



## ***Commentary***

### ***USP 40–NF 35***

November 1, 2016

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 the USP website 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 Notices to USP–NF](#)

**General Chapters:**

- [<89.1> Collagenase I](#)
- [<89.2> Collagenase II](#)
- [<127> Flow Cytometric Enumeration of CD34+ Cells](#)
- [<151> Pyrogen Test](#)
- [<659> Packaging and Storage Requirements](#)
- [<821> Radioactivity](#)
- [<531> Thiamine Assay](#)
- [<1039> Chemometrics](#)
- [<1602> Spacers and Valved Holding Chambers Used with Inhalation Aerosols—Characterization Tests](#)
- [<1821> Radioactivity—Theory and Practice](#)
- [<1823> Positron Emission Tomography Drugs—Information](#)

**Monographs:**

- [Acetaminophen and Diphenhydramine Citrate Tablets](#)
- [Acetaminophen and Tramadol Hydrochloride Tablets](#)
- [Alprazolam Orally Disintegrating Tablets](#)
- [Carboplatin](#)
- [Chlorhexidine Gluconate Topical Gel](#)
- [Cidofovir](#)
- [Cidofovir Injection](#)
- [Cisplatin](#)
- [Citrulline](#)
- [Demeclocycline Hydrochloride Tablets](#)
- [Desipramine Hydrochloride Tablets](#)
- [Doxercalciferol](#)
- [Doxycycline Hyclate Capsules](#)
- [Doxycycline Hyclate Tablets](#)
- [Heparin Sodium](#)
- [Hesperidin](#)
- [Hydroxyzine Hydrochloride](#)
- [Hydroxyzine Hydrochloride Tablets](#)
- [Isoflurane](#)
- [Ixabepilone](#)
- [Japanese Honeysuckle Flower](#)
- [Japanese Honeysuckle Flower Dry Extract](#)
- [Japanese Honeysuckle Flower Powder](#)

- [Methylene Blue](#)
- [Moxifloxacin Hydrochloride](#)
- [Nicotine Polacrilex](#)
- [Pemetrexed Disodium](#)
- [Pemetrexed for Injection](#)
- [Phenoxybenzamine Hydrochloride Capsules](#)
- [Polymyxin B Sulfate](#)
- [Potassium Hydroxide](#)
- [Prochloroperazine Maleate](#)
- [Quetiapine Extended-Release Tablets](#)
- [Selamectin](#)
- [Sodium Citrate and Citric Acid Oral Solution](#)
- [Sodium Succinate](#)
- [Tetrahydrozoline Hydrochloride](#)

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

**General Chapters:**

- <165> Prekallikrein Activator
- <481> Riboflavin Assay
- <670> Auxiliary Packaging Components
- <1015> Automated Radiochemical Synthesis Apparatus

**Monographs:**

- Aminobenzoate Potassium
- Aminobenzoate Potassium Capsules
- Azathioprine Sodium for Injection
- Acebutolol Hydrochloride Capsules
- Acetaminophen and Codeine Phosphate Oral Solution
- Acetaminophen and Codeine Phosphate Oral Suspension
- Acetaminophen, Chlorpheniramine Maleate, and Dextromethorphan Hydrobromide Tablets
- Acetaminophen, Dextromethorphan Hydrobromide, Doxylamine Succinate, and Pseudoephedrine Hydrochloride Oral Solution
- Acetaminophen, Diphenhydramine Hydrochloride, and Pseudoephedrine Hydrochloride Tablets
- Acetaminophen and Pseudoephedrine Hydrochloride Tablets
- Alprazolam Extended-Release Tablets
- Amiloxate
- Aminophylline
- Aminophylline Injection
- Aminophylline Oral Solution
- Aminophylline Tablets

- Ascorbic Acid Injection
- Ashwagandha Root
- Powdered Ashwagandha Root
- Powdered Ashwagandha Root Extract
- Betamethasone Valerate Cream
- Betamethasone Valerate Ointment
- Biperiden
- Biperiden Hydrochloride
- Biperiden Hydrochloride Tablets
- Biperiden Lactate Injection
- Calcium Phosphate, Tribasic
- Carboplatin for Injection
- Cisplatin for Injection
- Croscarmellose Sodium
- *Cryptocodinium cohnii* Oil
- Curcuminoids
- Cysteine Hydrochloride
- Eucalyptus Oil
- Fenbendazole
- Ibuprofen Oral Suspension
- Iodine Tincture
- Iodine Topical Solution
- Strong Iodine Tincture Iothalamate Sodium Injection
- Hydrocortisone Sodium Succinate
- Metoprolol Fumarate
- Monosodium Glutamate
- Olopatadine Hydrochloride
- Olopatadine Hydrochloride Ophthalmic Solution
- Penicillin G Procaine
- Pentazocine and Acetaminophen Tablets
- Potassium Gluconate
- Potassium Gluconate Oral Solution
- Potassium Gluconate Tablets
- Prompt Phenytoin Sodium Capsules
- Riboflavin Tablets
- Ringer's Injection
- Rutin
- Secobarbital Sodium and Amobarbital Sodium Capsules
- Secobarbital Sodium for Injection
- Secobarbital Sodium Injection
- Sodium Ferrous Citrate
- Sodium Hypochlorite Solution
- St. John's Wort

- Powdered St. John's Wort
- Powdered St. John's Wort Extract
- St. John's Wort Flowering Top Dry Extract Capsules
- St. John's Wort Flowering Top Dry Extract Tablets
- Sulfadoxine and Pyrimethamine Tablets
- Thiamine Hydrochloride Tablets
- Tienchi Ginseng Root and Rhizome Dry Extract Capsules
- Tienchi Ginseng Root and Rhizome Dry Extract Tablets
- Tienchi Ginseng Root and Rhizome Powder Capsules
- Tienchi Ginseng Root and Rhizome Powder Tablets
- Tinidazole
- Tissue Human Amnion Chorion Membrane Dehydrated
- Turmeric
- Powdered Turmeric
- Powdered Turmeric Extract

<b>General Notices/Sections:</b>	General Notices/Multiple Sections
<b>Expert Committee:</b>	Council of Experts
<b>No. of Commenters:</b>	2

### **3.10.30. Applicability of Standards to the Practice of Compounding**

**Comment Summary #1:** The commenter suggested changing the statutory reference from 503(b) to 503B.

**Response:** Comment incorporated.

### **5.50.10. Units of Potency (Biological)**

**Comment Summary #2:** The commenter suggested replacing the word "volume" with the word "potency" in the following sentence: "[t]he term "USP Units" can be used on product labeling consistent with USP compendial requirements, provided it is clear from the context that the volume is stated in terms of USP [product name] Units."

**Response:** Comment not incorporated. The Council of Experts will consider this as a Request for Revision.

### **5.80. USP Reference Standards**

**Comment Summary #3:** The commenter recommended that USP add a statement allowing the use of secondary reference standards, similar to that in the *European Pharmacopoeia*.

**Response:** Comment not incorporated. The USP policy regarding secondary reference standards can be found in the Frequently Asked Questions for Reference Standards, Question #7, which is posted on the USP website at: [https://www.usp.org/frequently-asked-questions/reference-standards#question\\_7](https://www.usp.org/frequently-asked-questions/reference-standards#question_7)

**General Chapter/Sections:** <89.1> Collagenase I and <89.2> Collagenase II/Multiple Sections [identical comments were received for both General Chapters]  
**Expert Committee:** Biologics Monographs 2—Proteins  
**No. of Commenters:** 3

### **Assay**

**Comment Summary #1:** The commenter requested correcting the unit definition of extinction coefficient ( $\epsilon$ ) from " $\mu\text{mol}^{-1} \cdot 1 \text{ cm}^{-1}$ " to " $1 \text{ cm}^2 \cdot \mu\text{mol}^{-1}$ ".

**Response:** Comment incorporated.

**Comment Summary #2:** The commenter suggested revising the system suitability requirement for the average calculated activity from 90%–110% to 85%–115% of the value on the label to accommodate the variability of the enzymatic assay.

**Response:** Comment incorporated.

### **Purity**

**Comment Summary #3:** The commenter suggested clarifying the description for the integration of peaks in the *Analysis* section.

**Response:** Comment incorporated. The description was revised to state, "All shoulders in the fronting and tailing of the main peak are integrated by dropping a perpendicular line at the inflection points and considered as separate impurities."

**Comment Summary #4:** The commenter suggested clarifying the description for the duration of integration in the *Analysis* section.

**Response:** Comment incorporated. The description was revised to state, "Disregard any peaks having retention times greater than 25 min."

### **Impurities, Clostripain Activity**

**Comment Summary #5:** The commenter recommended correcting the unit definition of extinction coefficient ( $\epsilon$ ) from  $\text{L} \cdot \text{mmol}^{-1} \cdot 1 \text{ cm}^{-1}$  to  $1 \text{ cm}^2 \cdot \text{mmol}^{-1}$ .

**Response:** Comment incorporated.

### **Trypsin Activity**

**Comment Summary #6:** The commenter recommended correcting the unit definition of extinction coefficient ( $\epsilon$ ) from " $\text{mmol}^{-1} \cdot 1 \text{ cm}^{-1}$ " to " $1 \text{ cm}^2 \cdot \text{mmol}^{-1}$ ".

**Response:** Comment incorporated.

### **Specific Tests, Protein Content**

**Comment Summary #7:** The commenter requested correcting the unit definition of extinction coefficient ( $\epsilon$ ) from " $A_{280}1\% \text{ cm}$ " to " $A_{280}0.1\%/\text{cm}$ ".

**Response:** Comment incorporated.

**General Chapter/Section:** <127> Flow Cytometric Enumeration of CD34+ Cells/Multiple Sections  
**Expert Committee:** Biologics Monographs 3—Complex Biologics  
**No. of Commenters:** 1

### ***Sample Preparation***

**Comment Summary #1:** The commenter suggested including a wash step to remove cryopreservative from frozen cell samples.

**Response:** Comment not incorporated. The proposed change is outside the scope of the method described in the General Chapter. The Expert Committee will consider future revisions to the General Chapter upon receipt of supporting data.

### ***Identification of CD34+ Hematopoietic Stem Cells***

**Comment Summary #2:** The commenter requested including forward scatter (FSC) or side scatter (SSC) area and width signals to allow for gating of single cells and discrimination of aggregates of cells which may also provide for resolution of aggregates of counting beads.

**Response:** Comment not incorporated. The sequential gating described in the General Chapter specifically selects for single cells. *Table 1, Step 8* allows for excluding or including aggregates (depending on the manufacturer's recommendations) of counting beads. Pulse area and width measurements are currently not part of the protocol. Incorporating a different way to select for singlets would be a change to the protocol that would require additional data and validation. The Expert Committee will consider future revisions to the General Chapter upon receipt of supporting data.

