



Commentary

USP 41–NF 36

November 13, 2017

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

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

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

- [General Notices to USP-NF](#)

General Chapters:

- [<661.1> Plastic Materials of Constructions](#)
- [<661.2> Plastic Packaging Systems for Pharmaceutical Use](#)
- [<671> Containers--Performance Testing](#)
- [<1079.1> Storage and Transportation of Investigational Drug Products](#)
- [<1210> Statistical Tools for Procedure Validation](#)
- [<1211> Sterilization and Sterility Assurance of Compendial Articles](#)

Monographs:

- [Acetazolamide for Injection](#)
- [Amikacin](#)
- [Amikacin Sulfate](#)
- [Amoxicillin Capsules](#)
- [Amoxicillin Tablets](#)
- [Atorvastatin Calcium Tablets](#)
- [Buprenorphine and Naloxone Sublingual Tablets](#)
- [Carbidopa and Levodopa Tablets](#)
- [Cefaclor](#)
- [Cefaclor Extended-Release Tablets](#)
- [Cefaclor for Oral Suspension](#)
- [Cetyl Esters Wax](#)
- [Conjugated Linoleic Acids-Free Fatty Acids](#)
- [Cyproheptadine Hydrochloride Oral Solution](#)
- [Dexamethasone Sodium Phosphate Compounded Injection](#)
- [Dexmedetomidine Injection](#)
- [Doxycycline for Oral Suspension](#)
- [Echinacea Species Powder Capsules](#)
- [Epoetin](#)
- [Ethyl Acetate](#)
- [Fluticasone Propionate Nasal Spray](#)
- [Gelatin](#)
- [Glimepiride Tablets](#)
- [Granisetron](#)
- [Hydroxyzine Pamoate](#)

- [Hydroxyzine Pamoate Capsules](#)
- [Indomethacin Capsules](#)
- [Itraconazole](#)
- [Ipratropium Bromide and Albuterol Sulfate Inhalation Solution](#)
- [Mefenamic Acid](#)
- [Menthol](#)
- [Metoprolol Succinate Extended-Release Tablets](#)
- [Morphine Sulfate Compounded Injection](#)
- [Moxifloxacin Ophthalmic Solution](#)
- [Mycophenolic Acid Delayed-Release Tablets](#)
- [Nilutamide](#)
- [Potassium Phosphates Compounded Injection](#)
- [Simvastatin Tablets](#)
- [Sodium Bicarbonate Compounded Injection](#)
- [Sodium Phosphates Compounded Injection](#)
- [Tangerine Peel](#)
- [Tangerine Peel Dry Extract](#)
- [Tangerine Peel Powder](#)
- [Telmisartan and Amlodipine Tablets](#)
- [Temozolomide Capsules](#)
- [Temozolomide for Injection](#)
- [Trandolapril Tablets](#)
- [Warfarin Sodium](#)
- [Zinc Oxide](#)
- [Zinc Oxide Powder](#)
- [Zolmitriptan Nasal Spray](#)

No comments were received for the following proposals:

General Chapters

- <227> 4-Aminophenol In Acetaminophen-Containing Drug Products
- <591> Zinc Determination

Monographs

- Amikacin Sulfate Injection
- Aminobenzoate Sodium
- Aminobenzoic Acid Topical Solution
- BCG Live
- Betamethasone Tablets
- Cefaclor Capsules
- Cefaclor Chewable Tablets
- Clomipramine Compounded Oral Suspension, Veterinary
- Cyanocobalamin Co 57 Capsules

- Cyanocobalamin Co 57 Oral Solution
- Cyanocobalamin Co 58 Capsules
- Divalproex Sodium Delayed-Release Tablets
- Glimepiride
- Isostearyl Isostearate
- Lorazepam Injection
- Milrinone Lactate Injection
- Octyldodecanol
- Paraldehyde
- Pentazocine Injection
- Raltegravir Potassium
- Sibutramine Hydrochloride
- Tacrine Capsules
- Tacrine Hydrochloride
- Trandolapril and Verapamil Hydrochloride Extended-Release Tablets
- Triacetin
- Verapamil Hydrochloride Extended-Release Capsules
- Zinc Oxide Neutral
- Zinc Sulfate Ophthalmic Solution

General Chapter/Section(s): General Notices/Multiple Sections
Expert Committee: Council of Experts
No. of Commenters: 4

6.20. Automated Procedures

Comment Summary #1: The commenters suggested replacing the word “validated” with “compendial” in the following sentence, “[a]utomated and manual procedures employing the same basic chemistry are considered equivalent provided the automated system is properly qualified as being suitable to execute the validated manual method and the analytical procedure is verified under the new equipment conditions”

Response: Comment incorporated.

6.30. Alternative and Harmonized Methods and Procedures

Comment Summary #2: The commenter indicated that results comparable to the compendial method are not always possible with an alternative method. The commenter also suggested that the most modern methods should be considered superior to the compendial method and that equivalency requirements should be removed when these methods are used.

Response: Comment not incorporated. The compendial method is conclusive and USP does not rank methods. USP also suggests those with alternative methods to submit them for inclusion in the monograph or Chapter where appropriate.

Comment Summary #3: The commenter suggested revising the section to link the function of an alternative method to the intended compliance with the monograph.

Response: Comment not incorporated. USP cannot give guidance on compliance when non-compendial methods are used.

General Chapter/Sections: <661.1> Plastic Materials of Construction
Expert Committee(s): General Chapters—Packaging, Storage and Distribution

No. of Commenters: 8

General

Comment Summary #1: The commenter recommended adding a risk-based approach to testing in the chapter.

Response: Comment incorporated. The chapter already has a risk based approach to testing. Test requirements are different for oral and topical dosage forms vs all other dosage forms.

Comment Summary #2: The commenter recommended incorporating the developed FAQ's into the chapter.

Response: Comment not incorporated. Based on the May 1, 2017 Revision Bulletin the FAQ's have been removed from the USP website.

Comment Summary #3: The commenter recommend aligning <661.1> and <661.2> with analogous chapters in the Ph. Eur.

Response: Comment not incorporated. Alignment between <661.1> and <661.2> with Ph Eur was actively sought and accomplished when possible. Alignment was not complete: certain tests required in the Ph Eur (for example, reducing substances) were either eliminated or replaced.

Because the Ph Eur does not address testing for extractable metals (other than those specifically targeted based on composition), USP included a more comprehensive extractable metals test to reflect current testing expectations.

Comment Summary #4: The commenter recommends that USP work with the appropriate regulatory agency to bring clarity around the topic of grandfathering the applicability of Table 1 of the FAQs posted on the USP website.

Response: Comment incorporated. In conjunction with discussions with the appropriate regulatory agency, USP has decided to remove the grandfather exemption, which was posted as a Revision Bulletin on May 1, 2017.

Introduction

Comment Summary #5: The commenter indicated that the chapter should not discuss safety.

Response: Comment incorporated. In the current revision proposal, the text mentioning safety has already been deleted.

Scope

Comment Summary #6: The commenter suggested re-introducing text on how to deal with materials not specifically addressed ("unaddressed materials") in the chapter.

Response: Comment incorporated.

Table 1

Comment Summary #7: The commenter recommends the removal of the Extractable Metals requirements for oral and topical dosage forms.

Response: Comment not incorporated. In the absence of sufficient data to address metals present in packaging for oral and topical dosage forms, this requirement will not be waived at the current time. However, the Packaging and Distribution Expert Committee will continue to have open dialogue on this topic.

Table 3

Comment Summary #8: The commenter suggested that the requirements for Polyamide 6 in Table 3 are inconsistent with the testing described later in the chapter and recommends this be addressed.

Response: Comment incorporated.

Identification— Cyclic Olefins

Comment Summary #9: The commenter indicated that there is a conflict with the specifications for cyclic olefins. It states that "it is neither recommended nor required that differential scanning calorimetry (DSC) be performed" and recommend this conflict be addressed.

Response: Comment incorporated.

Identification— High-density polyethylene and polypropylene

Comment Summary #10: The commenter recommends that a <197> (*Spectrophotometric Identification Tests*) chapter reference be added for HDPE and Polypropylene so the direction in which <197> should be utilized is clear.

Response: Comment incorporated.

Identification— Polyvinyl Chloride (PVC)

Comment Summary #11: The commenter noted that Plasticized PVC is an amorphous material, and the melting point (T_m) cannot be observed. Glass Transition Temperature (T_g) is more applicable and the commenter recommends this change be made to the chapter.

Response: Comment incorporated.

Absorbance

Comment Summary #12: The commenter recommended revising the text to provide flexibility for the prescribed Absorbance requirements for plastic material of construction. The prescribed absorbance limits should be presented as 'alert levels' to allow for appropriate identification and characterization studies.

Response: Comment incorporated.

Total Organic Carbon

Comment Summary #13: The commenter recommended revising the text to provide flexibility for the prescribed Total Organic Carbon requirements for plastic material of construction. The prescribed absorbance limits should be presented as 'alert levels' to allow for appropriate identification and characterization studies.

Response: Comment incorporated.

Extractable Metals

Comment Summary #14: The commenter suggested that the procedure for Extract Analysis specifies methods described in <233> *Elemental Impurities – Procedures*, which are ICP-OES and ICP-MS methods, directs the user to <730>, Plasma Spectrochemistry. Currently it directs the user to <852> (Atomic Absorption Spectroscopy). This reference should be revised.

Response: Comment incorporated.

Comment Summary #15: The commenter indicated that the metals specified in <661.1> are misaligned to <232> *Elemental Impurities--Limits* and suggested addressing the issue.

Response: Comment not incorporated. In deciding on elements to include the Expert Committee developed the concept of relevant elements, where a relevant element is one which is a known constituent of the material or component that could potentially arise from a starting material, additive, or manufacturing process and elements of known toxicological concern as outlined in <232>. The EC included nontoxic elements that are intentionally added because of potential drug product sensitivities and interactions.

Comment Summary #16: The commenter indicated that metal specifications in the chapter are not based on either a toxicological or quality perspectives and should be removed.

Response: Comment not incorporated. The General Chapters Packaging, Storage and Distribution Expert Committee (PD EC) continues to discuss the current specifications for certain metals in the chapter, with the goal of coming to a resolution and proposing a revision in 2018.

Comment Summary #17: The commenter indicated that <661.1> should directly reference <232> because the chapter already discusses the contributions of packaging components to the final drug product.

Response: Comment not incorporated. In <661.2>, the PD EC deemed it appropriate to reference <232>, because the chapter focuses on the testing of a specific packaging with a specific drug product, whereas <661.1> focuses on the testing of materials of construction. While it is clear the <232> limits don't apply, the focus has been on the risk assessment option. Using the risk assessment option, it was not evident how to get the necessary data to make a decision regarding the selection of a material. In the control of plastic materials, extractable metals are an important attribute to understand and testing seems to be the only way to obtain the necessary data.

Additives —Nonphenolic Antioxidants

Comment Summary #18: The commenter indicated that under “chromatographic system”, the cross reference reads “See Chromatography <621>, Liquid Chromatography”. This test is a TLC test and should reference <621> Thin Layer Chromatography.

Response: Comment incorporated.

Comment Summary #19: The commenter recommends adding a solution preparation for the alcoholic iodine solution used in the chapter.

Response: Comment incorporated.

Additives — Phenolic Antioxidants and Amides and Stearates for Poly{ ethylene-vinyl acetate)

Comment Summary #20: The commenter indicated that in the Amides and Stearates testing, "chloride" is missing from the description of Reference Solution R and should be added.

