Commentary

USP–NF 2022, Issue 2

February 1, 2022

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 *USPNF*.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

<56> Methods for Determination of Resistance of Microorganisms to Sterilization Processes
<852> Atomic Absorption Spectroscopy
<1117> Microbiological Best Laboratory Practices
<1223.1> Validation of Alternative Methods to Antibiotic Microbial Assays
<1229.18> Viral Clearance Methods
<1776> Image Analysis of Pharmaceutical Systems

Monographs

Activated Attapulgite
Amantadine Hydrochloride
Amiloride Hydrochloride
Aminocaproic Acid Oral Solution
Atazanavir Sulfate
Basic Fuchsin
Buprenorphine Hydrochloride
Calcipotriene Ointment
Carboprost Tromethamine Injection
Choline Citrate
Clocortolone Pivalate Cream
Colloidal Activated Attapulgite
Cromolyn Sodium Oral Solution
Diltiazem Hydrochloride Compounded Cream
Dopamine Hydrochloride
Ethosuximide
Indocyanine Green
Lindane
Lindane Shampoo
Lisinopril Tablets
Loxapine Capsules
Loxapine Succinate
Methyl Acrylate, Methyl Methacrylate, and Methacrylic Acid (7:3:1) Copolymer 280000 Dispersion
Mitotane
Mitotane Tablets
Nicardipine Hydrochloride
Nicotine
Olanzapine Orally Disintegrating Tablets
Palm Oil Tocotrienols and Tocopherols
Palonosetron Hydrochloride
Perindopril Erbumine
Potassium Citrate and Citric Acid Oral Solution
Ramipril

Riociguat Tablets
Sotalol Hydrochloride Tablets
Tannic Acid
Valproic Acid
Vardenafil Orally Disintegrating Tablets
White Wax

No comments were received for the following proposals:

General Chapters

<123> Glucagon Bioidentity Tests
<1229> Sterilization of Compendial Articles
<1229.2> Steam Sterilization of Aqueous Liquids
<1229.3> Monitoring of Bioburden
<1229.5> Biological Indicators for Sterilization
<1852> Atomic Absorption Spectroscopy-Theory and Practice

Monographs

Adipic Acid
Bacillus Coagulans
Bifidobacterium Longum Subsp. Infantis
Calcium Acetate Tablets
Calcium Citrate
Calcium Undecylenate
Chlorothiazide
Cimetidine
Citicoline Sodium
Famciclovir Tablets
Felodipine Extended-Release Tablets
Glucagon
Glucagon for Injection
Hydroflumethiazide
Indocyanine Green for Injection
Japanese Sophora Flower Bud
Japanese Sophora Flower Bud Powder
Lacticaseibacillus Casei
Lactobacillus Acidophilus
Lactobacillus Acidophilus La-14
Lactobacillus Acidophilus NCFM
Lactobacillus Paracasei LCP-37
Methazolamide
Methyldopate Hydrochloride
Methyldopate Hydrochloride Injection
Methylene Blue Injection
Milk Thistle
Milk Thistle Capsules
Milk Thistle Tablets
Pamidronate Disodium
Penicillin G Benzathine Oral Suspension

Penicillin G Benzathine Tablets
Potassium Bicarbonate and Potassium Chloride Effervescent Tablets for Oral Solution
Powdered Milk Thistle
Powdered Milk Thistle Extract
Prednisolone Sodium Phosphate
Prednisolone Tebutate
Probenecid
Propranolol Hydrochloride and Hydrochlorothiazide Tablets
Sennosides
Sitagliptin Tablets
Sodium Chloride Ophthalmic Ointment
Stannous Fluoride
Stannous Fluoride Gel
Sulfamethazine
Thiabendazole
Ticarcillin and Clavulanic Acid for Injection
Tolbutamide Tablets
Undecylenic Acid
Vinblastine Sulfate for Injection
Vincristine Sulfate for Injection
Vincristine Sulfate Injection
Yellow Wax
Zinc Undecylenate

General Chapters

General Chapter/Section(s):	<56> Methods for Determination of Resistance of Microorganisms to Sterilization Processes
Expert Committee:	General Chapters—Microbiology
No. of Commenters:	5

Title
Comment Summary #1: The commenter suggested changing the title to reflect the content more accurately since it does not include methods for determination of resistance to agents other than moist heat used for sterilization (radiation, ethylene oxide, etc.).
Response: Comment not incorporated. The chapter contains methods for the presence/absence test for spores and a reference to ISO 11138 has been added.

Introduction
Comment Summary #2: The commenter indicated that determination of resistance to sterilization processes is not the only requirement for parametric release and the text be modified accordingly.
Response: Comment incorporated.
Comment Summary #3: The commenter stated that a) the purpose of the chapter is not clearly defined and b) the chapter does not explain why “alternative practices” for resistance determination would be used instead of the procedure described in USP <55>.

Response: Comment not incorporated. In the opinion of the Expert Committee, the purpose of the chapter that is clearly indicated in the Introduction along with a reference to <1229> is to provide procedures to determine resistance of the bioburden to the sterilization process (with thepossible exception of overkill processes) is essential to confirm the efficacy of the sterilization process. Also, <55> only applies to high resistance microorganisms.
Comment Summary #4: The commenter suggested that the applicability of this chapter to bioburden-based (Bioburden or Product Specific/Combined Bioburden/BI) cycle design approaches should be clarified.
Response: Comment not incorporated; this topic is covered in <1229>.
Comment Summary #5: The commenter indicated that although heat resistance of microorganisms may be known, the specific surrounding environment may influence this heat resistance.
Response: Comment incorporated. Text suitably modified to include context of susceptibility to sterilization processes when present in or on pharmaceutical articles .
Comment Summary #6: The commenter recommended removal of all references to BI resistance testing from this chapter as there is limited value in the inclusion of BI resistance testing in this chapter. There are other more detailed existing references (e.g., <55>, ISO 11138 series) that provide complete and detailed coverage on this topic.
Response: Comment not incorporated. In the opinion of the Expert Committee, resistance specificity and information at 121 degrees C is not useful for Sterilization at lower temperatures.

