



Commentary

USP–NF 2022 Issue 1

November 1, 2021

In accordance with USP’s *Rules and Procedures of the Council of Experts (“Rules”)*, and except as provided in Section 9.02 *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, a summary of comments received and the appropriate Expert Committee’s responses, as well as Expert Committee-initiated changes, are published in the Proposal Status/Commentary section of USP.NF.com 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 or conflict between the contents of the *Commentary* and the official text, the official text prevails.

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

General Chapters

[<426> Histamine Test Method](#)

[<591> Zinc Determination](#)

[<665> Plastic Components and System Used to Manufacture Pharmaceutical Drug Products and Biopharmaceutical Drug Substances and Products](#)

[<921> Water Determination](#)

[<1001> In Vitro Release Test Methods for Parenteral Drug Preparations](#)

[<1220> Analytical Procedure Life Cycle](#)

[<1665> Characterization and Qualification of Plastic Components and Systems Used to Manufacture Pharmaceutical Drug Products and Biopharmaceutical Drug Substances and Products](#)

[<1790> Visual Inspection of Injections](#)

[<2740> Manufacturing Practices for Dietary Ingredients](#)

Monographs

[Acyclovir](#)

[Acyclovir Injection](#)

[Atenolol](#)

[Atenolol Tablets](#)

[Butorphanol Tartrate](#)

[Carbomer 934](#)

[Carbomer 934p](#)

[Carbomer 940](#)

[Carbomer 941](#)

[Carbomer 1342](#)

[Chrysanthemum Flower](#)

[Chrysanthemum Flower Dry Extract](#)

[Chrysanthemum Flower Powder](#)

[Dichlorphenamide](#)

[Doxycycline Hyclate](#)

[Dutasteride](#)

[Everolimus](#)

[Flucytosine](#)

[Flucytosine Capsules](#)

[Formoterol Fumarate](#)

[Furosemide Oral Solution](#)

[Galantamine Hydrobromide](#)

[Hydrochlorothiazide](#)

[Hydroxyzine Hydrochloride](#)

[Magnesium Sulfate](#)

[Malathion](#)

[Maltol](#)

[Meclofenamate Sodium Capsules](#)

[Methimazole](#)

[Naproxen Compounded Oral Suspension](#)

[Oxiconazole Nitrate](#)

[Phenoxybenzamine Hydrochloride](#)
[Phentermine Hydrochloride](#)
[Phentolamine Mesylate](#)
[Phentolamine Mesylate Injection](#)
[Prednisolone Sodium Phosphate Compounded Oral Solution](#)
[Propofol](#)
[Selegiline Hydrochloride Capsules](#)
[Stearoyl Polyoxylglycerides](#)
[Testosterone Compounded Cream](#)
[Tetrahydrozoline Hydrochloride](#)
[Wild Chrysanthemum Flower](#)
[Wild Chrysanthemum Flower Dry Extract](#)
[Wild Chrysanthemum Flower Powder](#)
[Zidovudine](#)
[Zidovudine Oral Solution](#)

No comments were received for the following proposals:

General Chapters

<401> Fats and Fixed Oils
<162> Diphtheria Antitoxin Potency Testing for Immune Globulins
<711> Dissolution

Monographs

Acetazolamide
Acetylcysteine and Isoproterenol Hydrochloride Inhalation Solution
Alprostadil
American Ginseng Root and Rhizome
American Ginseng Root and Rhizome Dry Extract
American Ginseng Root and Rhizome Powder
American Ginseng Capsules
American Ginseng Tablets
Aprotinin
Aprotinin Injection
Asian Ginseng Tablets
Astaxanthin Esters Capsules
Bacillus Clausii
Benzethonium Chloride Topical Solution
Calcium Acetate Capsules
Cefazolin in Dextrose Injection
Chlorhexidine Acetate
Chlorhexidine Acetate Topical Solution
Chlorhexidine Gluconate Oral Rinse
Chlorhexidine Gluconate Solution
Chlorhexidine Gluconate Topical Solution
Chlorhexidine Hydrochloride
Chlorophyllin Copper Complex Sodium
Citrulline
Desflurane
Enflurane
Fructose

Gemifloxacin Tablets
Guaifenesin Oral Solution
Hexylresorcinol
Isoflurane
Isosorbide Dinitrate Chewable Tablets
Isosorbide Dinitrate Sublingual Tablets
Lamivudine and Zidovudine Tablets
Lamotrigine Extended-Release Tablets
Lidocaine Topical Aerosol
Methenamine Tablets
Methoxyflurane
Methylene Blue Compounded Injection, Veterinary
Nitrofurazone Topical Solution
Omega-3-Acids Ethyl Esters
Oxaprozin
Papaverine Hydrochloride Tablets
Penicillin G Procaine, Dihydrostreptomycin Sulfate, and Prednisolone Injectable Suspension
Phendimetrazine Tartrate Capsules
Phenoxybenzamine Hydrochloride Capsules
Piperazine Adipate
Plantago Seed
Polyoxyl 40 Hydrogenated Castor Oil
Potassium Gluconate and Potassium Chloride Oral Solution
Potassium Gluconate and Potassium Chloride for Oral Solution
Potassium Gluconate and Potassium Citrate Oral Solution
Potassium Gluconate, Potassium Citrate, and Ammonium Chloride Oral Solution
Potassium Guaiacolsulfonate
Prednisolone Hemisuccinate
Prednisolone Sodium Succinate for Injection
Progesterone Injectable Suspension
Promazine Hydrochloride
Propylthiouracil
Roxarsone
Saccharin Sodium Oral Solution
Sodium Gluconate
Sodium Sulfate Injection
Sodium Phosphates Compounded Injection
Streptomycin Injection
Sulfamethizole
Sulfapyridine Tablets
Technetium Tc 99m (Pyro- and Trimeta-) Phosphates Injection
Tetrahydrozoline Hydrochloride Ophthalmic Solution
Theophylline Tablets
Thiabendazole Chewable Tablets
Tolbutamide
Trihexyphenidyl Hydrochloride Extended-Release Capsules
Trikares Oral Solution
Trimeprazine Oral Solution

General Chapters

General Chapter/Section(s): <426> Histamine Test Method/Multiple Sections
Expert Committee: Biologics Monographs 4
No. of Commenters: 2

INTRODUCTION

Comment Summary #1: The commenter suggested using the skeletal structure for display of the chemical structures.

Response: Comment incorporated.

Comment Summary #2: The commenter suggested modifying the final paragraph as follows for clarity: "This chapter contains an LC-MS method to determine the histamine content. This method is validated for use with gentamicin sulfate and must be validated for use with other drug substances."

Response: Comment incorporated.

PROCEDURE

Comment Summary #3: The commenter suggested changing the concentration of sensitivity solution from 1ng/mL to 2ng/mL because it is difficult to meet the requirement of S/N with 1ng/mL solution.

Response: Comment incorporated.

Comment Summary #4: The commenter suggested changing the histamine standard curve range from 1-20ng/mL to 2-20ng/mL with the same rationale above and preparing 3 standard solutions instead of NLT 5 standard solutions to reduce workload in routine tests.

Response: Comment incorporated.

Comment Summary #5: The commenter suggested changing "Mobile phase: See *Table 1*" to "Mobile phase gradient: See *Table 1*" because *Table 1* provides a linear gradient of the mobile phase.

Response: Comment incorporated.

Chromatographic system

Comment Summary #6: The commenter suggested reconsidering the display of m/z value of Single-Ion-Monitoring mode (SIM).

Response: Comment incorporated. The m/z was changed from 112.00 to 112.1 to reflect the sensitivity of MS instruments.

Comment Summary #7: The commenter suggested incorporating some critical parameters from <621> into the system suitability test, including retention time (RT), peak symmetry, matrix matching and resolution.

Response: Comment partially incorporated. There is no need to include the resolution and peak symmetry since only histamine peak was observed in the chromatogram and this peak never had significant tailing issue based on historical data. The expected retention time of histamine peak was added as an informational note, but not as a requirement.

System suitability

Comment Summary #8: The commenter suggested tightening the acceptance criteria of the percent recovery of the *check standard* from 80%-120% to 90%-110%.

Response: Comment not incorporated. Histamine in the check standard is at ppm level, so the range of 90%-110% would be too tight.

Comment Summary #9: The commenter suggested replacing the *Sample solution* with the *Standard solution* prepared at 10ng/mL (median concentration of the standard curve) to

evaluate %RSD of the method because it is not possible to meet %RSD requirement with the *Sample solution* if it has a very low level of histamine.

Response: Comment incorporated.

Comment Summary #10: The commenter suggested adding LOQ to the system suitability requirements.

Response: Comment not incorporated. LOQ can be affected by many factors, such as different labs, different types of equipment, etc. Therefore, it may not be appropriate to add LOQ as a criteria. Furthermore, S/N is included in the system suitability requirements, which should be sufficient to ensure the sensitivity of the method.

ANALYSIS

Comment Summary #11: The commenter suggested revising the calculation equation since ppm is typically expressed in µg/mL, not ng/mg.

Response: Comment not incorporated. PPM can be expressed in ng/mg (weight/weight). Furthermore, the equation is intended to calculate the histamine content in the gentamicin sulfate powder, therefore ng/mg is an appropriate expression.

General Chapter/Section: <591> Zinc Determination

Expert Committee(s): General Chapters- Chemical Analysis

No. of Commenters: 2

Comment Summary #1: Commenter suggested including text in the “Introduction” section to indicate that method validation and acceptance criteria with a robustness study is required for any proposed method.

Response: Comment not incorporated. All USP procedures are required to be validated or verified depending on how they are used/referenced. Therefore, it does not need to be stated in the chapter.

Comment Summary #2: Commenter suggested revising the instructions for “Drug product sample solution” under **Atomic Absorption Method** as follows:

If the sample is a suspension, resuspend and add 4–7 µL of 6 N hydrochloric acid to each mL of the suspension, ~~as needed~~ to dissolve prior to dilution.

Response: Comment partially incorporated. Committee retained “as needed” for flexibility.

Comment Summary #3: Commenter requested revising the text in **Atomic Absorption Method—Procedure—Zinc Calibration Standard Solutions**, for consistency with <852>, and require preparing no less than **five** calibration standard solutions at suitable concentrations.

Response: Comment not incorporated. The concentration range specified for the AA procedure is a factor of 8 from the lowest concentration to highest. Three calibration levels are sufficient to establish the slope and intercept accurately within that limited range (less than an order of magnitude), which adequately covers the assessment of the two parameters that are directly used to measure sample solution concentrations. Additional standards within that limited range may potentially propagate errors. The most critical specification provided in the AA procedure is the calibration concentration range. General Chapter <852> refers to validation of the procedure whereas AA method in <591> is an application of an already validated method.

General Chapter/Sections: <665> Plastic Components and Systems Used to Manufacture Pharmaceutical Drug Products and Biopharmaceutical Drug Substances and Products

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

No. of Commenters: 17

General

Comment Summary #1: The commenter suggested that USP postpone <665> until the ICH Q3E effort is finalized and then work to align <665> with ICH document.

Response: Comment not incorporated. When ICH Q3E is finalized, the Expert Committee (EC) will work to align the chapters.

Comment Summary #2: The commenter recommended that the various role notations (e.g., user, sponsor, applicant, assessor) be aligned between <665> and <1665>.

Response: Comment incorporated.

Comment Summary #3: The commenter recommended adding a clear statement to clarify further flexibility with respect to the level of testing proposed for low-risk items.

Response: Comment not incorporated. USP General Notices 6.30 describes alternative methods and procedures which may be used.

Comment Summary #4: The commenter recommended aligning with established risk-based approaches for packaging components and systems (e.g., as described in USP General Chapter <661.2>).

Response: Comment not incorporated. General Chapter <665> addresses manufacturing components, not packaging components.

Comment Summary #5: The commenter recommended including a clear statement that already/legacy qualified items (not changed) are out of scope.

Response: Comment not incorporated. USP does not give grandfathering exemptions.

Comment Summary #6: The commenter suggested clarifying that the chapter is intended for end-users and not single-use and multiple use system manufacturers.

Response: Comment not incorporated. Applicability of General Chapters are noted in the General Notices.

Comment Summary #7: The commenter noted that currently there is no USP chapter that covers manufacturing components/systems made of elastomers and encourage USP to develop such a chapter.

Response: Comment incorporated. Topic has been added to the EC's workplan for future consideration.

Title

Comment Summary #8: The commenter suggested the word "biopharmaceutical" in the title is misspelled and should be corrected.

Response: Comment incorporated.

Comment Summary #9: The commenter suggested the title refers to plastic components, but the text in the chapter extends beyond solely plastic components, i.e., filling needles are predominately stainless steel.

Response: Comment not incorporated. There are some plastic filling needles that are utilized by industry and therefore these filling needles would be within scope.

1.0 Introduction

Comment Summary #10: The commenter recommends adding information early in the chapter explaining that active pharmaceutical ingredients for small molecule drugs are intentionally out of scope.

Response: Comment not incorporated. The EC determined that the scope of the chapter is clear.

Comment Summary #11: The commenter recommended changing "leaching of extractables" to "release of extractables."

Response: Comment incorporated.

Comment Summary #12: The commenter suggested adding a discussion on safety to include with quality considerations.

Response: Comment not incorporated. USP standard typically focus on quality. Determination of safety is out of the scope of the chapter.

2.0 Scope

Comment Summary #13: The commenter recommends clarifying the term “biopharmaceuticals.”

Response: Comment incorporated.

Comment Summary #14: The commenter recommended clarifying what types of biological entities are in scope.

Response: Comment incorporated.

Comment Summary #15: The commenter suggested clarifying that all drug substances are manufactured whereas the drug substances for biologics are often formulated and contain buffers.

Response: Comment not incorporated. The EC determined that clarification on the topic was not necessary.

2.0 Scope (2nd bullet)

Comment Summary #16: The commenters recommended editorial changes to the bullet for clarity.

Response: Comment incorporated.

Comment Summary #17: The commenter suggested providing more clarification on which aspects are relevant to extractables and leachables. The text references thawing and a risk during this operation for leaching due to the presence of a liquid-solid interface.

Response: Comment incorporated.

2.0 Scope (4th bullet)

Comment Summary #18: The commenter suggested clarifying that elastomers are in scope.

Response: Comment incorporated.

Comment Summary #19: The commenter recommended adding text on how to assess diaphragm, gaskets, and O-rings.

Response: Comment incorporated.

Comment Summary #20: The commenter recommended that the term “elastomeric material” be defined either in the Scope or in the Introduction section.

Response: Comment incorporated.

2.0 Scope (6th bullet)

Comment Summary #21: The commenter recommended giving guidance on which level of risk should be mitigated.

Response: Comment not incorporated. The document establishes baseline testing which may be augmented as necessary and appropriate.

2.0 Scope (Table 1)

Comment Summary #22: The commenter suggested that at first glance it is not easy to determine if the “Extraction Duration” entries reflect what is experienced during the manufacturing process or the length of time recommended for extraction studies and recommends clarification.

Response: Comment incorporated.

2.0 Scope (Table1 Extraction Duration)

Comment Summary #23: The commenter recommended clarifying that the recommended durations and that the actual durations should be determined by the end user.

Response: Comment not incorporated. The durations in table are required, not suggested or recommended.

Comment Summary #24: The commenter suggested clarifying the instruction and the context of application of extraction duration.

Response: Comment incorporated.

2.0 Scope (Table1 Connectors and disconnectors, aseptic)

Comment Summary #25: The commenter recommended that if tubing is permanently connected to a component, then the duration of extraction should match the longest duration.

Response: Comment incorporated.

2.0 Scope (Table1 Closure for storage containers and container intended for storage)

Comment Summary #26: The commenter suggested adding cross reference to <661> for final containers and final container closure systems.

Response: Comment not incorporated. The suite of <661> chapters focus on testing of packaging component and systems for the final marketed drug product.

2.0 Scope (Table1 Filter)

Comment Summary #27: The commenter suggest clarification that only filters in contact with drug product or drug substance are in scope.

Response: Comment not incorporated. Components that contact gases are established as out of scope.

2.0 Scope (Table1 Port on containers not intended for storage)

Comment Summary #28: The commenter suggest it is not clear what is meant by “port on container”.

Response: Comment not incorporated. If a container has an access port, then it is a container with a port.

2.0 Scope (Table1 Tubing for fluid transport)

Comment Summary #29: Commenter suggested clarifying the difference between this tubing and all the other tubing listed and why 21 days extraction duration was determined.

Response: Comment incorporated.

2.0 Scope (Table1 NOTE)

Comment Summary #30: The commenter recommended clarifying times for low and moderate risk components.

Response: Comment incorporated.

3.0 Assessment Process

Comment Summary #31: The commenter suggested adding text regarding analytical evaluation threshold.

Response: Comment not incorporated. The EC determined that this level of detail is unnecessary in the chapter.

Comment Summary #32: The commenter suggested that a toxicological assessment is only possible for moderate and high-risk components and should be discussed in chapter.

Response: Comment not incorporated. The EC determined that this topic is out of scope of the chapter.

Comment Summary #33: The commenter suggested that while <665> is describing a 2-step approach of material characterization and component characterization, <1665> describes component characterization and system characterization. The chapters should be aligned.

Response: Comment incorporated.

Comment Summary #34: The commenter suggested that the requirements for toxicology assessment for all extractable profiles across different applications or intended molecule indication is significant and may not be sustainable. The commenter recommends updating the language to allow focus on leachables.

Response: Comment not incorporated. Section 4.2.3 describes alternate acceptance criteria, which could include a focus on leachables instead of extractables.

3.1 Assessment Process (Initial Assessment)

Comment Summary #35: The commenter suggested that the risk-based approach of an Initial Assessment seems to be appropriate for the evaluation of existing and new process components and systems. It was suggested to introduce the term "device families" (such as filter- or bag-families etc).

Response: Comment not incorporated. The EC determined that the introduction of the new term does not enhance understanding or implementation of this chapter.

Comment Summary #36: The commenter suggested discussing friction, the physical abrasion of solid-solid interfaces.

Response: Comment not incorporated. Friction is not leaching and not within scope.

3.1 Assessment Process (Initial Assessment-Figure 1)

Comment Summary #37: The commenter recommended revising box 4 in the left column to make it clear that not only can a comparator component or system be established but that a comparator has been established.

Response: Comment incorporated.

3.1 Assessment Process (Initial Assessment-5th bullet)

Comment Summary #38: The commenter suggested that comparator components tested under harsher conditions can also be used (e.g., sterilized at a higher temperature for a longer duration).

Response: Comment not incorporated. The concept of a comparator is to use as close a match as possible. The assumption that harsher conditions always produce a worst extractables profile is not borne out by experience.

3.1 Assessment Process (Initial Assessment-7th bullet)

Comment Summary #39: The commenter suggested that the current text does not consider the extracting power of the process stream (e.g., if the comparator drug product is 100% aqueous whereas the proposed drug product is 40% aqueous, the extracting power of the two process streams is drastically different).

Response: Comment incorporated.

3.1 Assessment Process (Initial Assessment)

Comment Summary #40: The commenter recommended adding a new paragraph about the combined impact of multiple plastic components used in the same manufacturing process.

Response: Comment not incorporated. The concept is addressed in the chapter.

Comment Summary #41: The commenter suggested giving clarification as to whether justification should include an adjusted toxicological assessment, or if no further toxicological assessment needed.

Response: Comment not incorporated. If there is no further chemical characterization, then there is no basis for further toxicological assessment.

3.2 Assessment Process (Risk Assessment)

Comment Summary #42: The commenter suggested that the phrase “chemically (or biologically) unsuited” needs clarification.

Response: Comment incorporated.

3.2 Assessment Process (Risk Assessment 1st and 2nd bullet)

Comment Summary #43: The commenter suggested that bullet 1 and 2 are closely linked, separating these points may drive risk assessor to consider these points separately.

Response: Comment not incorporated. The requirement is to consider the two points separately.

3.2 Assessment Process (Risk Assessment 5th bullet)

Comment Summary #44: The commenter suggested that the phrase “nature of the manufactured dosage form” can be interpreted in multiple ways and should be clarified so the position is clear.

Response: Comment incorporated.

4.1 Testing of Plastic Component and Systems

Comment Summary #45: The commenter suggested that it is important for <665> to describe the fundamental goal of the testing that is being performed; that is that the testing data (extraction profile) should be representative of the worst-case scenario.

Response: Comment not incorporated. General Chapter <665> does not guarantee that the extraction profile is a worst-case for every situation. Rather, it is likely to be a representative case.

4.1 Testing of Plastic Component and Systems (Table 2)

Comment Summary #46: The commenter suggested that as the risk level increases, there is no significant changes in the testing requirements.

Response: Comment not incorporated. The risk-based approach is detailed in Table 2. As risk increases two things change, the number of extraction solvents increases and the tests change from general chemistry tests to full extractables screening.

Comment Summary #47: The commenter recommended that text be added pertaining to the expectations with regards to testing for elemental impurities.

Response: Comment not incorporated. Comments have been received suggesting that testing for extracted elements is not appropriate. The requirement to test for extractable elements only at the high-risk level represents a compromise between these two conflicting viewpoints. Also note that the extraction solvent for medium risk (50% ethanol) does not lend itself well to extracted elements testing.

Comment Summary #48: Commenter suggested that using the term “extracted elemental impurities” instead of “extracted elements.”

Response: Comment not incorporated. Extracts are tested for extracted elements, not elemental impurities.

Comment Summary #49: The commenter recommended removing the text stating that extractable elements be tested as appropriate because with various polymeric materials, they have not found any elements of concern based on ICH Q3D limits.

