



## ***Commentary***

### ***USP 40–NF 35, Second Supplement***

June 1, 2017

In accordance with USP’s Rules and Procedures of the Council of Experts (“Rules”) and except as provided in Section 7.02 Accelerated Revision Processes, USP publishes proposed revisions to the *United States Pharmacopeia and the National Formulary (USP–NF)* for public review and comment in the *Pharmacopeial Forum (PF)*, USP’s free bimonthly journal for public notice and comment. After comments are considered and incorporated as the Expert Committee deems appropriate, the proposal may advance to official status or be re-published in *PF* for further notice and comment, in accordance with the Rules. In cases when proposals advance to official status without re-publication in *PF*, a summary of comments received and the appropriate Expert Committee's responses are published in the Revisions and Commentary section of USP.org at the time the official revision is published.

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 Expert Committees’ responses to public comments on proposed revisions. 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.

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**Comments were received for the following when they were proposed in Pharmacopeial Forum:**

**General Chapters:**

- [<161> Medical Devices-Bacterial Endotoxin and Pyrogen Tests](#)
- [<503> Acetic Acid in Peptides](#)
- [<781> Optical Rotation](#)
- [<1062> Tablet Compression Characterization](#)
- [<1080> Bulk Pharmaceutical Excipients–Certificate of Analysis](#)
- [<1229.14> Sterilization Cycle Development](#)
- [<1229.15>Sterilizing Filtration of Gases](#)

**Monographs:**

- [Acetylcysteine Compounded Solution](#)
- [Atropine Sulfate Ophthalmic Ointment](#)
- [Atropine Sulfate Ophthalmic Solution](#)
- [Hydrogenated Castor Oil](#)
- [Chia Seed Oil](#)
- [Cholesterol](#)
- [Cyclophosphamide Tablets](#)
- [Decoquinat Premix](#)
- [Dipyridamole](#)
- [Divalproex Sodium Extended-Release Tablets](#)
- [Docetaxel Injection](#)
- [Doxycycline Capsules](#)
- [Eleuthero Root And Rhizome Dry Extract Capsules](#)
- [Eleuthero Root And Rhizome Dry Extract Tablets](#)
- [Eleuthero Root And Rhizome Powder Capsules](#)
- [Eprosartan Mesylate](#)
- [Esomeprazole Strontium](#)
- [Estradiol Valerate](#)
- [Exenatide](#)
- [Fingolimod Hydrochloride](#)
- [Fluvoxamine Maleate](#)
- [Folic Acid Compounded Oral Solution](#)
- [Hydralazine Hydrochloride](#)
- [Leucovorin Calcium Compounded Oral Suspension](#)
- [Linezolid](#)
- [Methylnaltrexone Bromide](#)
- [Milbemycin Oxime](#)
- [Monensin Premix](#)
- [Morphine Sulfate Extended-Release Capsules](#)
- [Moxifloxacin Tablets](#)
- [Narasin Premix](#)
- [Nevirapine Extended Release Tablets](#)
- [Nimodipine](#)

- [Ondansetron Compounded Topical Gel](#)
- [Phenytoin Chewable Tablets](#)
- [Polyoxyl 35 Castor Oil](#)
- [Pramipexole Dihydrochloride](#)
- [Protriptyline Hydrochloride Tablets](#)
- [Rhodiola Crenulata Root And Rhizome](#)
- [Rhodiola Crenulata Root And Rhizome Dry Extract](#)
- [Rhodiola Crenulata Root And Rhizome Powder](#)
- [Salix Species Bark](#)
- [Salix Species Bark Dry Extract](#)
- [Salix Species Bark Powder](#)
- [Sodium Hydroxide](#)
- [Sodium Lauryl Sulfate](#)
- [Sodium Acetate](#)
- [Sodium Nitrite](#)
- [Silver Sulfadiazine](#)
- [Teriparatide](#)
- [Teriparatide Injection](#)

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

**General Chapters:**

- <91> Calcium Pantothenate Assay
- <115> Dexpanthenol Assay
- <503.1> Trifluoroacetic Acid (TFA) in Peptides
- <771> Ophthalmic Products - Quality Tests

**Monographs:**

- Acetaminophen And Aspirin Tablets
- Acetaminophen, Aspirin, And Caffeine Tablets
- Almond Oil
- Aluminum Monostearate
- Anagrelide Capsules
- Antipyrine And Benzocaine Otic Solution
- Ascorbic Acid Compounded Oral Solution
- Betamethasone Dipropionate Topical Aerosol
- Canola Oil
- Clonazepam Orally Disintegrating Tablets
- Cinoxacin
- Cinoxacin Capsules
- Corn Oil
- Cottonseed Oil
- Cytarabine
- Desoxycorticosterone Acetate
- Desoxycorticosterone Acetate Injection
- Desoxycorticosterone Acetate Pellets

- Dichlorodifluoromethane
- Dichlorotetrafluoroethane
- Dienestrol
- Dienestrol Cream
- Divalproex Sodium
- Doxycycline Calcium Oral Suspension
- Eleuthero
- Powdered Eleuthero
- Powdered Eleuthero Extract
- Flutamide Capsules
- Hydralazine Hydrochloride Tablets
- Hydrocortisone Injectable Suspension
- Hydrocortisone Acetate Injectable Suspension
- Hydrocortisone Acetate Ophthalmic Suspension
- Insulin Aspart
- Lactobacillus Paracasei Lpc-37
- Lorazepam
- Metoprolol Tartrate Tablets
- Metoprolol Tartrate And Hydrochlorothiazide Tablets
- Nandrolone Phenpropionate
- Nandrolone Phenpropionate Injection
- Nitrofurazone
- Ondansetron Orally Disintegrating Tablets
- Peanut Oil
- Polyoxyl 40 Hydrogenated Castor Oil
- Red Clover Aerial Parts Isoflavone Aglycones Dry Extract
- Reserpine Injection
- Reserpine Oral Solution
- Reserpine And Hydrochlorothiazide Tablets
- Riluzole Tablets
- Salmeterol Xinafoate
- Sodium Nitrite Injection
- Terbinafine Tablets
- Ziprasidone Capsules
- Zolpidem Tartrate Tablets
- Zonisamide Capsules

## General Chapters

**General Chapter/Section(s):** <161> Medical Devices—Bacterial Endotoxin and Pyrogen Tests/Multiple Sections

**Expert Committee:** General Chapters—Microbiology

**No. of Commenters:** 2

**Comment Summary #1:** The commenter suggested clarifying the length of exposure of the extraction fluid and the necessary temperature of the extraction fluid for the duration of the extraction process.

**Response:** Comment not incorporated. The information is covered in General Chapter <161>.

**Comment Summary #2:** The commenter indicated that the basis for the limit in the *Definitions* section for devices in contact with cerebrospinal fluid is unclear and the limit is inconsistent with FDA's current Guidance for Industry on Pyrogen and Endotoxins Testing.

**Response:** Comment not incorporated. The Expert Committee determined that this information is outside of the scope of the current revision and that the limit is identical to the one indicated in FDA's current guidance on Pyrogen and Endotoxins Testing.

**Comment Summary #3:** The commenter suggested expanding the critical factors that should be considered in the definition of product families in the *Definitions* section.

**Response:** Comment not incorporated. The Expert Committee determined that this information is outside of the scope of the current revision.

**General Chapter/Section:** <503> Acetic Acid in Peptides

**Expert Committee:** Biologics Monographs 1—Peptides/Method 1, Sample Solution

**No. of Commenters:** 1

**Comment Summary #1:** The commenter requested revising the Note to add clarification.

**Response:** Comment incorporated.

**General Chapter/Section(s):** <781> Optical Rotation/Introduction/Footnote

**Expert Committee(s):** General Chapters—Physical Analysis

**No. of Commenters:** 13

**Comment Summary #1:** The commenter suggested updating the statements about: 1) the use of Quartz Control Plates (QCPs) as an alternative for calibration; and 2) accredited laboratories that perform calibrations on QCPs.

**Response:** Comment incorporated. The footnote was modified to include information on: 1) suitable calibrators available from the National Institute of Standards and Technology (NIST); 2) calibration using a Polarization Reference Standard; and 3) signatory and accreditation for making calibrations.

**Comment Summary #2:** The commenter recommended keeping QCPs as an alternative for calibration.

**Response:** Comment incorporated.

**Comment Summary #3:** The commenter suggested adding instrument calibration/qualification information to the procedure including: 1) definition of standards that can be used; 2) acceptance criteria; and 3) statements on use of NIST traceable standards and manufacturers' instructions for instrument calibration.

**Response:** Comment partially incorporated. The quartz plate standards were kept but additional information about calibration and qualification is out of the scope of the General Chapter.

