



Commentary – USP 34-NF 29

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

No comments were received for the following proposals:

General Chapters:

- <11> Reference Standards
- <521> Sulfonamides
- <561> Articles of Botanical Origin
- <727> Capillary Electrophoresis
- <1053> Biotechnology-Derived Articles—Capillary Electrophoresis
- <1070> Emergency Medical Services Vehicles and Ambulances—Storage of Preparations
- <1230> Water for Hemodialysis Applications (formerly Water for Health Applications)
- <2030> Supplemental Information for Articles of Botanical Origin
- <2040> Disintegration and Dissolution of Dietary Supplements

Monographs

- Acetyltributyl Citrate
- Alpha Lipoic Acid Capsules
- Alpha Lipoic Acid Tablets
- Aluminum Oxide
- American Ginseng Capsules
- American Ginseng Tablets
- Amifostine for Injection
- Amphetamine Sulfate
- Arginine Capsules
- Asian Ginseng Tablets

No comments received for the following proposals (continued):

Monographs (continued)

Balsalazide Disodium Capsules
Black Cohosh Tablets
Cat's Claw Capsules
Cat's Claw Tablets
Chlorhexidine Acetate
Chlorhexidine Acetate Topical Solution
Chlorhexidine Gluconate Solution
Chlorhexidine Hydrochloride
Clotrimazole
Clotrimazole Cream
Desflurane
Diltiazem Hydrochloride Tablets
Diluted Nitroglycerin
Ethambutol Hydrochloride
Fish Oil Containing Omega-3 Acids Capsules
Gadodiamide Injection
Ginger Capsules
Glyburide and Metformin Hydrochloride Tablets
Halobetasol Propionate
Iodixanol Injection
Iohexol Injection
Letrozole
Letrozole Tablets
Levocabastine Hydrochloride
Levonorgestrel and Ethinyl Estradiol Tablets
L-Glutamic Acid, Hydrochloride
Lithium Carbonate Tablets
Methylphenidate Hydrochloride Extended-Release Tablets
Oil-Soluble Vitamins Capsules
Oil-Soluble Vitamins Tablets
Oxaliplatin
Paramethasone Acetate
Paramethasone Acetate Tablets
Polyethylene Oxide
Polyoxyl Stearyl Ether
Propafenone Hydrochloride
Pygeum Capsules
Quinidine Sulfate Oral Suspension
Saw Palmetto Capsules
Sertraline Tablets
Sevoflurane
Soy Isoflavones Capsules
Soy Isoflavones Tablets

No comments received for the following proposals (continued):

Monographs (continued)

Spironolactone
Sulfasalazine
Sulfasalazine Tablets
Terbinafine Tablets
Triethyl Citrate
Valerian Tablets
Venlafaxine Tablets
Water for Hemodialysis
Water for Injection

General Notices

Committee: Council of Experts Executive Committee

No. of Commenters: 2

Comment Summary #1: The commenter suggested that the language in 2.30 “Legal Recognition” be further clarified, with one commenter suggesting that identity standards not be described separately from the other compendial standards.

Response: Comments for further overall clarification accepted in part, to make clearer exactly which legal and regulatory sources apply to specific authority and text. The text retains a separate description of identity, with the addition of specific legal and regulatory citations.

Comment Summary #2: The commenter suggested that the language to allow the early adoption of revised standards in 3.10 “Applicability of Standards” make clear that the affected standards are those that have been published but are not yet official; and that USP also provide a specific mechanism for indicating when a standard is not appropriate for early adoption, as part of standard development.

Response: Comment incorporated.

Comment Summary #3: The commenter suggested that the language regarding articles being “stored as directed” in 3.10 “Applicability of Standards” delete the parenthetical phrase “(by the manufacturer, consistent with any applicable standards).”

Response: Comment incorporated

Comment Summary #4: The commenter indicated with regard to language including a reference to good manufacturing practice in the “Official products” paragraph of 3.10 “Applicability of Standards” that the existing exception for dietary supplements (unrelated to the subject of good manufacturing practice) would no longer be appropriate to the overall revised paragraph.

Response: The “Official Products” paragraph was amended with a parenthetical indicating the applicability of standards to dietary supplements is addressed in section 3.10.20. If further clarification to that section should prove advisable, it can be considered in a future revision.

Comment Summary #5: The commenter suggested that 5.40 “Identity Test” retain the existing stated purpose of being an aid in verifying that the article being tested is what

the labeled container purports it to be, but not as proposed to make USP “Identity” tests sufficient alone to establish proof of compendial identity.

Response: Comment accepted in part, to reinsert the original purpose statement, in conjunction with also establishing as a purpose, as proposed, compendial identity—whether an article is the article named in *USP-NF*.

Comment Summary #6: The commenter recommended deferring addition of 5.60.30 “Elemental Impurities in *USP* and *NF* Articles” until it can be more closely coordinated with the final publication of new General Chapters pertaining to limits and procedures (<232> and <233>).

Response Comment incorporated.

General Chapters

General Chapter: <1> *Injections*, section on Labeling of Ferrules and Cap Overseals

Expert Committee: Nomenclature

No. of Commenters: 6

Comment Summary #1: The commenter indicated that USP should seek and apply scientific concepts to this standard (e.g., human factors studies) and encouraged USP to test the final design standard on end-users to ensure its effectiveness in preventing medication errors and to maintain those data in support of the standard.

Response: The Expert Committee determined there was not sufficient reason to conduct or await any studies prior to the release of the standard. USP standards are in a process of continuous review and revision based upon new evidence, emerging public health concerns, and public requests for revision. The ongoing role of USP Expert Committees is to evaluate new data and to shape standards based upon the available evidence, public input and the Expert Committee’s expertise. Such standards are always subject to further revision as additional evidence becomes available.

Comment Summary #2: The commenter suggested that the proposed USP standard may have unintended consequences. The commenter provided a commissioned, unpublished human factors engineering (HFE) evaluation of 20 healthcare practitioners (HCPs) handling injectable products in a variety of simulated scenarios. The authors of the HFE evaluation concluded that 1) HCPs are generally not used to viewing cap labels; 2) HCPs made many errors, with or without cap labels; 3) Some HCPs indicated that they did not notice the cap labels in the study; 4) When cap labels were noticed and used, HCP performance was better and faster; and 5) When HCPs were trained to cross-check the vial label with the cap label, there was an increased benefit to drug selection accuracy and time. Post-interviews of HCP participants revealed a) belief that reducing the incidence of cap labels would actually further reduce the likelihood of HCPs noticing any label that does exist, b) preference of HCPs towards having cap labels, c) concern that removing cap labels may increase medication errors, and d) belief that cap labeling could be useful and improve patient safety if they were more common and HCPs were explicitly trained to make use of them. The results of the survey were presented to the Expert Committee for their review and consideration.

Response: The Expert Committee was not persuaded that the results of the HFE evaluation were in opposition to the proposed standard, as the experimental scenarios did not test the proposed standard. The Expert Committee did not agree with the commenter's suggestion that the results of the HFE evaluation warranted changes to the standard.

Comment Summary #3: Several commenters indicated that the proposed revision would increase risk to patients by forbidding the use of anticounterfeiting measures on the cap.

Response: Comments not incorporated. The Expert Committee determined that the proposed standard does not forbid the use of anticounterfeiting measures from appearing on the vial skirt, label, or cap and ferrule as long as it does not appear on the top (circle) surface of the vial and does not interfere with the cautionary statement.

Comment Summary #4: The commenter suggested minor wording changes to clarify the intent of the proposed revision. The suggestion was to add "cautionary statements" in place of "such statement" and add "free of nonessential information" in place of "clearly differentiated."

Response: Comment incorporated.

Comment Summary #5: The commenter suggested that the phrase "busy" healthcare practitioners implied that such practitioners are too busy to read labels. The commenter suggested removing the term "busy."

Response: Comment incorporated.

Comment Summary #6: The commenter indicated that additional examples such as "Not for Lock Flush" should be added to this section of the general chapter.

Response: Comment not incorporated. The two cautionary statements indicated in the general chapter are examples only.

General Chapter: <90> Fetal Bovine Serum-Quality Attributes and Functionality Tests

Expert Committee(s): Biologics and Biotechnology—Cell, Gene and Tissue Therapies

No. of Commenters: 4

Comment Summary #1: In the section on *Processing*, several commenters suggested that the use of closed system for FBS collection using an aseptic technique is not practical because true aseptic is difficult to attain in an abattoir situation.

Response: Comment incorporated.

Comment Summary #2: In the section on *Processing*, a commenter suggested revising the paragraph on mycoplasma testing, deleting the sentence "Large-volume sampling is important to detect low levels of mycoplasma" and provide clarification on how mycoplasma testing is performed on FBS samples.

Response: Comment incorporated. The whole paragraph describing mycoplasma testing was deleted and a reference was made to recently published chapter <63> *Mycoplasma Testing*, which provides detailed guidance on this type of testing.

Comment Summary #3: In *Packaging and Storage*, a commenter suggested that storage should not be temperature specific, as long as serum is frozen and propose changing "Store in sealed containers at a temperature of -10° or below." to "Store in sealed containers at frozen temperatures."

Response: Comment not incorporated because storage at temperatures below -10° is important for stability of FBS as stated on certificate of analysis provided by suppliers.

Comment Summary #4: On the USP FBS RS, a commenter suggested the possibility of using an in house RS in addition of the USP RS. Commenter is also asking if the RS will be irradiated.

Response: Comment not incorporated. If users want to use their in house RS, they can do so but they will not be able to claim compliance with tests with an official use of the RS. The USP RS will be irradiated and this information will be part of the CoA and RS package.

Comment Summary #5: A commenter suggested revising ranges for pH [from 7.00-8.00 to 6.9-8.00] and Osmolality [280–360 to 270-330 mOsm/Kg] because some manufacturers supply serum outside the specified ranges.

Response: Comment not incorporated. The proposed ranges were based on survey of manufacturers and confirmed or adjusted based on a laboratory study conducted by USP.

Comment Summary #6: A commenter suggested changing the limits on endotoxin to “less than 25 EU/mL” instead of “less than 10 EU/mL.” The rationale is to align with EP 2262. Some manufacturers have other specifications, and commenter proposes to extend the range to reflect field reality as this is a new chapter.

Response: Comment not incorporated. A limit of 25 EU is high because FBS is a product where endotoxin levels should be very low or absent. Besides the laboratory study on several lots of FBS showed that actual endotoxin levels are always ≤1 EU/mL.

Comment Summary #7: In the Identification test, a commenter suggested adding the following statement before the description of RID procedure: In the absence of a user-defined identification assay, the following test should be performed. Rationale is to leave it open for using other methods

Response: Comment not incorporated. The USP General Notices 6.30 states that alternative methods can be used provided these methods have been validated and found equivalent to the compendial procedure (although only those results obtained by the methods and procedures given in the compendium are conclusive).

Comment Summary #8: In Functionality Tests—Acceptance criteria, several comments suggested changing “The doubling time of the test sample should be no less than 90% of the doubling time of USP Fetal Bovine Serum RS.” Instead a commenter suggests using the following “Compare results between lots of FBS, and select a serum lot that is good for various types of cells and optimal for a specific cell culture application.”

Response: Comment not incorporated because the use of a USP FBS RS is prescribed as an official use in General Chapter <90>. Comparing FBS lots to be tested to other lots will not meet the requirement of official use.

General Chapter/Section(s): <621> Chromatography

Expert Committee(s): General Chapters

No. of Commenters: 8

Comment Summary #1: A commenter recommended including a short discussion on the importance of setting proper minimum acceptable plate number and corresponding minimum resolution requirements for critical peak pairs in a separation.

Response: Comment not incorporated because the Expert Committee does not consider it appropriate to include values for efficiency and resolution in the general chapter. Those values should be stated in the individual monograph and determined based on the intended use of the procedure and validation data.

Comment Summary #2: A commenter suggested that detailed information about different chromatographic techniques would be best placed in a general chapter greater than <1000>, as supporting information for General Chapter <621> *Chromatography*.

Response: Comment not incorporated. A greater number of commenters suggested *eliminating* this information from USP (see *Comment Summary #7*)

Comment Summary #3: A commenter suggested that the specific procedure for "spotting description" contains too much detail to be generally useful.

Response: Comment not incorporated because the committee felt this level of detail was necessary to assure the standardization of a pharmacopeial procedure.

Comment Summary #4: A commenter suggested that it would be helpful to add a short description of UHPLC, in order to accommodate this new LC method within this revision to anticipate and avoid future revisions on this topic.

Response: Comment not incorporated. The topic of UHPLC is discussed separately in a Stimuli article published in *PF* [see *Pharmacopeial Forum* 35(6), page 1622-1626, 2009].

Comment Summary #5: A commenter indicated that signal-to-noise ratio definition should be consistent with the European Pharmacopoeia (*PhEur*) and additional clarification for baseline drift and overlapping adjacent peaks could be added.

Response: Comment not incorporated. The definition of this parameter is under discussion both in the US and Europe. Depending on the results of these discussions a future revision could be presented

Comment Summary #6: Several commenters indicated their concerns about adopting the repeatability requirements from *PhEur* 2.2.46. The repeatability requirements do not need to be as stringent as described in *PhEur* 2.246. Furthermore, laboratories in industry may have problems meeting the requirements of the European Pharmacopoeia, especially some quality control laboratories, where older instrumentation may still be utilized.