Response: Comment incorporated.

Comment Summary #21: The commenter indicated that the requirements were missing from the Specifications section and should be added.

Response: Comment incorporated.

Additives — Phenolic Antioxidants and Amides and Stearates for (Polyethylene, Cyclic Olefins and Polypropylene)

Comment Summary #22: The commenter requested clarification for the mobile phase: it is unclear what the ratio of dehydrated trimethylpentane and alcohol should be.

Response: Comment incorporated.

Vinyl Chloride in Non-Plasticized and Plasticized PVC

Comment Summary #23: The commenter recommended that Plasticized and Non-Plasticized PVC should not be split into two sections.

Response: Comment not incorporated. The two PVCs are separated because they are two different materials.

Polycarbonate Bisphenol A test

Comment Summary #24: The commenter indicated that the method refers to a stainless steel capillary column, packed with 0.251-I G38, however this is not the appropriate column.

Response: Comment incorporated.

Comment Summary #25: The commenter indicated the sample solution will not reach 50°C under a reflux and the temperature should be revised to address this.

Response: Comment incorporated.

Poly(ethylene-vinyl acetate)--Vinyl Acetate method

Comment Summary #26: The commenter indicated that the correlation coefficient should be noted as r and not r^2 , which is consistent with terminology used throughout instrumental chapters for linearity acceptance criteria in validations.

Response: Comment incorporated.

Comment Summary #27: The commenter suggested that a procedure for preparing the Alcoholic Potassium Hydroxide solution should be added to the chapter.

Response: Comment incorporated.

The Free Base Function

Comment Summary #28: The commenter indicated that the procedure for yielding 70% phenol, is incorrect and needs to be revised.

Response: Comment incorporated.

Polycarbonate--Related Substance

Comment Summary #29: The commenter indicated that the specifications for residual solvents are given in mg/L, but should be in weight per weight.

Response: Comment incorporated.

General Chapter/Sections: <661.2> Plastic Packaging Systems for Pharmaceutical Use

Expert Committee(s): General Chapters—Packaging, Storage and Distribution

No. of Commenters: 7

General

Comment Summary #1: The commenter recommended that the committee use the first paragraph of the Introduction in <1661> *Evaluation of Plastic Packaging Systems and Their Materials of Construction with Respect to their User Safety Impact* or similar language to clearly communicate the scope of the chapter.

Response: Comment incorporated.

Comment Summary #2: The commenter recommended that the scope of <661.2> be expanded to allow for component testing.

Response: Comment incorporated.

Comment Summary #3: The commenter recommend that component testing be a substitute for full system testing.

Response: Comment incorporated. It is up to individual companies to justify their qualification strategy.

Introduction

Comment Summary #4: The commenter suggested that since the chapter is applicable to plastic packaging systems, the term “plastic” should be incorporated to accurately reflect the scope of the chapter.

Response: Comment incorporated. The title of the chapter already states the focus is plastic packaging systems.

Comment Summary #5: The commenter suggested harmonizing the definition of primary and secondary packaging with that in <659> *Packaging and Storage Requirements*.

Response: Comment incorporated. The definitions in <659>, USP 40, are harmonized with <661.2>.

Scope

Comment Summary #6: The commenter recommended that a procedure be added for components that can be tested via <661.2>.

Response: Comment incorporated.

Comment Summary #7: The commenter suggested deleting dry powder inhalers, metered dose inhalers, nebulizers, and prefilled syringes from the list of packaging systems that are included in the chapter.

Response: Comment not incorporated. Rationale for the exclusion of these packaging systems is needed in order to understand the need for removal from the list.

Comment Summary #8: The commenter indicated that a component may be intentionally chosen, but the materials for those components are not chosen by the pharmaceutical manufacturer. Thus, <661.1> should be applied to pharmaceutical manufacturers' primary packaging components, not materials of construction.

Response: Comment not incorporated. While it may not be the purview of the pharmaceutical manufacturer to make the selection of the materials, the pharmaceutical manufacturer should gain some understanding of the material to make a sound decision.

Test Methods—Biological Reactivity

Comment Summary #9: The commenter recommended that the required In vitro biological tests for Topical Delivery Systems, Topical Solutions and Suspensions, and Topical and Lingual Aerosols, Oral Solutions and Suspensions and Topical Powders, Oral Powders Oral Tablets and Oral (Hard and Soft Gelatin) Capsules be removed from the chapter.

Response: Comment incorporated. In the proposed revision, the in vitro biological test for oral and topical dosage forms requirement is being removed.

Comment Summary #10: The commenter indicated that it is unlikely that USP <87> *Biological Reactivity Tests, in Vitro* could readily be performed on an entire packaging system.

Response: Comment not incorporated. USP <87> could easily be done on packaging systems if the extraction were performed by filling the package with the nominal volume of extraction medium and then subjecting the filled package to the appropriate temperature and duration.

Comment Summary #11: The commenter suggested Class VI plastics are meant for use in implants. There is no reason and it is not ethically justified to meet this requirement for inhalation or parenteral.

Response: Comment not incorporated. The classification "external communicating devices, blood path indirect, permanent" could be applied to certain packaging systems. This would make them Class VI. The chapter does not require performing GC <88> testing, but only in cases where GC <87> *Biological Reactivity Tests, In Vivo* fails or classifying materials. There is a current USP effort to revise both <87> and <88> and comment will be discussed in light of future revisions to those chapters.

Test Method—Physiochemical Tests: Water Extraction

Comment Summary #12: The commenter requested clarification on whether the primary container or primary and secondary packaging need to be tested.

Response: Comment not incorporated. The introduction states that a system refers to both primary and secondary packaging, if there is a potential of the secondary packaging to interact with the drug product. In this example, the test article to prepare solution C1 would include the overwrap.

Comment Summary #13: The commenter suggested allowing flexibility in the use of other inert materials to cover the sample.

Response: Comment incorporated.

Comment Summary #14: The commenter suggested using packaging systems instead of bags.

Response: Comment incorporated.

Comment Summary #15: The commenter indicated that a volume of 4% of the nominal capacity of a 0.5mL would not be sufficient in many situations and recommends changing to a nominal volume.

Response: Comment incorporated.

Test Method—Physiochemical Tests: Total Terephthaloyl Moieties in Polyethylene Terephthalate and Polyethylene Terephthalate G Packaging Systems - Preparation

Comment Summary #16: The commenter suggested that n-heptane should be used for the extracting media and blank preparations.

Response: Comment incorporated.

Chemical Safety Assessment

Comment Summary #17: The commenter indicated that the wording about which combination of data would be acceptable is unclear. Since assessment of the material of construction is prescribed in <661.1> the current wording appears to be a contradiction.

Response: Comment incorporated.

Specifications—Physicochemical Tests

Comment Summary #18: The commenter indicated that n-heptane should be used for the extracting media and blank preparations

Response: Comment incorporated.

Specifications— Chemical Safety Assessment

Comment Summary #19: The commenter indicated that in some cases it may not be feasible to experimentally test the entire packaging system. Testing of individual components may be necessary and in some cases beneficial to understand where the highest chemical risk is. Component testing should not be omitted as an option.

Response: Comment incorporated. The option of component testing has been added and further discussion on the topic can be found in <1661> *Evaluation of Plastic Packaging Systems and Their Materials of Construction with Respect to Their User Safety Impact*.

General Chapter/Sections: <671> Containers – Performance Testing
Expert Committee(s): General Chapters—Packaging, Storage and Distribution

No. of Commenters: 11

General

Comment Summary #1: The commenter recommended adding back Table 1 from the older chapter.

Response: Comment incorporated.

Comment Summary #2: The commenter recommended adding a statement to indicate that the testing methodology can be applied to other testing conditions, which will give industry more flexibility.

Response: Comment incorporated.

Comment Summary #3: The commenter indicated that there needs to be some consistency in the uses of glass beads filled into “control” container samples.

Response: Comment incorporated.

Comment Summary #4: The commenter indicated that throughout the text the terms “Method 1, Method 2 and Method 3” are used multiple times with different meanings and request a revision to remove confusion

Response: Comment incorporated.

Comment Summary #5: The commenter recommended including the Spectral Transmission test <671>.

Response: Comment incorporated.

Introduction

Comment Summary #6: The commenter suggested adding a sentence to allow other dosage forms to reference this chapter, as applicable to the protection of product.

Response: Comment incorporated.

Comment Summary #7: The commenter indicated that the current text implies that manufacturers and packagers should be exclusively using the barrier determination method and that the text should be revised to allow other methods to be used.

Response: Comment incorporated. There is already a statement in the chapter that states the classification system can be used for manufacturers and packagers.

Comment Summary #8: The commenter suggested defining “plastic packaging systems” in the chapter.

Response: Comment not incorporated. The chapter references <659>, where all USP packaging definition are contained.

Moisture Vapor Transmission for Plastic Packaging Systems, Procedure: Method 1

Comment Summary #9: The commenter recommended deleting the text that requires weighing at the zero time point, because it not used in the calculation.

Response: Comment not incorporated. The time zero reading is useful for investigational purposes.

Packaging Systems for Solid Oral Dosage Forms and Liquid Oral Dosage Forms, Procedure, Method 1;

Comment Summary #10: The commenter requested that the text below be added back to the chapter, to reducing testing variability: “clean the sealing surfaces with a lint-free cloth, and close and open each container 30 times.”

Response: Comment incorporated.

Classification System for Plastic Packaging Systems: Packaging Systems for Solid Oral Dosage Forms and Liquid Oral Dosage Forms

Comment Summary #11: The commenter suggested clarifying what testing method is applicable to liquid dose packaging systems.

Response: Comment incorporated.

Packaging Systems for Liquid Oral Dosage Forms

Comment Summary #12: The commenter indicated that the calculation used for the liquid oral dosage forms method does not match the equation in the currently published chapter, or the equation in the current Errata text and recommends confirming equation.

Response: Comment incorporated

General Chapter/Sections: <1079.1> Storage and Transportation of Investigational Drug Products

Expert Committee(s): General Chapters—Packaging, Storage and Distribution

No. of Commenters: 18

General

Comment Summary #1: The commenter requests a definition for “container”, to provide clarity around the term.

Response: Comment incorporated.

Comment Summary #2: The commenter recommended changing “Investigational Drug Products” to “Investigational Medicinal Products” throughout the chapter.

Response: Comment not incorporated. In the review of FDA documents, the term used was “investigational drug products” and it needs to align with the FDA.

Scope

Comment Summary #3: The commenter recommended replacing the word “change” with the word “vary” in the following sentence. “Due to global security issues, regulations may change for the distribution of drug products and for IDPs as well.”

Response: Comment incorporated.

Number of Clinical Trail Sites

Comment Summary #4: The commenter recommends additional guidance regarding the redistribution of clinical materials between sites.

Response: Comment not incorporated. The topic was not within the scope of the chapter.

Depots and Subcontractors

Comment Summary #5: The commenter indicated that there is a need for equivalent and/or greater diligence at these facilities like at Clinical Trial Sites. More often than not, these facilities hold greater volumes of the inventory and language should be added to reflect this point.

Response: Comment not incorporated. More clarification is necessary to fully understand this request.

IDP Supply Chain Challenges

Comment Summary #6: The commenter suggested rewording the following sentence to remove the reference to “very quickly”: “The faster the trial enrolls, the larger the number of shipments become very quickly.”

