

AMENDED COMMENTARY– USP 32-NF 27 First Supplement

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

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

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No comments received for the following proposals:

General Chapters

<271> Readily Carbonizable Substances Test

Monographs

Albuterol Sulfate
Aluminum Subacetate Topical Solution
Anastrozole
Bupropion Hydrochloride Extended-Release Tablets
Calcium Citrate Tablets
Cefaclor Capsules
Chlorhexidine Acetate
Chlorhexidine Gluconate Oral Rinse
Chlorhexidine Gluconate Solution
Chlorhexidine Hydrochloride
Cisapride
Clonazepam Orally Disintegrating Tablets
Clozapine Tablets

AMENDED COMMENTARY– USP 32-NF 27 First Supplement

No comments received for the following proposals, continued

Monographs, continued

Estradiol Tablets

Fenoprofen Calcium

Fexofenadine Hydrochloride and Pseudoephedrine Hydrochloride Extended-Release
Tablets

Fluticasone Propionate Ointment

Fosphenytoin Sodium

Glucosamine Sulfate Potassium Chloride

Glucosamine Sulfate Sodium Chloride

Hydroxyzine Pamoate Capsules

Hydroxyzine Pamoate Oral Suspension

Isotretinoin Capsules

Ketoprofen

Levonorgestrel

Levorphanol Tartrate

Meclocycline Sulfosalicylate

Meclocycline Sulfosalicylate Cream

Mefenamic Acid

Methacholine Chloride

Mupirocin Cream

Naltrexone Hydrochloride

Omega-3 Acids Triglycerides

Orbifloxacin

Orphenadrine Extended Release Tablets

Pergolide Oral Suspension, Veterinary

Phenylephrine Hydrochloride

Potassium Citrate Tablets

Pravastatin Sodium

Pseudoephedrine Hydrochloride

Ranitidine Hydrochloride

Sodium Fluoride

Tazobactam

Tiagibine Hydrochloride

Tobramycin Inhalation Solution

Zinc and Vitamin C Lozenges

Zinc Citrate Tablets

AMENDED COMMENTARY– USP 32-NF 27 First Supplement

General Chapters

General Chapter/Section(s): <191> Identification Tests–General/Multiple Sections

Expert Committee(s): General Chapters

No. of Commenters: 1

Comment Summary #1: For both the *Acetate Identification* test and the *Ammonium Identification* test, the commenter requested including an “equivalent or better” analytical method for species identification and the presentation of a better profile from safety, health and cost effectiveness standpoint. The commenter recommended either leaving the identification test “as is” or eliminating the odor testing portion of the existing test and soliciting input from stakeholders on an identification test that is more innocuous.

Response: Comments not incorporated. The USP General Notices allows manufacturers to use alternative methods so it is not necessary to specify this in the chapter. With regard to the changes to the identification test, organoleptic tests are being removed from official text for safety reasons. The General Chapters Expert Committee is initiating a revision of all identification tests in General Chapter <191> to address safety concerns and clarify the procedures.

General Chapter/Section(s): <401> Fats and Fixed Oils/Multiple Sections

Expert Committee(s): Excipient General Chapters/Dietary Supplement-Non-Botanicals

No. of Commenters: 3

Comment Summary #1: The commenter suggested revising the *Saponification Value* section because the description of the calculation was incorrect. The corrected calculation formula reads: $[56.11(V_B - V_T) N]/W$.

Response: Comment incorporated.

Comment Summary #2: The commenter requested revising the *Polyunsaturated Fatty Acids Determination and Profile* section to include other types of polyunsaturated fatty acids in addition to “EPA, DHA, and the other chain-desaturated and/or chain-elongated members of the omega-3 family.”

Response: Comment incorporated by changing section title from “*Polyunsaturated Fatty Acids Determination and Profile*” to “*Omega-3 Fatty Acids Determination and Profile*.”

Comment Summary #3: The commenter requested revising the *Polyunsaturated Fatty Acids Determination and Profile* section to include “families of other fatty acids (i.e., the omega-6, omega-9, or omega-7).”

Response: Comment not incorporated because no supporting data was provided. The Expert Committee is willing to consider future changes to the General Chapter upon receipt of supporting data.

Comment Summary #4: The commenter requested revising the *Polyunsaturated Fatty Acids Determination and Profile* section changing analytical column from G-16 to a number of other “columns of choice due to their enhanced selectivity and separation characteristics.”

AMENDED COMMENTARY– USP 32-NF 27 First Supplement

Response: Comment not incorporated because no supporting data was provided. The Expert Committee is willing to consider future changes to the General Chapter upon receipt of supporting data.

General Chapter/Section(s): <467> Residual Solvents/Pressurization Time

Expert Committee(s): General Chapters

No. of Commenters: 1

Comment Summary #1: The commenter requested two changes to the *Pressurization time* section: 1) increase the syringe temperature range 5 to 10°C higher than the equilibration temperature and 2) add the phrase “if appropriate” because equilibration temperatures are typically used for injectors with a transfer line. Pressurization time is not applicable to syringe-based injectors.

Response: Comment incorporated.