Response: Comment not incorporated. The proposed precision requirements will apply only to those drug substances and excipient monographs where the maximum %RSD is not specified. Introducing this requirement in this way will improve the quality of new monographs without materially affecting those already official. Assay specifications for Drug substances are typically in the range of 98.0 to 102.0%. The GC EC believes that the maximum permitted %RSD should be derived from the compendial specifications. %RSD NMT 2.0 for the injection repeatability, usually adopted in USP monographs, is inconsistent with the assay specifications.

Comment Summary #7: Several commenters recommend that the information that is not critical or intended to be enforceable be removed from General Chapter <621> and from USP-NF altogether. This information is readily available in other sources outside compendia such as text books, training courses, and technical literature.

Response: Comment incorporated

Comment Summary #8: A commenter suggested including definitions for the parameters used in the formula for calculating the symmetry factor.

Response: Comment incorporated

Comment Summary #9: A commenter suggested that the calculations for resolution and efficiency using the tangent method not to be removed from General Chapter <621>. From the practical viewpoint, most chromatographic software programs still use the tangent method as an option for calculating both parameters.

Response: Comment incorporated

Comment Summary #10: A commenter suggested incorporating definitions of correction factor and response factor using wording as in *PhEur* 2.2.46.

Response: Comment not incorporated because adopting this approach will impact several existing monographs.

Expert Committee-initiated Change #1: The Expert Committee revised the definition of *Relative retention* and added a new entry for *Relative retention time* as this term is widely used in monographs.

Expert Committee-initiated Change #2: Under System suitability, at the end of the paragraph starting with "The signal-to-noise ratio, the phrase "after the injection or application of a blank" was deleted. The statement was unintentionally introduced during the preparation of the revision. This change reestablishes the original text.

General Chapter/Sections: <795> Pharmaceutical Compounding—Nonsterile Preparations/Multiple Sections

Expert Committee(s): Compounding Pharmacy

No. of Commenters: 22

Introduction

Comment Summary #1: The commenter suggested that the last sentence in the *Introduction* should be clarified so that the health care professional engaged in the compounding of drug preparations will comply with applicable state and federal laws, regulations and guidelines.

Response: Comment incorporated.

Definitions

Comment Summary #1: The commenter suggested that when referring to a "device," a more accurate description would be "medical device."

Response: Comment incorporated.

Comment Summary #2: The commenter indicated that the word "product" in the *Preparation* definition should be in quotation marks.

Response: Comment incorporated.

Comment Summary #3: The commenter suggested that under the examples of manufacturing, in the first example "for the promotion and marketing of such drugs or devices" be deleted.

Response: Comment incorporated.

Comment Summary #4: The commenter indicated that the fourth bullet under the definition of *Compounding* implies that preparing drugs for research purposes is

considered to be compounding. They note that drugs prepared for research purposes, when conducted under an FDA-sanctioned IND, must be done within the requirements of the IND and current Good Manufacturing Practice standards. The commenter recommended this clarification be added to this statement.

Response: Comment not incorporated. Expanding on this topic in General Chapter <795> would be redundant, may not reflect a particular IND protocol, and is beyond the scope of this chapter.

Comment Summary #5: The commenter suggested that the second bullet under the definition of *Compounding* be clarified to include that the preparation of drugs should be in limited quantities.

Response: Comment not incorporated. The Expert Committee finds the word “limited” to be vague. The existing wording limits quantities based on the pragmatic basis of routine, regularly observed prescribing patterns.

Comment Summary #6: The commenter indicated that under the definition of *Stability*, there could be interpretation problems with the phrasing that a preparation retains the “same” properties and characteristics. A clarifying definition was suggested as follows: "The extent to which a preparation retains acceptable properties and characteristics, from the time of initial compounding through the beyond use date."

Response: Comment not incorporated. The definition as presented harmonizes with the definition of *Stability* in USP General Chapter <1191> *Stability Considerations in Dispensing*.

Comment Summary #7: The commenter suggested that under the definition of *Compounding*, the fourth bullet point that mentions "research" should be expanded to "research (clinical or academic)", since it is known that some Clinical Research Organizations reference General Chapter <795> as the standard by which they produce compounded drug products for clinical studies.

Response: Comment incorporated.

Comment Summary #8: The commenter suggested that under the definition of *Manufacturing*, the statement “Given or sold for resale” is very broad and may indicate that some compounded items may be manufactured if a patient is billed for them after an office procedure or incidental to an office visit. Perhaps a better term might be “retailed” which contains the connotation of being placed on a wholesale shelf for purchase. This line may effectively eliminate office compounding without adjustment in the language.

Response: Comment incorporated.

Comment Summary #9: The commenter suggested that the NIOSH list mentioned in *Hazardous Drug* definition should be a suggested list and not all inclusive.

Response: Comment incorporated. Line now reads - "• New drugs that mimic existing hazardous drugs in structure or toxicity [for examples, see current National Institute for Occupational Safety and Health (NIOSH) publications]."

Comment Summary #10: The commenter asked if there was a need to specifically distinguish the definition of “Compounding” from prepacking definition.

Response: Comment not incorporated. Definition in General Chapter <795> parallels NABP Model Rules for Pharmaceutical Care.

Comment Summary #11: The commenter suggested coordinating the BUD definition with the definition that appears in General Chapter <797>.

Response: Comment not incorporated. In actuality General Chapter <797> harmonized with General Chapter <795>. The definition in General Chapter <797> has language specific to CSPs.

Categories of Compounding

Comment Summary #1: The commenter suggested that while they agreed that the preparation and use of a compounded preparation in which stability is unknown is a major concern, unknown stability is not an issue of preparation complexity. Therefore it was suggested that any references to "unknown stability" be removed from the *Categories* subsection and a discussion on the safety risk of the assignment of a BUD without adequate stability data be added to the section "*Stability Criteria and Beyond-Use Dating*."

Response: Comment not incorporated. The committee intentionally included knowledge-based components of compounding, which includes evaluation and judgment of stability and assigning beyond-use dates, not just the complexity and difficulty of the physical act of compounding, and the equipment and physical facilities needed.

Comment Summary #2: The commenter suggested that the first bullet under "*Categories of Compounding*" be revised to include "complexity" in the description. The statement would read, "degree of difficulty and complexity of the compounding process."

Response: Comment incorporated.

Categories

Comment Summary #1: The commenter suggested that the first sentence in the "Simple" category be revised as follows, "...compounding procedure and equipment, and stability data for that formulation with appropriate BUDs; reconstitution or manipulation of commercial products that may require the addition of one or more ingredients."

Response: Comment incorporated with edits to read "... compounding procedure and equipment, and stability data for that formulation with appropriate BUDs; or reconstituting or manipulating of commercial products that may require the addition of one or more ingredients as directed by the manufacturer."

Comment Summary #2: The commenter suggested considering adding stability indicating assay with potency testing to the "Simple" category. It would help define that potency testing is not stability testing.

Response: Comment not incorporated. In this definition, by using the words "USP compounding monograph" and "peer-reviewed journal article," it indicates that there has been stability-indicating testing done. Potency testing is beyond the scope of this chapter at this time.

Comment Summary #3: The commenter indicated that Simple preparations should be limited to noncomplicated procedures. The examples listed have several multi-step processes that could easily be performed incorrectly. The commenter suggested that Simple preparations be limited to less than 5 ingredients or manipulators.

Response: Comment not incorporated. The examples provided are simple preparations to compound if monographs or articles are followed as written.

Comment Summary #4: The commenter indicated that they would not consider the mixing together of commercial creams or ointments as moderate level compounding because it doesn't take special training or skill. It is true that you probably will not find stability information, but that is why you would follow the USP BUD standards. The commenter indicated that the indomethacin topical gel may be a Moderate compound instead of Simple because it may require preparing the base before incorporating the API. This type of compounding requires more training/education.

Response: Comment not incorporated; however, the "Moderate" category wording was changed by removing the words "including but not limited to those with a USP monograph or with a peer-reviewed journal article."

Comment Summary #5: The commenter indicated that in the description for the "Moderate" category the statement "...or making a preparation for which stability data for that specific formulation is not available" should be removed.

Response: Comment not incorporated. The committee intentionally included in the criteria for classification, not just the complexity and difficulty of the physical act of compounding, and the equipment and physical facilities needed, but also the knowledge-based components of compounding, which includes evaluation and judgment of stability and assigning beyond-use dates.

Comment Summary #6: The commenter suggested that it was not clear why there is a distinction between simple, moderate, and complex preparations. For example, the Complex preparation requires "special training, environment, facilities, equipment, and procedures" yet these requirements are not differentiated from the typical requirements outlined within the chapter. If the sections are retained the "Simple" category should include the words "including but not limited to" as written in the "Moderate" category.

Response: Comment not incorporated; however, the "Moderate" category wording was changed. See Comment Summary #6.

Responsibilities of the Compounder

Comment Summary #1: The commenter indicated that the second sentence of this section should be clarified to mention federal law and regulations.

Response: Comment incorporated as follows "...and in compliance with the requirements established by the applicable State Board of Pharmacy, federal law, and other regulatory agencies where appropriate."

Comment Summary #2: The commenter suggested removing, in the first sentence, the "and" before "in accordance", as it is not necessary.

Response: Comment incorporated.

Comment Summary #3: The commenter suggested adding USP General Chapter <1265> *Written Prescription Drug Information* to the list of other General Chapters. This chapter is extremely useful for constructing patient information.

Response: Comment incorporated.

General Principles of Compounding

Comment Summary #1: The commenter suggested that statement #1 should include the sentence, "Such training should be documented" adding more emphasis on retraining personnel and documenting such training.

Response: Comment incorporated.

Comment Summary #2: The commenter suggested that statement #2 be revised to read, "Compounding ingredients of the appropriate identity, purity, and quality are purchased from reliable sources. These sources are able to provide documentation that the ingredients trace back to FDA-registered facilities that have been recently to reflect their current operations. Ingredients are also properly stored according to manufacturer or USP specification."

Response: Comments incorporated as follows: First and third sentences accepted with edits. Second sentence not incorporated due to confusion and vagueness as to time frames, and would be difficult to implement.

Comment Summary #3: The commenter indicated that this subsection should be rewritten for clarity

Response: Comment not incorporated. The section as written is clear in its intent

Comment Summary #4: The commenter indicated that statement #7 should add examples such as process should be reproducible and meet minimum standards).

Response: Comment incorporated by adding the word "reproducible."

Comment Summary #5: The commenter suggested that statement #10 would benefit by adding the word "preventing" to the sentence so it would read, "Adequate procedures and records exists for investigating, correcting, and preventing failures..."

Response: Comment not incorporated. This is addressed in general principle #8.

Comment Summary #6: The commenter recommends an additional statement #11 to address appropriate documentation

Response: Comment not incorporated. This is addressed in general principle #9.

Comment Summary #7: The commenter suggested that an additional statement #12 should be added to prevent failures.

Response: Comment not incorporated (see comment #5).

Comment Summary #8: The commenter indicated that if statement #3 refers to a specific label then details should be provided.

Response: Comment incorporated as a reference because OSHA.gov describes the hazard labels, which are proprietary.

Comment Summary #9: The commenter made an inquiry about accomplishing General Principle #1 which states that "Personnel are appropriately trained, and are capable and qualified to perform their assigned duties?"

Response: USP will respond to this inquiry.

Comment Summary #10: The commenter asked what is the intention for "Only authorized personnel" ... in "immediate vicinity" in # 6. Most pharmacies are relatively short of space and must have all sorts of people in and about the non-sterile compounding areas from delivery to cleaning to visitors for meetings. This is not needed.

Response: Comment not incorporated. Wording is consistent with all accreditation standards and harmonizes with PCAB standards.

Comment Summary # 11: The commenter asked for specific examples on what must be documented in #9

Response: Comment incorporated in Section *Compounding Documentation* which defines the elements of the Master Formulation Record and Compounding Record.

Compounding Process

Comment Summary #1: The commenter suggested that USP define critical processes by providing examples such as weighing, mixing, etc

Response: Comment incorporated.

Comment Summary #2: The commenter suggested that the labeling requirements according to all applicable state and federal laws, including the BUD and storage and handling information as well as a statement that “this is a compounded preparation” be clearly stated.

Response: Comment incorporated to indicate that the label **shall** include the BUD and storage and handling information and **should** include a statement that “this is a **compounded** preparation.”

Comment Summary #3: The commenter indicated that the term “evaluated” needed a definition

Response: Comment not incorporated. The Expert Committee views the word “evaluated” as an inclusive term.

Criteria When Compounding Each Drug Preparation

Comment Summary #1: The commenter suggests providing a link to “list of federally recognized drugs that have been withdrawn or removed from the market for safety reasons.”

Response: Comment incorporated. Specific links are not included because they are subject to change.

Comment Summary #2: The commenter suggested that the Joint Commission term “clean, uncluttered and functionally separate” be used in number 3 for clarity.

Response: Comment incorporated.

Comment Summary #3: The commenter suggested adding a compounding template to an appendix.

Response: Comment not incorporated. The Expert Committee decided not to add templates for Compounding Records or Master Formulation Records because there are many possible variations of these records.