Response: Comment incorporated.

Timing

Comment Summary #7: The commenter recommends deleting or revising the information in this section that addresses “patient specimens” (biological samples), as it is not relevant to the subject of this proposed chapter

Response: Comment incorporated.

IDP Environmental Conditions

Comment Summary #8: The commenter suggested using “Safety Data Sheets” rather than “Material Safety Data Sheets” due to recent regulatory changes.

Response: Comment incorporated.

Unbinding

Comment Summary #9: The commenter recommends revising the section to make it clear that unbinding does not always mean quarantine.

Response: Comment incorporated.

Returned IDPs

Comment Summary #10: The commenter recommends removing the words “environmental monitoring” because they are not necessary.

Response: Comment not incorporated. It was deemed that the wording as written is appropriate.

Assessing Risk Early in the Distribution Process

Comment Summary #11: The commenter recommends the section be written to be less prescriptive.

Response: Comment incorporated.

Comment Summary #12: The commenter recommended omitting Figure 2 because it is too prescriptive.

Response: Comment incorporated.

General Chapter/Sections: <1210> Statistical Tools for Procedure
Validation/Multiple Sections
Expert Committee: General Chapters–Statistics
No. of Commenters: 15

Combination of Accuracy and Precision

Comment Summary #1: The commenter indicated that the variability associated with bias is not mentioned as part of the overall variability of the combined “Accuracy and Precision”.

Response: Comment not incorporated. Variability associated with the bias is already accounted for in the tolerance interval approach.

Comment Summary #2: The commenter indicated that it does not clearly state that the combined Accuracy/Precision approach should only be implemented when a matrix reference standard that simulates the actual tested sample matrix should be used in the combined Accuracy/Precision experiments.

Response: Comment not incorporated. Comment is specific to an organization’s standard and cannot be incorporated into a general chapter.

Comment Summary #3: The commenter indicated that in Section 3.1, having method validation criteria for accuracy and precision based on requiring confidence limits within pre-specified criteria, will have significant sample size implications if the results generated are truly representative.

Response: Comment incorporated.

Comment Summary #4: The commenter indicated that combining accuracy and precision into a single acceptance criterion is not a preferred approach to assessing the acceptability of an analytical method. Having separate criteria for accuracy and precision are more aligned with the expectations of ICH Q2 (R1) and analytical scientists. Moreover, conducting separate assessments of accuracy and precision allows for improved understanding if either one or both criteria are not met.

Response: Comment not incorporated. Combining accuracy and precision is only one approach. Details to qualify separately are provided in the chapter.

Comment Summary #5: A commenter indicated that Equation (9) refers (as requested by ICH Q2 (R1) guideline) to τ , the true or accepted reference value, which is unknown from real samples. So, the use of theoretical calculations described in <1210> does not allow using real samples during validation. An additional equation that could be used with data obtained from real samples would be interesting in order to calculate a tolerance interval from these data (still taking into account the systematic bias observed from spiked samples).

Response: Comment incorporated.

Comment Summary #6: The commenter indicated that if accuracy and precision are combined into a single acceptance criterion in Section 3.2, the confidence interval and Bayesian approaches mentioned in the final paragraph, seem more appropriate than the approaches that are emphasized in the section. As such, the confidence interval

and Bayesian approaches should be emphasized and expanded first as the appropriate approaches rather than what is emphasized in the text.

Response: Comment not incorporated. The method provided is more useful for most readers.

Comment Summary #7: The commenter suggested that the applicability of the combined validation approach for accuracy and precision in development and in QC laboratories is questionable because the true value of a sample is usually not known. Thus, the biggest objection to USP <1210> is that the reference point is most often missing, especially in development and generally for drug product test methods. It is impossible to address accuracy and precision in the same experimental set-up, as samples with known potencies over a given range are not available. Therefore, precision is generally investigated on real samples; whereas accuracy is addressed by spiking the material with various concentrations of the analyte(s). For drug product test methods, the sample preparation step is known to significantly impact the method variability and it is therefore not deemed adequate to address the method precision on spiked samples. Results of new statistical approaches are not compatible with the traditional way of specification setting.

Response: Comment incorporated with the addition of “The value of τ is assumed known in this chapter and approaches for validation without such knowledge are out of scope.”

Comment Summary #8: The commenter indicated that while prediction and tolerance intervals are proposed, no clear recommendation is done regarding the use of one or the other according to the study objective.

Response: Comment not incorporated. The selection of an interval will depend on the desire to validate either (i) or (ii) and a company’s risk profile.

Comment Summary #9: The commenter requested the rationale for including the prediction interval for method validation. The goal is to determine that the method is suitable for its intended use and not for its next measurement.

Response: Comment incorporated with the addition “Selection of an interval will depend on the desire to validate either (i) or (ii) and a company’s risk profile.”

Comment Summary #10: A commenter indicated that for the Target Measurement Uncertainty (TMU) calculation, a TMU for a sub-sample of a batch of tablets provides a mean and confidence interval for the sub-sample of that batch. The commenter added, a second sub-sample would have a different mean and confidence interval (although you would expect the range of the confidence interval to be similar) and if you took a sub-sample from a second batch of tablets you would expect a different mean with a different but similar confidence interval. The commenter mentioned it is not clear how you should (or indeed if you should) account for the variability from sampling or the production process of API and tablets, and whilst it is clear how you calculate the TMU for the method it is not clear how you apply that to the batch release process as there is no mention of specifications or guard bands etc.

Response: Comment not incorporated. There is no reference to TMU in the chapter.

Comment Summary #11: The commenter noted that the draft proposes a tolerance interval (TI) approach for simultaneously assessing accuracy and precision. While this approach has the benefit of providing a comprehensive measure of assay performance,

the draft did not address the critical issue of choice of lambda (acceptable limit of error, Eq. 9)

Response: Comment not incorporated. Setting acceptance criteria and confidence levels are out of the scope of the chapter.

Reportable Values

Comment Summary #12: The commenter indicated that precision is typically assessed by a point estimate of Coefficient of Variation. During the analytical procedure validation, the number of readings and their rule for averaging to obtain the reportable value must be identical compared to routine use of the method. Therefore, "as defined in the analytical procedure to be validated" should be added at the end of the definition.

Response: Comment incorporated by using the terms individual determinations and reportable value as defined in General Notices 7.10. Tables 1 and 2 have been modified.

Comment Summary #13: The commenter indicated that in Section 1 - the definition of "Reportable Value" in <1210> does not agree with that in <1225> *Validation of compendial Methods*. <1210> Table 1 defines "Reportable value" as "Average value of readings from one or more units of a test solution". Validation is required to be performed using the reportable value. <1225> defines "Reportable Value" as the final value that is compared to the acceptance criteria of a specification and differentiates it from a "test result". A "test result" is defined in <1225> as an observed value or a result calculated from several observed values. "A test result also can be the final, reportable value"

Response: Comment incorporated by using the terms "individual determinations" and "reportable value" as defined in General Notices 7.10. Tables 1 and 2 have been modified.

Comment Summary #14: The commenter indicated that in Table 2, the reportable value as an average value of four readings is not aligned with GMP's, which have moved away from averaging values to generate a reportable result.

Response: Comment not incorporated. The Expert Committee does not understand this as a GMP movement.

Linearity

Comment Summary #15: The commenter indicated that the original chapter was a step forward to help people move away from calculating linearity from the correlation coefficient. Since this is no longer included the misconceptions will remain.

Response: The linearity section is not in the current version of the chapter due to the feedback received. The section on "linearity" will be addressed in future updates of this chapter.

Comment Summary #16:

The last sentence, "Linearity may be inferred from accuracy or other statistical methods as deemed appropriate," is very confusing, particularly when compared with a sentence from ICH Q2 (paragraphs 4.1.1 c, and 4.1.2.c which state that for assay "accuracy may be inferred once precision, linearity and specificity have been established".

Response: Comment incorporated. Removed reference to inferring linearity.

Alignment with USP Documents

Comment Summary #17: The commenter requested that the content of this proposal be reviewed against related Chapters such as <1225>, <1220>, and ICH to ensure full alignment of requirements. The approach of inferring linearity from accuracy or other appropriate statistical methods presented in this proposal makes sense; however this approach should also be included in <1225>. In addition, the Stimuli Article entitled: "Proposed New USP General Chapter: The Analytical Procedure Lifecycle <1220>" contains valuable comments/explanations/clarification which are relevant to the understanding of this document.

Response: Comment not incorporated. This chapter is aligned with USP <1225>.

LOD

Comment Summary #18: The commenter indicated that Section 4.1 is based on the IUPAC/ISO model but provides only an LOD estimate (which is not unbiased) without any confidence interval methodology for providing the user information with respect to closeness of the estimate to the true LOD or alternatively closeness of beta to a desired $\beta = \beta_0$ for fixed alpha. Moreover the methodology involves estimating the calibration curve, which only adds variability and additional assumptions.

The worked out example represents the case of homogeneous variances and linear calibration curves, which cover only a small subset of analytical instruments. Although the methodology applies to linear calibration curves with heterogeneous variances, weighted least squares are not explained for the reader. For the more common case of nonlinear calibration curves, the document sends the reader to a statistician.

Response: Comment not incorporated. These comments offer extensions that are out of scope with the intentions.

Comment Summary #19: The commenter indicated that the definition of LOD introduces the notion of false-positive or false-negative decisions. LOD has to be determined for limit tests (category II). However, for limit tests, the final decision is not always based on LOD. Sometimes the final decision is based on the specification limit or reporting limit, which are usually significantly higher than LOD. Therefore, the relevance of this statistical approach is disputable. The important information is not the absolute value of the LOD, but if the LOD is sufficiently low to support the routine use of the analytical method, while taking the relevant specifications into account.

The described approach is only applicable, for a quantifiable signal for the blank. If no quantifiable signal for the blank is available, the statistical approach as described in <1210> cannot be applied.

Response: Comment not incorporated. The "fitness for use" definition implies that if the specification or reporting limit is above the LOD, the method is fit for use.

Comment Summary #20: The commenter suggested LOD and LOQ are changing every day of analysis. Just because the Noise changes every day also (changing a reagent, equipment or even one day after the other, as the lamp of the detector is getting older).

In this context, the calculations –proposed in <1210>, do not provide information in line with the intended use of the method and a commonly used validation strategy. For LOD from a regulatory point of view, authorities (and also analysts) only expect it to be sensitive enough to detect a compound that is far below the limit set in the

specifications (using a solution at 10% or even 50% of the specification limit). Again, searching for the “real” value is out of the scope for “intended use”. Furthermore, for both LOD and LOQ, the rounding of estimated values generates an error far higher than expected by analysts in the lab.

Response: Comment not incorporated. The Chapter deals with this uncertainty with the sentence, “This is corrected by using a statistical prediction interval that takes into account the uncertainty in the estimated line as well as the variability associated with a future observation.”

Comment Summary #21: The commenter indicated that this section suggests approaches for estimating an upper bound on LOD based on the imprecision in estimates for repeatability variance and the calibration curve. The formulas given, being upper bounds, will systematically overestimate LOD. While this has the benefit of providing a statistically-based upper bound, it may raise interpretational difficulties in the current context in which LOD estimates are typically based on either point estimates or more moderate adjustments for uncertainty. An alternate approach could consist of estimating LOD based on point estimates and applying the upper bound estimate as a form of sensitivity analysis to indicate the precision of the LOD estimate.