General Chapter/Section(s): <1010> Analytical Data-Interpretation and Treatment/
Multiple Sections

Expert Committee(s): Statistics

No. of Commenters: 3

Comment Summary #1: The commenter indicated that in the *Sampling Considerations* section, systematic random sampling is recommended as a sampling scheme that may be preferred to simple random sampling in certain situations. While the stated reasons are valid, there are analytical issues with variance estimation associated with data collected via systematic sampling. Although the last sentence of the sub-section states that the tests discussed in the remainder of the chapter assume that simple random sampling was performed, the commenter recommend including an additional statement recommending consultation with a statistician to identify the optimal sampling strategy.

Response: Comment incorporated.

Comment Summary #2: The commenter indicated that in Appendix C, the recommended approach assesses the data first for a single outlier (correctly), then tests the reduced dataset again, using the same approach, to ensure there are no other outliers on the same side of the mean. The commenter viewed this as incorrect because there are outlier tests designed for more than one outlier on the same side of the mean. However, the commenter noted the warning in the conclusion and suggested making the warning more prominent at the end or beginning of Appendix C.

Response: Comment incorporated. The following text was added under the *Dixon-Type Tests* subsection: “Dixon provides for testing for two outliers simultaneously; however, these procedures are beyond the scope of this Appendix. The stepwise procedure discussed below is not an exact procedure for testing for the second outlier as the result of the second test is conditional upon the first. Because the sample size is also reduced in the second stage, the end result is a procedure that usually lacks the sensitivity of Dixon's exact procedures.” The conclusion paragraph was replaced with the following text: “Therefore, 95.7 is declared to be an outlier but 99.5 is not an outlier.”

Comment Summary #3: The commenter indicated that Appendix E, *Sample Size* section, the formula for σ_L^2 should be revised throughout the entire chapter from “RSD” to “%RSD.”

Response: Comment incorporated.

AMENDED COMMENTARY– USP 32-NF 27 First Supplement

Expert Committee-initiated Change #1: Under Appendix B, the Expert Committee members proposed to revise the sentence from “Nevertheless, many statistical software packages can easily handle unequal replication” to “Many statistical software packages can easily handle unequal replication.”

General Chapter/Section(s): <1078> GMP for Bulk Pharmaceutical Excipients/Multiple Sections

Expert Committee(s): Excipient General Chapters

No. of Commenters: 3

Comment Summary #1: The commenter proposed replacing “In these cases, consultation and adaptation of detailed guidelines and compliance programs is recommended as necessary for the excipient in question,” with “In these cases, detailed information pertaining to the intended use of excipient as provided by the end-user can be useful in determining appropriate GMP.”

Response: Comment incorporated.

Comment Summary #2: The commenter proposed amending Appendix I to add a reference called *Application of GMP Principles* that provides a rationale for applying appropriate GMP concepts at various stages of the manufacturing process.

Response: Comment not incorporated because the proposal reflects the current approved marketed product.

Comment Summary #3: The commenter proposed replacing the statement “Customers and, if necessary, regulatory authorities (for example, for Drug Master Files [DMFs] or Certificates of Suitability to the *European Pharmacopoeia* [CEPs]) should be notified of significant changes ...” with “Customers should be notified and, where applicable, excipient regulatory submissions (e.g. DMFs) should be amended to reflect significant changes....”

Response: Comment incorporated.

Comment Summary #4: The commenter proposed replacing the statement “Water used in the manufacture of excipients should be demonstrated to be of a quality suitable for its intended use” with “Water used in the manufacture of excipients should be demonstrated to be of appropriate quality in consideration of purity requirements and intended use of the excipient.”

Response: Comment incorporated.

Comment Summary #5: The commenter proposed replacing the statement “Supplier approval by the quality unit should require an evaluation of the supplier’s quality management system, including adequate evidence that they can consistently agreed requirements” with “Supplier approval by the quality unit should require an evaluation of the supplier’s Quality Management System, including adequate evidence that they can consistently meet agreed upon specifications and maintain traceability.”

Response: Comment incorporated.

Comment Summary #6: The commenter proposed adding the sentence “Excipient manufacturers should also have adequate knowledge about the origin of any raw materials derived from plant or animal matter.”

Response: Comment incorporated.

AMENDED COMMENTARY– USP 32-NF 27 First Supplement

Comment Summary #7: The commenter proposed clarifying and expanding *Measurement, Analysis, and Improvement* section, *Expiry/Retest Periods* subsection to clearly describe the retest period and whether the stated retest period can be applied once or multiple times.

Response: Comment not incorporated because the manufacturer provides information on the expiry/retest period as appropriate with each excipient.

Comment Summary #8: The commenter proposed adding a statement regarding the periodic auditing of raw material manufacturers to support the use of identification testing only.

Response: Comment not incorporated because supplier auditing requirements are defined and enforced by certification and regulatory bodies.

Comment Summary #9: The commenter proposed adding a statement to Appendix 2, *Documentation and Record Keeping* subsection, suggesting an excipient manufacturer can provide documentation of the supplier’s manufacturing sites.

Response: Comment not incorporated because the suggestion is more specific than the regulatory requirements for who retains supplier manufacturing site documentation.

