Commentary

USP–NF 2021 Issue 1

November 2, 2020

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.

For further information, contact:
USP Executive Secretariat
United States Pharmacopeia
12601 Twinbrook Parkway
Rockville, MD 20852-1790 USA

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

General Notices to *USP-NF*

General Chapters

<191> *Identification Tests—General*
<210> *Monosaccharide Analysis*
<476> *Control of Organic Impurities*
< 601> *Inhalation and Nasal Drug Products: Aerosols, Sprays, and Powders—Performance Quality Tests*
<631> *Color and Achromicity*
<643> *Total Organic Carbon*
<915> *Measurement of Structural Strength of Semisolids by Penetrometry*
<922> *Water Activity*
<1051> *Cleaning Glass Apparatus*
<1086> *Impurities in Drug Substances and Drug Products*
<1088> *In Vitro and In Vivo Evaluation of Dosage Forms*
<1102> *Immunological Test Methods*
<1151> *Pharmaceutical Dosage Forms*
< 1153> *Drug Products Containing Nanomaterials*
<1195> *Significant Change for Bulk Pharmaceutical Excipients*
<1235> *Vaccines for Human Use—General Considerations*
<1238> *Vaccines for Human Use—Bacterial Vaccines*
<1239> *Vaccines for Human Use—Viral Vaccines*
<1711> *Oral Dosage Forms—Performance Tests*
<1788> *Methods for the Determination of Subvisible Particulate Matter*
<1788.1> *Light Obscuration Method for the Determination of Subvisible Particulate Matter*
<1788.2> *Membrane Microscope Method for the Determination of Subvisible Particulate Matter*
<1788.3> *Flow Imaging Method for the Determination of Subvisible Particulate Matter*
<1912> *Measurement of Hardness of Semisolids*

Monographs

Abacacvir Lamivudine and Zidovudine Tablets
Albuterol Inhalation Solution
Amlodipine Besylate Tablets
Atomoxetine Hydrochloride
Azithromycin for Oral Suspension
Baclofen Injection
Benazepril Hydrochloride and Hydrochlorothiazide Tablets
Benztropine Mesylate
Bifidobacterium Bifidum
Bifidobacterium Longum Subsp. Longum
Calcipotriene
Calcium Magnesium Citrate

Levofloxacin Tablets
Liothyronine Sodium
Loratadine Capsules
Maltitol
Maltitol Solution
Methylphenidate Hydrochloride
Minoxidil Tablets
Modafinil
Modafinil Tablets
Nefazodone Hydrochloride
Noncrystallizing Sorbitol Solution
Oil-and Water-Soluble Vitamins with Minerals Chewable Gels
Omeprazole Magnesium
Oxcarbazepine Tablets
Oxycodone Hydrochloride Oral Solution
Pindolol
Prazosil Hydrochloride
Pyrazinamide
Quinapril Tablets
Quinine Sulfate Capsules
Regorafenib
Rifabutin
Rifabutin Capsules
Risperidone Oral Solution
Sodium Phenylbutyrate Oral Powder
Sodium Phenylbutyrate Tablets
Sorafenib Tablets
Sorafenib Tosylate
Sorbitol
Sorbitol Solution
Sorbitol Sorbitan Solution
Spironolactone Compounded Oral Suspension
Sterile Purified Water
Sterile Water for Inhalation
Sterile Water for Injection
Sterile Water for Irrigation
Telmisartan
Tetraxetan
Tranexamic Acid
Urea C13
Vecuronium Bromide
Water-Soluble Vitamins Preparation

No comments were received for the following proposals:

Monographs

Acebutolol Hydrochloride
Betaxolol Hydrochloride
Bethanechol Chloride Injection
Butylated Hydroxytoluene
Carbachol
Carbachol Ophthalmic Solution
Cefonicid for Injection
Cefonicid Sodium
Cetylpyridinium Chloride
Ciprofloxacin Ophthalmic Ointment
Citicoline
Clotrimazole
Cyclopropane
Diazoxide
Dibucaine Hydrochloride
Dimenhydrinate Tablets
Doxepin Hydrochloride
Doxycycline Extended-Release Capsules
Epinephryl Borate Ophthalmic Solution
Ergotamine Tartrate Injection
Ethynodiol Diacetate and Mestranol Tablets
Flavoxate Hydrochloride
Flumethasone Pivalate
Flumethasone Pivalate Cream
Gallamine Triethiodide
Gallamine Triethiodide Injection
Gemifloxacin Mesylate
Guanethidine Monosulfate Tablets
Half-Strength Lactated Ringer's and Dextrose Injection
Haloperidol Decanoate
Hyoscyamine Tablets
Isoetharine Hydrochloride
Isoetharine Inhalation Solution
Isoetharine Mesylate
Isoxsuprine Hydrochloride Injection
Lactated Ringer's Injection
Lactated Ringer's and Dextrose Injection
L-alpha-Glycerylphosphorylcholine
Maprotiline Hydrochloride
Modified Lactated Ringer's and Dextrose Injection
Nandolol and Bendroflumethiazide Tablets
Naratriptan Hydrochloride
Nortriptyline Hydrochloride
Nortriptyline Hydrochloride Capsules
Nortriptyline Hydrochloride Oral Solution
Oxcarbazepine Oral Suspension
Oxymetholone
Oxymetholone Tablets
Paclitaxel Injection

