Furoate Ointment
Mometasone Furoate Topical Solution
Nitrofurantoin Capsules
Norethynodrel/Multiple Sections
Ofloxacin Tablets
Ondansetron Orally Disintegratinjg Tablets
Pea Starch
Polyvinyl Acetate
Potassium Iodide Delayed-Release Tablets
Pyrantel Pamoate
Ritonavir
Sibutramine Hydrochloride
Sulfinpyrazone
Tretinoin Gel
Valrubicin
Valrubicin Intravesical Solution
Vancomycin Hydrochloride Capsules
Vincristine Sulfate for Injection
Vincristine Sulfate Injection

General Chapters

General Chapter/Section(s): <63> Mycoplasma Tests/Culture Method/ Indicator Cell Culture Method
Expert Committee(s): Microbiology and Sterility Assurance
No. of Commenters: 2
Comment Summary #1: Stains other than Dienes could be used.
Response: Comment incorporated.
Comment Summary #2: The commenter suggested that the sentence "Mycoplasma are considered parasites, and many are....and plant hosts." be revised to "Mycoplasma are parasites and commensals, and some may be....plant host".
Response: Comment incorporated.
Comment Summary #3: The commenter suggested that the sentence "They may also cause...for aseptic processing" be deleted.
Response: Comment incorporated.
Comment Summary #4:
The commenter suggested that USP make clear in the chapter that testing must be performed by both the methods indicated and any alternate method should be validated against both methods.
Response: Comment incorporated.
Comment Summary #5:
The commenter suggested that an alternate method should not be required to be validated against the methods indicated in the chapter.
Response: Comment not incorporated. Alternative methodology is required to be validated against the methodology in the chapter.
Comment Summary #6:
The commenter suggested that the phrase "correct testing" be rephrased to "appropriate testing."

Response: Comment incorporated.
Comment Summary #7: The commenter suggested that that USP specify the minimum number of articles and minimum test article volume or refer to Center for Biologics Evaluation and Research (CBER) Guidance.
Response: Comment not incorporated. The establishment of these parameters is left to the discretion of the user.
Comment Summary #8: The commenter suggested that USP specify that the organisms listed are examples of suitable strains, and that other equivalent species and strains may be used.
Response: Comment not incorporated. Through *General Notice*s statements, other strains are allowed to be used if equivalence is demonstrated.
Comment Summary #9: The commenters suggested that microaerophilic conditions be clarified.
Response: Comment incorporated.
Comment Summary #10: The commenters suggested that to align with the *European Pharmacopoeia*, USP replace the acceptance criteria of 0.5 log unit range (a factor of 3.16) with "not differ by a factor greater than 5."
Response: Comment not incorporated. This would be a loosening of the specification.
Comment Summary #11: The commenters suggested that to align with *European Pharmacopoeia*, USP replace the requirement for neutralization of 0.5 log unit range (3.16 fold difference) with 5 fold difference.
Response: Comment not incorporated. This would be a loosening of the specification.
Comment Summary #12: The commenter suggested that USP clarify the condition for a valid test.
Response: Comment incorporated.
Comment Summary #13: The commenter indicated that the sentence "Include in the test positive controls….on agar medium or into broth medium" is not clear and suggested inoculating the positive control into broth and making subcultures or relying on only the "test for nutritive properties."
Response: Comment not incorporated.
Comment Summary #14: The commenter suggested that in tightly stoppered containers, the broths do not need specific atmospheric conditions.
Response: Comment not incorporated. The Expert Committee believes this is a critical requirement.
Comment Summary #15: The commenter recommended including sterilization instructions to specify which components need filter sterilization.
Response: Comment not incorporated. This information is available elsewhere.
Comment Summary #16: The commenter recommended using inactivated horse serum.
Response: Comment not incorporated. The composition described in the chapter is consistent with information in other pharmacopeias.
Comment Summary #17: The commenter suggested using fresh yeast extract, not powdered.
Response: Comment incorporated.
Comment Summary #18: The commenter suggested describing DNA-binding fluorochrome stains such as the Hoechst stain.
Response: Comment incorporated.

