COMMENTARY—*2ND SUPPLEMENT* TO *USP30 - NF25*

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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USP Monographs

Monograph/Sections: Acetaminophen, Chlorpheniramine and Dextromethorphan Hydrobromide Tablets/Assay
Expert Committee: MD-CCA
No. of Commenters: 1
Comment Summary: The commenter suggested rewriting the monograph so it does not reference other monographs, but instead includes all relevant information within the monograph itself.
Response: Comment incorporated.

Monograph/Section: Albuterol Sulfate/Assay
Expert Committee: AER
Expert Committee-initiated change: Column dimensions are corrected in the Assay section of the monograph. The proposal in PF 32(5) specified a 5.0- mm X 20-cm column but the correct dimensions are 4.6 mm X 20 cm.

Monograph/Section: Capecitabine/Multiple Sections
Expert Committee: MD-OOD
No. of Commenters: 1
Comment Summary #1: Commenter suggested including the test for residual solvents in the monograph because the Assay is calculated on the anhydrous and solvent free basis.
Response: Comment not incorporated. The Committee did not include the test for residual solvents because the *USP* General Notices require testing for residual solvents. That the test result is used in the Assay calculation.
Comment Summary #2: Commenter suggested that limit for heavy metals be expressed in % rather than in ppm.
Response: Comment not incorporated at this time because both % and ppm are used in the USP.
Comment Summary #3: The commenter suggested that the unit of concentration in the Assay be added after the calculation for clarification.
Response: Comment incorporated.

Monograph/Section: Capecitabine Tablets/Assay, Related compounds
Expert Committee: MD-OOD
No. of Commenters: 2
Comment Summary #1: Commenter suggested that the Assay limit is not consistent with the FDA-approved specification.
Response: Comment not incorporated. The Committee confirmed that the Assay limit in the monograph is consistent with the FDA-approved specification for shelf-life.
Comment Summary #2: In the test for Related compounds, commenter suggested that the wording "based on the assay of tablets" should be added for the test solution in the statement under the calculation for clarification.
Response: Comment incorporated, using the wording "based on the label claim."
Expert Committee-initiated change: In the Assay, change the wording from "to obtain a solution having a known concentration of about 0.6 mg per mL" to "to obtain a solution having a known concentration of about 0.6 mg per mL of capecitabine, based on the label claim." Change the wording from "Calculate the quantity, in percentage, of $C_{15}H_{22}FN_3O_6$ in the portion of Tablets taken by the formula" to "Calculate the quantity, in percentage of label claim, of $C_{15}H_{22}FN_3O_6$ in the portion of Tablets taken by the formula." Also change the wording from "C_U is the concentration of capecitabine in the Assay preparation" to "C_U is the concentration, in mg per mL, of capecitabine based on the label claim in the Assay preparation."

Monograph/Section: Citalopram Tablets/Identification
Expert Committee: MD-PP
Number of Commenters: 1
Comment Summary: Commenter requested deletion of Identification test C for bromide counter ion.
Response: Comment incorporated.
Expert Committee-initiated changes: Move the reference to <197K> to an appropriate location in the IR Identification to reflect that the extraction step precedes the KBr pellet preparation.

Monograph/Section: Dantrolene Sodium Capsules/Dissolution
Expert Committee: MD-PP
Number Commenters: 1
Comment Summary: Commenter recommended the addition of a note in the Dissolution section concerning pH adjustment of the dissolution medium.
Response: Comment incorporated
Expert Committee-initiated change: Add specific storage condition.

Monograph/Sections: Didanosine/Related compounds
Expert Committee: MD-AA
Expert Committee-initiated change: The Related compounds test which was already published in PF 32(3) was initially deferred because of the unavailability of the USP Reference Standards (RS) needed for this test. Since the quantitative and system suitability USP RSs are now available, the test has now been added to the monograph.

Monograph/Section: Fexofenadine Hydrochloride/Multiple sections
Expert Committee: MD-PS
No. of Commenters: 1
Comment summary: Commenter indicated that the impurity procedures (Limit of fexofenadine related compound B and the test for Related compounds) do not adequately resolve impurities specific to their product; and requested that an alternative Related compounds test be added to the monograph.
Response: Comment not incorporated at this time. The Committee will consider the addition of the alternative procedure when the commenter provides a complete submission.

Monograph/Section: Fexofenadine Hydrochloride Capsules/Multiple sections
Expert Committee: MD-PS
No. of Commenters: 1
Comment summary: See *Comment summary* section under Fexofenadine Hydrochloride.
Response: See *Response* under Fexofenadine Hydrochloride.
Expert Committee-initiated change: The Committee did not approve the test for Water because total water content is dependent upon the identity of the excipients, and it would be difficult to establish meaningful criteria that would apply to all formulations. Each manufacturer should establish limits for their product based on scientific evaluation of their own formulation performance and stability data.

Monograph/Section: Fexofenadine Hydrochloride and Pseudoephedrine Hydrochloride Extended-Release Tablets/ID, Related compounds
Expert Committee: MD-PS
No. of Commenters: 1
Comment Summary #1: Commenter requested that the infrared absorption Identification test be replaced with a thin-layer chromatographic procedure because the infrared absorption identification test is applicable only to bilayer tablets.
Response: Comment incorporated. The thin-layer chromatographic Identification procedure is added as an alternative identification test for non-bilayer tablets.
Comment Summary #2: - Change the impurity limits in the test for Related compounds as follows:
- related compound A from NMT 0.3% to NMT 0.4%,
- add 4-[4{4-(diphenymethylene)-1-piperidinyl}-1-hydroxybutyl]-2,2-dimethyl phenyl acetic acid (TRS-1) as a specified impurity with a limit of NMT 0.2%,
- total impurity limit from NMT 0.5% to NMT 0.8%

Response: Comment incorporated.
Expert Committee-initiated change: The Committee did not approve the test for Water because total water content is dependent upon the identity of the excipients, and it would be difficult to establish meaningful criteria that would apply to all formulations. Each manufacturer should establish limits for their product based on scientific evaluation of their own formulation performance and stability data.