Response: Comment not incorporated. ICH Q3D indicates that manufacturing systems are a potential source of elemental impurities and a potential contribution to the final drug product.

Comment Summary #50: The commenter recommended adding text that indicate at which level a risk must be mitigated.

Response: Comment not incorporated. The concept is not in scope of the chapter.

Comment Summary #51: The commenter suggested clarification that NVR/UV testing is needed for moderate and high risk.

Response: Comment incorporated.

Comment Summary #52: The commenter recommended deleting any testing requirement for low-risk testing and just mandate referencing material characterization requirements.

Response: Comment not incorporated. As explained in <1665>, the low-risk category needs to be confirmed by some level of testing. Tests like NVR and UV will indicate if there are a lot of organic extractables which would mean this component is not “low risk.”

Comment Summary #53: The commenter suggested adding a statement to justify additional techniques.

Response: Comment not incorporated. General Notices 6.30 allows for alternative methods and procedures to be used.

Comment Summary #54: The commenter recommended aligning the scouting methods and acceptance criteria between <665> and <661.2>.

Response: Comment not incorporated. General Chapter <661.2> is intended for the testing packaging system and components for final drug product packaging systems and is not applicable to this chapter.

Comment Summary #55: The commenter recommended not including an extraction solution or performing extraction for low-risk components because it is not necessary.

Response: Comment not incorporated. To do NVR and UV absorbance, there must be an extraction solution described.

Comment Summary #56: The commenter recommended clarifying what solution C1, C2 and C3 are in this table.

Response: Comment incorporated.

Comment Summary #57: The commenter recommended mentioning the maximum time limit between irradiation and extraction; or heat sterilization and extraction.

Response: Comment incorporated.

Comment Summary #58: The commenter suggested that some research shows that for components made from polycarbonate the actual process stream can be much stronger than the C1, C2, and C3 extraction systems. If there is agreement with this statement, then additional text needs to be added to this section.

Response: Comment not incorporated. Section 4.3.2 allows for alternative extraction solvents in extreme cases.

4.2.1 Extraction Procedures

Comment Summary #59: The commenter suggested discussing solution incompatibility, e.g., solvent fully dissolves material.

Response: Comment not incorporated. Topic is discussed in the chapter.

Comment Summary #60: The commenter suggested clarifying the testing condition for low and moderate risk components.

Response: Comment incorporated.

Comment Summary #61: The commenter recommended changing the term “solvent” to “solution.”

Response: Comment incorporated.

Comment Summary #62: The commenter recommended that <665> provide flexibility to select a proper solvent because C1 solution might not represent worst-case scenario.

Response: Comment not incorporated. Section 4.3.2 allows for alternative extraction solvents in extreme cases.

Comment Summary #63: The commenter recommended the ability to use denatured, as well as, absolute ethanol,

Response: Comment not incorporated. General Notices 6.70 specifies that unless otherwise specified, reagents conforming to the specifications set forth in the current edition of *Reagent Chemicals* published by the American Chemical Society (ACS) shall be used. Ethyl alcohol, absolute contains the required purity. Denatured alcohol contains additives.

Comment Summary #64: The commenter suggested adding the choice of 1:1 ethanol/water or the percent ethanol in the ethanol/water mixture which should be decided based on the solution/drug product formulation.

Response: Comment not incorporated. The use of alternatives is outlined in General Notices 6.30.

Comment Summary #65: The commenter suggested that if one adjusts the pH of 250 mL of the potassium chloride solution to 3 ± 0.1 and then dilute to 1 L with purified water, the pH will not remain 3 ± 0.1 . This needs to be corrected.

Response: Comment incorporated.

Comment Summary #66: The commenter suggested that the basic extraction, pH 10 provides for use of an alternative higher pH extraction solution in certain circumstances. However, as currently phrased, the use of the higher pH extraction solution is not required when these special circumstances exist. It is being recommended that the use of the higher pH extraction solution should be mandatory when those special circumstances exist.

Response: Comment not incorporated. Users should decide and justify the use of a higher pH solvent if the pH of their process stream is >10.5 .

Comment Summary #67: The commenter suggested clarifying the time and temperature for low and moderate risk components.

Response: Comment incorporated.

Comment Summary #68: The commenter suggested that the extraction profile at neutral conditions (approximately pH 7) can be theoretically different for some compounds than an intermediate between the extreme pH values. Therefore, buffered water at approximate pH 7 should also be listed as an alternative.

Response: Comment not incorporated. There is no theoretical means that an extractable would be at a higher concentration at pH 7 than at both pH 3 and pH 10.

Comment Summary #69: The commenter suggested that the text and Table 1 describes the expectations for a standard extraction protocol. However, sometimes higher temperatures or longer extraction times are necessary.

Response: Comment not incorporated. Section 4.3.2 allows for alternate extractions in extreme cases.

Comment Summary #70 The commenter suggested adding the degree units, i.e., 40°C .

Response: Comment not incorporated. USP General Notices 8.180 specifies that temperatures are expressed as Celsius without $^{\circ}\text{C}$.

4.2.2 Extraction Process

Comment Summary #71: The commenter recommended removing dynamic extraction (agitation or recirculation) and allow alternative extraction techniques (e.g., filled bags, sealed vessel or self-enclosed filters, filled tubes) without the necessity of further justification.

Response: Comment not incorporated. The EC disagrees with the assumption that there is no relevant difference in dynamic or static extraction. The majority of users, vendors and regulators prefer dynamic extractions.

Comment Summary #72: The commenter suggested including information pertaining to the evaporation of the extraction solvent(s) or another drying process following extraction for plastic bags with large volume, if applicable.

Response: Comment not incorporated. The chapter considers the issue of loss of extraction solutions. The instructions allow for the use of smaller bags if volume is an issue. Users can scale from big bags to small bags.

Comment Summary #73: The commenter suggested that a dynamic extraction is scientifically not required.

Response: Comment not incorporated. The EC disagrees with the assumption that there is no relevant difference between dynamic and static extraction.

Comment Summary #74: The commenter suggested that it is not always possible to maintain the suggested surface/volume ratio and that other options should be discussed.

Response: Comment not incorporated. The EC determined that listing all the viable options at this time was not feasible. .

Comment Summary #75: The commenter suggested that if the filter is rinsed, flushed, autoclaved or conditioned prior to use, even if the manufacturer does not specify to do so, that it is critical to similarly process the filter prior to extraction.

Response: Comment incorporated.

Comment Summary #76: The commenter recommended adding text stating that for tubing, a family (or comparator) approach can be taken instead of extractable profiling.

Response: Comment not incorporated. Such inconsistencies are covered in Alternate Extraction Protocol.

Comment Summary #77: The commenter suggested that for aseptic connectors that are irradiated it must be irradiated prior to the extraction study.

Response: Comment incorporated.

Comment Summary #78: The commenter suggested the term "inert" is used multiple times in the chapter and that a definition and a list of materials to be considered as inert could be added.

Response: Comment incorporated. Text added to section 4.2.2.

Comment Summary #79: The commenter recommended including the radius when discussing rpm.

Response: Comment incorporated.

Comment Summary #80: The commenter recommended mentioning the maximum time limit between irradiation and extraction; or heat sterilization and extraction.

Response: Comment incorporated.

Comment Summary #81: The commenter suggested it is not clear how results of scouting methods like non-volatile residue and UV absorbance should be interpreted.

Response: Comment incorporated. This is explained in <1665>; text added referring to <1665>.

Comment Summary #82: The commenter recommended stating the number of replicates needed.

Response: Comment not incorporated. The number of replicates should be determined by the analyst.

4.2.2 Extraction Process (Figure 2)

Comment Summary #83: The commenter recommended mentioning devices as examples only or remove examples.

Response: Comment incorporated.

Comment Summary #84: The commenter suggested that the extractions of filters be considered. The second picture from the left shows sterile connectors; this should be removed, or the Figure label adjusted.

Response: Comment incorporated.

4.2.3 Extract Testing

Comment Summary #85: The commenter suggested it is not clear how results of scouting methods like non-volatile residue and UV absorbance should be interpreted.

Response: Comment incorporated. This is explained in <1665>; text added referring to <1665>.

Comment Summary #86: The commenter suggested a more specific value of reporting threshold (e.g., 0.1 ppm for organic compounds and 20 ppb for elements)

Response: Comment incorporated.

Comment Summary #87: The commenter suggested that in many cases, the extraction solution is less than 50 mL. In those cases, the entire solution should be evaporated for NVR analysis. In some cases, sampling of 50 mL may not produce NVR amounts above detection limit and the NVR is considered as nondetectable. However, the NVR of the total extraction solution could be more than zero and sampling only 50 mL out of 1 L would be misleading. This is a very practical issue for reviewing NVR analysis.

Response: Comment not incorporated. If the extraction volume is less than 50 mL, then multiple units will need to be extracted and combined. This is addressed in section 4.2.2. There is a practical limit to the sample size that can be used for NVR.

Comment Summary #88: The commenter suggested that the volume, time, and temperature can vary and doesn't affect the overall outcome of the results unless the temperature is too high. It will cause volume loss due to boiling.

Response: Comment incorporated. Text added stating to avoid boiling.

Comment Summary #89: The commenter suggested aligning <665> and <661>

Response: Comment not incorporated. <661> is for packaging and <665> is for manufacturing.

Comment Summary #90: The commenter suggested that the unit mg for the NVR seems not to be adequate since volumes other than 50 mL are allowed.

Response: Comment incorporated. A statement has been added that if alternate volumes are used the result should be adjusted back to a 50 mL reference volume.

Comment Summary #91: The commenter suggested it is not clear how results of scouting methods like non-volatile residue and UV absorbance should be interpreted.

Response: Comment incorporated. This is explained in <1665>; text added referring to <1665>.

Comment Summary #92: The commenter suggested that the UV wavelength range be changed to 200-400 nm, which would be consistent with the UV wavelength region described in <857>.

Response: Comment incorporated.

Comment Summary #93: The commenter suggested that the organic profiling section should also refer to appropriate validation of the analytical methodology, when necessary.

Response: Comment not incorporated. This is beyond the scope of the <665>. This section of <665> references <1663>, where method qualification is considered.

Comment Summary #94: The commenter suggested extending scaling advice to extractables results of all components and to describe with more depth.

Response: Comment not incorporated. This is beyond the scope of <665>.

Comment Summary #95: The commenter suggested including a statement that alternative solvents and conditions can be used.

Response: Comment not incorporated. There is a provision in <665> that discusses use of another solvent.

Comment Summary #96: The commenter stated that as long as the leachables are below the safety threshold or qualified, the components are considered suitable for use. The commenter recommends providing additional information about how to proceed if the test results are above the acceptable parameters.

Response: Comment not incorporated. The EC determined that remediation for failed test result is out of the scope of the chapter.

Comment Summary #97: The commenter suggested that the requirements for toxicological assessment for all extractable profiles across a number of different applications or intended molecule indication is significant and may not be sustainable and recommended USP update the language to enable a focus on leachables.

Response: Comment not incorporated. <665> does not require the toxicological assessment of all extractables. <665> describes establishing an assessment threshold such as the AET and toxicologically assess only those extractables that are above the threshold.

4.3 Alternate Extraction

Comment Summary #98: The commenter suggested specifying if 40°C should be applied.

Response: Comment not incorporated. 40° is specified as the temperature for all extractions without exceptions.

4.3.2 Extreme Manufacturing Conditions

Comment Summary #99: The commenter expressed concern that it is not always suitable to use extraction conditions more aggressive than the manufacturing contact conditions. This type of testing could present a false risk hazard and lead to inaccurate conclusions about the toxicological risk. It was suggested that it should be recognized that there may be times when it is difficult to reach the correct conclusions if the standard extraction protocol is worse than the “the worst-case scenario.”

Response: Comment not incorporated. The extraction conditions in <665> were designed not to be excessively aggressive in most applications. If the standard extraction protocol produces an incompatibility, then less aggressive conditions can be used.

General Chapter/Sections: <921> Water Determination/Multiple Sections

Expert Committee: General Chapters—Chemical Analysis

No. of Commenters: 4

FIRST SECTIONS

Comment Summary #1: The commenter suggested that the proposed revision “where no method is specified in the monograph, determine the water by Method Ia” is redundant, as a similar statement is included under METHOD I (TITRIMETRIC).

Response: Comment incorporated. Statements were consolidated and captured in a single statement in the first section of the chapter.

Comment Summary #2: The commenter indicated that they propose that Method Ia be used when no method is listed as high impact and should be revised to allow users the free choice of method based on scientific rationale.

Response: Comment not incorporated. General Notices 6.30 allows the use of an alternative validated procedure when the results produced are comparable to the compendial method or procedure.

METHOD IA (DIRECT TITRATION)/REAGENT

Comment Summary #3: The commenter suggested that the General Chapter is not clear as to whether the water equivalency factor of 2.0 for a Reagent should be used for articles that have water content less than 1%, even if the specification is greater than 1%.

Response: Comment not incorporated. The statement in the General Chapters indicates that when water is less than 1% in the article, it is preferable (not requirement) to use a dilute reagent so that a significant volume of titrant is consumed. It is a general approach and does

not prevent the user from selecting the most convenient concentration of the reagent and to validate their procedures.

METHOD IA (DIRECT TITRATION)/TEST PREPARATION

Comment Summary #4: The commenter suggested that LOQ should be considered as a requirement in the general chapter, as the following statement “unless otherwise specified in the individual monograph, use an accurately weighed or measured amount of the specimen under test estimated to contain 2–250 mg of water” may indicate that any sample with water content greater than 2 mg can be accurately determined by the test procedure.

Response: Comment not incorporated. The user is responsible for accurate results and should validate or verify their procedures. LOQ may be a part of the validation/verification procedure, but in the general chapter, no specific requirement is given for LOQ.

General Chapter/Sections:	<1001> In Vitro Release Test Methods for Parenteral Drug Preparations
Expert Committee(s):	General Chapters—Dosage Form
No. of Commenters:	8

General

Comment Summary #1: The commenter suggested revising chapter’s title to be more geared towards modified or extended release parenterals because the chapter seem to be focused on these topics.

Response: Comment not incorporated. The EC will consider future revisions to the chapter to discuss this topic.

Comment Summary #2: The commenter recommended using a generic term for “dissolution,” “in vitro release,” “in vitro drug release,” “drug release” and “performance.”

Response: Comment not incorporated. The EC will consider this in future revisions to the chapter.

Comment Summary #3: The commenter recommended that in a future revision, the EC may want to consider including information for injectable foams in this chapter.

Response: Comment not incorporated. The EC will consider this in future revisions to the chapter.

Introduction

Comment Summary #4: The commenter recommended an edit suggesting that parenteral drugs be limited to those injected intravenously.

Response: Comment not incorporated. Parenteral drugs also include intramuscular, subcutaneous, and other routes of administration.

Comment Summary #5: The commenter recommended using the term “parenteral product” instead of “parenteral preparation.”

Response: Comment incorporated.

Comment Summary #6: The commenter recommends clarifying that stents are not solutions.

Response: Comment incorporated.

Common Principles

Comment Summary #7: The commenter recommends including references to develop a predictive dissolution method and build an IVVC/R which would be seen as the number one purpose of dissolution/IVR method.

Response: Comment not incorporated. The EC will consider this in future revisions to the chapter.

Comment Summary #8: The commenter agreed that USP <1092> is a good starting point for developing or selecting a suitable in vitro test procedure for parenteral products. However, suggests clarifying that it is just a starting point.

Response: Comment incorporated.

Comment Summary #9: The commenter recommended not adding the number of injections and performance test methods in The FDA's Dissolution Methods Database, because of the difficulty in maintaining an accurate number.

Response: Comment incorporated.

Comment Summary #10: The commenter suggested expanding the meaning of relevance, as it relates to accelerated in vitro release testing being a practical solution for QC testing.

Response: Comment incorporated.

Comment Summary #11: The commenter suggested that the reference to FDA's Center for Veterinary Medicine Guidance for Industry is only applicable to extended-release injectable products and request this clarification in the chapter.

Response: Comment incorporated.

Comment Summary #12: The commenter suggested that for some temperature sensitive formulations accelerated methods may not be possible and the text should reflect this point.

Response: Comment incorporated.

Comment Summary #13: The commenter suggested adding text that accelerated tests could conceal release rate differences.

Response: Comment not incorporated. The EC will consider this in future revisions to the chapter.

Comment Summary #14: The commenter noted that the FDA's Center for Veterinary Medicine Guidance for Industry is only applicable to extended-release injectable products. For clarity, it was recommended to include appropriate reference and placement in the chapter.

Response: Comment incorporated. Text was revised to address this comment.

Comment Summary #15: The commenter suggested deleting the following bullet, "Utilizes early sampling to characterize the initial burst." Retaining this statement could allow the opportunity to qualify a suboptimal product.

Response: Comment not incorporated. It is up to the developer to demonstrate a method performs as intended.

Comment Summary #16: The commenter suggested deleting the following statement, "if a reliable in-vitro in-vivo correlation (IVIVC) is established during drug development" because it is confusing.

Response: Comment incorporated.

Comment Summary #17: The commenter suggested removing reference to inclusion of organic solvents or at least stating that it should be avoided unless necessary.

Response: Comment not incorporated. There are occasions when organic solvents are necessary.

Comment Summary #18: For bullet #1 the commenter recommended providing a clear expectation of batch quality.

Response: Comment incorporated.

Comment Summary #19: For bullet #1 the commenter recommended using other terms besides "good and bad".

Response: Comment incorporated.

Comment Summary #20: The commenter recommends deleting bullet #3 because it is not obvious how to incorporate surrogates for organs or tissues in an IVR test.

Response: Comment incorporated.

Comment Summary #21: The commenter recommends omitting the following text, "Demonstrates the absence of drug release before reaching the target tissue or organ."

Response: Comment incorporated.

Table 1

Comment Summary #22: The commenter recommended including “nonspecific membrane adsorption” in the list of limitations in the “Dialysis” technique row.

Response: Comment incorporated.

Comment Summary #23: The commenter recommended including “nonspecific membrane adsorption” in the list of limitations in the “Reverse dialysis/microdialysis” technique row.

Response: Comment incorporated.

Comment Summary #24: The commenter recommended including “nonspecific membrane adsorption” in the list of limitations in the “Centrifugal filtration” technique row.

Response: Comment incorporated

Comment Summary #25: The commenter suggested that centrifugation and ultracentrifugation should be considered, and the difference should be made clear throughout the chapter.

Response: Comment incorporated.

Comment Summary #26: The commenter suggested 4 limitations for some nanosuspension products as it is impossible to retain the formulation in the cell unless a dialysis insert is used.

Response: Comment not incorporated. The EC will consider this in future revisions to the chapter.

Evaporation (Sub-bullet)

Comment Summary #27: The commenter suggested that some equipment (USP Apparatus 2) have very reproducible evaporation rates that can be measured and mathematically accounted for in the calculation of the results. Commenter recommends adding a discussion section on this topic.

Response: Comment not incorporated. This recommendation would add equipment specific information which is not within scope.

Microbial Growth (Sub-bullet)

Comment Summary #28: The commenter recommended including some examples of alternative antimicrobials.

Response: Comment not incorporated. Expert Committee will consider future revisions upon receipt of appropriate examples.

Chemical Degradation (Sub-bullet)

Comment Summary #29: The commenter suggested adding a discussion about when summing all drug-related peaks that a relative response factor may be needed if UV is used and there are differences.

Response: Comment not incorporated. Although a valid comments, it was deemed unnecessary to include such a discussion within the chapter at this time.

Suspensions

Comment Summary #30: The commenter recommended deleting the range listed, and either revising the sentence to indicate a size of less than 1000 nm or simply referring to these solids as “sub-micron.”

Response: Comment incorporated.

Comment Summary #31: The commenter recommended referring to filter openings as “pores” rather than “particles.”

Response: Comment incorporated.

Comment Summary #32: The commenter recommended replacing “size” with “weight.”

Response: Comment incorporated.

Comment Summary #33: The commenter recommended clarifying the intent of the following text: “This technique allows for placement of test article in the bulk media to, for example, minimize the aggregation effect.”

Response: Comment incorporated.

Comment Summary #34: The commenter suggested that it is unlikely that nanosuspensions would be used to prolong the drug release and recommends removing “nanosuspensions” from statement.

Response: Comment incorporated. Text was revised to clarify.

Comment Summary #35: The commenter suggested to remove choice of organic solvent from the media composition section unless caveats are added on the release mechanism being proven to be the same.

Response: Comment not incorporated. The EC felt that the inclusion of organic solvents in the media composition section was appropriate.

Comment Summary #36: Commenter suggested that for the sampling of nanosuspensions it would be worth mentioning ultracentrifugation and a comparison of non-centrifuged versus the ultra to determine % free drug released.

Response: Comment not incorporated. The EC felt that this was a development activity and out of the scope of the chapter.

Liposomes (Bullet 4)

Comment Summary #37: The commenter recommended editing the bullet to include the surface charge of liposome maintenance since the charge may affect the in vitro release and cellular transfection capability of liposomes designed for intracellular delivery.

Response: Comment not incorporated. The EC determined that the level of detail is not needed in the chapter.

Microparticles

Comment Summary #38: The commenter suggested deleting references to microspheres and replacing the threshold with 1000 nm.

Response: Comment not incorporated. Microsphere is a nomenclature name for contrast agents that are really a liposome and an emulsion stabilized with a lipid monolayer.

Emulsions

Comment Summary #39: The commenter recommended clarifying that the majority, not all, parenteral emulsions are oil-in-water emulsions.

Response: Comment incorporated.

Reference

Comment Summary #40: The commenter recommended correcting an error in the title for reference #12.

Response: Comment incorporated.