**Comment Summary #4:** The commenter suggested including analyst error if sucrose standard is prepared in-house.

**Response:** Comment not incorporated. This comment is out of the scope of the General Chapter.

**General Chapter/Sections:** <1062> Tablet Compression Characterization/Multiple Sections

**Expert Committee:** General Chapters–Physical Analysis

**No. of Commenters:** 3

### **Background**

**Comment Summary #1:** The commenter recommended revising the second paragraph by adding the phrase, “high friability, broken tablets.”

**Response:** Comment partially incorporated. Only the “high friability” phrase was added because the Expert Committee decided that the descriptions are examples and not necessarily used as a comprehensive list.

**Comment Summary #2:** The commenter recommended revising the second paragraph by adding the phrases, “excess variation in weight or dimension of compressed tablets” and “poor powder flow leading to content uniformity issues.”

**Response:** Comment not incorporated. The Expert Committee determined that the suggestions are related to powder flow, not to compression.

**Comment Summary #3:** The commenter recommended revising the third paragraph by replacing “can also influence” with “are also key factors that influence.”

**Response:** Comment incorporated.

### **Compression Phases**

**Comment Summary #4:** The commenter suggested revising *Figure 1* by adding specific dwell time, a sample curve of ejection force following compression time, and that pressure would be recorded on the lower punch.

**Response:** Comment partially incorporated. The Expert Committee determined that the dwell time should not be specified and pressure should be recorded on the lower punch.

**Comment Summary #5:** The commenter suggested revising the second paragraph by adding that particles vibrate.

**Response:** Comment not incorporated. The Expert Committee determined that the particles do not vibrate.

**Comment Summary #6:** The commenter suggested revising statements in the third paragraph regarding punch velocity and dwell time to reflect that tablet consolidation can continue as long as pressure is applied.

**Response:** Comment not incorporated. The Expert Committee determined that, as indicated, dwell time can also affect tablet mechanical properties.

**Comment Summary #7:** The commenter suggested revising the second paragraph by changing the statement regarding the punch velocity and dwell time to reflect that tablet consolidation can continue as long as pressure is applied.

**Response:** Comment not incorporated. The Expert Committee determined that, as indicated, dwell time can also affect tablet mechanical properties.

**Comment Summary #8:** The commenter suggested revising the second paragraph by adding “may” between “Tooling shape and size” and “also.”

**Response:** Comment incorporated.

### ***Tablet Compression Characterization Equipment***

**Expert Committee-initiated Change #1:** The Expert Committee replaced “precisely” with “necessarily.”

**Comment Summary #9:** The commenter suggested revising a sentence by adding “when the fill weight is in control” after “rotatory machines.”

**Response:** Comment not incorporated. The Expert Committee determined that this is related to powder flow, not compression, and is only relevant for force-time profile.

**Comment Summary #10:** The commenter suggested revising a sentence in 3.5 *Instrumented Production Tablet Press* by adding “(or tablet-in-tablet)” between “multi-layer tablet” and “capability.”

**Response:** Comment incorporated.

### ***Tooling***

**Comment Summary #11:** The commenter suggested revising the first paragraph by adding “and elongated oval shape” after “standard round concave tooling that produces convex-shaped tablets.”

**Response:** Comment not incorporated. The Expert Committee determined that the elongated oval shape is not commonly used.

**Comment Summary #12:** The commenter suggested revising the first paragraph by adding “if there has been a significant change in design” after “the tablet tooling design may affect the tablet mechanical integrity.”

**Response:** Comment not incorporated. The Expert Committee determined that more information about “change” is required and that the sentence contains “may.”

### ***Punch Displacement–Time Profiles***

**Expert Committee-initiated Change #2:** The Expert Committee deleted the sentence in the first paragraph, “Typical punch displacement–time profiles include the properties of a compressed powder.”

**Expert Committee-initiated Change #3:** The Expert Committee deleted the sentence in the third paragraph, “Because the compression set up and parameters can affect measured compact properties, it is important to specify the experimental details when reporting results.”

### ***Tablet Mechanical Strength***

**Comment Summary #13:** The commenter suggested revising the sentence in the first paragraph by adding “compression parameters” between “the particle–particle bond strength” and “true areas of contact.”

**Response:** Comment not incorporated. The Expert Committee determined that compression parameters affect tablet strength through influencing particle-particle bond strength and true areas of contact.

**Comment Summary #14:** The commenter suggested revising the first paragraph by adding a sentence regarding loading and breaking force for tablets of other shapes after the sentence regarding conventional round tablets with a circular cross-section.

**Response:** Comment not incorporated. The Expert Committee determined the description is already in General Chapter <1217>, *Tablet Breaking Force*.

**Comment Summary #15:** The commenter suggested revising the first paragraph by deleting the sentence regarding hardness in material science.

**Response:** Comment not incorporated. The Expert Committee retained the sentence because it explains why hardness should not be used to describe tablet breaking strength.

**Comment Summary #16:** The commenter suggested revising the sentence in the second paragraph regarding manufacturing process history to state that critical manufacturing process can also influence tablet strength.

**Response:** Comment not incorporated. The Expert Committee changed the sentence regarding critical manufacturing process to, "Problems in manufacturing processes, such as over-mixing or over-granulation, also can influence tablet strength."

**Expert Committee-initiated Change #4:** The Expert Committee deleted the word "also" in the second paragraph.

**Comment Summary #17:** The commenter suggested revising the third paragraph by replacing "are known to" with "may."

**Response:** Comment incorporated.

**Comment Summary #18:** The commenter suggested revising the third paragraph by adding "also."

**Response:** Comment incorporated.

**Comment Summary #19:** The commenter suggested revising the third paragraph by adding "depending on the compression parameters."

**Response:** Comment not incorporated. The Expert Committee determined that the addition of the phrase, "depending on the compression parameters" does not clarify or add value to the statement.

### ***Tablet Porosity and Solid Fraction***

**Comment Summary #20:** The commenter suggested revising the first paragraph by deleting, "Virtually all pharmaceutical compacts contain porous regions (pores)" and replacing "air" with "void space."

**Response:** Comment partially incorporated. The Expert Committee retained the text recommended for deletion but replaced "air" with "void space."

### ***Compatibility Profile***

**Expert Committee-initiated Change #5:** The second paragraph was modified by adding, "(solid fraction)" after "high porosity."

### ***Conclusions and Recommendations***

**Comment Summary #21:** The commenter suggested revising the first paragraph by adding "environment conditions, equipment" between "manufacturing process parameters" and "and tooling design."

**Response:** Comment incorporated.

**Comment Summary #22:** The commenter suggested revising *Table 1* by replacing "Key" with "Common" in the caption.

**Response:** Comment partially incorporated. The Expert Committee replaced "Key" with "Important."



**Comment Summary #23:** The commenter suggested revising *Table 1* by adding “Press Revolutions Per Minute (RPM)” or “Tablets Per Hour/Minute (TPH/M)” to the “Example Parameters in Common Use” under “Compression Speed.”

**Response:** Comment incorporated. The Expert Committee added “Tablets/Min.”

**Comment Summary #24:** The commenter suggested revising *Table 1* by adding three more parameters to the table that include “Die Material/Type,” “Tooling Material/Type,” and (importantly) “Compression Location in Die.”

**Response:** Comment partially incorporated. The Expert Committee added one new line in Table 1: Tablet press configuration with or without pre-compression setting. Adding die type (straight vs. tapered) may be useful, but it may not be necessary for tooling material and compression location in die. They are relevant but may not be key parameter to specify for all studies.

**Comment Summary #25:** The commenter suggested revising the discussion on pre-compression and adding parameters and examples to Table 1.

**Response:** Comment not incorporated. The information is covered in General Chapter <1062>.

### ***Machine Speed Sensitivity***

**Comment Summary #26:** The commenter suggested changing strain rate sensitivity in Table 1 to a general tablet property.

**Response:** Comment not incorporated. The Expert Committee determined that it is an example only and that the existing text is sufficient.

### ***Tablet Mechanical Strength***

**Comment Summary #27:** The commenter suggested adding a reference on determination of the tensile strength of elongated tablets.

**Response:** Comment not incorporated. The Expert Committee determined that no change is required because <1062> does not discuss tensile strength calculation.

### ***Conclusions and Recommendations***

**Expert Committee-initiated Change #6:** In *Table 1*, the Expert Committee changed “SRS:  $(P2 - P1)/P2$ ” to “SRS =  $(P2 - P1)/P2$ .”

### ***Glossary***

**Expert Committee-initiated Change #7:** The Expert Committee changed the definition for “Dwell time” from “Duration of time (in ms) that an applied compression pressure is  $\geq$  90% of maximum compression pressure, or duration of time (in ms) that the compression roll is in contact with the flat portion of the punch head” to “Duration of time (in ms) that the compression roll is in contact with the flat portion of the punch head.”