General Procedures
Comment Summary #7: The commenter indicated that if the material is inherently antimicrobial and viable microorganisms cannot be detected in the material, then D-value determination is not necessary and neutralization would only apply to the presence/absence of spores, rather than D-value determination.
Response: Comment incorporated. Text suitably modified to indicate neutralization would only apply to the presence/absence of spores.
Comment Summary #8: The commenter indicated that chapter <61> does not provide a sample preparation method for solid, water-insoluble, or immiscible products. In addition, the "Presence/Absence Test for Spores" and the "Resistance Estimation Test" require the samples to be exposed to moisture. Adding solid, water-insoluble, or immiscible products to a sterile screwcap tube without moisture will only expose any spores that may be present on the sample to dry heat, which will overestimate the thermal resistance of organisms on material subjected to moist heat sterilization processes.
Response: Comment not incorporated. General Chapter <61> does provide a sample preparation method for solid, water-insoluble, or immiscible products.
Comment Summary #9: The commenter indicated that the sample size should not be broadly prescribed and uniform for all products and should be based on risk assessment including specific product attributes (including manufacturing process considerations) and historical data. Additionally, it is not clear what pool of product should be considered when gathering 10 samples (is this per lot, per mix batch, per day, etc.).
Response: Comment partially incorporated. The text has been revised to clarify that composite samples may be used. In the opinion of the Expert Committee, the indicated sample size is uniform and related to reliability of results.
Comment Summary #10: The commenter suggested that only microorganisms that survive 95—100°C are of relevance and the resistance of these should be examined further, if found. Therefore, to avoid counting colonies of spore formers, which do not approach a resistance of BI's (D_{121}-value of 1 or more), the temperature exposure for test of bioburden for high F_0 sterilization (F_0 above 12) processes should be 95—100°C and not 70—75°C for example, 30 min.

Response: Comment not incorporated. The sensitivity of bioburden is generic to all sterilization processes, not moist heat alone.

Presence/Absence Test for Spores (All Sterilization Processes Except Filtration and Radiation)

Comment Summary #11: The commenter suggested providing a definition for “non-nutrient germinant” or providing a reference.

Response: Comment incorporated. Definition and examples provided.

Comment Summary #12: The commenter suggested that alternate spore heat shocking approaches should be permitted when properly supported by a scientific rationale, references and/or historical data.

Response: Comment not incorporated. Although alternative spore heat shocking approaches are not specifically incorporated, comparable alternate methods, suitably validated, are always allowed by USP *General Notices*.

Comment Summary #13: The commenter suggested that including a positive control which contains spores (not vegetative cells) would confirm that heat treatment and test conditions can recover spores and changing the heading of the sub-section to “Positive and Negative Controls”.

Response: Comment incorporated by requiring the use of a positive control and changing the heading of the sub-section.

Resistance Estimation (Moist Heat Processes Only)

Comment Summary #14: The commenter suggested that for consistency with the remainder of the chapter, identify the heat-shock method as the “boil test”.

Response: Comment incorporated.

Comment Summary #15: The commenter indicated that clarification is needed regarding the statement on the range of times used to estimate moist heat resistance.

Response: Comment incorporated. Statement clarified to indicate the application of the boil test over a range of times is used to estimate moist heat resistance.

Comment Summary #16: The commenter suggested to present maximum resistance estimation and preliminary resistance estimation procedures as options to be used as described in the first paragraph and list maximum resistance estimation second as a specific time duration.

Response: Comment incorporated. Changes made. The subsections were reorganized by placing the content on preliminary resistance estimation prior to maximum resistance estimation

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Comment Summary #17: The commenter indicated correlated D-Values in Table 1 cannot be unequivocally and objectively demonstrated for their appropriateness.

Response: Comment not incorporated. This table is adapted from <1229.2> and as the title suggests, this only provides an estimate that needs to be confirmed.

Comment Summary #18: The commenter suggested inserting a greater than equal symbol as a prefix to the values in Table 2.

Response: Comment incorporated. Change made.

Comment Summary #19: The commenter indicated that it is not clear as to why BIER vessels are not appropriate for determination of D-values.

Response: Comment not incorporated. Lower temperature in a BIER vessel is higher than the suggested use in this chapter (see ISO-18472).

***D*-Value Determination (Moist Heat Processes Only)**

Comment Summary #20: The commenter suggested to clarify temperature ranges used for the processes.
Response: Comment incorporated. Temperature ranges used have been clarified.
Comment Summary #21: The commenter suggested to clarify the use of these methods for bioburden isolates and recommended the use of Sterile Water in place of Purified Water as a diluent.
Response: Comment incorporated. Use of Sterile Water is included in place of Purified Water as a diluent
Comment Summary #22: The commenter suggested that the conditions for recovery of bioburden isolates may need to be modified as needed.
Response: Comment incorporated. A statement that suggests that the conditions for recovery of bioburden isolates may need to be modified as needed, has been included.

General Chapter/Section(s): <852> Atomic Absorption Spectroscopy
Expert Committee: General Chapters—Chemical Analysis
No. of Commenters: 3

General
Comment Summary #1: The commenter noted that the term “replicate” in the chapter is used in different contexts, such as in “replicate,” “replicate measurements,” and “replicate analyses” and noted that this could lead to confusion regarding the use of one sample solution analyzed for multiple readings or multiple sample preparations. The commenter recommended defining each of those terms and suggested that it could be done by adding a glossary.
Response: Comment partially incorporated. The Expert Committee, noting that there was no need for a glossary, revised the concerned text to include an explanation of the term “replicate” in parenthesis.

Procedure
Comment Summary #2: The commenter noted a typo in the second paragraph of the PROCEDURE section.
Response: Comment incorporated to fix the typo.

Validation and Verification
Comment Summary #3: The commenter suggested deleting the last sentence of the Accuracy, Repeatability and Quantitation Limit subsection of VALIDATION AND VERIFICATION section. The commenter suggested adding a note at the end of the first paragraph to direct users to the use of the appropriate value.
Response: Comment not incorporated. The Expert Committee, noting that it cannot be assumed that all users have the appropriate experience and background in conducting Method of Standard Additions analyses, determined that the current text is suitable.

General Chapter/Section(s): <1117> Microbiological Best Laboratory Practices
Expert Committee: General Chapters—Microbiology
No. of Commenters: 6

Comment Summary #1: The commenter indicated that the chapter contains a lot of recommendations that are already covered by other USP chapters and/or regulations suggested that such overlapping detail could be removed, and the chapter simplified.

Response: Comment not incorporated**.** In the opinion of the Expert Committee, the information is helpful in conjunction with the text of this chapter, and the content of other chapters may be reinforced as long as it is not contradictory.

Introduction
Comment Summary #2: The commenter suggested that the scope of the chapter be clarified and include a glossary of terms.
Response: Comment not incorporated. The text is sufficient as written.