General Chapter/Sections:	<1220> Analytical Procedure Life Cycle
Expert Committee:	General Chapters—Measurement and Data Quality
No. of Commenters:	26

GENERAL

Comment Summary #1: A commenter suggested that the chapter should be harmonized with all ISO/IEC 17025 requirements for laboratories. Specific focus should be on estimation of analytical results deviation in microbiology analysis and physical chemical analysis, based in reproducibility and repeatability study and sum of error calibration in equipment and glasses.

Response: Comment not incorporated. The principles in this chapter are more general but are in line with the specific requirements of ISO/IEC 17025. The goal and purpose of this chapter is to provide a framework for applying quality by design and systems thinking to analytical method development, qualification, and life cycle management, but avoids recommending specific requirements for these stages and activities. This approach provides room for flexible, innovative, and risk-based approaches during the method lifecycle.

Comment Summary #2: Commenters indicated the chapter, “method procedure validation” appears to be described and used differently from “method validation.” This intent can come off as confusing and could result in misinterpretation by regulators and users of the chapter. Where “method validation” is intended to be comprised of procedure validation as well as method transfers and method verifications, it is recommended that terminology be replaced with “method lifecycle monitoring” or “procedure performance qualification.” This would be consistent with “ATP” terminology used later in the chapter. Such a change will maintain clarity of terms.

Response: Comment not incorporated. A Glossary is added to the chapter.

Comment Summary #3: A commenter indicated that though <1220> is flexible enough to include multivariate methods, it appears that the chapter was written with chromatographic methods in mind.

Response: Comment not incorporated. The reason multivariate methods are not mentioned is to keep the chapter simple, so the important concepts are explained.

Comment Summary #4: A commenter suggested that the definitions of ATP have lost the reference to probability/coverage.

Response: Comment not incorporated. ATP is indirectly referring to probability, it does not always need a numerical value.

Comment Summary #5: The commenter suggested including examples from testing aerosols and other drug-device combination products.

Response: Comment not incorporated. The EC will consider adding this to a future training program.

Comment Summary #6: The commenter, noting that there are not any cross-references to guide “good sampling practice,” the sampling uncertainty may potentially be by far the largest single component of overall uncertainty and the biggest factor in overall PPQ.

Response: Comment not incorporated. The EC determined that sampling does not belong to the analytical procedure, therefore it is outside the scope of <1220>.

Comment Summary #7: The commenter noted that an example of analytical procedure with ATP statement, MODR and example analytical performance attributes including SST to be monitored for CPPV would be very helpful for the users. The commenter suggested adding such an example for assay/deg method for drug product.

Response: Comment not incorporated. The EC will consider adding this to a future training program.

Comment Summary #8: Several commenters suggested to expand the chapter in certain areas, add new topics, and examples.

Response: Comment not incorporated. Appropriate areas indicated in the introduction.

Comment Summary #9: A commenter suggest clarifying the scope and whether concepts can be applied to biologics.

Response: Comment not incorporated. The Introduction indicated that the procedure life cycle approach is applicable to all types of analytical procedures,

Comment Summary #10: A commenter indicated that ICH is developing guidelines on this topic and the USP should align with ICH when published and signed off by the regulators.

Response: Comment not incorporated. It is indicated in the Briefing of PF 46(5) that the chapter may be revise as new ICH guidelines are published.

Comment Summary #11: The commenter, suggested to incorporate the *PF* Briefing into the text of the chapter referring to the objective of the chapter as stated in the briefing, stated that it would be helpful if USP can provide clarification and specific guidelines if and how it applies to medical devices and combination products.

Response: Comment incorporated. Some text of the briefing has been incorporated into the introduction.

Comment Summary #12: Several commenters suggested the convenience of incorporating a glossary.

Response: Comment incorporated.

Comment Summary #13: A commenter mentioned that the current version describes the procedure life cycle management, but a link to the product life cycle management should be considered

Response: Comment incorporated. Figure 1 has been modified to include a link to the QTPP.

Comment Summary #14: The commenter noted that the use of the acronym “PPQ” (Procedure Performance Qualification) can be confused with “process performance qualification,” especially when read in context with other guidance documents.

Response: Comment incorporated. The term “analytical procedure performance qualification” (APPQ) is being use in the final document

Comment Summary #15: The commenter, noting that the description of Stage 1, 2, and 3 in the Introduction is presented in detail both in the body of the document as well as in Figure 1, making the introduction section long with duplicate information, recommend consolidating all aspects into one Stage 1, one Stage 2, and one Stage 3 sections.

Response: Comment not incorporated. The EC believes that a summary in the Introduction may help the reader.

Comment Summary #16: A commenter indicated that the document does not include definition difference for qualification vs. validation.

Response: Comment incorporated. The terms are included in the glossary.

Comment Summary #17: The commenter noted that the document should describe application of decision rule weighted against criticality of quality attribute, i.e., CQA vs. pCQA vs. Non-CQA

Response: Comment incorporated.

Comment Summary #18: Commenters recommended consideration of FDA’s 2015 Guidance for Industry Analytical Procedures and Methods Validation for Drugs and Biologics

Response: Comment incorporated.

Comment Summary #19: A commenter recommended including a comprehensive overview of qualitative and quantitative calculations used in data analysis. Additionally, commenter suggested to consider including calculations for the following: equipment (IR, UV, TLC, HPLC, GC AA, MS, etc.); apparatus (viscosity, distillation, etc.); and potency or label claim (RF, RRF, RRT, etc.).

Response: Comment not incorporated. This aspect will be covered in a training program USP will develop.

Comment Summary #20: A commenter noted that the chapter does not include any discussion on preventative maintenance of in-use equipment. Including text describing appropriate precautions for equipment use may help readers avoid out of specification results (and an ensuing investigation report).

Response: Comment not incorporated. The EC determined that this topic is outside the scope of <1220> and may be covered in other USP chapters

Comment Summary #21: The commenter indicated that while the level of details within the chapter is good, there could be value in some examples around execution to help visualize at least some concepts and approaches.

Response: Comment not incorporated. The EC determined that this type of topics will be included in a future training program.

Comment Summary #22: A commenter noted the value in providing examples around execution in addition to providing framework consistent with developing ICH Q2 and Q14 guidance documents.

Response: Comment not incorporated. Training material to address examples is being developed.**Comment Summary #23:** Commenter noted that this current document certainly has relevance to both chromatographic and non-chromatographic methods, and it will be important to maintain and even further promote this notion.

Response: Comment not incorporated. The text indicates that.

Comment Summary #24: The commenter noted that the document reasonably allow flexibility by not necessarily defining which activities fall in which stage. However, there may be value in explicitly allowing items such as robustness in Stage 1 and not tying robustness to validation – which is being captured in the current ICH Q2/Q14 draft guidance documents.

Response: Comment not incorporated. Robustness is not mentioned in Stage 2

INTRODUCTION

Comment Summary #25: A commenter suggested to introduce in the chapter the sentence from the briefing indicating that this approach should be considered optional.

Response: Comment incorporated.

Comment Summary #26: A commenter suggested to incorporate into the document references to the applicable ICH guidances.

Response: Comment not incorporated. While this information is indicated in the Briefing, this information may change relatively soon.

Comment Summary #27: A commenter indicated that often not all CQAs or specification are known until the time of submission for marketing authorization. There are often iterations of design, develop, and evaluate activities that happen along the way.

Response: Comment not incorporated. This is handled by change control and discussed in the section "Examples of Change."

Comment Summary #28: The commenter indicated that the chapter is very focused on quantitative methods. It would be very useful to extend the recommendations for ATP and Procedure Performance Qualification and Verification to qualitative methods.

Response: Comment not incorporated. The EC determined that the statement in the introduction is sufficient. Specific examples will be developed as part of the training material.

Comment Summary #29: The commenter, referring that the use of “formal validation” is confusing when one is trying to shift the paradigm from validation being the one-time test assessment vs the lifecycle approach where validation refers to the entire analytical method lifecycle process. It may be better to adopt different terminology that is aligned with the stages of process validation described in FDA guidance, where what is referred to here as formal validation could be called qualification as it is in the process validation lifecycle guidance. This would eliminate the ambiguity of validation used in the lifecycle sense and the one-time test assessment sense.

Response: Comment not incorporated. The term is used to describe the current status of the regulatory requirement.

Comment Summary #30: The commenter noting that the term “replication strategy for samples and standards” is used, but it was not clearly explained

Response: Comment incorporated. The section on control strategy has been expanded.

Comment Summary #34: The commenter noted that selectivity and sensitivity are not part of typical validation characteristics which should be considered as defined in ICH Q2(R1).

Response: Comment incorporated. The terms were change to specificity and quantitation limit.

Comment Summary #35: The commenter noted that “conditions that minimizes bias” may imply that bias should be reduced to an unnecessary limit.

Response: Comment incorporated. The text has been amended to indicate “conditions that minimizes bias to a suitable level.”

Comment Summary #36: The commenter suggested publishing general chapters to provide acceptance criteria of analytical characteristics for HPLC, ICP-MS, etc.

Response: Comment not incorporated. The EC determined that this very specific technical detail, which may be relevant in certain cases, is outside the scope of the chapter.

Comment Summary #37: The commenter indicated that the examples in the parenthesis under Stage 1 point 2 appear to be related to chromatographic procedures. Examples should not be limited to chromatography.

Response: Comment not incorporated. The EC determined that the current text is correct considering the objective of the chapter's section.

Comment Summary #38: Several commenters noted that column for stage 3 in Figure 1 'Continued Procedure Performance Verification' should be in line with the text further below under 'Stage 3.'

Response: Comment partially incorporated. Figure 1 is being modified accordingly.

Comment Summary #39: A commenter indicated that to confirm ATP, both accuracy and precision need to be assessed. This would be challenging especially for drug products. During routine use one can assess precision (when there are replicate sample preparations) but not accuracy. Accuracy involves repeating spike and recovery experiments which is not practical over 10-20 years of product lifecycle.

Response: Comment not incorporated. Depending upon the risk analysis, a suitable control strategy should be used for accuracy. Only periodic recovery checks are needed.

Comment Summary #40: A commenter indicated that under Introduction, Stage 2, it is stated “*Procedure performance qualification consists of studies designed to demonstrate that the procedure is suitable for its intended purpose in the laboratory.*” As the PPQ integrates the analytical transfer, it would be good to delete “in the laboratory” as several laboratories can be involved in PPQ.

Response: Comment incorporated.

Comment Summary #41: A commenter suggest to delete the expression in parentheses (lifecycle change management).

Response: Comment incorporated.

ANALYTICAL TARGET PROFILE (ATP)

Comment Summary #42: A commenter stated that the term “bias” is listed as interchangeable with “accuracy.” While a definition is given for Bias as: “how close the measurement is, on average, to the true value that is being measured,” it is also clear throughout the chapter that “bias” is to be controlled and kept to a minimum.

Response: Comment not incorporated. Here the term “accuracy” is used as it is defined in ICH Q2. A definition of “bias” is also added in the new glossary.

Comment Summary #43: The commenter recommended adding text about running development experiments to investigate procedure performance around the appropriate and applicable ICH characteristics (e.g., specificity, precision and accuracy requirements).

Response: Comment not incorporated. The EC considered this is outside the scope of the chapter.

Comment Summary #44: The chapter makes reference to “total analytical error.” This is called “total variance” and “total error” in <1210>.

Response: Comment not incorporated. The EC determined that the term is consistent with the proposed ICH Q14 guidance

Comment Summary #45: A commenter stated that the ATP describes performance requirements for the measurement and should not be restricted to a certain analytical procedure

Response: Comment not incorporated. It is indicated in the text under Stage 1 that “Any technique that is capable of meeting the ATP criteria can be selected.”

Comment Summary #46: A commenter recommend including discussion on establishing a link to attribute range in Stage 1 by providing detailed interpretation and examples with numbers, as that will facilitate ATP understanding and execution.

Response: Comment not incorporated. Training material to address examples is being developed.

Comment Summary #47: Commenters indicated that concept of ATP is abstract and difficult to understand and encouraged USP to issue a new general chapter to elaborate on ATP.

Response: Comment not incorporated. Training material to address how to develop the ATP is being developed.

Comment Summary #48: Commenters suggested introducing an approach of establishing the bias (accuracy) and precision of the procedure with respect to the product specification.

Response: Comment incorporated. The section on decision rules have been revised and addresses this comment.

Comment Summary #49 A commenter suggested to add alternative examples of ATP from different sources.

Response: Comment not incorporated. The EC consider that there are multiple sources of ATP examples and not all can be included in the chapter

Comment Summary #50: A commenter suggested including examples on calculation of the maximum allowable combined bias and precision.

Response: Comment not incorporated. A detailed example is described in USP <1210>

BIAS AND PRECISION

Comment Summary #51: A commenter stated that an evaluation of equipment performance to verify that the equipment used is adapted with the expected method performance should be included.

Response: Comment not incorporated. The EC consider that this topic is outside the APL process

Comment Summary #52: A commenter indicated that procedures should be developed to have an appropriate bias (not the smallest possible).

Response: Comment incorporated.

Comment Summary #53: A commenter suggested replacing the term validation in the first sentence for qualification.

Response: Comment incorporated.

Comment Summary #54: The commenter indicated that it would be useful to establish a link between method uncertainty concepts, ATP and the decision rules and to clarify whether the USP considers TAE as being the same as, or fundamentally different to, standard error.

Response: Comment not incorporated. The EC decided to expand on these topics as part of the training/education. A series of podcasts discussing TAE and MU have been launched. The first episode can be heard here: <https://www.usp.org/our-science/evolving-quality-standards>

SPECIFICATIONS AND DECISION RULES

Comment Summary #55: The commenter instructed USP to align Scenario 2 and Scenario 3 text with Figure 4.

Response: Comment incorporated.

Comment Summary #56: A commenter suggested deleting the majority of the section or moving it to another USP chapter.

Response: Comment not incorporated. The EC decided to keep the section in a rewritten format.

Comment Summary #57: The commenter suggested including examples on

TAE calculation and its distribution, and how to determine guard bands and indecision zone

Response: Comment not incorporated. The EC determined that this type of topics will be included in a future training program.

Comment Summary #58: The commenters identified conflict between current OOS procedures used in industry and current nonalignment guidelines (e.g., FDA Guidance for Industry Investigating Out-of-Specification)

Response: Comment not incorporated. Since <1220> is based on science and statistical approaches, it does not contradict FDA guidances.

Comment Summary #59: Commenters instructed USP to either remove the decision rules out of the chapter or provide more clarity with applicable analytical examples.

Response: Comment partially incorporated. The section was rewritten for clarity.

Comment Summary #60: The commenter requested clarification regarding use of guard bands.

Response: Comment not incorporated. The EC determined that this type of topic will be included in a future training program.

Comment Summary #61: The commenter recommended that a definition of “safe and efficacious range” should be added to the glossary.

Response: Comment not incorporated. The EC determined that the term is self-explanatory, and the definition is outside the scope of the chapter.

Comment Summary #62: The commenter indicated that “total analytical error” is referenced but not defined.

Response: Comment incorporated. The term is added to the glossary

Comment Summary #63: The commenter recommended changing Figure 2 accordingly: “*Figure 2. Relationship between bias, precision, Total Analytical Error and reportable value distribution*”

Response: Comment not incorporated. The EC considered the suggested change as not correct because it incorporates variability twice (once as precision and once as Total Error).

Comment Summary #64: Commenter noted that under *Specifications and Decision Rules* the term “analytical measurement variability” is used without proper definition.

Response: Comment incorporated.

Comment Summary #65: A commenter expressed that it is unclear the connection between decision rules and ATP.

Response: Comment incorporated. The section has been rewritten.

Comment Summary #66: The commenter stated that scenarios in Figure 4 don't account for process variability. There's no consideration of "acceptable process capability" in the figure or text. RV2 and RV3 (with appropriate acknowledgement of process variability) might be acceptable if the lab is satisfied.

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

Comment Summary #67: A commenter noted that in Scenarios 2 and 3 in Figure 4, it is less clear that the true quality characteristic is actually above or below the upper acceptance criterion and there is significant probability that the true value of the quality characteristic is actually inside (Scenario 2) or outside (Scenario 3) the specification acceptance range.

Response: Comment incorporated. Figure 4 and text is modified to address the comment.

Comment Summary #68: A commenter noted that guard bands, as shown in the figure, ensure an absence false acceptance, but do not prevent a false rejection. This should be made clear in the associated text.

Response: Comment not incorporated. Considering the risks of false acceptance and false rejection, false acceptance would be a much less desirable outcome. The use of guard bands is a more conservative approach that is specifically designed to prevent false acceptance, at the

cost of potentially higher false rejection rates. The alternative approach of using an indecision zone in combination with a multistage testing procedure helps to mitigate the false rejection risk.

STAGE 1 PROCEDURE DESIGN

Comment Summary #69: A commenter suggested including an example of method development report, MODR, etc.

Response: Comment not incorporated. The EC determined that this exceeded the level of detail proposed in the document and considered that this should be addressed by training material.

Comment Summary #70: A commenter indicated that the use of the ATP should be encouraged but not be mandatory.

Response: Comment not incorporated. The introduction states that life cycle approach can be considered optional, and any of the elements can be applied on the basis of how the procedure is used.

Comment Summary #71: A commenter indicated that it is important to define the objective of development in terms of the desired levels of robustness.

Response: Comment incorporated.

Comment Summary #72: A commenter indicated that “optimize variability” is not an appropriate term.

Response: Comment incorporated.

Comment Summary #73: A commenter suggested further describing the use of heat maps and Ishikawa diagrams.

Response: Comment not incorporated. The EC determined that this type of topics will be included in a future training program.

Comment Summary #74: A commenter requested that the sentence “*Some procedures may not require modelling ...*” be moved later in the section.

Response: Comment incorporated.

Comment Summary #75: A commenter suggested replacing the term “mechanistic modeling.”

Response: Comment not incorporated. The EC considered that the term is correct.

Comment Summary #76: A commenter suggested to use the term “fishbone diagram” when defining Ishikawa diagram.

Response: Comment not incorporated. The EC considered that the term is widely used.

Comment Summary #77: A commenter suggested to consider including some discussion of the following: sample compartment and temperature requirements; detector usage time (signal range check); pump maintenance; signal sensitivity output; and calculation errors.

Response: Comment not incorporated. The EC considered that the suggestion is too detailed for this document.

Comment Summary #78: A commenter suggested including an additional Ishikawa diagram formatted by method step as an alternative format. This would align with a procedure process map.

Response: Comment not incorporated. The EC preferred to keep only one as an example.

Comment Summary #79: The commenter noted that the use of “*analytical unit of operation*” as header for column 1 in Table 1 seems unnecessary and should be replaced by another term.

Response: Comment not incorporated. The term is corrected to “unit operation” but kept in the text.

Comment Summary #80: A commenter proposed to add column in Table 1 for cleaning protocols and/or column performance. Both variables can substantially affect the performance of an analytical procedure.

Response: Comment incorporated.

Comment Summary #81: A commenter suggested that rating the impact of each variable/potential hazard on total method uncertainty (TMU) may be simpler and just as effective

for specific technologies. It would be helpful to acknowledge this approach as equally valid in the text.

Response: Comment not incorporated. The heat map is demonstrating the concept and is not meant to be a comprehensive. **Comment Summary #82:** A commenter suggested changing the phrase *“This approach is generally powerful for exploring a larger number of procedure parameters”*

to *“This approach is generally powerful for exploring procedure parameters...”*

Response: Comment incorporated.

Comment Summary #83: Under *Quality Risk Management (QRM) and the Analytical Procedure*, a commenter suggested clarifying which methods belong to simple technology.

Response: Comment not incorporated. It is mentioned several times in the text that the extent of these tools will vary depending on several factors including method complexity.

Comment Summary #84: A commenter stated that one sentence introduces the concept of FMEA but does not describe or reference another document to aid the user in this strategy.

Response: Comment not incorporated. There are many references available on FMEA as a risk management tool that can be consulted.

Comment Summary #85: A commenter suggested adding multivariate analysis (MVA) as a tool for stage 1, which allows user to rank parameters which cannot be systematically evaluated experimentally.

Response: Comment not incorporated. The EC considered that <1220> is not meant to be a complete list of all tools available for method development. MVA and other techniques can be used even though they are not mentioned in the chapter.

Comment Summary #86: Under *Robustness and MODR*, a commenter suggested further expanding the liquid chromatography example. An additional non-chromatographic example would also aid further understanding.

Response: Comment not incorporated. The topic can be expanded with training material.

Comment Summary #87: Under *Robustness and MODR*, a commenter suggested to modify the phrase *“If the MODR relates to attributes that are linked to the elimination of bias ...”* to *“If the MODR relates to attributes that are linked to the reduction of bias.”*

Response: Comment not incorporated. The EC considered the term appropriate.

Comment Summary #88: Commenters requested clarification if a deliberate change in the set points can be made as long as it remains into MODR.

Response: Comment not incorporated. The EC refers the commenter to the text on managing changes: *“An adjustment in a procedure parameter to a value”*

Comment Summary #89: A commenter requested clarity if the replication strategy is also defined based on expected procedure performance and risk of taking a wrong decision.

Response: Comment not incorporated. The section describes the Replication strategy for the reportable value. The link to the performance requirements is already mentioned (“which may enable the procedure to more easily meet the criteria of the ATP for the reportable value”). The title section title is change to “Replication strategy for the reportable value.”

Comment Summary #90: A commenter suggest clarifying that robustness studies should be completed beyond the method development stage in order to provide a full scope of robustness.