### ***Enumeration Considerations***

**Comment Summary #3:** The commenter recommended confirming that the CD34+ cells are identified equally with and without antibody wash steps.

**Response:** Comment not incorporated. The proposed change is out of the scope of the General Chapter method. Equivalent results are achieved without a wash step if the General Chapter antibody titration and sample preparation procedures are followed.

### ***Flow Cytometer Instrument Setup and Considerations***

**Comment Summary #4:** The commenter suggested that using fixed cells mixed with fresh cells provides for a better control sample to set up the flow cytometer for the 7AAD detection.

**Response:** Comment not incorporated. The proposed change is out of the scope of the General Chapter method. As per *General Notices*, alternative methods can be used as long as the results are equivalent to or better than the method in the General Chapter.

### ***Sample Preparation***

**Comment Summary #5:** The commenter suggested permitting the use of additional antibodies for phenotypic analysis of other, non-CD34+ cells.

**Response:** Comment not incorporated. The proposed change is out of the scope of the General Chapter method. As per *General Notices*, alternative methods can be used as long as the results are equivalent to or better than the compendial method.

### ***Data Acquisition and Analysis***

**Comment Summary #6:** The commenter suggested including FSC or SSC area and width signals for gating single cells versus aggregates.

**Response:** Comment not incorporated. The proposed change is out of the scope of the General Chapter method. The Expert Committee will consider future revisions to the General Chapter upon receipt of supporting data.

**Comment Summary #7:** The commenter suggested changing “R1” to “R2” in *Table 1* row 2, column 4.

**Response:** Comment incorporated.

**Comment Summary #8:** The commenter suggested permitting the use of alternate fluorescence channels other than those used for CD45 and CD34, to detect counting beads.

**Response:** Comment not incorporated. The procedure in the General Chapter is designed to be executed on a flow cytometer with a minimum of three independent detectors for fluorescence (‘fluorescence channels’); therefore, the method measures counting beads using the same detectors as those used for CD45 and CD34 to eliminate the need for more detectors. *Table 2* states that other fluorescence channels may be used to detect counting beads, depending on the flow cytometer configuration. As per *General Notices*, alternative methods can be used as long as the results are equivalent to or better than the method in the General Chapter.

**Comment Summary #9:** The commenter indicated that there may be considerable differences when gating fresh or frozen cell samples and not “slight differences” as stated in the text.

**Response:** Comment incorporated. The word “slightly” was removed. The statement now reads, “Dot plots may vary, depending on the cell sample, flow cytometer, and software used.”

**Expert Committee-initiated Change #1:** The reference standard name was changed from USP CD34+ Cells RS to USP CD34+ Cell Enumeration System Suitability RS to more accurately reflect the composition of the reference standard.

**Expert Committee-initiated Change #2:** Editorial changes were made to the text of *Table 1* for clarification and to eliminate redundancy.

**Expert Committee-initiated Change #3:** The figures in Step 2 and Step 3 of *Table 1* were revised to ensure that the gating included all CD34+ cells.



**General Chapter/Section:** <151> Pyrogen Tests  
**Expert Committee:** General Chapters—Microbiology  
**No. of Commenters:** 2  
**Comment Summary #1:** The commenter recommended adding names of specific in vitro pyrogen tests that are currently available commercially.  
**Response:** Comment not incorporated. It is intentional that specific technologies are not indicated. This is to ensure that the user has the option of choosing suitable technologies that may become available at a later date.  
**Comment Summary #2:** The commenter suggested including additional specifications for the use of healthy adult rabbits in the test.  
**Response:** Comment not incorporated. The suggested revision is beyond the scope of the current revision proposal.

**General Chapter/Section:** <531> Thiamine Assay  
**Expert Committee:** Non-Botanical Dietary Supplements  
**No. of Commenters:** 1  
**Comment Summary #1:** The commenter suggested that the proposed column dimensions (4.6-mm x 25-cm) in *Chromatographic Methods, Procedure 4* be harmonized with the column dimensions (4.0-mm x 30-cm) of a similar method in the Thiamine Hydrochloride monograph unless the proposed column size provides better resolution.  
**Response:** Comment not incorporated. The proposed column size, 4.6-mm x 25-cm, does give better resolution than the 4.0-mm x 30-cm size and is also more readily available commercially for users to purchase.

**General Chapter/Sections:** <659> Packaging and Storage  
Requirements/Multiple Sections  
**Expert Committee(s):** General Chapters—Packaging and Distribution  
**No. of Commenters:** 6

### ***Introduction***

**Comment Summary #1:** The commenter recommended adding back the text stating that every monograph in the *USP* and *NF* shall have packaging and storage requirements.

**Response:** Comment incorporated.

**Comment Summary #2:** The commenter recommended adding additional examples to better reflect the variety of products that are considered to be combination products.

**Response:** Comment incorporated.

**Comment Summary #3:** The commenter suggested referencing <661> Plastic Packaging Systems and Their Materials of Construction.

**Response:** Comment incorporated.

### ***Poison Prevention Packaging Act (PPPA)***

**Comment Summary #4:** The commenter suggested deleting the reference to 16 *CFR* 1700.16, because this regulation does not exist.

**Response:** Comment incorporated.

**Comment Summary #5:** The commenter recommended changing the term “non-closable” to “non-reclosable.” The term “non-closable” is not used in the *Poison Prevention Packaging Act*.

**Response:** Comment incorporated.

#### ***Packaging Definitions, Packaging System***

**Comment Summary #6:** The commenter suggested revising the definition of “packaging system” to align with the FDA Guidance, which defines the packaging system (container-closure system) as “the sum of packaging components that together contain and protect the dosage form.” This includes primary packaging components and secondary packaging components, but not tertiary.

**Response:** Comment incorporated.

#### ***Packaging Definitions, Container***

**Comment Summary #7:** The commenter suggested expanding the list of examples to include some devices.

**Response:** Comment incorporated.

#### ***Packaging Definitions, Closure***

**Comment Summary #8:** The commenter recommended adding examples of the various closures.

**Response:** Comment incorporated.

#### ***Packaging Definitions, Packaging Component***

**Comment Summary #9:** The commenter recommended using the term “syringe” instead of “pre-filled syringe.”

**Response:** Comment incorporated.

**Comment Summary #10:** The commenter suggested adding “container liners” to the list of examples.

**Response:** Comment incorporated.

#### ***Packaging Definitions, Child-resistant packaging***

**Comment Summary #11:** The commenter recommended that a reference to 16 *CFR* 1700.15 be added to this definition

**Response:** Comment incorporated.

#### ***Packaging Definitions, Tight Container***

**Comment Summary #12:** The commenter suggested that the list “Well-closed container” and “Light-resistant container” and “Tight container” be separate entries.

**Response:** Comment incorporated.

**Comment Summary #13:** The commenter suggested adding the definition for hermetic container back to the General Chapter.

**Response:** Comment incorporated.

### ***Injection Packaging Systems***

**Comment Summary #14:** The commenter recommended revising the definitions that begin with “A packaging system” to state, “A container” or “A container-closure system,” because these terms are meant for primary packaging components.

**Response:** Comment incorporated.

### ***Injection Packaging Systems, Pharmacy bulk package***

**Comment Summary #15:** The commenter recommended revising the definition to align with the final version proposed by the FDA.

**Response:** Comment incorporated.

### ***Non-Injection Packaging Systems***

**Comment Summary #16:** The commenter recommended revising the definitions that begin with “A packaging system” to state, “A container” or “A container-closure system,” because these terms are meant for primary packaging components.

**Response:** Comment incorporated.

### ***Non-Injection Packaging Systems, Unit-of-use container***

**Comment Summary #17:** The commenter recommended referencing General Chapter <7> Labeling, because there is a labeling requirement in the definition.

**Response:** Comment incorporated.

### ***Miscellaneous, Dispenser***

**Comment Summary #18:** The commenter suggested changing the term “Dispenser” to “Dispensing party” to avoid misinterpretation because the term dispenser is often used for an associated component to dispense the drug product.

**Response:** Comment not incorporated. The Expert Committee determined that changing the term could cause additional confusion.

### ***Associated Components***

**Comment Summary #19:** The commenter recommended that the General Chapter specify that the associated components must be composed of safe materials.

**Response:** Comment incorporated.

**Comment Summary #20:** The commenter recommended restoring the following statement, which had been removed from the General Chapter, “Each liquid preparation has unique surface and flow characteristics. Consequently, the volume delivered from a measurement/dosing component may vary for each preparation.”

**Response:** Comment incorporated.

**Comment Summary #21:** The commenter recommended revising the text to clearly state that the metric requirement also applies to OTC products, to avoid confusion.

**Response:** Comment incorporated.

**Comment Summary #22:** The commenter recommended delaying the implementation of the requirement that metric units are marked on associated components.

**Response:** Comment incorporated.

### ***Temperature and Storage, Temperature and Storage Definitions, Freezer***

**Comment Summary #23:** The commenter recommended revising the definition to permit use of temperatures colder than -10.

**Response:** Comment incorporated.

**General Chapter/Sections:** <821> Radioactivity/Multiple sections  
**Expert Committee:** Chemical Medicines Monographs 4  
**No. of Commenters:** 2

#### ***1. Introduction***

**Comment Summary #1:** The commenter suggested including a statement saying that the General Chapter should be used as guidance for establishing best practices for each setting where radioactivity is measured, taking into consideration the needs of the particular setting.

**Response:** Comment not incorporated. This is an enforceable General Chapter and the use of the requested language would make it unenforceable.

**Comment Summary #2:** The commenter recommended including the statement, “The use of technologies, techniques, materials, and procedures other than those described in this chapter is not prohibited so long as they have been proven to be equivalent or superior with statistical significance to those described herein.”

**Response:** Comment not incorporated. Requirements for alternative procedures are covered in *General Notices 6.30, Alternative and Harmonized Methods and Procedures*.

#### ***2. Personnel Training and Qualification***

**Comment Summary # 3:** The commenter suggested separating the qualification of personnel from the qualification of instruments.

**Response:** Comment incorporated. The section was revised to remove instrument qualification and present it as an introductory paragraph in Section 3, *Qualification of instruments*.

#### ***3.2 Operational Qualifications***

**Comment Summary # 4:** The commenter requested inclusion of the definition of “major repair.”

**Response:** Comment not incorporated. The Expert Committee indicated that this phrase is subjective. Not including the definition allows the user flexibility to define the type of repair according to their established policies.

#### ***3.4 Geometry Testing***

**Comment Summary # 5:** The commenter suggested replacing the term “dose calibrator” with “radionuclide calibrator” to be consistent with *AAPM Report 181*.