Monograph/Section: Fluticasone Propionate Nasal Spray/Multiple sections
Expert Committee: AER
Number of Commenters: 0
Expert Committee-initiated changes:

- Revise the USP Reference standards section of the monograph to replace USP Fluticasone Propionate Related Compound D RS and USP Fluticasone Propionate Related Compound F RS with USP Fluticasone Propionate Related Compound Mixture RS. This change was made because of the unavailability of the individual impurity standards.
- Incorporate USP Reference Standards for USP Fluticasone Propionate Nasal Spray Resolution Mixture RS, USP Docusate Sodium RS and USP Benzalkonium Chloride RS.
- Modify the tests for Delivered dose uniformity (within container), Related compounds, Content of benzalkonium chloride, and Assay to accommodate and reflect the changes in USP Reference standards section.
- Modify the microbial limit section to include USP indicator microorganisms and to reflect current limit standards for such products.
- Clarify the Particle size section to indicate measurement of the drug substance particles.
- Add tests for Droplet size distribution and Spray pattern. These are considered critical attributes for the performance of the pump and drug product. Different factors can affect the outcome of these tests including the size and shape of the nozzle, the design of the pump, the size of the metering chamber, and formulation and manufacturing related characteristics.

Acceptance criteria for these tests have not been included because the information is unavailable and because they may be product specific, based on the source of the drug product and its demonstrated safety and effectiveness.

Monograph/Section: Fluticasone Propionate Nasal Spray/Microbial limits
Expert Committee: MSA
Number of Commenters: 1
Comment Summary: Consistent with the product approval specifications, commenter suggested modifying the Microbial Limit requirements to also include absence of E. coli and Salmonella, changing the total aerobic microbial count to not exceed 25 cfu per mL, and changing the total combined molds and yeasts count to not exceed 25 cfu per mL.
Response: Comment incorporated.

Monograph/Section: Glipizide/Related compounds, Assay
Expert Committee: MD-GRE
No. of Commenters: 4
Comment summary #1: Commenter suggested that Test 1 under Related compounds be deleted because Test 2 appears to be capable of separating the specified impurity that is being quantitated using Test 1.
Response: Comment not incorporated. The Expert Committee reviewed all of the data that it received and concluded that the proposed change would require additional supporting data. Although the Committee is not delaying approval of the monograph for official status on this point, the Committee is willing to consider publishing this proposal in a future *PF* for public review and comment.
Comment summary #2: Commenter requested the proposal to be deferred from becoming official until the required USP Reference Standards are available for sale so that the Commenter can evaluate the proposed method.
Response: Comment not incorporated because the required Reference Standards will be available by the time the 2nd Supplement to *USP 30* becomes official. Although the Committee is not delaying approval of the monograph for official status on this point, the Committee is willing to consider further changes to this monograph in the future if the commenter submits a Request for Revision.
Comment Summary #3: Commenter suggested that a clarification to use the anhydrous grade of dibasic sodium phosphate in the preparation of *0.02 M Phosphate Buffer* be added.
Response: Comment incorporated.
Comment Summary #4: Commenter suggested that the Note regarding the use of low-actinic glassware be revised to specify that the solutions containing glipizide related compounds should also be protected from light.
Response: Comment incorporated.

Monograph/Section: Glipizide and Metformin Hydrochloride Tablets /Multiple sections
Expert Committee: MD-GRE
Number of Commenters: 3
Comment summary #1: Commenter suggested that a second identification test for Metformin Hydrochloride employing Infrared Absorption spectroscopy be included in the monograph, in addition to the retention time agreement in the HPLC Assay for Metformin Hydrochloride.
Response: Comment not incorporated. Having only one identification test for a dosage form is common in USP monographs and was judged by the Committee to be acceptable for a public standard.
Comment summary #2: Commenter requested the proposal to be deferred from becoming official until the Commenter can evaluate whether the proposed methods work for the Commenter's product.
Response: Comment not incorporated. Although the Committee is not delaying approval of the monograph for official status on this point, the Committee is willing to consider further changes to this monograph in the future if the commenter submits a Request for Revision.

Comment Summary #3: Commenter suggested that the redundant filtering step for the Assay for Metformin Hydrochloride be eliminated, and the column temperature requirement be omitted.
Response: Comment incorporated.

Monograph/Section: Lidocaine and Prilocaine Cream/Related compounds
Expert Committee: MD-PS
Number of Commenters: 1
Comment Summary #1: Commenter suggested clarifying the definitions of the terms r_u, r_s, and L, used in the formula for calculating impurities.
Response: Comment incorporated.
Comment Summary #2: Commenter suggested that process related impurities should not be specified in the test.
Response: Comment not incorporated at this time because the process related impurities are not controlled in the current drug substance monographs.
Comment Summary #3: Commenter suggested the following changes based on their approved product:

- change the limit of o-toluidine from NMT 0.1% to NMT 2.0%
- change the limit of 2,6-dimethylaniline from NMT 0.1% to NMT 0.04%.

Response: Comment partially incorporated. The limit of o-toluidine was increased as requested but 2,6-dimethyaniline limit was not tightened.