Comment Summary #4: The commenter suggested that number 12 in this section should be changed because there is not enough room on the prescription label for all the information indicated. Commenter also questioned the second use of the word “label” as to determine if it refers to documents that accompany the prescription as well as the prescription label on the container.

Response: Comment incorporated and revised to read: The labeling **shall** include the BUD and storage and handling information. The labeling **should** indicate that this is a compounded preparation.

Comment Summary #5: The commenter indicated that # 2 in this section should be changed to “must be readily available” because it is not realistic in a typical pharmacy setting to read the MSDS/Certificates of Analysis each time the compound is made.

Response: Comment not incorporated. The Expert Committee determined that number 2 does not imply each time.

Comment Summary #6: The commenter indicated that most pharmacies do not compound huge amounts at one time for resale, but one-off-batches to fill specific

order/prescription requirements. Item number 10 describing how the final preparation should be assessed will add unneeded burden to the compounding practice.

Response: Comment not incorporated. This item is part of accepted good compounding practices.

Comment Summary #7: The commenter indicated that there was no benefit in adding the statement “this is a compounded preparation.” This would be another specialized sticker on a product that probably has 2-3 stickers already applied to the container. The addition of this erroneous information just means that the patient is more likely not to read ANY of the information applied to the container.

Response: Comment addressed by changing “shall” to “should” indicate that this is a compounded preparation.

Comment Summary #8: The commenter suggested removing "when available" in reference to Certificate of Analysis. A Certificate of Analysis should always be available for bulk chemicals.

Response: Comment incorporated.

Comment Summary #9: The commenter suggested adding potency either within monograph limits or \pm 10%.

Response: Comment incorporated by changing "expected" to "accepted" so sentence now readsthe finished preparation has its accepted potency, purity, quality..... Specific ranges vary with the monograph.

Comment Summary #10: The commenter suggested incorporating the information that should be on all prescription labels as well as preparations made for anticipatory orders.

Response: Comment not incorporated as regulations vary by state.

Comment Summary #11: The commenter suggested that this section should note that the Master Formulation record should be created prior to compounding, and that the Compounding Record be utilized for the preparation of the compounded drug. Also, the review of the Master Formulation Record and the Compounding Record in step 13 should be revised to add to the end of the sentence “...and the preparation is suitable for use.”

Response: Comment “and the preparation is suitable for use” incorporated.

Comment Summary #12: The commenter suggested that statement # 1 should be amended to read, "The dose, safety, and intended use of the preparation or drug delivery device, or device has been evaluated... of the components, dosage form, *therapeutic effectiveness*, and route of administration..."

Response: Comment incorporated by adding the words “therapeutic appropriateness” as manufacturers test for therapeutic effectiveness, not pharmacists. Comment on the term “device” was not incorporated since our use of this term is consistent with that used in the NABP *Model State Pharmacy Act and Model Rules of the National Association of Boards of Pharmacy (Model Act)*.

Comment Summary #13: The commenter suggested that statement #3 should be amended to read, "Compounding is done in an appropriately clean and sanitized area dedicated to this activity."

Response: Comment incorporated.

Comment Summary #14: The commenter suggested that statement #7 needs clarification and should read, "Personnel engaged in compounding maintain good

sanitation habits, and wear clean clothing...for prevention of drug contamination and minimization of burden of the preparation."

Response: Comment incorporated by changing the wording to harmonize with USP General Chapter <797>.

Comment Summary #15: The commenter suggested clarifying statement #10 so that the sentence would read, "...odor, color, consistency, pH and analytical testing, as appropriate..."

Response: Comment incorporated.

Compounding Facilities

Comment Summary #1: The commenter suggested adding "and updates" to the NIOSH Alert publication to be sure current information is included.

Response: Comment incorporated.

Comment Summary #2: The commenter indicated adding a note about checking Pyrogen levels in the section describing different types of water.

Response: Comment not incorporated. This is addressed in the applicable water monographs and in General Chapter <797>.

Comment Summary #3: The commenter indicated that they were unclear about how separate storage of hazardous drugs offers prevention from contamination and exposure for personnel. All drugs must be handled to prevent contamination and exposure.

Response: Comment incorporated. Sentence now reads "Hazardous drugs shall be stored, prepared, and handled by appropriately trained personnel under conditions that protect the healthcare workers and other personnel."

Comment Summary #4: The commenter asked what is USP's definition of "Purified Water." The commenter stated that most pharmacies use distilled water, but purified could have many meanings. The commenter questioned why the sudden need to wash equipment/rinse with purified water? The commenter asked if there is evidence that trace amounts of minerals, biologicals, etc. that remain on the surface interact in a meaningful way with the compounded drugs. They see this as an unnecessary expense to the pharmacy and patient. The commenter asked that the USP rephrase the sentence from "*Purified Water* must be..." to "*Purified Water* should be..."

Response: Comment incorporated

Comment Summary #5: The commenter suggested defining purified water.

Response: Comment incorporated by reference to *Purified Water* Monograph and Chapter <1231> *Water for Pharmaceutical Purposes*.

Comment Summary #6: The commenter suggested adding the need to record temperature and humidity daily.

Response: Comment incorporated.

Comment Summary #7: The commenter suggested that hazardous drug is too broad and should be changed to read cytotoxic drugs should be stored separately. There is no risk for poisonous, irritating and reproductive chemicals to be stored in a separate location as long as the chemical is in sealed containers. These types of chemicals are only hazardous upon opening the container and should be opened in powder containment areas.

Response: Comment incorporated.

Comment Summary #8: The commenter indicated that ASHP has a very clear and precise published guideline for hazardous (sterile and nonsterile) compounding and should be cited as a reference for hazardous compounding because it is specifically for pharmacy practice settings.

Response: Comment not incorporated as general chapter references both the OSHA Technical Manual and the NIOSH Alert.

Comment Summary #9: The commenter suggested that in this section, there appears to be no mention of the documentation or record keeping that needs to accompany the various operations. The commenter suggested adding recommendations for maintaining records of facility design (i.e., blueprints or other documents showing location of plumbing, electrical, air-handling and other utility systems), qualification and maintenance of the facility ventilation and cooling system. Maintaining and referring to facility blueprints would assist in the cleaning and maintenance of the utility system within a pharmacy and aid in any investigation of the cause of compounding failures that might be due to environmental contamination. In addition, SOPs should be required that define the requirements and procedures to adequately address contamination of compounded preparations by dust and other particles.

Response: Comment not incorporated. This is beyond the scope of this general chapter.

Comment Summary #10: The commenters indicated that there is no direct statement that temperature and humidity controls are important for maintenance of drug product integrity and suggested adding a statement, "Appropriate temperature and humidity controls need to be maintained as required for certain compounded dosage forms."

Response: Comment incorporated with edits and now reads as: "Appropriate temperature and humidity monitoring should be maintained as required for certain components and compounded dosage forms."

Comment Summary #11: The commenter suggested that the paragraph that begins, "Hazardous drugs ..." be revised as follows; "Hazardous drugs shall be prepared and handled by appropriately trained personnel, for administration only under..."

Response: Comment incorporated and now reads: "Hazardous drugs shall be stored, prepared, and handled by appropriately trained personnel under conditions that protect the healthcare workers and other personnel."

Comment Summary #12: The commenter indicated that throughout this section, there is mention of cleaning compounding equipment, but it does not specify that the equipment should also be sanitized with an agent that will not leave a residue upon drying. They recommend reinforcing this concept where the cleaning of equipment is mentioned.

Response: Comment not incorporated. Sanitization with each use is not appropriate for all compounding equipment.

Compounding Equipment

Comment Summary #1: The commenter suggested using NIOSH terms following antibiotics cytotoxic and other hazardous drugs.

Response: Comment incorporated.

Comment Summary #2: The commenter suggested that a new paragraph be added when discussing compounding preparations that require special precaution and in the

last sentence revise the wording to read, "Special equipment should be dedicated for such use..." Additionally, a final sentence should be added, "If possible, the use of disposable equipment should be utilized to reduce chances of bioburden and cross-contamination."

Response: Comments incorporated.

Component Selection, Handling, and Storage

Comment Summary #1: The commenter suggested that FCC grade be defined.

Response: Comment incorporated.

Comment Summary #2: The commenter indicated that a compounder may not know if an organization is an FDA-registered facility.

Response: Comment not incorporated because not content related to the chapter.

Comment Summary #3: The commenter indicated that "expiration date" should be changed to "beyond-use date" when describing components in containers that are received from the manufacturer or distributor.

Response: Comment not incorporated. BUDs are for compounded preparations dispensed by a pharmacist based on the triad relationship. This statement describes components in containers that have an expiration date from the manufacturer or distributor.

Comment Summary #4: The commenter indicated that the word "future" in the following "... and a future expiration date to be acceptable" should be removed.

Response: Comment incorporated. The word "future" was removed.

Comment Summary #5: The commenter indicated that cosmetic is mentioned for the first time in this section and questions if it should be listed prior to this.

Response: Comment incorporated.

Comment Summary #6: The commenter indicated that a link to the "list of federally recognized drugs that have been withdrawn or removed from the market for safety reasons" should be added.

Response: Comment not incorporated. General Chapter <795> does not include specific links because these are subject to change.

Comment Summary #7: The commenter suggested referencing the British Pharmacopeia

Response: Comment not incorporated. Referencing other pharmacopeias is not a USP policy.

Comment Summary #8: The commenter indicated that labeling a preparation "USP" would require that the preparation be tested according to the USP or NF as well, not just the individual ingredients.

Response: Comment not incorporated. Testing is not a requirement to label a product or preparation "USP."

Comment Summary #9: The commenter suggested adding a note about air oxidization, light sensitivity, and hygroscopy.

Response: Comment incorporated by adding reference to General Chapter <1191> *Stability Considerations in Dispensing Practice*.

Comment Summary #10: The commenter suggested adding a note about a chemical's retest or re-evaluation date as an acceptable expiration date. Also chemical

company's expiration dates are for properly stored unopened containers so a note indicating that opening the chemical container requires a reevaluation of a company's labeled expiration date is needed. This could be further limited to chemicals that are sensitive to oxidation, hydrolysis, or light.

Response: Comments incorporated.

Comment Summary #11: The commenter indicated that the "transfer date" on a container has no benefit and the BUD date would be better.

Response: Comment not incorporated. BUD is not applicable in this case (BUDs are for dispensed compounded preparations).

Comment Summary #12: The commenter indicated a concern about the 3-year BUD for components that do not have expiration dates assigned by the manufacturer or supplier because many of these chemicals come in huge containers that are appropriately stored under light/tight conditions. For the small pharmacies that do limited compounding thus increases waste & expense. Manufacturers/distributors should be encouraged to sell these products in smaller amounts. Landfills are already being filled with drug waste products and this increases that type of expensive waste.

Response: Comment not incorporated. This is consistent with information in the *Expiration and BUD* section of *USP General Notices*. Text edited to include this reference.

Comment Summary #13: The commenter suggested that a compounder may not have the expertise/equipment to assign an expiration date. As long as the container is of same or better quality the original manufactured expiration date should still apply. Expiration dates are assigned from defined stability studies produced by a manufacturer and therefore do not apply to a compounder."

Response: Comment incorporated.

Comment Summary #14: The commenter indicated that this section needed to be altered to read "API's that do not have expiration dates...not to exceed three years" "Excipients, dietary, and cosmeceuticals that do not have expiration dates...not to exceed five years." These changes would be consistent with typical pharmaceutical manufacturer expiration dates as most excipients contain an expiration date of 3-5 years.

Response: Comment not incorporated. Section consistent with information in the *Expiration and BUD* section of *USP General Notices*. Text edited to include this reference.

Comment Summary #15: The commenter indicated that cosmetics have defined requirements in the Food Drug and Cosmetic Act and should be subjected to USP General Chapter <795>.

Response: Comment not incorporated. The word "cosmetic" was removed from the chapter entirely.

Comment Summary #16: The commenter suggested extending the 3-year date for components delivered without an expiration date because there are numerous components that will be viable nearly forever. It would perhaps be better to require an analysis for extended use for expensive components thus clearing out inventory of old inexpensive viable items such as sodium chloride, and allowing the use of more costly ingredients that should not be casually disposed of.

Response: Comment not incorporated. This is consistent with information in the *Expiration and BUD* section of *USP General Notices*. Text edited to include this reference.

Comment Summary #17: The commenter indicated that a distinction needs to be made between "manufactured drug product that may be used in compounding and bulk chemicals.

Response: Comment not incorporated. This is covered under the use of the word "product" in preparations definition.

Comment Summary #18: The commenter suggested that the usage of the term "preferred" in statement #1 term "preferred" to describe the source of ingredients implies that other types of ingredients that are not USP, NF, or FCC grade are suitable for use and that it should be replaced with "recommended."

Response: Comment incorporated.

Comment Summary #19: The commenter indicated that in statement #2 the sentence beginning, "When components are not obtainable...", should be deleted and insert a requirement that the registered facility should be a facility that has recently been inspected by FDA. A firm that is not regularly inspected by FDA may not have adequate controls to ensure the quality of the drug components. Quality issues can have serious consequences for patient safety.

Response: Comment not incorporated. There are instances when components are not available from FDA-registered facilities. Note that this section addresses all components, not just APIs.