Media Preparation and Quality Control
Comment Summary #3: The commenter indicated that the section on media preparation only addresses commercially obtained media and recommended clarification around in-house prepared media.
Response: Comment incorporated to include recommendations around in-house prepared media.
Comment Summary #4: The commenter indicated that media may also overheat when an autoclave is slow to cool after the cycle and therefore recommended that the text be modified to address this topic.
Response: Comment incorporated.
Comment Summary #5: The commenter suggested to clearly indicate that pH of media should always be checked post-sterilization.
Response: Comment incorporated.
Comment Summary #6: The commenter recommended to clarify that media plates containing agar should not be stored at or below 0°.
Response: Comment incorporated.
Comment Summary #7: The commenter recommended that media plates should not be subjected to conditions that allow for condensation or loss of moisture.
Response: Comment incorporated. Text modified as appropriate.
Comment Summary #8: The commenter recommended that remelting of solid media should be performed by methods that do not compromise media quality.
Response: Comment incorporated.
Comment Summary #9: The commenter indicated that restricting the hold time for molten media to 4 hours (from the current, well-established time of 8 hours) would have an impact on lab operations.
Response: Comment incorporated. Change made to revert to the original recommendation for a hold time of 8 hours for molten media.
Comment Summary #10: The commenter recommended that the term “non-traditional format” should be deleted since these types of media have not been in use for a while.
Response: Comment incorporated.
Comment Summary #11: The commenter indicated that the statement “For qualitative and quantitative comparison, direct physical comparison with a previously tested batch is not necessary” may result in introducing a second variable associated with use of different lot(s) and/or preparation(s).
Response: Comment not incorporated. Such a requirement already exists in USP <61> and <62>.
Comment Summary #12: The commenter suggested clarifying that if plates are incubated in storage and transport bags, growth promotion should be performed to qualify that bag incubation does not impact recovery

Response: Comment not incorporated. In the opinion of the Expert Committee, storage and transportation conditions should be part of validation, and therefore there is no need to perform growth promotion.

Microbiological Media Incubation Times
Comment Summary #13: The commenter suggested clarifying the meaning of "at that same time of day."
Response: Comment incorporated.

Maintenance of Microbiological Cultures
Comment Summary #14: The commenter suggested defining a clear storage range for cultures stored at –70°.
Response: Comment incorporated.

Laboratory Equipment
Comment Summary #15: The commenter suggested referencing 21 CFR Part 11 for data integrity of electronic records.
Response: Comment incorporated.
Comment Summary #16: The commenter recommended that equipment that is difficult to sanitize should be segregated from aseptic operations.
Response: Comment incorporated to explain that difficult to sanitize equipment should be segregated from aseptic operations.

Laboratory Layout and Operations
Comment Summary #17: The commenter recommended that areas in which microbiological test samples are handled and incubated should be maintained completely free of live cultures, if possible.
Response: Comment incorporated to make this recommendation.
Comment Summary #18: The commenter recommended that the reference to laminar flow hood be deleted; it would never be used for containment purposes.
Response: Comment incorporated.
Comment Summary #19: The commenter recommended clarifying that lab coats should be dedicated and should not be worn outside the micro lab and personnel should wash and sanitize their hands upon exit.
Response: Comment incorporated.
Comment Summary #20: The commenter suggested clarifying that Sterility tests should preferably be carried out in an isolator with ISO 5 classification.
Response: Comment incorporated.
Comment Summary #21: The commenter recommended clarifying the quality of Laminar air flow.
Response: Comment incorporated.

Sample Handling
Comment Summary #22: The commenter recommended clarifying the hold time for bioburden samples at 2—8°.
Response: Comment incorporated.
Comment Summary #23: The commenter indicated that environmental monitoring samples includes sample types other than plates.
Response: Comment incorporated.

Comment Summary #24: The commenter indicated that the recommendation for not storing environmental samples at refrigerated conditions is not consistent with standard practice, especially if it cannot be tested or shipped externally for testing.
Response: Comment incorporated.
Comment Summary #25: The commenter indicated that all tests are expected to be completed before release of the product.
Response: Comment incorporated to note that all tests must be completed before product release.
Comment Summary #26: The commenter recommended clarifying that the samples should be protected during transport to minimize contamination.
Response: Comment incorporated.
Comment Summary #27: The commenter recommended that the storage condition of samples be part of the documentation submitted to the microbiology laboratory.
Response: Comment incorporated.

Incubation Temperature Excursions

Comment Summary #28: The commenter recommended that a brief section should be added on how to deal with incubation temperature excursions.
Response: Comment incorporated. A brief section on incubation temperature excursions was included.

Considerations for Microbiological Risk Assessments
Comment Summary #29: The commenter recommended clarifying that an investigation to determine the source of a recovered species of concern and its contamination risk may be required to be completed before a drug product is released to the market.
Response: Comment incorporated. A statement, that an investigation to determinethe source of a recovered species of concern andits contamination risk may be requiredtobe completed before a drug product is released to the market has been added.

Laboratory Resources
Comment Summary #30: The commenter recommended that USP <60> testing be added to the list of compendial tests that contract laboratories are expected to perform and the ability to conduct an on-site audit.
Response: Comment incorporated. <60> has been added to the list.
Comment Summary #31: The commenter recommended clarifying that the controls in place for testing/inspection of incoming lab supplies are key to supply control.
Response: Comment incorporated. A sentence to that effect has been added in the section on Oversight of Suppliers.

Method Transfer
Comment Summary #32: The commenter recommended that for clarity the term “method transfer” should be used instead of “analytical method transfer”.
Response: Comment incorporated.

Documentation
Comment Summary #33: The commenter indicated that many microbial methods have method steps that if not completed correctly will lead to failed tests. These steps should be documented to be able to reconstruct what happened during the test.
Response: Comment incorporated. A statement that documentation of the significant method steps has been included in the Lab write up, has been included.

Comment Summary #34: The commenter recommended clarifying the expression "microbiology is a logarithmic science".
Response: Comment incorporated. Reference to USP <1223>, which has information on the usage of this expression, has been added.
Comment Summary #35: The commenter indicated that the section that discusses investigations is missing the title.
Response: Comment incorporated. A title has been added.

General Chapter/Section(s):	<1223.1> Validation of Alternative Methods to Antibiotic Microbial Assays/Multiple Sections
Expert Committee:	Biologics Monographs 4
No. of Commenters:	1

Approach I
Comment Summary #1: For #2 in Approach 1, the commenter suggested revising "Active moieties including process impurities and degradation products at levels below 1% of antimicrobial activity may be disregarded" to "Active moieties including process impurities and degradation products at levels not more than 1% of antimicrobial activity may be disregarded" for clarity.
Response: Comment incorporated.
Comment Summary #2: For #2 in Approach 1, the commenter suggested expanding the statement of "Active moieties including process impurities and degradation products at levels below 1% of antimicrobial activity may be disregarded" to include some discussion for special situations (e.g., situations where multiple impurities each contribute less than 1%, but total an antibiotic potency well over 1%).
Response: Comment not incorporated. For #8 in Approach 1, there was a statement on what should be done if the bridging study fails, including investigating impurities below 1%. Approach 2 references Approach 1 if the bridging study fails.
Comment Summary #3: For #3 in Approach 1, the commenter suggested considering accommodating a broader recommendation because the variation range may be quite wide. Also, isolating minor components to very low levels for testing may not be technically feasible.
Response: Comment partially incorporated. The word "full" was deleted and the statement of "This step is done before testing the samples using the two methods to evaluate the variation of the production and help selection of representative batches for the bridging study" was added.
Comment Summary #4: For #4 in Approach 1, the commenter suggested revising the statement of "Forced degradation products or out-of-specification (OOS) lots may be introduced in the study to strengthen its robustness" to "Lots within the process limits, forced degradation products, and out-of-specification (OOS) lots should be introduced in the study to strengthen its robustness" for clarity.
Response: Comment partially incorporated. The statement of "Successful method comparability necessitates testing lots with variation in activity and purity" was added.
Comment Summary #5: For #8 in Approach 1, the commenter suggested clarifying what specific steps to take when the bridging study fails. The current text may not have enough information for the reader.
Response: Comment incorporated. The statement of "Additional analysis may also be required to evaluate the accuracy of measured purity of isolated impurity samples" was added.
Comment Summary #6: The commenter suggested that #6 in Approach II is also applicable to Approach I.