Response: Comment incorporated. Under Stage 2 the 5th bullet point has been revised to *“Acceptable performance and robustness under routine use.”*

Comment Summary #91: Under *Replication strategy* a commenter suggested to add the phrase: *“when averaging individual replicates, one should consider additional criteria in order to control variation.”*

Response: Comment incorporated.

Comment Summary #92: A commenter suggested to expand on ACS to include change management procedures.

Response: Comment not incorporated. The EC determined that the level of detail in this chapter is appropriate.

Comment Summary #93: A commenter suggested to move the sentence *Stage 2 involves confirming (or qualifying) ... samples and standards* into Stage 2 section.

Response: Comment incorporated.

Comment Summary #94: A commenter suggested to use the term “precision” instead of “replication strategy.”

Response: Comment not incorporated. “Replication” is the correct term in the routine use of the procedure to obtain an average reportable value.

Comment Summary #95: A commenter proposed emphasizing that at Stage 1 a preliminary ACS is developed.

Response: Comment incorporated.

STAGE 2: ANALYTICAL PROCEDURE PERFORMANCE QUALIFICATION (APPQ)

Comment Summary #96: Several commenters suggest using the term “*Analytical Procedure Validation*” instead of “*Procedure Performance Qualification*.”

Response: Comment not incorporated. The EC decided to align with process validation terminology.

Comment Summary #97: A commenter suggest expanding on the development of a protocol.

Response: Comment not incorporated. It is up to each company (and regulators) to define what kind of documentation is being included in the protocol.

Comment Summary #98: A commenter request to clarify the term “Procedure Performance Qualification.”

Response: Comment incorporated. The term is being added in the glossary.

Comment Summary #99: A commenter proposed to add definitions to clarify the following terms: qualification, verification, validation, and transfer.

Response: Comment incorporated. A glossary is added to the chapter.

Comment Summary #100: A commenter indicated that it might be useful to further clarify that in case of transfer of analytical procedures or implementation of compendial methods, the receiving site may adjust the analytical control strategy and/or replication strategy as part of Stage 2.

Response: Comment not incorporated. The ACS should control method parameters or instructions.

Comment Summary #101: A commenter indicated that PPQ is a common acronym in the pharmaceutical industry, it might be helpful to use the acronym APPQ for “analytical procedure performance qualification” to limit confusion.

Response: Comment incorporated.

Comment Summary #102: Under *Protocol and study design*, a commenter indicated that the following phrase should be change “*The acceptance criteria needed to meet the ATP (e.g. accuracy, precision, range)...*”. It is critical to include the ‘e.g.’ since ATP criteria will be vary dependent on method, approach to defining ATP etc.

Response: Comment incorporated.

Comment Summary #103: A commenter proposed clarifying the text as follows: “*The acceptance criteria needed to meet a technology independent ATP (accuracy, precision, range) and procedure-specific performance characteristics (e.g., specificity, calibration model, quantitation limit).*”

Response: Comment not incorporated. Accuracy, precision, and range are also valid for an ATP with technology restrictions.

Comment Summary #104: A commenter indicated that the examples (accuracy, precision, range, specificity, calibration model, quantitation limit) may lead to the interpretation that the requirements for verification and transfer are the same as for method validation. It is suggested

that the examples are deleted since the same study design is not feasible for the different types of activities.

Response: Comment not incorporated. These are illustrative examples.

Comment Summary #105: A commenter suggested including a sentence which excludes reinitiation when the replication format has been changed to yield results that satisfy the ATP.

Response: Comment not incorporated. It is stated under *Changes to an Analytical Procedure*.

STAGE 3: ONGOING PROCEDURE PERFORMANCE VERIFICATION (OCPV)

Comment Summary #106: A commenter proposed clarifying the text as follows: “*The acceptance criteria needed to meet a technology independent ATP (accuracy, precision, range) and procedure-specific performance characteristics (e.g., specificity, calibration model, quantitation limit).*”

Response: Comment not incorporated. The EC determined that the text is sufficiently clear as written.

Comment Summary #107: A commenter noted that under “*Routine monitoring*” SSTs are covered twice in the same sentence and only need to be covered once.

Response: Comment incorporated.

Comment Summary #108: A commenter suggest adding a statement indicating that low risk or simple procedures need not be routinely monitored or trended.

Response: Comment not incorporated. The EC considered this implicit in the current text.

Comment Summary #109: Under Routine monitoring, a commenter proposed to modify the text as follows: “*The monitored data and information should be evaluated on an ongoing basis.*”

Response: Comment not incorporated. While ongoing evaluation may be ideal, it is impractical to state this is always necessary.

Comment Summary #110: Under Analytical control attributes it is suggested to modify the text as follows “*....such as HPLC column replacement, or provision of supporting data for root cause investigation of unexpected observations or trends.*”

Response: Comment not incorporated. The EC considered that this should be part of a training program.

Comment Summary #111: Under Analytical control attributes it is noted that for simple control measures established limits may be the best and a more effective tool.

Response: Comment not incorporated. The use of other approaches is not expressly prohibited. An attribute is generally controlled by a limit, control charts is only a way to visualize the performance .

Comment Summary #112: Under Analytical control attributes a commenter suggested including further flexibility for selection and design of control samples.

Response: Comment not incorporated. The EC determined that the appropriate level of flexibility is implied.

Comment Summary #113: A commenter indicated that the description of Figure 8 contains a factor of 3.64 with no indication on how it is derived.

Response: Comment incorporated. The factor has been deleted.

Comment Summary #114: A commenter suggest expanding on the example under *Changes to an Analytical Procedure*.

Response: Comment not incorporated. Items are presented to demonstrate an approach only.

Comment Summary #115: A commenter noted that it is not expected that further risk assessment or experimentation would be required, considering that the method performance is guaranteed.

Response: Comment not incorporated. Often additional work will not be needed, but if the method is sensitive to one or more parameters or if ranges are very narrow, it's a good idea to confirm the robustness of the new conditions with respect to those parameters.

Comment Summary #116: A commenter suggest that in the *Examples of change* subsection, to include some discussion of additional factors affecting validation qualification attributes, including: reagents, standards, equipment, and change in apparatus supply chain.

Response: Comment not incorporated. The EC determined that no additional detail is necessary in the examples.

Comment Summary #117: A commenter indicated that while the user based set up for an ATP is necessary for the testing of new drug substances/new drug products, it's not deemed necessary for existing monographs due to already predefined requirements.

Response: Comment not incorporated. Even for existing monographs, Stage 3 can be applied (as described) as well as for non-compendial methods.

General Chapter/Sections: <1665> Characterization of Plastic Components and Systems Used to Manufacture Pharmaceutical Drug Products and Biopharmaceutical Drug Substances and Products

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

No. of Commenters: 11

General

Comment Summary #1: The commenter suggested it will be helpful for USP to indicate that <665> testing of elastomers, such as silicone tubing, represents a reasonable characterization of these components.

Response: Comment incorporated. A new chapter dedicated to silicone elastomers is under consideration.

Comment Summary #2: The commenter suggested that more information be given on the testing of systems/assemblies vs. components.

Response: Comment not incorporated. It is more challenging to specify test conditions for assemblies and systems.

Comment Summary #3: The commenter recommended re-organizing a table to capture/summarize alternate solutions that could be used and in what situations they could be used.

Response: Comment incorporated.

Comment Summary #4: The commenter recommended adding information about what plastic additive are to be expected in each component.

Response: Comment not incorporated. USP does not have access to such information.

Comment Summary #5: The commenter recommended to not include autoclaved components as high risk by default.

Response: Comment not incorporated. High heat causes polymer additives to degrade, producing extractables.

Comment Summary #6: For mitigating factors, the commenter suggested ensuring that the presence of a purification step that has a demonstrated impact on the clearance of extractables and leachables are taken into consideration to reduce the risk from one level.

Response: Comment incorporated.

Comment Summary #7: The commenter suggested providing clarification that extraction conditions can apply to components and single use assemblies.

Response: Comment incorporated.

Title

Comment Summary #8: The commenter suggested the title refers to plastic components, but often the text in this document starts to reach out beyond solely plastic components, i.e., filling needles which are predominately stainless steel.

Response: Comment not incorporated. Plastic filling needles are utilized within the industry and thus these needles are within scope.

Comment Summary #9: The commenter suggested that the chapter also includes information about qualification and the word “qualification” should be added to the title.

Response: Comment incorporated.

1.0 Introduction

Comment Summary #10: The commenter suggested it would be helpful to include some information on the types of polymers used in pharmaceutical and biopharmaceutical manufacturing as well as high level information on their expected extractables.

Response: Comment not incorporated. A list of polymer types containing a generalized list of expected additives is not possible.

Comment Summary #11: The commenter recommended that this introduction be revised to be consistent with the text in the Introduction of <665>.

Response: Comment incorporated.

Comment Summary #12: The commenter suggested adding links to the discussion of molecular weight.

Response: Comment incorporated.

Comment Summary #13: The commenter recommends not overlooking the impact on drug product quality, particularly when discussing CQAs.

Response: Comment incorporated.

Comment Summary #14: The commenter suggested that altering critical quality attributes has the potential to affect efficacy as well as safety which should be reflected in the text.

Response: Comment incorporated.

2.0 Scope

Comment Summary #15: The commenter recommended clarifying if cell and gene therapies are in scope.

Response: Comment incorporated.

Comment Summary #16: The commenter recommends removing the term “traditional” as it does not add to understanding of “small molecules” or “biologics.”

Response: Comment not incorporated. The EC determined that the term as utilized is appropriate.

Comment Summary #17: The commenter recommended spelling out API the first time it is mentioned in the chapter.

Response: Comment incorporated.

Comment Summary #18: The commenter recommends avoiding the misconception that biologics are highly purified products.

Response: Comment incorporated.

Comment Summary #19: The commenter suggested reviewing the section to ensure the proper use of the term “extractables.”

Response: Comment incorporated.

Comment Summary #20: The commenter suggested adding text to clarify whether this chapter is meant to provide guidance on how to apply <665>.

Response: Comment incorporated.

Comment Summary #21: The commenter recommended making it clear that pharmaceutical substances are within scope.

Response: Comment incorporated

2.0 Scope (6th Bullet)

Comment Summary #22: The commenter suggested that it is preferable to describe the components by its function rather than its size.

Response: Comment incorporated.

3.1 Discussion (2nd Bullet)

Comment Summary #23: The commenter suggested that bullet be revised to be consistent with the other cited entries.

Response: Comment incorporated.

3.1 Discussion

Comment Summary #24: The commenter recommended adding that <665> also references good scientific judgment by the applicant/risk assessor where the standard testing requirements are not suitable.

Response: Comment not incorporated. Chapter established good scientific judgment as one of the testing requirements.

3.2 Material Characterization

Comment Summary #25: The commenter suggested removing elastomeric components from the chapter because it is not within the scope of <665>.

Response: Comment not incorporated. This discussion is about what happens before <665> is used.

4.1 Initial Assessment

Comment Summary #26: The commenter suggested that bullets 1 and 2 be switched. It would be more logical to first ask if the component is in contact with the process stream, then ask if it interacts with the process stream.

Response: Comment incorporated.

Comment Summary #27: The commenter recommended clarifying bullet 2 and whether process streams include starting materials and reagents.

Response: Comment incorporated.

Comment Summary #28: The commenter recommended ensuring that the term “extractables” is being used properly.

Response: Comment incorporated.

Comment Summary #29: The commenter recommended mentioning semisolids.

Response: Comment incorporated.

Comment Summary #30: The commenter suggested that some solid or gaseous process streams might be reactive with the plastic components and cause the migration or leaching of PERLs.

Response: Comment not incorporated. The EC is not aware of any examples.

Comment Summary #31: The commenter suggested adding drug substance and product to the discussion regarding liquid process streams and intermediates.

Response: Comment incorporated.

Comment Summary #32: Commenter suggested clarifying if products contact time frozen would be included in the chapter.

Response: Comment incorporated.

Comment Summary #33: The commenter recommended clarifying if chapter applies to sterile powders.

Response: Comment incorporated.

Comment Summary #34: The commenter recommended mentioning the influence of sterilization.

Response: Comment incorporated.

Comment Summary #35: The commenter suggested clarity as to whether the 4th bullet include the same sterilization method (e.g., autoclave, irradiation and ETO).

Response: Comment incorporated.

4.2 Risk Assessment of Components

Comment Summary #36: The commenter recommended aligning tables in <665> and <1665>.

Response: Comment incorporated.

Comment Summary #37: The commenter recommended adding parentals to the examples of products that would be considered high risk.

Response: Comment incorporated.

4.2.1 Development and Application of the Risk Evaluation Matrix

Comment Summary #38: The commenter suggested that PERLs do not always have to persist until the end of drug product manufacturing to impact product quality and should be mentioned.

Response: Comment incorporated.

Comment Summary #39: The commenter recommends adding additional detail to bullet 3 to improve clarity.

Response: Comment incorporated.

Comment Summary #40: The commenter recommends revising bullet 4 and 5 to align with <665>.

Response: Comment incorporated. Edits have been made to <665>.

4.2.2 Linking Risk Characterization Methodologies

Comment Summary #41: The commenter suggested adding elemental impurities to align with <665>.

Response: Comment incorporated.

Comment Summary #50: The commenter suggested that testing for extracted elements may also be necessary for both the moderate and high-risk levels.

Response: Comment not incorporated. It is difficult to measure extractables elements in 50% ethanol, therefore extractable elements are only relevant for high-risk.

Comment Summary #51: The commenter suggest that it is not clear what “bracketing” means in the high-risk bullet and should be clarified.

Response: Comment incorporated.

4.3.1 Low Risk Assessment

Comment Summary #52: The commenter suggested that it might be necessary to revise the text to simply refer to “Solution C1” or use some other terminology to allow for other extraction solvents.

Response: Comment not incorporated. Solution C1 is an ethanol/water, 50/50 v/v solution. Although <665> allows the composition of the solution to be modified with justification, it does not change this designation. If an alternate to C1 is used it is not called C1, it is an alternate to C1.

Comment Summary #53: The commenter recommended giving examples where items deemed low risk would not need to be tested.

Response: Comment not incorporated. Data for low risk is necessary to verify that low risk is the correct classification.

Comment Summary #54: The commenter suggested outlining the strength and limitations of NVR and UV absorbance.

Response: Comment not incorporated. The EC determined that the recommendation is not in scope of the chapter.

Comment Summary #55: The commenter suggested applying analytical evaluation threshold to NVR and UV absorbance.

Response: Comment not incorporated. The EC determined that it is not appropriate to use the analytical evaluation threshold in this manner.

Comment Summary #56: The commenter recommended adding an acceptance criterion for NVR and UV absorbance.

Response: Comment not incorporated. The EC determined that this addition is not appropriate to the current revision of the chapter.

Comment Summary #57: The commenter recommended listing NVR as just for informational purposes only.

Response: Comment not incorporated. The Expert Committee see value in collecting NVR data and using it to inform decision regarding the use of a component or system.

4.3.2 Moderate Risk Assessment

Comment Summary #58: The commenter recommended adding text around the C1 solution that it may not always represent the worst-case scenario for certain formulations.

Response: Comment not incorporated. This point is addressed in section 5.1.5 Non Standard Extractions.

4.3.3 High Risk Assessment

Comment Summary #59: The commenter recommends acknowledging that there are exceptions to the rule regarding the standard extraction protocol.

Response: Comment not incorporated. This point is addressed in section 5.1.5 Non Standard Extractions.

5.1.1 Extraction Solution

Comment Summary #60: The commenter recommended adding clarity on when pH 10 extraction solution can be replaced.

Response: Comment incorporated.

Comment Summary #61: The commenter suggested that water may possess a stronger extracting power than the C1 solvent, so C1 may not provide worst case.

Response: Comment not incorporated. A comparison list of compounds extracted with water and ethanol/water will be heavily biased toward ethanol/water.

Comment Summary #62: The commenter suggested adding water as an extraction solvent.

Response: Comment not incorporated. Water does not add anything more to the extraction profile beyond what you would see with the low and high pH solvents.

Comment Summary #63: The commenter recommended conveying that C1 solution is not restricted to just a 50% by volume ethanol solution.

Response: Comment incorporated. This is discussed in section 5.1.5 Non Standard Extractions.

Comment Summary #64: The commenter recommended addressing process streams that are nonaqueous or oil based.

Response: Comment incorporated. This is discussed in section 5.1.5 Non Standard Extractions.

Comment Summary #65: The commenter suggested the section is overly wordy and confusing and should be revised.

Response: Comment incorporated.

5.1.2 Extraction Temperature

Comment Summary #66: The commenter suggested that acceleration for single use and multiple use systems is not necessary because real contact time can be used for extraction.

Response: Comment not incorporated. Acceleration may not be necessary for duration of 1 day, but for 7 and 21 days it was agreed to be too long and thus acceleration is acceptable.

Comment Summary #67: The commenter suggested that the effect of higher temperature on extraction kinetics and the identity of the extraction vehicle(s) should be considered carefully if exaggerated extraction temperatures are used.

Response: Comment not incorporated. This is discussed in section 5.1.5 Non Standard Extractions.

5.1.3 Extraction Duration

Comment Summary #68: The commenter recommended clarifying if the Arrhenius Law is applicable to frozen products subjected to freeze-thaw cycles.

Response: Comment incorporated.

Comment Summary #69: The commenter recommended clarifying if the maximum process time needs to be exceeded by extractables testing.

Response: Comment incorporated.

Comment Summary #70: The commenter recommended reviewing equation 2 for accuracy.

Response: Comment incorporated.

5.1.4 Accomplishing the Extraction

Comment Summary #71: The commenter recommended adding an acceptance criterion for NVR and UV absorbance. The aim is to use the data to justify a component's use in a particulate application and setting an acceptance criterion would negate the ability to determine suitability base on risk.

Response: Comment not incorporated.

Comment Summary #72: The commenter suggested that surface-area-to solution volume should be moved up in the chapter because it is a key extraction consideration.

Response: Comment incorporated.

5.1.5 Non Standard Extraction

Comment Summary #73: The commenter suggested it should be recognized that there may be times when it is difficult to reach the correct conclusion if the standard extraction protocol is worse than worst-case scenario or the worst-case scenario data overly exaggerates the risk.

Response: Comment incorporated.

5.2.1 Organic Extractables

Comment Summary #74: The commenter recommended editing section heading to delete PERLs because it is not appropriate.

Response: Comment incorporated.

Comment Summary #75: The commenter recommended allowing for the identification of organic extractables of interest on a case-by-case basis.

Response: Comment not incorporated. The Expert Committee determined that this was not necessary.

Comment Summary #76: The commenter suggested that the analytical evaluation threshold is specific to drug products and depends on various parameters that do not directly correlate to manufacturing systems. This point needs to be removed from the chapter.

Response: Comment not incorporated. An analytical evaluation threshold for a drug product can almost always be translated into an analytical evaluation threshold for manufacturing PERLs, if proper process knowledge is known.

Comment Summary #77: The commenter recommended making it clear that the extractable test method needs to be validated if the extractable data alone is used to qualify the component without leachables data.

Response: Comment incorporated.

5.2.2 Extracted Elements (Elemental PERLs)

Comment Summary #78: The commenter recommended editing the section heading, so that it accurately reflects the section.

Response: Comment incorporated.

5.3 Implementing the Standard Extraction Protocol

Comment Summary #79: The commenter recommended checking the section to make sure PERLs is properly used.

Response: Comment incorporated

6.1 General

Comment Summary #80: The commenter recommended adding text on the scientific approach to scale from components to the entire assembly.

Response: Comment incorporated.

6.3 Alternate Approaches for Qualification

Comment Summary #81: The commenter recommended additional text around the event of changing any engineering control to lower the risk of leachables from the manufacturing component or system by establishing a mitigation strategy to justify lower risk.

Response: Comment not incorporated. The EC determined that the comment is not within scope.

Appendix (Table A-1)

Comment Summary #82: The commenter suggested that the table should be the same as Table 2 in <665>.

Response: Comment not incorporated. Table A-1 does not correlate to the low, medium, and high-risk level.

Comment Summary #83: The commenter suggested that for Level 3, Chemical Composition of the Process Stream – Neutral pH (buffered water) should be included.

Response: Comment not incorporated. pH 7 is not a high-risk solution for leaching.

Appendix (Temperature)

Comment Summary #84: The commenter recommended revising the subsection heading to “Temperature of contact to be consistent with the entry in Table A-1.”

Response: Comment incorporated.

Appendix (Extraction Solution)

Comment Summary #85: The commenter recommended revising the subsection heading.

Response: Comment incorporated.

Comment Summary #86: The commenter recommended revising subsection heading for more clarity.

Response: Comment incorporated.

Comment Summary #87: The commenter suggested that if the process stream contains exactly 5% by weight of lipids or proteins, then both bullets 2 and 3 apply.

Response: Comment incorporated.

Comment Summary #88: The commenter suggested that “niacinamide” be add to the list of solubilizers, because niacinamide and its derivatives are known for solubility enhancement.

Response: Comment incorporated.

Appendix (Risk Evaluation Matrix)

Comment Summary #89: The commenter suggested considering further dimension that address the risk that a plastic component will be leached to such an extent that its extractables may be impactful.

Response: Comment not incorporated. The Risk Evaluation Matrix provided in the Appendix is an example and users may modify the dimensions if they want to include additional dimensions.

Comment Summary #90: The commenter suggested PERLs do not always have to persist until the end of drug product manufacturing to impact product quality.

Response: Comment not incorporated. PERLs must persist in order to have a direct patient safety effect.

Appendix (Risk Evaluation Matrix-Clinical Use)

Comment Summary #91: The commenter suggested discussing whether it is appropriate to refer to a solid oral/topical dosage form.

Response: Comment incorporated.