Comment Summary #19: The commenter suggested aligning with the *European Pharmacopoeia* requirement of incubation temperature of 35-38°C.
Response: Comment not incorporated. USP requirement is 35-37 C and is consistent with current regulatory guidelines in the United States.
Comment Summary #20:
The commenter suggested that "must " in the sentence "Complete confluence….must be avoided." be replaced by "should " since complete confluence is difficult to define.
Response: Comment not incorporated.

General Chapter/Section(s): <223> Dimethylaniline/Multiple Sections
Expert Committee(s): Monograph Development-Antibiotics
No. of Commenters: 1
Comment Summary #1: The commenter suggested replacing the procedure with another validated procedure.
Response: Comment not incorporated since the procedure has not been evaluated for all the monographs impacted by this chapter.

Monographs

Monograph/Section(s): Acetaminophen and Tramadol Hydrochloride Tablets/ Multiple Sections
Expert Committee(s): Monograph Development Cough, Cold and Analgesics
No. of Commenters: 2
Comment Summary #1: The commenter suggested lowering the limit of p-Aminophenol, a possible mutagen and teratogen.
Response: Comment not incorporated. The Expert Committee is willing to consider future changes to the monograph upon receipt of supporting data.
Comment Summary #2: The commenter suggested adopting a single HPLC procedure for the *Assay, Organic Impurities* and *Limit of p-Aminophenol* tests.
Response: Comment not incorporated. The Expert Committee is willing to consider future changes to the monograph upon receipt of supporting data.

Monograph/Section(s): Amiodarone Hydrochloride/Assay
Expert Committee: Monograph Development Cardiovascular
No. of Commenters: 3
Comment Summary #1: The commenter suggested revising the *Assay* limits from 98.5-101.0% to 98.0-102.0%, based on the generally accepted instrument error for an HPLC procedure of about 2.0%.
Response: Comment not incorporated because the commenter has an approved product in the market with the same *Assay* acceptance range of 98.5 – 101.0% as stated in the *PF* proposal.
Comment Summary #2: The commenter suggested adding a melting point range test.
Response: Comment not incorporated because typically the melting point test is done to address polymorphic issues if any or to verify the purity of the product. These two issues are addressed in the monograph via identification using more specific IR test and also an Organic Impurities test using HPLC.

Comment Summary #3: The commenter suggested adding a quantitative chloride test with a limit.
Response: Comment not incorporated because the monograph has a qualitative test for the chloride counter ion an *Identification* test. The addition of a quantitative test may not add value to ensure the product quality.
Comment Summary #4: The commenter suggested adding a quantitative iodide test with limit.
Response: Comment partially incorporated. A limit of 150 ppm is added to the test for iodide that is already included in the monograph proposal.
Comment Summary #5: The commenter suggested revising the preparation of the *Monitor solution* in the test for *Heavy metals* as follows: Replace " Dilute 2 mL of *Test solution* with "Dilute 2mL of *Standard solution.*"
Response: Comment incorporated.

Monograph/Section(s): Amlodipine Besylate Tablets/Organic Impurities
Expert Committee(s): Monograph Development Cardiovascular
No. of Commenters: 3
Comment Summary #1: The commenter suggested revising the limit for any other individual impurity from NMT 0.10% to NMT 0.2% to be consistent with their approved specifications.
Response: Comment incorporated.
Comment Summary #2: The commenter suggested replacing the Organic Impurities procedure as they experienced foaming during sample preparation and the injection precision published in the *Pharmacopeial Forum* proposal is greater than that observed with their procedure.
Response: Comment not incorporated because the injection precision is consistent with the FDA approved product and the Expert Committee concluded that there is no significant advantage in replacing the current procedure.