Penbutolol Sulfate
Penbutolol Sulfate Tablets
Penicillin V Benzathine
Penicillin V Benzathine Oral Suspension
Penicillin V for Oral Suspension
Penicillin V Tablets
Pilocarpine Ocular System
Potassium Chloride in Lactated Ringer's and Dextrose Injection
Proparacaine HCl
Quinapril Hydrochloride
Ropinirole Extended-Release Tablets
Ropinirole Hydrochloride
Rufinamide Tablets
Sertraline Hydrochloride
Sodium Chloride Tablets
Sodium Chloride Tablets for Solution
Tetracycline Hydrochloride Compounded Oral Suspension
Thioridazine Hydrochloride
Ticarcillin and Clavulanic Acid Injection
Tizanidine Hydrochloride
Tomato Extract Containing Lycopene
Trifluprom azine Oral Suspension
Trioxsalen
Trioxsalen Tablets
Zalcitabine
Zalcitabine Tablets
Zinc Carbonate

General Notices

Monograph/Sections: *General Notices and Requirements*/Multiple Sections
Expert Committee: Council of Experts
No. of Commenters: 3

Section 1. Title and Revision
Comment Summary #1: The commenter supported USP's continuing efforts to transition the *USP* and *NF* compendia to a fully electronic format, with the latest revisions to the *General Notices* completing this timely effort.
Response: Comment incorporated. The Council of Experts (CoE) acknowledged the supportive comment.
Comment Summary #2: The commenter suggested adding the months in which the compendia become official to the example titles: "*USP–NF* 2021 Issue 1: Published November 1, 2020; Official May 1, 2021."
Response: Comment not incorporated. The six-month implementation period does not apply to all standards that are published in each issue (e.g., delayed implementation or accelerated revisions), thus including it in the title would not be accurate.

Section 3.10 Applicability of Standards

Comment Summary #3: The commenter disagreed that chemical information should be provided in monographs solely for informational purposes. The commenter proposed any changes to chemical structures be published in *Pharmacopeial Forum* for public comment and proposed adding information to the *General Notices* from the Mission and Preface, noting the graphical representation of the chemical compound structure in the monograph is understood to represent one of many possible ways to depict the molecule.
Response: Comment not incorporated. The revision specifically aligns USP policy with the intention of providing chemical information and structures for informational purposes. In cases where any specifications represented by chemical information are critical to establishing identity, purity, potency, or another quality attribute of an official article, the monograph will include such specifications in the text that states requirements. The CoE agreed that chemical and structural information in a monograph must be subject to stringent quality checks. Certain details (e.g., molecular weights, CAS numbers, chemical structures) are updated continually by organizations outside of USP and thus are not subject to further editing based on public comments.
Comment Summary #4: The commenter suggested revising the proposal for clarity to state: *"In either format, information that appears before the double arrow symbol, before the section titled "Definition," or in or after the section titled "Auxiliary Information" is provided for informational purposes.*"
Response: Comment partially incorporated. The title was added as it is a required portion of the monograph and the following text was used: *"In either format, information that appears: (1) after the title but before the double arrow symbol; (2) after the title but before the section titled "Definition,"; or (3) in or after the section titled "Auxiliary Information" is provided for informational purposes.*"
Comment Summary #5: The commenter encouraged completion of monograph redesign for all remaining "classic style" monographs.
Response: Comment incorporated. USP continues to redesign "classic style" monographs as they are revised.
Comment Summary #6: The commenter noted that there were compliance challenges in instances in which a monograph *Definition* section contained specification information without providing an associated compendial procedure or referencing a procedure in a relevant General Chapter.
Response: Comment not incorporated. The comment is outside the scope of this revision, but the CoE will review additional information from the commenter as a request for revision.

Section 3.10.40 Applicability of Global Health Monographs
Comment Summary #7: The commenter expressed support for Global Health Monographs in the compendia and the newly added GN provision 3.10.40, in keeping with the organization's ongoing efforts to provide quality standards for essential medicines in the global market.
Response: Comment incorporated. The Council of Experts (CoE) acknowledged the supportive comment.

General Chapters

General Chapter: <191> *Identification Tests—General*
Expert Committee: General Chapters–Chemical Analysis
No. of Commenters: 2

Comment Summary #1: The commenter recommended that *Identification Test Procedures A and B for Chloride* should remain separate, and that Identification Test C could be specifically prescribed within a monograph as needed. The impact of consolidating both *Identification* procedures would require a significant investment for internal change control.
Response: Comment not incorporated. The recommendation is not in conflict with the scientific or technical aspects of the test, and no change to the procedure is proposed. A notice of intent to revise was published on July 27, 2018 (see: https://www.uspnf.com/notices/general-chapter-191-id-test-general-nitr). The target official date is August 1, 2020. This extended implementation period provides additional time to implement change control as needed.
Comment Summary #2: The commenter suggested introducing colorimetric instrumental determinations of chloride based on matrices to achieve reliable results.
Response: Comment not incorporated. The second paragraph of the *Introduction* of the General Chapter reads, "Instrumental techniques described in this chapter may be used in lieu of chemical identification tests. Those instrumental techniques are not exhaustive and other techniques, such as nuclear magnetic resonance, ion-selective electrodes, and near-infrared, may be used in lieu of a chemical identification test provided that they are suitable and validated." In addition, the EC will consider including additional instrumental techniques in future revisions of the chapter.