Monograph/Section: Modafinil/Multiple sections
Expert Committee: MD-PS
Number of Commenters: 8
Comment Summary #1: Commenters requested the following changes: delete the Particle size test; change the limit of impurities in the Related compounds test; widen the limits for the Assay; increase the limit for the Residue on ignition test; add an alternative Related compounds test, and change the procedures for the Heavy metals and Water tests.
Response: Comment not incorporated in the official monograph at this time.
Expert Committee-initiated change: The Committee will consider the test for Particle size for future addition to the monograph.

Monograph/Section: Modafinil Tablets/Related compounds
Expert Committee: MD-PS
Expert Committee-initiated change: The Committee removed Modafinil ester [2-[(diphenylmethyl)sulfinyl]acetic acid methyl ester], a process related impurity that is already controlled in the drug substance monograph, from the list of specified impurities in the Related compounds test.

Monograph/Sections: Nevirapine Oral Suspension/pH and Viscosity
Expert Committee: MDAA
No. of Commenters: 2
Comment Summary #1: Commenter suggested omitting the pH and Viscosity requirements from the monograph because these specifications are formulation-dependent and may not be appropriate for other suspension drug products with different formulations.
Response: Comment incorporated.
Comment Summary #2: Commenter suggested including a test for checking consistency within the same dosage unit, as suspension dosage form drug products using some suspending agents might settle on storage.
Response: Comment not incorporated because the sponsor indicated that the approved NDA allows this test to be omitted after the first three production scale batches.

Comment Summary #3: Commenter suggested deleting the <905> Uniformity of Dosage Units test from the monograph because the test only applies to suspensions that are in unit dose containers. Nevirapine Oral Suspension is only packaged in a multi-dose bottle.
Response: Comment incorporated.

Monograph/section: Nevirapine Oral Suspension/Microbial limits
Expert Committee: MSA
Number of Commenters: 2
Comment Summary #1: Commenter noted that due to the method's limitations, it is difficult for oral suspension products to meet the total yeast and mold count limit of 10cfu per mL.
Response: Comment incorporated. The total yeast and mold count has been changed to 50 cfu per mL.
Comment Summary #2: Commenter suggested adding a requirement for the absence of total coliforms.
Response: Comment not incorporated. Currently, General Chapter <61> Microbial Limit Tests does not contain tests for Total coliforms. Only tests specified in the chapter are included as monograph requirements.

Monograph/Section: Ondansetron Injection/Definition
Expert Committee: MD-PP
Number of Commenters: 1
Comment Summary: Commenter requested the expansion of the definition to allow the use of ondansetron free base.
Response: Comment incorporated.

Monograph/Section: Pravastatin Sodium Tablets/Packaging and storage
Expert Committee: MD-GRE
Number of Commenters: 1
Comment Summary: Commenter suggested that the Packaging and storage section state that the Tablets should be stored protected from moisture and light.
Response: Comment incorporated.

Monograph/Section: Risperidone/Assay
Expert Committee: MD-PP
Number of Commenters : 1
Comment Summary: Commenter recommended rewording the system suitability criteria for clarity.
Response: Comment incorporated.

Monograph/Section: Risperidone Tablets/Multiple sections
Expert Committee: MD-PP
Number of Commenters: 1
Comment Summary #1: Commenter requested that the monograph include 9-hydroxyrisperidone as an identified impurity with appropriate limits.
Response: Comment not incorporated because 9-hydroxyrisperidone is a process impurity and is controlled in the drug substance.
Comment Summary#2: Commenter suggested renaming the "unidentified impurity" as "unspecified degradation product" to be consistent with ICH guidelines.
Response: Comment incorporated.
Expert Committee-initiated change: Moved the reference to <197K> to an appropriate location in the IR Identification to reflect that extraction step precedes the KBr pellet preparation.

Monograph/Section: Thalidomide Capsules/Microbial limits
Expert Committee: MSA
Number of Commenters: 1
Comment Summary: The Commenter suggested that the Microbial Limits requirements for solid oral dosage forms is of no added value and should be deleted.
Response: Comment not incorporated. The microbial contamination of solid oral dosage forms can be a health hazard, especially to certain sections of the population.

Monograph/section: Tiamulin Fumarate/Multiple sections
Expert Committee: VET
No. of Commenters: 1
Comment summary: Commenter requested that the Committee not increase the total impurity limit from “not more than 2.0%” to “not more than 3.0%.”
Response: Comment not incorporated. The Committee noted that FDA-approved articles are already in distribution with the “not more than 3.0%” limit as part of the regulatory filing.

General Chapters

General Chapter/Section: <401> Fats and Oils
Expert Committee: EGC
Number of Commenters: 1
Comment Summary: Commenter questioned inconsistency for molecular weight for potassium hydroxide used in this chapter. In Acid Value section, “56.1” is used, however, “56.11” is used in the other sections.
Response: Comment incorporated. The Committee changed “56.1” to “56.11” throughout the chapter.