Monograph/Sections(s): Ampicillin/Organic Impurities
Expert Committee(s): Monograph Development-Antibiotics
No. of Commenters: 2
Comment Summary #1: Commenters suggested revising the *Organic impurities* test with one that is more appropriate for their impurity profiles.
Response: Comment not incorporated. The Expert Committee is willing to consider future changes to the monograph upon receipt of supporting data.

Monograph/section(s): Budesonide/Organic Impurities
Expert Committee(s): Monograph Development Pulmonary and Steroids
No. of Commenters: 1
Comment Summary #1: The commenter suggested that the chemical name for D-homobudesonide be changed from 16α,17-[(1*RS*)-Butylidenebis(oxy)]-11b-hydroxy-17-(hydroxymethyl)-*D*-homoandrosta-1,4-diene-3,17α-dione to 16α,17-[(1*RS*)-Butylidenebis(oxy)]-11β-hydroxy-17-(hydroxymethyl)-*D*-homoandrosta-1,4-diene-3,17α-dione in the footnote to the Table.
Response: Comment incorporated.

Monograph/Section(s): Cefazolin Sodium/Organic Impurities
Expert Committee(s): Monograph Development-Antibiotics
No. of Commenters: 1
Comment Summary 1: The commenter suggested revising the *Organic Impurities* test to improve selectivity.
Response: Comment not incorporated. The Expert Committee is willing to consider future changes to the monograph upon receipt of supporting data.

Monograph/Section(s): Endotoxin Indicator for Depyrogenation/Carrier
Expert Committee(s): Microbiology and Sterility Assurance
No. of Commenters: 1
Comment Summary #1: The commenter suggested that the phrase "complies with" be clarified.
Response: Comment incorporated.
Comment Summary #2: The commenter suggested the requirement "if the carrier cannot be depyrogenated" be further elaborated.
Response: Comment incorporated.

Monograph/Section(s): Ketoprofen Extended–Release Capsules/Assay.
Expert Committee(s): Monograph Development Cough, Cold and Analgesics
No. of Commenters: 1
Comment Summary #1: The commenter suggested that the instructions for *Sample preparation* be reworded for clarity and to change the size of the volumetric flask from 200 mL to 100 mL to achieve the desired concentration.
Response: Comment incorporated.

Monograph/Section(s): Mesna/Limit of Sulfate and Organic Impurities
Expert Committee(s): Monograph Development Cough, Cold and Analgesics
No. of Commenters: 1
Comment Summary #1: The commenter suggested changing the concentration of the *Sulfate standard solution* in the *Limit of sulfate* test from 0.181 mg/mL to 1.81 mg/mL. This change in concentration is a correction to the original text and corresponds to the procedure in the *European Pharmacopoeia* version of this monograph.
Response: Comment incorporated.
Comment Summary #2: The commenter suggested incorporating the relative response factors for the three named impurities into the calculations and listed in Impurity Table 1.
Response: Comment incorporated.

Monograph/Section(s): Mycophenolate Mofetil/Organic Impurities
Expert Committee(s): Monograph Development Ophthalmics, Oncology, Dermatology
No. of Commenters: 2
Comment Summary #1: The commenter suggested the column length be changed from 15 cm to 25 cm so that the mycophenolate mofetil z-isomer can be resolved from mycophenolate mofetil. The same procedure in the *European Pharmacopoeia* version of this monograph uses a 25-cm column.

Response: Comment incorporated.
Comment Summary #2: The commenter suggested a correction to the chemical name of a related compound from 1-Morpholinoethoxy to 1-Morpholinoethoxy.
Response: Comment incorporated.