Response: Comment incorporated. The statement “Stability samples with varying amounts of active moieties should have a change in potency that directly correlates to the alternative method” was added to #4 in Approach I.

DATA EVALUATION

Comment Summary #7: The commenter noted that the two assay ranges (80—125%) are asymmetric. Ranges are typically noted as 100 ± x, with x being a specific integer.
Response: Comment not incorporated. The range of 80—125% is from natural log scale of the activity confidential interval of -0.09691 to 0.09691 and it is symmetric on the natural log scale.

APPENDIX 1

Comment Summary #8: The commenter recommended revising Equation 3 to include a consideration where an inequality could be equal to zero.
Response: Comment not incorporated. Equation 3 is written statistically correct; it is two one-sided tests. See USP <1010> which describes two one-sided tests.
Comment Summary #9: The commenter suggested including additional data points in Example 1 because a fully validated HPLC method typically includes at least six data points, which are necessary for appropriate statistical analyses.
Response: Comment not incorporated. This example is for the bridging study, not validation. The chapter states a minimum of three replicates are needed for HPLC analysis. Example 1 is aligned with the minimum recommendation in the chapter. A note of “Results for one sample lot” was added for clarity.

APPENDIX 2

Comment Summary #10: The commenter suggested including additional data points in Example 2 because a fully validated HPLC method typically includes at least six data points, which are necessary for appropriate statistical analyses.
Response: Comment not incorporated. This example is for the bridging study, not validation. The chapter states a minimum of three replicates are needed for HPLC analysis. Example 2 is aligned with the minimum recommendation in the chapter. A note of “Results for multiple sample lots” was added for clarity.

APPENDIX 4

Comment Summary #11: The commenter suggested clarifying $Z_{\beta/2}$ in Table 1 as $Z_{\beta/2}$ could be misinterpreted to be a value and cause confusion.
Response: Comment incorporated. Table 1 was revised as follows:

Power	$Z_{\beta/2}$	d	s	N
80%	0.842	30	50	35
		40	50	20
		50	50	13
		60	50	9
		70	50	7
		80	50	5
90%	1.282	30	50	48
		40	50	27
		50	50	18

Power	$Z_{\beta/2}$	d	s	N
		60	50	12
		70	50	9
		80	50	7

Comment Summary #12: The commenter suggested correcting the N value in Table 1 that have been rounded down as the general rule is to round up.
Response: Comment incorporated. Table 1 was revised as follows:

Power	$Z_{\beta/2}$	d	s	N
80%	0.842	30	50	35
		40	50	20
		50	50	13
		60	50	9
		70	50	7
		80	50	5
90%	1.282	30	50	48
		40	50	27
		50	50	18
		60	50	12
		70	50	9
		80	50	7

General Chapter/Section(s): <1229.18> Viral Clearance Methods
Expert Committee: General Chapters—Microbiology
No. of Commenters: 5

Title
Comment Summary #1: The commenter suggested changing the title of the chapter to *Viral Clearance Methods,* consistent with its content.
Response: Comment incorporated. Title Changed.

Introduction
Comment Summary #2: The commenter indicated that this chapter proposal does not add any additional value to the topic as related chapters <1050> and <1050.1> already exist and suggested not to move ahead with this new chapter. The commenter instead suggested adding necessary information to USP <1050>and <1050.1>.
Response: Comment not incorporated. In the opinion of the Expert Committee, a separate chapter on viral clearance methods is needed. However, a sentence has been added at end of first paragraph directing the reader to <1050> and <1050.1>.
Comment Summary #3: The commenter recommended that the scope of the chapter be clarified to avoid confusion. A glossary of terms (e.g., susceptible products, etc.) is recommended to help clarify focus.
Response: Comment not incorporated. A reference to USP <1050> and <1050.1> was added.
Comment Summary #4: The commenter suggested to modify the definition of viruses.
Response: Comment incorporated.

Comment Summary #5: The commenter suggested only including names of diseases caused by viruses or the names of both the virus and the disease caused.
Response: Comment incorporated.
Comment Summary #6: The commenter recommended clarifying the types of products susceptible to viral contamination.
Response: Comment incorporated. Text modified and reference added to <1050> and <1050.1>.
Comment Summary #7: The commenter suggested to provide clarity as to why virus removal is of concern for materials of animal origin and biological processes that require the use of mammalian cell culture.
Response: Comment incorporated.
Comment Summary #8: The commenter suggested replacing the term “biological material” with “natural biological material” in the context of prevention of viral contamination.
Response: Comment incorporated.
Comment Summary #9: The commenter suggested adding viral inactivation in addition to removal in the context of prevention of viral contamination.
Response: Comment incorporated.
Comment Summary #10: The commenter suggested to clarify the difference in scope of <1050> and the present chapter <1229.18>.
Response: Comment incorporated.
Comment Summary #11: The commenter suggested to clarify the execution of viral clearance studies.
Response: Comment incorporated.
Comment Summary #12: The commenter suggested to clarify whether actual processes are expected to be challenged with virus, or a simulation/scale-down model is intended.
Response: Comment incorporated.
Comment Summary #13: The commenter recommended to clarify whether a panel of viruses are needed to be challenged for each discrete viral clearance step.
Response: Comment partially incorporated. Minor change made to indicate challenge studies should include endogenous and non-endogenous viruses as appropriate.
Comment Summary #14: The commenter indicated that spiking studies do not need to include both endogenous and non-endogenous viruses. The important thing to consider is the virus type and whether or not it is endogenous.
Response: Comment incorporated. Text has been added to clarify that challenge studies should include endogenous and non-endogenous viruses as appropriate.
Comment Summary #15: The commenter recommended that for consistency with ICH Q5A, changing the term “viral removal” to “virus removal”.
Response: Comment incorporated.
Comment Summary #16: The commenter suggested adding radiation methods in the list of most widely used methods for virus removal.
Response: Comment incorporated.
Comment Summary #17: The commenter suggested adding methods such as pH treatment (chemical methods) in the list of most widely used methods for virus removal.
Response: Comment incorporated.