Comment Summary #20: The commenter indicated that the American Chemical Society (ACS) does not certify reagents; it develops general quality standards for chemicals. The chemical standards used for analytical and ACS-grade reagents are not designed to determine the suitability of a chemical for human or animal use, whether topically or by ingestion. Therefore, the use of ACS-grade reagents could have serious safety repercussions when the chemicals are used in humans.

Response: Comment incorporated.

Comment Summary #21: The commenter suggested that in statement #6, it is not clear what the rationale is for the three year time frame for expiry.

Response: Comment incorporated by adding reference to the *Expiration Date and BUD* section of the *USP General Notices*.

Comment Summary #22: The commenter suggested that statement #7 should emphasize that an FDA-approved drug product must be used, and that the effect of manipulating a manufactured FDA-approved drug product on bioavailability and stability of the components needs to be considered when compounding.

Response: Comment incorporated.

Comment Summary #23: The commenter indicated that in statement #9, suppliers may have a difficult time providing written assurances that ruminant animals were certified free of BSE or TSE. Suppliers should, however, be able to provide assurances that material is either derived from a closed herd in which BSE is not known, or that the material has been sourced from geographical regions in which risk of BSE is considered either negligible or controlled. The U.S. is currently classified by the World Organization for Animal Health (OIE) as having the risk of BSE under control. Also, as there are other forms of TSE, the simple reference to BSE should be changed to BSE and other

TSE Supplier should be required to provide written assurance that the source animals were of a young age, overall health, found suitable for human consumption, and from countries that have a negligible or controlled risk of bovine or other transmissible spongiform encephalopathy as determined by OIE.

Response: Complete comment not incorporated. This suggestion is confusing and would be impossible to implement. As suggested, USP has edited the section to remove the word "certified."

Comment Summary #24: The commenter suggested that statement #10 should be clarified to include products that have been withdrawn or removed from the market for safety and effectiveness reasons by the FDA.

Response: Comment incorporated by adding the word "removed" but "effectiveness" not incorporated because this may depend on individual patient requirements and responses.

Comment Summary #25: The commenter suggested that statement #11 should be amended to include controlling humidity as a storage condition.

Response: Comment incorporated.

Comment Summary #26: The commenter indicated the need for an additional statement, as this section does not mention batch testing and qualification of active pharmaceutical ingredients (API). Verification of the quality of an API that will be used in a drug product should not be overlooked

Response: Comment not incorporated. While end-product testing is appropriate for high-risk sterile preparations, these are very special cases as indicated by the term "high-risk;" this sort of testing is not required for any other risk categories of sterile preparations and should not be required for non-sterile preparations. General Chapter <795> is a general chapter for all sizes of compounding facilities and many different types of non-sterile dosage forms, and designating parameters for end-product testing is beyond the scope of this chapter.

Stability Criteria and Beyond-Use Dating

Comment Summary #1: The commenter suggested harmonizing the BUD definition with that in General Chapter <797>.

Response: Comment not incorporated. In actuality, General Chapter <797> harmonized with General Chapter <795>. The definition in General Chapter <797> has language specific to CSPs.

Comment Summary #2: The commenter suggested clarifying the phrase "directly to assign a BUD" in ...the product expiration date cannot be used directly to assign a BUD for the compounded preparation.

Response: Comment incorporated by changing the word "directly" to the word "solely."

Comment Summary #3: The commenter suggested adding bioburden and long term stability as factors in the second sentence of the second paragraph.

Response: Comment incorporated by adding reference to General Chapter <1191> *Stability Considerations in Dispensing Practice*.

Comment Summary #4: The commenter suggested revising the second paragraph of this section because it does not mention the therapeutic principles that are the basis for the need for accurate beyond-use dating.

Response: Comment incorporated.

Comment Summary #5: The commenter indicated that the statement "...the compounder is also to use his or her pharmaceutical education and experience" be changed to "that all beyond-use dates be derived directly from documented stability data for a particular drug."

Response: Comment not incorporated. This is not possible in many cases, especially with new drug products for which compounding is particularly needed because of the lack of variety of manufacturer dosage forms needed by geriatric, pediatric, and special needs patients.

General Guidelines for Assigning Beyond-Use Dates

Comment Summary #1: The commenter suggested that since ophthalmics are listed, shouldn't all dosage forms listed in General Chapter <797> be listed.

Response: Comment not incorporated. Ophthalmics were added simply as a reminder that they are required to be sterile preparations. This information is intuitive for the various parenteral preparations listed in General Chapter <797>.

Comment Summary #2: The commenter suggested changing API to "any ingredient." This would match the rest of the document.

Response: Comment not incorporated. This is addressed by the sentence in the footnote that reads: "The BUD shall not be later than the expiration date on the container of any component."

Comment Summary #3: The commenter suggested adding concern about hydrolysis decomposition. It appears that not having a preservative is the only consideration for BUD determination.

Response: Comment incorporated.

Comment Summary #4: The commenter suggested changing the "controlled cold temperature" since many of today's newer reconstituted antibiotics are stored at controlled room temperature.

Response: Comment incorporated.

Comment Summary #5: The commenter suggested addressing aqueous internal-use preparations, e.g., vaginal creams/gels, nasal sprays, otics...etc

Response: Comment incorporated.

Comment Summary #6: The commenter suggested that the start of the second full paragraph be modified to read, "If there is not sufficient antimicrobial data available, water-containing preparations should contain suitable antimicrobial agents..." In some cases, there may be published data which negates the requirement for utilizing antimicrobial preservatives.

Response: Comment incorporated.

Comment Summary #7: Numerous commenters expressed concern that the restrictions on Beyond-Use Dates were too stringent and arbitrary.

Response: Comment incorporated for Nonaqueous Formulations. The "25% of the time remaining until the earliest expiration date of any API" restriction was eliminated. Comments not incorporated for other recommendations. The Expert Committee believes the dating, as listed, is reasonable based on their experience conducting and reviewing stability studies of a wide variety of compounded preparations.

Packaging and Drug Preparation Containers

Comment Summary #1: The commenter suggested that the container supplier should provide verification of USP container compliance. Compounders are not going to do the necessary container testing in the detail outlined in USP.

Response: Comment incorporated with the addition of the following sentence “Compounders are not expected to perform the tests described in these chapters but should be knowledgeable about the standards described therein.”

Comment Summary #2: The commenter indicated that General Chapters <661> and <671> should be removed from requirements that compounded preparations must meet.

Response: Comment not incorporated. Theses are for reference purposes and the Expert Committee also provided packaging chapters that are targeted to compounders.

Master Formulation Record

Comment Summary #1: The commenter suggested including the assigned name in the Master Formulation Record, if the compounder has assigned a name.

Response: Comment incorporated.

Comment Summary #2: The commenter suggested including references for the formulation.

Response: Comment already incorporated as references were included in the fourth bullet.

Comment Summary #3: The commenter suggested adding expected final appearance

Response: Comment incorporated.

Compounding Record

Comment Summary #1: The commenter suggested including the assigned name to the Compounding Record, if the compounder has assigned a name.

Response: Comment incorporated.

Comment Summary #2: The commenter suggested including who performed the test.

Response: Comment incorporated.

Comment Summary #3: The commenter suggested that they hoped that this section was referring to large scale manufacturers. And that this is a little onerous to expect a pharmacy to check the pH of reconstituted liquids.

Response: Comment incorporated.

Comment Summary #4: The commenter indicated that the list of requirements under Compounding Record lacked a number of key elements necessary to adequately document the compounding process for a drug. Some of these elements include:(1) Including actual weights (or measures) of components used in a compounded drug, (2) Identification of major pieces of equipment used, (3) Documentation, including date and time, of the execution of each critical compounding step (e.g., time events occurred within specification, heating steps occurred at the specified temperature, etc.), (4) Labeling, including a description of the finish drug preparation container label and the outer container label, (5) Documented results of any investigation conducted regarding quality control and follow-up investigation. Inclusion of these statements will allow for a more complete record of the compounding process and facilitate the identification of potential issues of a root cause analysis is necessary due to product quality concern.

Response: Comments incorporated.

Comment Summary #5: The commenter indicated that the Compounding Record subsection is inadequate. The development and documentation of SOPs is important to the implementation of every standard listed in the draft chapter. The need for SOP development and documentation should be emphasized throughout the chapter.

Response: Comment not incorporated. General Chapter <795> is a general chapter for all compounding, not just large compounding operations. The Expert Committee added an additional item in the section Compounding Process, Criteria When Compounding Each Drug Preparation; this requires that a Master Formulation Record and a Compounding Record be completed before making a compounded preparation.

Standard Operating Procedures

Comment Summary #1: The commenter suggested that this section does not mention whether SOP's should be written as later parts of the document do.

Response: Comment incorporated.

Compounding Controls

Comment Summary #1: The commenter indicated that in the Compounding Control subsection the document fails to mention the importance of doing checks and rechecks at each stage of the process to assure a positive therapeutic outcome by ensuring that each compounded product contains an appropriate concentration of the active ingredient.

Response: Comment not incorporated. This chapter sets standards for quality compounded preparations. It is beyond the scope of the chapter to define therapeutic outcomes.

Comment Summary #2: The commenter suggested a rewording to ... shall incorporate an independent double check ...

Response: Comment incorporated with addition of the following second sentence: "If possible, a trained second person should verify each critical step in the compounding process."

Comment Summary #3: The commenter recommended verification by a second trained person when possible, and indicated that it was not clear if compounder equaled R.Ph. and if the intent is to have two checks for each stage.

Response: Comments incorporated

Comment Summary #4: The commenter suggested that "validate" should be "verify" in #5.

Response: Comment incorporated.

Comment Summary #5: The commenter suggested that in step 2, the sentence, "The written procedures shall be followed in execution of the compounding process" should be clarified to indicate related documentation

Response: Comment incorporated.

Comment Summary #6: The commenter suggested that in step 3, the sentence "The compounder shall check and recheck each procedure at each stage of the process" should be clarified to refer to a second person verifier. Suggested wording: "A trained second person shall verify each critical step within Compounding Record at each stage

of the process." This would be consistent with the requirements outlined in the TRAINING section.

Response: Comment incorporated with edits. Second sentence now reads "If possible, a trained second person should verify each critical step in the compounding process."

Patient Counseling

Comment Summary #1: The commenter suggested adding: "At the time of dispensing a prescription..." to distinguish it from an order for a bed patient in an institution. In the situation of an order, it is often the person administering the medication (who is not the patient's agent) who needs to be aware of the issues.

Response: Comment incorporated.

Comment Summary #2: The commenter suggested adding a statement that adverse events be documented, as well as documenting any investigation and corrective action taken as a result of an adverse event. These documents should be retained for a time period equal to that required by state law for prescriptions.

Response: Comment incorporated.

Training

Comment Summary #1: The commenter suggested adding a statement that staff be trained at least annually, and that all training should be documented.

Response: Comment incorporated. The requirement for documentation is included in the fourth bullet point.

Comment Summary #2: The commenter indicated that this is excessive for training a technician to compound "magic mouthwash," but might be advisable for a manufacturer. Pharmacies already have a lot of training to accomplish to get their employees up and running. This adds extra time/steps without any real benefit. Change "shall" to "should" throughout the section to place proper emphasis without providing an unfunded mandate ... it is difficult enough to get all the training done while ensuring the patient's needs are met.

Response: Comment not incorporated. The committee gave careful consideration of each "should" and "shall" and believes the wording is appropriate.

Comment Summary #3: The commenter suggested rewording to incorporate newer technology for oversight – cameras, etc.

Response: Comment not incorporated. The Expert Committee determined that a pharmacist needs to be present.

Comment Summary #4: The commenter indicated that it was not clear if compounder equaled R.Ph.

Response: USP defines compounder as a professional authorized by the appropriated jurisdiction to perform compounding pursuant to a prescription or medication order by a licensed prescriber.

Compounding for Animal Patients

Comment Summary#1: Section needs more details to clarify.

Response: Comment not incorporated. Additional coverage of this topic is beyond the scope of this chapter.

General Chapter/Section: <1163> Quality Assurance in Pharmaceutical Compounding/Multiple Sections
Expert Committee(s): Compounding Pharmacy
No. of Commenters: 4

Introduction

Comment Summary #1: The commenter suggested that it would be helpful to convey that pharmacy compounding is an acceptable approach (perhaps under an IND, exploratory IND, or as an investigator-initiated study), to perform compounding as a means to prepare small quantities of clinical trial materials. It is suggested to add that compounding can be performed "...as an incident to, research (clinical or academia), teaching, or chemical analysis."

Response: Comments incorporated with edits. Harmonized with responsibilities of the compounder and compounding personnel in General Chapters <795> and <797> by referencing those general chapters.

Comment Summary #2: The commenter suggested that although radiopharmaceuticals are mentioned as a potential application for performing compounding, it would be helpful to also indicate that compounding is an approach that is appropriate for the preparation of radiolabeled materials, as well (which are commonly used in early clinical trials – e.g., for ADME studies). As defined by the FDA, radiopharmaceuticals do not encompass radiolabeled materials. It is suggested to add the preparation of radiolabeled materials as a potential application for compounding

Response: Comments incorporated with edits. Sentence now includes radiolabeled materials

Comment Summary #3: The commenter indicated that General Chapter <795> should be mentioned in the introduction as a reference.

Response: Comment not incorporated as General Chapter <795> was already referenced in the first paragraph of the *Introduction* section.