Monograph/Section(s): Nateglinide/Multiple Sections
Expert Committee(s): Monograph Development–Gastrointestinal, Renal and Endocrine
No. of Commenters: 2
Comment Summary #1: The commenter suggested that some of the impurities listed in Table 1 are "process-specific" impurities and they should be deleted from the Table and be classified under "other impurities."
Response: Comment not incorporated. The Expert Committee will consider it in the future if additional information regarding impurities pertaining to alternative impurity profile(s) is received.
Comment Summary #2: The commenter suggested lowering the limit of "any other impurity" to NMT 0.10%, to be consistent with ICH Q3A.
Response: Comment not incorporated. The limit included in the monograph (NMT 0.1%) is consistent with the sponsor's regulatory filing.
Comment Summary #3: The commenter suggested deleting the test for Specific rotation, as the methods in the monograph already control possible stereoisomers such as Related compound B and Related compound C.
Response: Comment incorporated.
Comment Summary #4: The commenter indicated that their material is a different polymorphic form with the moisture content which is outside of the proposed limits, and suggested USP widen the specification from "NMT 0.2%" to "NMT 0.5%."
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.

Monograph/Section(s): Olive Oil/Multiple Sections
Expert Committee(s): Excipient Monographs 2
No. of Commenters: 1
Comment Summary #1: In the *Alkaline Impurities*, the commenter suggested deleting "Neutralize the solution to a green color if necessary with 0.01 N hydrochloric acid or 0.01 N sodium hydroxide" because "a green color" was not practically observed.
Response: Comment incorporated. In addition to deletion of that sentence, the Expert Committee added "freshly opened" before "acetone" for the solvent.
Comment Summary #2: In the *Acid Value*, the commenter suggested using petrol ether instead of ethylic ether. Ethylic ether is prohibited from labs for safety reasons and results are equivalent with petrol ether.
Response: Comments incorporated. In the *Acid Value*, the Expert Committee added a note as [NOTE—Petroleum ether can be used to replace ether in the test.]
Comment Summary #3: In the *Unsaponifiable Matter*, the commenter suggested using petrol ether instead of ethylic ether. Ethylic ether is prohibited from labs for safety reasons and results are equivalent with petrol ether.

Response: Comments incorporated. In the *Unsaponifiable Matter*, the Expert Committee added a note as [NOTE—Petroleum ether can be used to replace ether in the test.]

Monograph/ Section(s): Oseltamivir Phosphate/Assay
Expert Committee (s): Monograph Development-Antivirals and Antimicrobials
No. of Commenters: 1
Comment Summary #1: The commenter suggested removing the tailing factor criterion for oseltamivir peak from the system suitability requirement.
Response: Comment not incorporated because this criterion is needed to check column performance in the absence of the resolution requirement for the system suitability.

Monograph/ Section(s): Oseltamivir Phosphate Capsules/Multiple Sections
Expert Committee(s): Monograph Development- Antivirals and Antimicrobials
No. of Commenters: 1
Comment Summary #1: The commenter suggested removing the tailing factor criterion for oseltamivir peak from the system suitability requirement in the *Assay* procedure.
Response: Comment not incorporated because his criterion is needed to check column performance in the absence of the resolution requirement for the system suitability.
Comment Summary #2: The commenter suggested revising the relative response factor (F) from 1.0 to 0.9 for impurity C in the organic impurities procedure.
Response: Comment incorporated.

Monograph/Section(s): Oxaliplatin for Injection/Multiple Sections
Expert Committee(s): Monograph Development Ophthalmics, Oncology, Dermatology
No. of Commenters: 3
Comment Summary #1: The commenter suggested adding the *Limit for constitution time* to reflect the specification for the approved product.
Response: Comment not incorporated. The Expert Committee noted that the monograph gives adequate direction via reference to General Chapter <1> Injections.
Comment Summary #2: The commenter suggested adding an *Identification* test by UV to reflect the specification for the approved product.
Response: Comment not incorporated. The Expert Committee noted that the UV identification test is not definitive and specific.
Comment Summary #3: The commenter suggested the sensitivity requirement be added in the test for Limit of oxalic acid to be consistent with the Oxaliplatin monograph.
Response: Comment incorporated.
Comment Summary #4: 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, unspecified impurity, total unspecified impurities and total impurities.
Response: Comment not incorporated because the limits in the monograph reflect the specifications for the approved product. The Expert Committee will consider addressing this comment as part of the USP Pending Monographs initiative.