Filtration and Chromatographic Methods
Comment Summary #18: The commenter indicated that the virus retentive filters do not often state a molecular weight cutoff (MWCO), but rather an average pore size is included for viral removal.
Response: Comment incorporated.

Thermal Methods
Comment Summary #19: The commenter suggested modification of the section on Thermal Methods for clarity and consistency with ICH Q5A.
Response: Comment incorporated.
Comment Summary #20: The commenter indicated that not all viruses are susceptible to destruction by thermal means.
Response: Comment incorporated.
Comment Summary #21: The commenter indicated a concern that there is a possibility that the heat treatment described and applied at cell culture stages could be confused with downstream virus clearance.
Response: Comment not incorporated. In the opinion of the Expert Committee, there is no need to be explicit as to where a particular method is utilized in a USP informational chapter. Regardless, it would still require validation on the manufacturing scale.

Radiation Methods
Comment Summary #23: The commenter recommended moving the sentence emphasizing that the sum of the viral clearance efforts do not adversely affect the biological drug substance, to later in the paragraph.
Response: Comment incorporated.

References
Comment Summary #24: The commenter indicated that in the references section, the references 1 and 4 appear to be the same document.
Response: Comment incorporated. The duplicate reference #4 was deleted.

General Chapter/Section(s): <1776> Image Analysis of Pharmaceutical Systems
Expert Committee: General Chapters—Physical Analysis
No. of Commenters: 2

Expert Committee-initiated Change #1: The Expert Committee added the following entry at the end of subsection 2.4 Particle Quantitation and Identification of "Foreign Particulate Matter": "The maximum number of particles that are permissible in a specific mass or volume of sample is addressed in Particulate Matter in Injections <788>, Visible Particulates in Injections <790>, Methods for the Determination of Subvisible Particulate Matter <1788>, and Visual Inspection of Injections <1790>."

INTRODUCTION AND SCOPE
Comment Summary #1: The commenter, referring to the first sentence of the first paragraph, suggested revising it to add "qualitative or" before the quantitative and replace "assessment of an image" with "characterization of two- or three-dimensional digital images."
Response: Comment incorporated.
Comment Summary #2: The commenter, referring to the second sentence of the first paragraph, reasoned that it may not be true for scientific image measurement and recommended revising the entry.
Response: Comment not incorporated. The Expert Committee determined that the text is suitable. The entry is there for a comparative purpose of automated image analysis with the very laborious manual process. The next sentence of the chapter states that this is out of scope of the chapter.

Comment Summary #3: The commenter, referring to the entries under 1.1 Image, suggested including confocal scanning microscopy (CSM) in the parenthetical list of the microscopy bullet, and micro-CT in the parenthetical list of electromagnetic reflection, detection, and illumination bullet.
Response: Comment incorporated.
Comment Summary #4: The commenter, referring to the surface texture or roughness bullet of 1.2 Image Analysis, reasoning that the existing text seemed to imply that the surface texture and surface roughness are synonymous recommended revising the entry to add additional identifiers.
Response: Comment not incorporated. The Expert Committee revised the text to state "Surface texture and/or roughness".

2. APPLICATIONS OF IMAGE ANALYSIS OF PARTICLES

Comment Summary #5: The commenter, referring to the first sentence of subsection 2.1, reasoning that the examples there do not explain why the image analysis of particles can help for the given context, recommended including a better explanation with relevant examples.
Response: Comment not incorporated. The Expert Committee determined that current text is suitable and additional detailed explanation on how the examples are applied is out of scope.
Comment Summary #6: The commenter, referring to the first paragraph of subsection 2.3 Characterization of Raw Materials in Development, suggested including some discussion from the scientific image measurement and analysis perspective and proposed revised text.
Response: Comment not incorporated. The Expert Committee determined that the text is suitable because the suggested content is already discussed.
Comment Summary #7: The commenter, referring to the second paragraph of subsection 2.4 Particle Quantitation and Identification of "Foreign Particulate Matter," recommended deleting the statement concerning the defect levels.
Response: Comment incorporated.
Comment Summary #8: The commenter, referring to subsection 2.5 Assessing Crystal Growth, Milling, and Dissolution, suggested including some mention of different process analytical technology tools for monitoring in-situ and real time crystallization processes, for improved clarity to the reader.
Response: Comment not incorporated. The Expert Committee determined that the current text is suitable, and the suggestion is out of scope of the chapter.
Comment Summary #9: The commenter, referring to subsection 2.8 Evaluating the Chemical Composition of Materials, noted a typographical error in the punctuations.
Response: Comment incorporated. The typo has been corrected.
Comment Summary #10: The commenter, referring to the last sentence of subsection 2.8 Evaluating the Chemical Composition of Materials, suggested revising this statement to include definitions and/or examples of "chemical evolution", "process transformation", and "possible contamination," and provided proposed text.
Response: Comment partially incorporated. The Expert Committee revised the sentence to state "These techniques may also be useful for understanding the ~~chemical evolution of~~ changes in a formulation over time ~~through process transformations or stability~~, and in investigations of possible contamination."

4. DATA PROCESSING, INTERPRETATION, AND REPORTING

Comment Summary #11: The commenter, referring to the last paragraph of subsection 4.1 Data Processing, suggested expanding that statement and proposed a replacement text.
Response: Comment partially incorporated. The Expert Committee, noting that the text already includes parts of the suggestion, incorporated an alternative revised text.

6. METHOD DEVELOPMENT AND VALIDATION

Comment Summary #12: The commenter, referring to section 6 on Method Development and Validation, suggested including a discussion of the appropriate statistical evaluation process to ensure accurate, representative results.
Response: Comment not incorporated. The Expert Committee, noting that the suggestion is an application issue and addressed on a case-by-case basis, determined that the current text is suitable.
Comment Summary #13: The commenter, referring to the bullet on "Level of assurance needed for accuracy and precision" in section 6 on Method Development and Validation, requested to elaborate on parameters to measure level of assurance.
Response: Comment not incorporated. See response to comment 12.

Comment Summary #14: The commenter, referring to the validation discussion of section 6 on Method Development and Validation, requested to elaborate the validation section to include acceptance criteria for each parameter.
Response: Comment not incorporated. The Expert Committee, noting that the acceptance criteria depend on the specific application and are addressed on a case-by-case basis, determined that the request is out of scope of the chapter.
Comment Summary #15: The commenter, referring to section 6 on Method Development and Validation, requested to elaborate the section for better understanding of the applicability of the general chapter.
Response: Comment not incorporated. The Expert Committee, noting that the method development and validation are application specific and addressed on a case-by-case basis, determined that additional text would not provide added clarity.