Comment Summary #92: The commenter suggested that expressing the dose threshold in mL/kg makes it easier to translate to comparable terms for smaller patients or smaller veterinary species.

Response: Comment not incorporated. The EC recognized the comment but noted that the requested change is not trivial to implement, and the chapter does not cover safe levels for various patient populations.

Appendix (Chemical Composition of the Component)

Comment Summary #93: The commenter recommended removing autoclaving from the list of parameters that would automatically place it in a higher risk category as compared to not autoclaving.

Response: Comment not incorporated. This is one aspect of a four-dimension risk matrix. It is still very possible that the component would be deemed low risk based on the other three dimensions. Any exposure to high temperature such as autoclaving is a cause of additives to degrade and produce more soluble extractables.

Comment Summary #94: The commenter suggested adding text stating that if data are available demonstrating that an additive(s) greater than 1% does not impact the full extraction protocol profiles, then the materials risk score can be one lower.

Response: Comment not incorporated. Statements on the relative safety of additives are outside of the scope of the risk assessment matrix.

Appendix (Table A-2)

Comment Summary #95: The commenter suggested considering how to appropriately deal with drug products that are high-risk simply because of their route of administration.

Response: Comment not incorporated. The product dosage form is one consideration in the risk assessment. However, it cannot be the overriding factor. If all the other dimensions are rated as low risk, then the dosage form itself being high risk is not enough to require the entire situation to be classified as high risk. It is one factor, not the only factor.

Appendix (Table 2)

Comment Summary #96: The commenter suggested deleting any testing for low- risk testing, and reference material characterization requirements.

Response: Comment not incorporated. <665> allows the use of an alternate approach.

General Chapter/Sections: <1790> Visual Inspection of Injections
Expert Committee(s): General Chapters—Dosage Form

No. of Commenters: 4

General

Comment Summary #1: The commenter recommended adding some discussion on multiple container inspections.

Response: Comment not incorporated. Multiple container inspection should be developed as a comparative inspection which is not within the scope of the chapter.

1.1 Introduction

Comment Summary #2: The commenter suggested adding text to note that guidance for situations where visual examination may be impossible (e.g., preparations having reduced clarity, high viscosity solutions, opaque solutions or packages).

Response: Comment incorporated.

2.2 Patient Risk

Comment Summary #3: The commenter suggested emphasizing particulate burden studies that focuses on sub-visible particulate matter since porosity used for in-line filters are 0.2µm and 1.2µm.

Response: Comment incorporated.

3.1 100% Inspection

Comment Summary #4: The commenter recommends mentioning <1> *Injections and Implanted Drug Products (Parenterals)—Product Quality Tests* as primary chapter requiring 100% Visual Inspection.

Response: Comment not incorporated. General chapter <1> is mentioned in *Introduction*.

Comment Summary #5: The commenter suggested being less restrictive with the association of a device in case of multiple container inspection.

Response: Comment not incorporated. Multiple container inspections are not within the scope of chapter.

3.2 Acceptance Sampling and Testing

Comment Summary #6: The commenter suggested that the probability of acceptance of batches having a density of defects equal to the claimed AQL vary from 88% to 99%, depending on the inspection type and inspection level and suggests adding “approximately” to the 95% value.

Response: Comment not incorporated. The EC determined that this editorial change would not add clarity.

Comment Summary #7: The commenter suggested considering the overall processes capabilities in the outcome of the AQL after visual inspection.

Response: Comment not incorporated. The EC felt that including this point would create less clarity around the topic.

Comment Summary #8: The commenter recommended adding an allowance for small sampling plans in the S plans.

Response: Comment not incorporated. S plans for testing are outside of the scope.

Comment Summary #9: The commenter recommended clarifying text to suggest representative samples only.

Response: Comment not incorporated. There is no indication of industry confusion around this point.

3.3 Remedial and Alternative Practices - Reinspection

Comment Summary #10: The commenter recommends emphasizing that lack of defect prevention can lead to too much reinspection.

Response: Comment incorporated.

5.1 Defect Classification

Comment Summary #11: The commenter suggested particles detected after visual inspection are representative of visible contaminants of the marketed units and recommends considering a holistic approach for such event.

Response: Comment not incorporated. This point is made elsewhere in the chapter.

Comment Summary #12: The commenter suggested adding commentary based on <1> to ensure that visual inspection methods follow the requirement in <1>.

Response: Comment not incorporated. The focus of <1> is injectable drug products not manufacturing components.

Comment Summary #13: The commenter suggested that the presence of visible particles in a container is classified as at least a 'major defect.'

Response: Comment not incorporated. Not every particle is a major defect (e.g., suspension).

5.2 Unique Product and Container Considerations

Comment Summary #14: The commenter suggested that difficult-to-inspect products are not as amenable to defect reduction even by an optimized 100% inspection process and this point should be noted in chapter.

Response: Comment incorporated.

Comment Summary #15: The commenter suggested adding text that while zero particles remain the goal, the probabilistic nature and random occurrence of visible particles often leads to detecting single particles in a single unit.

Response: Comment not incorporated. This requirement has been in place for 15 years and should not reduce the expectation for zero particles in such a small sample.

6.1 Manual Visual Inspection

Comment Summary #16: The commenter suggested adding guidance regarding the additional time that may be required to adequately inspect product for multiple defects.

Response: Comment incorporated.

7.2 Preparing Defect Standard

Comment Summary #17: The commenter recommended adding intrinsic product-specific particle defects identified during pharmaceutical development as potential defect standards.

Response: Comment incorporated.

7.5 Test Set

Comment Summary #18: The commenter recommends adding language clarifying that container closure integrity defects are critical but that combining defects does not mean there is one overarching acceptance criteria.

Response: Comment incorporated.

Comment Summary #19: The commenter recommended removing the 10% limit for defect proportion in the test set and replace with Knapp guidance.

Response: Comment incorporated.

7.6 Type of Test Sets

Comment Summary #20: The commenter recommended adding specific clarity for method development and size threshold evaluation for particulate defects prior to qualification of operators and incorporate into a particulate risk assessment.

Response: Comment incorporated.

7.7 Training and Qualification of Human Inspectors

Comment Summary #21: The commenter suggested that near-vision performance should be measured using Jaeger charts or equivalent, with no impairment of color vision.

Response: Comment incorporated.

7.8 Inspector Qualification Requirements – Rejection Zone Efficiency Qualification Method

Comment Summary #22: The commenter suggested stating that requirements for detection for defects can also be based on AQL classifications using fixed percentage criteria and risk assessment.

Response: Comment not incorporated. Chapter allows other qualification methods with justification.

Comment Summary #23: The commenter suggested that the rationale of defects within the defect set should be not more than 25%.

Response: Comment not incorporated. Change at this time would alter the test requirements stated in chapter.

Comment Summary #24: The commenter recommended going beyond the rejection zone efficiency and allowing the use of statistical variability of operators from the reference group to qualify an operator.

Response: Comment not incorporated. Suggested change is an alternative method that is permitted by the chapter as written.

Comment Summary #25: The commenter suggested that a false reject rate depends on the set size and its detection requirements and as a business risk and no GMP-risk, thus no number should be given.

Response: Comment not incorporated. The EC disagree that this is a “business risk” and that the limit as stated is practical.

9.0 Conclusion/Recommendations

Comment Summary #26: The commenter suggested clarifying text for the following:

“Identification of the type or types of particles found during product development and routine manufacturing is an important aid in source identification and reduction.”

Response: Comment incorporated.

General Chapter/Sections:	<2740> Manufacturing Practices for Dietary Ingredients/ Multiple Sections
Expert Committee:	Non-Botanical Dietary Supplements and Botanical Dietary Supplements & Herbal Medicines
No. of Commenters:	1

1.0 General Provisions

Comment Summary #1: The commenter suggested adding continuous production under 4.0 *Production operations and control systems*.

Response: Comment incorporated.

Comment Summary #2: The commenter suggested adding on-site label printing under 5.0 *Packaging and labeling operations and controls system*.

Response: Comment incorporated.

2.0 Quality Management

Comment Summary #3: The commenter suggested adding a separate sentence “that Quality

unit delegate responsibility to production with oversight to ensure their review is proper” under Section 2.2.2 *Responsibilities of Quality unit* since both provisions are needed.

Response: Comment not incorporated. The EC determined that quality unit should be responsible for the review and not production.

Comment Summary #4: The commenter suggested adding “has been exposed to communicable disease” under Section 2.2.7 Personal responsibilities 2.2.7.1. Preventing microbial contamination.

Response: Comment incorporated. The statement was rephrased as “or has a communicable disease that could be transmissible through food.”

Comment Summary #5: The commenter recommended adding “during performances of their duties” under Section 2.2.7.2 *Hygienic practices*.

Response: Comment incorporated.

Comment Summary #6: The commenter wanted clarity on what jewelry is not secured under Section 2.2.7.2 *Hygienic practices*.

Response: EC recommended rephrasing the statement as “removing all jewelry that is not adequately secured or tight fitting.”

Comment Summary #7: The commenter recommended adding an additional sentence “if bare hands or gloves have the potential to come into contact with these materials during the performance of their duties” under Section 2.2.7.2 *Hygienic practices*.

Response: Comment incorporated.

Comment Summary #8: The commenter suggested modifying the sentence “Wearing when appropriate and in an effective manner hair net, caps, beard covers, or other hair restraints” to “Wearing when appropriate such as where the raw material, in-process material or ingredient is exposed, and in an effective manner” under Section 2.2.7.2 *Hygienic practices*.

Response: Comment incorporated.

Comment Summary #9: The commenter suggested adding “taking personal medication” under Section 2.2.7.2 *Hygienic practices*.

Response: Comment incorporated.

Comment Summary #10: The commenter recommended revising the statement “All dates must include the day, month, and year in a consistent format (e.g., DD-MM-YYYY) to “All dates must include the day, month, and year in a consistent and unambiguous format such as establishing a date format or spelling out the month format (e.g., DD-MM-YYYY)” under Section 2.3 *Documentation and Records*, 2.3.1 *General*.

Response: Comment incorporated

Comment Summary #11: The commenter suggested adding “Documentation should be readily retrievable” under Section 2.3 *Documentation and Records*, 2.3.2 *General*.

Response: Comment incorporated

Comment Summary #12: The commenter suggested defining “Critical deviations” under Section 2.5 *Deviations and material review*, 2.5.1 *Deviations*.

Response: Comment not incorporated. The EC recognized there is no official definition for “Critical deviations” and recommended removing “critical” and replace it with “deviations”.

Comment Summary #13: The commenter proposed adding “Rework procedures should be approved by the QU and the reworked ingredient should be inspected to verify the material has the same composition and stability as virgin ingredient. Also, customers should be informed the lot was reworked” under Section 2.5 *Deviations and material review*, 2.5.2 *Material Review*.

Response: Comment not incorporated. EC recommended Quality agreements between manufacturers and customers should define what information is handled with each batch, including reworking, deviations. The chapter describes the commenter’s remarks.

Comment Summary #14: The commenter suggested providing examples for cGMPs under Section 2.7 Hazard Analysis and Risk-Based Preventive Controls (HARPC), 2.7.3.6 *Other controls*

Response: Comment not incorporated. The EC was of the opinion not to provide any specific examples of cGMPs.

Comment Summary #15: The commenter suggested providing an allowance for certification at the acceptor site, i.e., ISO 17025, in lieu of audit under Section 2.8 Contract Manufacturers and Contract Laboratories.

Response: Comment not incorporated. The EC opined that audit are the basis for supplier qualification.

Comment Summary #16: The commenter wanted to indicate an established timeframe for completion or permission to extend the investigation under Section 2.9 Complaints.

Response: Comment not incorporated. The EC concluded that manufacturers should have procedures describing how to handle investigations that are extended in time and what to include in the internal audit.

Comment Summary #17: The commenter proposed adding a statement that internal audit should verify that those computer systems that have an audit trail have this feature enable under Section 2.10 *Internal (self-inspection) audits*.

Response: Comment incorporated.

Comment Summary #18: The commenter suggested adding associated metadata to be kept as original records under Section 2.12.2 *Records*.

Response: Comment incorporated

Comment Summary #19: The commenter suggested adding “content of the training or reference to a document that describes the content” under Section 2.12.2 *Records*.

Response: Comment incorporated

Comment Summary #20: The commenter opined that records for external audits, customer or regulators must be made and kept adding under Section 2.12.2 *Records*.

Response: Comment not incorporated. The EC recommended that audits and inspections received from USP, customers or regulators should not be described in the chapter.

3.0 Physical plant and design

Comment Summary #21: The commenter wanted a clarity on product types described under *section 3.2 Physical plant design, 3.2.1 Separate and defined areas* and was wondering if molecular weight is a determinant in grouping products based on types.

Response: Comment not incorporated. The EC opined that the section relates to composition to minimize the potential for cross-contamination or cross-contact where such occurrence could create a health hazard, such as the introduction of an undeclared allergen.

Comment Summary #22: The commenter opined that in chemical ingredient plants, contact surfaces are seldom sanitized. The processing conditions are harsh enough to prevent microbial growth described under *section 3.2 Physical plant design, 3.2.1 Separate and defined areas*.

Response: Comment incorporated. The statement was rephrased to “cleaning and sanitizing food contact surface as necessary.”

Comment Summary #23: The commenter suggested adding “one or more individuals demonstrated to be competent by education or training” for sanitation supervisor under *section 3.3 Physical plant sanitation and facilities*.

Response: Comment not incorporated. The EC recommend no change as competency would be self-evident through education, training or experience.

Comment Summary #24: The commenter suggested treating cleaning compounds, sanitizing agent, pesticides and other toxic materials as any raw material, ID and COA review under *section 3.3.1 Cleaning compounds, sanitizing agents, pesticides and other toxic materials*.

Response: Comment not incorporated. The EC recommend no change to GC as the intent of this is to make sure that non-production materials or processing aids, cleaning agents, etc, are clearly labeled and stored in a manner that protects against contamination when not in use.

Comment Summary #25: The commenter recommended adding “Scientifically justified

frequency” to sanitation of food-contact surfaces under *section 3.3.3 Sanitation of contact surfaces*.

Response: Comment not incorporated. The EC recommended rephrasing the statement to “must be cleaned and sanitized as necessary to prevent contamination.”

Comment Summary #26: The commenter proposed defining “suitable temperature” under *section 3.3.4 Water Supply*.

Response: Comment not incorporated. The EC opined that this is a standard statement for food processing facilities. Temperature could be important in many different scenarios, especially if water is used in a clean-in-place operation under high temperature and high pressure to sanitize the equipment and achieve the appropriate microbial kill.

Comment Summary #27: The commenter recommended adding “trash must be collected and stored in containers clearly identified as containing waste” under *section 3.3.6. Sewage and trash disposal*.

Response: Comment not incorporated. The EC found the current wording of the statement appropriate.

Comment Summary #28: The commenter proposed adding “and” to cleaning sanitizing schedules as needed under *section 3.4.4. Cleaning and Maintenance*.

Response: Comment incorporated.

Comment Summary #29: The commenter suggested defining “high-risk areas” under *section 3.4.4. Cleaning and Maintenance*.

Response: Comment not incorporated. The EC suggested high-risk areas should be defined by the manufacturer.

Comment Summary #30: The commenter recommended adding “Multi-use utensils such as sample scoops should be stored clean and protected from contamination such as in a clean, sealed plastic bag for single service articles under *section 3.4.4. Cleaning and Maintenance*.”

Response: Comment not incorporated. The EC noted that this is covered in another section and need not be repeated.

Comment Summary #31: The commenter suggested adding “Test records should not be written to erasable media not covered by audit trail such as thumb drives” under *section 3.4.6. Computerized systems*.

Response: Comment incorporated. The EC recommended modifying the sentence to “Data can be recorded by a second means in lieu of a computer system failure. Test records should not be written to erasable media not covered by audit trail such as thumb drives.”

Comment Summary #32: The commenter suggested adding “Should allow for hybrid systems where unique login is not possible or presents a safety hazard such as in certain chemical processing. In those instances, a written log of users should be implemented” under *section 3.4.6.2 Electronic signatures*.

Response: Comment not incorporated. The EC determined that each organization needs to adopt a system that works for their organization. Usually, all electronic systems require separate users to have their own ID and password protected signature.

Comment Summary #33: The commenter questioned the requirement for maintaining drawings of utility systems under *section 3.5.2 Records* and opined those drawings will present an obstacle to chemical manufacturers in large facilities. Historically, many plants did not update their Piping and Instrumentation Diagrams (P&ID).

Response: Comment not incorporated. The EC believed chemical manufacturers should update their P&ID.

Comment Summary #34: The commenter recommended removing the compendial requirements of water to potable or deionized water under *section 3.5.2 Records*.

Response: Comment incorporated. The EC recommended revising the sentence to “Demonstrating that water, when used as a component of a dietary ingredient, meets all federal,

state, and local standards of potability (some intended uses of water in dietary ingredients may require the use of compendial grade *Purified Water*).

Comment Summary #35: The commenter suggested removing the requirement for maintaining documentation of individual equipment logs of the date of use, maintenance, cleaning and sanitizing of equipment, unless such documentation is kept with the batch record under section 3.5.2 *Records*.

Response: Comment not incorporated. The EC was of the opinion that companies have different approaches to maintaining records, as long as they are readily retrievable and meet the appropriate Standard of Evidence.

4.0 Materials Management

Comment Summary #36: The commenter suggested removing the requirement that stated “Raw materials must meet a recognized standard of quality [e.g., American Chemical Society (ACS) reagent grade, or other compendial grade]” since not all raw materials used to make dietary ingredients have a recognized standard of quality. ACS reagent grade or monograph or such grade is expensive and not readily available under section 4.1.1 *Raw material and other ingredient specifications*.

Response: Comment incorporated. The EC modified the sentence to “Starting materials and processing aids used to manufacture dietary ingredients should be of suitable quality to ensure that the finished dietary ingredient meets appropriate standards of Identity, Strength, Purity, Composition and Limits on Contaminants.”

Comment Summary #37: The commenter suggested referencing <232> for elemental impurities under section 4.1.1 *Raw material and other ingredient specifications*.

Response: Comment not incorporated. The EC instead referenced <2232> *Elemental Contaminants in Dietary Ingredients*.

Comment Summary #38: The commenter proposed adding reprocessed ingredients under section 4.1.1 *Raw material and other ingredient specifications*.

Response: Comment not incorporated. The EC was of the opinion that “rework” and “reprocessed” are redundant and section already refers to rework.

Comment Summary #39: The commenter recommended not including identity specification for in-process dietary ingredient since full testing of intermediates are expected under section 4.1.4 *In-Process dietary ingredient specifications*.

Response: Comment not incorporated. The EC believed that Intermediate products are controlled with in-process controls of production steps and raw material specifications. The need to develop specifications of intermediates is to be evaluated by the manufacturer. Statements were added with modifications.

Comment Summary #40: The commenter recommended that the “QC unit must conduct an OOS investigation prior to the release of the ingredient” under section 4.2 *Determining compliance with specifications, 4.2.1 General*.

Response: Comment incorporated. Statements were added with modifications.

Comment Summary #41: The commenter wanted to add on-site printed label to the section 4.2.6 *Packaging material and labelling* as this would be the most likely label type for dietary ingredients.

Response: Comment not incorporated. The EC recommended that all labels requires inspection and approval before use.

Comment Summary #42: The commenter wanted clarity on one of the statements (When the dietary ingredient was received from a supplier for packaging or labeling as a dietary ingredient and for distribution rather than return to the supplier, but without sufficient assurance provided to adequately identify the product and to determine that the product is consistent with its purchase order) that the ingredient was produced in confirmation to the chapter under section 4.2.9 *Treatments, In-Process adjustments and reprocessing*.

Response: Comment not incorporated. The EC determined that there is no need to state conformance to chapter, as this is evident if one is claiming conformance to USP standards.

Comment Summary #43: The commenter wanted to add “For raw materials received in bulk truck or railcar this should include verification the vehicle is dedicated to that service or that the vehicle has been properly cleaned and that the prior load does not pose a risk of contamination” under section 4.3 *Receiving and release of materials, 4.3.1 Raw materials, other ingredients, packaging materials and labels Treatments*.

Response: Comment incorporated. Statement added with modification.

Comment Summary #44: The commenter expressed that representative samples of each unique shipment of raw materials that are hazardous cannot be collected and stored under section 4.3 *Receiving and release of materials, 4.3.1 Raw materials, other ingredients, packaging materials and labels Treatments*.

Response: Comment not incorporated. A procedure should be in place for these raw materials. Fast analysis should be implemented, and pre-samples should be agreed upon for compliance with the full specification.

Comment Summary #45: The commenter wanted clarity on a requirement that “any lot of raw materials and other ingredients that are produced, must be identified in a manner that allows a person to trace the lot to the supplier by the date received; the name and status (e.g., quarantined, approved, or rejected) of the raw material, other ingredient, packaging material, and label; as well as to the dietary ingredient that was manufactured and distributed” and was wondering how would this work where the raw material is offloaded to a storage tank prior to use under section 4.3 *Receiving and release of materials, 4.3.1 Raw materials, other ingredients, packaging materials and labels Treatments*.

Response: Comment not incorporated. It is understood in the industry that bulk stored materials that are stored in tanks, silos, etc. will have comingling from one lot to the next. This is unavoidable and is accepted in the Food Industry. Most railcar, bulk truck deliveries have specific procedures for identifying and confirming the raw material prior to releasing the material to the bulk storage location.

Comment Summary #46: The commenter suggested that requiring representative samples of each lot of packaged and labelled dietary ingredients to determine whether the packaging used and the label applied complies with the master packaging record is impractical and costly under section 4.4 *Representative and reserve samples, 4.4.1 Representative samples*.