General Chapter: <210> *Monosaccharide Analysis*
Expert Committee: General Chapters–Biological Analysis
No. of Commenters: 1

General Comments
Comment Summary #1: The commented requested to change the requirement of coefficient of determination (R^2) to NLT 0.98.
Response: Comment incorporated.

General Chapter: <476> *Control of Organic Impurities*
Expert Committee: General Chapters–Chemical Analysis
No. of Commenters: 12

Introduction
Comment Summary #1: The commenter requested removing the word “policies” in the opening sentence for clarity and to avoid confusion with documents that are issued by regulators and which are developed by a different process.
Response: Comment incorporated.
Comment Summary #2: The commenters recommended clarifying the timing and applicability of this chapter, whether it will be implemented by referencing the chapter in individual monographs or through inclusion of a statement in the USP *General Notices* that will define applicability more broadly.
Response: Comment incorporated. The following sentence was introduced: “This chapter applies to drug substances and drug products described in the USP where referenced in the individual monograph.”
Comment Summary #3: The commenter recommended presenting ICH Q3A(R2) and ICH Q3B(R2) as the core reference, including a clarification on scope and exclusions to avoid confusion and the need to keep updating contents with potential ICH revisions/updates.
Response: Comment partially incorporated. Several parts of the *Introduction* and the scope were changed in this chapter and in the companion General Chapter <1086> by adapting the text to USP scope and stating the relationship with both guidelines from the ICH.

Comment Summary #4: The commenter requested deleting “(process impurities and degradation products)” in the scope of the chapter to avoid confusion that Q3B could also apply to process impurities.
Response: Comment incorporated.
Comment Summary #5: The commenter suggested excluding enantiomeric impurities in this chapter, as per ICH Q3B guideline.
Response: Comment not incorporated. The scope of this chapter is wider than ICH Q3B guideline, including drug substances and drug products. Enantiomeric impurities could be by-products and therefore are covered under drug substances.
Comment Summary #6: The commenters recommended clarifying the exclusion of addressing genotoxic impurities (or adding a statement about the ICH M7 guideline) in this chapter to avoid confusion.
Response: Comment incorporated. The following sentence was added: “This chapter does not cover mutagenic impurities as described in ICH M7 guideline - Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk.”
Comment Summary #7: The commenter recommended clarifying explicitly the exclusion of impurities in excipients (concomitant component, other component, added substance, excipient impurity) in the scope of this chapter to avoid confusion.
Response: Comment not incorporated. The chapter already states that it is not applicable to impurities in excipients.
Comment Summary #8: The commenter suggested removing “alternate/additional procedure” or replacing it with "new procedure” because when there is no procedure in the monograph, any procedure submitted is considered alternate or additional.
Response: Comment partially incorporated. The text was changed to “alternative/new procedure.”

Identification of Impurities
Comment Summary #9: The commenters requested clarifying “all reasonable attempts” to identify impurities present above the identification threshold because it deviates from ICH Q3, which states that a summary of the laboratory studies demonstrating such attempts made should be included in the application. If an impurity is over the identification threshold, it should be identified.
Response: Comment not incorporated. The justification can be done in different ways. The chapter refers to ICH Q3A and Q3B, which describes what information should be included in this scenario.
Comment Summary #10: The commenter recommended listing the “current applicable regulatory references” mentioned in this section.
Response: Comment incorporated. The guidelines ICH Q3A and Q3B are listed in the *Introduction* and “or other acceptable scientific means" was added for consistency within the chapter.
Comment Summary #11: The commenter requested clarifying that higher thresholds may be applied if scientifically justified as per ICH Q3A and ICH Q3B.
Response: Comment incorporated.

Analytical Procedures for Impurities
Comment Summary #12: The commenter suggested including the sentence related to setting the acceptance criteria for an analytical method that includes setting the limits of detection and quantitation also in the “setting acceptance criteria” section.
Response: Comment not incorporated. The information is already included in the relevant *Analytical Procedures* section.

Comment Summary #13: The commenter recommended including the need to consult the regulatory guidelines in order to establish limits for impurities that are known or suspected to be highly toxic (e.g., genotoxic) or that produce undesired pharmacological effects.
Response: Comment incorporated.

Reporting Impurities
Comment Summary #14: The commenter requested deleting "and it is included in the individual monograph" because establishment of the reporting threshold in individual monographs can be complicated and is affected by different factors (e.g., incomplete impurity profile, maximum daily dose, inclusion of process impurities in drug product monographs, unusually toxic impurities). The reporting threshold should remain a general principle in this chapter instead of being included in each monograph.
Response: Comment incorporated.
Comment Summary #15: The commenter recommended removing the reference to USP *General Notices* 7.20. Rounding Rules to avoid potential discrepancies in the reporting threshold with ICH guidelines.
Response: Comment not incorporated. The rules in both the General Notices and the chapter are complementary.
Comment Summary #16: The commenter suggested removing the definition of the total impurities as it could be viewed as a definition of a limit. In the individual monographs, total impurities are determined based on the impurities profile and specifications that are set as described by FDA and listed in the specific monograph.
Response: Comment not incorporated. The total impurities is a critical element of the monograph and it provides useful information as a public standard. The inclusion of total impurities does not negate FDA specifications.
Comment Summary #17: The commenter requested clarifying that total degradation product acceptance criteria for OTC monographs have no value added if specified and unspecified are separately controlled since manufacturers likely have a different set of impurities in their products based on their formulation variations.
Response: Comment partially incorporated. A sentence was changed to: "All impurities at a level greater than (>) the reporting threshold shall be summed and reported as a value for total impurities, unless otherwise indicated in the monograph." to emphasize that the monograph specification supersedes this chapter. Stakeholders should use a scientific approach when dealing with OTC products with multiple-active ingredients.