Response: Comment not incorporated. These comments offer extensions that are out of scope with the intentions.

Prevalidation

Comment Summary #22: The commenter indicated that the second section on pre-validation procedure development is not relevant in such details for a chapter on statistical tools. It includes several aspects from the analytical method lifecycle approach (procedure design and development). It would be better included in a chapter on analytical procedure lifecycle.

Response: Comment not incorporated. This is not viewed as life cycle but as informative.

General Chapter/Sections:	General Chapter <1211> Sterilization and Sterility Assurance of Compendial Articles
Expert Committee:	General Chapters—Microbiology
No. of Commenters:	3

Comment Summary #1: The commenter requested that the word “substantially” be removed in the Aseptic Processing section since all exposed skin should be covered. Furthermore, including the word “substantially” implies that an undefined portion of skin is acceptable for exposure.

Response: Comment incorporated. Change made.

Comment Summary #2: The commenter indicated that there is no mention of control of endotoxins (or pyrogens) and asked if this should be acknowledged here. The commenter also noted that control of these parameters will influence the control of endotoxins, which is linked to sterility assurance.

Response: Comment not incorporated. Endotoxin and its control is addressed in <1228> *Depyrogenation*.

Comment Summary #3: The commenter recommended that the chapter should more strongly emphasize the increased risk that can be associated with the manufacturing of aseptically

processed products compared to the manufacturing of terminally sterilized products, and suggested including language in the chapter to highlight this issue.

Response: Comment not incorporated. This is outside the scope of this revision. USP is currently developing entirely new content on Sterility Assurance <1211>, which will address this topic.

Comment Summary #4: The commenter recommended including more explicit wording to emphasize the requirements and importance of trending environmental monitoring data.

Response: Comment not incorporated. This is outside the scope of this revision. USP is currently developing entirely new content on Sterility Assurance <1211>.

Comment Summary #5: The commenter indicated that the text on “Media Fills” could be interpreted as discounting the utility of media fills and also noted that the performance of media fills is not important in assessing the aseptic manufacturing process. The commenter therefore suggested either expanding on this statement in greater detail and supporting it with a reference or deleting it entirely.

Response: Comment not incorporated. This is outside the scope of this revision. USP is currently developing entirely new content on Sterility Assurance <1211> which will address the topic.

Comment Summary #6: The commenter indicated that it would be helpful to have some discussion of the level of risk associated with the use of or lack of use of other advanced technologies (e.g. isolators) and therefore include language in this section to cover this topic.

Response: Comment not incorporated. This is outside the scope of this revision. USP is currently developing entirely new content on Sterility Assurance <1211>. That new content addresses this topic.

Comment Summary #7: The commenter suggested adding more explicit details around minimizing operator interactions with products in the section on barrier systems.

Response: Comment not incorporated. This is outside the scope of this revision. USP is currently developing entirely new content on Sterility Assurance <1211>.

Comment Summary #8: The commenter suggested revising the sentence on Areas of Critical Concern to better fit with the paragraph or to revise the paragraph in its entirety.

Response: Comment not incorporated. USP is currently developing an entirely new content on Sterility Assurance <1211>.

Monograph/Section(s): Acetazolamide for Injection/Organic Impurities

Expert Committee(s): Chemical Medicines 3

No. of Commenters: 2

***Comment Summary #1:** The commenter requested widening the limit of acetazolamide related compound D from NMT 0.2% to NMT 2.0%, and the Total impurities limit from NMT 2.0% to NMT 3.0% to be consistent with FDA approved acceptance criteria.

Response: Comment incorporated.

Monograph/Section(s): Amikacin/Organic Impurities

Expert Committee(s): Chemical Medicines 1

No. of Commenters: 1

***Comment Summary #1:** The commenter recommended adding a test for *Organic Impurities* with acceptance criteria for specified impurities. The commenter also recommended including the chemical structures for the identified impurities.

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

Monograph/Section(s): Amikacin Sulfate/Multiple Sections
Expert Committee(s): Chemical Medicines 1
No. of Commenters: 1

***Comment Summary #1:** The commenter indicated that the chemical structure and CAS number are not consistent with the chemical names and formulas. The chemical structure and CAS number are only for the 1:2 sulfate. However, the chemical names and formulas are for the 1:2 and 1:1.8 sulfates.

Response: Comment incorporated. The chemical structure was revised to include both 1:2 and 1:1.8 sulfates. The CAS number for the 1:1.8 sulfates was added.

***Comment Summary #2:** The commenter recommended adding a test for *Organic Impurities* with acceptance criteria for specified impurities and including the chemical structures of the identified impurities.

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

Monograph/Section(s): Amoxicillin Capsules/Organic Impurities
Expert Committee(s): Chemical Medicines 1
No. of Commenters: 3

***Comment Summary #1:** The commenters requested widening the acceptance criteria for specified impurities, unspecified impurities, and total impurities so that they are consistent with FDA approved requirements.

Response: Comment incorporated. The acceptance criteria for amoxicillin related compounds D, E, F, J, any individual unspecified degradation product, and total impurities were revised from NMT 1.5%, 2.0%, 0.5%, 1.5%, 0.2% and 5.0% to NMT 2.4%, 3.6%, 1.0%, 2.0%, 1.0% and 7.0% respectively, based on FDA approved limits.

Monograph/Section(s): Amoxicillin Tablets/Organic Impurities
Expert Committee(s): Chemical Medicines 1
No. of Commenters: 3

***Comment Summary #1:** The commenters requested widening the acceptance criteria for specified impurities, unspecified impurities, and total impurities to be consistent with FDA approved requirements.

Response: Comment incorporated. The acceptance criteria for amoxicillin related compounds D, E, F, J, any individual unspecified degradation product and total impurities were revised from NMT 1.5%, 2.0%, 0.5%, 2.0%, 0.5% and 4.5% to NMT 2.0%, 5.0%, 1.0%, 2.5%, 1.0% and 10.0% respectively, based on FDA approved limits.

Monograph/Sections: Atorvastatin Calcium Tablets/Multiple sections
Expert Committee: Chemical Medicines 2
No. of Commenters: 10

Comment Summary #1 *: The commenter recommended revising the chemical formula for the labeled amount of atorvastatin from (C₃₃H₃₄FN₂O₅) to (C₃₃H₃₅FN₂O₅)₂ based on the label claim, under the *Definition*.

Response: Comment not incorporated. The Expert Committee determined that the chemical formula in the proposal accurately represents the label claim in the FDA approved drug products.

Comment Summary #2: The commenter recommended clarifying the preparation of the *Standard solution* and the *Sample solution* in the *Assay* and *Dissolution* to indicate that the *Standard solution* concentration is based on the anhydrous atorvastatin calcium and the *Sample solution* is based on 2 moles of atorvastatin anhydrous free acid [(C₃₃H₃₅FN₂O₅)₂].

Response: Comment not incorporated. The Expert Committee determined that the Standard solution and Sample solution stated in the proposal are accurate and meet the FDA approved drug product requirements.

Comment Summary #3: The commenter recommended revising the calculation statement in the Assay and Dissolution to contain the appropriate molecular formula.

Response: Comment not incorporated. The Expert Committee determined that the calculations described in the proposal are consistent with the FDA approved drug product requirements.

Comment Summary #4: The commenter recommended revising the chemical name of Atorvastatin amide to be consistent with the drug substance monograph.

Response: Comments not incorporated. The Expert Committee will consider future revision to the drug substance monograph as the name in the drug product monograph is consistent with the USP's current naming convention.

Comment Summary #5: The commenter recommended revising the chemical name of Atorvastatin epoxy pyrrolooxazin 7-hydroxy analog as the structure cannot be easily generated.

Response: Comment not incorporated. The Expert Committee determined that the proposed name is consistent with the USP's current naming convention.

Comment Summary #6: The commenter recommended including a known oxidative degradation impurity, ATV-FX1 into the monograph.

Response: Comment not incorporated. The Expert Committee determined that the proposed impurities and the corresponding acceptance criteria are in accordance with the FDA approved drug product requirements.

Comment Summary #7: The commenter indicated that the total impurities limit is not in accordance with the FDA approved drug products.

Response: Comment not incorporated. The Expert Committee determined that the total impurities limit is in accordance with the FDA approved drug product requirements and will consider a future revision as needed.

Comment Summary #8: The commenter requested widening the disregard limit from NMT 0.05% to NMT 0.1% to be consistent with their FDA approved drug product.

Response: Comment incorporated. The Expert Committee determined to delete the disregard limit in accordance with the current USP practice.

Comment Summary #9: The commenter requested including an additional dissolution test as the current procedures are not suitable to test their product.

Response: Comment not incorporated. The Expert Committee will consider a future revision based on the supporting documentation.

Comment Summary #10: The commenter requested increasing the limit for epoxy THF analog impurity to NMT 1.0% as their product cannot meet the proposed acceptance criteria of NMT 0.25%.

Response: Comment not incorporated. The Expert Committee will consider future revisions upon receiving the supporting data.

Comment Summary #11: The commenter indicated that under Organic Impurities, it is not very clear how the relative retention times of impurities are calculated. The run time should be more than 65 minutes if RRTs of all peaks eluting after Atorvastatin related compound H peaks are calculated with respect to related compound H peak as stated in the proposal.

Response: Comment incorporated. The Expert Committee was determined to clarify the relative retention times and indicate in Table 4 that the relative retention time for Atorvastatin related compound H is 1.0 and consequently revise the relative retention times of impurities eluting after the Atorvastatin related compound H.

Comment Summary #12: The commenter requested revising the Definition acceptance criterion from NLT 94.5% and NMT 105.0% to NLT 90.0%-NMT 110.0% because of the unstable nature of the drug substance and the possible presence of antioxidants.

Response: Comment not incorporated. The Expert Committee determined that the proposed acceptance criteria are consistent with the FDA approved drug product requirements.

Comment Summary #13: The commenter recommended harmonizing the impurity names with European Pharmacopeia impurity names.

Response: Comment not incorporated. The Expert Committee determined the proposed names are consistent with the current USP naming convention.

Comment Summary #14: The commenter indicated that under Organic Impurities, the relative response factor for epoxy THF analog and the Atorvastatin related compound D is 1.29 and not 1.12.

Response: Comment not incorporated. The proposed relative response factors are consistent with the validation data. The Expert Committee will consider future revisions upon receiving supporting data and as needed.

Comment Summary #15: The commenter indicated that Atorvastatin Methyl ester and Atorvastatin epoxy pyrroloxazin 7-hydroxy analog are coeluting under the proposed conditions for Organic Impurities

Response: Comment not incorporated. The Expert Committee will consider future revisions upon receiving supporting data and as needed.

Comment Summary #16: The commenter indicated that there is filter bias in preparing the sample under the Dissolution test and recommends including the centrifugation step vs filtration.

Response: Comment incorporated. The Expert Committee determined to provide flexibility to use either centrifugation or suitable filter.

Comment Summary #17: The commenter recommended including a Sample stock solution under Assay because large volume flasks are needed for higher tablet strengths.

Response: Comment incorporated. To be consistent with the sponsor's original documentation the Expert Committee determined to include a sample stock solution.

Comment Summary #18: The commenter indicated that there is back pressure and changing retention times while using the Assay procedure.

Response: Comment not incorporated. The Expert Committee determined that the proposed procedure is consistent with the sponsor's original documentation.