<b>General Chapter/Section:</b>	<1080> Bulk Pharmaceutical Excipients—Certificate of Analysis Tests/Multiple Sections
<b>Expert Committee:</b>	Excipient Monographs 1
<b>No. of Commenters:</b>	2

### ***General Guidance***

**Comment Summary #1:** The commenter recommended revising the first paragraph by deleting the sentence that the Certificate of Analysis (COA) should be reflective of the user-specified quality requirements because a typical COA does not have user specified requirements.

**Response:** Comment incorporated.

**Comment Summary #2:** The commenter recommended revising the second paragraph by removing the sentences that suggest that the onus is on the excipient manufacturer to agree to the specifications.

**Response:** Comment incorporated.

### ***Design and Required Elements of a COA***

**Comment Summary #3:** The commenter recommended revising the third paragraph by removing the sentence that indicates the best practice is to include a reference to the user's current specification on the COA because this would be difficult for the excipient manufacturer to implement.

**Response:** Comment incorporated.

### ***Identifying Information***

**Comment Summary #4:** The commenter recommended including a CAS number as a non-ambiguous identifier that is readily available for excipients.

**Response:** Comment not incorporated. A CAS number cannot be used as a non-ambiguous identifier because many excipients are complex entities.

### ***Certification and Compliance Statements***

**Comment Summary #5:** The commenter suggested deleting the number signifying the revision year from NSF/IPEC/ANSI 363-2014.

**Response:** Comment incorporated.

### ***Data Versus Conformance***

**Comment Summary #6:** The commenter suggested using numbers instead of bullets to describe the source of measurements reported on a COA.

**Response:** Comment incorporated.

**Comment Summary #7:** The commenter suggested revising the sentence on describing how the test result was obtained to read, "Where number 2 or number 3 apply, the technique for how the test result was obtained should be described."

**Response:** Comment incorporated.

### ***Distributor information***

**Comment Summary #8:** The commenter recommended retaining the first two sentences and deleting the rest of the paragraph because it did not reflect the current practice.

**Response:** Comment incorporated.

**Expert Committee-initiated Change #1:** In the *Glossary* section, definitions were updated for Continuous process or processing, Excipient, Impurity, Specification, and Stable process; and new definitions were added for Skip lot (periodic) testing, Stability, Storage, and Supply chain.

**Expert Committee-initiated Change #2:** The Expert Committee updated references throughout the general chapter and in the *References* section.

**General Chapter/Sections:** <1229.14> Sterilization Cycle Development/Multiple Sections

**Expert Committee:** General Chapters—Microbiology

**No. of Commenters:** 3

**Comment Summary #1:** The commenter suggested clarifying that the bioburden evaluation and resistance test is unnecessary for process development of overkill approaches or bioburden/biological indicator-based processes.

**Response:** Comment not incorporated. Knowledge of the bioburden and its resistance to the sterilization process is a major consideration in the establishment of a sterilization process.

**Comment Summary #2:** The commenter recommended providing additional guidance and/or references regarding materials compatibility with radiation.

**Response:** Comment incorporated. This is addressed with an added reference in the appropriate section.

**Comment Summary #3:** The commenter indicated that Equation 2 in the proposed new General Chapter is incorrect.

**Response:** Comment incorporated. The equation has been rectified.

**Comment Summary #4:** The commenter recommended that the definition of PNSU in Equation 2 be revised for greater clarity.

**Response:** Comment incorporated. The definition has been revised for greater clarity.

**Comment Summary #5:** The commenter suggested including a reference to Association for the Advancement of Medical Instrumentation document TIR17 to support the section on *Formal Material Evaluation*.

**Response:** Comment incorporated. The reference has been added.

**General Chapter/Section:** <1229.15> Sterilizing Filtration of Gases/General

**Expert Committee:** General Chapters—Microbiology

**No. of Commenters:** 1

**Comment Summary #1:** The commenter recommended including guidance on frequency of integrity testing based on formal risk assessment and pre-use integrity testing.

**Response:** Comment not incorporated. This is already discussed in the cross-referenced General Chapter <1229.4> *Sterilizing Filtration of Liquids*.

### **Monographs**

**Monograph/Sections:** Acetylcysteine Compounded Solution/Multiple Sections

**Expert Committee:** Compounding

**No. of Commenters:** 1

**Comment Summary #1:** The commenter recommended omitting the monograph because there are several FDA-approved generic acetylcysteine solution products commercially available.

**Response:** Comment not incorporated. The compounded preparation monograph was developed to ensure consistency in compounding in the event of product unavailability or drug shortages.

**Comment Summary #2:** The commenter recommended changing references from “single-dose” to “single-unit” throughout the monograph because “single-dose” is a packaging term for an article intended for parenteral administration.

**Response:** Comment incorporated.

**Expert Committee-initiated Change #1:** The *Definition* and acceptance criteria in the Assay were revised to state that the preparation must contain NMT 110% of the labeled amount of acetylcysteine.

**Expert Committee-initiated Change #2:** The designation for the HPLC column was changed to L96.

**Monograph/Sections:** Atropine Sulfate Ophthalmic Ointment/Assay and Organic Impurities

**Expert Committee:** Chemical Medicines Monographs 4

**Expert Committee-initiated Change #1:** The designation for the HPLC column was changed from L1 to L96.

**Monograph/Section(s) :** Atropine Sulfate Ophthalmic Solution/Assay and Organic Impurities

**Expert Committee:** Chemical Medicines Monographs 4

**Expert Committee-initiated Change #1:** The designation for the HPLC column was changed from L1 to L96.

**Monograph/Section:** Chia Seed Oil/Fatty Acid Composition

**Expert Committee:** Non-Botanical Dietary Supplements

**Expert Committee-initiated Change #1:** The acceptance criteria for gamma-linolenic acid was changed from 0.2%–0.4% to 0.0%–0.4% in *Table 1* of the test for *Fatty Acid Composition*.

**Monograph/Section(s):** Cholesterol/Limit of Related Sterols and Other Impurities

**Expert Committee(s):** Excipients Monographs 1

**No. of Commenters:** 1

**Comment Summary #1:** The commenter recommended revising the acceptance criteria for the limit of desmosterol from “≤3%” to “≤4%.”

**Response:** Comment incorporated.

**Monograph/Section:** Cyclophosphamide Tablets/Organic Impurities

**Expert Committee:** Chemical Medicines Monographs 3

**No. of Commenters:** 1

**Comment Summary #1:** The commenter recommended including a test for organic impurities with appropriate acceptance criteria.

**Response:** Comment not incorporated. The Expert Committee will consider future revisions to the monograph upon receipt of supporting data.

**Monograph/Sections:** Decoquinat Premix/Multiple Sections

**Expert Committee:** Chemical Medicines Monographs 3

**No. of Commenters:** 1

**Comment Summary #1:** The commenter requested that the official date of the Title change be changed from June 1, 2020 to December 1, 2017. The commenter provided data to support that manufacturers are already using Decoquinatate Type A Medicated Article.

**Response:** Comment incorporated.

**Comment Summary #2:** The commenter requested that the *Labeling* section be revised to remove “Label it to indicate that it is for veterinary use only”.

**Response:** Comment not incorporated. This section of the monograph was not proposed for revision in the *Pharmacopeial Forum* proposal. The Expert Committee will consider the comment in a future revision of the monograph.

**Monograph/Section:** Dipyridamole/Organic Impurities

**Expert Committee:** Chemical Medicines Monographs 2

**No. of Commenters:** 5

**Comment Summary #1:** The commenter requested widening the acceptance criteria for Dipyridamole Related Compound A from NMT 0.1% to NMT 0.50% and widening the acceptance criteria for Dipyridamole Related Compound B from NMT 0.1% to NMT 0.50% to match their approved specifications.

**Response:** Comment incorporated.

**Comment Summary #2:** The commenter requested widening the acceptance criteria for Dipyridamole Related Compound D from NMT 0.1% to NMT 0.2% and widening the acceptance criteria for Dipyridamole Related Compound E from NMT 0.1% to NMT 0.2% to match their approved specifications.

**Response:** Comment incorporated.

**Comment Summary #3:** The commenter requested replacing the proposed method with the validated HPLC procedure that separates all listed impurities.

**Response:** Comment not incorporated. The Expert Committee determined that the proposed method is suitable for determining impurities in dipyridamole.

**Comment Summary #4:** The commenter indicated that the peak shapes of Dipyridamole Related Compound B and Dipyridamole Related Compound F were poor and that the quantification of impurities was done against the individual impurity standards, which consumes multiple impurity standards.

**Response:** Comment not incorporated. The Expert Committee determined that the proposed method is suitable for determining impurities in dipyridamole.