Setting Acceptance Criteria for Impurities
Comment Summary #18: The commenters requested deleting the parenthesis excluding the impurities due to the drug product manufacturing process or interaction with the packaging systems or interaction with the excipients because they are considered as degradation products per ICH Q3B.
Response: Comment incorporated.
Comment Summary #19: The commenter suggested clarifying the use of relative retention times in this context because unspecified identified process impurities are more common.
Response: Comment incorporated. The reference to relative retention times was deleted from this sentence: "Drug product monographs may include a note that certain drug substance process-related impurities should not be included in the total degradation products."
Comment Summary #20: The commenter suggested changing "identification thresholds" to "reporting thresholds" although the acceptance criteria for impurities between the reporting threshold and the identification threshold will be set at the identification level; nevertheless, there will be an acceptance criteria.
Response: Comment incorporated.

Comment Summary #21: The commenter requested adding that the acceptance criteria for the total degradation product is not required for complex OTC products or that the manufacturer of these products establish and justify the use of acceptance criteria for total degradation product based upon the manufacturing experience.
Response: Comment not incorporated. These statements are out of the scope of this chapter.
Comment Summary #22: The commenter recommended revising the paragraph to read as follows: "Unless otherwise indicated, total degradation products in the drug product monographs are the sum of all specified (identified and unidentified) and unspecified degradation products above the reporting threshold."
Response: Comment incorporated.

Qualification of Impurities
Comment Summary #23: The commenter recommended specifying where to find the toxicologic endpoints that need to be addressed by "scientific rationale." An example would be the following: "Refer to ICH M7, ICH Q3A, and ICH Q3B regarding guidance on elements of an adequate qualification (e.g., point mutation assay, chromosomal aberration assay, and 90-day animal study)."
Response: Comment not incorporated. This level of detail is out of the scope of this chapter. References to ICH guidelines are already provided.
Comment Summary #24: The commenter requested adding that degradation products that are also significant metabolites present in human studies are generally considered qualified.
Response: Comment not incorporated. A similar statement was removed previously based on public comments. It was added to <1086> instead for general consideration.

Organic Impurities in Drug Substances
Comment Summary #25: The commenter recommended unifying the policy on reporting threshold between <476>, ICH Q3A, and <621>.
Response: Comment not incorporated. The purpose of this chapter is to align with ICH Q3 in terms of safety. General Chapter <621> is focused on analytical capabilities.
Comment Summary #26: The commenter recommended changing "acceptance criteria shall be set for all impurities present above the identification threshold" to "acceptance criteria shall be set for all impurities present above the reporting threshold, including specified (identified and unidentified) impurities" because acceptance criteria should also be set for specified unidentified impurities (using relative retention times as identifiers), although their levels are lower than the identification threshold.
Response: Comment partially incorporated. The sentence was removed to avoid confusion because the proposed sentence applies to an identified impurity, but if it is unidentified, it can be captured as an unspecified impurity.

Organic Impurities in Drug Products
Comment Summary #27: The commenter recommended adding guidelines when drug products with multiple indications have different impurity limits relative to different maximum daily doses per labeled indication.
Response: Comment not incorporated. These cases, when identified, are individually addressed in the particular monograph (e.g., ramipril capsules with different strengths). It is not a general rule.
Comment Summary #28: The commenter suggested removing the first sentence of the section, as the second sentence is more consistent with ICH Q3B. In the second sentence, they suggested inserting "usually" at the beginning of the sentence (e.g., "Usually, the impurities to be controlled in the drug product are only the degradation products resulting from the degradation of the drug substance or the interaction of the drug substance with…") because in

some cases drug substance process impurities are also included in the drug product specification.
Response: Comment incorporated.
Comment Summary #29: The commenter suggested providing an example of when drug substance process impurities should be included in the drug product specification.
Response: Comment not incorporated. This is determined on a case-by-case basis. It is not illustrative nor appropriate to provide a specific example.
Comment Summary #30: The commenter suggested revising the sentence that states: “the amount of drug substance administered per day is based upon the manufacturer's recommended labeled dosage per day for the over-the-counter (OTC) monograph drug product” because this principles also applies for prescription products. Also, it was recommended changing “manufacturer’s recommended labeled dosage” to “manufacturer’s maximum recommended labeled dosage.”
Response: Comment incorporated.
Comment Summary #31: The commenter recommended the following revisions to Table 2 to align with ICH Q3B: “i) Maximum daily dose row, second cell: replace “1-10 mg” with 1-<10 mg; ii) Add a new column for a 10 mg maximum daily dose and list the following: 0.05% for reporting threshold, 0.5% (20 µg) for identification threshold, and 0.5% (200 µg) for qualification threshold."
Response: Comment incorporated.
Comment Summary #32: The commenter recommended adding language to clarify that the duration of use is sometimes not reflected in the labeled use for OTC monograph products because the duration of animal qualification studies depends on the duration of clinical use.
Response: Comment not incorporated. The use of nonprescription drugs is not in the scope of this chapter.
Comment Summary #33: The commenter requested clarifying how limits may be established based on grouping of impurities in cases of a multiple drug substance product.
Response: Comment partially incorporated. The sentence was changed to: “In cases of complex impurity profiles, limits may be established based on grouping of impurities, if appropriate and scientifically justified (according to ICH Q3B (R2) guidelines).”
Comment Summary #34: The commenter recommended clarifying content to address impurity controls for complex multi-active drug products, particularly around the challenges of assignment of unknown peaks to the appropriate drug substance and the determination of total degradation limits.
Response: Comment partially incorporated. The text was changed to: “For drug products that contain multiple drug substances, degradation products from each active ingredient should be controlled. Manufacturers should provide rationale and supporting data to justify the acceptance criteria for impurities associated with each drug substance, as applicable.”