Monographs

Monograph/Section(s): Activated Attapulgite/Impurities
Expert Committee: Small Molecules 3
No. of Commenters: 1

Comment Summary: The commenter recommended that USP retain tests for "Arsenic" and "Lead" as Activated Attapulgite is an ingredient of natural origin sourced from ores and therefore may contain high levels of elemental impurities.
Response: Comment not incorporated. Removal of elemental impurity tests is to align with the concept of General Chapter <232>. The elemental impurities will be controlled in the drug product using the risk-based approach specified in the General Chapter <232>. The risk-based approach is used to determine the presence of an elemental impurity (in components of the formulation or in the drug product) and the appropriate level of control needed. Therefore, it is redundant to include the test and acceptance criteria in the monograph.

Monograph/Section(s): Amantadine Hydrochloride/Organic Impurities
Expert Committee: Small Molecules 1
No. of Commenters: 1

Comment Summary #1: The commenter noted that amantadine related compound A is poorly soluble in water and in the preparation of sample solution there is no assurance that this poorly soluble impurity will be evenly distributed or dissolved in the initial aqueous dilution.

Response: Comment not incorporated. The comment is outside the scope of the proposed revisions. The Expert Committee will consider future revisions to the monograph upon receipt of the necessary supporting data.

Monograph/Section(s): Amiloride Hydrochloride/Multiple sections
Expert Committee: Small Molecules 2
No. of Commenters: 2

Comment summary #1: The commenter recommended revising the chemical name in the Chemical Information section to “Amiloride (free base)” instead of “Amiloride Hydrochloride (free base)”.
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.

Monograph/Section(s): Aminocaproic Acid Oral Solution/Multiple Sections
Expert Committee: Small Molecules 2
No. of Commenters: 1

Comment Summary #1: The commenter suggested including a procedure and acceptance criteria for *Organic impurities* by contacting the FDA approved applicants to obtain relevant information.
Response: Comment not incorporated. At this time the EC does not have supporting data to support adding such acceptance criteria. The Expert Committee will consider future revisions to this monograph upon receipt of supporting data.
Comment Summary #2: The commenter suggested adding a Burkholderia Capcia Complex (BCC) test based on the General Chapter <60>.
Response: Comment not incorporated. At this time the EC does not have supporting data to add such a test. The Expert Committee will consider future revisions to this monograph upon receipt of supporting information.

Monograph/Section(s): Atazanavir Sulfate/Organic Impurities
Expert Committee: Small Molecules 1
No. of Commenters: 2

Comment Summary #1: The commenter recommended revising the diluent in *Organic Impurities, Procedure 1* from Solution A: Solution B (50:50) with their in-house diluent acetonitrile: buffer (25:75) as one of the impurities, atazanavir hydrazine analog impurity peak shape split with the proposed diluent.
Response: Comment not incorporated. The Expert Committee determined that the proposed concentration is consistent with validation data and suitable for its intended use.
Comment Summary #2: The commenter recommended removal of the reporting threshold from the monograph as it will vary based on product-specific factors and the FDA would address this as an application assessment issue.
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.

Monograph/Section(s): Basic Fuchsin/Impurities
Expert Committee: Small Molecules 3
No. of Commenters: 1

Comment Summary #1: The commenter requested that USP retain tests for “Arsenic” and “Lead” in the monograph to allow for elemental impurity control at the ingredient level because there may not be USP drug product monographs which apply to all marketed Basic Fuchsin products.
Response: Comment not incorporated. Removal of elemental impurity tests is to align with the concept of General Chapter <232>. The elemental impurities will be controlled in the drug product using the risk-based approach specified in the General Chapter <232>. The risk-based approach is used to determine the presence of an elemental impurity (in components of the formulation or in the drug product) and the appropriate level of control needed. Therefore, it is redundant to include the test and acceptance criteria in the monograph.

Monograph/Section(s): Buprenorphine Hydrochloride/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.

Monograph/Section(s): Calcipotriene Ointment/Organic Impurities
Expert Committee: Small Molecules 3
No. of Commenters: 1

Comment Summary #1: The commenter recommended keeping the currently official acceptance criterion for Calcipotriene Impurity B for consistency with what has been approved.
Response: Comment incorporated. The current limit of NMT 0.50% for Calcipotriene impurity B remains unchanged.
Comment Summary #2: The commenter recommended revising the acceptance criteria for Calcipotriene Impurity D and “Any individual unspecified impurity” for consistency with what has been approved.
Response: Comment not incorporated. The EC is not aware of any information indicating that the acceptance criteria is inconsistent with what has been approved.
Comment Summary #3: The commenter recommended removal of “Specified unknown impurity” or providing the structure of it.
Response: Comment incorporated. The “Specified unknown impurity” was deleted from Table 1.
Comment Summary #4: 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.

Expert Committee-initiated Change #1: Change from “Any individual unspecified impurity” to “Any unspecified impurity”.

Monograph/Section(s): Carboprost Tromethamine Injection/Multiple sections
Expert Committee: Small Molecules 5
No. of Commenters: 1

Comment Summary #1: The commenter recommended including tests for tromethamine content and Organic Impurities for consistency with what has been approved.
Response: Comment not incorporated. The EC is not aware of supporting information to support this revision. The Expert Committee will consider future revisions to the monograph upon receipt of supporting data.

Monograph/Section(s): Choline Citrate/Multiple Sections
Expert Committee: Non-botanical Dietary Supplements

Expert Committee-initiated change #1: An additional note to the *Related Compounds* procedure to help users distinguish, identify, and address artifact and impurity peaks in the HPLC-CAD chromatograms was incorporated.
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Expert Committee-initiated change #2: Instructions for the *Standard response line* in the test procedure for the *Limit of Total Amines* contain error in representation of the accurate. cumulative concentrations after each addition of the *Standard solution,* which should be calculated by taking into account the accurate total volume of the solution in the vessel.

Monograph/Section(s): Clocortolone Pivalate Cream/Organic Impurities
Expert Committee: Small Molecules 5
No. of Commenters: 2

Comment Summary #1: The commenter recommended revising the acceptance criteria for clocortolone and total impurities to be consistent with what has been approved.
Response: Comment incorporated. The acceptance criterion for clocortolone was revised from NMT 0.1% to NMT 0.2% and the acceptance criterion for total impurities was revised from NMT 0.5% to NMT 0.80%.

Monograph/Section(s): Colloidal Activated Attapulgite/Impurities
Expert Committee: Small Molecules 3
No. of Commenters: 1

Comment Summary #1: The commenter recommended that USP retain tests for “Arsenic” and “Lead” as Colloidal Activated Attapulgite is an ingredient of natural origin sourced from ores and therefore, may contain high levels of elemental impurities.
Response: Comment not incorporated. Removal of elemental impurity tests is to align with the concept of General Chapter <232>. The elemental impurities will be controlled in the drug product using the risk-based approach specified in General Chapter <232>. The risk-based approach is used to determine the presence of an elemental impurity (in components of the formulation or in the drug product) and the appropriate level of control needed. Therefore, it is redundant to include the test and acceptance criteria in the monograph.