Monograph/Sections: Buprenorphine and Naloxone Sublingual Tablets
/Multiple Sections

Expert Committee: Chemical Medicine 2

No. of Commenters: 4

Comment Summary #1: The commenter indicated that the acceptance criteria for Assay are not consistent with the FDA approved specification.

Response: Comment not incorporated. The Expert Committee determined that the acceptance criteria are consistent with the FDA approved specifications in the sponsor's application and will consider future revisions upon receipt of supporting data.

Comment Summary #2: The commenter recommended tightening the acceptance criterion for unspecified degradation products in *Organic impurities*.

Response: Comment not incorporated. The Expert Committee determined that the acceptance criterion is consistent with the FDA approved specifications in the sponsor's application.

Comment Summary #3: The commenter recommended including the chemical names and structures for Naloxone degradation product 1, Naloxone degradation product 2, Naloxone degradation product 3, and Buprenorphine degradation product 1, specified by relative retention times in *Organic impurities*

Response: Comment not incorporated. The Expert Committee determined that the Naloxone degradation product 1, Naloxone degradation product 2, Naloxone degradation product 3, and Buprenorphine degradation product 1 are specified but unidentified impurities and the corresponding chemical names and structures are unknown based on the sponsor's approved application.

Comment Summary #4: The commenter indicated that the molecular weight of buprenorphine in Assay, *Dissolution and Organic Impurities* should be corrected from 469.55 to 467.65.

Response: Comment incorporated.

Comment Summary #5: The commenter indicated that dealkylbuprenorphine is a potential degradation product and recommends including it in total degradation products.

Response: Comment not incorporated. The proposed specifications are consistent with the FDA approved specifications in the sponsor's application and the Expert Committee will consider future revisions upon receipt of supporting data.

Comment Summary #6: The commenter requested adding their method and specifications to Organic Impurities test to accommodate the specifications of their drug product.

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

Comment Summary #7: The commenter indicated that there are placebo interferences and coelution of peaks related to impurities listed in the corresponding European Pharmacopoeia drug substance monographs.

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

Comment Summary #8: The commenter recommended that the acceptance criteria for specified and unspecified impurities should be based on the maximum daily dose.

Response: Comment not incorporated. The proposed specifications are consistent with the FDA approved specifications in the sponsor's application and the Expert Committee will consider future revisions upon receipt of supporting data.

Monograph/Sections: Carbidopa and Levodopa Tablets/ Multiple Sections

Expert Committee: Chemical Medicines Monographs 4

No. of Commenters: 4

Comment Summary #1: The commenter requested adding an identification test which uses infrared spectroscopy.

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

Comment Summary #2: The commenter requested tightening the acceptance criteria in the Assay for consistency with what has been approved.

Response: Comment not incorporated. The acceptance criteria in the monograph are consistent with an approved drug product.

Comment Summary #3: The commenter requested revising the acceptance criteria within the test for *Organic Impurities* for dihydroxybenzaldehyde, dihydroxyphenylacetone, levodopa related compound A, methyldopa, and Total degradation products for consistency with what has been approved.

Response: Comment incorporated as follows. Dihydroxybenzaldehyde, dihydroxyphenylacetone, and levodopa related compound A are identified as process impurities. The acceptance criterion for Total degradation products is widened for consistency with what has been approved. The acceptance criterion for methyldopa is retained because it is consistent with an approved drug product.

Expert Committee-initiated Change #1: In the test for *Organic Impurities*, the references to dihydroxybenzaldehyde, dihydroxyphenylacetone, and levodopa related compound A are removed from the calculations, and the statements identifying which compounds are associated with carbidopa or levodopa are removed because they are no longer needed.

Expert Committee-initiated Change #2: In the test for *Organic Impurities*, the following statements were replaced "disregard peaks less than 0.1% of carbidopa" and "disregard peaks less than 0.05% of levodopa" with "the reporting thresholds are 0.1% and 0.05% for peaks associated with carbidopa and levodopa, respectively", to make it consistent with the ICH Q3B terminology.

Monograph/Section(s): Cefaclor/Organic Impurities

Expert Committee: Chemical Medicines 1

No. of Commenters: 1

Comment Summary #1: The commenter recommended including specified impurities in the test for *Organic Impurities*.

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

Monograph/Section(s): Cefaclor Extended Release Tablets/Organic Impurities
Expert Committee: Chemical Medicines 1
No. of Commenters: 1
Comment Summary #1: The commenter recommended including specified impurities in the test for *Organic Impurities*.
Response: Comment not incorporated. The Expert Committee will consider a future revision to this monograph upon receipt of supporting data.

Monograph/Section(s): Cefaclor for Oral Suspension/Multiple Sections
Expert Committee: Chemical Medicines 1
No. of Commenters: 1
Comment Summary #1: The commenter recommended adding a test for *Dissolution*.
Response: Comment not incorporated. The Expert Committee will consider future revisions upon receipt of supporting data.
***Comment Summary #2:** The commenter recommended adding “controlled room temperature” as the storage temperature condition under *Packaging and Storage*.
Response: Comment not incorporated. The Expert Committee will consider future revisions upon receipt of supporting data.

Monograph/Section(s): Cetyl Esters Wax/Multiple Sections
Expert Committee(s): Excipients Monographs 1
No. of Commenters: 1
Comment Summary #1: In the test for *Total Fatty Esters and Cetyl Palmitate* under the Assay, the commenter recommended adding a C26 ester. This is a component that might be expected in some of the products that conform to this monograph. The commenter provided the data in support of the recommendations.
Response: Comment incorporated. In the test for *Total fatty Esters and Cetyl Palmitate*, add the text “Fatty esters with carbon chain length of carbon number 26 with Relative Retention Times of 0.72” in Table 2. In the *Suitability requirements*, add “Reference solution D” in the *Resolution*. In the section of *Analysis*, add “fatty esters with carbon chain length of carbon number 26” after “Calculate the percentage of each individual group of fatty esters” and before “fatty esters with carbon chain length of carbon number 28”. In the definition of r_U , add “fatty esters with carbon chain length of carbon number 26” after “peak area of each individual group of fatty ester” and before “fatty ester with carbon chain length of carbon number 28”.
Comment Summary #2: In the Labeling, the commenter recommended adding “fatty esters with carbon chain length of carbon number 26” after “Label to indicate the percentages of” and before “fatty esters with carbon chain length of carbon number 28”.
Response: Comment incorporated.

Monograph/Section(s): Conjugated Linoleic Acids-Free Fatty Acids
Expert Committee: Non-Botanical Dietary Supplements
No. of Commenters: 3

Definition:

Comment Summary #1: The commenter suggested increasing the lower limit content of conjugated linoleic acids from NLT 78% to NLT 78.5%.

Response: Comment not incorporated. Major manufacturers of the Conjugated Linoleic Acids-Free Fatty Acids would be locked out if the specification is changed from NLT 78% to NLT 78.5%.

Comment Summary #2: The commenter suggested removing the upper limit of NMT 84% for the conjugated linoleic acids content.

Response: Comment incorporated.

Comment Summary #3: The commenter suggested removing the ratio 1:1 requirement for the conjugated linoleic isomers in the Definition section.

Response: Comment not incorporated. The ratio 1:1 is a defined characteristic of the conjugated linoleic acids products and therefore it should be stated in the Definition of the monograph.

Impurities:

Comment Summary #4: The commenter suggested adding a note “if appropriate to the manufacturing process” to the residual solvent test for hexane.

Response: Comment not incorporated. The note is not needed as the acceptance criteria for hexane and methanol are covered by the General Chapter <467> and General Notices.

Comment Summary #5: The commenter suggested removing the test for *Elemental Impurities - Procedure <233>* because beginning Jan 1, 2018, dietary ingredient monographs won't require this test anymore.

Response: Comment incorporated.

Specific Tests:

Comment Summary #6: The commenter suggested adding the test for *Water content* to the proposed monograph.

Response: Comment incorporated.

Comment Summary #7: The commenter suggested adding the test for *Unaponifiable matter* to the monograph.

Response: Comment not incorporated. This test has no value-added to the standard.

Comment Summary #8: The commenter suggested changing the requirement for the peroxide value from NMT 10 to NMT 5.

Response: Comment incorporated.

Comment Summary #9: The commenter suggested replacing the limits for individual conjugated linoleic acid isomers in Table 1 with a limit for total conjugated linoleic isomers of NLT 74.7%.

Response: Comment not incorporated. Setting the required limits for individual active conjugated linoleic acid isomers would reflect the 1:1 ratio stated in the Definition.

Comment Summary #10: The commenter suggested increasing the limit of trans trans isomer from NMT 2.0% to NMT 3% in Table 1.

Response: Comment not incorporated. Because trans trans isomer is an impurity, keeping its limit of NMT 2.0% is essential to the quality of the conjugated linoleic acids products.

Monograph/Sections: Cyproheptadine Hydrochloride Oral Solution/Organic impurities

Expert Committee: Chemical Medicine 5

No. of Commenters: 1

***Comment Summary #1:** The commenter indicated that the Acceptance criterion for *Total degradation products* is different from what has been approved by the FDA.

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

Monograph/Section(s): Dexamethasone Sodium Phosphate Compounded Injection

Expert Committee(s): Compounding

No. of Commenters: 1

Comment Summary #1: The commenter suggested adding storage temperature in the *Packaging and Storage* section of the monograph.

Response: Comment incorporated.

Comment Summary #2: The commenter suggested using the term “single-dose container” instead of “containers for single use in one patient only” in the *Packaging and Storage* section of the monograph to clarify that the compounded preparation is intended as a single-dose as it does not contain any preservatives.

Response: Comment incorporated.

Comment Summary #3: The commenter requested that light-resistant containers be required for storage of the compounded preparation.

Response: Comment incorporated.

Comment Summary #4: The commenter requested that the *Labeling* section requires protection from light.

Response: Comment incorporated.

Expert Committee-initiated Change #1: Instructions for preparing *Solution A* was clarified to indicate that 6N potassium hydroxide is used to adjust the pH.

Monograph/Sections: Dexmedetomidine Injection /Multiple sections

Expert Committee: Chemical Medicines 2

No. of Commenters: 3

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

Response: Comments not incorporated. The Expert Committee determined that the specified limit for total impurities is consistent with the sponsor’s FDA approved limits.

Comment Summary #2: The commenter indicated that the acceptance criterion for bacterial endotoxins is not consistent with the FDA approved limits.

Response: Comments incorporated. The Expert Committee determined that the acceptance criterion be widened from **NMT 0.70 USP Endotoxin Units/μg** to NMT 2.5 Eu/ug of dexmedetomidine free base to be consistent with the FDA approved limits.

Comment Summary #3: The commenter requested including the salt form in the monograph title.

Response: Comment not incorporated. The monograph title is consistent with the USP's salt nomenclature policy and as approved by the relevant Expert Committee.

Comment Summary #4: The commenter indicated that methyl paraben, used to prepare the system suitability solution under Organic Impurities, is not soluble in water and that it needs to be dissolved in methanol before dilution.

Response: Comments incorporated. The Expert Committee determined to include the Butyl Paraben Solution to be consistent with the sponsor's procedure.

Comment Summary #5: The commenter requested clarifying the Sample solution preparation under *Organic Impurities*, which states that any dilution of the drug product is not needed prior to use.

Response: Comments incorporated. The Expert Committee determined it necessary to restate the sample solution preparation to indicate that the Injection is used as is without dilution.