Comment Summary #4: The commenter suggested adding the following sentence: "The authority and responsibility for the Quality Assurance program should be clearly defined and implemented."

Response: Comments incorporated.

Comment Summary #5: The commenter suggested that the first sentence does not clearly address the intent of a quality assurance program and there appears to be an overemphasis on *scientific measurements* (e.g., 'testing in quality'), and on ***maintenance*** of safe preparations as opposed to proactively creating a system to ensure consistent and safe preparations.

Response: Comments incorporated.

Comment Summary #6: The commenter suggested revising the numerical list on page 250 for clarification as follows: I. "(1) training" should read "(1) training in QA functions and responsibilities." ii. "(6) cleaning and disinfecting" should be revised to include safety as a component, e.g. "(6) cleaning, disinfecting, and safety," iii. Item 7 should include the term "labeling." iv. A new component number 8 should be added as follows, "... (8) responsible personnel; and (9) outsourcing."

Response: Comments incorporated except # 1 as it is already addressed in the section titled training; ii) incorporated; iii) incorporated; iv) incorporated.

Comment Summary #7: The commenter suggested that since many sites don't use outsourcing this term should be included.

Response: Comment incorporated.

Comment Summary #8: The commenter suggested that the chapter should specify for whom the prescription or medication is specifically intended.

Response: Comment incorporated by reference to the definition of compounding in General Chapter <795>.

Comment Summary #9: The commenter indicated that the QA program should include appropriate *facilities and equipment, defined responsibilities, and appropriate materials*. "Cleaning and disinfecting" could be replaced with "facilities and equipment." Sections on "materials" and "responsibilities" should be added.

Response: Comments not incorporated. Comments do not match with suggestions.

Comment Summary #10: The commenter suggested removing the word "conditions" from the sentenceappropriate formulation, conditions, and procedures.....because it appears vague and unclear.

Response: Comment incorporated.

Comment Summary #11: The commenter suggested removing or clarifying the sentence "The water used in all aspects of compounding should meet the requirements of <1231> *Waters for Pharmaceutical Purposes*" as the phrase "all aspects" is too broad for the application being presented.

Response: Comment not incorporated. Filtration systems are readily available, easy to install, and relatively inexpensive.

Training

Comment Summary #1: The commenter suggested that organizational responsibilities should be mentioned prior to discussing an individual's training requirements. Move the "Responsibilities of the Compounder" section from General Chapter <1075> to the section *prior to Training*" since clear responsibilities is an important part of a modern quality system.

Response: Comment incorporated.

Comment Summary #2: The commenter indicated that the first sentence of this section should reflect the appropriate staffing level for the complexity of compounding. The commenter also suggested an additional statement should be added after the second sentence as follows: "In addition, the authority and responsibility for the QA program should be clearly defined as implemented.

Response: The first comment not incorporated as it is not within USP's scope to suggest staffing levels which can be regulated by State Boards of Pharmacy. Second comment incorporated.

Standard Operating Procedures

Comment Summary #1: The commenter indicated that it is not clear how the SOPs on Patient monitoring, complaints, and adverse events, Patient or caregiver education and training, and Purchasing are pertinent for pharmaceutical compounding as they do not describe how to perform routine and expected tasks in the compounding environment: •.

Response: Comment not incorporated. The Expert Committee feels that SOPs are needed for all areas listed.

Comment Summary #2: The commenter suggested that the “Quality assurance” bullet point it is not clear and suggested changing the “Quality assurance” bullet point to “Documentation.”

Response: Comment incorporated by adding “Continuous Quality and Monitoring” to quality assurance and documentation bullet.

Comment Summary #3: The commenter suggested that an additional item be added to the bulleted list to reflect component quality evaluation.

Response: Comment incorporated.

Comment Summary #4: The commenter suggested removing “Chemical and physical stability” from the bulleted list of SOPs.

Response: Comment not incorporated as it would be out of harmonization with other standards.

Comment Summary #5: The commenter indicated that the description of the task should only be included in the SOP if something about that SOP were unusual or unique.

Response: Comment not incorporated. Even routine tasks should be in SOPs for consistency and accuracy.

Comment Summary #6: The commenter suggested that the first sentence of the second paragraph should be expanded for clarity and read, "SOPs must be reviewed regularly and updated as necessary. Auditing and verifying compliance with established SOPs should be performed periodically."

Response: Comment incorporated.

Comment Summary #7: The commenter suggested that the statement “The SOP should be specific to each device, process, and decision used in compounding” is too restrictive. An SOP for each balance, hood, pH meter, etc is not practical or required. Thousands of different formulas are compounded and SOP for each “process” is not necessary. That is why instructions are included in each formula. The commenter also suggested removing the word “decision” as these are often made on an individual basis using “professional judgment.”

Response: Comment to remove the word "decision" incorporated.

Documentation

Comment Summary #1: The commenter indicated that to enter information on the compounding record as specific tasks are being performed is an interruption in the process causing potential errors.

Response: Comment incorporated by adding the word "ideally" to the sentence so it states that “Information on the compounding record should ideally be entered...”

Comment Summary #2: The commenter indicated that the wording “permanent record” means to never discard the record and suggested rewording to reflect compliance with acceptable record retention policy (or other defined date).

Response: Comment incorporated with edits by deleting the word "permanent."

Comment Summary #3: The commenter indicated that the phrase “all aspects” is too broad and suggested using a phrase such as “significant steps in the compounding process.”

Response: Comment not incorporated because the Expert committee determined that all components of the compounding procedure require documentation.

Comment Summary #4: The commenter suggested adding a procedural statement after the second sentence of this section as follows, "...entered as the tasks are performed. Compounding records should be reviewed for accuracy and completeness and approved by QA personnel, prior to dispensing. Additionally, beyond-use dating..."

Response: Comment incorporated.

Comment Summary #5: The commenter indicated that the establishment of BUD should be based on empirical studies without extrapolation, so the last bulleted statement from this section should be removed.

Response: Comment not incorporated. The Expert Committee determined that pharmacists are trained to evaluate science and chemistry in order to make professional judgments.

Comment Summary #2: The commenter suggested clarifying that only one of the items listed as bullet points would be sufficient to support beyond-use dating thus suggested rewording the sentence to add *one or more of the following*:

Response: Comments incorporated with edits to read: “.....at least one of the following:”

Verification

Comment Summary #1: The commenter indicated that this section is confusing in that it is addressing two different aspects of verification – (1) verifying another person’s work and (2) verification that equipment is performing properly and suggested creating separate sections (paragraphs) to discuss these two different verification concepts.

Response: Comment incorporated.

Comment Summary #2: The commenter suggested moving the sentence “The compounding facilities and equipment should be of appropriate capacity and should be designed for the compounding being performed to the equipment/facility section.

Response: Comment incorporated with statement added to Cleaning, Disinfecting and Safety section stating “This section applies to both equipment and facilities.....”

Comment Summary #3: The commenter suggested clarification on “the quality of ingredients should be verified prior to each use.” Currently, if a bulk powder or liquid is stored according to USP guidelines and the expiration date is adhered to, the quality does not have to be tested before use.

Response: Comment incorporated by deleting “...verified prior to each use” and adding “verified upon receipt (e.g. Certificate of Analysis, manufacturer’s label on commercial products, etc.).

Testing

Comment Summary #1: The commenter indicated that periodic weight, volume, and color testing seemed reasonable during the compounding process but anything beyond that seemed impractical and unnecessary.

Response: Comments already addressed in first paragraph of the Testing section by stating that compounded preparations should include testing as described in chapters <795> and <797>.

Comment Summary #2: The commenter suggested that this section include documenting prior to performing the testing and clarifying that specifications (acceptance criteria) must be documented (prior to testing).

Response: Comment incorporated.

Comment Summary #3: The commenter indicated that the list of 1-7 items was unnecessary and did not add any value with the reference to <795> and <797> already present thus suggested replacing with "...and know the applications of testing in the overall quality program in the compounding facility."

Response: Comment not incorporated. Emphasizing components, as listed, is designed to strengthen a testing program.

Comment Summary #4: The commenter suggested with regard to in-house testing, that the sentence be revised to, "Some testing can be conducted in-house by an expert with a good understanding of pharmaceutical analysis, with proper training..."

Response: Comment incorporated.

Comment Summary #5: The commenter suggested that this section should indicate that glassware of appropriate accuracy should be utilized when performing testing and refer to the USP chapter on glassware (chapter <660>).

Response: Comment incorporated.

Comment Summary #6: The commenter suggested that one of the duplicate references to the need for contract laboratories registration with the FDA be deleted.

Response: Comment incorporated.

Comment Summary #7: The commenter suggested eliminating the word "speed" as a testing procedure requirement.

Response: Comments incorporated.

Comment Summary #8: The commenter suggested that any testing method used should have accuracy, speed, reproducibility, and specificity.

Response: Comment incorporated.

Comment Summary #9: The commenter suggested that the word "and" was not needed in the sentence: "...and storage/shipping of the sample..."

Response: Comment incorporated.

Comment Summary #10: The commenter suggested revising the first bullet to simply state, "Quantity of preparation being compounded, for a specific prescription."

Response: Comment not incorporated as the Expert Committee determined that this was unrealistic and not possible in direct patient care.

Comment Summary #11: The commenter indicated that the decision to provide the complete formulation to the contract laboratory should be left up to the individual pharmacy and should not be mandated.

Response: Comment not incorporated. The Expert Committee determined that it is important for the testing laboratory to know the quantity of all ingredients in a preparation.

Comment Summary #12: The commenter indicated that in Table 2 *Testing Method, Endotoxin Testing for Ophthalmics* should be changed from a “minus” to a “plus.”

Response: Comment not incorporated in order to maintain harmonization with <797>.

Comment Summary #13: The commenter suggested that in Table 2 *Testing Method* it requires testing using gas chromatography and HPLC of small batches of compounded preparations, which is time consuming, impractical and expensive and does not distinguish between single or batch preparations.

Response: Comment incorporated.

Physical Testing of Dosage Units

Comment Summary #1: The commenter indicated that this section should include discussion of "performance testing" such as dissolution or disintegration of solid oral dosage forms (USP General Chapters <711> or <701>), and deliverable volume (General Chapter <698>) for oral liquids. The text should include why these performance characteristics are important product quality attributes to achieve positive therapeutic outcomes.

Response: Comment not incorporated as this is beyond the scope of the chapter.

Comment Summary #2: The commenter suggested changing “multidose” to “multiple-dose” as in other general chapters.

Response: Comment incorporated.

Weight and Volume Assessment

Comment Summary #1: The commenter indicated that this section is titled “Weight and Volume Assessment”, yet the paragraph only refers to gravimetric verification.

Response: Comment incorporated.

Comment Summary #2: The commenter suggested that the text does not require that samples that failed to meet the weight limits be segregated and discarded and this should be added.

Response: Comments not incorporated. Destroying the batch is already instructed, which is a tighter requirement than the manufacturing industry.

Comment Summary #3: The commenter suggested adding sections on Emulsions, Solutions, and Suspensions as well as Suppositories which are included in chapter <795>.

Response: Comments not incorporated. Suppositories have their own section. Emulsions, Solutions and Suspensions are in Table 2.

Comment Summary #4: The commenter suggested removing the sentence “First, zero or tare the balance.”

Response: Comment not incorporated. The first sentence, “First, zero or tare the balance” applies to all the dosage forms that follow in this section and was added to eliminate repetition.

Comment Summary #5: The commenter indicated replacing the entire section on *Hard Capsules, Other Solids and Semi-Solids* with a reference to USP <905>, “Uniformity of Dosage Units.”

Response: Comment not incorporated. General Chapter <905> was evaluated and found to primarily pertain to pharmaceutical manufacturers. Relevant sections that did pertain to General Chapter <1163> were extracted and used.

Microbiological Testing

Comment Summary #1: The commenter indicated that this section should discuss the need for the microbial limit testing, either on the part of the component supplier, the pharmacy, or contract laboratory and include references to USP General Chapters <61> *Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests*, and <62> *Microbiological Examination of Nonsterile Products: Tests for Specified Microorganisms*. In addition it should reference General Chapter <1111> *Microbiological Examination of Nonsterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use*, to assist the pharmacists in setting meaningful microbial limits for nonsterile products.

Response: Comment not incorporated since the information appears in Table 1 with reference to General Chapters <61> and <62> and in Table 2 with reference to General Chapter <1111>.

Comment Summary #2: The commenter suggested that the Preservative Effectiveness Testing “must support a beyond-use date (BUD).” be changed to “must support the beyond-use date of the compounded preparation.”

Response: Comment incorporated.

Cleaning, Disinfecting, and Safety

Comment Summary #1: The commenter suggested changing the title to Facilities and Equipment and refer to General Chapters <795> and <797> since there are additional requirements for equipment other than just cleaning and disinfecting.

Response: Comment incorporated.

Containers, Packaging, Repackaging, and Storage

Comment Summary #1: The commenter suggested adding references to General Chapter <1079> *Good Storage and Shipping Practices*, and General Chapter <1> *Injections*, to the bulleted list in this section on page 257.

Response: Comment not incorporated, as both chapters are already on the bulleted list.

Outsourcing

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

Expert Committee(s): Compounding Pharmacy

No. of Commenters: 1

Comment Summary #1: The commenter suggested that the term "suppliers" be replaced with "pharmacies that prepare."

Response: Comment incorporated.