Comment Summary #10: The commenter proposed deleting statements or sections that are redundant throughout the chapter.

Response: Comment not incorporated because the Expert Committee determined the redundancy ensured clarity.

Comment Summary #11: The commenter proposed adding a statement on the use of a second person to verify the operation or data in the control of documents section.

Response: Comment not incorporated because the record review requirements are defined and enforced by certification and regulatory bodies.

Comment Summary #12: The commenter proposed adding a statement to strengthen the notification process in the change control subsection under the *Quality Management System: Excipient Quality Systems*.

Response: Comment not incorporated because the suggestion is more specific than the regulatory requirements to ensure change control is appropriately communicated.

Comment Summary #13: The commenter proposed removing the phrases “whenever feasible” and “otherwise verified prior to use” throughout the chapter.

Response: Comment not incorporated because the Expert Committee determined the General Chapter wording is appropriate and allows for appropriate flexibility.

General Chapter/Section(s): <1195> Significant Change Guide for Bulk
Pharmaceutical Excipients/ Multiple Sections

Expert Committee(s): Excipient General Chapters

No. of Commenters: 1

Comment Summary #1: The commenter proposed revising the *Significant Change* section, *Evaluation criteria* subsection to include language discussing the impact of organizational changes on the purchaser of pharmaceutical excipients.

Response: Comment not incorporated because the Expert Committee determined the recommended change is beyond the scope of the General Chapter.

AMENDED COMMENTARY– USP 32-NF 27 First Supplement

Comment Summary #2: The commenter proposed adding text in *Significant Change* section, *Determination of Significance* subsection, criterion 7 impact to the pharmaceutical excipient manufacturer when there is a change to the source of raw material.

Response: Comment not incorporated because the Expert Committee determined the recommended change is beyond the scope of the General Chapter.

Comment Summary #3: Commenter proposed adding text in the *Reporting Requirements* section, *Notification* subsection that requires the raw materials supplier to assess and disclose impact of changes to the purchaser of pharmaceutical excipients.

Response: Comment not incorporated because the Expert Committee determined recommended change is beyond the scope of the General Chapter.

General Chapter/Section(s): <1225> Validation of Compendial Procedures/Multiple Sections

Expert Committee(s): General Chapters

No. of Commenters: 2

Comment Summary #1: A commenter suggested incorporating additional information to Chapter <1225> regarding the concept of Reportable Value.

Response: Comment not incorporated because the Expert Committee refers to the General Notices for the definition of reportable value.

Comment Summary #2: A commenter indicated that the use of the words “average” and “median” is inconsistent and also mentioned that the test result *normally* is, but need not be, the final, reportable value.

Response: Comment not incorporated because the Expert Committee determined that the current wording is accurate and appropriate for the intent of the chapter.

General Chapter/Section(s): <1237> Virology Test Methods/Detection of Viable Viruses

Expert Committee(s): Biologics and Biotechnology-Vaccines and Virology

No. of Commenters: 2

Comment Summary #1: The commenter suggested revising the *Detection of Viable Viruses* section by adding “There may be instances where the test material is toxic to the indicator cells and as such a preliminary enhancement of the test material may be necessary to eliminate the toxic effect.”

Response: Comment incorporated.

Comment Summary #2: The commenter suggested revising the *Detection of Viable Viruses* section by adding a discussion regarding steps needed to prevent bacterial or fungal overgrowth on animal-based raw materials before samples of the raw materials are tested for unwanted viable viruses.

Response: Comment incorporated. The following sentence was added: “The possibility that animal-derived raw materials may contain bacterial or fungal contaminants should be considered. In some cases, it may be necessary to treat the samples with antibiotics or to filter the samples (0.22 or 0.45 micron pore size) prior to inoculation in order to prevent bacterial or fungal outgrowth in the test system.”

AMENDED COMMENTARY– USP 32-NF 27 First Supplement

Comment Summary #3: The commenter suggested revising the *Detection of Viable Viruses* section by reducing the percentage of cell confluency to less than 50%.

Response: Comment incorporated.

Comment Summary #4: The commenter suggested revising the chapter to offer several appropriate methods, such as shell vial culture and electron microscopy, in addition to visible cytopathic effects (CPE). Viral growth in cell culture is most often detected from microscopically visible CPE. Some viruses, however, can grow to high titer without producing visible CPE and so must be detected by other methods.

Response: Comment incorporated by adding the following sentence “For instance, some viruses can grow to high titers without producing visible cytopathic effects and so must be detected using other endpoints.”

Comment Summary #5: The commenter proposed adding virological test detection methods (e.g., differential display, deoxyribonucleic acid (DNA) sequencing, and DNA microarray) as a safety measure to the new General Information Chapter. The additional tests may be needed to detect spontaneous viral oncogene mutations incorporating into the continuous cell lines. Although the risk is hypothetical, the potentially high impact deserves consideration because the continuous cell lines are highly mutable, and therefore could be difficult to develop an effective vaccine and because there are no clear studies that demonstrate whether using permanent cell lines as vaccine substrates may somehow transfer cancer-causing properties.