**Comment Summary #5:** The commenter indicated that the upper impurity limit for specified impurities should be NMT 0.15%.

**Response:** Comment not incorporated. The Expert Committee will consider future revisions to the monograph upon receipt of supporting data.

**Comment Summary #6:** The commenter indicated that UPLC is not a universal method in the pharmaceutical industry and that the retention times obtained using different brands of UPLC columns could vary significantly.

**Response:** Comment not incorporated. The Expert Committee determined that the proposed method is suitable for determining impurities in dipyridamole.

**Comment Summary #7:** The commenter indicated that the proposed method is costly because it requires six impurity reference standards in the test for organic impurities.

**Response:** Comment not incorporated. The Expert Committee determined that the proposed method is suitable for determining impurities in dipyridamole.

**Monograph/Section:** Divalproex Sodium Extended-Release Tablets/Dissolution  
**Expert Committee:** Chemical Medicines Monographs 4

**Expert Committee-initiated Change #1:** In *Dissolution Test 1*, the word “diluted” in front of phosphoric acid is repeated to provide clarity that diluted sodium hydroxide or diluted phosphoric acid may be used to adjust the pH of the solution to 5.5.

**Expert Committee-initiated Change #2:** In *Dissolution Test 10*, the references to “Medium” in the descriptions of the *Acid stage standard solution* and *Buffer stage standard solution* were replaced for clarity, and the references to “Medium” in the definition of “V” were replaced for clarity .

**Monograph/Section:** Docetaxel Injection/Bacterial Endotoxins  
**Expert Committee:** Chemical Medicines Monographs 3

**No. of Commenters:** 1

**Comment Summary #1:** The commenter recommended tightening the acceptance criteria for *Bacterial Endotoxins* so that they are consistent with FDA approval.

**Response:** Comment not incorporated. The acceptance criteria for *Bacterial Endotoxins* in the currently official monograph are consistent with the FDA-approved limits.

**Monograph/Section:** Doxycycline Capsules/Organic Impurities  
**Expert Committee:** Chemical Medicines Monographs 1

**No. of Commenters:** 1

**Comment summary #1:** The commenter recommended including its in-house process impurity to the test for *Organic Impurities*.

**Response:** Comment not incorporated. The Expert Committee will consider future revisions to the monograph upon receipt of supporting data.

**Comment summary #2:** The commenter indicated that doxycycline coelutes with 2-acetyl-2-decarbamoylexycycline impurity, which is detected in the commenter’s product.

**Response:** Comment not incorporated. Based on the validation data, the Expert Committee determined that the procedure adequately resolves organic impurities.

**Expert Committee-initiated Change #1:** The chemical information for USP Doxycycline Related Compound A RS was revised to include information for the hydrochloride salt.

**Expert Committee-initiated Change #2:** The relative retention times of the impurities in the test for *Organic Impurities* were revised to be consistent across the family of monographs.

**Monograph/Sections:** Eleuthero Root and Rhizome Dry Extract Capsules/Multiple Sections

**Expert Committee:** Non-Botanical Dietary Supplements

**No. of Commenters:** 2

**Comment Summary #1:** The commenter proposed adding synonyms and chemical formulas to Eleutheroside B and Eleutheroside E for improved clarity in the monograph definition.

**Response:** Comment incorporated.

**Comment Summary #2:** The commenter proposed revising the proportion of methanol and water to 30% methanol and 70% water (instead of 60% methanol and 40% water)

in the final standard and sample solutions for improved robustness of the assay procedure; and using wavelength of 220 nm (instead of 215 nm).

**Response:** Comment incorporated.

**Monograph/Sections:** Eleuthero Root and Rhizome Dry Extract Tablets/Multiple Sections

**Expert Committee:** Non-Botanical Dietary Supplements

**No. of Commenters:** 2

**Comment Summary #1:** The commenter proposed adding synonyms and chemical formulas to Eleutheroside B and Eleutheroside E for improved clarity in the monograph definition.

**Response:** Comment incorporated.

**Comment Summary #2:** The commenter proposed revising the proportion of methanol and water to 30% methanol and 70% water (instead of 60% methanol and 40% water) in the final standard and sample solutions for improved robustness of the assay procedure; and using wavelength of 220 nm (instead of 215 nm).

**Response:** Comment incorporated.

**Monograph/Sections:** Eleuthero Root and Rhizome Powder Capsules/Multiple Sections

**Expert Committee:** Botanical Dietary Supplements and Herbal Medicines

**No. of Commenters:** 1

**Expert Committee-initiated Change #1:** Expert Committee proposed to incorporate comments received for Eleuthero Root and Rhizome Dry Extract Capsules and Eleuthero Root and Rhizome Dry Extract Tablets.

**Response:** Comment incorporated.

**Monograph/Section:** Eprosartan Mesylate/Organic Impurities

**Expert Committee:** Chemical Medicines Monographs 2

**No. of Commenters:** 1

**Comment Summary #1:** The commenter indicated that the total impurities acceptance criterion is not consistent with the FDA-approved specification.

**Response:** Comment not incorporated. The proposed limits are consistent with the FDA-approved limits in the sponsor's application.

**Monograph/Sections:** Esomeprazole Strontium/Multiple Sections

**Expert Committee:** Chemical Medicines Monographs 3

**No. of Commenters:** 1

**Comment Summary #1:** The commenter indicated that the impurity profile in the test for *Organic Impurities* is different from what has been approved by FDA.

**Response:** Comment not incorporated. The impurity profile is consistent with FDA approved requirements.

**Comment Summary #2:** The commenter indicated that the acceptance criteria for *Enantiomeric Purity* are different from what has been approved by FDA.

**Response:** Comment not incorporated. The acceptance criteria in the proposal are consistent with FDA-approved requirements.

**Monograph/Section:** Estradiol Valerate/Impurities/Additional Requirements

**Expert Committee:** Chemical Medicines Monographs 5

**No. of Commenters:** 2

**Comment Summary #1:** The commenter indicated that Impurity-G (not listed in the proposal) and Impurity-C (Estradiol-9-ene Valerate) were closely eluting, and that artifact peaks from the blank were observed at the retention time of Impurity-B, Estradiol Valerate, and Impurity-H peaks.

**Response:** Comment not incorporated. The Expert Committee will consider future revisions to the monograph upon receipt of supporting data.

**Comment Summary #2:** The commenter recommended revising the organic impurities limits to be consistent with what has been approved by the FDA.

**Response:** Comment incorporated. The limit for estradiol was widened from NMT 0.2% to NMT 0.5%; the limit for estradiol-9-ene valerate was widened from NMT 0.2% to NMT 0.5%; the limit for 4-methylestradiol valerate was widened from NMT 0.4% to NMT 0.5%, and the total impurity limit was widened from NMT 0.5% to NMT 1.0%.

**Comment Summary #3:** The commenter recommended adding “controlled room temperature” under Package and Storage.

**Response:** Comment incorporated.

**Monograph/Sections:** Exenatide/Multiple Sections

**Expert Committee:** Biologics Monographs 1–Peptides

**No. of Commenters:** 5

**Comment Summary #1:** The commenter stated that alternative hydrolysis approaches are acceptable for *Amino Acid Analysis* and recommended extending the options for this procedure.

**Response:** Comment incorporated. A note was added stating, “Use a suitable, validated hydrolysis, separation and calculation procedure including amino acids used in the calculation (see *Biotechnology-Derived Articles—Amino Acid Analysis (1052)*).”

**Comment Summary #2:** The commenter recommended adding a statement that the *Amino Acid Analysis* method and calculations in the monograph were only a representative method and also proposed different acceptance criteria for the Ser and Trp limits in Method B (AAA).

**Response:** Comment not incorporated. Per *General Notices* 6.30, alternative methods may be used in certain circumstances. In addition, the proposed Ser and Trp limits are based on the FDA-approved specifications.

**Comment Summary #3:** Two commenters recommended stating whether or not Trp is present without specifying the limits.

**Response:** Comment not incorporated. The proposed limit is based on the FDA-approved specifications.

**Comment Summary #4:** The commenter recommended changing “glutamine” to “glutamic acid” and “asparagine” to “aspartic acid” in *Table 1* for the *Amino Acid Analysis Identification* procedure, since they are produced by the hydrolysis step.

**Response:** Comment incorporated.

**Comment Summary #5:** The commenter recommended including total peptide content determination by nitrogen analysis instead of HPLC for the Assay.

**Response:** Comment not incorporated. HPLC is a universally used method in the peptide industry and can be used for testing both Drug Substance and Drug Product.

**Comment Summary #6:** The commenter recommended adding more details regarding the base used to prepare the Assay Solution A.