Monograph/Section(s): Oxcarbazepine/Organic Impurities
Expert Committee(s): Monograph Development Psychiatrics & Psychoactive
No. of Commenters: 4
Comment #1: The commenter indicated that the impurities profile of the drug substance manufactured by their company is different from the profile included in the *PF* proposal. The procedure in *PF* cannot be used due to co-elution of peaks.
Response: Comment not incorporated because a revision to the *Related compounds* procedure will be published as a flexible monograph in a future volume of *PF* for public comments.
Comment #2: Two commenters indicated the possible errors in the identification of peaks and their relative retention times.
Response: Comment not incorporated because there are plans to publish a revision to the *Organic Impurities* test in a future volume of *PF* and the necessary corrections will be made at that time.
Comment#3: The commenter suggested that the proposal needs a limit for Total unspecified impurities.
Response: Comment not incorporated because there is no requirement per ICH guidelines Q3A R2 for limit of total unspecified impurities.

Monograph/Section(s): Oxycodone Hydrochloride/Organic Impurities
Expert Committee(s): Monograph Development Cough, Cold and Analgesics
No. of Commenters: 2
Comment Summary #1: Commenters suggested reporting the limits of the organic impurities in percent instead of ppm.
Response: Comment incorporated.
Comment Summary #2: The commenter suggested stating the limit for all specified impurities as 0.15% and to reduce total impurities from 0.2% to 0.1%.
Response: Comment not incorporated. The Expert Committee is willing to consider future changes to the monograph upon receipt of supporting data.
Comment Summary #3: The commenter suggested replacing the *Limit of alcohol* test with compliance to <467> *Residual Solvents*.
Response: Comment not incorporated because the monograph limit of not more than 1.0% ethanol exceeds the 0.5% limit stated in <467> *Residual Solvents.* In this situation, the limit stated in the monograph takes precedence over the chapter requirement.

Monograph/Section(s): Peanut Oil/Multiple Sections
Expert Committee(s): Excipient Monographs 2
No. of Commenters: 1
Expert Committee-initiated Change #1: The Expert Committee changed *Water* determination method from *Method Ia* to *Method Ic* (Coulometric Titration), and deleted a suggestion for a solvent system used. *Water* <921> offers users flexibility to use suitable solvents.
Expert Committee-initiated Change #2: In the *Alkaline Impurities*, a commenter recommended deleting “Neutralize the solution to a green color if necessary with 0.01 N hydrochloric acid or 0.01 N sodium hydroxide” because “a green color” was not

practically observed. In addition to deletion of that sentence, the Expert Committee added “freshly opened” before “acetone” for the solvent.

Monograph/Section(s): Polyoxyl 15 Hydroxystearate/*Free Polyethylene Glycols*
Expert Committee(s): Excipient Monographs 2
No. of Commenters: 0
Expert Committee-initiated Change: In the *Free Polyethylene Glycols*, the Expert Committee changed the analytical column designation from “L25” to “L39.”

Monograph/Section(s): Polyvinyl Acetate Dispersion/*Limit of Vinyl Acetate*
Expert Committee(s): Excipient Monographs 2
No. of Commenters: 1
Comment Summary#1: The commenter suggested changing “0.2-mm membrane filter” to “0.2-μm membrane filter” under “*Sample solution.*”
Response: Comment incorporated.