**Response:** Comment not incorporated. *AAPM Report 181* is suggested as a reference in the General Chapter. Dose calibrator is a commonly accepted and used term in the nuclear medicine community. The definition for radionuclide calibrator has been included in the *Glossary*.

#### **4. Ongoing Performance Tests**

**Comment Summary # 6:** The commenter suggested revising the introductory paragraph to state, “Ongoing performance tests for other instruments used for radiation measurements should be designed as appropriate to each instrument, testing the parameters which are pertinent to assuring the performance of the instrument, considering its application and the level of precision of measurement required” in order to allow flexibility.

**Response:** Comment incorporated.

#### **4.3 Operational Tests—Background and Contamination Test**

**Comment Summary # 7:** The commenter recommended revising the text to indicate that it is especially important to verify if the minimum detectable activity increases or decreases because the limit of detection is a function of the background level. The commenter also recommended including the point that even with a higher background level, the instrument may still be suitable for use in performing measurement, depending upon the order of magnitude for the expected measurement, even if the minimum detectable activity (MDA) has increased.

**Response:** Comment incorporated.

#### **4.3 Operational Tests—Accuracy Test**

**Comment Summary # 8:** The commenter suggested revising the following statement to read, “If the dose calibrator is used to measure the quantity of multiple radionuclides, two or three different radioactive calibration sources with different energies should be included to cover the energy range of the radionuclides expected to be measured.”

**Response:** Comment incorporated.

#### **4.3 Operational Tests—Linearity Test**

**Comment Summary # 9:** The commenter recommended emphasizing the practice of measuring linearity of detector response across the full range of radioactivity levels expected to be measured, from the highest expected activity measurement to the lowest.

**Response:** Comment not incorporated. The Expert Committee determined that the text is clear and additional details are not necessary.

**Comment Summary # 10:** The commenter recommended the deletion of the line item from Table 1 Supplier Equivalence.

**Response:** Comment incorporated.

#### **5.1 Half-life Determination**

**Comment Summary # 11:** The commenter suggested revising the following statement to read, “The quantity of radioactivity in the sample should be sufficient to allow measurements over the time frame of the test and in consideration of the statistical precision of the instrument to result in half-life estimation within the allowable error.” It was suggested that the General Chapter should include the concept that different types of instruments could be used for half-life determination, and the selection of the

instrument should consider the known half-life of the radionuclide, to which the measurement would be compared. The commenter also requested inclusion of guidance that one should avoid an instrument with substantial dead time.

**Response:** Comment not incorporated. The Expert Committee determined that the text is clear, and additional details are not necessary.

### **5.2 Gamma Ray Spectrometry**

**Comment Summary # 12:** The commenters requested revising the text to indicate that some positron emitting radionuclides, in addition to annihilation radiation of 511 keV, also have characteristic gamma rays that allow them to be identified. Examples of such are Ge-69 and Na-22.

**Response:** Comment incorporated.

### **6.4 Liquid Scintillation Counter**

**Comment Summary # 13:** The commenter suggested revising the text, “a sample may require a scintillation fluid,” because to use liquid scintillation the sample does require a scintillation media, because this is how LSC accomplishes its measurement, i.e., detection of fluorescence. Scintillation fluid is widely used as the media, but certain solid matrix scintillants are also available. It should also be noted that the selection of the type of scintillant depends upon several factors, including the radionuclide to be measured.

**Response:** Comment not incorporated. The word “may” refers to the use of cocktails as needed, because the section deals with liquid scintillation counters, solid scintillants are out of context. Additionally, solid scintillants are not widely used.

## **7. Glossary**

**Comment Summary # 14:** The commenter requested removal of the word “essentially” from the definitions of Alpha and Beta particles.

**Response:** Comment incorporated.

**Comment Summary # 15:** The commenter requested deletion of the definition of Bremsstrahlung, because the term does not appear in the General Chapter.

**Response:** Comment incorporated.

**Comment Summary # 16:** The commenter requested revision of the definition of “Radioactivity” to be consistent with the commonly accepted definition.

**Response:** Comment incorporated.

**Expert Committee-initiated Change:** The Expert Committee removed the following definitions because they are not relevant within the scope of the General Chapter: Beyond Use Date, Carrier Free, No Carrier Added, and Specific Activity.

**General Chapter/Sections:** <1039> Chemometrics/Multiple Sections  
**Expert Committee:** General Chapters—Chemical Analysis  
**No. of Commenters:** 4

### **1. Introduction**

**Comment Summary #1:** The commenter suggested adding Linearity and Range to the Normal validation glossary branch in *Figure 1*.

**Response:** Comment incorporated.

**Comment Summary #2:** The commenter suggested replacing the word “Development” with “Feasibility” in *Figure 1*, first tier categories, because the term development is normally synonymous with “calibration” and calibration is already used in the figure.

**Response:** Comment not incorporated. The Expert Committee determined that the existing text was suitable.

**Expert Committee-initiated Change #1:** The second sentence of the *Introduction* was revised for clarity to state, “Established chemometric practices, including calibration and validation, for applications using different analytical technologies (e.g. spectroscopic, chromatographic, and others) and for different purposes (e.g. fingerprinting, identification, classification, properties prediction, and others) are discussed under a lifecycle approach.”

### **2. What Is Chemometrics?**

**Comment Summary #3:** The commenter suggested revising the phrase “chemical sensor-based multidimensional data.”

**Response:** Comment incorporated. The phrase was replaced with, “multidimensional data collected from an analytical instrument”.

**Comment Summary #4:** The commenter suggested revising the caption for *Figure 2* to better reflect the portrayed chemometric technique.

**Response:** Comment incorporated. The caption was revised to indicate that “latent projection techniques” are portrayed.

**Comment Summary #5:** The commenter suggested removal of *Figure 2*.

**Response:** Comment not incorporated. The Expert Committee determined that this figure is beneficial for users unfamiliar with chemometrics.

**Comment Summary #6:** The commenter suggested revising the second paragraph, in which it states, “unsupervised (i.e. qualitative) or supervised (i.e. quantitative) purposes,” because not all qualitative models are unsupervised.

**Response:** Comment incorporated. The committee removed the terms “i.e. qualitative” and “i.e. quantitative.”

### **3. Model Lifecycle**

**Comment Summary #7:** The commenter suggested defining the term “analytical target profile (ATP)” by adding information about established conditions to enhance clarity.

**Response:** Comment not incorporated. A definition appears at the end of the first paragraph.

**Comment Summary #8:** The commenter suggested revising *Figure 3* to be representative of the workflow described in the text.

**Response:** Comment incorporated.

**Comment Summary #9:** The commenter suggested rearranging the order of sections in the text to convey the order of the model lifecycle.

**Response:** Comment partially incorporated. *Figure 3* was revised to indicate the suggested flow of the order. The order of the sections was not revised because the Expert Committee determined that sufficient explanation was provided to tell readers that the order presented in this section does not always represent the order of operations.

**Expert Committee-initiated Change #2:** The term “model” was replaced with “method” in the sentence, “The model update may also be triggered by the necessity of performing method transfer.”

### ***3.1 Model Lifecycle, Model Development: Calibration***

**Comment Summary #10:** The commenter suggested removing or replacing the term “statistical model,” because not all chemometric models can be called or accepted as “statistical models.”

**Response:** Comment incorporated.

**Comment Summary #11:** The commenter suggested revising the sentence describing the response variables, because not all reference methods may have response variables (e.g. gravimetric or volumetric).

**Response:** Comment incorporated.

**Comment Summary #12:** The commenter suggested rearranging the order of sub-sections in the text to convey the order of the model lifecycle.

**Response:** Comment incorporated.

### ***3.1 Model Lifecycle, Model Development: Calibration, Sample Selection***

**Expert Committee-initiated Change #3:** The Expert Committee revised the second paragraph to clarify that representative distributions are more broadly sought, even though uniform distributions may be preferred. To assure probability of correct results, the samples should mimic the expected distribution of unknowns.

**Expert Committee-initiated Change #4:** A cross reference to *Figure 2* was added to the sentence, “Data obtained from selected samples (i.e., a selected number of rows of the X matrix in figure 2) should undergo further triage.”

**Comment Summary #13:** The commenter suggested providing a short explanation of the term “outlier.”

**Response:** Comment not incorporated. The term “outlier” is defined in the text.

**Expert Committee-initiated Change #5:** The term “model hyperspace” was replaced with “model subspace” to clarify the metric.

### ***3.1 Model Lifecycle, Model Development: Calibration, Preprocessing***

**Expert Committee-initiated Change #6:** A cross reference to *Figure 2* was included in the first sentence and it was clarified that pre-processing works on the column of X matrix.



**Comment Summary #14:** The commenter suggested clarifying the sentence describing the use of mean-centered data in the regression model. This function does not necessarily result in parsimonious models.

**Response:** Comment incorporated.

### **3.1 Model Lifecycle, Model Development: Calibration, Variable Selection**

**Expert Committee-initiated Change #7:** The first sentence was revised to reference *Figure 2* and show that the columns on the X matrix represent the predictor variables.

**Comment Summary #15:** The commenter suggested revising the section to highlight methods that can avoid bias in the selection process, such as genetic algorithms and stimulated annealing.

**Response:** Comment not incorporated. The text describes manual methods.

**Comment Summary #16:** The commenter stated that the discussion of genetic algorithms separates them from other multivariate methods such as PLS and PCR.

**Response:** Comment not incorporated. There are two categories of variable selection.

The text stated genetic algorithms as an example of leveraging variable selection before PLS and PCR and as an example to conduct variable weighting inside PLS and PCR.

**Comment Summary #17:** The commenter stated that because a large portion of the text is devoted to overfitting, this discussion should be moved to a separate section.

**Response:** Comment not incorporated. Variable selection could be viewed as additional leverage to choose the optimal model parameter.

**Comment Summary #18:** The commenter recommended using consistent nomenclature to refer to the measurement channels as predictor variables.

**Response:** Comment incorporated.

**Comment Summary #19:** The commenter suggested elaborating on the performance attributes in the last sentence of the first paragraph by adding a robustness model.

**Response:** Comment incorporated.

**Comment Summary #20:** The commenter suggested a revision to the sentence, “Typically in chemometrics, the number of predictor variables is not...”

**Response:** Comment incorporated.

**Comment Summary #21:** The commenter suggested revising the following sentence for clarity: “The latent variables methods – PLS and PCR– avoid overfitting by generating a smaller number of new variables.”

**Response:** Comment incorporated.

### **3.1 Model Lifecycle, Model Development: Calibration, Cross-Validation**

**Expert Committee-initiated Change #8:** A reference to *Figure 2* was included in the sentence, “This is accomplished by repetitive splitting of the data (i.e., the number of rows of the X matrix in Figure 2) into a calibration set...” to indicate rows in the X matrix are split into calibration and validation sets.