Response: Comment not incorporated. The EC found the existing wording of the section appropriate for representative and reserve samples.

Comment Summary #47: The commenter recommended to add “reprocessed” under section 4.5 *Holding, Distribution and Transportation, 4.5.1 Holding*.

Response: Comment not incorporated. The EC found the existing word “rework” is sufficient.

Comment Summary #48: The commenter stated that the most common practice to store reserve samples of the ingredient is in a closed glass container without confirmation it protects as does the market container-closure under section 4.5 *Holding, Distribution and Transportation, 4.5.1 Holding*.

Response: Comment incorporated. Statement was added with modifications.

Comment Summary #49: The commenter suggested that undesirable materials can be added during the shipping process without the manufacturer's knowledge and outside their control under section 4.5 *Holding, Distribution and Transportation, 4.5.5 Transportation operations*.

Response: Comment not incorporated. The EC found the existing wording of the section sufficient and recommended that this is a standard requirement of all companies and is a FSMA requirement that contracts be engaged to ensure that food ingredients and foods are not shipped with dangerous or hazardous chemicals.

5.0 Production operations and controls

Comment Summary #50: The commenter stated that it is not possible to generate a batch record each time a batch of dietary ingredient is manufactured during continuous processing as stated under section 5.2 *Executed batch production records*.

Response: Comment not incorporated. The EC recommended making changes to the statement.

Comment Summary #51: The commenter questioned the requirement to add the identity of equipment and processing lines used in producing the batch if the ingredient is produced in a dedicated line in one site under section 5.2 *Executed batch production records*.

Response: Comment incorporated. The EC recommended making changes to the statement.

Comment Summary #52: The commenter recommended adding “release” under section 5.2 *Executed batch production records*.

Response: Comment incorporated.

Comment Summary #53: The commenter proposed adding “rework” under section 5.2 *Executed batch production records*.

Response: Comment not incorporated. Statements contain reprocessing. Rework and reprocessing are used synonymously.

6.0 Packaging and labelling operations and controls

Comment Summary #54: The commenter suggested adding the address of the manufacturer on the CoA rather than the label as allowed by ANSI under section 6.3 Labelling, 6.3.1 *General procedure*.

Response: Comment not incorporated. The EC recommended that the manufacturer address needs to be on the label attached to the package.

Comment Summary #55: The commenter proposed adding “Repackaged or relabeled ingredient should retain the original retest or expiry date” under *section 6.6 Repackaging and relabeling*.

Response: Comment incorporated.

7.0 Laboratory Operations and Controls

Comment Summary #56: The commenter suggested adding “Repackaged or relabeled ingredient should retain the original retest or expiry date” under *section 6.6 Repackaging and relabeling*.

Response: Comment incorporated.

Comment Summary #57: The commenter proposed adding “may blend uniformly” under *section 7.6 Reduced testing, 7.6.1 General procedures*.

Response: Comment not incorporated. Statement was modified for clarity.

Comment Summary #58: The commenter proposed adding “relying on the supplier CoA for those tests not performed in a given lot” under *section 7.6 Reduced testing, 7.6.2 Reduced Testing requirements*.

Response: Comment incorporated. Statement was modified as “the dietary ingredient CoA should clearly disclose when reduced testing principles are applied” for clarity.

Comment Summary #59: The commenter suggested adding “shown to provide the same level of protection to the ingredient but not be more protective. A cross-study should be performed before switching from the market container to the alternate container” under *section 7.8 Stability testing*.

Response: Comment incorporated. Statement was rephrased as “If multiple container/closure systems are used, stability and expiry date assignment can be satisfied by testing the container/closure system with the least desirable barrier properties” for clarity.

Comment Summary #60: The commenter proposed extending the stability testing to 60 months under *section 7.8 Stability testing*.

Response: Comment not incorporated. The EC suggested that this is not required but can be

done at the discretion of the product owner.

Comment Summary #61: The commenter proposed adding “retest” under *section 7.9 Laboratory testing*.

Response: Comment incorporated. The EC suggested modifying the sentence to “recommended retest date, analytical method reference for each attribute”.

Comment Summary #62: The commenter proposed adding “electronic signatures” in certificate of analysis under *section 7.9 Laboratory testing*.

Response: Comment not incorporated. The EC suggested electronic signature is self-evident in the statement.

Monographs

Monograph/Section: Acyclovir/Organic impurities
Expert Committee: Small Molecules 1
No. of Commenters: 5

Comment Summary #1: The commenter recommended removing the ‘Specified impurity 1’ and ‘Specified impurity 2’ from the Table 2 as they are neither qualified, nor controlled at ICH Q3A identification threshold limits.

Response: Comment not incorporated. The ‘Specified impurity 1’ and ‘Specified impurity 2’ are identified as EP impurity N and EP impurity O respectively. The footnote for these impurities is updated, from unknown impurity to unknown structure, to be consistent with the *Ph. Eur.* name.

Comment Summary #2: The commenter commented correcting the typo in Table 2 from retention time to relative retention time.

Response: Comment incorporated.

Comment Summary #3: The commenter suggested confirming the impurity at RRT 2.67 is indeed the ‘N,O-Diacetyl acyclovir-N⁷-isomer (EP Impurity M) and not the ‘N,O-Diacetyl acyclovir N⁹-isomer (EP Impurity G), as the proposed method is similar to that in *Ph. Eur.*

Response: Comment incorporated. The impurity at RRT 2.67 in Table 2 was updated from ‘N,O-Diacetyl acyclovir-N⁷-isomer to ‘N,O-Diacetyl acyclovir N⁹-isomer. The chemical name in the footnote h was also updated.

Comment Summary #4: The commenter suggested that the impurity ‘N,O-Diacetyl acyclovir N⁹-isomer (EP Impurity G) be included with an acceptance criteria of NMT 0.1%.

Response: Comment incorporated. The impurity at RRT 2.67 in Table 2 is updated from ‘N,O-Diacetyl acyclovir-N⁷-isomer to ‘N,O-Diacetyl acyclovir N⁹-isomer.

Comment Summary #5: The commenter recommended removing the reporting threshold as it will vary based on product-specific factors.

Response: Comment not incorporated. Based on comments received on a proposed policy for reporting thresholds, USP determined that removal of reporting thresholds from monographs needs further stakeholder engagement. USP intends to do further stakeholder engagement.

Comment Summary #6: The commenter proposed adding a USP Reference Standard including ‘Specified impurity’ and ‘Specified impurity 2’ for identification of these two impurities.

Response: Comment not incorporated. The ‘Specified impurity 1’ and ‘Specified impurity 2’ are identified as EP impurity N and EP impurity O. The EC will consider future revisions to the monograph upon receipt of the necessary supporting data.

Comment Summary #7: The commenter commented that the relative retention times for Acyclovir related compound F and Acyclovir related compound A should be 1.79 and 1.83, respectively.

Response: Comment incorporated.

Comment Summary #8: The commenter suggested including the *Ph. Eur.* naming for Impurities K+R rather than only Bis-acyclovir in Table 2.

Response: Comment not incorporated. The EC determined that the proposal is consistent with the validation data and will consider future revisions to the monograph upon receipt of the necessary supporting data.

Monograph/Section: Acyclovir Injection/Organic impurities

Expert Committee: Small Molecules 1

No. of Commenters: 1

Comment Summary #1: The commenter recommended changing the term “any other individual impurity” to “any individual unspecified impurity” in Table 2.

Response: Comment incorporated.

Monograph/Sections: Atenolol/Organic Impurities

Expert Committee: Small Molecules 2

No. of Commenters: 1

Comment Summary#1: The commenter recommended removing the reporting threshold as it will vary based on product-specific factors.

Response: Comment not incorporated. Based on comments received on a proposed policy for reporting thresholds, USP determined that removal of reporting thresholds from monographs needs further stakeholder engagement. USP intends to do further stakeholder engagement.

Comment Summary #2: The commenter recommended revising the acceptance criteria for the specified impurities and the total impurities to be consistent with what has been approved.

Response: Comment not incorporated. The proposed acceptance criteria are consistent with the sponsor’s FDA-approved application and the EC will consider future revision to the monograph upon receipt of supporting data.

Monograph/Sections: Atenolol Tablets/Organic Impurities

Expert Committee: Small Molecules 2

No. of Commenters: 2

Comment Summary #1: The commenter requested revising the acceptance criteria for atenolol related compound G from NMT 0.20% to NMT 0.25% and for any unspecified impurity from NMT 0.10% to NMT 0.2% to be consistent with their approved specification.

Response: Comment incorporated.

Comment Summary #2: The commenter indicated that atenolol related compound A, atenolol related compound B, atenolol related compound E, and atenolol related compound F should not be reported or included in the total impurities because these are process-related impurities.

Response: Comment not incorporated. These impurities and the corresponding acceptance criteria are part of the approved specification.

Comment Summary #3: The commenter recommended removing the reporting threshold as it will vary based on product-specific factors.

Response: Comment not incorporated. Based on comments received on a proposed policy for reporting thresholds, USP determined that removal of reporting thresholds from monographs needs further stakeholder engagement. USP intends to do further stakeholder engagement.

Comment Summary #4: The commenter recommended revising the acceptance criteria for any unspecified impurity and total impurities for consistency with ICHQ3B and what has been approved.

Response: Comment incorporated. The acceptance criterion for any unspecified impurity is widened from NMT 0.10% to NMT 0.2% and the acceptance criterion for total impurities is widened from NMT 0.50% to NMT 0.60% (also see Comment Summary #1).

Monograph/Section: Butorphanol Tartrate / Multiple sections
Expert Committee: Small Molecules 2
No. of Commenters: 2

Comment Summary #1: The commenter recommended revising the structure of butorphanol tartrate with the correct chiral structure for tartaric acid in the chemical information section to be consistent with what is in the current monograph.

Response: Comment incorporated. The incorrect structure in the proposal was inadvertently introduced during publication.

Comment Summary #2: The commenter recommended replacing the term 'Any individual impurity' with 'Any unspecified impurity' in the test of *Organic Impurities* to be consistent with ICH terminology.

Response: Comment incorporated.

Comment Summary #3: The commenter recommended removing the reporting threshold from the test of *Organic Impurities* as it will vary based on product-specific factors.

Response: Comment not incorporated. Based on comments received on a proposed policy for reporting thresholds, USP determined that removal of reporting thresholds from monographs needs further stakeholder engagement. USP intends to do further stakeholder engagement on the topic.

Comment Summary #4: The commenter requested adopting their method for *Organic Impurities* which is more sensitive and has a shorter run time than the proposed *Organic Impurities* method.

Response: Comment not incorporated. The EC determined that the proposed method for *Organic Impurities* is suitable for the intended use.

Monograph/Section(s): Carbomer 934/Multiple sections
Expert Committee(s): Complex Excipients
No. of Commenters: 1

Comment Summary #1: The commenter recommended keeping the original value of 30,500 mPa·s for the lower limit of the viscosity acceptance criteria in the *Viscosity – Rotational Methods <912>* test and in the *Definition*.

Response: Comment incorporated.

Comment Summary #2: In the *Carboxylic Acid Content* test, a commenter indicated that the units for equivalency factor for the carboxylic acid (–COOH) group should be changed to mg/mEq.

Response: Comment incorporated.

Comment Summary #3: In the *Limit of Benzene* test, the commenter suggested replacing the "Teflon-lined butyl rubber septum" with just "Teflon-lined rubber septum."

Response: Comment incorporated.

EC-initiated Change #1: The Carbomer 934 structure in the chemical information section was updated.

EC-initiated Change #2: In the *Identification C*, the text "or use the method described in *Viscosity—Rotational Methods*" was replaced with "follow the procedure described in the test for *Viscosity—Rotational Methods* until neutralization is complete and the final pH of 7.3 - 7.8 is reached" to provide more clarity for a step in the test procedure at which a very viscous gel is produced.

EC-initiated Change #3: A footnote stating "If formation of a very viscous gel is observed at pH of 7.3 – 7.8, the tested material conforms to *Identification C*" is added to the *Viscosity—Rotational Methods* to connect the step in the test procedure at which a very viscous gel is formed with *Identification C*.

EC-initiated Change #4: In the *Carboxylic Acid Content* test, the phrase “on the dried basis” was deleted from the *Acceptance criteria* because the analysis is conducted on a previously dried sample. This will avoid correcting the content of carboxylic acid for moisture twice.

EC-initiated Change #5: *Standard stock solution* was deleted from *Samples* in the *Analysis* section of the *Limit of Benzene* test because it is only used in preparation of other standard solutions, and it is not intended to be used in the analysis.

EC-initiated Change #6: The equation for calculating the percentage of free acrylic acid in the *Limit of Acrylic Acid* test was corrected. The ratio of the peak response of acrylic acid from the *Sample solution* to the response factor is divided by the concentration of Carbomer 934 in the *Sample solution*.

EC-initiated Change #7: A particle size of 5- μ m was added to the column description in the *Limit of Acrylic Acid* test.

EC-initiated Change #8: In the *Analysis* section of the *Carboxylic Acid Content* test, further clarification as to whether to keep the propeller in the sample mixture or remove it after stirring was added.

Monograph/Section(s): Carbomer 934P/Multiple sections

Expert Committee(s): Complex Excipients

No. of Commenters: 2

Comment Summary #1: The commenter suggested to specify number of injections for *Standard solution A* and *Standard solution C* in the test for *Limit of Acrylic Acid*.

Response: Comment not incorporated. It is understood from the *Analysis* section of the test that *Standard solution A*, *Standard solution B*, and *Standard solution C* should be analyzed once for plotting a calibration curve.

Comment Summary #2: The commenter indicated that the equation for calculating the percentage of free acrylic acid in the *Limit of Acrylic Acid* test is not correct. The ratio of the peak response of acrylic acid from the *Sample solution* to the response factor should be divided by the concentration of Carbomer 934P in the *Sample solution*.

Response: Comment incorporated.

Comment Summary #3: The commenter requested adding a particle size of 5- μ m to the column description in the *Limit of Acrylic Acid* test.

Response: Comment incorporated.

Comment Summary #4: The commenter recommended adding a reference to <621> *Chromatography* to the *Chromatographic system* section in the *Limit of Acrylic Acid* test.

Response: Comment incorporated.

Comment Summary #5: In the *Analysis* section of the *Carboxylic Acid Content* test, the commenter recommended to provide further clarification as to whether to keep the propeller in the sample mixture or remove it after stirring.

Response: Comment incorporated.

Comment Summary #6: In the *Carboxylic Acid Content* test, a commenter indicated that the units for equivalency factor for the carboxylic acid (–COOH) group should be changed to mg/mEq.

Response: Comment incorporated.

Comment Summary #7: The commenter suggested to specify number of injections for *Standard solution A* and *Standard solution C* in the test for *Limit of Benzene*.

Response: Comment not incorporated. It is understood from the *Analysis* section of the test that *Standard solution A*, *Standard solution B*, and *Standard solution C* should be injected once.

Response: Comment incorporated.

Comment Summary #8: In the *Limit of Benzene* test, the commenter suggested replacing the “Teflon-lined butyl rubber septum” with just “Teflon-lined rubber septum.”

Response: Comment incorporated.

EC-initiated Change #1: The Carbomer 934P structure in the chemical information section was updated.

EC-initiated Change #2: In the *Identification C*, the text “or use the method described in *Viscosity—Rotational Methods*” was replaced with “follow the procedure described in the test for *Viscosity—Rotational Methods* until neutralization is complete and the final pH of 7.3 - 7.8 is reached” to provide more clarity for a step in the test procedure at which a very viscous gel is produced.

EC-initiated Change #3: A footnote stating “If formation of a very viscous gel is observed at pH of 7.3 – 7.8, the tested material conforms to *Identification C*” is added to the *Viscosity—Rotational Methods* to connect the step in the test procedure at which a very viscous gel is formed with *Identification C*.

EC-initiated Change #4: In the *Carboxylic Acid Content* test, the phrase “on the dried basis” was deleted from the *Acceptance criteria* because the analysis is conducted on a previously dried sample. This will avoid correcting the content of carboxylic acid for moisture twice.

EC-initiated Change #5: *Standard stock solution* was deleted from *Samples* in the *Analysis* section of the *Limit of Benzene* test because it is only used in preparation of other standard solutions, and it is not intended to be used in the analysis.

Monograph/Section(s): Carbomer 940/Multiple sections

Expert Committee(s): Complex Excipients

No. of Commenters: 2

Comment Summary #1: In the *Carboxylic Acid Content* test, a commenter indicated that the units for equivalency factor for the carboxylic acid (–COOH) group should be changed to mg/mEq.

Response: Comment incorporated

Comment Summary #2: In the *Limit of Benzene* test, the commenter suggested replacing the “Teflon-lined butyl rubber septum” with just “Teflon-lined rubber septum.”

Response: Comment incorporated.

Comment Summary #3: A commenter proposed an in-house procedure for the *Limit of Benzene* test claiming that it is more precise.

Response: Comment not incorporated. The EC will consider the recommendations proposed in the commenter’s procedure and will consider a future revision.

EC-initiated Change #1: The Carbomer 940 structure in the chemical information section was updated.

EC-initiated Change #2: In the *Identification C*, the text “or use the method described in *Viscosity—Rotational Methods*” was replaced with “follow the procedure described in the test for *Viscosity—Rotational Methods* until neutralization is complete and the final pH of 7.3 - 7.8 is reached” to provide more clarity for a step in the test procedure at which a very viscous gel is produced.

EC-initiated Change #3: A footnote stating “If formation of a very viscous gel is observed at pH of 7.3 – 7.8, the tested material conforms to *Identification C*” is added to the *Viscosity—Rotational Methods* to connect the step in the test procedure at which a very viscous gel is formed with *Identification C*.

EC-initiated Change #4: In the *Carboxylic Acid Content* test, the phrase “on the dried basis” was deleted from the *Acceptance criteria* because the analysis is conducted on a previously dried sample. This will avoid correcting the content of carboxylic acid for moisture twice.

EC-initiated Change #5: *Standard stock solution* was deleted from *Samples* in the *Analysis* section of the *Limit of Benzene* test because it is only used in preparation of other standard solutions, and it is not intended to be used in the analysis.

EC-initiated Change #6: The equation for calculating the percentage of free acrylic acid in the *Limit of Acrylic Acid* test was corrected. The ratio of the peak response of acrylic acid from the

Sample solution to the response factor is divided by the concentration of Carbomer 940 in the *Sample solution*.

EC-initiated Change #7: A particle size of 5- μ m was added to the column description in the *Limit of Acrylic Acid* test.

EC-initiated Change #8: In the *Analysis* section of the *Carboxylic Acid Content* test, further clarification as to whether to keep the propeller in the sample mixture or remove it after stirring was added.

Monograph/Section(s): Carbomer 941/Multiple sections

Expert Committee(s): Complex Excipients

No. of Commenters: 2

Comment Summary #1: The commenter suggested to specify number of injections for *Standard solution A* and *Standard solution C* in the test for *Limit of Acrylic Acid*.

Response: Comment not incorporated. It is understood from the *Analysis* section of the test that *Standard solution A*, *Standard solution B*, and *Standard solution C* should be analyzed once for plotting a calibration curve.

Comment Summary #2: The commenter indicated that the equation for calculating the percentage of free acrylic acid in the *Limit of Acrylic Acid* test is not correct. The ratio of the peak response of acrylic acid from the *Sample solution* to the response factor should be divided by the concentration of Carbomer 941 in the *Sample solution*.

Response: Comment incorporated.

Comment Summary #3: The commenter requested adding a particle size of 5- μ m to the column description in the *Limit of Acrylic Acid* test.

Response: Comment incorporated.

Comment Summary #4: In the *Analysis* section of the *Carboxylic Acid Content* test, the commenter recommended to provide further clarification as to whether to keep the propeller in the sample mixture or remove it after stirring.

Response: Comment incorporated.

Comment Summary #5: In the *Carboxylic Acid Content* test, a commenter indicated that the units for equivalency factor for the carboxylic acid (–COOH) group should be changed to mg/mEq.

Response: Comment incorporated.

Comment Summary #6: The commenter suggested to specify number of injections for *Standard solution A* and *Standard solution C* in the test for *Limit of Benzene*.

Response: Comment not incorporated. It is understood from the *Analysis* section of the test that *Standard solution A*, *Standard solution B*, and *Standard solution C* should be injected once.

Response: Comment incorporated.

Comment Summary #7: In the *Limit of Benzene* test, the commenter suggested replacing the “Teflon-lined butyl rubber septum” with just “Teflon-lined rubber septum.”

Response: Comment incorporated.

EC-initiated Change #1: The Carbomer 941 structure in the chemical information section was updated.

EC-initiated Change #2: In the *Identification C*, the text “or use the method described in *Viscosity—Rotational Methods*” was replaced with “follow the procedure described in the test for *Viscosity—Rotational Methods* until neutralization is complete and the final pH of 7.3 - 7.8 is reached” to provide more clarity for a step in the test procedure at which a very viscous gel is produced.

EC-initiated Change #3: A footnote stating “If formation of a very viscous gel is observed at pH of 7.3 – 7.8, the tested material conforms to *Identification C*” is added to the *Viscosity—Rotational Methods* to connect the step in the test procedure at which a very viscous gel is formed with *Identification C*.

EC-initiated Change #4: In the *Carboxylic Acid Content* test, the phrase “on the dried basis” was deleted from the *Acceptance criteria* because the analysis is conducted on a previously dried sample. This will avoid correcting the content of carboxylic acid for moisture twice.

EC-initiated Change #5: *Standard stock solution* was deleted from *Samples* in the *Analysis* section of the *Limit of Benzene* test because it is only used in preparation of other standard solutions, and it is not intended to be used in the analysis.