General Chapter/Section: <466> Ordinary Impurities
Expert Committee: GC
Number of Commenters: 3
Comment Summary #1: Several commenters suggested slight changes in grammar, terminology, and other editorial changes to clarify or improve upon the requirements or to eliminate redundancies or inconsistencies. Some of the suggested changes were more editorial and stylistic and do not warrant a detailed discussion.
Response: Comments incorporated as appropriate. The Expert Committee reviewed each of these editorial and language changes to determine whether it offered an improvement in clarity or definition and promoted consistency with other portions of the *USP-NF*.
Comment Summary #2: The three commenters suggested that the new section on Reporting and Specifications is unclear regarding the general limit that applies to "total" ordinary impurities rather than "individual" ordinary impurities. One Commenter disagrees with the replacement of the older very clear text with regard to the limit for substances under the class “ordinary impurities” ("The *total* of any ordinary impurities observed does not exceed 2.0%....") with the new wording (".. .value of 2.0%...general limit on ordinary impurities..." is a summation). Two commenters suggested changing the sentence to read, "The value of 2.0%, unless otherwise specified in the individual monograph, was selected as the general limit on total/the total amount of ordinary impurities...."
Response: Comments incorporated. The statement that a 2% limit pertains to the total of all ordinary impurities will be reinserted. This change was inadvertent and should have remained in the draft chapter, as <466> is an evaluation of total ordinary impurities not individual impurities. The statement has been revised to clarify that a 2% limit pertains to the total of all ordinary impurities.
Comment Summary #3: One commenter suggested that the Chapter state that the analytical procedure is used to "evaluate” instead of "control" the presence of ordinary impurities.
Response: Comment incorporated.

Comment Summary #4: Because the Ordinary impurities specification cannot be used (alone) to monitor individual unidentified impurities, one Commenter suggested that General Chapter <466> be revised to convey some discussed risks and shortcomings of the Ordinary Impurities test.
Response: Comment incorporated. The Committee added an additional disclaimer regarding the risks of the Ordinary impurities test.
Comment Summary #5: Commenter is in general agreement with the proposal, but suggested that the <466> either define the term "concomitant components" or reference the definition in <1086>.
Response: Comment incorporated. The definition for "concomitant components" will be copied from <1086> and placed in <466>.

General Chapter: <467> Residual Solvents
Expert Committee: GC
Number of Commenters: 6
Comment Summary #1: One Commenter suggested deleting the statement in the Introduction that indicates that the chapter applies to non-official articles.
Response: Comment incorporated.
Comment Summary #2: Several commenters said that the correction of assay value for residual solvents content will change the compendial definition for those articles for which the assay value is reported on the "as is" basis.
Response: Comment incorporated.
Comment Summary #3: One Commenter suggested reverting to the original language stating that "some solvents" that cause unacceptable toxicities should be avoided. The word "some" would indicate that other toxic solvents might not have to be avoided.
Response: Comment incorporated.
Comment Summary #4: The Veterinary Expert Committee suggested including a statement that higher levels for the PDE can be justified for veterinary products based upon the actual target species.
Response: Comment incorporated.
Expert Committee-Initiated Change: Under *Options for Describing limits of class 2 residual solvents* the formula to calculate the cc of residual solvents was revised to introduce units to the factor 1000.

General Chapter: <621> Chromatography
Expert Committee: GC
Number of Commenters: 1
Comment Summary: Commenter suggested clarifying that system suitability must be demonstrated throughout the run and at the end of the analysis.
Response: Comment incorporated.

Chapter/Section: <660> Containers
Expert Committee: PS
Number of Commenters: 13
Comment Summary #1: One Commenter suggested that the last paragraph of the introductory text (which was added) fails to reflect that the requirement for arsenic testing also applies to Type I containers. It was recommended that the last paragraph be modified as follows:

"The quality of glass containers is defined by measuring their resistance to chemical attack. In addition, Type I containers for aqueous parenteral preparations are tested for arsenic release, and colored glass containers are tested for light transmission."

Response: Comment incorporated
Comment Summary #2: One Commenter suggested revising the current "Powdered Glass Test" methodology so that commercially available autoclaves can be used in testing. Currently, the method calls for the use of manual functions of an autoclave, but it has become increasingly difficult to find an autoclave that allows manual operation.

Response: Comment not incorporated. The Committee does not believe that the current wording of the methodology prevents the use of modern autoclaves.

Comment Summary #3: One Commenter suggested that the sections on "Water Attack at 121° C" and "Surface Glass Test are redundant as they both address the same interior surface issue. The Commenter suggested that if the "Surface Glass Test" is to be added, the "Water Attack at 121° C" should be removed as the two tests have different limit specifications that are not compatible

Response: Comment incorporated. The Committee has made the "Water Attack at 121° C" an optional test to qualify Type II Glass.

Comment Summary #4: One Commenter noted that Table II does not reflect any requirement for the "Surface Glass Test" in classifying containers and suggested that if the "Surface Glass Test" is intended as a required test, the table should reference it and its limits.

Response: Comment not incorporated. The testing limits for the Surface Glass Test are given in Table 3.

Comment Summary #5: One Commenter noted that the specifications for "High-Purity Water" require in-line monitoring of conductivity at the time of dispensing. This precludes the use of bottled water of suitable quality in situations where a deionized water system is not available. This specification would limit the overall applicability of the test.

Response: Comment not incorporated. The Committee will investigate and see if the specification for "High Purity Water" limits the overall applicability of the test. If it is determined to be an industry issue, the Committee will consider revising the Chapter.

Comment Summary #6: One Commenter suggested that the language describing the determination of fill volume for the "Surface Glass Test" is unclear. It is left to the reader to determine how to get from the mass of water contained in the container to the equivalent volume in mL. While it is reasonable to assume that the volume should be the mass divided by the ambient temperature density of 1.00 g/ml, the Commenter suggested that it would not hurt to say so.

Response: Comment not incorporated. The Committee determined this not to be an issue in performing the test.

Comment Summary #7: One Commenter felt that the language describing the rinsing process for the "Surface Glass Test" is unclear and requested clarification. The Commenter inquired whether the water used in the rinsing process should be left in the container and discarded immediately before testing, and inquired about the volume of water to be used in rinsing.