**Comment Summary #22:** The commenter stated that cross-validation is a measure of model performance only when the calibration set is homogenous. The commenter suggested adding a cautionary statement about the predictive nature of cross-validation and also adding some metrics that may better evaluate performance.

**Response:** Comment incorporated.

**Expert Committee-initiated Change #9:** In the third paragraph the term “regression” was replaced with “calibration.”

**Expert Committee-initiated Change #10:** In the third paragraph, the term “incorporated” was replaced with “added.”

**Comment Summary #23:** The commenter suggested clarifying that any batch and its replicates could be used either in the calibration or in the cross validation, but the same batch or replicates cannot be used in both processes at the same time.

**Response:** Comment incorporated.

### ***3.2 Method Validation***

**Comment Summary #24:** The commenter indicated that the terms “model validation” and “method validation” are used throughout the section and suggested revising the text for clarity.

**Response:** Comment not incorporated. The terminology was addressed in the text.

### ***3.2 Method Validation, Performance Characteristics for Method Validation***

**Expert Committee-initiated Change #11:** The word chemometrics was removed from the phrase “chemometrics method validation” throughout.

**Comment Summary #25:** The commenter suggested including a sentence in the lead-in to the characteristics, to highlight the fact that the validation sample set should be as independent as possible from the calibration sample set.

**Response:** Comment not incorporated. Similar statements appear in the text.

### ***3.2 Method Validation, Performance Characteristics for Method Validation, Accuracy***

**Comment Summary #26:** The commenter suggested that the comparable orders of RMSEP, RMSEC, and RMSECV be described.

**Response:** Comment incorporated.

### ***3.2 Method Validation, Performance Characteristics for Method Validation, Precision***

**Expert Committee-initiated Change #12:** The replicate analysis is clarified to indicate that these are independent replicates of the sample.

**Expert Committee-initiated Change #13:** A reference to Section 4.1 *Figure 6* was added to the discussion regarding the ROC curve metric.

### ***3.2 Method Validation, Performance Characteristics for Chemometrics Method Validation, Specificity***

**Comment Summary #27:** The commenter suggested adding criteria to bolster the claims.

**Response:** Comment not incorporated. The Expert Committee determined that the level of detail is sufficient for an informational General Chapter.

### **3.2 Method Validation, Performance Characteristics for Method Validation, Linearity**

**Expert Committee-initiated Change #14:** Slope was added to the commonly used measures of model fit.

### **3.2 Method Validation, Performance Characteristics for Method Validation, Robustness**

**Comment Summary #28:** The commenter suggested conveying robustness in terms of the stability of performance relative to the controlled changes and conveying ruggedness relative to changes that normally occur in routine use.

**Response:** Comment incorporated.

**Expert Committee-initiated Change #15:** The paragraph regarding specificity was moved to the *Method Validation, Performance Characteristics for Method Validation, Specificity* section

**Comment Summary #29:** The commenter suggested including weighing and mixing of powders as a reference method in the list of examples.

**Response:** Comment incorporated.

### **3.4 Model Update and Transfer**

**Expert Committee-initiated Change #16:** The section title was changed from *Model Update and Transfer* to *Model Update and Method Transfer*

### **3.4 Model Update and Transfer, Calibration Expansion**

**Comment Summary #30:** The commenter suggested indicating that assessment of the diagnostics limits defined during model development is also an effective approach.

**Response:** Comment incorporated.

### **4.1 Applications of Chemometrics, Qualitative, General Aspects**

**Expert Committee-initiated Change #17:** The sentence was revised to clarify that chemometric models may be incorporated into compendial procedures or procedures that are alternatives to compendial methods.

**Expert Committee-Initiated Change #18:** A sentence was added to the last paragraph to address the case dependency of using the overall error rate or the error rates of all the classification categories.

### **4.1 Applications of Chemometrics, Qualitative/Qualitative Tools, PCA**

**Comment Summary #31:** The commenter suggested revising the sentence containing the phrase “so called latent variable” for clarity.

**Response:** Comment incorporated.

**Expert Committee-initiated Change #19:** A cross reference to *Figure 2* was included in the second sentence to highlight the Principal Components (PCs) visually.

### **4.1 Applications of Chemometrics, Qualitative, Qualitative Tools, Clustering Algorithms**

**Expert Committee-initiated Change #20:** The metric Mahalanobis distance was included to address statistical distance as a parameter used to assess (dis)similarity between objects or clusters.

**Comment Summary #32:** The commenter suggested rotating the axis in *Figure 5* for optimum clarity.

**Response:** Comment not incorporated. The Expert Committee determined that the figure, as drawn, provides sufficient detail.

#### ***4.1 Applications of Chemometrics, Qualitative, Qualitative Application Examples, Exploratory analysis***

**Expert Committee-initiated Change #21:** A sentence was added to describe design of experiment (DoE) approaches.

#### ***4.1 Applications of Chemometrics, Qualitative, Qualitative Application Examples, Analysis of DoE data***

**Expert Committee-initiated Change #22:** The section was removed because the explanation was inadequate to provide useful information. A sentence was included in the *Exploratory analysis* subsection to highlight that this approach exists.

#### ***4.1 Applications of Chemometrics, Qualitative, Qualitative Application Examples, Material identity testing***

**Expert Committee-initiated Change #23:** The last paragraph was revised for clarity by replacing “make up the success rate” with “provide the basis for the sensitivity and specificity”.

#### ***4.1 Applications of Chemometrics, Qualitative, Qualitative Application Examples, Classification***

**Expert Committee-initiated Change #24:** The term “probabilities” was replaced with “likelihood” in the sentence “Soft classification estimates the class conditional probabilities explicitly and then makes the class assignment based on the largest estimated probability.” Conditional probabilities depend on the population being tested (e.g., the prior multinomial class distribution in the tested population); therefore, soft classification requires additional considerations.

**Expert Committee-initiated Change #25:** The last paragraph was revised to indicate that an outlier should be investigated.

#### ***4.2 Quantitative, Quantitative Tools, Multi-linear regression (MLR)***

**Expert Committee-initiated Change #26:** The MLR subsection title was revised.

**Expert Committee-initiated Change #27:** MLR subsection text was revised to acknowledge that other appropriate alternatives to the adjusted  $R^2$  statistic metric may be used.

**Expert Committee-initiated Change #28:** The sentence “A limitation of MLR is the inability to model collinear variables” was revised and the explanation was expanded to clarify that the difficulty is not unique to MLR, rather the key with any predictive approach is to avoid collinearity in the calibration set.

#### **4.2 Quantitative, Quantitative Tools, PLS**

**Comment Summary #33:** The commenter suggested revising the description of PLS-2 to include its case to be used when two or more variables are correlated.

**Response:** Comment not incorporated. The Expert Committee determined that the existing text was sufficiently detailed.

#### **4.2 Quantitative, Quantitative Application Examples, Pharmaceutical dosage form assay and/or uniformity of content**

**Comment Summary #34:** The commenter suggested revising the sentence, “For example, models developed using NIR or Raman data must be calibrated relative to a primary reference technique such as HPLC or NMR spectroscopy” to account for cases where the calibration is performed by mixing amounts of the two forms and there is no alternative technique sensitive enough for a reference measurement.

**Response:** Comment incorporated.

**Comment Summary #35:** The commenter suggested expanding the discussion to include assay procedures that are based on weighing and mixing of powders as the reference method, because sometimes few alternatives are available for quantitative modeling.

**Response:** Comment incorporated. The Expert Committee added to the paragraph beginning “Most spectrophotometric methods...” to acknowledge these additional examples.

#### **4.2 Quantitative, Quantitative Application Examples, Impurity limit tests**

**Expert Committee-initiated Change #29:** The last paragraph was revised to expand on the definition of LOD as an estimator for PLS models.

**Comment Summary #36:** The commenter stated that testing for degradation products is usually not done as a limit test, because extrapolation would not be feasible. The commenter suggested revising the text to clarify.

**Response:** Comment incorporated.

**Comment Summary #37:** The commenter suggested revising the text to clarify that although it is possible to develop a spectroscopic method for impurities, it may be impractical, and a method like this needs careful development and feasibility studies.

**Response:** Comment incorporated.

#### **4.2 Quantitative, Quantitative Application Examples, Dissolution testing**

**Expert Committee-initiated Change #30:** The first sentence was revised to clarify the purposes of dissolution performance testing.

**Comment Summary #38:** The commenter suggested adding the alternative case where the whole profile can be modeled by several responses from different time points on the dissolution curve (for example, using PLS-2).

**Response:** Comment incorporated.

**General Chapter/Section:** <1602> Spacers and Valved Holding Chambers Used With Inhalation Aerosols—Characterization Tests/Multiple Sections  
**Expert Committee:** General Chapters—Dosage Forms  
**No. of Commenters:** 4

### **1.1 Introduction, Background**

**Comment Summary #1:** The commenter recommended deleting the phrase “poor inhalation technique” because it does not contribute to the scope of the General Chapter.

**Response:** Comment partially incorporated. The Expert Committee determined that the phrase is relevant to the scope of the General Chapter, because some of the tests included relate to what might happen with poor inhalation coordination; however, the text was clarified to explain what was meant by “poor inhalation technique.”

### **1.4 Test Method Selection, Recommendations**

**Comment Summary #2:** The commenter suggested revising the second paragraph to state, “The evaluation of face mask performance has two aspects: i) aerodynamic performance assuming good fit and ii) check and optimization of fit to the patients face. It requires.....or adult, ” because depending on the intention it may be necessary to model skin properties in addition to face surface geometry.

**Response:** Comment not incorporated. The Expert Committee determined that the comment was a valid point, but considered it a little too much detail for the General Chapter. In addition, the proposed text is not directly related to this revision and the Expert Committee did not consider it necessary, because the fit of the face mask to the face will already be assessed in part through the performance results determined with a ‘realistically’ achieved optimum fit.

### **1.5 Introduction, Definitions of Key Terms Relating to This Chapter**

**Comment Summary #3:** The commenter recommended deleting the definition of terms section, because the description of common spacers and VHCs is not relevant to the General Chapter.

**Response:** Comment not incorporated. This background information assists the reader in determining what types of tests may be appropriate.

## **2. Test Method Selection**

**Comment Summary #4:** The commenter recommended adding the statement, “The tests are not meant to serve as batch release tests, neither for the pMDI nor for the spacer/VHC nor for the facemask,” and deleting the statement, “and this chapter may be used to develop specifications that could be used in a quality control environment” in section 2, because the quality of a pMDI is not defined by a VHC, and there is no need to use VHCs in the quality control of pMDIs. The commenter also noted that there seemed to be a contrast between the statements “for characterizing” and “may be used for quality control.”

**Response:** Comment partially incorporated. The statement “and this chapter may be used to develop specifications that could be used in a quality control environment” was deleted; however, the suggested statement was not added because the Expert Committee considered it to be unnecessary and also too prescriptive.