General
Comment Summary #35: The commenter suggested reorganizing the chapter to separate contents/discussions related to drug substance and drug products. Independent discussion/presentation will help avoid contents mix-up and confusion, clarify expectations, and facilitate potential application.
Response: Comment incorporated.
Comment Summary #36: The commenter recommended prioritizing the implementation of this chapter in monographs, in coordination with relevant stakeholders because of its broad and significant impact.
Response: Comment incorporated. The following sentence “This chapter applies to drug substances and drug products described in the USP where referenced in the individual

monograph," was changed to clarify that this chapter will be only applicable when referenced in individual monographs, on a case-by-case basis.

General Chapter: <601> *Inhalation and Nasal Drug Products: Aerosols, Sprays, and Powders—Performance Quality Tests*
Expert Committee: Dosage Forms
No. of Commenters: 4

Section A.1.1.1
Comment Summary #1: The commenter suggested deleting "The volume of air sampled per actuation should not exceed 2.0 L." as this requirement adds unnecessary testing variability since there would be a short duration (~4 seconds for a 2 L limit) where airflow is present through the test apparatus. If the testing analyst actuated the MDI prior to or near the end of the airflow, incomplete capture of the dose could occur. A 2 L volume limit might be applicable for DDU testing of a breath actuated MDI since the airflow is what triggers the delivery of the dose.
Response: Comment not incorporated. The volume of 2 L is proposed to incorporate a procedural standard and to be consistent with the FDA guidance.
Comment Summary #2: The commenter suggested removing the two-way solenoid valve and timer from Figure 1a.
Response: Comment not incorporated. The existing arrangement provides optimum control of sampling duration.
Comment Summary #3: The commenter stated that it is odd to have the same component described as both "Connector A" and "Vacuum Tubing D" in Figures 1a and 1b, given that they have different specifications and entries in Table 1. The same comment applies to Figure 7c and Table 5.
Response: Comment not incorporated. Dimensional information is provided in Tables 1 and 5. The figure is a schematic representation to support the dimensional detail contained in the table.
Comment Summary #4: The commenter suggested editing the bolded text in the following sentence from "The actuations between the two test samples (i.e. beginning and end of **container** life)" to "The actuations between the two test samples (i.e. beginning and end of **unit** life)" in order to be consistent with the wording used in other paragraphs.
Response: Comment incorporated.

Table 1
Comment Summary #5: The commenter recommended the inclusion of other types of filters in Table 1, such as "stainless steel fiber filter; and microfiber polypropylene filter" besides "glass fiber filter." These filters are frequently used by product manufacturers.
Response: Comment incorporated.
Comment Summary 6#: The commenter suggested adding a description of "vacuum pump" for Apparatus A.
Response: Comment incorporated.
Comment Summary #7: The commenter recommended including nasal sprays under Description in Table 1 or excluding it from Figure 1a, since the Figure 1a caption includes nasal sprays.
Response: Comment incorporated. Nasal spray was added to Table 1 Sampling Apparatus A description.
Comment Summary #8: The commenter requested clear specification of the drug products that Figure 2 applies to in the caption.
Response: Comment incorporated. The caption was revised to include nasal aerosols, sprays, and powders.

Comment summary #9: The commenter indicated that all tubing has been lumped together as Vacuum Tubing Code D and this could be an issue. In the case of Apparatus B, for the testing of inhalation powders where critical sonic flow is required, the tubing used between the solenoid valve and the pump should be as short and wide as possible. The text in the current chapter, under Vacuum Pump Code F, reflects this and similar text, such as "Short, wide vacuum tubing should be used to minimize pump capacity requirements." should be used here. A 16 mm ID is typically used here instead of the 10 mm ID tubing used elsewhere in the set-up to achieve the required sonic flow rates. The requirement for 25 ± 5 mL volume of tubing between the SCT and flow control valve has been removed. The assumption is that it is intentional. These issues have been raised previously, so please refer to the previous comments regarding the ramp-up rate.
Response: Comment incorporated. Table 1 has been revised.
Comment summary #10: The commenter indicated that the solenoid valve is shown in Figure 1a, which is consistent with the new text for Apparatus A "(e.g., a timer solenoid valve can be used to achieve the required volume)". However, since this seems to be optional, the recommendation is that "N/A" be replaced with "Optional" or "Recommended," followed by the same text as for Apparatus B.
Response: Comment incorporated. "N/A" is replaced with "optional."
Comment summary #11: The commenter suggested that Code F under Apparatus B should say required flow rate "under critical (sonic) conditions (P3/P2 < 0.5)," since the vacuum pump for Apparatus A is also required to draw the required flow rate through the apparatus, but this statement is not made there.
Response: Comment incorporated.
Comment summary #12: The commenter indicated that the timer shown in Figure 1a seems to be optional, therefore "N/A" for Code G, Apparatus A should be replaced with "Optional" or "Recommended", followed by the same text as for Apparatus B.
Response: Comment incorporated. "N/A" is replaced with "optional."