Monograph/Section(s): Carbomer 1342/Multiple sections

Expert Committee(s): Complex Excipients

No. of Commenters: 2

Comment Summary #1: The commenter recommended keeping the original value of 9500 mPa·s for the lower limit of the viscosity acceptance criteria in the *Viscosity – Rotational Methods <912>* test and in the *Definition*.

Response: Comment incorporated.

Comment Summary #2: The commenter proposed keeping the original sample weight of 5.0 g in the *Viscosity – Rotational Methods <912>* test. The acceptance criteria for viscosity in the test was historically established on 1% dispersion of Carbomer 1342.

Response: Comment incorporated.

Comment Summary #3: The commenter suggested to specify number of injections for *Standard solution A* and *Standard solution C* in the test for *Limit of Acrylic Acid*.

Response: Comment not incorporated. It is understood from the *Analysis* section of the test that *Standard solution A*, *Standard solution B*, and *Standard solution C* should be analyzed once for plotting a calibration curve.

Comment Summary #4: The commenter indicated that the equation for calculating the percentage of free acrylic acid in the *Limit of Acrylic Acid* test is not correct. The ratio of the peak response of acrylic acid from the *Sample solution* to the response factor should be divided by the concentration of Carbomer 1342 in the *Sample solution*.

Response: Comment incorporated.

Comment Summary #5: The commenter requested adding a particle size of 5-µm to the column description in the *Limit of Acrylic Acid* test.

Response: Comment incorporated.

Comment Summary #6: In the *Analysis* section of the *Carboxylic Acid Content* test, the commenter recommended to provide further clarification as to whether to keep the propeller in the sample mixture or remove it after stirring.

Response: Comment incorporated.

Comment Summary #7: In the *Carboxylic Acid Content* test, a commenter indicated that the units for equivalency factor for the carboxylic acid (–COOH) group should be changed to mg/mEq.

Response: Comment incorporated.

Comment Summary #8: The commenter suggested to specify number of injections for *Standard solution A* and *Standard solution C* in the test for *Limit of Benzene*.

Response: Comment not incorporated. It is understood from the *Analysis* section of the test that *Standard solution A*, *Standard solution B*, and *Standard solution C* should be injected once.

Response: Comment incorporated.

Comment Summary #9: In the *Limit of Benzene* test, the commenter suggested replacing the “Teflon-lined butyl rubber septum” with just “Teflon-lined rubber septum.”

Response: Comment incorporated.

EC-initiated Change #1: The Carbomer 1342 structure in the chemical information section was updated.

EC-initiated Change #2: In the *Identification C*, the text “or use the method described in *Viscosity—Rotational Methods*” was replaced with “follow the procedure described in the test for

Viscosity—Rotational Methods until neutralization is complete and the final pH of 7.3 - 7.8 is reached” to provide more clarity for a step in the test procedure at which a very viscous gel is produced.

EC-initiated Change #3: A footnote stating “If formation of a very viscous gel is observed at pH of 7.3 – 7.8, the tested material conforms to *Identification C*” is added to the *Viscosity—Rotational Methods* to connect the step in the test procedure at which a very viscous gel is formed with *Identification C*.

EC-initiated Change #4: In the *Carboxylic Acid Content* test, the phrase “on the dried basis” was deleted from the *Acceptance criteria* because the analysis is conducted on a previously dried sample. This will avoid correcting the content of carboxylic acid for moisture twice.

EC-initiated Change #5: *Standard stock solution* was deleted from *Samples* in the *Analysis* section of the *Limit of Benzene* test because it is only used in preparation of other standard solutions, and it is not intended to be used in the analysis.

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

Identification A

Comment Summary #1: The commenter suggested rephrasing HPTLC System Suitability Requirements and Acceptance Criteria to accommodate multiple HPTLC plates.

Response: Comment incorporated.

Composition

Comment Summary #2: The commenter suggested making following changes based on the investigation test results from USP laboratories for USP *Chrysanthemum × morifolium* Flower Dry Extract RS.

1. Add 0.1% glacial acetic acid in *Solution B* to keep *pH* consistent for the gradient mobile phases.
2. Extend 10 min more to wash the column after HPLC gradient to clean the column sufficiently before next injection.
3. Change column temperature from 25° to 20° to increase resolution between peaks of isochlorogenic acid A and apigenin-7-O-glucoside.
4. Change isochlorogenic acid B to an identification marker from a quantitative marker since it was partially co-eluted with unknown peaks.
5. Change RRT for luteolin-7-O-glucuronide to 1.1 - 1.2.
6. Add a theoretical plate number of NLT 10000 in System Suitability Requirements to make sure a sufficient column efficiency.
7. Add “Before injection test solutions, equilibrate the column more than 1 h” under analysis.

Response: Comments incorporated.

Comment Summary #3: The commenter suggested changing isochlorogenic acid C to an identification marker from a quantitative marker because LC/MS results from USP laboratory displayed that isochlorogenic acid C was co-eluted with other components.

Response: Comment incorporated. The acceptance criteria for total caffeoyquinic acids were changed to NLT 0.8% accordingly.

Comment Summary #4: The commenter requested to change diosmetin-7-O-glucoside to luteolin-7-O-malonylglucoside because LC/MS results from USP Lab showed the peak at around 42.3 min (RRT 1.8) was luteolin-7-O-malonylglucoside not diosmetin-7-O-glucoside.

Response: Comment incorporated.

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

Identification A

Comment Summary #1: The commenter suggested rephrasing HPTLC System Suitability Requirements and Acceptance Criteria to accommodate multiple HPTLC plates.

Response: Comment incorporated.

Composition

Comment Summary #2: The commenter suggested doing following changes based on the investigation test results from USP laboratories for USP *Chrysanthemum × morifolium* Flower Dry Extract RS.

1. Add 0.1% glacial acetic acid in *Solution B* to keep *pH* consistent for the gradient mobile phases.
2. Extend 10 min more to wash the column after HPLC gradient to clean the column sufficiently before next injection.
3. Change column temperature from 25° to 20° to increase resolution between peaks of isochlorogenic acid A and apigenin-7-O-glucoside.
4. Change isochlorogenic acid B to an identification marker from a quantitative marker since it was partially co-eluted with unknown peaks.
5. Change RRT for luteolin-7-O-glucuronide to 1.1 - 1.2.
6. Add a theoretical plate number of NLT 10000 in System Suitability Requirements to make sure a sufficient column efficiency.
7. Add "Before injection test solutions, equilibrate the column more than 1 h" under analysis.

Response: Comments incorporated.

Comment Summary #3: The commenter suggested changing isochlorogenic acid C to an identification marker from a quantitative marker because LC/MS results from USP laboratory displayed that isochlorogenic acid C was co-eluted with other components.

Response: Comment incorporated. The acceptance criteria for total caffeoyquinic acids were changed to NLT 0.8% accordingly.

Comment Summary #4: The commenter requested to change diosmetin-7-O-glucoside to luteolin-7-O-malonylglucoside because LC/MS results from USP lab showed the peak at around 42.3 min (RRT 1.8) was luteolin-7-O-malonylglucoside not diosmetin-7-O-glucoside.

Response: Comment incorporated.

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

Identification A

Comment Summary #1: The commenter suggested rephrasing HPTLC System Suitability Requirements and Acceptance Criteria to accommodate multiple HPTLC plates.

Response: Comment incorporated.

Composition

Comment Summary #2: The commenter suggested doing following changes based on the investigation test results from USP laboratories for USP *Chrysanthemum × morifolium* Flower Dry Extract RS.

1. Add 0.1% glacial acetic acid in *Solution B* to keep *pH* consistent for the gradient mobile phases.
2. Extend 10 min more to wash the column after HPLC gradient to clean the column sufficiently before next injection.
3. Change column temperature from 25° to 20° to increase resolution between peaks of isochlorogenic acid A and apigenin-7-O-glucoside.
4. Change isochlorogenic acid B to an identification marker from a quantitative marker since it was partially co-eluted with unknown peaks.
5. Change RRT for luteolin-7-O-glucuronide to 1.1 - 1.2.
6. Add a theoretical plate number of NLT 10000 in System Suitability Requirements to make sure a sufficient column efficiency.
7. Add "Before injection test solutions, equilibrate the column more than 1 h" under analysis.

Response: Comments incorporated.

Comment Summary #3: The commenter suggested changing isochlorogenic acid C to an identification marker from a quantitative marker because LC/MS results from USP laboratories displayed that isochlorogenic acid C was co-eluted with other components.

Response: Comment incorporated.

Comment Summary #4: The commenter requested to change diosmetin-7-O-glucoside to luteolin-7-O-malonylglucoside because LC/MS results from USP Lab showed the peak at around 42.3 min (RRT 1.8) was luteolin-7-O-malonylglucoside not diosmetin-7-O-glucoside.

Response: Comment incorporated.

Monograph/Section: Dichlorphenamide/Organic impurities

Expert Committee: Small Molecules 3

No. of Commenters: 1

Comment Summary #1: The commenter requested removing the "reporting threshold" as it will vary based on product-specific factors.

Response: Comment not incorporated. Based on comments received on a proposed policy for reporting thresholds, USP determined that removal of reporting thresholds from monographs needs further stakeholder engagement. USP intends to do further stakeholder engagement.

Monograph/Section: Doxycycline/Multiple Sections

Expert Committee: Small Molecules 1

No. of Commenters: 3

Comment Summary #1: The commenter requested removing the reporting threshold from the test for *Organic Impurities* as it will vary based on product-specific factors.

Response: Comment not incorporated. Based on comments received on a proposed policy for reporting thresholds, USP determined that removal of reporting thresholds from monographs needs further stakeholder engagement. USP intends to do further stakeholder engagement on the topic.

Comment Summary #2: The commenter requested including <197K> in *Identification A* and allowing the flexibility of using either <197A> or <197K> as proposed in the Doxycycline Hyclate monograph.

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

Comment Summary #3: The commenter recommended using the same USP standard of doxycycline, in the tests for *Assay* and *Organic Impurities* in both Doxycycline and Doxycycline Hyclate monographs.

Response: Comment not incorporated. The EC determined the use of USP Doxycycline Monohydrate RS is suitable for Doxycycline monograph.

Comment Summary #4: The commenter indicated there are slight differences in the relative retention times and relative response factors for *Organic Impurities* test between Doxycycline and Doxycycline Hyclate monographs and recommended using the same values of relative retention times and relative response factors in both monographs.

Response: Comment not incorporated. The EC determined the relative retention times and relative response factors are consistent with the validation data.

Monograph/Section: Doxycycline Hyclate/Multiple Sections

Expert Committee: Small Molecules 1

No. of Commenters: 2

Comment Summary #1: The commenter requested removing the reporting threshold from the test for *Organic Impurities* as it will vary based on product-specific factors.

Response: Comment not incorporated. Based on comments received on a proposed policy for reporting thresholds, USP determined that removal of reporting thresholds from monographs needs further stakeholder engagement. USP intends to do further stakeholder engagement on the topic.

Comment Summary #2: The commenter recommended adopting the same acceptance criteria of 4.3%-6.0% for both human and veterinary products in the test for *Content of Ethanol*.

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

Comment Summary #3: The commenter recommended using the same USP standard of doxycycline, in the tests for *Assay* and *Organic Impurities* in both Doxycycline and Doxycycline Hyclate monographs.

Response: Comment not incorporated. The EC determined the use of USP Doxycycline Hyclate RS in both tests is suitable for Doxycycline Hyclate monograph based on the supporting data.

Comment Summary #4: The commenter indicated there are slight differences in the relative retention times and relative response factors for *Organic Impurities* test between Doxycycline and Doxycycline Hyclate monographs and recommended using the same values of relative retention times and relative response factors in both monographs.

Response: Comment not incorporated. The EC determined the relative retention times and relative response factors are consistent with the validation data.

Monograph/Section: Dutasteride/Multiple sections

Expert Committee: Small Molecules 5

No. of Commenters: 1

Comment Summary #1: The commenter recommended revising the acceptance criteria for *Water Determination* under *Specific Tests* to be consistent with what has been approved.

Response: Comment not incorporated. The comment is outside of the scope of the revision. The EC will consider future revisions to the monograph upon receipt of supporting data.

EC Initiated Change #1: Revise “Any other individual impurity” to “Any unspecified impurity.” In *Organic Impurities, Procedure 1, Table 3* and *Organic Impurities, Procedure 2, Table 4* to be consistent with ICH Q3A terminology.

Monograph/Sections: Everolimus/Multiple sections

Expert Committee: Small Molecules 1

No. of Commenters: 2

Comment Summary #1: The commenter requested removing the redundant entries for “Everolimus” from Table 4 in the test for *Limit of Sirolimus*.

Response: Comment Incorporated

Comment Summary #2: The commenter requested removing the reporting threshold from the tests for *Organic Impurities* and *Limit of Sirolimus* as it will vary based on product-specific factors.

Response: Comment not incorporated. Based on comments received on a proposed policy for reporting thresholds, USP determined that removal of reporting thresholds from monographs needs further stakeholder engagement. USP intends to do further stakeholder engagement on the topic.

Comment Summary #3: The commenter requested removing the detector temperature information under the Note in the test for *Limit of Sirolimus*.

Response: Comment not incorporated. The EC determined that the detector temperature information under the Note is useful to the user as demonstrated by the supporting data.

EC-Initiated Change #1: In the test for *Organic Impurities*, the formula for calculating the percentage of each impurity was updated with the relative response factor (F) in the denominator instead of the numerator to be consistent with USP style and the values for *Relative Response Factor* listed in Table 2.

Monograph/Section: Flucytosine/Multiple Sections

Expert of Committee: Small Molecules 1

No. of Commenters: 3

Comment Summary #1: The commenter recommended addition of an IR test for *Identification*.

Response: Comment not incorporated. The comment is outside of the scope of the revision. The EC will consider future revisions to the monograph upon receipt of supporting data.

Comment Summary #2: The commenter requested removing the reporting threshold from *Organic Impurities* test as it will vary based on product-specific factors.

Response: Comment not incorporated. Based on comments received on a proposed policy for reporting thresholds, USP determined that removal of reporting thresholds from monographs needs further stakeholder engagement. USP intends to do further stakeholder engagement.

Comment Summary #3: The commenter indicated the proposed *Organic Impurities* method is not specific for the impurity “2,4-Dichloro-5-fluoropyrimidine.”

Response: Comment not incorporated. The comment is outside of the scope of the revision. The EC will consider future revisions to the monograph upon receipt of supporting data.

Comment Summary #4: The commenter recommended that their method for *Organic Impurities* test should be adopted for this monograph as their method provides higher capacity than the proposed method.

Response: Comment not incorporated. The EC determined that the proposed method is suitable for the intended use.

Monograph/Section: Flucytosine Capsules/ Organic Impurities

Expert of Committee: Small Molecules 1

No. of Commenters: 1

Comment Summary #1: The commenter requested removing the reporting threshold as it will vary based on product-specific factors.

Response: Comment not incorporated. Based on comments received on a proposed policy for reporting thresholds, USP determined that removal of reporting thresholds from monographs needs further stakeholder engagement. USP intends to do further stakeholder engagement.

Monograph/Sections: Formoterol Fumarate/Organic Impurities

Expert Committee: Small Molecules 4

No. of Commenters: 1

Comment Summary #1: The commenter recommended removing the “reporting threshold” as it will vary based on product-specific factors.

Response: Comment not incorporated. The comment is outside of the scope of the revision. Based on comments received on a proposed policy for reporting thresholds, USP determined that removal of reporting thresholds from monographs needs further stakeholder engagement. USP intends to do further stakeholder engagement.

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

Expert Committee: Small Molecules 2

No. of Commenters: 1

Comment Summary #1: The commenter requested adding acceptance criteria for other specified degradation products, unspecified degradation products, and total degradation products to the *Impurities* section of the monograph to be consistent with what has been approved.

Response: Comment not incorporated. This comment is outside of the scope of the proposed revisions. The EC will consider future revisions to this monograph upon the receipt of the necessary supporting data.

EC-initiated Change #1: Show the inadvertently omitted revision mark-up around the *Signal-to-noise ratio* requirement within the test for the *Limit of Furosemide Related Compound B*. This revision was acknowledged in the *Briefing* when published in *PF*

Monograph/Section(s): Galantamine Hydrobromide/Multiple Sections

Expert Committee: Small Molecules 4

No. of Commenters: 1

Comment Summary #1: The commenter recommended removing the “reporting threshold” in the test for *Organic Impurities* as it will vary based on product-specific factors.

Response: Comment not incorporated. The comment is outside of the scope of the revision. Based on comments received on a proposed policy for reporting thresholds, USP determined that removal of reporting thresholds from monographs needs further stakeholder engagement. USP intends to do further stakeholder engagement.

Comment Summary #2: The commenter requested revising the acceptance criterion in the test for the *Loss on Drying* for consistency with what has been approved.

Response: Comment not incorporated. This comment is outside of the scope of the proposed revisions. The EC will consider future revisions to this monograph upon the receipt of the necessary supporting data.

Monograph/Section(s): Hydrochlorothiazide/Organic Impurities

Expert Committee: Small Molecules 2

No. of Commenters: 1

Comment Summary #1: The commenter requested replacing the term “any other individual impurity” with “any unspecified impurity” and revising the acceptance criterion.

Response: Comment not incorporated. This comment is outside of the scope of the proposed revisions. The EC will consider future revisions to this monograph upon the receipt of the necessary supporting data.

Comment Summary #2: The commenter requested removing the reporting threshold as it will vary based on product-specific factors.

Response: Comment not incorporated. Based on comments received on a proposed policy for reporting thresholds, USP determined that removal of reporting thresholds from monographs needs further stakeholder engagement. USP intends to do further stakeholder engagement.

Monograph/Sections: Hydroxyzine Hydrochloride/Organic Impurities

Expert Committee: Small Molecules 4

No. of Commenters: 1

Comment Summary #1: The commenter requested removing the “reporting threshold” as it will vary based on product-specific factors.

Response: Comment not incorporated. Based on comments received on a proposed policy for reporting thresholds, USP determined that removal of reporting thresholds from monographs needs further stakeholder engagement. USP intends to do further stakeholder engagement.

Monograph/Section: Malathion/ Organic Impurities

Expert of Committee: Small Molecules 1

No. of Commenters: 1

Comment Summary #1: The commenter requested removing the reporting threshold as it will vary based on product-specific factors.

Response: Comment not incorporated. Based on comments received on a proposed policy for reporting thresholds, USP determined that removal of reporting thresholds from monographs needs further stakeholder engagement. USP intends to do further stakeholder engagement.

Monograph/Section(s): Maltol/Organic impurities

Expert Committee(s): Simple Excipients

No. of Commenters: 4

Comment Summary #1: The commenter recommended making a distinction between impurities and concomitant components in the excipient monograph.

Response: Comment incorporated. This approach aligns with the Excipient ECs’ proposed definitions for impurities and concomitant components reflecting its current general principles and practices as appearing in the 2018 USP Stimuli article on Excipient Composition and Impurities titled “*The Complexity of Setting Compendial Specifications for Excipient Composition and Impurities*” in PF 44(3).

Comment Summary #2: The commenter recommended setting impurity/component specification based on toxicological assessment.

Response: Comment incorporated. Excipient ECs modernized the Maltol monograph. Additionally, the term, “unspecified impurity” was changed to “unidentified impurity” in the *Organic Impurities* test.

Comment Summary #3: The commenter requested not to apply an approach intended to address impurities in APIs, such as ICH Q3A, to excipients.

Response: Comment incorporated. Excipient ECs do not apply ICH Q3A for any excipient compendial standard studied, including Maltol. Excipient ECs follow the USP Request for Revision guideline, https://www.usp.org/sites/default/files/usp/document/get-involved/submission-guidelines/excipients_rfr_guideline-28apr16.pdf as well as the general principles and practices that were proposed in the 2018 *Stimuli* article on Excipient Composition and Impurities in PF 44(3).

Comment Summary #4: The commenter requested including rationale for the proposed organic impurity specifications (i.e., NMT 0.1% for any individual unspecified impurity and NMT 1.0% total impurities) in the briefing.

Response: Comment incorporated. In future, Excipient ECs will provide additional clarity in the briefing section of the *PF* proposal in similar instances.

Comment Summary #5: The commenter recommended adding an additional section to the *General Notices* that would address excipient composition and impurities

Response: Comment not incorporated. The Excipient ECs are currently working on developing a policy/strategy on excipient impurities and have been actively engaging stakeholders through the 2018 Stimuli article, survey, open fora, stakeholder fora, etc. to develop such a policy and develop future revisions to the USP *General Notices*. USP will consider future updates to the USP General Notices to include requirements for excipient composition and impurities targeted for proposal in a future *PF*.

Comment Summary #6: The commenter recommended forming an advisory panel or collaborative working group for excipient impurities.

Response: Comment incorporated. In the current revision cycle, the USP Excipients Impurities Joint Subcommittee is working with stakeholders on the formation of an Excipients impurities project team or similar group that will include experts from industry, regulators and other key stakeholders.

Comment Summary #7: The commenter recommended having a meeting with USP to discuss the subject of excipient impurities and composition in greater detail.

Response: Comment incorporated. USP hosted several stakeholder engagement meetings in both the previous and current revision cycles, including the 2019 Excipients Stakeholder Forum, and the Excipient Open Forum in Feb 2021 at which the presentation titled “USP Addressing Maltol *PF* 46 (2) comments” was presented on behalf of the Simple Excipients EC. The 2021 Excipient Open Forum meeting summary and the presentation can be referenced from <https://www.usp.org/get-involved/provide-input/stakeholder-forums/excipients-stakeholder-forum-feb-2021> .