Comment Summary #2: The commenter suggested the term "purchasers" should be replaced with "facilities that receive."

Response: Comment incorporated.

Comment Summary #3: The commenter suggested that the users of this chapter would benefit from an additional section regarding "Responsible Personnel." The commenter recommended the following text be added to a newly proposed section that would follow the **OUTSOURCING** section:

The responsibility and authority for the quality assurance program should be clearly defined and implemented. Personnel responsible for the quality assurance program should have the education, training, an experience necessary to perform the assigned functions. Quality Assurance personnel should be independent of the compounding Personnel. Quality assurance personnel should assure that SOPs documentation, verification, and testing are performed in accordance with written policies and procedures. The commenter also suggested that if deviations from approved policies and procedures occur, it is the responsibility of the quality assurance personnel to investigate and to implement appropriate corrective action. Documentation of any investigations and corrective actions is the responsibility of the quality assurance personnel. The importance of having responsible personnel in the quality assurance program is to assure the safety, identify, strength, quality, and purity of compounded drug products before they are dispensed.

Response: Comment incorporated in a new section titled *Responsible Personnel*.

Responsible Personnel

Expert Committee-initiated Change #1: See above Comment Summary #3 in *Outsourcing*.

Summary

Comment Summary #1: The commenter suggested that the second sentence of this section be edited for clarification as, "A sound quality assurance program includes detailed SOPs, documentation, verification, analytical and microbiological testing as appropriate to particular compounded preparations, and responsible quality assurance personnel."

Response: Comment incorporated.

Comment Summary #2: The commenter suggested changing the sentence "A sound quality assurance program includes..." by removing the word "sound" as it is vague.

Response: Comment not incorporated. The word "sound" as used here is synonymous with "thorough" and "complete."

Comment Summary #3: The commenter suggested emphasizing that the types of testing and degree of testing should be documented by adding a statement similar to what is added to the Testing section.

Response: Comment incorporated by changing "decide" to "determine."

General Chapter/Section(s): <1788> Methods for the Determination of Particulates Matter in Parenteral Injections and Ophthalmic Solutions
Title/Introduction/LO Calculation/Enumeration of Particles/Test Procedure/Test Preparation/Dry or Lyophilized Preparation

Expert Committee(s): General Chapters–Pharmaceutical Dosage Forms

No. of Commenters: 5

Comment Summary #1: The commenter suggested that the definition surrounding extrinsic and intrinsic material was confusing.

Response: The Expert Committee agreed with the comment and revised to clarify intent.

Comment Summary #2: The commenter suggested that the calculation examples in the LO Calculation and Enumeration of Particles section be changed to represent only the USP size ranges applicable to this general chapter.

Response: The Expert Committee agreed with the comment and revised to clarify intent.

Comment Summary #3: The commenter felt that the general chapter only deals with sub-visible particles, thus the title should be changed to reflect this.

Response: Comment not incorporated. The Expert Committee believes that there is not distinct size boundary between visible and sub-visible and thus the title is appropriate.

Comment Summary #4: The commenter suggested that the reference to the requirement in chapter <1> *Injections* for visible particles be removed because it confuses the purpose of the general chapter.

Response: Comment not incorporated. The Expert Committee believes there is crossover of General Chapters <1> and <788> size domains.

Comment Summary #5: The commenter suggested that instead of providing general instructions on how to prepare dry or lyophilized samples for testing, a reference to the drug product label is all that is needed.

Response: Comment incorporated.

Comment Summary #6: The commenter suggested that the information that currently resides in <788> should not be repeated in General Chapter <1788> and should be removed.

Response: Comment incorporated.

Comment Summary #7: The commenter suggested that the text in General Chapters <788> and <1788> on how dry or lyophilized preparations are prepared for testing is contradictory.

Response: Comment incorporated.

Comment Summary #8: The commenter suggested that it is not clear if the statement “nonshedding garments...are worn throughout the preparation of samples” is applicable to the preparation of all three steps and thus wanted clarification.

Response: Comment incorporated.

Comment Summary #9: The commenter suggested that clarification was needed on whether plastic, nonshredding labels are included in the statement “remove or tap over label.”

Response: Comment incorporated.

Monographs

Monograph/ Section(s): Amifostine/Organic Impurities

Expert Committee(s): Monograph Development-Cardiovascular

No. of Commenters: 1

Comment Summary #1: The commenter requested revising the requirement for relative standard deviation from NMT 4.0% to NMT 15.0% to be consistent with their FDA-approved specifications.

Response: Comment incorporated.

Monograph/Section(s): Amoxicillin/Multiple Sections
Expert Committee(s): Monograph Development-Antibiotics
No. of Commenters: 2

Comment Summary #1: The commenter requested replacing the proposed *Organic impurities* procedure with a different FDA-approved procedure.

Response: Comment not incorporated. The Expert Committee considers the proposed procedure to be adequate for the public standard.

Comment Summary #2: The commenter requested including relative response factors in the proposed *Organic impurities* procedure.

Response: Comment not incorporated. The approved limits are based on calculations that do not include relative response factors.

Expert Committee initiated change #1: The Assay was revised to delete column efficiency and capacity factor as system suitability requirements. The remaining criteria are adequate for evaluating system suitability.

Expert Committee initiated change #2: A *Note* was added to the *Sample solution* in the *Organic impurities* procedure to indicate that the solution should be used within 4 hour if stored at 4°, based on the validation data for the procedure.

Monograph/Section(s): Azithromycin/Organic Impurities
Expert Committee(s): Monograph Development-Antibiotics
No. of Commenters: 4

Comment Summary #1: The commenter requested replacing the *Organic impurities* procedure with the commenter's FDA-approved procedure.

Response: Comment not incorporated. The proposed procedure is based on validation data from two FDA-approved sponsors and on the *European Pharmacopoeia (PhEur)* procedure. The Expert Committee considers the selectivity of the proposed procedure to be adequate for the public standard.

Comment Summary #2: The commenter requested not to delete the current *Procedure 1*, and to retain the flexible monograph approach in the *Organic impurities* procedure to allow for different analytical technologies.

Response: Comment incorporated as follows: The current *Procedure 1* was retained in the monograph; the limit for 'Any unspecified impurity' was deleted because it is not consistent with the sponsor's FDA-approved specifications. The proposed procedure was designated as *Procedure 2*, and the *Note* about the selection of the appropriate *Organic impurities* procedure was updated for clarity. The statement in the *Labeling* section about the *Organic impurities* procedure was retained.

Comment Summary #3: The commenter requested revising the relative response factors to be consistent with the values in the *PhEur* monograph.

Response: Comment incorporated.

Monograph/Section(s): Benzalkonium Chloride/Multiple Sections
Expert Committee(s): Excipient Monographs 2
No. of Commenters: 2

Comment Summary #1: In the Assay, *Procedure 1: Ratio of Alkyl Components*, the commenter observed *NF* and *PhEur* relative retention times (RRTs) for the C₁₄ and C₁₆

homologs are different and could lead to a confusion and possible errors in peak identification. The commenter realized that the differences might result from the use of different columns allowed in the *NF* and *PhEur* monographs, but the commenter recommended these RRTs need to be clarified and/or aligned to avoid the confusion.

Response: Comment incorporated. The Expert Committee added a statement in the NOTE, "Relative retention times are provided for information only, and the standard should be used to ensure appropriate peak identification." The EC agrees that since RRTs are provided for information only, the qualifying statement will help to clarify concerns regarding slight variations in the Relative Retention Times depending on the chromatographic conditions of use.

Comment Summary #2: In the *Organic Impurities, Procedure 1: Limit of Amines and Amine Salts*, the commenter suggested that the sentence in the beginning: "Dissolve the *Sample* with heating carefully on top of a steam bath with water as the steam source " be modified to "Dissolve the *Sample*, heating carefully, e.g., on top of a steam bath with water as the steam source"

Response: Comment incorporated.

Comment Summary #3: In the *Organic Impurities, Procedure 1: Limit of Amines and Amine Salts*, the commenter recommended an alternative titration which can be performed in an aqueous solution with sodium hydroxide as the base, and without use of nitrogen.

Response: Comment not incorporated due to a lack of validation report and data. The Expert Committee will consider and evaluate this alternative method once the supporting data are received.

Comment Summary #4: In the *Organic Impurities, Procedure 2: Limit of Benzyl Alcohol, Benzaldehyde, and Chloromethyl Benzene*, the commenter recommended modifying the multiplication factor from "0.7" to "1.3"

Response: Comment incorporated. The Expert Committee also added a NOTE to clarify this factor.

Monograph/Section(s): Benzalkonium Chloride Solution/Multiple Sections

Expert Committee(s): Excipient Monographs 2

No. of Commenters: 2

Comment Summary #1: In the *Identification B*, the commenter suggested using the sample preparation from the *Identification A* to perform the Chlorides identity test.

Response: Comment not incorporated. The Expert Committee recommended preparing fresh samples for the Chloride test to avoid potential cross contamination.

Comment Summary #2: In the *Assay, Procedure 1: Ratio of Alkyl Components*, the commenter observed *NF* and *PhEur* relative retention times (RRTs) for the C₁₄ and C₁₆ homologs are different. The commenter realized that the differences might result from the use of different columns allowed in the *NF* and *PhEur* monographs, but the commenter recommended these RRTs need to be clarified and/or aligned to avoid the confusion.

Response: Comment incorporated. The Expert Committee added a statement in the NOTE, "Relative retention times are provided for information only, and the standard should be used to ensure appropriate peak identification." The EC agrees that since RRTs are provided for information only, the qualifying statement will help to clarify

concerns regarding slight variations in the Relative Retention Times depending on the chromatographic conditions of use.

Comment Summary #3: In the *Assay, Procedure 1: Ratio of Alkyl Components*, the commenter commented that in the absence of scientific justification, they recommend changing the injection volume from “20 µL” to “10 µL”, not including C₁₀ homolog into the calculation, and changing the calculation formula and acceptance criteria.

Response: Comment not incorporated due to a lack of validation data. The *NF* test in the *PF35(6)* is supported by a validation report and data together with scientific justification.

Comment Summary #4: In the *Assay, Procedure 2: Total Alkylbenzyltrimethylammonium Chlorides*, the commenter suggested a volume equivalent to 500 mg solid in Benzalkonium Chloride Solution in order to align with Benzalkonium Chloride monograph.

Response: Comment incorporated based on supporting data.

Comment Summary #5: In the *Other Components, Alcohol Content (If Added)*, the commenter recommended deleting this test from the monograph.

Response: Comment not incorporated. In the *NF* monograph *Definition*, it describes “... .. It may contain a suitable coloring agent and may contain NMT 10% of alcohol.” As such, the specification and the test for alcohol (if added) are necessary in the monograph and cannot be deleted.

Comment Summary #6: In the *Organic Impurities, Procedure 1: Limit of Amines and Amine Salts*, the commenter suggested that the sentence in the beginning: “Dissolve the *Sample* with heating carefully on top of a steam bath with water as the steam source” be modified to “Dissolve the *Sample*, heating carefully, e.g., on top of a steam bath with water as the steam source.”

Response: Comment incorporated.

Comment Summary #7: In the *Organic Impurities, Procedure 1: Limit of Amines and Amine Salts*, the commenter recommended an alternative titration which can be performed in an aqueous solution with sodium hydroxide as the base, and without use of nitrogen.

Response: Comment not incorporated due to a lack of validation data. The Expert Committee will consider and evaluate this alternative method once the supporting data are received.

Comment Summary #8: In the *Organic Impurities, Procedure 1: Limit of Amines and Amine Salts*, the commenter recommended removing the statement “corresponding to NMT 0.1 mmol/g of amines and amine salts.”

Response: Comment not incorporated. A corresponding test limit for a wet chemical method such as titration is needed for compendial use. As such, the Expert Committee believes that this statement is necessary for the *USP-NF* compendial users.

Comment Summary #9: In the *Organic Impurities, Procedure 2: Limit of Benzyl Alcohol, Benzaldehyde, and Chloromethyl Benzene*, the commenter questioned why the *NF* method contains different system suitability requirements than those present in the Ph. Eur. Method and suggested deleting the relative standard deviation for replicate injections.

Response: Comment not incorporated. The Expert Committee will consider to include the use of other system suitability parameters upon receipt of validation data. “Relative

standard deviation for replicate injections” is required in most *USP-NF* monographs if HPLC and GC tests are being used.

Comment Summary #10: In the *Organic Impurities, Procedure 2: Limit of Benzyl Alcohol, Benzaldehyde, and Chloromethyl Benzene*, the commenter recommended modifying the multiplication factor from “0.7” to “1.3”

Response: Comment incorporated. The Expert Committee also added a NOTE to clarify this factor.

Comment Summary #11: In the *Specific Tests, Acidity and Alkalinity*, the commenter recommended the *NF* proposal be revised to require titration of the specific amount of benzalkonium chloride (i.e., 500 mg) rather than providing a specific concentration of benzalkonium chloride, to account for the different solution concentrations allowed.

Response: Comment incorporated.

Monograph/Section(s): Buspirone Hydrochloride/Chloride Content

Expert Committee(s): Monograph Development–Psychiatrics and Psychoactives

Number of Commenters: 1

Comment Summary #1: The commenter suggested retaining of the test for *Content of chloride*

Response: Comment not incorporated. The Expert Committee believes that the quantitative test for the counter-ion content is not necessary as *USP* monographs usually include only an identification test for a counter-ion. The identification test for the chloride (*Identification-C*) has already been added in the proposal.