Figure 2
Comment summary #13: The commenter inquired why the dimensioned version of this drawing (b) has been reinstated, given that the critical dimensions were transferred to Table 1 to simplify matters for users and to be consistent with Apparatus B.
Response: Comment not incorporated. Necessary information is in Table 1. The figure is merely to assist in visualization of the table and is not intended as an engineering drawing.
Comment summary #14: The commenter inquired whether Figure 2 applies to all nasal products or to just nasal aerosols.
Response: Comment incorporated. The caption in Figure 2 was revised to include all nasal products.

Section A 2.1
Comment Summary #15: The commenter recommended modifying the last sentence in the first paragraph to read as follows: "A dose in this test is defined as the minimum recommended number of actuations specified in the product labeling or instructions for use but NMT 2 actuations per determination." The term "actuation" (as opposed to spray) would describe the actions of both nasal aerosols and nasal sprays. Additionally, it is in line with the FDA guidance for Industry Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action and USP <5> which use the term "number of actuations."
Response: Comment incorporated.

Section A.2.1.2
Comment summary #16: The commenter requested removal of the following sentence

as it is redundant: “The dose should be delivered into a suitable container (e.g. scintillation vial) in which quantitative transfer from the drug product can be accomplished.”
Response: Comment incorporated.

Section A .3
Comment Summary #17: The commenter suggested revising the following sentence to avoid any misunderstanding: “Data are reported as amount delivered and as a percentage of target-delivered ~~label claim~~ dose (or of labelled delivered dose).”
Response: Comment not incorporated. In all cases, DDU is the amount and percent of target delivered label claim, which is specified when tested under defined experimental conditions. On the other hand, label claim is the nominal overall strength stated on the label.

Section A 3.1
Comment summary #18: The commenter suggested revising the first sentence of the third paragraph as follows, to be consistent with other paragraphs in the chapter: “Unless otherwise directed in the individual monograph, the drug content of the delivered dose will be collected at the beginning and the end of the unit life per label claim.”
Response: Comment incorporated.

Section A.3.1.1
Comment Summary #19: The commenter proposed modifying the following sentence as follows for clarity: “The flow rate should not be changed to compensate for device-to-device variability for the same product in flow resistance.”
Response: Comment incorporated.
Comment Summary #20: The commenter recommended modifying the following phrase as follows for clarity: “where n is the number of inhalations defined in the labeling as the minimum recommended dose”.
Response: Comment incorporated. The phrase was revised with the following modification: “where n is the number of ~~inhalations~~ actuations defined in the labeling as the minimum recommended dose.”

Section A.4.1.1
Comment Summary #21: The commenter requested modifying the following sentence for consistency: “The two separate determinations (NMT 2 actuations) include samples of the first dose and the dose corresponding to the last labeled dose from each of 10 units.” The revision would be: “The two separate determinations (NMT 2 actuations) include samples of the beginning and the end of the unit life corresponding to the label claim from each of 10 units.”
Response: Comment incorporated.
Comment Summary #22: The commenter requested modifying the following sentence for consistency: “The doses between the two sequential beginning and end test samples”
to read “The discharges between the two sequential beginning and end test samples.”
Response: Comment incorporated.
Comment Summary #23: The commenter suggested revising the final sentence that reads: “DDU sampling apparatus B (Figure 1b and Figure 2) is recommended for nasal powders.” to include a reference to Table 1 as it is pertinent to DDU sampling apparatus B for nasal powders.
Response: Comment incorporated. The sentence was revised as follows: “DDU sampling apparatus B (Table 1, Figure 1b, and Figure 2) is recommended for nasal powders.”

Section B
Comment Summary #24: The commenter requested modifying the following sentence for consistency: “the emitted droplet/particle size distribution should be determined for the

delivered plume subsequent to delivery." The revision would be "the emitted droplet/particle size distribution should be determined for the discharged plume subsequent to delivery."
Response: Comment incorporated.
Comment Summary #25: The commenter suggested revising Figure 3 caption to read "Figure 3. Conversion of light-scattering data into a droplet/particle size distribution by laser diffractometry." This would be more in line with the title of Section B.1. Furthermore, PSD has been defined in the gray box of Figure 3, making its definition here unnecessary.
Response: Comment incorporated.
Comment Summary #26: The commenter suggested specifying the types of products in Figure 4 caption in order to exclude nasal powder drug products. The revised caption should read as follows: "Setup for laser diffractometry with a nasal aerosol or nasal spray drug product."
Response: Comment Incorporated.

Section B.2
Comment Summary #27: The commenter requested clarification of whether aerodynamic particle size distribution (APSD) testing of nasal sprays is included in the chapter as stated under Briefing.
Response: Comment not incorporated. The table of contents of this chapter clearly shows that APSD testing of nasal sprays is not part of this chapter.

Section C
Comment Summary #28: The commenter suggested revising the section title to include droplet size distribution, since the section is written for inhalation aerosols, sprays and powders, and nasal aerosols and powders. The modification reads as follows: *"Aerodynamic Particle Size Distribution/Droplet Size Distribution—Inhalation Aerosols."*
Response: Comment incorporated.