Monograph/Sections: Magnesium Sulfate/Multiple Sections

Expert Committee(s): Small Molecules 5

No. of Commenters: 2

Comment Summary #1: The commenter recommended retaining the currently official procedures for *Assay* and *Identification* test with adopting the widened assay acceptance criteria of 98.0 - 102.0%. The current titration procedure under *Assay* is suitable for testing and cost effective.

Response: Comment not incorporated. The EC determined that the proposed ion chromatography-based procedure is specific compared to the current titration-based procedure.

Comment Summary #2: The commenter recommended replacing the current manual titration method under *Assay* with the use of automatic titrator having potentiometric detection of the point of equivalence.

Response: Comment not incorporated. The EC determined that the proposed ion chromatography-based procedure is more specific and it would strengthen the compendial standard.

Comment Summary #3: The commenter indicated that the assay acceptance criteria were widened without justification. Such change would require users to establish system suitability requirements for separating magnesium and calcium ions and tailing factor for such chromatograph system.

Response: Comment not incorporated. The EC determined that the proposed acceptance criteria is to reflect the change in the *Assay* from titration to chromatography. Magnesium and calcium ions are well separated by this proposed ion chromatography-based procedure with relative retention times for the magnesium and calcium ions as 1.0 and 1.3, respectively.

Comment Summary #4: The commenter indicated that the new *Identification* test for *Magnesium* based on retention time agreement obtained from the proposed ion chromatography-based procedure is less specific than the chemical test in the current monograph.

Response: Comment not incorporated. The EC determined that the proposed ion chromatography-based procedure is more specific and it would strengthen the compendial standard.

Monograph/Section: Meclofenamate Sodium Capsules/Organic Impurities

Expert Committee: Small Molecules 2

No. of Commenters: 1

Comment Summary #1: The commenter requested removing the reporting threshold as it will vary based on product-specific factors.

Response: Comment not incorporated. Based on comments received on a proposed policy for reporting thresholds, USP determined that removal of reporting thresholds from monographs needs further stakeholder engagement. USP intends to do further stakeholder engagement.

Monograph/Section: Methimazole/Organic impurities

Expert Committee: Small Molecules 3

No. of Commenters: 1

Comment Summary #1: The commenter requested removing the “reporting threshold” as it will vary based on product-specific factors.

Response Comment not incorporated. The comment is outside of the scope of the revision. Based on comments received on a proposed policy for reporting thresholds, USP determined that removal of reporting thresholds from monographs needs further stakeholder engagement. USP intends to do further stakeholder engagement.

Monograph/Section: Naproxen Compounded Oral Suspension

Expert Committee: Compounding

Number of Commenters: 2

Comment Summary #1: A commenter indicated that the monograph uses proprietary ingredients in the formulation where there is no information about the identity of the excipient provided in the monograph.

Response: Comment not incorporated. USP does not provide information on proprietary ingredients. Information on the content of proprietary ingredient is generally available from suppliers.

Comment Summary #2: A commenter recommended the monograph contain the labeling indicating the preparation be shaken well before use.

Response: Comment incorporated

Monograph/Section: Oxiconazole Nitrate/Multiple sections

Expert Committee: Small Molecules 1

No. of Commenters: 2

Comment Summary #1: The commenter noted that the proposed acceptance criteria for *Assay* and *Residue on Ignition* are different from those in some of the FDA-approved applications.

Response: Comment not incorporated. The acceptance criteria are consistent with the sponsor’s FDA-approved application. The EC will consider future revision to the monograph upon receipt of supporting data.

Comment Summary #2: The commenter noted that the proposed acceptance criterion for *Loss on Drying* is different from the FDA-approved applications.

Response: Comment incorporated. The acceptance criterion for *Loss on Drying* was widened from NMT 0.5% to NMT 1.0%.

Comment Summary #3: The commenter requested adding an alternate column and revising the tailing factor for oxiconazole nitrate from NMT 2.0 to NMT 2 in the *Assay*.

Response: Comment not incorporated. The EC determined that the

proposed method is suitable for the intended use as a public standard. The EC will consider revisions in the future upon receipt of supporting data.

Comment Summary #4: The commenter commented that the acceptance criteria for Oxiconazole related compound A, Oxiconazole related compound B, and Total impurities in the test for *Organic Impurities* are different from those in some of the FDA-approved applications.

Response: Comment not incorporated. The acceptance criteria are consistent with the sponsor's FDA-approved application. The EC will consider a future revision to the monograph upon receipt of supporting data.

Comment Summary #5: The commenter commented that the impurity of Oxiconazole related compound E in the test for *Organic Impurities* is a potential genotoxic impurity. The acceptance criterion of NMT 0.15% for this impurity is very high.

Response: Comment not incorporated. The EC determined that the Oxiconazole related compound E impurity is not considered genotoxic based on sponsor's Bacterial Reverse Mutation Assay. The EC will consider future revisions to the monograph upon receipt of the necessary supporting data.

Monograph/Sections: Phenoxybenzamine Hydrochloride/Organic Impurities

Expert Committee: Small Molecules 2

No. of Commenters: 4

Comment Summary #1: The commenter recommended revising the acceptance criterion of NMT 0.10% for phenoxybenzamine alcohol to be consistent with what has been approved by the agency and to be in line with ICH Q3A.

Response: Comment not incorporated. The specification in the monograph reflects an FDA-approved requirement. The EC will consider future revisions upon the receipt of supporting data.

Comment Summary #2: The commenter requested adding a note so that an unknown peak associated with USP Phenoxybenzamine RS is not integrated.

Response: Comment not incorporated. The EC determined that the observed peak is an artifact from the diluent.

Comment Summary #3: The commenter indicated that the procedure does not account for all process impurities.

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

Comment Summary #4: The commenter requested revising the acceptance criteria for a compound eluting with a relative retention time of about 0.34 and indicated that the test may not be suitable to quantitate this impurity.

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

Monograph/Section: Phentermine Hydrochloride/Organic Impurities

Expert Committee: Small Molecules 2

No. of Commenters: 4

Comment Summary #1: The commenter requested removing the reporting threshold as it will vary based on product-specific factors.

Response: Comment not incorporated. The comment is outside of the scope of the revision. Based on comments received on a proposed policy for reporting thresholds, USP determined that removal of reporting thresholds from monographs needs further stakeholder engagement. USP intends to do further stakeholder engagement.

Comment Summary #2: The commenters indicated that the acceptance criteria for phentermine related compound A, phentermine alcohol, phentermine related compound C and total impurities are different from what have been approved.

Response: Comment incorporated. Based on the available information from the FDA-approved applications (see the Comment Summary #3 and #4), the acceptance criteria were revised from NMT 0.10% to NMT 0.15% for phentermine related compound A; from NMT 0.10% to NMT 0.1% for both phentermine alcohol and phentermine related compound C and from NMT 0.50% to NMT 1.0% for total impurities.

Comment Summary #3: The commenter indicated that the acceptance criteria should be revised from 0.10% to NMT 0.15% for phentermine related compound A and from NMT 0.50% to NMT 1.0% for total impurities based on their FDA-approved application.

Response: Comment incorporated.

Comment Summary #4: The commenter indicated that the acceptance criteria should be revised from 0.10% to NMT 0.1% for both phentermine alcohol and phentermine related compound C based on their FDA-approved application.

Response: Comment incorporated.

Comment Summary #5: The commenter indicated that the impurity “N-N-Acetyl- α,α -dimethylphenethylamine” controlled at NMT 0.10% for their API is not specified in this monograph.

Response: Comment not incorporated. The EC determined that the control of this impurity at NMT 0.10% which is equivalent to the limit for any unspecified impurity doesn't need to be specified in this monograph as a public standard.

EC-Initiated Change #1: The reagent name “sodium 1-heptanesulphonate” in the *Buffer* for *Organic Impurities* test and the *Buffer* for the *Limit of Phentermine Related Compound C* test will be corrected to “sodium 1-heptanesulfonate.”

Monograph/Sections: Phentolamine Mesylate/Organic Impurities

Expert Committee: Small Molecules 2

No. of Commenters: 1

Comment Summary #1: The commenter recommended removing the reporting threshold as it will vary based on product-specific factors.

Response: Comment not incorporated. Based on comments received on a proposed policy for reporting thresholds, USP determined that removal of reporting thresholds from monographs needs further stakeholder engagement. USP intends to do further stakeholder engagement.

Comment Summary #2: The commenter recommended revising the acceptance criterion for phentolamine keto analog to be consistent with what has been approved.

Response: Comment not incorporated. The specification in the monograph reflects an FDA-approved requirement. The EC will consider revisions in the future upon the receipt of supporting data.

Monograph/Sections: Phentolamine Mesylate Injection (published in *PF* as Phentolamine Injection)/Multiple Sections

Expert Committee: Small Molecules 2

No. of Commenters: 1

Comment Summary #1: The commenter recommended revising the monograph title from “Phentolamine Injection” to “Phentolamine Mesylate Injection.”

Response: Comment incorporated.

Comment Summary #2: The commenter recommended removing the reporting threshold in the test for *Organic Impurities* as it will vary based on product-specific factors.

Response: Comment not incorporated. Based on comments received on a proposed policy for reporting thresholds, USP determined that removal of reporting thresholds from monographs needs further stakeholder engagement. USP intends to do further stakeholder engagement.

EC-initiated Change #1: The *Definition* section was updated to reflect the monograph title change.

Monograph/Section: Prednisolone Sodium Phosphate Compounded Oral Solution
Expert Committee: Compounding
Number of Commenters: 1

Comment Summary #1: A commenter indicated that the monograph uses proprietary ingredients in the formulation where there is no information about the composition of the proprietary ingredients in the monograph.

Response: Comment not incorporated. USP does not provide information on proprietary ingredients. Information on the content of proprietary ingredient is generally available from suppliers.

Monograph/Section(s): Propofol/Multiple Sections
Expert Committee: Small Molecules 5
No. of Commenters: 1

Comment Summary #1: The commenter recommended changing “Any other individual impurity” to “Any unspecified impurity” in both Procedure 1 and Procedure 2 in *Organic Impurities* tests to be consistent with ICH Q3A terminology.

Response: Comment incorporated.

Comment Summary #2: The commenter recommended tightening the limit of any unspecified impurity from NMT 0.1% to NMT 0.10% in *Procedure 1* in *Organic Impurities* test.

Response: Comment not incorporated. This comment is outside the scope of the revision. Furthermore, tightening the limit requires republishing in *PF* for comments. The EC will consider a future revision to the monograph upon receipt of the supporting data.

Comment Summary #3: The commenter recommended tightening the RSD requirements in both Procedure 1 and Procedure 2 under *Assay* to align with General Chapter <621> requirement.

Response: Comment not incorporated. This comment is outside the scope of the revision. Tightening RSD requires republishing in *PF* for comments. The EC will consider a future revision to the monograph upon receipt of the supporting data.

Monograph/Sections: Selegiline Hydrochloride Capsules/Organic Impurities
Expert Committee: Small Molecules 4
No. of Commenters: 1

Comment Summary #1: The commenter recommended removing the “reporting threshold” as it will vary based on product-specific factors.

Response: Comment not incorporated. Based on comments received on a proposed policy for reporting thresholds, USP determined that removal of reporting thresholds from monographs needs further stakeholder engagement. USP intends to do further stakeholder engagement.

Comment Summary #2: The commenter requested tightening the acceptance criterion for “Any individual unspecified degradation product” to be consistent with the identification threshold in ICH Q3B and what has been approved by the agency.

Response: Comment not incorporated. This comment is outside the scope of the revision. The specification in the monograph reflects an FDA-approved requirement. The EC will consider future revisions upon the receipt of supporting data.

EC-initiated Change #1: “Any individual unspecified degradation product” was revised to “Any unspecified degradation product” to be consistent with ICH Q3B terminology.

Monograph/Section(s): Stearoyl Polyoxylglycerides/Acid Value
Expert Committee(s): Complex Excipients

EC-initiated Change#1: The wording “Sum of 16 and 18 above” in table 1 was changed to “Sum of palmitic acid (C16:0) and stearic acid (C18:0)”.

Monograph/Section: Testosterone Compounded Cream

Expert Committee: Compounding

Number of Commenters: 4

Comment Summary #1: A commenter indicated that this preparation is essentially a copy of an FDA-approved product.

Response: Comment not incorporated. This was designed as a bracketed study to allow for a range of concentrations to be compounded.

Comment Summary #2: A commenter indicated that that monograph uses proprietary ingredients in the formulation where there is no information about the composition of the ingredient in the monograph.

Response: Comment not incorporated. USP does not provide information on proprietary ingredients. Information on the content of proprietary ingredients are generally available from suppliers.

Comment Summary #3: A commenter suggested consideration be given to clarifying what is considered a “suitable calibrated dispenser” in order for this preparation be dispensed in a way that allows for dosing consistency.

Response: Comment not incorporated. USP to share input with the Packaging and Labeling EC about providing a definition for a suitable calibrated dispenser.

Comment Summary #4: A commenter recommended the monograph contain the labeling indicating to wash hands with soap and water immediately after applying Testosterone Compounded Cream, to cover application site(s) with clothing, to wash the application site(s) thoroughly with soap and water prior to skin-to-skin contact of the application site with another person, and to avoid contact with others and the unwashed or unclothed application site(s).

Response: Comment not incorporated. USP will share input with the Nomenclature and Labeling EC about adding labeling to warn of secondary exposure to children and animals and will consider provide additional safety labeling to all future monographs and revisions.

Monograph/Section(s): Tetrahydrozoline Hydrochloride/Organic impurities

Expert Committee: Small Molecules 3

No. of Commenters: 1

Comment Summary #1: The commenter requested removing the “reporting threshold” as it will vary based on product-specific factors.

Response: Comment not incorporated. Based on comments received on a proposed policy for reporting thresholds, USP determined that removal of reporting thresholds from monographs needs further stakeholder engagement. USP intends to do further stakeholder engagement on the topic.

EC-initiated Change #1: The calculation for the percentage of naphthyl imidazoline is removed and the calculation for the percentage of any individual impurity was updated to remove the exclusion for naphthyl imidazoline.

Monograph/Section(s): Wild Chrysanthemum Flower/Multiple Sections

Expert Committee: Botanical Dietary Supplements and Herbal Medicines

No. of Commenters: 4

Identification A

Comment Summary #1: The commenter suggested rephrasing HPTLC System Suitability Requirements and Acceptance Criteria to accommodate multiple HPTLC plates. The commenter also suggested removing *Standard solution C* to simplify the test.

Response: Comments incorporated.

Composition

Comment Summary #2: The commenter suggested doing following changes based on the investigation test results from USP laboratory for USP *Chrysanthemum × morifolium* Flower Dry Extract RS.

8. Add 0.1% glacial acetic acid in *Solution B* to keep *pH* consistent for the gradient mobile phases.
9. Extend 10 min more to wash the column after HPLC gradient to clean the column sufficiently before next injection.
10. Change column temperature from 25° to 20° to be consistent with that in *Chrysanthemum Flower* monograph.
11. Change isochlorogenic acid B to an identification marker from a quantitative marker since it was partially co-eluted with unknown peaks.
12. Add a theoretical plate number of NLT 10000 in System Suitability Requirements to make sure a sufficient column efficiency.
13. Add “Before injection test solutions, equilibrate the column more than 1 h” under analysis.

Response: Comments incorporated.

Comment Summary #3: The commenter suggested changing luteolin-7-*O*-glucuronide to a non-quantitation peak because LC/MS results from USP laboratory displayed that luteolin-7-*O*-glucuronide was co-eluted with other components.

Response: Comment incorporated. The acceptance criteria for total flavone glycosides were changed to NLT 0.20% accordingly.

Comment Summary #4: The commenter suggested removing *Standard solution D* to simplify the test.

Response: Comment incorporated.

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

Identification A

Comment Summary #1: The commenter suggested rephrasing HPTLC System Suitability Requirements and Acceptance Criteria to accommodate multiple HPTLC plates. The commenter also suggested removing *Standard solution C* to simplify the test.

Response: Comments incorporated.

Composition

Comment Summary #2: The commenter suggested doing following changes based on the investigation test results from USP laboratories for USP *Chrysanthemum × morifolium* Flower Dry Extract RS.

1. Add 0.1% glacial acetic acid in *Solution B* to keep *pH* consistent for the gradient mobile phases.
2. Extend 10 min more to wash the column after HPLC gradient to clean the column sufficiently before next injection.
3. Change column temperature from 25° to 20° to be consistent with that in *Chrysanthemum Flower* monograph.
4. Change isochlorogenic acid B to an identification marker from a quantitative marker since it was partially co-eluted with unknown peaks.

5. Add a theoretical plate number of NLT 10000 in System Suitability Requirements to make sure a sufficient column efficiency.
6. Add “Before injection test solutions, equilibrate the column more than 1 h” under analysis.

Response: Comments incorporated.

Comment Summary #3: The commenter suggested changing luteolin-7-O-glucuronide to a non-quantitation peak because LC/MS results from USP laboratory displayed that luteolin-7-O-glucuronide was co-eluted with other components.

Response: Comment incorporated. The acceptance criteria for total flavone glycosides were changed to NLT 0.20% accordingly.

Comment Summary #4: The commenter suggested removing *Standard solution D* to simplify the test.

Response: Comment incorporated.

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

Identification A

Comment Summary #1: The commenter suggested rephrasing HPTLC System Suitability Requirements and Acceptance Criteria to accommodate multiple HPTLC plates. The commenter also suggested removing *Standard solution C* to simplify the test.

Response: Comments incorporated.

Composition

Comment Summary #2: The commenter suggested doing following changes based on the investigation test results from USP laboratory for USP *Chrysanthemum × morifolium* Flower Dry Extract RS.

1. Add 0.1% glacial acetic acid in *Solution B* to keep *pH* consistent for the gradient mobile phases.
2. Extend 10 min more to wash the column after HPLC gradient to clean the column sufficiently before next injection.
3. Change column temperature from 25° to 20° to be consistent with that in Chrysanthemum Flower monograph.
4. Change isochlorogenic acid B to an identification marker from a quantitative marker since it was partially co-eluted with unknown peaks.
5. Add a theoretical plate number of NLT 10000 in System Suitability Requirements to make sure a sufficient column efficiency.
6. Add “Before injection test solutions, equilibrate the column more than 1 h” under analysis.

Response: Comments incorporated.

Comment Summary #3: The commenter suggested changing luteolin-7-O-glucuronide to a non-quantitation peak because LC/MS results from USP laboratory displayed that luteolin-7-O-glucuronide was co-eluted with other components.

Response: Comment incorporated.

Comment Summary #4: The commenter suggested removing *Standard solution D* to simplify the test.

Response: Comment incorporated.

Monograph/Section: Zidovudine/Multiple sections
Expert Committee: Small Molecules 1

No. of Commenters: 4

Comment Summary #1: The commenter recommended revising the acceptance criterion for Zidovudine related compound G (dimer) to be consistent with what has been approved in the test for *Organic Impurities*.

Response: Comment not incorporated. The acceptance criterion is consistent with the sponsor's FDA-approved application. The EC will consider future revisions to the monograph upon the receipt of supporting data

Comment Summary #2: The commenter requested the rationale for tighter limit of NMT 0.15% for Zidovudine related compound G in the test for *Organic Impurities* compared with the limit of NMT 0.5% for the same impurity (EP impurity G) in the EP monograph.

Response: Comment not incorporated. The acceptance criterion is consistent with the sponsor's FDA-approved application. The EC will consider future revisions to the monograph upon the receipt of supporting data.

Comment Summary #3: The commenter requested revising the statement in the calculation to include calculate the percentage of triphenylmethanol instead of individual impurity in the *Limit of Triphenylmethanol* test.

Response: Comment incorporated.

Comment Summary #4: The commenter recommended removing the disregard statement "Disregard any peak eluting before triphenylmethanol and any peak below 0.05%" in the *Limit of Triphenylmethanol* test as the method is specific for content of triphenylmethanol.

Response: Comment incorporated

Comment Summary #5: The commenter requested revising the *Specific Optical Rotation* acceptance criteria from "+60.5° to +63°" to +60.5° to +63.5°.

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

Comment Summary #6: The commenter commented that in the *Assay*, the gradient is too long and their in-house impurity eluted closely with zidovudine peak in the *Assay*.

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

Comment Summary #7: The commenter commented that the proposed *Organic Impurities* method is not specific for their in-house impurities.

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

Monograph/Section: Zidovudine Oral Solution /Multiple sections

Expert Committee: Small Molecules 1

No. of Commenters: 1

Comment Summary #1: The commenter recommended ensuring that all the approved manufacturers are able to meet the requirements in the proposed monograph to avoid potential drug shortage.

Response: Comment not incorporated. USP reached out to the FDA-approved manufacturers and received no response or objection. The EC will consider future revisions to the monograph upon the receipt of supporting data.

Comment Summary #2: The commenter recommended verifying with FDA-approved applicants about the addition of specified impurity "3-Amino-3'-deoxythymidine" in the test for *Organic impurities*, prior to making the proposal official.

Response: Comment not incorporated. USP reached out to the FDA-approved manufacturers and based on the response received, the EC determined that the proposed changes are

consistent with the available FDA-approval information. The EC will consider future revisions to the monograph upon the receipt of supporting data.

Comment Summary #3: The commenter commented that the note “On the basis of the synthetic route, perform either *Organic Impurities, Procedure 1 or Procedure 2*” in the test for *Organic Impurities* is not appropriate for a drug product monograph.

Response: Comment incorporated. The note is revised to “On the basis of knowledge of the product, perform either *Organic Impurities, Procedure 1 or Procedure 2.*”