**Response:** Comment incorporated. The Expert Committee added to the monograph that pH is adjusted by the addition of 0.0375% ammonia.

**Comment Summary #7:** The commenter recommended revising the Product Related Substances and Impurities note by adding “regulatory review sought.”

**Response:** Comment not incorporated. The additional phrase is implied and does not need to be explicitly stated.

**Comment Summary #8:** The commenter recommended implementing the identification and qualification threshold limits for peptide impurities from the *European Pharmacopeia* monograph on *Substances for Pharmaceutical Use*.

**Response:** Comment not incorporated. These general limits are not accepted by the FDA.

**Comment Summary #9:** The commenter recommended adding a note to Procedure 1 of the *Product Related Substances and Impurities* section to clarify that subtle variations to the elution profile are acceptable.

**Response:** Comment not incorporated. Adding the note is not necessary because General Chapter <621> *Chromatography* allows slight variations in elution profile and the retention times are not requirements.

**Comment Summary #10:** The commenters recommended rewording the subsection heading Product Related Substances and Impurities for improved clarity.

**Response:** Comment incorporated. The section was renamed *Impurities*.

**Comment Summary #11:** The commenter recommended adding the chemical name of Impurity A to the *Product Related Substances and Impurities* section.

**Response:** Comment partially incorporated. The Expert Committee omitted this impurity because the structure of this impurity cannot be definitively determined.

**Comment Summary #12:** The commenter indicated that the acceptance criteria for [Glu<sup>13</sup>]-exenatide and the Sum of [Asp<sup>28</sup>]-exenatide and [Met(O)<sup>14</sup>]-exenatide in the *Product Related Substances and Impurities* section were inconsistent with FDA approvals and ICH Q3B limits and recommended standard nomenclature for the impurity names.

**Response:** Comment not incorporated. The Expert Committee determined that the limits and naming were appropriate.

**Comment Summary #13:** The commenter recommended adding the reporting limit to Procedure 1 in the *Product Related Substances and Impurities* section.

**Response:** Comment incorporated. The reporting limit of 0.05% was added.

**Comment Summary #14:** The commenter recommended widening the relative retention times for Exenatide, [Glu<sup>13</sup>]-exenatide, and the Sum of [Asp<sup>28</sup>] and [Met(O)<sup>14</sup>]-exenatide in Procedure 1 in the *Product Related Substances and Impurities* section.

**Response:** Comment not incorporated. The Expert Committee determined that General Chapter <621> *Chromatography* allows slight variations in elution profile and that retention times are not requirements.

**Comment Summary #15:** The commenter recommended clarifying that the Standard solution is prepared in duplicate in the RSD requirement in Procedure 2 of the *Product Related Substances and Impurities* section.

**Response:** Comment incorporated.

**Comment Summary #16:** The commenter recommended widening the retention time for *N*-Acetyl-His<sup>1</sup>-exenatide in *Procedure 2* of the *Product Related Substances and Impurities* section.

**Response:** Comment not incorporated. The Expert Committee determined that General Chapter <621> *Chromatography* allows slight variations in elution profile and that retention times are not requirements. The Expert Committee will consider future revisions to the monograph upon receipt of supporting data.

**Comment Summary #17:** The commenter recommended using its alternative method to the *Procedure 3* of the *Product Related Substances and Impurities* section for the determination of *N-Acetyl-His<sup>1</sup>-exenatide*.

**Response:** Comment not incorporated. The Expert Committee will consider future revisions to the monograph upon receipt of supporting data.

**Comment Summary #18:** The commenter recommended changing the column to designate L-Chirasil Val for *Procedure 3* of the *Product Related Substances and Impurities* section.

**Response:** Comment partially incorporated. The L-Chirasil Val column designation was removed and replaced with the packaging designation G49.

**Comment Summary #19:** The commenter recommended changing “Standard solution” a to “System suitability solution” in *Procedure 3* of the *Product Related Substances and Impurities* section.

**Response:** Comment incorporated. Standard solution was renamed System suitability solution A and the previous System suitability solution was renamed System suitability solution B.

**Comment Summary #20:** Three commenters recommended changing the column length, optimization, and system suitability in *Procedure 3* of the *Product Related Substances and Impurities* section.

**Response:** Comment not incorporated. The Expert Committee determined that the types of modifications are within the variability allowed by General Chapter <621> *Chromatography*.

**Comment Summary #21:** The commenter recommended adding “the mass fragment of 379 is used to detection” to *Procedure 3* in the *Product Related Substances and Impurities* section.

**Response:** Comment incorporated.

**Comment Summary #22:** The commenter recommended clarifying that the limit of phosphate only applies if phosphate reagents are used in the manufacturing process.

**Response:** Comment not incorporated. The Expert Committee finds the current wording of this statement to be sufficient.

**Comment Summary #23:** The commenters recommended increasing the specification for acetic acid content.

**Response:** Comment not incorporated. The Expert Committee determined that the specifications in the monograph reflect FDA-approved specifications.

**Comment Summary #24:** The commenters recommended removing reference to General Chapter <62> *Microbiological Examination of Nonsterile Products: Tests for Specified Microorganisms* in the *Microbial Enumeration Tests* section.

**Response:** Comment not incorporated. The Expert Committee determined that General Chapter <62> is referenced by General Chapter <61> *Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests* for the purpose of preparing media.

**Comment Summary #25:** The commenter recommended widening the specification of the water content to NMT 10.0%.

**Response:** Comment not incorporated. The Expert Committee determined that the proposed change is inconsistent with the FDA-approved specifications.

**Expert Committee-initiated Change # 1:** A note was added to the *Standard Solution* of the Assay section stating: “The retention time for the exenatide peaks is approximately 14–20 min.”

**Expert Committee-initiated Change # 2:** The Expert Committee recommended widening the relative retention time of [*N*-Acetyl-His<sup>1</sup>]-exenatide in *Table 5* to a range of 1.10 to 1.13 based on further review of laboratory data.

**Expert Committee-initiated Change # 3:** The Expert Committee removed the USP Endotoxin RS reference in the *Additional Requirements* section as it is already referenced in General Chapter <85> *Bacterial Endotoxins Test*.

**Monograph/Sections:** Fingolimod Hydrochloride/Multiple Sections

**Expert Committee:** Chemical Medicines Monographs 3

**No. of Commenters:** 4

**Comment Summary #1:** The commenter recommended deleting the impurity *O*-acetyl fingolimod from *Table 2* in the test for *Organic Impurities* because it differs from what has been approved by the FDA.

**Response:** Comment incorporated. The relative retention time for *O*-acetyl fingolimod was deleted from *Table 2* and added as a note in the *System Suitability* section.

**Comment Summary #2:** The commenter indicated that the procedure inadequately resolves *O*-acetyl fingolimod from fingolimod nonyl homolog.

**Response:** Comment not incorporated. The Expert Committee determined that the resolution requirement is suitable for the intended purpose.

**Comment Summary #3:** The commenter recommended including General Chapter <921> *Water Determination* as an alternative procedure for moisture determination.

**Response:** Comment incorporated.

**Comment Summary #4:** The commenter requested widening the acceptance criteria for *Loss on Drying* from NMT 0.5% to NMT 0.70%.

**Response:** Comment not incorporated. The acceptance criteria for *Loss on Drying* are consistent with the FDA-approved specifications. The Expert Committee will consider future revisions to this monograph upon receipt of supporting data.

**Comment Summary #5:** The commenter recommended including additional tests for identification in the monograph.

**Response:** Comment not incorporated. The Expert Committee determined that the tests in the monograph are suitable for the intended purpose.

**Monograph/Section:** Fluvoxamine Maleate/Organic Impurities

**Expert Committee:** Chemical Medicines Monographs 4

**No. of Commenters:** 2

**Comment Summary # 1:** The commenters requested correcting the chemical names of aminoethyl fluvoxamine, succinyl fluvoxamine, and Z-isomer.

**Response:** Comment partially incorporated. The Expert Committee corrected the chemical name of Aminoethyl Fluvoxamine, found that the chemical name of Z-isomer was added in *PF 42(5)* [Sep.–Oct. 2016], and determined that the chemical name of Succinyl fluvoxamine is consistent with the information provided by the sponsor.

**Monograph/Section:** Folic Acid Compounded Oral Solution/Definition  
**Expert Committee:** Compounding  
**No. of Commenters:** 1

**Comment Summary #1:** The commenter recommended revising the compounding table by clarifying that a sufficient quantity of Purified Water should be added to bring to a final volume of 100 mL.

**Response:** Comment incorporated.

**Monograph/Section:** Hydralazine Hydrochloride/Organic Impurities  
**Expert Committee:** Chemical Medicines Monographs 2  
**No. of Commenters:** 1

**Comment Summary #1:** The commenter indicated that a process-related impurity is late eluting and difficult to quantify.