Response: Comment not incorporated because the Expert Committee has addressed the safety issues specifically related to vaccine manufacturing in General Chapter <1235> *Vaccines for Human Use-General Considerations* proposed in the *Pharmaceutical Forum* volume 34(5).

Comment Summary #6: The commenter recommend adding the viral interference assay in order to exclude false negative results when an interference phenomenon occurs in the viral culture.

Response: Comment not incorporated because the General Chapter already addresses false negative cultures for the two general types of interferences listed. The appropriate text is in the chapter: “The failure to observe viral particles in electron microscopic analysis of fixed cells should not be considered absolute proof of the absence of infectious virus in the cells. In a general sense, the same is true for each of the detection endpoints discussed above. Each endpoint has a detection limit below which a virus may be present but not detected.”

Monographs

Monograph/Section(s): Amino Methacrylate Copolymer/Multiple Sections

Expert Committee(s): Excipient Monographs 2

No. of Commenters: 1

Comment Summary #1: The commenter recommended revising the *Packaging and Storage* section to read “store at a temperature below 30°.”

Response: Comment incorporated.

Expert Committee-initiated Change #1: The Expert Committee revised the *Chemical Information* section by adding the chemical structure, chemical names and CAS number to the monograph.

AMENDED COMMENTARY– USP 32-NF 27 First Supplement

Expert Committee-initiated Change #2: Expert Committee revised the *Definition* section to delete the sentence: “This copolymer has a mean relative molecular mass of about 150,000. The ratio of (2-dimethylaminoethyl) methacrylate groups to butyl methacrylate and to methyl methacrylate groups is about 2:1:1.”

Expert Committee-initiated Change #3: The Expert Committee clarified the *Viscosity* test.

Monograph/Section(s): Betamethasone Oral Solution/Multiple Sections

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

No. of Commenters: 1

Amended Comment Summary #1: The commenter requested revising the *Standard solution* and ~~*Test solution*~~ in *Identification Test A* to correct the diluent from “chloroform:methanol (1:1)” to “~~chloroform:alcohol~~” “alcohol.”

Response: Comment incorporated.

Amended Comment Summary #2: The commenter requested revising the *Sample solution* in *Identification Test A* to reinstate previously official text, “Evaporate 1 mL of the resulting solution on a steam bath just to dryness, and dissolve the residue in 0.5 mL of alcohol.”

Response: Comment incorporated.

Note: Comment Summary #1 was amended and Commentary Summary #2 was added on July 6, 2009. Comment Summary #1 corrects the original comment. Only “alcohol” is used as the diluent in the *Standard solution* and therefore replaces “chloroform:methanol (1:1).” Amended Commentary Summary #2 is newly added for further clarification.

Expert Committee-initiated Change #1: The text of *Identification Test A* was revised to simplify the preparation procedure and omit the need for multiple extractions as this test does not need to be quantitative. The revision was approved by the monograph sponsor.

Expert Committee-initiated Change #2: The term “degradation product” in the *Related compounds* test was replaced with “related compound” since the relevant impurities are synthetic process impurities that are not adequately controlled in the drug substance monograph.

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

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

No. of Commenters: 1

Comment Summary #1: The commenter requested replacing the 0.7 micron filter used in the *Dissolution* test with the word “suitable.”

Response: Comment incorporated.

Comment Summary #2: The commenter requested the Assay procedure be revised to include an optional sample filtration step.

Response: Comment incorporated via the addition of a note.

AMENDED COMMENTARY– USP 32-NF 27 First Supplement

Monograph/Section(s): Doxycycline Hyclate Delayed-Release Tablets/Multiple Sections

Expert Committee(s): Monograph Development-Antibiotics

No. of Commenters: 1

Comment Summary #1: The commenter requested to revise the name of one of the reference standards from “USP Doxycycline Related Compound A RS” to “USP 6-Epidoxycycline RS” in the *USP Reference Standards* section and in the *Related Compounds* test.

Response: Comment not incorporated because the Reference Standard name follows current USP Reference Standard naming convention.

Comment Summary #2: The commenter requested to delete *Identification Test A* because the sponsor does not test the product with *Identification Test A*.

Response: Comment incorporated.

Comment Summary #3: The commenter requested revising the *Related compounds* test replace the test for the proposed *resolution* criterion between Doxycycline and 6-epidoxycycline with a resolution criterion between Doxycycline and any adjacent peak to ensure resolution from unidentified impurities.

Response: Comment not incorporated because the proposed resolution criterion is more appropriate for a public standard.

Comment Summary #4: The commenter requested to replace the signal-to-noise ratio criterion in the *Related compounds* test with a requirement that the peak is integrated and properly detected.

Response: Comment not incorporated because the proposed signal-to-noise criterion is more appropriate for a public standard.

Monograph/Section(s): Enalaprilat Injection/ Benzyl Alcohol Content and Related Compounds

Expert Committee(s): Monograph Development-Cardiovascular

No. of Commenters: 1

Comment Summary #1: The commenter requested to revise both the upper and the lower limits for benzyl alcohol.