Response: Comment not incorporated. The Committee does not feel that this needs to be rewritten.

Comment Summary #8: One Commenter noted that the "Surface Glass Test, Cleaning" procedure calls for carbon dioxide free water, but this term is not defined in <660>.

Response: Comment incorporated. The Committee added a definition.

Comment Summary #9: One Commenter noted that the autoclave cycles for both the "Powdered Glass Test" and the "Surface Glass Test" are effectively the same other than the hold time, and requested that the same description be used for both. The Commenter suggested using the more general description of the "Powdered Glass Test" for both.

Response: Comment not incorporated. The Committee does not feel that a rewrite is needed.

Comment Summary #10: One Commenter suggested that the section "Arsenic" refer to a test preparation prepared as under "Surface Glass Test."

Response: Comment incorporated.

Comment Summary #11: Commenter noted that the titration under "Surface Glass Test" is difficult because the volume of methyl red solution specified is the same as that prescribed in EP 3.2.1, but the concentration of the methyl red solution used is significantly lower (1.86 mM EP, 0.83 mM USP).

Response: Comment incorporated. The protocol for making a 1.86 mM Methyl red Solution was added to the Reagent Section.

Comment Summary #12: One Commenter suggested that the restrictive wording under "Mortar and Pestle" implies that a device exactly matching the stated dimensional specifications must be used, and should be broaden to allow the use of any similar steel mortar and pestle.

Response: Comment incorporated, mortar and pestle diagram was updated.

Comment Summary #13: The revision of the "Powdered Glass Test" protocol provides an opportunity to refer to reference materials which can be used by laboratories in validation of their work. NIST provides two Standard Reference Materials (622, Type III and 623, Type I) with certified values for the powdered glass test. It has been the commenter's experience that these are helpful for laboratories and analysts in evaluating the quality of their test results.
Response: Comment not incorporated at this time. The Committee will look into the various reference materials for glass that are currently available and will consider including these standard in the chapter in the future.

General Chapter/Section: <661> Containers—Plastics/Multiple Internal Reflectance
Expert Committee: PS
Number of Commenters: 1
Comment Summary: Currently, suppliers call Multiple Internal Reflectance by different names. Commenter suggests changing "Multiple Internal Reflectance" to "Multiple Internal Reflectance (MIR) Spectrophotometry (also known as Attenuated Total Reflectance (ATR) Spectroscopy)."
Response: Comment not incorporated at this time. The Committee will consult with the General Chapters Expert Committee on the interchangeability of Multiple Internal Reflectance (MIR) Spectrophotometry and Attenuated Total Reflectance (ATR) Spectroscopy and will consider including the terms in the chapter in the future if they are interchangeable.

General Chapter/Section: <671>Containers- Permeation
Expert Committee: PS
Number of Commenters: 2
Comment Summary #1: Commenter felt that a section on "Single-Unit Containers and Unit Dose Containers for Capsules and Tablets" should be included.
Response: There is a section on Single-Unit Containers and Unit Dose Containers for Capsules and Tablets in chapter.
Comment Summary #2: Commenter was concerned with the removal of the following exemption from performance testing:

"Where the manufacturer's unopened multiple unit, single unit, or unit dose packages are used for dispensing the drug, such containers are exempt from the requirements of the test"

It was noted that the performance test requires opening and closing containers 30 times prior to addition of desiccant. This requirement would not be practical for PS-22 lined or induction sealed bottles, where the seal integrity would be damaged with opening and closing. Thus, the exemption would allow the avoidance of this test on containers for which the exemption is applicable.
Response: With the current testing methods the manufacturer has the option of testing the unopened and opened container.

Chapter/Section: <681> Repackaging Into Single-Unit Containers and Unit-Dose Containers for Nonsterile Solid and Liquid Dosage Forms/ An Official Dosage
Expert Committee: PS
Number of Commenters: 4
Comment Summary #1: One commenter suggested that the exemption of repackaged drugs from expiration date labeling be clarified to state that the exemption is only allowable as long as the assigned expiry is within the assigned manufacturer or distributor original package. Recommended rewrite:

"Because the expiration date stated on the manufacturer's or distributor's package has been determined for the drug in that particular and is not intended to be applicable to the product where it has been repackaged in a different container, repackaged drugs dispensed pursuant to a prescription are exempt from this expiration date labeling requirement <u>as long as the assigned expiry is within that assigned by the manufacturer or distributor in the original package.</u>

Response: Comment incorporated.

Comment Summary #2: One commenter noted that the expiration date assigned by the manufacturer should be taken into account when determining expiration dates for repackaged dosage forms.
Response: Comment incorporated.
Comment Summary #3: One commenter suggested that the upper relative humidity limit of 75% for repackaging and storage should be lowered to 60% RH for consistency with ICH guidelines for long-term stability. The commenter also suggested removing the 23° temperature range because controlled room temperature is already specified.
Response: Comment incorporated.
Comment Summary #4: One commenter suggested that the moisture permeation requirement for patient med pak containers be clarified and/or re-stated because the reference to Class B single-unit or unit-dose container (see Container-Permeation <671>)" needs revision due to the concurrent update of <671> in PF 32 (4). The commenter felt that this section should require the moisture permeation characteristics of the patient med pak package to be at least equivalent to that of the original manufacturer's packaging, to ensure that the product is not unduly exposed to conditions detrimental to product stability
Response: Comment not incorporated. There has been no change in the Class B designation for single-unit or unit-dose container as outlined in Container-Permeation <671> and therefore there is no need to clarify requirements for patient med paks.