### **2.1 Test Method Selection, Spacer/VHC Configurations**

**Comment Summary #5:** The commenter recommended deleting condition C from *Table 1*, and indicated that inclusion of mouthpiece testing in the General Chapter is not relevant.

**Response:** Comment not incorporated. Mouthpiece testing *is* indeed considered relevant to the purpose and content of the General Chapter.

**Comment Summary #6:** The commenter recommended deleting conditions B and D stated that from *Table 1* and onwards and indicated that the inclusion of a face mask testing in the General Chapter is not relevant, because the available face models needed for the tests are well spread, not defined, nor accepted within the scientific community.

**Response:** Comment not incorporated. Devices incorporating face masks are routinely used for young children and potentially the elderly; therefore, test methodologies to assess their performance are considered relevant. Face models have been used in the scientific literature for some time to assess facemask products and have started to become available commercially.

### **2.2 Test Method Selection, Comments on Test Methods**

**Comment Summary #7:** The commenter suggested including the text, “Depending on the aim of the test, the tightness of the facemask may be reinforced (e.g. tape, glue, clamps) or achieved by skin models.” In the latter case it is important that the surfaces have mechanical characteristics (i.e. deformability).

**Response:** Comment not incorporated. The existing General Chapter text already captures the valid points made regarding appropriate skin modelling. In addition, it is considered inappropriate to artificially clamp or tape face masks to the face.

**Comment Summary #8:** The commenter indicated that for delay testing, it may be sufficient to use a 10-s delay only, as opposed to using 2-s, 3-s, and 10-s delays.

**Response:** Comment not incorporated. The Expert Committee noted that the specific delays mentioned (2-, 5-, and 10-s delays) are not stated as being mandatory, however, there is value in testing at a number of different delay intervals.

### **4.2 Mass of Drug Delivered from a Spacer/VHC While Simulating Patient Tidal Breathing, With Facemask**

**Comment Summary #9:** The commenter recommended changing the volumetric flow rate from NLT 90% to NLT 95% to be consistent with other sections of the General Chapter, unless it is difficult to achieve for this specific test.

**Response:** Comment not incorporated. This is a test of mask-to-face seal and is indeed difficult to achieve and can depend on the design of the mask. In fact, even the 90% flow may be difficult to achieve in some cases. The text was therefore revised slightly to state ‘ideally’ NLT 90%.

<b>General Chapter/Sections:</b>	<1821> Radioactivity—Theory & Practice/ Multiple sections
<b>Expert Committee:</b>	Chemical Medicines Monographs 4
<b>No. of Commenters:</b>	2

## ***2. Types of Decay***

**Comment Summary #1:** The commenter recommended deleting or revising the statement, “however, X-rays are the result of interactions between radiation from the nucleus and the orbital electrons,” because it is technically incorrect.

**Response:** Comment incorporated. The reference to X-Rays was deleted because X-Rays are out of the scope of the General Chapter.

## ***3.5 Statistics of Counting and 3.6 Minimum Detectable Activity***

**Comment Summary #2:** The commenter noted that in the unit, “dps” and “cps” have been used interchangeably and this should be corrected.

**Response:** Comment incorporated. The term dps was replaced with cps wherever applicable.

## ***3.8 Counting Losses***

**Comment Summary #3:** The commenter requested including the following statement, “most modern counting systems have the ability to account for dead time but dead time may still be a factor to consider in some circumstances.”

**Response:** Comment incorporated.

## ***3.11 Production of Radionuclides***

**Comment Summary #4:** The commenter recommended deleting the cost analysis because it is out of the scope of the General Chapter

**Response:** Comment not incorporated. This is an informational chapter and thus it is in the scope of the chapter.

## ***3.13 Radiochemical Purity***

**Expert Committee-initiated Change #1:** The section was revised to also include the use of the Radiochemical Identity section based on comment summary #5.

## ***3.14 Radionuclidic Purity***

**Comment Summary #5:** The commenter requested clarifying the text and including the use of this section for Radionuclidic Identity as well.

**Response:** Comment incorporated.

## ***3.16 Labeling***

**Comment Summary #6:** The commenter requested inclusion of the following statement, “Additional Labeling requirements may apply for Investigational New Drugs



and/or for unapproved radiopharmaceuticals prepared and administered under the auspices of an institution's Radioactive Drug Research Committee.”

**Response:** Comment incorporated.

#### **4.1. Ionization Chambers**

**Comment Summary #7:** The commenter requested addition of information about the potential inaccuracies caused by container attenuation in alpha emitters, beta emitters, and low-energy gamma emitters.

**Response:** Comment not incorporated. This information is already in the section.

#### **4.3 Nuclear Spectroscopy Systems/Gamma Ray Spectrometry**

**Comment Summary #8:** The commenters noted that the reference to Ge(Li) is incorrect because high-purity germanium detectors are not doped with lithium.

**Response:** Comment incorporated. The reference to Ge(Li) was deleted.

### **5. Glossary**

**Comment Summary #9:** The commenter recommended removing the word “essentially” from the definition of Alpha and Beta particles.

**Response:** Comment incorporated.

**Comment Summary #10:** The commenter recommended revising the definition of Bremsstrahlung as follows: “Bremsstrahlung: electromagnetic radiation produced by the acceleration or especially the deceleration of a charged particle after passing through the electric and magnetic fields of a nucleus.”

**Response:** Comment incorporated.

**Comment Summary #11:** The commenter recommended deleting the definitions for Geiger-Muller counter, Isobars, and Isotones, because they are not used anywhere in the General Chapter.

**Response:** Comment not incorporated. These important aspects do belong in this informational chapter.

**Comment Summary #12:** The commenter suggested replacing the term “Isotopic Carrier” with just “Carrier.”

**Response:** Comment partially incorporated. The term Carrier was added as an alternative term.

**Comment Summary #13:** The commenter recommended deleting the terms Beyond-use-Date and Expiration date because they refer to drug products.

**Response:** Comment incorporated.

**Comment Summary #14:** The commenter recommended deleting the term “Radiopharmaceuticals” because it refers to finished dosage forms.

**Response:** Comment not incorporated. This term indicates the connection between the radioactive element and the dosage form.

**Comment Summary #15:** The commenter recommended revising the definition of “Radioactivity” to be consistent with the commonly accepted definition.

**Response:** Comment incorporated.

**General Chapter/Sections:** <1823> Positron Emission Tomography  
Drugs—Information/Multiple sections  
**Expert Committee:** Chemical Medicines Monographs 4  
**No. of Commenters:** 2

### ***Introduction***

**Comment Summary #1:** The commenter recommended changing the word “photons” in the first paragraph to “radionuclides”.

**Response:** Comment incorporated.

**Comment Summary #2:** The commenter requested clarification of the text regarding similarity to biological systems.

**Response:** Comment incorporated.

**Comment Summary #3:** The commenter requested revision of the statement in the paragraph (following the production scheme) about bioburden to minimize over interpretation.

**Response:** Comment incorporated.

**Comment Summary #4:** The commenter requested inclusion of the word “quality” in the paragraph following the production scheme finished product testing.

**Response:** Comment incorporated.

**Comment Summary #5:** The commenter recommended modifying the bullet regarding PET drug product handling environments to highlight the different requirements from different agencies.

**Response:** Comment incorporated.

### ***3.3 Quality Assurance, Validation***

**Comment Summary #6:** The commenter requested the inclusion of guidance on which parameters of control systems should be validated for computer software used for automated equipment.

**Response:** Comment not incorporated. There is a variety of automated equipment which may require different parameters to be validated.

### ***4.1 Production/Equipment for Manual Synthesis***

**Comment Summary #7:** The commenter indicated that depyrogenation should not be required when the physical cleaning process is validated, robust, and shown to result in low levels of endotoxins.

**Response:** Comment not incorporated. This is an informational chapter and the text does not mandate depyrogenation. It states, “depyrogenated as appropriate.”

### ***6.4 Analytical Methodologies, Radiation Detectors used in Chromatographic Techniques***

**Comment Summary # 8:** The commenter indicated that unless the detectors are used for quantification of radioactivity, calibration is not required.

**Response:** Comment incorporated. The phrase, “for quantitative measurements” was added to the statement.

### **7.1 Quality Attributes, Appearance**

**Comment Summary #9:** The commenter requested revising the text to include the statement “free from visible particulate matter,” because manufacturing of PET drug products that are entirely free of particulate matter is unachievable. The primary purpose of <788> is to ensure low levels of particulates.

**Response:** Comment incorporated. The statement, “free from particulate matter” was included in the section.

### **7.5 Quality Attributes, Radionuclidic Purity**

**Comment Summary #10:** The commenter indicated that PET drug products may contain a dozen or more long-lived radionuclides at very low levels. Validation of the removal of all of these during the manufacturing process would be onerous and would require handling and licensing of long-lived radionuclides.

**Response:** Comment incorporated. The following statement was added: “Other approaches may be appropriate depending on the characteristics and source of the radionuclidic impurities”.

### **7.7 Quality Attributes, Chemical Purity**

**Comment Summary #12:** The commenter indicated that ingredients added to the formulation intentionally, such as excipients and stabilizers, should not be included the assessment of PET drug product purity.

**Response:** Comment incorporated. The words, “stabilizers and excipients” were removed from the sentence.

### **7.8 Quality Attributes, Total Mass of Active Pharmaceutical Ingredient and Specific Activity**

**Comment Summary #13:** The commenter raised concerns about the inability to measure total mass of the API under certain conditions.

**Response:** Comment incorporated. The statement was revised as follows: “the total mass of the API contained in a patient dose should be defined for PET products where mass-related localization or toxicity concerns require such assessment, which may be determined by HPLC or GC. On the basis of the mass of the API, the specific activity may be calculated.”

### **8.3 Sterility Assurance, Pre-Sterilized Components.**

**Comment Summary #14:** The commenter indicated that PET drug products are not, in fact, “produced” in a commercially available container-closure system. Rather, the title of this section suggests that several pre-sterilized components may be used in the production of PET drug products, and the container-closure system is only one.

**Response:** Comment incorporated.

### **8.4 Sterility Assurance, Environmental Controls**

**Comment Summary #15:** The commenter requested clarification of the parameters that require control per any standard such as ISO 5, etc.

**Response:** Comment incorporated. To allow flexibility, the statement was revised as follows: “These controls may include temperature, humidity, ventilation and air filtration, cleaning and disinfection, equipment maintenance, proper garb, and microbiological monitoring.”

### **8.6 Quality Assurance, Suitability of Media**

**Comment Summary #16:** The commenter objected to the requirement that media be used within 3 months.

**Response:** Comment incorporated. The statement was revised as follows, “Media should be used within the manufacturer’s expiration date.”