Response: The comment regarding the lower limit of benzyl alcohol range was changed from “80.0%” to “75.0%.” The upper limit of 120.0%, however, was retained because the sponsor confirmed it was the approved upper limit for benzyl alcohol.

Comment Summary #2: The commenter also requested to verify the content of the gradient table under the *Related compounds* test.

Response: The gradient table under the *Related compounds* test was confirmed to be correct as published by the sponsor.

Monograph/Sections(s): Estradiol Vaginal Inserts/ Multiple Sections

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

No. of Commenters: 1

Comment Summary: The commenter requested to revise the tests for *Identification Test A*, *Chromatographic purity* test and the *Assay* to reflect the requirements for a product with a different strength.

AMENDED COMMENTARY– USP 32-NF 27 First Supplement

Response: Comment not incorporated because the Expert Committee did not receive supporting data. The Expert Committee will consider revising the tests if supporting data is provided.

Monograph/ Section(s): Fluconazole Injection/Multiple Sections
Expert Committee (s): Monograph Development-Antivirals and Antimicrobials and Microbiology and Sterility Assurance

No. of Commenters: 2

Comment Summary #1: The commenter requested the monograph specifications be changed to reflect the specifications for multiple approved products.

Response: Comment not incorporated because the information supporting this revision was not available to the Expert Committee. The Expert Committee will consider revising the specifications upon notification by other sponsors.

Comment Summary #2: The commenter requested clarification of whether *Test 1* or *Test 2* or both tests are performed in the *Related compounds* tests.

Response: Comment not incorporated because both *Test 1* and *Test 2* for the *Related compounds* must be performed unless otherwise stated in the monograph.

Comment Summary #3: The commenter requested adding additional acceptance criteria for known individual impurities and total (known and unknown) impurities in the *Related compounds* tests.

Response: Comment not incorporated because the information supporting this revision was not available to the Expert Committee. The Expert Committee will consider revising the limits when data is submitted by the monograph sponsor.

Comment Summary #4: The commenter proposed reducing the endotoxin limit from “0.88 EU/mg” to “0.416 EU/mg” because the new limit is consistent with pediatric dosing limits.

Response: Comment incorporated.

Monograph/Section(s): Fluticasone Propionate Cream/Multiple Sections
Expert Committee(s): Monograph Development-Pulmonary and Steroids
No. of Commenters: 0

Expert Committee-initiated Change: The composition of the mobile phase for the Assay was revised from “50:35:15 methanol:pH 3.5 buffer:acetonitrile” to “46:40:14 methanol:pH 3.5 buffer:acetonitrile” according to the updated information provided by the monograph sponsor.

Monograph/Section(s): Fosinopril Sodium/Related Compounds
Expert Committee(s): Monograph Development-Cardiovascular
No. of Commenters: 1

Comment Summary: The commenter requested to lower the limit for *Fosinopril related compound A* from “0.75%” to “0.3%.”

Response: Comment not incorporated because there is another approved marketed product with a limit of 0.75% for *Fosinopril related compound A*.

AMENDED COMMENTARY– USP 32-NF 27 First Supplement

Monograph/Section(s): Glucosamine Hydrochloride/Assay
Expert Committee(s): Dietary Supplements-Non-Botanicals
No. of Commenters: 1

Comment Summary #1: The commenter requested revising the liquid chromatograph retention times.

Response: Comment not incorporated because supporting data was not provided. The Expert Committee is willing to reconsider revising the liquid chromatograph retention time if supporting data is provided.

Monograph/Section(s): Haloperidol Decanoate/Multiple Sections
Expert Committee(s): Monograph Development-Psychiatrics and Psychoactives
No. of Commenters: 2

Comment Summary #1: The commenter requested the definition of the *Assay* range be changed to “98.0-102.0%.”

Response: Comment not incorporated due to lack of supporting data. The Expert Committee will consider changing the range if supporting data is provided.

Comment Summary #2: The commenter requested increasing the *Heavy Metals* limit from “10 ppm” to “20 ppm” to reflect their approved application.

Response: Comment incorporated.

Comment Summary #3: The commenter requested adding additional specified impurities with appropriate limits to the *Related Compounds* test.

Response: Comment incorporated.

Comment Summary #4: Two commenters requested the limits for specified, unspecified and total impurities to be tightened without specifying any proposed limits.

Response: Comment incorporated to reflect all currently approved marketed products.

Comment Summary #5: The commenter requested increasing the standard and sample solution concentrations in the *Assay* from “0.2 mg/mL” to “0.5 mg/mL.”

Response: Comment not incorporated due to lack of supporting data. The Expert Committee will consider changing these specifications if supporting data is provided.

Monograph/Section(s): Hydrogenated Coconut Oil/Limit of Nickel
Expert Committee(s): Excipient Monographs 2
No. of Commenters: 0

Expert Committee-initiated Change: The Expert Committee rewrote the *Standard solution* and *Procedure* subsections for clarity.

Monograph/Section(s): Hydroxyzine Pamaote/Residue on Ignition
Expert Committee(s): Monograph Development-Psychiatrics and Psychoactives
No. of Commenters: 2

Comment Summary: The commenters requested the limit for *Residue on ignition* be raised from the proposed value of “0.1%” to “0.2%” based on the historical data provided for 20 batches.