General Chapter/Section: <721> Distilling Range
Expert Committee: GC
Number of Commenters: 1
Comment Summary #1: Commenter suggested changes in grammar and reinsertion of deleted text to clarify or improve upon the requirements as stated in the General Chapter.
Response: Comment incorporated. The Committee reviewed each of these language changes to determine whether it offered an improvement in clarity or definition or otherwise identified textual problems that were not previously noted by USP. They agreed with the suggested changes.
Comment Summary #2: One commenter stated that the ASTM numbers for specific thermometers should not be changed.
Response: Comment incorporated.
Comment Summary #3: The commenter suggested that the Committee reinsert the statement "and apply the emergent stem correction where necessary" in the Procedure section since this is a necessary correction.
Response: Comment incorporated. The Committee agrees with all comments.

General Chapter/Section: <1086> Impurities in Official Articles
Expert Committee: GC
Number of Commenters: 5
Comment Summary #1: Several commenters suggested changes in language, grammar, terminology, punctuation, sentence structure, and other editorial changes to clarify or improve upon the requirements as stated in the General Chapter or to eliminate redundancies or inconsistencies. Those proposals that raised significant policy questions, suggested changes in the substance of the General Chapter, or otherwise required, in the Committee's opinion, a specific response, are discussed individually below. Many of the suggested changes, however, were more editorial and stylistic and do not warrant a detailed discussion.
Response: Comment partially incorporated. The Committee reviewed each of these numerous editorial and language changes to determine whether it offered an improvement in clarity or definition, eliminated an obvious error or redundancy, promoted consistency with other portions of the *USP-NF*, or otherwise identified textual problems that were not previously noted by USP. Where the proposed alternative language or other changes suggested were superior to the proposal, they were adopted in substance or verbatim. Where they did not offer any improvement the Committee declined to accept

them. The decisions made by the Committee do not change the spirit of the documents that were published in the *PF* proposal.

Comment Summary #2: Commenter feels that the portion of this chapter providing updated classification and definition of the types of impurities that might be included in a typical USP monograph specification is appropriate.

Response: Comment appreciated.

Comment Summary #3: The commenter doesn't see a need for the chapter to characterize the approach used for setting specifications in existing or non-monograph articles during the various phases. They think that ICH Q3A, Q3B, and related ICH documents, as well as FDA guidance, provide Investigational New Drug (IND), New Drug Application (NDA), and Abbreviated New Drug Application (ANDA) applicants and holders adequate advice on setting appropriate limits for impurities at during a product's development and lifecycle. This Chapter could simply reference the CDER public website.

Response: Comment not incorporated. The information on INDs, NDAs, and ANDAs will not be removed. This information has been included since the beginning of the development of this chapter. The information does not contradict ICH or FDA guidance. Reference to a public website is risky because websites change over time.

Comment Summary #3: Two commenters made recommendations to improve the clarity of the wording. Commenters asked for the wording "uniquely different" to be changed to "significantly different."

Response: Comments incorporated. In general, they appear to be acceptable and consistent within the context of the General Chapter. The statement about the impurity profile being "uniquely different" will be changed to "significantly higher" for the lots used for the additional studies. The wording could be changed to "significantly different." The use of the word "significant" implies statistics. The section is not talking about quantitation, but an overall profile. Surprise impurities should not appear later.

Comment Summary #4: One commenter proposes the inclusion of the ICH 3A (R2) thresholds based on the daily doses, preferably under General Notices or in both General Notices and <1086>. The ICH general acceptance criteria for any unspecified impurity of Not more Than (NMT) 0.10% for doses <= 2 g/day or NMT 0.05% for doses > 2 g/day are those established already in the European Pharmacopoeia. The commenter thinks that the inclusion of these standards would align with their current practice, and be a reasonable approach for any company already in compliance with ICH and Ph. Eur. requirements.

Response: Comment partially incorporated. A sentence such as "Other information for setting limits can be found at…." will be added. The ICH 3A (R2) impurity thresholds based on the daily doses will not be included, as this would not be consistent with the General Notices and is not appropriate for an information chapter. The added sentence could refer the user to the ICH guidance without including the numbers.

Comment Summary #5: Another commenter suggests incorporating requirements for Reporting, Identification and Qualification thresholds based on Total Daily intake for Drug substances and Drug Products; the addition of guidance in setting of specifications limits for drug substances of Semi-synthetic routes of synthesis and their corresponding drug products, as well as specific guidance on Antibiotics; and including, with the list of parameters on which the setting of the limits for impurities depends, details of how the setting up of the limits are affected by each parameter mentioned.

Response: Comment not incorporated. Specific guidance on antibiotics or semi-synthetic routes of synthesis will not be included. The introductory section states that <1086> does not apply to biologics, radiopharmaceuticals, or more complex products.

General Chapter/Section: <1163> Quality Assurance In Pharmaceutical Compounding

Expert Committee: CRX

Number of Commenters: 1

Comment Summary #1 : Commenter noted that the General Chapter as written relies more on analytical testing and not enough on personnel training, evaluation of data obtained by lab scientists, and action taken after deviations. A Quality Assurance must have quality built into the system and not

have quality tested by finished product testing. It is important to have adequate QA programs and staff.

Response: Comment partially incorporated. For example, there are additions on training, reviewing for accuracy, what to do when deviation occurs or when preparations do not meet specifications, and investigations and corrective actions extended to other possible preparations. In the STANDARD OPERATING PROCEDURES section, the Committee added that a statement of what to do if a deviation occurs is a necessary part of standard operating procedures for pharmaceutical compounding.