Monograph/Section(s): Doxycycline for Oral Suspension/Multiple Sections

Expert Committee: Chemical Medicines 1

No. of Commenters: 2

Comment Summary #1: The commenter recommended including their specified unidentified impurity to the test for *Organic Impurities*.

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

Comment Summary #2: To be consistent with the validated procedure, the commenter recommended correcting the preparation of Solution A in the *Dissolution* test to use 75 g of tert-butyl alcohol rather than 0.75 g.

Response: Comment incorporated.

Comment summary #3: The commenter recommended updating the acceptance criteria for 4-Epidoxycycline and total Impurities to be consistent with FDA approved limits.

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

Monograph/Section(s): *Echinacea* Species Powder Capsules

Expert Committee: Botanical Dietary Supplements and Herbal Medicines

No. of Commenters: 1

Comment Summary #1: The commenter proposed to revise the *Definition* to eliminate cross reference to the related ingredients monographs and be consistent with the *Echinacea* Species Dry Extract Capsules and Tablets monographs.

Response: Comment incorporated.

Comment Summary #2: The commenter proposed to calculate the Assay value of cynarin against a suitable grade of cynarin (1,3-di-O-caffeoylquinic acid) instead of using the conversion factor of 0.729 for cynarin.

Response: Comment incorporated.

Monograph/Sections: Epoetin/Assay
Expert committee: Biologics Monographs 2
No. of Commenters: 1

Comment summary #1: The commenter noted that specific activity should be expressed as Units/mass instead of Units/absorbance.

Response: Comment not incorporated. As expressed, specific activity is consistent with regulatory filing for US licensed product.

Epoetin/Identification B-Peptide mapping

Comment Summary #2: The commenter noted that Lys-C reagent from different suppliers may have different specific activities with impact on digest efficiency.

Response: Comment incorporated. A note will be added regarding appropriate source of Lys-C with specific activity.

Comment Summary #3: The commenter asked if the system suitability window could be narrowed. The current requirement of 1.2 minute retention time is a large window.

Response: Comment not incorporated. The test is consistent with method validation provided by US approved license holder.

Comment Summary #4: The commenter noted that the system suitability criterion for retention time is difficult to interpret.

Response: Comment incorporated. Additional text was added for clarification.

Epoetin/Specific Test –Isoform distribution

Comment Summary #5: The commenter noted that in the acceptance criteria, Isoforms 10 + 11 NLT 52% is not consistent with the other isoform requirements.

Response: Comment incorporated. The acceptance criterion was corrected to NMT 52%.

Epoetin/Impurities – Limit of high molecular weight proteins

Comment Summary #6: The commenter observed that the specification of 0.1% for aggregates and dimer is too low.

Response: Comment not incorporated. The proposed specification is consistent with the regulatory filing for US licensed product.

Monograph/Section(s): Ethyl Acetate /Multiple Sections
Expert Committee(s): Excipients Monographs 1
No. of Commenters: 1

Comment Summary #1: The commenter recommended harmonizing the chromatographic method used in the Assay and *Chromatographic Purity* tests with the gas chromatographic method specified for ethyl acetate within the current edition Food Chemicals Codex (FCC) (M-1b).

Response: Comment not incorporated. The method specified in FCC is generic and does not address any impurities in Ethyl Acetate.

Comment Summary #2: The commenter recommended changing the acceptance criteria for *Relative standard deviation* in the Assay from the value of NMT 0.7% proposed in *PF 42(5)* to NMT 2.0%, which is more appropriate for a chromatographic method.

Response: Comment incorporated.

Comment Summary #3: In the *Chromatographic purity* test, the commenter recommended injecting a neat sample instead of a *Sample solution*, stating that the dilution of a sample will negatively impact the accuracy of impurity assay quantifications.

Response: Comment not incorporated. The method development and validation results showed that the proposed procedure provides sufficient sensitivity and accuracy for determining content of different impurities in Ethyl Acetate.

Comment Summary #4: The commenter was concerned by the length of the run time in the proposed chromatographic method and stated that this would significantly increase the time required for analysis and batch release for pharmaceutical customers.

Response: Comment not incorporated. The Expert Committee acknowledged that the run time in the commenter's method was shorter than in the proposed method.

However the proposed method is also capable of separating and detecting methyl compounds. The implementation of the new chromatographic method eliminates the manual wet chemistry test for Limit of Methyl Compounds. Additionally, the proposed method was developed to analyze Ethyl Acetate produced by other manufacturers.

Comment Summary #5: The commenter expressed concerns that implementation of the proposed method, that calls for the use of methyl ethyl ketone (MEK) and N,N-dimethylacetamide, would introduce safety risks to the employees conducting the test.

Response: Comment not incorporated. The Expert Committee evaluated information listed in MSDS and other sources to determine whether or not extra measures were required to handle these compounds in addition to normal safety requirements to working with solvents, and concluded that when MEK and N,N- dimethylacetamide are handled using appropriate personal protective equipment and hoods, they should not introduce safety risks greater than the safety risk of exposure to ethyl acetate.

Comment Summary #6: The commenter recommended implementing their in-house gas chromatographic method.

Response: Comment not incorporated. The recommended method was developed specifically for Ethyl Acetate produced by the commenter and has not been shown to address impurities in Ethyl Acetate produced by other manufacturing processes.

Expert Committee-initiated Change #1: Because in Comment Summary #2, the recommendation to change the acceptance criteria for *Relative standard deviation* in the Assay from NMT 0.7% to NMT 2.0% was incorporated, the acceptance criteria for the Assay was also changed to NLT 98.0% and NMT 102.0%.

Monograph/Sections: Fluticasone Propionate Nasal Spray/Multiple Sections

Expert Committee: Chemical Medicines 4

No. of Commenters: 1

Comment Summary #1: The commenter requested the reinstatement of pH adjustment to 3.5 ± 0.1 .

Response: Comment not incorporated because the available supporting data supports the use of buffer pH in the range of 3.3-3.7, which corresponds to a pH range 3.5 ± 0.2 consistent with the general chapter <621> Chromatography.

Monograph/Section(s): Gelatin/Identification
Expert Committee(s): Excipients Monographs 2
No. of Commenters: 4

Comment Summary #1: The commenter recommended not including the Identification (ID) by infrared (IR) test in the monograph because of the expensive instrumentation such as infrared spectroscopy and the burden of testing, although the commenter understands the new ID by IR test could further strengthen the identification of gelatin. In addition, since melamine adulteration above levels of 1% would negatively alter the physical characteristics of gelatin and would be cost-prohibitive, they don't believe the IR test needs to be included in the monograph to prevent melamine contamination/adulteration.

Response: Comment not incorporated. The Expert Committee recommended including the new ID by IR test in the NF monograph because the IR test is more specific compared to existing ID tests in the current Gelatin monograph and it would strengthen the compendial standard for gelatin. Generally, the instrumentation of infrared spectroscopy is widely available in the pharmaceutical industry and the detection of melamine contamination/adulteration using IR has been demonstrated by both USP and FDA lab results. This update is based on FDA's request and comments.

Comment Summary #2: The commenter has the same comments as Commenter #1.

Response: Comment not incorporated. See above response to Commenter #1.

Comment Summary #3: The commenter noted that the proposed changes of including a new ID by IR test in the identification section are not consistent with the current harmonized standard in PDG. In addition, the proposed changes did not go through the official PDG process.

Response: Comment not incorporated. The Expert Committee recommended including the IR test for ID in the monograph with the above described reasons to Commenter #1. This will be a local requirement in USP, which has been gone through the regular revision process in USP, not the harmonization process in PDG.

Comment Summary #4: The commenter commented on another existing ID test for distinguishing gelling grade from non-gelling grade of Gelatin. They recommended changing the temperature from 0°C to a wider range in order to help avoid unclear results.

Response: Comment will be incorporated. The Expert Committee recommended publishing a Stage 4 proposal for public comments on this change. It will be revised through PDG harmonization.

Monograph/Section: Glimepiride Tablets /Organic Impurities
Expert Committee: Chemical Medicines 3

Expert Committee-initiated Change: The Note, "Disregard any peak less than 0.1%" in the test for Organic Impurities was replaced with "Reporting threshold for impurities is 0.1%" to make it consistent with the current *USP style*.

Monograph/Section: Granisetron/Organic Impurities

Expert Committee: Chemical Medicines 3

No. of Commenters: 1

Comment Summary #1: The commenter recommended revising the acceptance criterion for 9-desmethyl granisetron impurity to be consistent with FDA approved limits.

Response: Comment incorporated. The acceptance criterion was widened from NMT 0.15% to NMT 0.2%, based on the FDA-approved specifications.

Comment Summary #2: The commenter recommended re-evaluating the relative response factor for the 1-desmethyl granisetron impurity (granisetron related compound B).

Response: Comment incorporated. The relative response factor is revised from 0.59 to 1.0 based on the supporting information.

Expert Committee-initiated Change: The term “reporting level for impurities” in the test for Organic Impurities was replaced with “reporting threshold for impurities” to make it consistent with current *USP style*.

Monograph/Sections : Hydroxyzine Pamoate/ Multiple Sections

Expert Committee: Chemical Medicines 4

No. of Commenters: 2

Comment Summary #1: The commenters requested revising the acceptance criteria within the test for *Organic Impurities* for: declozine, hydroxyzine related compound A, and total impurities with what has been approved.

Response: Comment incorporated.

Comment Summary #2: The commenter requested delaying the Expert Committee’s consideration of the proposal to allow more time for evaluation.

Response: Comment not incorporated. The Expert Committee discussed and balloted the proposal a year after the close of the PF public comment period.

Expert Committee-initiated Change #1: The reference to “chromatographic acetonitrile” in the *Assay* was replaced with a reference to “acetonitrile” because the proposal to add an entry to the reagent section for “chromatographic acetonitrile” has been cancelled.

Expert Committee-initiated Change #2: The relative retention time for 4-chlorobenzophenone is provided in the *System suitability* section of the *Assay* and test for *Organic Impurities*.

Expert Committee-initiated Change #3: In the test for *Organic Impurities*, references to 4-chlorobenzophenone are removed from the Relative standard deviation requirement, the calculations, and from Table 2.

Expert Committee-initiated Change #4: To make the test for *Organic Impurities* consistent with the ICH Q3B terminology, the following statement was replaced: “Disregard peaks less than 0.05%” with the statement “the reporting threshold is 0.05%”.

Monograph/Sections: Hydroxyzine Pamoate Capsules/ Multiple Sections
Expert Committee: Chemical Medicines 4
No. of Commenters: 1

Comment Summary #1: The commenter requested that the acceptance criteria for hydroxyzine related compound A and total degradation products be revised to make them consistent with their approved specifications.

Response: Comment incorporated.

Expert Committee-initiated Change #1: The references to “chromatographic acetonitrile” in the *Assay* and to “chromatographic methanol” in the test for *Dissolution* were replaced with references to “acetonitrile” and “methanol”, respectively because the proposals to add entries to the reagent section for “chromatographic acetonitrile” and “chromatographic methanol” have been cancelled.

Expert Committee-initiated Change #2: The relative retention times for declozine and 4-chlorobenzophenone are provided in the *System suitability* sections of the *Assay* and test for *Organic Impurities*.

Expert Committee-initiated Change #3: In the test for *Organic Impurities*, the reference to 4-chlorobenzophenone is removed from the Relative standard deviation requirement; the references to declozine and 4-chlorobenzophenone are removed from the calculations and from Table 2.