**Response:** Comment not incorporated. The Expert Committee will consider future revisions to this monograph upon receipt of supporting data.

**Monograph/Section(s):** Hydrogenated Castor Oil/Multiple Sections  
**Expert Committee(s):** Excipient Monographs 1  
**No. of Commenters:** 2

**Comment Summary #1:** The commenter recommended extending the centrifugation time to “5 min to 15 min” in *Identification test A, Identity by Fatty Acid Composition*.

**Response:** Comment incorporated.

**Comment Summary #2:** The commenter recommended changing “upper” layer to “organic” layer, eliminating “(the upper layer),” and replacing “lower” with “aqueous” in *Identification test A, Identity by Fatty Acid Composition*.

**Response:** Comment incorporated.

**Comment Summary #3:** The commenter recommended changing “NLT 10” to “NLT 5” for *Resolution*, in *Identification test A, Identity by Fatty Acid Composition*.

**Response:** Comment incorporated.

**Comment Summary #4:** The commenter recommended replacing “unidentified fatty acid” with “unspecified fatty acid or impurity” in *Table 3 in Identification test A, Identity by Fatty Acid Composition*.

**Response:** Comment incorporated.

**Comment Summary #5:** The commenter recommended replacing “Hydrogenated Castor Oil” with “USP Hydrogenated Castor Oil RS” in preparation of *System suitability solution* in the *Assay, Triglyceride Composition*.

**Response:** Comment incorporated.

**Comment Summary #6:** The commenter recommended replacing “and allow to cool to room temperature” with “The titration can be performed on a warm solution of 50°–65° to avoid a flocculation of the substance” in General Chapter <401> *Fats and Fixed Oils, Hydroxyl Value*.

**Response:** Comment incorporated.

**Comment Summary #7:** The commenter recommended increasing the upper limit from 162 to 163 in General Chapter <401> *Fats and Fixed Oils, Hydroxyl Value*.

**Response:** Comment incorporated.

**Monograph/Sections:** Leucovorin Calcium Compounded Oral Suspension/Multiple Sections

**Expert Committee:** Compounding

**No. of Commenters:** 1

**Comment Summary #1:** The commenter recommended verifying that the pH acceptance criteria are aligned with the pH adjustment specified in the compounding procedures.

**Response:** Comment not incorporated. Addition of Syrup to the formulation decreases the pH of the preparation; therefore, the pH acceptance criteria are slightly lower than the range specified in the formula. The stability for the formulation has been established by a validated stability-indicating assay.

**Expert Committee-initiated Change #1:** A note was added to *Solution A* in the Assay to specify that tetrabutylammonium phosphate appearing wet should not be used because it may co-elute with the leucovorin.

**Monograph/Sections:** Linezolid/Multiple Sections

**Expert Committee:** Chemical Medicines Monographs 1

**No. of Commenters:** 3

**Comment summary #1:** The commenter requested including a limit for *Total impurities* in the test for *Organic Impurities*.

**Response:** Comment not incorporated. The Expert Committee will consider a future revision to this monograph upon receipt of supporting data.

**Comment summary #2:** The commenter recommended including the run time for the *Enantiomeric purity* test.

**Response:** Comment incorporated.

**Comment summary #3:** The commenter recommended changing “Any other individual impurity” to “Any individual unspecified impurity” in the test for *Organic impurities*.

**Response:** Comment incorporated.

**Comment summary #4:** The commenter indicated that the test for *Organic impurities* did not adequately resolve its in-house impurities.

**Response:** Comment not incorporated. The Expert Committee will consider a future revision to this monograph upon receipt of the supporting data.

**Comment summary #5:** The commenter recommended updating the test for *Organic impurities* by adding “if present” for linezolid *N*-oxide and desfluoro linezolid impurities because these impurities were not observed in their impurity profile.

**Response:** Comment incorporated. The Expert Committee determined that “if present” should only be applied to the desfluoro linezolid impurity because linezolid *N*-oxide is a degradation product rather than a process impurity.

**Comment summary #6:** The commenter indicated that the test for *Enantiomeric purity* did not adequately resolve an in-house impurity from the *R*-isomer.

**Response:** Comment not incorporated. The Expert Committee will consider a future revision to this monograph upon receipt of supporting data.

**Comment summary #8:** The commenter recommended including the polymorphic type of USP Linezolid RS.

**Response:** Comment incorporated by adding information about polymorphic normalization to the test for *Identification by Infrared Spectroscopy*.

**Comment summary #9:** The commenter requested revising the resolution requirement from NLT 2.0 to NLT 1.5 in the test for *Enantiomeric purity*.

**Response:** Comment incorporated.

**Comment summary #10:** The commenter recommended using the coulometric method (*Method Ic*) in the test for *Water Determination*.

**Response:** Comment incorporated.

**Monograph/Sections:** Methylaltraxone Bromide/Multiple Sections

**Expert Committee:** Chemical Medicines Monographs 3

**No. of Commenters:** 2

**Comment Summary #1:** The commenter recommended revising the acceptance criteria for *Organic impurities* to be consistent with what have been approved by the agency.

**Response:** Comment not incorporated. The acceptance criteria for *Organic impurities* are consistent with FDA-approved limits.

**Comment Summary #2:** The commenter recommended revising the acceptance criteria for *Bacterial Endotoxins*.

**Response:** Comment incorporated. The numerical value for the acceptance criteria was replaced with statements regarding the level of bacterial endotoxins and a statement was added to the *Labeling* section.

**Comment Summary #3:** The commenter requested changing the units for the concentration of the *Standard solution* in the *Analysis* section of the test for *Limit of Methylaltraxone Related Compound A* from “mg/mL” to “µg/mL.”

**Response:** Comment incorporated.

The numerical value for the acceptance criteria is replaced with statement regarding the level of bacterial endotoxins when Methylaltraxone Bromide is used. The *Labeling* section is updated.

**Monograph/Section(s):** Milbemycin Oxime/Multiple Sections

**Expert Committee(s):** Chemical Medicines Monographs 3

**No. of Commenters:** 3

**Comment Summary #1:** The commenter indicated that the limits in the *Definition* section were not consistent with those in the *Assay*.

**Response:** Comment incorporated. The *Assay* limits were aligned with the *Definition* to 95.0% - 102.0%, which are consistent with the FDA approved acceptance

**Comment Summary #2:** The commenter requested changing the acceptance criteria in the *Assay* for the ratio of Milbemycin A<sub>4</sub> Oxime: Milbemycin A<sub>3</sub> Oxime from NMT 0.80: NLT 0.20 to NMT 0.75: NLT 0.25 to reflect FDA approved limits.

**Response:** Comment incorporated as follows: the acceptance criterion is changed to NLT 0.75 for Milbemycin A<sub>4</sub> Oxime. The acceptance criterion for Milbemycin A<sub>3</sub> Oxime is removed.

**Comment Summary #3:** The commenter requested revising the acceptance criteria for total organic impurities in the test for *Organic Impurities* from NMT 5.0% to NMT 3.5% (excluding Milbemycin Oxime D) to reflect FDA approved limits.

**Response:** Comment incorporated.

**Comment Summary #4:** The commenter requested revising the acceptance criteria in the test for *Water Determination* from NMT 2.0% to NMT 3.0% to reflect FDA approved limits.

**Response:** Comment incorporated.

**Monograph/Section(s):** Monensin *Premix* / Multiple Sections

**Expert Committee:** Chemical Medicines Monographs 3

**No. of Commenters:** 1

**Comment Summary #1:** The commenter requested that the official date of the Title Change be changed from June 1, 2020 to December 1, 2017. The commenter provided data to support that manufacturers are already using Monensin Type A Medicated Article.

**Response:** Comment incorporated.

**Comment Summary #2:** The commenter requested that the *Labeling* section be revised to remove “Label it to indicate that it is for veterinary use only”.

**Response:** Comment not incorporated. This section of the monograph was not proposed for revision in the *PF* proposal. The Expert Committee will consider the comment in a future revision of the monograph.

**Monograph/Section:** Morphine Sulfate Extended-Release Capsules/Assay

**Expert Committee:** Chemical Medicine Monographs 2

**No. of Commenters:** 1

**Comment Summary #1:** The commenter indicated that the mixing time of NLT 30 min and the sonication time of NLT 5 min should be more defined to avoid degradation during the preparation of sample stock solution.

**Response:** Comment not incorporated. The Expert Committee determined that the flexibility allowed for mixing time and sonication time is necessary to cover all approved products. The Expert Committee will consider future revisions to this monograph upon receipt of supporting data.