Comment Summary #2: Commenter recommended that irrigants (irrigations) be added to Table 2: Suggested Analytical Methods for Various Dosage Forms, Depending upon the Active Drug in the Testing Methods section. The last paragraph in this section which lists the various analytical methods should be moved immediately above Table 2.

Response: Comment incorporated. Irrigations as a dosage form is added to Table 2, with the same analytical methods as inhalations and injections. The last paragraph was moved above Table 2, which is now Table 1 (see below).

Expert Committee-Initiated Change: In the Verification section, the Committee removed the condition that the responsibility for assuring that equipment performance is verified resides with compounding personnel, but may be performed by the contractors. Instead, the Committee inserted the following: The responsibility for assuring that equipment performance is verified, including work completed by contractors, resides with the compounder.

The title of the Testing section was changed to Testing of Finished Compounded Preparations and a statement (7) what to do if the preparations listed do not meet specifications is added.

The Committee removed the requirement 21 CFR Part 58, FDA's Good Laboratory Practices for external laboratories since that CFR is specific for non-clinical studies in support of drug applications submitted to FDA.

Table 1, Classification of Analytical and Microbiological Methods was changed to a listing titled Classification of Analytical Methods. Table 2, Suggested Analytical Methods for Various Dosage Forms, Depending Upon the Active Drug was relabeled Table 1.

A footnote of microbial limits by *Microbial Limit Tests* <61> was added for Nasals dosage form.

Under Microbiological Testing, Microbial Limit Testing was added as a subsection and part of microbiological testing for pharmacy compounding that also includes Sterility Testing and Endotoxin Testing in the section Microbiological Testing.

General Chapter: <1226> Verification of Compendial Procedures

Expert Committee: GC

Number of Commenters: 6

Comment Summary: Commenters generally supported the desirability of this General Information Chapter, and consider this proposal published in PF 32(4) much improved from the previous version. Most of the commenters suggested changes in language, grammar, terminology, and other editorial changes to clarify or improve the General Chapter or to eliminate redundancies or inconsistencies. Those proposals that raised significant policy questions, suggested changes in the substance of the General Chapter, or otherwise required, in the Expert Committee's opinion, a specific response, are discussed individually below. Other changes were more editorial and stylistic and do not warrant a detailed discussion.

Response:

- Under the introduction and in others parts of the chapter the word "laboratories" was deleted to indicate that the purpose of the verification process is to challenge the sample matrix not the laboratory.
- Under Verification process, the reference on how to establish acceptance criteria for the verification process was eliminated indicating that it is the user's responsibility to assure that the procedure will perform suitably as intended

General Chapter/Section: <1231> Water for Pharmaceutical Purposes/Type of Water
Expert Committee: PW
Number of Commenters: 2
Comment Summary #1: Commenter suggested removal of the reference to “clean steam” in the first paragraph because it may be misleading.
Response: Comment not incorporated. The Expert Committee felt that the language used to describe potential uses of Pure Steam is adequate to provide the intended guidance, and is not likely to result in interpretation errors.
Comment Summary #2: Commenter suggested clarification of the term “porous” and the inclusion of examples.
Response: Comment not incorporated. The Expert Committee accepted the general descriptive terms and further descriptive text in the paragraph as sufficient, without cited examples.
Comment Summary #3: Commenter proposed the inclusion of “particulate matter” as an additional source of undesirable contaminants.
Response: Comment not incorporated. Though particulates themselves are undesirable contaminants of *Pure Steam*, the sentence in question is referring to "sources of undesirable contaminants." Particulate contaminants almost certainly are among the "residues from the steam production and distribution system" since that is their most likely origin. Therefore, particulate contaminants are already inferred as a resulting contaminant from the sentence you have targeted for change. We feel that the existing attribute tests will adequately control all the undesirable contaminants arising from the sources listed in that sentence. Furthermore, since particulates are not an attribute of *Pure Steam* (nor of *Water for Injection*, the basis of the *Pure Steam* attributes), it would be inappropriate to specifically name them as a potential contaminant in the informational chapter without providing a specification for them in the monograph.
Comment Summary #4: Commenter suggested revision of the second paragraph to promote the concept that the contaminants should be removed before the production of Pure Steam.
Response: Comment not incorporated. There is an assumption throughout all USP monographs, including Pure Steam, that the contaminants as detected by the prescribed tests must be controlled in order to meet the requirements of those tests.
Comment Summary #5: Commenter suggested revision of the second paragraph to remove the phrase “or other applications where the pyrogenic content must be controlled” since the monograph only requires bacterial endotoxin testing.
Response: Comment not incorporated. The wording of this sentence was carefully chosen to include in general terms all other potential applications without specifically naming each one and risk leaving some out, which might create even more confusion.
Comment Summary #6: Commenter suggested revision of the final paragraph to make it more understandable.
Response: Comment not incorporated. Though the wording may be difficult for some to understand, the words were carefully chosen to unambiguously represent most of the situations where plant steam would be appropriate.
Comment Summary #7: Commenter suggests additional text be added to the Note in order to provide guidance with respect to the application of plant steam and pure steam.
Response: The Expert Committee felt that the suggested additional text did not materially clarify the intent of this portion of the chapter and that the wording of the section should remain unchanged.