Expert Committee-initiated Change #4: In the test for *Organic Impurities*, the statement “Disregard peaks less than 0.05%” was replaced with the statement “the reporting threshold is 0.05%”, to make it consistent with the ICH Q3B terminology.

Monograph/Section: Indomethacin Capsules/Impurities
Expert Committee: Chemical Medicine 2
No. of Commenters: 1

Comment Summary #1: The commenter indicated that the acceptance criteria for indomethacin related compound A, indomethacin related compound B, unspecified impurity, and total impurities are not consistent with the FDA approved specification.

Response: Comment not incorporated. The Expert Committee determined that the acceptance criteria are consistent with the FDA approved specifications in the sponsor’s application and will consider future revisions if necessary.

Expert Committee-Initiated Change #1: The word “impurity” or “impurities” in *Organic Impurities* was replaced with “degradation product” or “degradation products” to be consistent with ICH terminology and the sponsor’s approved specifications.

Monograph/Sections: Ipratropium Bromide and Albuterol Sulfate Inhalation Solution / Multiple
Expert Committee: Chemical Medicines 4
No. of Commenters: 2

Comment Summary # 1: The commenter indicated that the statement in the Definition –“a chelating agent” is not needed to achieve suitable stability of the drug product.

Response: Comment not incorporated as the definition is consistent with what has been approved by the FDA.

Comment Summary # 2: The commenter indicated that the acceptance criterion of Levalbuterol Related Compound D should be tightened from NMT 0.1% to NM T 0.10%.

Response: Comment not incorporated as the limit of Levalbuterol related compound D is consistent with what has been approved by the FDA.

Comment Summary # 3: The commenter indicated that the pH range is not consistent with what has been approved by FDA.

Response: Comment incorporated. The pH range was widened from 3.5-4.5 to 3.4-4.5 to be consistent with what has been approved by FDA.

Comment Summary # 4: The commenter indicated that the limit for any individual unspecified degradation product is inconsistent with what has been approved by the FDA.

Response: Comment not incorporated. The limit of any individual unspecified degradation product is consistent with the sponsor's approved specifications.

Monograph/Section(s): Itraconazole/Multiple¹
Expert Committee: Chemical Medicines Monographs 1
No. of Commenters: 1

Comment summary #1: The commenter recommended harmonizing the mobile phase preparation in the Assay and test for Organic impurities.

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

Comment summary #2: The commenter recommended including the system suitability solution in the Assay to ensure separation of closely eluting impurity peaks.

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

Comment summary #3: The commenter recommended revising the relative standard deviation from NMT 2.0% to NMT 0.73% as per general chapter <621> in the Assay.

Response: Comment not incorporated. The Expert committee determined that the suitability requirements in the Assay are consistent with the validation data.

Monograph/Section: Mefenamic Acid/Impurities
Expert Committee: Chemical Medicine Monographs 2
No. of Commenters: 1

Comment Summary #1: The commenter recommended revising the terminology under *Acceptance criteria*, from "Individual impurity" to "Any unspecified impurity".

Response: Comment not incorporated. The Expert Committee determined that the terminology of "individual impurity" is consistent with the intended use and includes both specified and unspecified impurities.

Monograph/Section(s): Menthol/Related compounds
Expert Committee: Botanical Dietary Supplements and Herbal Medicines
No. of Commenters: 3

¹ Commentary added November 10, 2017 based on omission from the text posted on November 1, 2017

Comment Summary #1 & 2: The commenter indicated there is no retention time (RRT) for isomenthol as listed.

Response: Relative retention time (RRT = 1.08) for isomenthol has been included.

Expert Committee-initiated Change #1: The “Tailing factor” in System suitability has been removed.

Monograph/Sections: Metoprolol Succinate Extended-Release
Tablets/Organic Impurities

Expert Committee: Chemical Medicines 2

No. of Commenters: 4

Comment Summary #1: The commenter requested to provide their in-house procedure in the compendium as an alternate procedure to the currently proposed methods.

Response: Comment not incorporated. The Expert Committee determined that the proposed procedure is adequate to monitor the quality of the drug product. A future revision will be considered upon receipt of supporting data.

Comment Summary #2: The commenter requested to adopt their organic impurity method for the USP monograph.

Response: Comment not incorporated. The Expert Committee determined that the proposed procedure is suitable to monitor the quality of all the FDA approved drug product requirements.

Comment Summary #3: The commenter requested revising the acceptance criteria for the *Organic impurities* in Table 6 as they are not consistent with their ANDA pending FDA approval.

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

Comment Summary #4: The commenter requested including the specific grade of sodium dodecyl sulfate, the reagent used in the mobile phase as there is a variation in the retention time of the metoprolol when different grades of sodium dodecyl sulfate are used.

Response: Comment not incorporated. The Expert Committee determined that the proposal describes the relative retention times and is consistent with the current USP practice.

Monograph/Section(s): Morphine Sulfate Compounded Injection

Expert Committee(s): Compounding

No. of Commenters: 1

Comment Summary #1: The commenter suggested including labeling statements to indicate that the compounded preparation is intended to be administered through a pump.

Response: Comment not incorporated. Route of administration is out of the scope of the monograph and <797> *Pharmaceutical Compounding – Sterile Preparations* which is referenced in the monograph. The Compounding Expert Committee noted that limitations in the space on labeling would prohibit such requirements.

Monograph/Section(s): Moxifloxacin Ophthalmic Solution/Organic impurities

Expert Committee: Chemical Medicines 1

No. of Commenters: 1

Comment Summary #1: The commenter requested including run time to control the appearance of late eluting impurities in the test for *Organic impurities – Late eluting related compounds*.

Response: Comment incorporated. The run time of NLT 5 times the retention time of moxifloxacin peak is added.

Monograph/Section: Mycophenolic Acid Delayed-Release Tablets/ Multiple Sections

Expert Committee: Chemical Medicines 3

No. of Commenters: 2

Comment Summary #1: The commenters recommended widening the acceptance criteria for mycophenolate mofetil related compound B, ethyl ester of mycophenolate, and total impurities in the test for *Organic Impurities* from NMT 0.1%, 0.1% and 0.4% to NMT 0.2%, 0.2% and 1.0% respectively, based on the FDA approved limits.

Response: Comment incorporated.

Expert Committee-initiated Change #1: Statements were added to the *Acid stage* and *Buffer stage* in *Dissolution* to clarify that one of the two analytical procedures (spectrophotometric or chromatographic) may be used.

Expert Committee-initiated Change #2: “Disregard any impurity peak less than 0.05%” is replaced with “The reporting threshold is 0.05%” in the test for *Organic Impurities* to be consistent with current *USP style*.

Expert Committee-initiated Change #3: The footnote (a) in Table 2 is updated to clarify that process impurities are controlled in the drug substance and they are listed in the table for identification only.

Expert Committee-initiated Change #4: The chemical name for USP Mycophenolate Mofetil Related Compound B RS is corrected in *USP Reference Standards <11>*.

Monograph/Sections: Nilutamide/Multiple

Expert Committee: Chemical Medicines 5

No. of Commenters: 2

Comment Summary #1: In the test for Assay, the commenter suggested changing the flow rate from 1.5 mL/min to 1.3 mL/min, and the Run time from NLT 5 times to NLT 3 times the retention time of Nilutamide.

Response: Comment not incorporated. Flow rate changes are covered in general chapter <621>. The proposed run time ensures all impurities are eluted from the chromatographic column.

Comment Summary #2: In the test for Organic impurities, the commenter suggested changing the concentration of USP Nilutamide RS and USP Flutamide Related Compound A RS from 0.04 mg/mL to 0.05 mg/mL in the System suitability solution.

Response: Comment not incorporated. The proposed concentration for USP Nilutamide RS and USP Flutamide Related Compound A RS has no impact on the method performance.

Comment Summary #3: In the test for Organic impurities, the commenter requested the Total Impurities limit be increased from NMT 0.3% to NMT 0.5%.

Response: Comment incorporated.

Comment Summary #4: The commenter requested “Store at controlled room temperature” be added under *Packaging and Storage*.

Response: Comment incorporated.

Monograph/Section(s): Potassium Phosphates Compounded Injection

Expert Committee(s): Compounding

No. of Commenters: 2

Comment Summary #1: The commenter suggested adding storage temperature in the *Packaging and Storage* section of the monograph.

Response: Comment incorporated

Comment Summary #2: The commenter suggested using the term “single-dose container” instead of “containers for single use in one patient only” in the *Packaging and Storage* section of the monograph to clarify that the compounded preparation is intended as a single-dose as it does not contain any preservatives.

Response: Comment incorporated.

Comment Summary #3: The commenter suggested adding labeling requirements that reflect those in the monograph for *Potassium Phosphates Injections* to indicate that the compounded preparation should not be used for direct injection or must be diluted before use.

Response: Comment not incorporated. The Compounding Expert Committee indicated that the labeling statement is out of scope of the monograph and limitations on the space on labeling would prohibit such requirements. They also did not want to imply that monographs for compounded preparations were equivalent to the product with having the same labeling requirements in the monographs.

Comment Summary #4: The commenter suggested adding a statement in the *Definition* that the preparation contains no bacteriostat or other preservative.

Response: Comment incorporated

Comment Summary #5: The commenter suggested that the column packing is IonPac AS19 L103.

Response: Comment incorporated

Monograph/Sections: Simvastatin Tablets/Organic Impurities²

Expert Committee: Chemical Medicines Monographs 2

No. of Commenters: 1

Comment Summary #1: The commenter requested clarifying that the Cs in the definition list under calculations refer to the tenivastatin.

Response: Comment not incorporated. The Expert committee determined that the description of the Cs as written is suitable for the intended purpose.

Monograph/Section(s): Sodium Bicarbonate Compounded Injection

Expert Committee(s): Compounding

No. of Commenters: 1

Comment Summary #1: The commenter suggested using the term “single-dose container” instead of “containers for single use in one patient only” in the *Packaging and*

² Commentary added November 13, 2017 based on omission from the text posted on November 1, 2017

Storage section of the monograph to clarify that the compounded preparation is intended as a single-dose as it does not contain any preservatives.

Response: Comment incorporated.

Comment Summary #2: The commenter suggested adding labeling requirements reflecting the requirements in the monograph for *Sodium Bicarbonate Injection* to indicate that the compounded preparation should not be used for direct injection or must be diluted before use.

Response: Comment not incorporated. The Compounding Expert Committee indicated that the labeling statement is out of scope of the monograph and limitations on the space on labeling would prohibit such requirements. They also did not want to imply that monographs for compounded preparations were equivalent to the product with having the same labeling requirements in the monographs.

Expert Committee-initiated Change #1: The Committee suggested adding a statement in the *Definition* to state that the preparation contains no bacteriostat or other preservative.

Monograph/Section(s): Sodium Phosphates Compounded Injection

Expert Committee(s): Compounding

No. of Commenters: 2

Comment Summary #1: The commenter suggested adding storage temperature in the *Packaging and Storage* section of the monograph.

Response: Comment incorporated.

Comment Summary #2: The commenter suggested using the term “single-dose container” instead of “containers for single use in one patient only” in the *Packaging and Storage* section of the monograph to clarify that the compounded preparation is intended as a single-dose as it does not contain any preservatives.

Response: Comment incorporated.

Comment Summary #3: The commenter suggested adding labeling requirements reflecting the requirements in the monograph for *Sodium Phosphates Injections* to indicate that the compounded preparation should not be used for direct injection or must be diluted before use.