Monograph/Section(s): Cromolyn Sodium Oral Solution/Multiple sections
Expert Committee: Small Molecules 5

No. of Commenters: 1

Comment Summary #1: The commenter recommended revising the acceptance criteria for the *Assay* to be consistent with what has been approved.
Response: Comment incorporated. The acceptance criteria for the *Assay* were revised from NLT 95.0% and NMT 105.0% to NLT 90.0% and NMT 110.0%, based on supporting information.
Comment Summary #2: The commenter recommended including common degradation products controlled in approved products in the test for *Organic Impurities*.
Response: Comment not incorporated. The proposed acceptance criteria are consistent supporting data given used by the Expert Committee. The Expert Committee will consider future revisions to the monograph upon receipt of additional supporting data.
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.
Expert Committee-initiated Change #1: The acceptance criterion for total impurities in the test for *Organic Impurities* was revised from NMT 0.50% to NMT 0.5% to be consistent with what supporting data regarding what has been approved.
Expert Committee-initiated Change #2: "Any other individual unspecified impurity" was revised to "Any unspecified impurity" in the test for *Organic Impurities* to be consistent with ICH terminology.

Monograph/Section(s): Diltiazem Hydrochloride Compounded Cream
Expert Committee(s): Compounding
No. of Commenters: 2

Comment summary #1: A commenter indicated the monograph lists diltiazem hydrochloride as the API but omits the source of the API, bulk API, or an approved drug.
Response: Comment not incorporated. When API is used in the formula, USP *General Notices* and <795> requires that compounders source ingredients which meet the requirements of a USP API monograph.
Comment summary #2: A commenter indicated that the monograph uses proprietary ingredients as excipients where there is no information about the identity of the excipient provided in the monograph.
Response: Comment not incorporated. USP does not generally provide information on commercially available excipients. Information on the content of excipients is readily available from suppliers.

Monograph/Section(s): Dopamine Hydrochloride/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.

Monograph/Section(s): Ethosuximide/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.

Monograph/Section(s): Indocyanine Green/Chemical Information
Expert Committee: Small Molecules 4
No. of Commenters: 1
Comment #1: The commenter recommended retaining the chemical information in the currently official monograph, which does not indicate a specific isomer, because multiple isomers may be appropriate.
Response: Comment partially incorporated. The third chemical name describing a specific isomer is not added to the monograph. A chemical structure that reflects a non-specific isomeric configuration and that is consistent with current USP style was added to the monograph.

Monograph/Section(s): Lindane/Organic Impurities
Expert Committee: Small Molecules 1
No. of Commenters: 2

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.
Comment Summary #2: The commenter requested widening the limit of any individual, unspecified impurity from NMT 0.10% to NMT 0.1%.
Response: Comment not incorporated. The commenter has not provided data to support widening the limit and indicated that the limit in the proposed monograph can be met.

Monograph/Section(s): Lindane Shampoo/Organic Impurities
Expert Committee: Small Molecules 1
No. of Commenters: 1

Comment Summary #1: The commenter recommended that USP works with the manufacturers of marketed products to ensure that they will be able to meet the requirements in the proposed monograph to avoid a drug shortage.
Response: Comment incorporated. Generally, USP works with applicable members of industry to ensure that a proposed monograph revision will not result in compliance issues. In this case,, no compliance issue is expected.
Comment Summary #2: 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.

Monograph/Section(s): Lisinopril Tablets/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.

Monograph/Section(s): Loxapine Capsules/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 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.
Comment Summary #2: The commenter requested removal of process impurities Amoxapine and Loxapine related compound A from Table 2 in the *Organic Impurities* section.
Response: Comment incorporated. Both impurities have been removed from Table 2 and their relative retention times have been added to the Note in *System Suitability* section.
Comment Summary #3: The commenter recommended revising the limits for both Loxapine *N*-oxide and "Any unspecified degradation product" to be consistent with ICH Q3B.
Response: Comment incorporated. The limits for both Loxapine *N*-Oxide and "Any unspecified degradation product" are widened to NMT 0.2%.

Monograph/Section(s): Loxapine Succinate/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.

Monograph/Section(s): Methyl Acrylate, Methyl Methacrylate, and Methacrylic Acid (7:3:1) Copolymer 280000 Dispersion/Multiple sections
Expert Committee: Complex Excipients

Expert Committee-initiated Change #1: The wording of "average molecular weight" was changed to "weight-average molecular weight" through the monograph to offer clarity.

Monograph/Section(s): Mitotane/Organic Impurities
Expert Committee: Small Molecules 3
No. of Commenters: 1

Comment Summary #1: The commenter requested removing the 'reporting threshold'.

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.

Monograph/Section(s): Mitotane Tablets/Organic impurities
Expert Committee: Small Molecules 3
No. of Commenters: 1

Comment Summary #1: The commenter noted that the acceptance criteria for "Mitotane" should be removed as it is not an impurity.
Response: Comment incorporated.

Monograph/Section(s): Nicardipine Hydrochloride/Organic Impurities
Expert Committee: Small Molecules 2
No. of Commenters: 2

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.
Comment Summary #2: The commenter indicated that the observed elution order was different from the proposed elution order for nicardipine related compound D and nicardipine related compound C.
Response: Comment not incorporated. As the commenter acknowledged, observed elution order became consistent with the proposed elution order when the LC column listed in the *PF* briefing was used.
Comment Summary #3: The commenter requested that the *Relative standard deviation* requirement be widened from NMT 2% to NMT 5.0% due to the low solution concentration.
Response: Comment not incorporated. The commenter did not provide detailed supporting information. The Expert Committee will consider future revisions upon receipt of supporting data.

Monograph/Section(s): Nicotine/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 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.

Monograph/Section(s): Olanzapine Orally Disintegrating Tablets/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 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.
Comment Summary #2: The commenter indicated that the impurity profile missed degradation products and recommended working with approved manufacturers to include degradation products with limits consistent with what has been approved.
Response: Comment not incorporated. The revision is based on existing data. The Expert Committee will consider future revisions to the monograph upon receipt of additional supporting data.

Monograph/Section(s): Palm Oil Tocotrienols and Tocopherols
Expert Committee: Non-botanical Dietary Supplements
No. of Commenters: 1

Definition
Commenter summary #1: The commenter indicated that squalene and phytosterol are naturally present in Palm Oil. Therefore, the following statement should be included in the Definition: “It also consists of Phytosterols and Squalene which are naturally present in Palm Oil.”
Response: Comment incorporated.