**Monograph/Sections:** Moxifloxacin Tablets/Multiple Sections

**Expert Committee:** Chemical Medicines Monographs 1

**No. of Commenters:** 2

**Comment Summary #1:** The commenter requested widening the acceptance criteria in the Assay for from 95.0%–105.0% to 90.0%–110.0% to be consistent with FDA-approved limits.

**Response:** Comment incorporated.

**Comment Summary #2:** The commenter requested replacing the resolution requirement with a peak-to-valley ratio, which is more appropriate in for the peaks in question.

**Response:** Comment incorporated.

**Monograph/Sections:** Narasin Premix/Multiple Sections

**Expert Committee:** Chemical Medicines Monographs 3

**No. of Commenters:** 1

**Comment Summary #1:** The commenter requested that the official date of the Title Change be changed from June 1, 2020 to December 1, 2017. The commenter provided data to support that manufacturers are already using Narasin Type A Medicated Article.

**Response:** Comment incorporated.

**Comment Summary #2:** The commenter requested that the *Labeling* section be revised to remove “Label it to indicate that it is for veterinary use only”.

**Response:** Comment not incorporated. This section of the monograph was not proposed for revision in the *PF* proposal. The Expert Committee will consider the comment in a future revision of the monograph.

**Monograph/Section:** Nevirapine Extended Release Tablets/Organic Impurities  
**Expert Committee:** Chemical Medicines Monographs 1  
**No. of Commenters:** 1

**Comment Summary #1:** The commenter indicated that the acceptance criteria for *Total impurities* differ from FDA-approved requirements.

**Response:** Comment not incorporated. The acceptance criteria for *Total impurities* are consistent with FDA-approved requirements.

**Monograph/Sections:** Nimodipine/Impurities  
**Expert Committee:** Chemical Medicines Monographs 2  
**No. of Commenters:** 1

**Comment Summary #1:** The commenter requested changing “Individual impurities” to “any unspecified impurity” to match ICH terminology.

**Response:** Comment incorporated.

**Monograph/Section:** Ondansetron Compounded Topical Gel/Assay  
**Expert Committee:** Compounding  
**No. of Commenters:** 1

**Expert Committee-initiated Change #1:** The *Sample Solution* preparation instruction in the Assay was revised to indicate that it should be prepared on a weight basis instead of a volume basis.

**Monograph/Sections:** Phenytoin Chewable Tablets/Organic Impurities  
**Expert Committee:** Chemical Medicines Monographs 4  
**No. of Commenters:** 3

**Comment Summary # 1:** The commenters indicated that the acceptance criteria for any individual unspecified degradation products and total degradation products are not consistent with FDA-approved specifications.

**Response:** Comment incorporated. The acceptance criteria for any individual unspecified degradation product and total degradation products were revised to reflect FDA-approved specifications.

**Monograph/Section(s):** Polyoxyl 35 Castor Oil/Multiple Sections  
**Expert Committee(s):** Excipients Monographs 1  
**No. of Commenters:** 1

**Comment Summary #1:** The commenter recommended revising the acceptance criteria for linoleic acid (C18:2) from “1.0–5.0” to “≤5.0%” in *Identification C.*, *Identity by Fatty Acid Composition*.

**Response:** Comment incorporated.

**Expert Committee-initiated Change #1:** The Expert Committee added the test title “*Constituting Fatty Acids*” for *Identification B*.

**Monograph/Sections:** Pramipexole Dihydrochloride/Limit of Pramipexole Related Compound D, Organic Impurities  
**Expert Committee:** Chemical Medicines Monographs 4  
**No. of Commenters:** 1



**Comment Summary # 1:** The commenter requested adding “(as monohydrate)” to the definition for  $C_U$  to make it consistent with the definition in the Assay and Organic impurities tests.

**Response:** Comment incorporated. The variable definition has been clarified.

**Comment Summary # 2:** The commenter requested confirmation of the Relative Response Factor (RRF) value for Pramipexole Related compound A or deleting RRF for specified impurities.

**Response:** Comment not incorporated. The RRF value in the proposal is consistent with the sponsor’s data.

**Monograph/Sections:** Protriptyline Hydrochloride Tablets/Organic Impurities

**Expert Committee:** Chemical Medicines Monographs 4

**No. of Commenters:** 1

**Comment Summary # 1:** The commenter indicated that the acceptance criteria for any individual unspecified degradation products and total degradation products are inconsistent with the FDA-approved specifications.

**Response:** Comment incorporated. The acceptance criteria for any individual unspecified degradation product was widened from NMT 0.15% to NMT 0.2% and total degradation products from NMT 0.20% to NMT 1.0%.

**Monograph/Sections:** Rhodiola crenulata Root and Rhizome/Multiple Sections

**Expert Committee:** Botanical Dietary Supplements and Herbal Medicines

**No. of Commenters:** 2

**Comment Summary #1:** The commenter indicated that there was no LOD typical condition listed in current General Chapter <731> *Loss on Drying* and suggested adding the dry condition under Loss on Drying.

**Response:** Comment incorporated. The monograph was revised by adding drying condition.

**Comment Summary #2:** The commenter suggested that the USP Laboratories project indicated that the HPTLC test results showed that the *Standard solution* displayed two bands with different color but not two gray bands.

**Response:** Comment incorporated by removing the word “gray.”

**Monograph/Sections:** Rhodiola crenulata Root and Rhizome Dry Extract/Multiple Sections

**Expert Committee:** Botanical Dietary Supplements and Herbal Medicines

**No. of Commenters:** 2

**Comment Summary #1:** The commenter indicated that there was no LOD typical condition listed in current General Chapter <731> *Loss on Drying* and suggested adding the dry condition under Loss on Drying.

**Response:** Comment incorporated. The monograph was revised by adding the drying condition.

**Comment Summary #2:** The commenter suggested that USP Laboratories project indicated that the HPTLC test results showed that the *Standard solution* displayed two bands with different color but not two gray bands.

**Response:** Comment incorporated by removing the word “gray.”

**Monograph/Sections:** Rhodiola crenulata Root and Rhizome Powder/Multiple Sections

**Expert Committee:** Botanical Dietary Supplements and Herbal Medicines

**No. of Commenters:** 2

**Comment Summary #1:** The commenter indicated that there was no LOD typical condition listed in current General Chapter <731> *Loss on Drying* and suggested adding the dry condition under Loss on Drying.

**Response:** Comment incorporated. The monograph was revised by adding the drying condition.

**Comment Summary #2:** The commenter suggested that USP Laboratories project indicated that the HPTLC test results showed that the *Standard solution* displayed two bands with different color but not two gray bands.

**Response:** Comment incorporated. The monograph was revised by deleting “gray.”

**Monograph/Section:** Salix Species Bark/Definition

**Expert Committee:** Botanical Dietary Supplements and Herbal Medicines

**Expert Committee-initiated Change #1:** In accordance with the current botanical nomenclature, the Latin binomial for *Salix humboldtiana* Willd. was updated to *Salix chilensis* Molina.

**Expert Committee-initiated Change #2:** In acknowledgement of the tendency of the willow species to freely hybridize, Salix species hybrids were included in the enumeration of acceptable botanical sources.

**Expert Committee-initiated Change #3:** In *Composition/Content* of Salicin and in *Specific Tests/Salicylates Profile* procedures, the diluent was introduced to replace methanol and weaken the eluotropic strength of the injection solvent, which tended to introduce artifacts in chromatographic systems with a low dwell volume.

**Monograph/Sections:** Salix Species Bark Powder/Multiple Sections

**Expert Committee:** Botanical Dietary Supplements and Herbal Medicines

**Expert Committee-initiated Change #1:** In *Composition/Content* of Salicin and in *Specific Tests/Salicylates Profile* procedures, the *diluent* was introduced to replace methanol and weaken the eluotropic strength of the injection solvent, which tended to introduce artifacts in chromatographic systems with a low dwell volume.

**Monograph/Sections:** Salix Species Bark Dry Extract/Multiple Sections

**Expert Committee:** Botanical Dietary Supplements and Herbal Medicines

**Expert Committee-initiated Change #1:** In *Composition/Content* of Salicin and in *Specific Tests/Salicylates Profile* procedures, the diluent was introduced to replace methanol and weaken the eluotropic strength of the injection solvent, which tended to introduce artefacts in chromatographic systems with a low dwell volume.

**Monograph/Sections:** Silver Sulfadiazine/Multiple Sections

**Expert Committee:** Chemical Medicines Monographs 1

**No. of Commenters:** 1

**Comment summary #1:** The commenter recommended revising the relative response factor for acetylsulfadiazine from 1.0 to 1.24 in the *Organic Impurities*.

**Response:** Comment not incorporated. Relative response factors from 0.8 to 1.2 are rounded to 1.0; the Expert Committee determined that it would be acceptable to round from 1.24 to 1.0 in this instance.