Excipients

Monograph/Section: Almond Oil/Fatty acid composition
Expert Committee: EM2
Number of Commenters: 1
Comment Summary #1: New specifications for Fatty acid composition were suggested and supporting data were provided.
Response: Comment incorporated
Expert Committee-initiated change: CAS no [8007-69-0] is added into the monograph
Expert Committee-initiated change: In order to eliminate the source for Bitter Almond Oil, the monograph definition has been changed as follows: "Almond Oil is the refined fixed oil obtained by expression from the kernels of varieties of *Prunus dulcis* (Miller) D.A. Webb (formerly known as *Prunus amygdalus* Batsch) (Fam. Rosaceae), except for *Prunus dulcis* (Miller) D.A. Webb var. amara (De Candolle) Focke. It may contain suitable antioxidants."

Monograph/Section: Carbomer Copolymer/Limit of benzene
Expert Committee: EM2
Number of Commenters: 1
Comment Summary: Based on the calculation used in Limit of benzene test**,** incorrect result will be generated.
Response: Comment incorporated. Calculation in Limit of benzene is revised

Monograph/Section: Palm Kernel Oil/Multiple sections
Expert Committee: EM2
Number of Commenters: 3
Comment Summary #1: Briefing section: The new monograph is stated to be derived from the Cottonseed Oil, NF and Palm Kernel Oil, FCC monographs. Incorporating certain tests from the current FCC monograph would make this proposed monograph inconsistent with analogous vegetable oil USP-NF monographs. A general recommendation is to consider making all vegetable oil monographs (for example, Peanut Oil, NF; Olive Oil, NF) similar with regard to the battery of tests performed.
Response: In the briefing for Palm Kernel Oil monograph, "Cottonseed Oil NF" should not be taken as a basis because the text was simply following the Briefing of "Canola Oil" *PF* 31(6) [Nov-Dec 2005] that was developed in previous convention cycle. Coconut Oil (*PF* 32(2) [Mar-Apr 2006]) was the first new oil monograph developed through current Committee and should be an example. Revision for Almond Oil (PF 32(4) [Jul-Aug 2006]) brought this outdated monograph to a current status. In the continued efforts, the Committee developed and proposed new oil monographs: Palm Kernel Oil in PF32(5) [Sept-Oct 2006], Fully Hydrogenated Rapeseed Oil and Superglycerinated Fully Hydrogenated Rapeseed Oil in PF32(6) [Nov-Dec 2006]. The Committee is working on a position paper for setting test specifications for these oil articles. Based on the paper, these existing, outdated oil monographs will be revised.
Comment Summary #2: In the Packaging and storage section, commenter recommended removing the statement "No storage requirements specified." This is because this oil is typically shipped and stored in large bulk containers that are continually heated to prevent congealing, and excessive heating can lead to degradation of the oil.
Response: Comment incorporated. The Committee decided to remove the statement "No storage requirements specified" as recommended and add "Do not store above 45°C".
Comment Summary #3: Residual Solvents: Commenter suggested that the monograph include some type of reference to the *General Notices* residual solvents test requirement, to be consistent with several other NF vegetable oil monographs that currently reference the <467> OVI test. A reference to the new *General Notices* section is desirable here because it is possible that solvents may be used by certain manufacturers to extract the oil. Manufacturers of palm kernel oil (or any

compendial article) will still retain the option to certify absence of solvents if none are used, and therefore not be required to routinely perform this testing.
Response: Comment not incorporated. The monograph sponsor does not extract this oil using solvent. The "Residual Solvents" requirement in USP General Notices soon will be mandatory for all compendial articles.

Monograph/section: Corn Syrup Solids
Expert Committee: EM2
Number of Commenters: 1
Comment Summary: Under Packaging and Storage, product should be stored in a "cool" dry place (can melt between 90-100° F).
Response: Comment incorporated.
Expert Committee-initiated change: In the *Labeling* section, change "mg per Kg" to "μg per g".
Expert Committee-initiated change: In *Limit of sulfuric dioxide, Limit of lead,* and *Assay for reducing sugars*, eliminate the reference to Corn Syrup monograph and provide detailed procedures in the monograph to make it an independent monograph.

Monograph/Section: Carboxymethylcellulose Sodium, Carboxymethylcellulose Sodium Paste, Carboxymethylcellulose Calcium
Expert Committee: EM2
Number of Commenters: 1
Comment Summary: Commenter questioned about four revisions for Carboxymethylcellulose Sodium, Carboxymethylcellulose Sodium Paste, Carboxymethylcellulose Calcium, Carboxymethylcellulose Sodium 12: *PF* 31(5) Page 1349 and Page 1420. Heavy metals tests have to be aligned with the official publication and not *PF* proposal in *PF* 31(5).
Response: The revision to the Heavy metals chapter proposed in *PF* 31(5) is not official. The IRA for that chapter published in *PF* 32(3) stated "In response to comments from industry, USP is reverting back to the Heavy Metals text that appeared in *USP 28-NF 23* for *Heavy Metals*, *Method II*. The *USP 28-NF 23* test has been used in industry for some time. The search continues for a more robust and practical method." As shown in the following texts, the Committee decided to keep the original test by eliminating the reference to "*Methylcellulose*" in order to form an independent text in each monograph.
Expert Committee-initiated change: An inconsistent statement was found in the revision for Labeling with Viscosity specs. The following text is suggested by the Committee.
"Labeling—Label it to indicate the nominal viscosity in solutions of stated concentrations of either 1% (w/w) or 2% (w/w). The indicated viscosity may be in the form of a range encompassing 80.0% to 120.0% of the nominal viscosity, where the solution concentration is ~~1% (w/w)~~ 2% (w/w); ~~and~~ or 75.0% to 140.0% of the nominal viscosity, where the solution concentration is ~~2% (w/w)~~ 1%(w/w)."