**Monograph/Sections:** Acetaminophen and Diphenhydramine Citrate  
Tablets/Assay for acetaminophen  
**Expert Committee:** Chemical Medicines Monographs 6  
**No. of Commenters:** 1

**Comment Summary #1:** The commenter suggested tightening the % Relative Standard Deviation of the System suitability requirement in the test for the Assay from NMT 2.5% to NMT 2.0% to be consistent with the Acetaminophen, Diphenhydramine Hydrochloride, and Pseudoephedrine Hydrochloride Tablets monograph.

**Response:** Comment not incorporated. The Expert Committee determined that the comment is outside the scope of the revision and a future revision will be considered as needed upon evaluating the specifications in the other monographs of the family.

**Monograph/Sections:** Acetaminophen and Tramadol Hydrochloride  
Tablets/Organic Impurities  
**Expert Committee:** Chemical Medicines Monographs 6  
**No. of Commenters:** 2

**Comment Summary #1:** The commenter indicated that the proposed limit for total degradation products is different from the FDA-approved specifications.

**Response:** Comment not incorporated. The Expert Committee determined that the comment is outside the scope of the revision. Future revision will be considered upon receipt of supporting data.

**Comment Summary #2:** The commenter indicated that Acetaminophen Related Compound B is co-eluting with O-Desmethyl Tramadol, and Acetaminophen Related Compound D is co-eluting with Tramadol.

**Response:** Comment not incorporated. The Expert Committee determined that the comment is outside the scope of the revision. Future revision will be considered upon receipt of supporting data.

**Monograph/Section:** Alprazolam Orally Disintegrating  
Tablets/Dissolution <711>  
**Expert Committee:** Chemical Medicines Monographs 4  
**Expert Committee-initiated change #1:** The solution descriptions for the *Standard stock solution* and *Standard solution* within *Dissolution, Test 1* and *Dissolution, Test 2*

were revised for consistency with the units in the corresponding calculations and current USP style.

**Monograph/Section(s):** Carboplatin/Organic Impurities  
**Expert Committee(s):** Chemical Medicines Monographs 3  
**No. of Commenters:** 2

**Comment Summary #1:** The commenter recommended tightening the acceptance criterion for *any individual unspecified impurity* in the test for *Organic Impurities*.

**Response:** Comment not incorporated. The acceptance criterion for *any individual unspecified impurity* is consistent with FDA-approved requirements.

**Comment Summary #2:** The commenter recommended including 1,1-cyclobutanedicarboxylic acid in *Table 1* and adding a footnote that it is not included in the calculation of *total impurities* in the test for *Organic impurities*.

**Response:** Comment not incorporated. 1,1-cyclobutanedicarboxylic acid is not detected in the test for *Organic impurities*. The test for *Limit of 1,1-cyclobutanedicarboxylic acid* is used for the determination of this impurity.

**Monograph/Sections:** Chlorhexidine Gluconate Topical Gel/Multiple Sections  
**Expert Committee:** Chemical Medicines Monographs 6  
**No. of Commenters:** 2

**Comment Summary #1:** The commenter recommended publishing this proposal in a different compendium (other than *USP–NF*) or placing it in a separate section in *USP–NF*, because the drug product is not marketed in the United States, which could cause confusion and misuse.

**Response:** Comment incorporated. A new *Global Health Monographs* section was created in the *USP–NF* for drug products not marketed in the United States.

**Comment Summary #2:** The commenter suggested clarifying that the acceptance criterion for the p-chloroaniline in the test for *Limit of p-Chloroaniline* is based on w/w % of chlorhexidine gluconate.

**Response:** Comment not incorporated. The Expert Committee determined that the current description in the proposal adequately describes the specification limit.

**Comment Summary #3:** The commenter requested revising the acceptance criterion for p-chloroaniline from NMT 0.25% to NMT 0.35% based on the stability data.

**Response:** Comment incorporated.

**Comment Summary #4:** The commenter suggested adding an organic impurities test based on their validated test procedures.

**Response:** Comment not incorporated. The Expert Committee will consider adding an organic impurities test in a future revision.

**Comment Summary #5:** The commenter requested flexibility in the concentration of the *Sample solution* used in the test for pH <791> to allow the sample to be used without dilution.

**Response:** Comment not incorporated. The Expert Committee determined that the preparation of *Sample solution* as described in the proposal is adequate for all the marketed products.

**Monograph/Sections:** Cidofovir/Multiple Sections  
**Expert Committee:** Chemical Medicines Monographs 1  
**No. of Commenters:** 1  
**Comment Summary #1:** The commenter indicated that the *Acceptance criteria* for Cidofovir diol analog and cidofovir enantiomer 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.  
**Comment Summary #2:** The commenter indicated that the acceptance criterion for *Water Determination* is different from what has been approved by FDA.  
**Response:** Comment not incorporated. The acceptance criterion in the proposal is consistent with FDA-approved requirements.  
**Comment Summary #3:** The commenter indicated that the limit for *total combined molds and yeasts count* is 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(s):** Cidofovir Injection/Multiple Sections  
**Expert Committee(s):** Chemical Medicines Monographs 1  
**No. of Commenters:** 1  
**Comment Summary #1:** The commenter indicated that the acceptance criteria for Assay 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.  
**Comment Summary #2:** The commenter indicated that the acceptance criteria for Cidofovir uracil analog and total impurities 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.  
**Comment Summary #3:** The commenter indicated that the acceptance criteria for *Bacterial Endotoxins Test* are different from what has been approved by FDA.  
**Response:** Comment incorporated. The limit for *Bacterial Endotoxins Test* was widened from NMT 0.93 to NMT 1 USP Endotoxin Unit/mg based on FDA-approved limits.  
**Comment Summary #4:** The commenter indicated that the acceptance criteria for *pH* are different from what has been approved by FDA.  
**Response:** Comment not incorporated. The acceptance criteria for *pH* in the proposal are consistent with FDA-approved limits.  
**Comment Summary #5:** The commenter indicated that the limit for *total combined molds and yeasts count* is different from what has been approved by FDA.  
**Response:** Comment not incorporated. A limit for *total combined molds and yeasts count* is not relevant for parenteral dosage forms.  
**Comment Summary #6:** The commenter recommended defining the correct storage temperature, to provide clarity.

**Response:** Comment not incorporated. *Controlled Room Temperature* is defined in General Chapter <629>.

**Monograph/Section(s):** Cisplatin/Multiple Sections  
**Expert Committee(s):** Chemical Medicines Monographs 3  
**No. of Commenters:** 1  
**Comment Summary #1:** The commenter recommended harmonizing the monograph with the *European Pharmacopoeia* monograph.  
**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 defining the number of injections used to determine the system suitability requirement of the relative standard deviation in the Assay.  
**Response:** Comment not incorporated. Monograph users can find this information in General Chapter <621> *Chromatography*.

**Monograph/Section:** Citrulline/Impurities  
**Expert Committee:** Non-Botanical Dietary Supplements  
**No. of Commenters:** 1  
**Comment Summary #1:** The commenter recommended adding 'delta-acetyornithine' to the *Related Compounds* test as a potential impurity of citrulline.  
**Response:** Comment incorporated.

**Monograph/Sections:** Desipramine Hydrochloride Tablets/Multiple Sections  
**Expert Committee:** Chemical Medicines Monographs 4  
**Expert Committee-initiated Change #1:** The references to "Chromatographic acetonitrile" and "Chromatographic methanol" in the Assay and in the test for *Organic Impurities* were replaced with references to "acetonitrile" and "methanol," respectively, because the proposal to add entries to the reagent section for "Chromatographic acetonitrile" and "Chromatographic methanol" was cancelled.

**Monograph/Sections:** Demeclocycline Hydrochloride Tablets/Multiple Sections  
**Expert Committee:** Chemical Medicines Monographs 1  
**No. of Commenters:** 1  
**Comment Summary #1:** The commenter recommended adding an orthogonal *Identification* test.  
**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 adding the volume of the *Medium* to correct the formula in the test for *Dissolution*.  
**Response:** Comment incorporated.  
**Comment Summary #3:** The commenter recommended adding specified impurities with appropriate acceptance criteria to this monograph.

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

**Monograph/Sections:** Doxercalciferol/Multiple Sections  
**Expert Committee:** Chemical Medicines Monographs 3  
**No. of Commenters:** 2

**Comment Summary #1:** The commenter recommended revising the acceptance criteria for *trans*-doxercalciferol impurity and for the total impurities in the test for *Organic Impurities*.

**Response:** Comment not incorporated. The acceptance criteria for *trans*-doxercalciferol and for total impurities are consistent with FDA-approved requirements.

**Comment Summary #2:** The commenter indicated that the test for *Loss on Drying*, based on the thermogravimetric analysis performed from ambient temperature to 150°, is not suitable for doxercalciferol, which has a melting point of about 140°.

**Response:** Comment not incorporated. The proposed procedure is consistent with <891> *Thermal Analysis*, which states that the thermogravimetric analysis should be performed “over a wide range of temperatures (typically, room temperature to decomposition temperature, or about 10° to 20° above the melting point).”

**Monograph/Section:** Doxycycline Hyclate Capsules/Identification  
**Expert Committee:** Chemical Medicines Monographs 1  
**No. of Commenters:** 1

**Comment Summary #1:** The commenter indicated that the observed infrared spectrum bands are significantly different from those proposed in *Identification A*.

**Response:** Comment incorporated. The Expert Committee canceled the proposed infrared identification test and also deleted the TLC identification test from the monograph. The Expert Committee will consider future revisions to the monograph upon receipt of supporting data.

**Monograph/Section(s):** Doxycycline Hyclate Tablets/Identification  
**Expert Committee(s):** Chemical Medicines Monographs 1  
**No. of Commenters:** 1

**Comment Summary #1:** The commenter indicated that the observed infrared spectrum bands are significantly different from those proposed in *Identification A*.

**Response:** Comment incorporated. The Expert Committee canceled the proposed infrared identification test and also deleted the TLC identification test from the monograph. The Expert Committee will consider future revisions to the monograph upon receipt of supporting data.

**Monograph/Sections:** Heparin Sodium /Multiple Sections  
**Expert committee:** Biologics Monographs 3—Complex Biologics  
**No. of Commenters:** 1

**Comment summary #1:** The commenter suggested adding the information found in General Chapter <191> regarding sodium identification, specifically by specifying the quantity of sample in water and the quantities of K<sub>2</sub>CO<sub>3</sub> and potassium pyroantimonate that should be added.



**Response:** Comment not incorporated. The monograph was revised to contain only the flame test for sodium. The additional information requested is for a precipitation test and therefore is not required.

**Comment Summary #2:** The commenter suggested revising the volume of solution used for the benzonase found in the footnote so that the concentration of benzonase would be consistent with the current official version.