Response: Comment not incorporated. The Compounding Expert Committee felt that the labeling statement is out of scope of the monograph and limitations on the space on labeling would prohibit such requirements. They also did not want to imply that monographs for compounded preparations were equivalent to the product with having the same labeling requirements in the monographs.

Comment Summary #4: The commenter suggested that the column packing is IonPac AS19 L103.

Response: Incorporated.

Expert Committee-initiated Change #1: The Committee corrected the *Standard solution* in the assay for phosphate to use USP Dibasic Potassium Phosphate.

Monograph/Section(s): Tangerine Peel/Multiple Sections

Expert Committee: Botanical Dietary Supplements and Herbal Medicines

No. of Commenters: 4

Comment Summary #1: The commenter indicated that the material is the rind or peel not the complete pericarp.

Response: In monograph definition, “dried ripe pericarp” was changed into “dried exocarp and mesocarp of the ripe fruit”; also added “partly freed from the white spongy tissue of the mesocarp” to be consistent with the monograph in Europe Pharmacopoeia.

Comment Summary #2: The commenter noted that USP Lab project test results showed that on the HPTLC plate, Naringin and Narirutin co-eluted as having exactly the same R_F and same dark green bands. The distinct lighter green band above hesperidin in the *Citrus Reticulata* sample closely matched the R_F of Naringin and Narirutin which made the test inconclusive of the presence or absence of Naringin. The commenter also noted that another discrepancy is the missing faint band between hesperidin and the blue band above.

Response: The monograph was revised by deleting "There is not another dark green band due to naringin above the hesperidin band (distinct from the *Citrus wilsonii* Fruit and *Citrus maxima* Pericarp, these two plants do not contain hesperidin while containing naringin)" and rewording colors of the bands.

Comment Summary #3: The commenter expressed confusion by the following sentence in the HPLC identification acceptance criteria, the sentence of "The *Sample solution* does not exhibit a principle peak due to naringin at a relative retention time of about 0.9 relative to hesperidin (a distinction from *Citrus maxima* Peel and *Citrus wilsonii* Fruit)."

Response: In the HPLC identification part, the description was changed as “No other peak between narirutin and tangeretin is more intense than the peak corresponding to didymin (distinction from other *Citrus* species; *Citrus maxima* Peel and *Citrus wilsonii* Fruit show a principal peak for naringin).” In the HPLC assay part, relative retention time of 0.90 and content ratio of <0.02 for naringin were added in *Table 2*.

Comment Summary #4: The commenter indicated that detecting wavelengths for assay were clearly displayed as Detector: UV 283 nm (0–17 min) and 330 nm (17–28 min). The commenter felt that the wavelengths listed in *Table 1* were confusing and should be deleted.

Response: Comment incorporated.

Monograph/Section(s): Tangerine Peel Dry Extract/Multiple Sections
Expert Committee: Botanical Dietary Supplements and Herbal Medicines
No. of Commenters: 4

Comment Summary #1: The commenter indicated that the material is the rind or peel not the complete pericarp.

Response: In monograph definition, “dried ripe pericarp” was changed into “dried exocarp and mesocarp of the ripe fruit”; also added “partly freed from the white spongy tissue of the mesocarp” to be consistent with the monograph in Europe Pharmacopoeia.

Comment Summary #2: A commenter noted that USP Lab project test results showed that on the HPTLC plate, Naringin and Narirutin co-eluted as having exactly the same R_F and same dark green bands. The distinct lighter green band above hesperidin in the *Citrus Reticulata* sample closely matched the R_F of Naringin and Narirutin which made the test inconclusive of the presence or absence of Naringin. The commenter also noted that the faint band between hesperiding and the blue band above is missing.

Response: The monograph revised by deleting "There is not another dark green band due to naringin above the hesperidin band (distinct from the *Citrus wilsonii* Fruit and *Citrus maxima* Pericarp, these two plants do not contain hesperidin while containing naringin)" and rewording colors of the bands.

Comment Summary #3: The commenter expressed confusion by the following sentence in HPLC identification acceptance criteria: "The *Sample solution* does not exhibit a principle peak due to naringin at a relative retention time of about 0.9 relative to hesperidin (a distinction from *Citrus maxima* Peel and *Citrus wilsonii* Fruit)."

Response: In HPLC identification part, the description was changed as "No other peak between narirutin and tangeretin is more intense than the peak corresponding to didymin (distinction from other *Citrus* species; *Citrus maxima* Peel and *Citrus wilsonii* Fruit show a principal peak for naringin)." In HPLC assay part, relative retention time of 0.90 for naringin was added in *Table 2*.

Comment Summary #4: The commenter indicated that detecting wavelengths for assay were clearly displayed as Detector: UV 283 nm (0–17 min) and 330 nm (17–28 min). The commenter also noted that the wavelengths listed in *Table 1* were confusing and should be deleted.

Response: Comment incorporated

Monograph/Section(s):	Tangerine Peel Powder/Multiple Sections
Expert Committee:	Botanical Dietary Supplements and Herbal Medicines
No. of Commenters:	4

Comment Summary #1: The commenter indicated that the material is the rind or peel not the complete pericarp.

Response: In monograph definition, "dried ripe pericarp" was changed into "dried exocarp and mesocarp of the ripe fruit"; also added "partly freed from the white spongy tissue of the mesocarp" to be consistent with the monograph in Europe Pharmacopoeia.

Comment Summary #2: The commenter noted that USP Lab project test results showed that on the HPTLC plate, Naringin and Narirutin co-eluted as having exactly the same R_F and same dark green bands. The commenter also observed that the distinct lighter green band above hesperidin in the *Citrus Reticulata* sample closely matched the R_F of Naringin and Narirutin, which made the test inconclusive of the presence or absence of Naringin. Another discrepancy is the missing faint band between hesperidin and the blue band above.

Response: The monograph revised by deleting "There is not another dark green band due to naringin above the hesperidin band (distinct from the *Citrus wilsonii* Fruit and *Citrus maxima* Pericarp, these two plants do not contain hesperidin while containing naringin)" and rewording colors of the bands.

Comment Summary #3: The commenter expressed confusion by the following sentence in HPLC identification acceptance criteria: "The *Sample solution* does not exhibit a principle peak due to naringin at a relative retention time of about 0.9 relative to hesperidin (a distinction from *Citrus maxima* Peel and *Citrus wilsonii* Fruit)."

Response: In HPLC identification part, the description was changed to "No other peak between narirutin and tangeretin is more intense than the peak corresponding to didymin (distinction from other *Citrus* species; *Citrus maxima* Peel and *Citrus wilsonii* Fruit show a principal peak for naringin)." In HPLC assay part, relative retention

time of 0.90 and content ratio of <0.02 for naringin were added in *Table 2*. **Comment Summary #4:** The commenter indicated that detecting wavelengths for assay were clearly displayed as Detector: UV 283 nm (0–17 min) and 330 nm (17–28 min). The commenter also noted that the wavelengths listed in *Table 1* were confusing and should be deleted.

Response: Comment incorporated

Monograph/Sections: Telmisartan and Amlodipine Tablets/Multiple sections

Expert Committee: Chemical Medicine 2

No. of Commenters: 1

Comment #1: The commenter requested revising the relative response factor for “Amlodipine mannitol adduct” to be consistent with the validation data.

Response: Comments not incorporated. The Expert Committee will consider future revisions upon receipt of the supporting data.

Comment #2: The commenter requested including other process related impurities in the table 2 under *Organic Impurities*.

Response: Comments not incorporated. The Expert Committee determined that future revisions may be considered upon receiving the supporting data.

Comment #3: The commenter requested deleting the resolution requirement from the organic impurities procedure because telmisartan and amlodipine are well separated.

Response: Comment incorporated.

Comment #4: The commenter requested revising the percent *Diluent* added initially to prepare the *Sample solution* under *Assay* from about 80% to about 60%.

Response: Comment not incorporated. The Expert Committee determined that the proposed text in the procedure adequately describes the sample preparation.

Monograph/Section: Temozolomide Capsules/Organic Impurities

Expert Committee: Chemical Medicines 3

Expert Committee-initiated Change #1: The term, “reporting level” is replaced with “reporting threshold” in the test for Organic Impurities to be consistent with current *USP style*.

Monograph/Section: Temozolomide for Injection/ Multiple Sections

Expert Committee: Chemical Medicines 3

No. of Commenters: 1

Comment Summary #1: The commenter recommended adding the pH test with associated acceptance criteria.

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

Expert Committee-initiated Change #1: The term, “reporting level” is replaced with “reporting threshold” in the test for Organic Impurities to be consistent with current *USP style*.

Monograph/Sections: Trandolapril Tablets

Expert Committee: Chemical Medicines 2

No. of Commenters: 1

Comment #1*: The commenter requested revising the acceptance criteria for any unspecified degradation product from NMT 0.2% to NMT 1.0% to be consistent with the FDA approved drug product.

Response: Comments incorporated.

Monograph/Section(s): Warfarin Sodium/Specific Tests

Expert Committee: Chemical Medicines 3

No. of Commenters: 1

Comment Summary #1: The commenter recommended changing the headspace vial size from 10mL to 20mL and adding the GC cycle time of 65 minutes based on their instrument capabilities in the test for *Isopropyl Alcohol Content*.

Response: Comment not incorporated. The Expert Committee determined that vial size and GC cycle time are instrument specific requirements and recommended deleting the headspace vial size of 10 mL.

Monograph/Sections: Zinc Oxide/Multiple sections

Expert Committee(s): Chemical Medicines 6

No. of Commenters: 1

Comment summary #1: The commenter recommended using the currently official Zinc Identification Tests - General <191> and not replacing with the proposed IC based procedure.

Response: Comment not incorporated. The Expert Committee determined that the proposed procedure is more specific than the currently official nonspecific identification test based on the General Chapter <191>.

Comment summary #2: The commenter recommended retaining the currently official titration based Assay as it is consistent with the *PharmEuropa* method and supports harmonization.

Response: Comment not incorporated. The Expert Committee determined that the proposed procedure is more specific than the currently official titration based procedure and is suitable as written.

Monograph/Sections: Zinc Oxide Powder/Multiple sections

Expert Committee(s): Chemical Medicines 6

No. of Commenters: 1

Comment summary #1*: The commenter recommended including an additional and specific *Identification test*

Response: Comment not incorporated. The Expert Committee will consider a future revision upon receiving the supporting documentation.

Comment summary #2*: The commenter recommended revising the acceptance criteria under the Assay and noted that the current zinc oxide drug substance monograph have much tighter limits than the proposed limits for Zinc oxide powder.

Response: Comment not incorporated. The Expert Committee determined that the proposed Assay limits are adequate for the drug product.

Monograph/Sections: Zolmitriptan Nasal Spray/ Multiple

Expert Committee: Chemical Medicines 4

No. of Commenters: 1

Comment Summary #1: The commenter requested the calculation formula for Delivered Dose Uniformity be revised to correctly reflect the percentage of the labeled amount of zolmitriptan in each does of Nasal Spray.

Response: Comment incorporated.

Comment Summary #2: The commenter requested the details for preparing the System suitability solution be added in the test for Delivered Dose Uniformity.

Response: Comment incorporated.

Comment Summary #3: The commenter indicated that the Osmolality range in the proposal is inconsistent with the information on the package insert.

Response: Comment incorporated by deleting the Osmolality requirement as it is a manufacturing process parameter that does not impact the quality of the finished dosage form.