Section C.1
Comment Summary #29: The commenter recommended revising the title of this section as follows, to include droplet size distribution, since the section is written for inhalation aerosols, sprays and powders, and nasal aerosols and powders: *"General Principles of Aerodynamic Particle Size Distribution/Droplet Size Distribution Measurement."*
Response: Comment incorporated.
Comment Summary #30: The commenter suggested removal of "and separators" from the last sentence of this section as it is not currently a specification for <u>all</u> commercially available pre-separators (e.g., NGI).
Response: Comment incorporated.

Section C.1.2
Comment Summary #31: The commenter suggested that the last sentence of this section (stated below) applies only to the ACI since the NGI is designed to have wall losses <5% in all cases and is not designed for recovery from impactor nozzles, seal body or inter-stage passageways. This is a departure from the current methodology where ACI stage deposition (wall losses) are included with the associated collection plate. As these are generally small, they are not considered to skew the APSD.
The aforementioned sentence is "Wall losses on a particular stage should not be combined with the plate deposition to assay the mass deposited on a specific stage. It is appropriate to include wall deposition in the determination of the mass balance."
Response: Comment not incorporated. The sizes of the particles deposited on the wall has no relation to the sizes of the particles deposited in the adjacent collection plates/collection cups.

Section C.1.3
Comment Summary #32: The commenter suggested revising the following phrase in the second paragraph, “by using appropriate assay methods” to read “by using validated analytical methods” This change will clearly convey the expectation that good analytical practices are to be followed.
Response: Comment incorporated.
Comment Summary #33: The commenter suggested revising the following phrase in the second paragraph for consistency: “determine aerodynamic particle size distributions for drugs leaving the mouthpieces.” The modification would be: “determine aerodynamic particle size distributions for drug leaving the mouthpieces.”
Response: Comment incorporated.

Section C.1.4
Comment Summary #34: The commenter suggested revising the following phrase in the first paragraph, “is within an acceptable range around the measured delivered dose,” to read “is within an acceptable range around the target delivered dose.” This would be more consistent with the text in the following paragraph which reads, “NLT 85% and NMT 115% of the target-delivered label claim.”
Response: Comment incorporated.

Section C.1.5
Comment Summary #35: The commenter requested revision of the following sentence for clarity: “Generation Impactor with pre-separator are intended for use with inhalation and nasal powders.” For clarity, the suggestion is to revise the sentence to read *“*Generation Impactor with pre-separator are intended for use with inhalation powders and nasal powders.”
Response: Comment incorporated.
Comment Summary #36: The commenter suggested revising the title for Table 3a as it appears unnecessarily wordy. The modification for consistency should read as follows: “Cut-off Diameters (µm) for Andersen Cascade Impactor with and without Pre-Separator at 28.3, 60 and 90L/min” to be consistent with the title used for Table 3b.
Response: Comment incorporated.
Comment Summary # 37: The commenter suggested revising the sentence below for better understanding by providing an example as follows: “The version of Stage 0 used at 60 and 90 L/min (i.e. - 0) has external modifications, permitting another stage rather than the inlet adapter cone to be fitted above it. [….]”
Response: Comment incorporated.
Comment Summary #38: The commenter recommended removing “or other suitable material” from the Note included in Figure 6b in order to be consistent with the text in C.2.1. first paragraph. The revised text should read, *“*1) Material may be aluminum or stainless steel.”
Response: Comment incorporated.
Comment Summary #39: The commenter suggested including the apparatus numbers as in earlier versions (Table 2). The impactors were previously named but also referenced with an apparatus number. The approach to remove the apparatus numbers is not recommended for a variety of reasons.
Response: Comment not incorporated. The descriptive title is the clearest way of defining the apparatus associated with each test procedure and does not require cross referencing for the reader.

Section C. 2.2
Comment Summary #40: The commenter suggested revising the following sentence in the first paragraph, “Attach mouthpiece/nosepiece adapter **to the end of induction port** to produce an

airtight seal.", to include the bolded text as it would provide some clarity and would be consistent with the text found in other paragraphs.
Response: Comment incorporated.
Comment Summary #41: The commenter indicated that the following sentence, "Unless otherwise prescribed in the patient instructions, shake the product for 5s and discharge one actuation to waste.", is unclear as it makes no reference to priming. It is not clear if the intended instruction is to discharge one actuation after (i.e., in addition to) priming. It should be replaced with the following text**:** "Prepare the product for use according to the label instructions for shaking, priming and firing. Unless otherwise..."
Response: Comment incorporated.
Comment Summary #42: The commenter recommended removing "The data from analysis of deposition on the other components should only be used for the purpose of establishing the determination of mass balance and should not be combined with the plate deposition for determination of aerodynamic particle size distribution." as it is inaccurate and contradicts current FDA practice. The FDA requires applicants to control product APSD profile with grouping data which includes data collected from all the components of the CI tests.
Response: Comment not incorporated. The size of the particles collected on the internal surfaces of the impactor does not correlate with the size of particles collected on the corresponding stages. In addition, a 5% loss to the impactor surface has been incorporated. It is the burden on the user to justify a loss greater than 5%.

Comment Summary #43: The commenter suggested replacing the phrase "Using the method of analysis specified in the individual monograph…" with "Using a validated method of analysis…" as in-house methods may be necessary.
Response: Comment incorporated.
Comment Summary # 44: The commenter requested revising the following sentence by adding the bold text for clarity: "With the vacuum pump running, insert the mouthpiece/nosepiece **of the inhaler** into the mouthpiece/nosepiece adapter."
Response: Comment incorporated.