Composition
Expert Committee-initiated Change #1: The following Table footnote has been added to *Table 1* for clarity: “The Relative Response Factors (F) were calculated based on the molecular weight of the different tocotrienols isomers relative to the molecular weight of α-Tocopherol”.
Comment summary #2: In *Content of Tocotrienols and Tocopherols* under *Composition,* the commenter proposed the possibility of using individual isomers as reference standards in addition to the USP proposed calculations of the individual tocopherols and tocotrienols isomers using relative response factors (F) based on USP α-tocopherol RS.
Response: Comment not incorporated. The monograph will not be revised to add a reference standard that is not a USP reference standard, consistent with *General Notices and Requirements 5.80. USP Reference Standards,* which states: “USP Reference Standards are authentic specimens that have been approved as suitable for use in USP or NF tests and assays (see USP Reference Standards ⟨11⟩). Where USP or NF tests or assays call for the use of a USP Reference Standard, only those results obtained using the specified USP Reference Standard are conclusive”.
Comment summary #3: In *Content of Tocotrienols and Tocopherols* under *Composition*, the commenter suggested that the purity of USP α-tocopherol RS is missing in the equation, and that it is necessary to correct the content calculations.
Response: Comment not incorporated. According to *General Notices and Requirements 5.80. USP Reference Standards:* “Unless otherwise directed in the procedure in the individual monograph or in a general chapter, USP Reference Standards are to be used in accordance with the instructions on the label of the Reference Standard”. As such, the value of USP Reference Standard provided in the vial label and accompanying Certificate of Analysis needs to be considered when calculating the concentration of the *Standard Solution*.

Contaminants
Expert Committee-initiated Change #2: The following *Note* has been added to the *Contaminants Section*: “Chloropropanols can be formed if the Palm Oil is treated at high temperature”.

Specific Tests
Comment summary #4: In *Content of Squalene* under *Specific tests*, the commenter proposed to change the reagent *Alcohol* to *Ethanol*. Alcohol is too wide range where it might influence the separation or elution time.
Response: Change not incorporated. According to *USP Reagents Specifications, Alcohol* is defined as: Ethanol, Ethyl Alcohol, C_2H_5OH 46.07 [64-17-5].Use a suitable grade with a content of NLT 92.3% and NMT 93.8%, by weight, corresponding to NLT 94.9% and NMT 96% by volume, at 15.56°. Therefore, the reference to the reagent *Alcohol* is intended to incorporate reagents within the applicable definition.

Monograph/Section(s): Palonosetron Hydrochloride
Expert Committee: Monographs – Small Molecules 3
No. of Commenters: 1

Comment Summary #1: The commenter requested removing the reporting threshold because 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.

Monograph/Section(s): Perindopril Erbumine/Multiple Sections
Expert Committee: Small Molecules 2
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. Based on comments received on a proposed policy for reporting thresholds, USP determined that removal of reporting thresholds from monographs needs further stakeholder engagement.
Expert Committee-initiated Change #1: The chemical name for USP Perindopril Related Compound I RS is updated to reflect that the material is available in the tert-butyl salt form in the USP Reference Standards <11> section.

Monograph/Section(s): Potassium Citrate and Citric Acid Oral Solution/Assay
Expert Committee: Small Molecules 5
No. of Commenters: 1

Comment summary #1: The commenter recommended that USP work with the manufacturers of marketed products to ensure that they will be able to meet the requirements in the proposed monograph in order to avoid a drug shortage.
Response: Comment incorporated. To the extent feasible, USP seeks information from manufacturers of marketed products before publishing a monograph. As applicable, the Expert Committee will consider future revisions to the monograph upon the receipt of new supporting data.

Monograph/Section(s): Ramipril/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.

Monograph/Section(s): Riociguat Tablets/Organic Impurities
Expert Committee: Small Molecules 5
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.
Comment Summary #2: The commenter recommended removal of process impurities, Riociguat related compound A and Riociguat related compound C, from Table 1 in the test for *Organic Impurities*.
Response: Comment incorporated. Both impurities along with the information for the relative retention times were removed from Table 1 and added to the Note under the System Suitability section. The footnote indicating riociguat related compound A and riociguat related compound C as process impurities was also removed.
Expert Committee-initiated Change #1: "Any individual unspecified degradation product" was revised to "Any unspecified degradation product" in the test for *Organic Impurities* to be consistent with ICH terminology.

Monograph/Section(s): Sotalol Hydrochloride Tablets/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.

Monograph/Section(s): Tannic Acid/Impurities
Expert Committee: Small Molecules 3
No. of Commenters: 1

Comment summary #1: The commenter recommended that USP retain the test for "Arsenic" in the monograph to allow for elemental impurity control at the ingredient level because tannic acid is sourced from natural origin and is listed as an ingredient under the FDA OTC monograph under several therapeutic categories. There may not be USP drug product monographs which apply to all marketed Tannic Acid products.
Response: Comment not incorporated. Removal of elemental impurity tests is to align with the concept of General Chapter <232>. The elemental impurities will be controlled in the drug product using the risk-based approach specified in the General Chapter <232>. The risk-based approach is used to determine the presence of an elemental impurity (in components of the formulation or in the drug product) and the appropriate level of control needed. Therefore, it is redundant to include the test and acceptance criteria in the monograph.

Monograph/Section(s): Valproic Acid/Organic Impurities
Expert Committee: Small Molecules 4
No. of Commenters: 1

Comment summary #1: The commenter recommended to retain the current procedure as procedure 1 and to include the proposed procedure as procedure 2 because the valproic acid related compound K cannot be formed in their manufacturing process.
Response: Comment not incorporated. The proposed procedure can separate more impurities, including valproic acid related compound K, than the current official procedure. The Expert Committee determined that the proposed procedure is suitable for intended use and the manufacturer can use alternative procedures, as applicable, as described in USP *General Notices* 6.30. [*Alternative and Harmonized Methods and Procedures*.]

Monograph/Section(s): Vardenafil Orally Disintegrating Tablets/Multiple Sections
Expert Committee: Small Molecules 5
No. of Commenters: 1

Comment Summary #1: The commenter recommended widening the acceptance criterion for the test of *Disintegration* to be consistent with the FDA Guidance for Industry Orally Disintegrating Tablets.
Response: Comment incorporated. The acceptance criterion was widened from NMT 25 s to NMT 30 s, consistent with the FDA Guidance for Industry Orally Disintegrating Tablets.
Comment Summary #2: 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.
Comment Summary #3: The commenter recommended removal of process impurities, 7-methyl vardenafil and vardenafil dimer, from Table 2 in the test for *Organic Impurities*.
Response: Comment incorporated. Both impurities along with the information for the relative retention times were removed from Table 2 and added to the Note under the System suitability section. The footnote indicating 7-methyl vardenafil and vardenafil dimer as process impurities was also removed.
Expert Committee-initiated Change #1: "Any individual unspecified degradation product" was revised to "Any unspecified degradation product" in the test for *Organic Impurities* to be consistent with ICH terminology.

Monograph/Section(s): White Wax/Ester value
Expert Committee: Complex Excipients
No. of Commenters: 1

Comment Summary #1: The commenter suggested changing the lower limit of the ester value test from 70 to 68 with supporting data.
Response: Comment incorporated consistent with the supporting data.