Response: Comment incorporated.

Monograph/Section(s): Ivermectin and Pyrantel Pamoate Tablets/Multiple Sections
Expert Committee(s): Veterinary Drugs/Microbiology and Sterility Assurance

AMENDED COMMENTARY– USP 32-NF 27 First Supplement

No. of Commenters: 2

Comment Summary #1: The commenter requested revising the section for <61> *Microbial Limits* to incorporate the requirements for the absence of *Salmonella* and for the *Limit of total Coliforms*.

Response: Comment not incorporated because the limits proposed in the monograph are consistent with the harmonized acceptance criteria for this class of products and route of administration. Testing for the absence of *Salmonella* is not a recommended minimal requirement for this route of administration. In addition, the *USP-NF* does not have a test method for total *Coliforms*.

Comment Summary #2: The commenter requested revising the *Uniformity of dosage units* section with additional specific requirements, which are representative of approved marketed products.

Response: Comment incorporated.

Comment Summary #3: The commenter requested revising the *pH* specification range from “4.0 to 6.0” to “4 to 6” to represent approved marketed products. The commenter also proposed adding the option to use 0.01 N sodium hydroxide or 0.01 N hydrochloric acid in the *Diluent* as a pH adjuster.

Response: Comment incorporated.

Comment Summary #4: The commenter requested that minor changes and corrections be made under the *Assay for ivermectin* to achieve consistency with their current approved specifications. The changes affected subsections for *Alumina column*, *Standard stock solution*, *Standard preparation*, *Assay stock preparation*, *System suitability requirements*, and *Procedure*.

Response: Comment incorporated.

Comment Summary #5: The commenter requested that minor changes and corrections be made under the *Assay for pyrantel pamoate* to achieve consistency with their current approved specifications. The changes affected subsections for *Extraction solvent*, *Standard preparation*, *Assay preparation*, *System suitability requirements*, and *Procedure*.

Response: Comment incorporated.

Monograph/Section(s): Lamotrigine/Related Compounds

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

No. of Commenters: 1

Comment Summary #1: The commenter suggested including a test for a significant specified impurity.

Response: Comment not incorporated because none of the approved marketed products contain any additional impurities other than those listed in the proposal.

Comment Summary #2: The commenter suggested the limit for any unspecified impurity be tightened from 0.1% to 0.10% to be consistent with International Committee for Harmonization (ICH) guidelines.

Response: Comment not incorporated because there was concern that revising the limit could potentially conflict with the limits for the approved marketed products.

Monograph/Section(s): Methotrexate/Related Compounds

AMENDED COMMENTARY– USP 32-NF 27 First Supplement

Expert Committee(s): Monograph Development-Ophthalmics, Oncology, Dermatology

No. of Commenters: 1

Comment Summary #1: The commenter requested the limit for any unknown impurity be changed from “0.05%” to “0.10%” because the new limit would be consistent with their specification.

Response: Comment incorporated.

Comment Summary #2: The commenter requested the limits for other specified impurities from their product specification be added to be consistent with their Drug Manufacturing File (DMF).

Response: Comment not incorporated because these impurities cannot be tested by the current method. The Expert Committee will consider a future revision to the monograph.

Monograph/ Section(s): Metronidazole/Related Compounds

Expert Committee(s): Monograph Development-Antivirals and Antimicrobials

No. of Commenters: 2

Comment Summary: The commenters proposed revising the acceptance criteria from “not more than 0.05%” to “not more than 0.1%” for any single unspecified impurity because the revised limit is consistent with the approved limit for the marketed product.

Response: Comment incorporated.

Monograph/ Section(s): Metronidazole Capsules/Related Compounds

Expert Committee(s): Monograph Development-Antivirals and Antimicrobials

No. of Commenters: 1

Comment Summary: The commenter proposed revising the acceptance criteria for any single unspecified degradation product from “not more than 0.1%” to “not more than 0.10%” because the revised limit is more consistent with the International Committee for Harmonization (ICH) guideline.

Response: Comment not incorporated because the acceptance criterion of 0.1% is consistent with the approved marketed product.

Monograph/Section(s): Olanzapine/Multiple Sections

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

No. of Commenters: 5

Comment Summary #1: Two commenters requested including additional impurities and an option to use *Loss on drying* in addition to the *Karl Fischer* method for moisture determination. The commenters also indicated that one of the specified impurities is not well resolved from the olanzapine peak.

Response: Comment not incorporated because the proposal reflects the current approved marketed product.

Comment Summary #2: The commenter suggested using the *System suitability solution* instead of *Standard preparation* for determining the relative standard deviation measurement in the *Assay*.

Response: Comment not incorporated because the concentrations are same in both solutions.

AMENDED COMMENTARY– USP 32-NF 27 First Supplement

Comment Summary #3: The commenter requested the replacement of the prescriptive sample preparation instructions with a final solution concentration to allow analyst flexibility.

Response: Comment incorporated.