**Response:** Comment not incorporated. The revised concentration of benzonase is consistent with the validated method.

**Monograph/Section(s):** Hesperidin  
**Expert Committee:** Non-Botanical Dietary Supplements  
**Expert Committee-initiated Change #1:** The chemical names of the three potential impurities in the *Related Compounds* test—Isonaringin, Neohesperidin, and Didymin—were changed to be consistent with those of the Reference Standards.

**Monograph/Sections:** Hydroxyzine Hydrochloride/Multiple Sections  
**Expert Committee:** Chemical Medicines Monographs 4  
**No. of Commenters:** 1

**Comment Summary #1:** The commenter indicated that the proposed test for *Organic Impurities* is not specific for two process impurities and suggested replacing this test with a specific in-house procedure that has not yet been validated.

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

**Expert Committee-initiated Change #1:** The references to “Chromatographic acetonitrile” in the *Assay* were replaced with references to “acetonitrile” because the proposal to add an entry to the reagent section for “Chromatographic acetonitrile” was cancelled.

**Expert Committee-initiated Change #2:** The placement of the additional chemical name for USP Hydroxyzine Related Compound A RS was changed within the *USP Reference Standards* <11> section.

**Monograph/Sections:** Hydroxyzine Hydrochloride Tablets/Multiple Sections

**Expert Committee:** Chemical Medicines Monographs 4

**Expert Committee-initiated Change #1:** Within the *Analysis* section of the test for *Organic Impurities*, the phrase “For impurities detected at UV 230 nm” was replaced with the phrase, “For degradation products detected at UV 230 nm” for consistency with the associated calculation and *Acceptance criteria*.

**Expert Committee-initiated Change #2:** The trivial name for the impurity with a relative retention time of 0.87 in *Table 2* within the test for *Organic Impurities* was corrected from declocixine to decloxizine.

**Expert Committee-initiated Change #3:** Another chemical name for USP Hydroxyzine Related Compound A RS was added to the *USP Reference Standards* <11> section.

**Monograph/Section:** Isoflurane/Organic Impurities

**Expert Committee:** Chemical Medicines Monographs 5  
**No. of Commenters:** 1  
**Comment Summary #1:** The commenter noted that the impurity profile is not consistent with that approved by the FDA.  
**Response:** Comment not incorporated. The impurity profile is consistent with the sponsor's approved profile.

**Monograph/Section(s):** Ixabepilone/Packaging and Storage  
**Expert Committee(s):** Chemical Medicines Monographs 3  
**Expert Committee-initiated Change #1:** The *Packaging and Storage* section was updated to include "store at 2°–8°" to be consistent with FDA requirements.

**Monograph/Section(s):** Japanese Honeysuckle Flower/Multiple Sections  
**Expert Committee:** Botanical Dietary Supplements and Herbal Medicines

**No. of Commenters:** 3  
**Comment Summary #1:** The commenter indicated that in the *Definition* section, only *Lonicera japonica* Thunb. is mentioned; however, several textbooks mention the dried flower buds of *L. hypoglauca* Miq., *L. confusa* DC., and *L. dasystyla* Rehd. as acceptable TCM substitutes. The commenter asked whether the monograph's acceptance criteria would cover these other two (or three) species.

**Response:** Comment not incorporated. The monograph of Japanese Honeysuckle Flower (Chinese Jin-Yin-Hua) only includes *L. japonica* Thunb. The Wild Honeysuckle Flower (Chinese Shan-Yin-Hua) in the *ChP* includes species of *L. macranthoides* Hand.-Mazz, *L. hypoglauca* Miq., and *L. confusa* DC. Jin-Yin-Hua is different from Shan-Yin-Hua, the monograph's acceptance criteria do not cover the other three species. The specific test of *Limit of Triterpenoid Saponins* in the monograph is to distinguish Jin-Yin-Hua from Shan-Yin-Hua.

**Comment Summary #2:** The commenter indicated that it is redundant to also include the part of the plant following the *Title*, because the part of the plant in the monograph cited is already noted in the *Title*.

**Response:** Comment incorporated.

**Comment Summary #3:** The commenter suggested revising the specifications for the container from "well-closed, along with protecting from moisture" to "tight container." The commenter indicated that "tight container" may be preferable if moisture is of special concern.

**Response:** Comment not incorporated. The Expert Committee determined that the specification "well-closed container and protected from moisture" is similar to and more appropriate than "tight container."

**Expert Committee-initiate Change #1:** The monograph was revised based on USP Lab project test results which indicated that the conversion factor for 3,4-di-O-caffeoylquinic acid was 0.81 not 0.92.

**Monograph/Section:** Japanese Honeysuckle Flower  
Powder/Multiple Sections  
**Expert Committee:** Botanical Dietary Supplements and Herbal  
Medicines

**No. of Commenters:** 3

**Comment Summary #1:** The commenter indicated that in the *Definition*, only *Lonicera japonica* Thunb. is mentioned; however, several textbooks mention the dried flower buds of *L. hypoglauca* Miq., *L. confusa* DC., and *L. dasystyla* Rehde as acceptable TCM substitutes. The commenter asked whether the monograph's acceptance criteria would cover these other two (or three) species.

**Response:** Comment not incorporated. The monograph of Japanese Honeysuckle Flower (Chinese Jin-Yin-Hua) only includes *L. japonica* Thunb. The Wild Honeysuckle Flower (Chinese Shan-Yin-Hua) in the *ChP* includes species of *L. macranthoides* Hand.-Mazz, *L. hypoglauca* Miq., and *L. confusa* DC. Jin-Yin-Hua is different from Shan-Yin-Hua, and the monograph's acceptance criteria do not cover the other three species. The specific test for *Limit of Triterpenoid Saponins* in the monograph is to distinguish Jin-Yin-Hua from Shan-Yin-Hua.

**Comment Summary #2:** The commenter indicated that it is redundant to state the part of the plant following the *Title*, because the part of the plant in the monographs cited is already noted in the *Title*.

**Response:** Comment incorporated.

**Comment Summary #3:** The commenter suggested revising the specifications for the container from “well-closed, along with protecting from moisture” to “tight container.” The commenter indicated that “tight container” may be preferable if moisture is of special concern.

**Response:** Comment not incorporated. The Expert Committee determined that the specification “well-closed container and protected from moisture” is similar to and more appropriate than “tight container.”

**Expert Committee-initiate Change #1:** The monograph was revised based on USP Lab project test results which indicated that the conversion factor for 3,4-di-O-caffeoylquinic acid was 0.81 not 0.92.

**Monograph/Section(s):** Japanese Honeysuckle Flower Dry  
Extract/Multiple Sections  
**Expert Committee:** Botanical Dietary Supplements and Herbal  
Medicines

**No. of Commenters:** 4

**Comment Summary #1:** The commenter suggested adding the statement, “Japanese Honeysuckle Flower Dry Extract may contain suitable added substances as carriers” in the *Definition*.

**Response:** Comment incorporated.

**Comment Summary #2:** The commenter indicated that in the *Definition* only *Lonicera japonica* Thunb is mentioned; however, several textbooks mention the dried flower buds of *L. hypoglauca* Miq., *L. confusa* DC., and *L. dasystyla* Rehde as acceptable TCM

substitutes. The commenter asked whether the monograph's acceptance criteria would cover these other two (or three) species.

**Response:** Comment not incorporated. The monograph of Japanese Honeysuckle Flower (Chinese Jin-Yin-Hua) only includes *L. japonica* Thunb. The Wild Honeysuckle Flower (Chinese Shan-Yin-Hua) in the *ChP* includes species of *L. macranthoides* Hand.-Mazz, *L. hypoglauca* Miq., and *L. confusa* DC. Jin-Yin-Hua is different from Shan-Yin-Hua, the monograph's acceptance criteria do not cover the other three species. The specific test of *Limit of Triterpenoid Saponins* in the monograph is to distinguish Jin-Yin-Hua from Shan-Yin-Hua.

**Comment Summary #3:** The commenter indicated that it is redundant to also include the part of the plant following the *Title*, because the part of the plant in the monographs cited is already noted in the *Title*.

**Response:** Comment incorporated.

**Comment Summary #4:** The commenter suggested revising the specifications for the container from "well-closed, along with protecting from moisture" to "tight container." The commenter indicated that "tight container" may be preferable if moisture is of special concern.

**Response:** Comment not incorporated. The Expert Committee determined that the specification "well-closed container and protected from moisture" is similar to and more appropriate than "tight container."

**Expert Committee-initiate Change #1:** The monograph was revised based on USP Lab project test results which indicated that the conversion factor for 3,4-di-O-caffeoylquinic acid was 0.81 not 0.92.

<b>Monograph/Sections:</b>	Methylene Blue/Multiple Sections
<b>Expert Committee:</b>	Chemical Medicines Monographs 2
<b>No. of Commenters:</b>	3

**Comment Summary #1:** The commenter requested revising the suitability requirements for signal-to-noise ratio from NLT 3.0 to NLT 10.0 in the *Organic Impurities* section, to be consistent with the FDA-approved specifications.

**Response:** Comment incorporated.

**Comment Summary #2:** The commenter requested deleting the % Relative Standard Deviation of System suitability requirement in the *Organic Impurities* test using the *Standard solution*, as the impurities are quantitated as a percentage of the total area.

**Response:** Comment incorporated.

**Comment Summary #3:** The commenter recommended adding a specification for solubility (NLT 1%) under the Assay, because of the possibility of different solubility profiles for different hydrated forms, which might affect the potency of the drug product.

**Response:** Comment not incorporated. The Expert Committee determined that the proposal accurately reflects the FDA-approved specifications.

**Comment Summary #4:** The commenter requested widening the acceptance criterion for azure B under the *Organic Impurities* section, from NMT 2.5% to NMT 5.0%, to be consistent with the monograph requirements in the *European Pharmacopoeia* and *British Pharmacopoeia*.

**Response:** Comment not incorporated. The Expert Committee determined that the proposed specifications are consistent with the FDA-approved specifications.

**Comment Summary #5:** The commenter requested adding an equilibration step of 5 min to *Table 1* under the Assay, as the retention times might be shortened in the subsequent injections.

**Response:** Comment incorporated.

**Comment summary #6:** The commenter indicated that the proposed methods and acceptance criteria for Assay and *Organic Impurities* are not suitable for their marketed product.

**Response:** Comment not incorporated. The Expert Committee determined that the proposed methods and acceptance criteria are consistent with the FDA-approved specifications.

**Monograph/Section(s):** Moxifloxacin Hydrochloride/Multiple Sections  
**Expert Committee(s):** Chemical Medicines Monographs 1  
**No. of Commenters:** 1

**Comment Summary #1:** The commenter recommended using a 4.6-mm x 25-cm dimension column instead of a 4.0-mm x 25-cm column in the Assay and test for *Organic impurities*.