Monograph/Section(s): Propafenone Hydrochloride/Organic Impurities
Expert Committee(s): Monograph Development Cardiovascular
No. of Commenters: 1
Comment Summary #1: The commenter suggested revising the preparation of *Solvent A* from monobasic potassium phosphate trihydrate to dipotassium hydrogen phosphate trihydrate. This change reflects the validation data.
Response: Comment incorporated.
Comment Summary #2: The commenter suggested revising the concentration of the *Resolution solution* from 1 mg/ml to 0.1 mg/mL. This correction to the concentration is consistent with the original data.
Response: Comment incorporated.

Monograph/Section(s): Sertraline Hydrochloride/Multiple Sections
Expert Committee(s): Monograph Development Psychiatrics & Psychoactive
No. of Commenters: 1
Comment #1: The commenter suggested changing the *Residue on ignition* limit from 0.1% to 0.3% to be consistent with the approved application.
Response: Comment incorporated.
Comment #2: The commenter suggested changing the *Heavy metals* limit from 20 ppm to 30 ppm to be consistent with the approved application.
Response: Comment incorporated.
Comment #3: The commenter suggested changing the *Limit of (**R, R**) sertraline hydrochloride* from 0.3% to 1.5% to be consistent with the approved application.
Response: Comment incorporated.
Comment #4: The commenter suggested changing the *Assay* limits from 98.0-102.0% to 97.0-102.0% to be consistent with the approved application..
Response: Comment incorporated.
Comment #5: The commenter suggested replacing the HPLC procedure for inorganic impurities with the GC procedure included in the *European Pharmacopoei*a monograph.
Response: Comment not incorporated. The Expert Committee is willing to consider future changes to the monograph upon receipt of supporting data.

Monograph/Section(s): Topiramate Tablets/Multiple Sections
Expert Committee(s): Monograph Development Psychiatrics & Psychoactive
No. of Commenters: 2
Comment #1: The commenter indicated that the procedures in *PF* are not consistent with the approved application.
Response: Comment not incorporated. The Expert Committee is willing to consider future changes to the monograph upon receipt of supporting data.
Comment #2: The commenter indicated that the test for *Limit of Sulfate/Sulfamate* does not work for their formulation.
Response: Comment not incorporated because no supporting data were provided**.** The Expert Committee is willing to consider future changes to the monograph upon receipt of supporting data.
Comment #3: The commenter suggested replacing the *Assay* procedure with their procedure which has a shorter run time.
Response: Comment not incorporated because the commenter's procedure does not offer any significant advantages.

Monograph/Section(s): Tramadol Hydrochloride/Limit of Tramadol Related Compound B.
Expert Committee(s): Monograph Development Cough, Cold and Analgesics
No. of Commenters: 1
Comment Summary #1: The commenter suggested changing the concentration of the *Standard solution* from 0.05 mg/mL to 0.1 mg/mL to correspond with the acceptance criterion of 0.2%.
Response: Comment incorporated.

Monograph/Section(s): Tramadol Hydrochloride Tablets/Organic Impurities
Expert Committee(s): Monograph Development Cough, Cold and Analgesics
No. of Commenters: 1
Comment Summary #1: The commenter suggested changing the limit for any individual unspecified impurity from 0.15% to 0.2% to be consistent with their approved application.
Response: Comment incorporated.

Monograph/Section(s): Zolpidem Tartrate/Identification and Organic Impurities
Expert Committee(s): Monograph Development Psychiatrics & Psychoactive
No. of Commenters: 1
Comment #1: The commenter suggested removing *Identification B.*
Response: Comment not incorporated because this Identification procedure does not pose any additional burden to the users.
Comment #2: The commenter indicated that the precision requirement (%RSD) is high and should be replaced with a S/N ratio.
Response: Comment not incorporated. The Expert Committee is willing to consider future changes to the monograph upon receipt of supporting data.

Comment #3: The commenter suggested removing the use of an external standard for Organic Impurities procedure because it is considered to be of limited value.
Response: Comment not incorporated. The Expert Committee is willing to consider future changes to the monograph upon receipt of supporting data.