Comment Summary #4: The commenter requested modifying the mobile phase composition from “50:50 (buffer:organic)” to “53:47(buffer:organic)” to facilitate meeting the resolution requirement.

Response: Comment incorporated.

Comment Summary #5: The commenter requested the molecular weight of Olanzapine be lowered from “312.44” to “312.43.”

Response: Comment not incorporated because the currently specified molecular weight of 312.44 is consistent with the United States Adopted Names (USAN) information.

Comment Summary #6: The commenter requested capitalizing the word “thieno” in the chemical name.

Response: Comment not incorporated because the name in the proposal is consistent with the USAN name.

Comment Summary #7: The commenter requested the *Standard solution* preparation be modified to reflect the validated method.

Response: Comment incorporated.

Comment Summary #8: The commenter requested the percent relative standard deviation requirement in the Assay be lowered from “1.0%” to “0.73%.”

Response: Comment not incorporated due to lack of supporting data. The Expert Committee will consider revising the requirement if supporting data is provided.

Comment Summary #9: The commenter requested the total impurities be lowered from “0.4%” to “0.2%.”

Response: Comment not incorporated because the lowering of the total impurities level might conflict with approved marketed products.

Comment Summary #10: The commenter requested the number of injections required for the RSD measurement in the *Related compounds* test for the relative standard deviation be specified as “4” to be consistent with the validated method.

Response: Comment incorporated.

Comment Summary #11: The commenter requested the inclusion of a *Note* to facilitate the use of correct solvent system for moisture determination by *Karl Fischer* titration.

Response: Comment incorporated.

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

Expert Committee(s): Veterinary Drugs

No. of Commenters: 1

Comment Summary #1: The commenter requested changing the storage requirement in the *Packaging and storage* section from “store at controlled room temperature” to “store between 2° and 30°” to meet current labeled storage conditions for the approved marketed product.

Response: Comment incorporated.

Comment Summary #2: The commenter informed the Expert Committee that the original HPLC column used in the development of the methods for the Assay and

AMENDED COMMENTARY– USP 32-NF 27 First Supplement

Chromatographic purity test has been discontinued. The commenter also submitted information about the replacement column and requested minor changes to the mobile phase ratio, flow rate, and relative retention times for the impurities as suitable for the new column.

Response: Comment incorporated. The updated column information will be listed in the *Chromatographic Reagents* database.

Comment Summary #3: The commenter requested revising the list of specified impurities and their relative response factors, to reflect recent changes in the sponsor's regulatory filing.

Response: Comment incorporated.

Monograph/Section(s): Pilocarpine Hydrochloride Tablets/Related Compounds

Expert Committee(s): Monograph Development-Ophthalmics, Oncology, Dermatology

No. of Commenters: 1

Comment Summary: The commenter requested the limits of Isopilocarpine be changed from "0.5%" to "1.0%" and of total impurities be changed from "1.0%" to "1.2%" to be consistent with their approved specifications.

Response: Comment incorporated.

Monograph/ Section(s): Proguanil Hydrochloride/Related Compounds

Expert Committee(s): Monograph Development-Antivirals and Antimicrobials

No. of Commenters: 1

Comment Summary: The commenter proposed using a higher concentration of proguanil hydrochloride in the *Standard solution* to reduce the percent relative standard deviation requirement (% RSD) from 10.0% to 2.0% for replicate injections.

Response: Comment not incorporated because the lower concentration of the *Standard solution* and the corresponding percent relative standard deviation are more appropriate and typical for the determination of low levels of impurities.

Monograph/Section(s): Rocuronium Bromide/Multiple Sections

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

No. of Commenters: 2

Comment Summary #1: The commenter requested adding a test and specification for the limit of acetic acid.

Response: Comment not incorporated because the proposal reflects the current approved marketed product. The USP Pending Monographs website includes a proposed addition of a *Limit of Acetic Acid* test as an "authorized" standard.

Comment Summary #2: The commenter requested the pH range be widened from "8.9-9.5" to "7.0-9.5."

Response: Comment not incorporated because the commenter does not have an approved product. A proposal with the wider pH range exists on the USP Pending Monographs website as an "authorized" standard.

Comment Summary #3: The commenter suggested the *Color of solution* test be revised to be consistent with the *European Pharmacopoeia* monograph.

Response: Comment not incorporated because the proposal reflects the current approved marketed product.

AMENDED COMMENTARY– USP 32-NF 27 First Supplement

Comment Summary #4: The commenter requested making the *Limit of 2-propanol* an optional test to allow the flexibility of not testing if 2-propanol is not used in the manufacturing process.

Response: Comment incorporated by adding a note to the test.

Comment Summary#5: The commenter requested the elimination of the retention time in the HPLC *Identification test*.

Response: Comment not incorporated due to inadequate justification.

Comment Summary #6: The commenter requested the *Karl Fischer Water* test be changed from “*Method I*” to “*Method Ic*.”

Response: Comment incorporated.

Comment Summary #7: The commenter requested the linear velocity of 25 cm/sec be included if nitrogen is used as the carrier gas in the *Limit of 2-propanol* test.

Response: Comment incorporated.