Monograph/Section: Butylated Hydroxyanisole/Assay

Expert Committee(s): Excipient Monograph 1 (EM1)

No. of Commenters: 2

Comment Summary: The commenters suggested the peak elution order was reversed for the 3-tert-butyl-4-hydroxyanisole and 2-tert-butyl-4-hydroxyanisole isomers in the note for the system suitability section in the Assay.

Response: Comment incorporated. The Expert Committee determined the elution order was reversed for the isomers.

Monograph/Section(s): Cabergoline/Residue on Ignition

Expert Committee(s): Monograph Development–Psychiatrics and Psychoactives

Number of Commenters: 1

Comment Summary #1: The commenter requested the increase of limit for *Residue on Ignition* from NMT 0.1% to NMT 0.2%.

Response: Comment not incorporated because the commenter subsequently withdrew their request.

Monograph/Section(s): Capreomycin Sulfate/Composition of Capreomycin

Expert Committee(s): Monograph Development-Antibiotics

No. of Commenters: 1

Comment Summary #1: The commenter requested revising the column dimensions and mobile phase composition in the test for *Composition of Capreomycin* to improve resolution.

Response: Comment not incorporated. The Expert Committee is willing to consider a revision in the future upon the receipt of the necessary supporting data.

Monograph/Section(s): Capreomycin for Injection/Composition of Capreomycin
Expert Committee(s): Monograph Development-Antibiotics
No. of Commenters: 1

Comment Summary #1: The commenter requested revising the column dimensions and mobile phase composition in the test for *Composition of Capreomycin* to improve resolution.

Response: Comment not incorporated. The Expert Committee is willing to consider a revision in the future upon the receipt of the necessary supporting data.

Monograph/Section(s): Cetirizine Hydrochloride and Pseudoephedrine Hydrochloride Extended-Release Tablets/Multiple sections
Expert Committee(s): Monograph Development-Pulmonary and Steroids
No. of Commenters: 2

Comment Summary #1: The commenter requested revising the chromatographic conditions in *Procedure 1* under *Organic Impurities* to be consistent with the commenter's FDA-approved procedure.

Response: Comment incorporated.

Comment Summary #2: The commenter requested the relative response factor for cetirizine acetic acid be revised from 1.2 to 1.1, to correct the rounding error.

Response: Comment incorporated.

Comment Summary #3: The commenter requested that a second identification test, based on a TLC procedure, be added to the monograph.

Response: Comment not incorporated. The Expert Committee considers a single identification test based on HPLC retention time agreement be adequate for a drug product monograph.

Comment Summary #4: The commenter suggested that the *Uniformity of Dosage Units* test be added to the monograph.

Response: Comment incorporated.

Monograph/Section(s): Chlorhexidine Gluconate Topical Solution/Packaging and Storage
Expert Committee(s): Veterinary Drugs
No. of Commenters: 1

Comment summary #1: The commenter recommended adding a storage statement "Store at controlled room temperature," to be consistent with the *Chlorhexidine Gluconate Solution* monograph.

Response: Comment incorporated.

Monograph/Section(s): Dactinomycin for Injection/Multiple Sections
Expert Committee(s): Monograph Development-Antibiotics
No. of Commenters: 1

Comment Summary #1: The commenter agreed with the proposed changes.

Response: No action required.

Monograph/Section(s): Deferoxamine Mesylate/Multiple Sections
Expert Committee(s): Monograph Development–Gastrointestinal, Renal and Endocrine

No. of Commenters: 2

Comment summary #1: The commenter indicated their concern with the proposed change of assay limit from 98.0%-102.0% to 95.0%-102.0%, and indicated that more information is needed to ensure that the relaxation of the lower assay limit can be attributed to the levels of drug-related impurities.

Response: Comment not incorporated. The proposed Assay limits are consistent with the limit of total impurities which is NMT 5.0%.

Comment summary #2: The commenter indicated that the proposed requirement for relative standard deviation for replicate injections of the *Standard solution* under *Organic impurities* is NMT 5.0% which is considered high for an HPLC procedure.

Response. Comment not incorporated. The concentration of the *Standard solution* is established at 1% level of the concentration of the *Sample solution*, and the proposed requirement for relative standard deviation is acceptable for diluted solutions.

Comment summary #3: The commenter indicated that the current USP monograph reflects the quality of the material produced by fermentation which contains about 5% of total impurities, while the commenter produces high purity API using synthetic route with average 1.0% of total impurities.

Response: Comment not incorporated at this time. The Expert Committee will consider creating a flexible monograph with tighter impurity limits for the material which is produced by synthetic route and is labeled as “high purity.”

Comment summary #4: The commenter suggested revising concentration and range under *pH*, to harmonize with the procedure in the *European Pharmacopoeia*.

Response: Comment not incorporated at this time. The Expert Committee will consider revising the *pH* in a future PF publication.

Monograph/Section(s): Donepezil Hydrochloride/Multiple Sections
Expert Committee(s): Monograph Development–Psychiatrics and Psychoactives
Number of Commenters: 3

Comment Summary #1: The commenter requested correcting the chemical name of donepezil related compound A.

Response: Comment incorporated.

Comment summary #2: The commenter requested revising the resolution requirement in the *Organic Impurities* from NLT 1.7 to NLT 1.5, to make it consistent with the resolution requirement under the Assay.

Response: Comment incorporated.

Comment Summary #3: The commenter indicated that donepezil related compound A has very low response, which may lead to reproducibility issues.

Response: Comment not incorporated because the validation report does not support this observation.

Comment Summary #4: The commenter requested the addition of three specified impurities - donepezilbenzyl bromide, dehydrodeoxydonepezil hydrochloride and deoxydonepezil hydrochloridew—which are included in the *Authorized USP Pending monograph* for Donepezil Hydrochloride.

Response: Comment not incorporated at this time. The Expert Committee will consider incorporating these impurities into the official text once the commenter's product receives full FDA approval.

Comment Summary #5: The commenter suggested revising the specifications for *Water* and *Identification* test to make them consistent with the *Authorized USP Pending monograph* for Donepezil Hydrochloride.

Response: Comment not incorporated at this time. The Expert Committee will consider these changes once the commenter's product receives full FDA approval.

Comment Summary #6: Two commenters requested the description to be changed from "white crystalline powder" to "off-white to white crystalline powder."

Response: Comment incorporated.

Comment Summary #7: The commenter requested revising the solubility in chloroform from "freely soluble" to "soluble to freely soluble."

Response: Comment incorporated.

Monograph/Section(s): Flavoxate Hydrochloride/Organic Impurities

Expert Committee(s): Monograph Development–Psychiatrics and Psychoactives

Number of Commenters: 1

Comment Summary #1: The commenter requested correcting the error in the gradient table.

Response: Comment incorporated.

Monograph/Section(s): Galantamine Hydrobromide/Organic Impurities, Limit of 4R,8R-Stereoisomer /

Expert Committee(s): Monograph Development–Psychiatrics and Psychoactives

Number of Commenters: 3

Comment Summary #1: The commenter indicated that the HPLC procedure for the *Limit of 4R,8R-Stereoisomer* is not sufficiently selective. The commenter did not provide alternative recommendations.

Response: Comment not incorporated. The validation data does not indicate lack of selectivity.

Comment Summary #2: The commenter indicated that the terms "Background Electrolyte" and "Run Buffer" are not consistent with their internal procedure.

Response: Comment not incorporated because these terms are generally accepted for the capillary electrophoresis technique.

Comment Summary #3: The commenter requested the addition of a *Note* to the impurities table indicating that narwedine is a process impurity.

Response: Comment incorporated.

Monograph/Section(s): Hydromorphone Hydrochloride Oral Solution/Multiple Sections

Expert Committee(s): Monograph Development-Cold, Cough and Analgesics

No. of Commenters: 1

Comment Summary #1: The commenter requested removing the statement "containing the expected concentration of excipients" from the *Blank* under *Identification-A*.

Response: Comment incorporated.

Comment Summary #2: The commenter requested removing any reference to excipients from the *Standard solution* under *Identification-A*.

Response: Comment incorporated.

Comment Summary #3: The commenter requested clarifying the composition of the *Solution A* and *Solution B* under the *Assay*.

Response: Comment incorporated.

Comment Summary #4: The commenter requested that a *Note* be added to the *Standard solution* and *Sample solution* of the *Assay*, indicating that these solutions should be kept in a cool place protected from light.

Response: Comment incorporated.

Comment Summary #5: The commenter requested that a *Quantitation limit solution* be added to the *Organic impurities* section.

Response: Comment incorporated.

Comment Summary #6: The commenter requested that a *Note* be added to the *Standard solution*, *Sample solution*, *Quantitation limit solution* and *System suitability solution* of the *Organic impurities* section, indicating that these solutions should be kept in a cool place protected from light.

Response: Comment incorporated.

Comment Summary #7: The commenter requested that the concentration of USP Hydromorphone Related Compound A RS in the *System suitability solution* of the *Organic impurities* section be revised from 0.8 mg/mL to 0.8 ug/mL to be consistent with the sponsor's submission.

Response: Comment incorporated.

Monograph/ Section(s): Irbesartan and Hydrochlorothiazide Tablets/Multiple Sections

Expert Committee(s): Monograph Development-Cardiovascular

No. of Commenters: 3

Comment Summary #1: The commenter suggested revising the pH of the *Buffer solution* in the *Assay* test from 3.0 to 3.0±0.1 to be consistent with the FDA-approved procedure.

Response: Comment incorporated.

Comment summary # 2: The commenter requested correcting the acceptance criteria under *Organic impurities* as follows: the limit of benzothiadiazine related compound A be changed from NMT 0.3% to NMT 1.0%, the limit of irbesartan related compound A be changed from NMT 1.0% to NMT 0.3%, and the limit of any other individual impurity be changed from NMT 0.1% to NMT 0.2%, to be consistent with the commenter's FDA-approved specifications.

Response: Comment incorporated.

Comment summary # 3: The commenter requested adding a detailed procedure for preparing the sample in the *Identification-A* test.

Response: Comment incorporated.

Monograph/Section(s): Lamotrigine Tablets/Organic Impurities

Expert Committee(s): Monograph Development–Psychiatrics and Psychoactives

No. of Commenters: 2

Comment Summary #1: Two commenters requested including lamotrigine related compound C in the Impurity Table 1 with the FDA-approved limit of NMT 0.5%.

Response: Comment incorporated.

Monograph/Section(s): Levetiracetam Tablets/Organic Impurities

Expert Committee(s): Monograph Development–Psychiatrics and Psychoactives

No. of Commenters: 6

Comment Summary #1: Four commenters requested widening the limit of levetiracetam acid from NMT 0.1% to NMT 0.3%

Response: Comment incorporated.

Comment Summary #2: Two commenters suggested adding a test for *Chiral purity* to control the amount of *R-enantiomer* in this drug product.

Response: Comment not incorporated. The *R-enantiomer* is a process impurity which is already controlled in the drug substance monograph.

Comment Summary #3: The commenter requested increasing the limit of total impurities from NMT 0.5% to NMT 0.6% to be consistent with the commenter's FDA-approved specifications.

Response: Comment incorporated.

Comment Summary #4: The commenter requested increasing the limit of total impurities from NMT 0.5% to NMT 1.0%.

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): Levofloxacin/Multiple Sections

Expert Committee(s): Monograph Development-Antivirals

No. of Commenters: 1

Comment Summary #1: The commenter suggested adding a new impurity in the *Organic Impurities* to match the impurity specified in the *Authorized USP Pending Monograph*.

Response: Comment not incorporated at this time. The Expert Committee will consider incorporating this impurity into the official text once the commenter's product receives full FDA approval.

Comment Summary #2: The commenter suggested reducing the signal to noise ratio for the *Sensitivity solution* in the *Organic Impurities* because they could not meet this system suitability requirement.

Response: Comment not incorporated because this criterion was met by the original sponsor and other laboratories.

Comment Summary #3: The commenter suggested changing the acceptance limit for the *Water* to match the limit specified in the *Authorized USP Pending Monograph*.

Response: Comment not incorporated at this time. The Expert Committee will consider addressing this once the commenter's product receives full FDA approval.

Comment Summary #4: The commenter suggested deleting separate injection of the *Standard solution* for calculation of the *Assay* result and instead using the average area

counts obtained from the *Standard solution* injected as part of the system suitability requirement.

Response: Comment not incorporated because *Tests* and *Assays* are based on single determination unless otherwise specified in the monograph. However, the decision to use replicates (averaging of area counts in this case) can better be handled by the manufacturer's release testing standard operating procedures.

Comment Summary #5: The commenter requested correcting a typographical error for the chemical name of N-desmethyl levofloxacin.

Response: Comment incorporated.

Monograph/Section(s): Methylphenidate Hydrochloride/Assay and Organic Impurities

Expert Committee(s): Monograph Development–Psychiatric and Psychoactives

No. of Commenters: 4

Comment Summary #1: The commenter indicated that their specifications include the threo isomer as an additional specified impurity.

Response: Comment not incorporated at this time. The Expert Committee is willing to consider future changes to the monograph upon receipt of the necessary supporting data.