**Comment summary #2:** The commenter recommended including an identification solution in the *Organic Impurities* containing an impurity that is observed in the *European Pharmacopoeia* monograph for *Sulfadiazine*.

**Response:** Comment not incorporated. The Expert Committee will consider a future revision to this monograph upon receipt of supporting data.

**Comment summary #3:** The commenter recommended including a reference standard for acetylsulfadiazine in the *System Suitability* solution for peak identification.

**Response:** Comment not incorporated. The Expert Committee will consider a future revision to this monograph upon receipt of supporting data.

**Monograph/Section:** Sodium Acetate/Impurities  
**Expert Committee:** Chemical Medicines Monographs 5  
**No. of Commenters:** 1

**Comment Summary #1:** The commenter requested clarification regarding the required concentration of 0.020 N sulfuric acid TS.

**Response:** Comment incorporated. A new volumetric solution entry was created to specify the process necessary to standardize the solution to the appropriate concentration for use in the monograph and the monograph text was updated to refer to the volumetric solution, rather than the test solution.

**Monograph/Sections:** Sodium Hydroxide Tests/Multiple Sections  
**Expert Committee:** Excipients Monographs 1  
**No. of Commenters:** 4

**Comment Summary #1:** The commenter recommended correcting a typographical error in the expression of the concentration of the *Sample stock solution* in the *Content of Sodium* test from 130.3 mg/mL to 1.303 mg/mL.

**Response:** Comment incorporated.

**Comment Summary #2:** The commenter recommended changing the requirement for the correlation coefficient in the *Content of Sodium* test from “NLT 0.999” to “NLT 0.995” to align with that specified in General Chapter <852> *Atomic Absorption Spectroscopy*.

**Response:** Comment incorporated.

**Comment Summary #3:** The commenter suggested changing the concentration of the *Standard stock solution* in the test for *Potassium* from 186.37 mg/mL of potassium chloride to 1.907 mg/mL of potassium chloride.

**Response:** Comment incorporated.

**Comment Summary #4:** The commenter recommended changing the requirement for the correlation coefficient in the test for *Potassium* from “NLT 0.995” to “NLT 0.99” to align with that specified in General Chapter <852> *Atomic Absorption Spectroscopy*.

**Response:** Comment incorporated.

**Comment Summary #5:** The commenter noted that it was unclear whether an emission mode or absorbance mode was used in the description of the *Instrumental conditions* in the *Content of Sodium* test and indicated that if an instrument is operated in the emission mode, then no lamp is necessary.

**Response:** Comment not incorporated. All *Instrumental conditions* listed in the procedure are correct. The sodium emission line was included under *Analytical*

*wavelength* to show that 589.0 nm is a specific emission line for sodium hollow-cathode lamp.

**Comment Summary #6:** The commenter recommended changing the concentration of the first calibration standard from 0.05 µg/mL to 0.10 µg/mL because of the low absorbance at that level impacting the correlation coefficient.

**Response:** Comment incorporated.

**Comment Summary #7:** The commenter suggested specifying the solvent used in the preparation of the *Sample stock solution* in the test for *Potassium*.

**Response:** Comment not incorporated. The use of water as solvent in the preparation of solutions is covered by *General Notices 6.50.20. Solutions*, which states, "Unless otherwise specified, all solutions shall be prepared with Purified Water."

**Comment Summary #8:** The commenter requested specifying that the absorbance mode was used in the test for *Potassium*.

**Response:** Comment not incorporated. It is clear that an instrument is operated in the absorbance mode because Potassium hollow-cathode lamp is used in the procedure.

**Expert Committee-initiated Change #1:** A description that 766.5 nm corresponds to the potassium emission line was added to the test for *Potassium*.

**Monograph/Section(s):** Sodium Lauryl Sulfate/Identification

**Expert Committee(s):** Excipient Monographs 2

**No. of Commenters:** 2

**Comment Summary #1:** The commenter indicated that the proposed changes in the *Identification* section are inconsistent with the current harmonized standard in PDG and that the proposed changes did not go through the official PDG process.

**Response:** Comment partially incorporated. The Expert Committee agreed to not delete the two existing Identification (ID) tests (C and D) in the monograph but recommends including the IR test for ID in the monograph. This will be a local requirement in USP, which has undergone the regular revision process in USP, but not the harmonization process in PDG.

**Comment Summary #2:** The commenter recommended using the previous indicator (potassium chromate TS) for the Limit of Sodium Chloride test instead of the indicator (Fluorescein sodium solution) to resolve difficulty in determining the endpoint of titration.

**Response:** Comment not incorporated. The Expert Committee determined that no alternative indicator or procedure is currently available for this test.

**Monograph/Section:** Sodium Nitrite/Limit of Alkyl Naphthalene Sulfonates

**Expert Committee:** Chemical Medicines Monographs 2

**Expert Committee-initiated Change #1:** The Expert Committee determined to delete the test for Limit of alkyl naphthalene sulfonates as it is not relevant in a public standard.

**Monograph/Sections:** Teriparatide/Multiple Sections

**Expert Committees:** Biologics Monographs 1–Peptides

**No. of Commenters:** 1

**Comment Summary #1:** The commenter recommended revising the *Definition* and *Labeling* sections to cover synthetic teriparatide produced by chemical synthesis.

**Response:** Comment not incorporated. The only approved product in the U.S. is recombinantly produced teriparatide. The Expert Committee will consider future

revisions to the monograph upon receipt of supporting data based on approval of synthetic teriparatide drug products.

**Comment Summary #2:** The commenter recommended using amino acid analysis and mass spectrometry instead of peptide mapping and bioidentity as part of *Identification* tests for synthetic teriparatide.

**Response:** Comment not incorporated. The Expert Committee will consider future revisions to the monograph upon receipt of supporting data based on approval of synthetic teriparatide drug products.

**Comment Summary #3:** The commenter recommended adoption of its analytical procedures for *Assay* and the test for *Product-Related Impurities*.

**Response:** Comment not incorporated. The option of using alternative methods and/or procedures is covered in *General Notices 6.30 Alternative and Harmonized Methods and Procedures*. The Expert Committee will consider future revisions to the monograph upon receipt of supporting data based on approval of synthetic teriparatide drug products.

**Comment Summary #4:** The commenter recommended including a specification for acetate content of NMT 10.0% and excluding requirement for chloride content for synthetic teriparatide.

**Response:** Comment not incorporated. The Expert Committee will consider future revisions to the monograph upon receipt of supporting data based on approval of synthetic teriparatide drug products.

**Comment Summary #5:** The commenter recommended deleting the reference to the General Chapter <62> *Microbiological Examination of Nonsterile Products: Tests for Specified Microorganisms* because specifications of specified microorganism only apply for dosage forms as recommended in General Chapter <1111> *Microbiological Examination of Nonsterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use*.

**Response:** Comment not incorporated. The existing text does not mean that tests under <62> are required when the monograph calls for total aerobic microbial count because the description of the media for use in General Chapter <61> *Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests* is contained in <62>.

**Monograph/Sections:** Teriparatide Injection/Multiple Sections

**Expert Committees:** Biologics Monographs 1—Peptides

**No. of Commenters:** 2

**Comment Summary #1:** The commenter recommended that the *Definition* and *Labeling* sections cover synthetic teriparatide produced by chemical synthesis and include a statement that bioidentity test is only applicable for recombinant teriparatide products.

**Response:** Comment not incorporated. The only approved product in the U.S. is recombinantly produced teriparatide. The Expert Committee will consider future revisions to the monograph upon receipt of supporting data based on approval of synthetic teriparatide drug products.

**Comment Summary #2:** The commenter recommended adoption of its analytical procedures for *Assay* and the test for *Product-Related Impurities*.

**Response:** Comment not incorporated. The option of using alternative methods and/or procedures is covered in *General Notices 6.30 Alternative and Harmonized Methods*

*and Procedures*. The Expert Committee will consider future revisions to this monograph upon receipt of supporting data.

**Comment Summary #3:** The commenter requested clarification as to why the method including the mobile phase gradient for the test of *Product-Related Impurities* is different from the one in the drug substance monograph.

**Response:** Comment not incorporated. The mobile phase gradient was modified for the drug product to allow separation of specific cleavage impurities derived from teriparatide in solution with pH at 4.

**Comment Summary #4:** The commenter requested clarification as to why the limits of the impurities listed in the drug substance monograph are not mentioned in the drug product monograph.

**Response:** Comment not incorporated. Those oxidation impurities listed in the drug substance monograph are considered part of total impurities and may be the largest other impurity.

**Comment Summary #5:** The commenter requested clarification as to why USP does not supply the impurity reference standards.

**Response:** Comment not incorporated. It is unnecessary to supply the impurity reference standards because the relative retention times for those specified impurities are provided in the monograph.