Comment Summary #8: The commenter requested the replacement of the *Resolution* requirement in the *Related compounds* test with peak-to-valley ratio because the required *USP Rocuronium Peak Identification Mixture RS* contains 500-fold excess of the major component making the resolution of 1.5 unattainable.

Response: Comment incorporated.

Comment Summary #9: The commenter requested the relative retention times listed in the *Related compounds* test for related compounds E, F and G be revised to match the *European Pharmacopoeia* monograph.

Response: Comment incorporated.

Comment Summary #10: The commenter requested the RSD requirement in the *Assay* be lowered from “2.0%” to “1.0%.”

Response: Comment not incorporated due to lack of supporting data. The Expert Committee will consider revising the requirement if supporting data is provided.

Monograph/Section(s): Simethicone Emulsion/Assay

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

No. of Commenters: 3

Comment Summary #1: The commenters stated that they successfully used a wrist shaker for the *Assay*, and requested to allow the use of a wrist-action shaker along with the currently specified reciprocal shaker.

Response: Comment incorporated. A *Note* is added that both reciprocal and wrist-action shakers were found suitable.

Comment Summary #2: The commenter requested listing centrifuge speed and time as suggestions only, and allowing for centrifuge speeds and times to be used if found suitable.

Response: Comment incorporated.

Monograph/Section(s): Trandolapril/ Related Compounds and Assay

Expert Committee(s): Monograph Development-Cardiovascular

No. of Commenters: 1

Comment Summary #1: The commenter requested to revise the anhydrous acetic acid to glacial acetic acid in the *Assay*.

AMENDED COMMENTARY– USP 32-NF 27 First Supplement

Response: Comment incorporated.

Comment Summary #2: The commenter requested revising the relative response factor (RRF) for unspecified impurities from “1” to “1.0” to maintain consistency with other RRF values presented in the table.

Response: Comment incorporated.

Monograph/Section(s): Travoprost/Multiple Sections

Expert Committee(s): Monograph Development-Ophthalmics, Oncology, Dermatology

No. of Commenters: 1

Comment Summary #1: The commenter requested the applied volume of *Standard solution* and *Test solution* be changed from “20 µL” to “5 µL” on the thin layer chromatography (TLC) plate in the test of *Identification A* to keep the spot size small.

Response: Comment incorporated.

Comment Summary #2: The commenter requested the resolution requirement be changed from “between Travoprost and any adjacent peak” to “between Travoprost and 5,6-*trans*-isomer” in the test for *Related compounds*.

Response: Comment incorporated.

Expert Committee-initiated Change #1: The committee corrected the chemical name of travoprost from “(Z)-7-[(1R,2R,3R,5S)-3,5-Dihydroxy-2-[(1E,3R)-3-hydroxy-4-[(a,a,a-trifluoro-*m*-isopropyl-tolyl)oxy]-1butenyl]cyclopentyl]-5-heptenoate” to “Isopropyl (Z)-7-[(1R,2R,3R,5S)-3,5-dihydroxy-2-[(1E,3R)-3-hydroxy-4-[(α,α,α-trifluoro-*m*-tolyl)oxy]-1-butenyl]cyclopentyl]-5-heptenoate.”

Expert Committee-initiated Change #2: The committee changed the *Assay* calculation from mg to percentage to be consistent with the format of USP monograph redesign.

Monograph/Section(s): Travoprost Ophthalmic Solution/Multiple Sections

Expert Committee(s): Monograph Development-Ophthalmics, Oncology, Dermatology

No. of Commenters: 1

Comment Summary #1: The commenter requested the cautionary statement be changed for clarification.

Response: Comment incorporated.

Comment Summary #2: The commenter requested “light resistant” be deleted from the *Packaging and storage* statement because the container carton, the secondary packing, is required.

Response: Comment incorporated.

Comment Summary #3: The commenter requested the *Resolution* requirement be changed from “between travoprost and any adjacent peak” to “between Travoprost and 5,6-*trans*-isomer” in the test for *Related compounds*.

Response: Comment incorporated.

Comment Summary #4: The commenter requested changing *Assay* calculation from mg to percentage because the latter is USP preferred convention.

Response: Comment incorporated.

AMENDED COMMENTARY– USP 32-NF 27 First Supplement

Monograph/Section(s): Zinc Citrate/Multiple Sections

Expert Committee(s): Dietary Supplement-Non-Botanicals

No. of Commenters: 1

Comment Summary #1: The commenter requested “not less than 33.3 percent” be changed to “not less than 31.3 percent” because 31.3 percent is the theoretical maximum.

Response: Comment incorporated.

Comment Summary #2: The commenter requested either removing the text “calculated on the dried basis” or replacing the text with “determined on the previously dried substance” because the assay method requires analysis of the “previously dried” material.

Response: Comment not incorporated because the proposed language is consistent with *General Notices, Tests and Assays, Procedures*.

Comment Summary #3: The commenter requested doubling the concentrations of the standard used in the test for *Limit of arsenic, cadmium, and lead* because the standard concentration would then be equal to the acceptance criteria maximum.

Response: Comment not incorporated because the proposed procedure requires calculation of the quantity of arsenic, cadmium, and lead present.