**Response:** Comment not incorporated. The column dimensions are consistent with validation data. In addition, General Chapter <621> allows analysts to change column dimensions in the laboratory; therefore, there is no need for changes to the public standard.

**Comment Summary #2:** The commenter indicated that the relative standard deviation of NMT 2.0% in the test for *Organic Impurities* was difficult to meet.

**Response:** Comment not incorporated. The Expert Committee determined that the system suitability requirements are consistent with validation data and the RSD was found to be achievable.

**Comment Summary #3:** The commenter indicated that the signal-to-noise ratio requirement in the test for *Enantiomeric purity* was difficult to meet.

**Response:** Comment incorporated. The signal-to-noise ratio requirement has been revised from NLT 10 to NLT 5 based on available data.

**Monograph/Section:** Nicotine Polacrilex/ Nicotine Release  
**Expert Committee:** Chemical Medicines Monographs 4  
**No. of Commenters:** 1

**Comment Summary #1:** The commenter requested that the units for the specific absorbance of nicotine at 259 nm be changed from “ $323 \text{ cm}^{-1}\text{mL}^{-1}\text{g}$ ” to “ $323 \text{ mLg}^{-1}\text{cm}^{-1}$ .”

**Response:** Comment incorporated.

**Monograph/Sections:** Pemetrexed Disodium/Multiple Sections  
**Expert Committee:** Chemical Medicines Monographs 3  
**No. of Commenters:** 2

**Comment Summary #1:** The commenter recommended revising the storage conditions to be consistent with FDA-approved requirements.

**Response:** Comment not incorporated. The Expert Committee determined that the storage conditions in the monograph are consistent with FDA-approved requirements. The Expert Committee will consider future revisions to the monograph upon receipt of supporting data.

**Comment Summary #2:** The commenter requested including amorphous pemetrexed disodium standard for infrared identification of the amorphous compound.

**Response:** Comment not incorporated. General Chapter <197> *Spectrophotometric Identification Tests* contains a procedure to be used if a difference between the analyte and the standard appears in the infrared spectra.

**Comment Summary #3:** The commenter indicated that the test for *Organic impurities* cannot adequately determine an individual impurity in the amorphous compound.

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

**Comment Summary #4:** The commenter indicated that the observed retention time of pemetrexed in the test for *Enantiomeric purity* is different from the value stated in the *Briefing*.

**Response:** Comment not incorporated. The Expert Committee determined that the retention time stated in the *Briefing* is for information only, and retention time may vary with the chromatographic conditions.

**Comment Summary #5:** The commenter requested introducing flexibility in the limits for *Water determination* to accommodate the amorphous form.

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

**Comment Summary #6:** The commenter requested including <921> *Water Determination, Method Ia* as an alternate procedure for *Water determination*.

**Response:** Comment incorporated.

**Expert Committee-initiated Change #1:** The Expert Committee added <197A> to *Identification A* to provide flexibility to the monograph users.

**Monograph/Section:** Pemetrexed for Injection/Organic Impurities

**Expert Committee:** Chemical Medicines Monographs 3

**No. of Commenters:** 1

**Comment Summary #1:** The commenter requested revising the acceptance criterion for ketopemetrexed.

**Response:** Comment not incorporated. The Expert Committee determined that the acceptance criterion for ketopemetrexed is consistent with the FDA-approved requirement.

**Expert Committee-initiated Change #1:** The Assay was revised to include the diode array detector when the chromatographic system is used for *Identification B*.

**Monograph/Section:** Phenoxybenzamine Hydrochloride Capsules/  
Organic Impurities

**Expert Committee:** Chemical Medicines Monographs 2

**No. of Commenters:** 1

**Comment Summary #1:** The commenter indicated that the acceptance criteria for phenoxybenzamine tertiary amine, unspecified impurities and total impurities, are not consistent with the FDA-approved specifications.

**Response:** Comment not incorporated. The Expert Committee determined that the comment is outside the scope of the revision. Future revision would be considered upon receipt of supporting data.

**Monograph/Section:** Polymyxin B Sulfate/Assay  
**Expert Committee:** Chemical Medicines Monographs 1  
**No. of Commenters:** 1

**Comment summary #1:** The commenter recommended revising the acceptance criteria in the Assay.

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

**Monograph/Sections:** Potassium Hydroxide/Multiple Sections  
**Expert Committees:** Excipient Monographs 1

**Expert Committee-initiated Change #1:** In the *Definition*, the percentage of potassium in Potassium Hydroxide were changed from 85.0% to 59.9% to reflect the true content of potassium in Potassium Hydroxide. The originally stated 85.0% was a typo.

**Expert Committee-initiated Change #2:** In the *Content of Potassium* test, added a requirement for the correlation coefficient was added for the plot of “absorbance values versus corresponding concentrations ( $\mu\text{g/mL}$ ) of potassium” as NMT 0.999. This requirement will help users evaluate the instrument system suitability during the analysis.

**Expert Committee-initiated Change #3:** In the *Analysis* section of the *Content of Potassium* test, the equation used to calculate the percentage of potassium in the portion of Potassium Hydroxide was corrected. The originally proposed equation was designed to calculate the percentage of potassium hydroxide in the portion of Potassium Hydroxide, which was not the goal of the test.

**Expert Committee-initiated Change #4:** The acceptance criterion in the *Content of Potassium* test was changed from 85.0% to 59.9% to reflect the true content of potassium in Potassium Hydroxide. The originally stated 85.0% was a typo.

**Expert Committee-initiated Change #5:** In the Limit of Sodium test, added a requirement for the correlation coefficient for the plot of “absorbance values versus corresponding concentrations ( $\mu\text{g/mL}$ ) of sodium” as NMT 0.995. This requirement will help users evaluate the instrument system suitability during the analysis.

**Expert Committee-initiated Change #6:** In the Standard solutions section of the *Limit of Sodium* test the highest volume of the Standard stock solution was changed from 20.0 mL to 15.0 mL. The Expert Committee did not see a reason for covering such a wide range based on the results for content of sodium obtained from the analysis of commercial samples. Correspondingly, changed the concentration of the highest Standard solution from 1.00  $\mu\text{g/mL}$  to 0.75  $\mu\text{g/mL}$ .

**Expert Committee-initiated Change #7:** In the Analysis section of the Limit of Sodium test, corrected the unit for concentration of Potassium Hydroxide in the Sample solution from g/mL to µg/mL.

**Monograph/Section:** Prochlorperazine Maleate/Organic Impurities  
**Expert Committee:** Chemical Medicines Monographs 3  
**No. of Commenters:** 1

**Comment Summary #1:** The commenter recommended revising the acceptance criteria for prochlorperazine sulfoxide and perazine impurities in the test for *Organic Impurities*.

**Response:** Comment not incorporated. The acceptance criteria for prochlorperazine sulfoxide and perazine impurities are consistent with FDA limits.

**Monograph/Sections:** Quetiapine Extended-Release Tablets/Multiple Sections

**Expert Committee:** Chemical Medicines Monographs 4

**No. of Commenters:** 3

**Comment Summary # 1:** The commenter suggested adding a drying step in the *Identification* Test A.

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

**Comment Summary # 2:** The commenter stated that the resolution requirements in the *Assay* and *Organic Impurities* sections could not be met.

**Response:** Comment not incorporated. The resolution requirements for the *Assay* and *Organic Impurities* are consistent with the validation data.

**Comment Summary # 3:** The commenter stated that the sample preparation procedure is not adequate and suggested it be modified.

**Response:** Comment not incorporated. The proposed sample preparation is consistent with a validated method. The Expert Committee will consider future revisions to the monograph upon receipt of supporting data.

**Comment Summary # 4:** The commenter stated that the sample solution is difficult to filter with nylon.

**Response:** Comment not incorporated. The monograph does not specify the type of filter. Any suitable filter can be used.

**Comment Summary # 5:** The commenter suggested changing the standard solution from quetiapine fumarate to quetiapine to eliminate the need for molecular weight correction in the calculations.

**Response:** Comment not incorporated. The molecular weight correction is required because the product label is in terms of quetiapine and the reference standard is a fumarate salt.



**Monograph/Section:** Selamectin/Organic Impurities  
**Expert Committee:** Chemical Medicines Monographs 3  
**No. of Commenters:** 1  
**Comment Summary #1:** The commenter requested revision of the relative response factor for selamectin aglycone from 1.0 to 1.2 in the test for *Organic impurities*.  
**Response:** Comment incorporated.

**Monograph/Section:** Sodium Citrate and Citric Acid Oral Solution/ Identification  
**Expert Committee:** Chemical Medicines Monographs 6  
**No. of Commenters:** 1  
**Comment Summary #1:** The commenter recommended revising the acceptance criterion in *Identification C* from “Meets the requirements” to a more specific acceptance criterion as approved by the FDA.  
**Response:** Comment incorporated.  
**Expert Committee-initiated Change #1:** The *Potassium stock solution* was deleted from the test for *Assay, Sodium*, because it is not used in the determination of sodium content.  
**Expert Committee-initiated Change #2:** The *Potassium stock solution* was deleted from the preparation of *Standard stock solution* in the test for *Assay, Sodium*.

**Monograph/Sections:** Sodium Succinate/Multiple Sections  
**Expert Committee:** Excipient Monographs 1  
**Expert Committee-initiated Change #1:** In *Identification A*, the statement “and USP Anhydrous Sodium Succinate RS” was deleted, because the data demonstrate that the IR spectra are the same under the conditions of “as is” and the proposed drying procedure.  
**Expert Committee-initiated Change #2:** In the *Assay*, the sentence “Dry USP Anhydrous Sodium Succinate RS at 120° for 2 h before use” in the preparations of System suitability solution and Standard solution was deleted. Users should follow the instructions on the reference standard label.  
**Expert Committee-initiated Change #3:** In the *Limit of Sodium Acetate, Sodium Maleate*, and *Sodium Fumarate*, the sentence “Dry USP Anhydrous Sodium Succinate RS at 120° for 2 h before use” in the preparation of System suitability solution was deleted. Users should follow the instructions on the reference standard label

**Monograph/Section(s):** Tetrahydrozoline Hydrochloride/Multiple Sections  
**Expert Committee:** Chemical Medicines Monographs 6  
**No. of Commenters:** 1  
**Comment Summary #1:** The commenter requested revising the acceptance criteria for *Total Impurities* to be consistent with the FDA-approved specifications.  
**Response:** Comment not incorporated. The acceptance criteria are consistent with the total impurity limits of the drug substance used in the currently marketed nonprescription drug products.

**Comment Summary #2:** The commenter suggested including storage conditions under the *Packaging and Storage* section and adding the statement, “store at controlled room temperature.”

**Response:** Comment incorporated.