Comment Summary #2: The commenter indicated the need to control the pH of the mobile phase between 4.05 and 4.15.

Response: Comment not incorporated because the validation data suggests that the procedure is robust in the pH range of 3.6-4.6.

Comment Summary #3: The commenter suggested tightening of relative standard deviation requirement for system suitability from NMT 2.0% to NMT 0.73%

Response: Comment not incorporated because stated value is consistent with the validation data.

Comment Summary #4: The commenter indicated that unspecified impurity limit and erythro isomer limit in *Organic Impurities Procedure 2* are inconsistent with the FDA-approved limits.

Response: Comment not incorporated because the limits in the monograph are based on the sponsor's FDA-approved regulatory filing.

Comment Summary #5: The commenter requested replacing the current *Assay* procedure with the HPLC procedure included in *Organic Impurities Procedure 2*.

Response: Comment not incorporated. The *Assay* procedure in the *PF* proposal uses a simple isocratic procedure while the procedure suggested by the commenter uses a gradient elution procedure.

Comment Summary #6: The commenter requested deleting the *Organic Impurities Procedure 1*, and use the HPLC procedure employed in *Organic Impurities Procedure 2* to control all impurities.

Response: Comment not incorporated because the *Procedures 1* and *2* are intended to monitor the impurity profiles of drug substance manufactured by different synthetic routes.

Comment Summary #7: Two commenters requested correcting the chemical name for bismethylphenidate impurity.

Response: Comment incorporated.

Monograph/Section(s): Mycophenolate Mofetil for Injection/Assay
Expert Committee(s): Monograph Development–Ophthalmology, Oncology, and Dermatology

No. of Commenters: 1

Comment Summary #1: The commenter indicated that the Assay procedure is not consistent with the FDA-approved procedure. No revision to the procedure was requested.

Response: Comment not incorporated because the Assay procedure in the monograph is based on the sponsor’s FDA-approved regulatory filing.

Monograph/Section(s): Mycophenolate Mofetil for Oral Suspension/Multiple Sections
Expert Committee(s): Monograph Development–Ophthalmology, Oncology, and Dermatology

No. of Commenters: 1

Comment Summary #1: The commenter suggested adding a test for *Loss on Drying* in the monograph with an appropriate limit.

Response: Comment not incorporated because the specifications for the *Loss on Drying* are formulation specific and should not be included in the dosage form monograph.

Expert Committee-initiated Change: The general chapter number for *Deliverable Volume* was corrected to <698>.

Expert Committee-initiated Change: The *Constituted Solution* test was deleted because it is not applicable to this dosage form.

Monograph/ Section(s): Oseltamivir Phosphate/Organic Impurities

Expert Committee(s): Monograph Development-Antivirals

No. of Commenters: 2

Comment Summary #1: The commenter requested changing the UV detector wavelength from 207 nm to 210 nm in *Procedure 2* to be consistent with the sponsor’s FDA- approved regulatory filing.

Response: Comment incorporated.

Comment Summary #2: The commenter suggested deleting the note stating that the *Sample solution* under *Procedure 2* can be stored at room temperature for 7 days because of potential degradation of oseltamivir related compound A during the storage.

Response: Comment incorporated.

Monograph/Section(s): Partially-Neutralized Methacrylic Acid and Ethyl Acrylate Copolymer/Multiple Sections

Expert Committee(s): Excipient Monographs 2

No. of Commenters: 2

Comment Summary #1: In the Assay, the commenter recommended with supporting data, changing “previously dried” to “calculated on the dried basis”

Response: Comment incorporated.

Comment Summary #2: For the *Residue on Ignition*, the commenter suggested developing a test for *Degree of Neutralization* in order to distinguish this partially-

neutralized copolymer from the acidic copolymer (Methacrylic acid and Ethyl Acrylate Copolymer).

Response: Due to interference of additives, the test for *Degree of Neutralization* cannot be developed at this time. The Expert Committee agreed to change the specification for *Residue on Ignition* from “0.5%–3.0%” to “2.0%–3.5%” based on data submitted. With this change, the partially-neutralized copolymer can be differentiated from the acidic copolymer (Methacrylic acid and Ethyl Acrylate Copolymer).

Comment Summary #3: In the test for *Viscosity*, the commenter provided clarifications for sample preparation and recommended changing “Transfer the *Sample* to the beaker very slowly under gentle stirring (avoid lumps). Ensure a homogeneous solution by gently stirring at room temperature for 3 h and taking care to avoid mixing in excess air.” to “Transfer the *Sample* to the beaker very slowly to ensure that the stirring is very effective (to avoid lumps) at the beginning and that at the same time the powder is immersed very slowly. Once the powder is dispersed and no lumps are visible, gentle stirring is then sufficient. Ensure a colloidal dispersion (milky white liquid) by stirring at room temperature for 3 h and taking care to avoid mixing in excess air.”

Response: Comment incorporated.

Monograph/Section(s): Pilocarpine Hydrochloride/Melting Range or Temperature
Expert Committee(s): Monograph Development–Ophthalmology, Oncology, and Dermatology

No. of Commenters: 1

Comment Summary #1: The commenter requested that the *Melting Range or Temperature* test not to be deleted from the monograph, and indicated that it may serve as an additional test to control unknown impurities.

Response: Comment not incorporated. The Expert Committee believes the HPLC *Organic Impurities* procedure adequately controls the impurities.

Monograph/Section(s): Pioglitazone Hydrochloride/Multiple Sections
Expert Committee(s): Monograph Development–Gastrointestinal, Renal and Endocrine

No. of Commenters: 10

Comment summary #1: The commenters requested correcting the name of the General Chapter <191> under the *Identification-B* from “*Chloride and sulfate*” to “*General Identification tests, Chloride.*”

Response: Comment incorporated.

Comment summary #2: The commenters requested widening the *Assay* limits from “NLT 99.0 and NMT 101.0%” to “NLT 98.0 and NMT 102.0%” which is typical for the chromatographic assays, and to calculate the limits on anhydrous basis.

Response: Comment incorporated.

Comment Summary #3: The commenters requested revising the *Assay*, to omit the use of internal standard in the *Sample solution* and the *Standard solution*.

Response: Comment incorporated.

Comment Summary #4: The commenters suggested reporting specified impurities under *Organic Impurities* to two decimal places.

Response: Comment incorporated.

Comment Summary #5: The commenter requested correcting the preparation of the *Standard solution* under *Organic impurities*, to delete the reference to USP Pioglitazone Hydrochloride RS.

Response: Comment incorporated

Comment Summary #6: The commenters requested increasing the limit of total impurities under *Organic impurities* from NMT 0.4% to NMT 0.5%, which is consistent with the FDA-approved specifications.

Response: Comment incorporated.

Comment Summary #7: The commenters requested reporting the limit for *Residue on ignition* rounded off to one decimal place.

Response: Comment incorporated.

Comment Summary #8: The commenters requested increasing the limit of *Water* from NMT 0.20% to NMT 0.5%, and submitted supporting information to indicate that there is no stability issues associated with the moisture content at 0.5% level.

Response: Comment incorporated.

Comment summary #9: The commenters indicated that the impurity profile of the drug substance manufactured by their companies is different from the profile included in the PF proposal, and the proposed *PF* procedure does not separate their impurities.

Response: Comment not incorporated at this time 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.

Comment summary #10: The commenter suggested revising the *Packaging and storage* section, to change the packaging from "well-closed" to "tight" containers and the storage from "room temperature" to "controlled room temperature."

Response: Comment not incorporated. The *Packaging and storage* requirements in the proposal are consistent with the sponsor's regulatory filing.

Monograph/Section(s): Pioglitazone Tablets/Multiple Sections

Expert Committee(s): Monograph Development–Gastrointestinal, Renal and Endocrine

No. of Commenters: 3

Comment summary #1: The commenters requested revising the *Assay*, to omit the use of internal standard in the *Sample solution* and the *Standard solution*.

Response: Comment incorporated.

Comment summary #2: The commenter suggested changing the final concentration of the *Standard solution* under *Dissolution* test from "L/1000" to "L/900", to be consistent with the volume of the *Medium*.

Response. Comment incorporated.

Comment summary #3:. The commenter indicated that the procedure and acceptance criteria for individual and total impurities under *Organic impurities* are not consistent with those approved by the FDA.

Response: Comment not incorporated. Based on the information received from the sponsor, the acceptance criteria under *Organic impurities* are based on the stability data, and the company is in the process of updating their regulatory filing to incorporate this information.

Monograph/Section(s): Rivastigmine Tartrate/Identification and Organic Impurities
Expert Committee(s): Monograph Development–Gastrointestinal, Renal and Endocrine

No. of Commenters: 7

Comment Summary #1: The commenter indicated that the proposed *Identification-C* test is based on the retention time agreement in the non-chiral *Assay* procedure, and recommended to replace it with a more specific test based on the retention time agreement in the chiral procedure under *Enantiomeric purity*.

Response: Comment incorporated.

Comment Summary #2: The commenters suggested deleting the *Identification-B* test for tartrate since this counter-ion can be detected by the *Identification-A* test which is based on infrared absorption.

Response: Comment incorporated.

Comment summary #3: The commenter indicated that the run time for chromatographic procedure under *Organic impurities* is very long, and suggested to replace it with a different procedure employing a shorter run time.

Response: Comment not incorporated. The procedure proposed in PF is shown to separate late-eluting impurities which are not present in the drug substance manufactured by the commenter's company. The Expert Committee will consider establishing a flexible monograph to accommodate a different impurity profile upon receipt of the necessary supporting data.

Comment summary #4: The commenters requested correcting the order of footnotes containing chemical names under *Organic impurities, Procedure 1*.

Response: Comment incorporated.

Monograph/Section(s): Rivastigmine Tartrate Capsules/Organic Impurities
Expert Committee(s): Monograph Development–Gastrointestinal, Renal and Endocrine

No. of Commenters: 3

Comment Summary #1: The commenters suggested adding a test for chiral purity to control the amount of *R*-isomer in this drug product.

Response: Comment not incorporated. The *R*-isomer is a process impurity which is already controlled in the drug substance monograph.

Comment Summary #2: The commenter requested revising a chemical name for the phenol impurity, to make it consistent with the name in the monograph for Rivastigmine Tartrate.

Response: Comment incorporated.

Monograph/Section(s): Ropinirole Hydrochloride/Assay and Organic Impurities
Expert Committee(s): Monograph Development–Psychiatrics and Psychoactives

No. of Commenters: 1

Comment Summary #1: The commenter requested widening the *Assay* acceptance criteria from 98.0%-102.0% to 97.0%-103.0% to be consistent in the specifications in the commenter's DMF.

Response: Comment not incorporated. The ANDA holders who reference the commenter's DMF did not indicate that this correction is needed, as the majority of the batched manufactured by the commenter meets the proposed acceptance criteria.

Comment Summary #2: The commenter requested revising the *Organic Impurities* to allow the monitoring of additional process impurities.

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 via publication in PF in the future.

Monograph/Section(s): Ropivacaine Hydrochloride/Specific Rotation

Expert Committee(s): Monograph Development-Pulmonary and Steroids

No. of Commenters: 1

Comment Summary #1: The commenter requested that the *Specific rotation* test not be deleted from the monograph, and indicated that it is essential to confirm that the correct enantiomer is present.

Response: Comment not incorporated. The Expert Committee determined that the *Specific rotation* test is redundant and that the chiral purity is adequately controlled by *Procedure 3: Enantiomeric Purity*.

Monograph/Section(s): Simethicone Emulsion/Identification

Expert Committee(s): Monograph Development–Gastrointestinal, Renal and Endocrine

No. of Commenters: 1

Comment summary #1: The commenter indicated that for older instruments with a low sensitivity, a larger sample (25 drops instead of 5 drops) may be necessary, and requested specifying that a larger sample size may be used.

Response. Comment incorporated.

Comment summary #2: The commenter suggested allowing alternative options for evaporating the toluene solvent from the solution in the ATR trough, in addition to using a stream of nitrogen.

Response: Comment incorporated.

Monograph/Section(s): Sodium Fluoride Gel/Definition

Expert Committee(s): Monograph Development–Gastrointestinal, Renal and Endocrine

No. of Commenters: 1

Comment summary #1. The commenter suggested adding a *Note* indicating that this monograph is only applicable to *Preventive treatments gels* and is not applicable to *Dentifrices*, as defined under 21 CFR 355.3.

Response: Comment incorporated.

Monograph/ Section(s): Terbinafine Hydrochloride/Organic Impurities

Expert Committee (s): Monograph Development-Antivirals

No. of Commenters: 3

Comment Summary #1: The commenter requested to correct a typographical error for references to individual and the total impurities.

Response: Comment incorporated.

Monograph/Section(s): Venlafaxine Hydrochloride/Multiple sections

Expert Committee(s): Monograph Development–Psychiatrics and
Psychoactives

No. of Commenters: 3

Comment Summary #1: The commenter requested including the procedure for polymorphic equalization similar to the one in the *European Pharmacopoeia* under the *Identification*.

Response: Comment incorporated.

Comment Summary #2: The commenter requested including references to both *Method I* and *Method II* under the *Heavy Metals* test.

Response: Comment incorporated.

Comment Summary #3: The commenter requested correcting the composition of the *Mobile phase* under *Assay*, to be consistent with the sponsor's approved procedure.

Response: Comment incorporated.