Section C. 3.1
Comment Summary #45: The commenter indicated that depending on the ACI configuration, the top stage will not necessarily be Stage 0. It could be Stage 0 (28.3 L/min), -1 (60 L/min) or -2 (90 L/min), as in Table 3a. Therefore, the first sentence of this section should be modified accordingly.
Response: Comment incorporated.
Comment Summary #46: The commenter requested clarification that there are 3 different versions of the ACI pre-separator, one each for 28.3, 60, and 90 L/min operation, not just a single version.
Response: Comment not incorporated. The statement included is clear that there are different pre-separators.
Comment Summary #47: The commenter recommended revising the following sentence in the third paragraph for grammatical correctness and readability: "Under steady-state flow conditions at the valve at the air flow rate to be used during testing by using the following procedure." The revision would read as follows: "Under steady-state flow conditions at the air flow rate the valve is used by the following procedure."
Response: Comment incorporated.
Comment Summary #48: The commenter suggested revising the following phrase in the third paragraph for grammatical correctness, *"*based on determination of duration of T seconds*"* to read "based on determined duration of T seconds."
Response: Comment incorporated.

Comment Summary #49: The commenter requested guidance as to which configuration to use when flow is in-between 28.3 and 60 L/min and in-between 60 and 90 L/min.
Response: Comment not incorporated. The scope of the chapter is limited to providing guidance on established flow rates only.
Comment Summary #50: The commenter requested making Table 5 consistent with Table 1.
Response: Comment incorporated.

Section C. 3.2
Comment Summary #51: The commenter requested adding text on "the reduction of wall loss by coating" in the following sentence in the first paragraph to read as follows: "Coat the particle collection surface of each of the stages of the cascade impactor appropriately to ensure that particles that have impacted on a given stage are not re-entrained in the flowing airstream or to reduce particle bouncing to the walls unless this has been shown to be unnecessary."
Response: Comment incorporated.
Comment Summary #52: The commenter suggested modifying the use of the term "induction port" at several places in the text as it is inappropriate for this context. The text should be changed from "into the induction port mouthpiece/nosepiece adapter" (second paragraph, line 2, line 7 and line 11; C.5.2. sixth paragraph, line 2, line 7 and line 11) to "into the mouthpiece/nosepiece adapter."
Response: Comment incorporated.
Comment Summary #53: The commenter suggested revising the first sentence of the third paragraph for accuracy to read as follows: "Carefully disassemble the apparatus. Using a suitable solvent, rinse the drug from mouthpiece /nosepiece adapter, induction port, pre-separator, each stage, and the collection plate of each stage or the filter immediately into appropriately sized flasks."
Response: Comment incorporated.
Comment Summary #54: The commenter suggested removing "The data from analysis of deposition on the other components should only be used for the purpose of establishing the determination of mass balance and should not be combined with the plate deposition for determination of aerodynamic particle size distribution." as it is inaccurate and contradicts current FDA practice. FDA requires applicants to control product APSD profile with grouping data which includes data collected from all the components of the CI tests
Response: Comment not incorporated. The size of the particles collected on the internal surfaces of the impactor does not correlate with the size of particles collected on the corresponding stages. In addition, a 5% loss to the impactor surface has been incorporated. It is the burden on the user to justify a loss greater than 5%.
Comment Summary #55: The commenter suggested revising the following phrase: "Using the method of analysis specified in the individual monograph…" to read "Using a validated method of analysis…" The reasoning is to address the use of in-house methods, which may be necessary.
Response: Comment incorporated.

Section 4.1
Comment Summary #56: The commenter suggested adding "...or other suitable material" text in the following sentence, "Material can be aluminum or stainless steel." The reasoning is a large part of the NGI is nickel-plated aluminum, not virgin aluminum.
Response: Comment incorporated. The sentence was deleted. The material for the NGI is specified in the design paper published in the *Journal of Aerosol Medicine* 2003;16(3):283-299.

Table 6

Comment Summary #57: The commenter indicated that the precision of the numerical values is not aligned in terms of number of decimal places for nozzle diameter (mm) in Table 6. For example, the value 2.185 ± 0.02 is given. It should be expressed either as 2.19 ± 0.02 or 2.185 ± 0.020.
Response: Comment incorporated. Values were revised to align decimal places (e.g., 2.185 ± 0.02 revised to 2.185 ± 0.020).

Section C.4.2
Comment Summary #58: The commenter suggested changing the following sentence from "Unless otherwise prescribed in the patient instructions, shake the product for 5s and discharge one actuation to waste." to "Prepare the product for use according to the label instructions for shaking, priming and firing. Unless otherwise..." for clarity (as the sentence makes no reference to priming).
Response: Comment incorporated.
Comment Summary #59: The commenter suggested to add the bolded text to the third line of the first paragraph in order to be consistent with C.2.2: "Connect the USP induction port (Figure 6b) to the impactor inlet. ***Attach a mouthpiece/nosepiece adapter to the end of the induction port to produce an airtight seal between the products mouthpiece/nosepiece and the induction port as shown in Figure 6a.*** Use a mouthpiece/nosepiece adapter that ensures that the tip of the product's mouthpiece/nosepiece is flush with the open end of the induction port. Turn on the vacuum pump to draw air through the impactor and calibrate the airflow through the system with an appropriate flowmeter attached to the open end of the induction port."
Response: Comment incorporated.
Comment Summary #60: The commenter suggested revising the second line of the third paragraph from "Remove the induction port and mouthpiece/ nosepiece adapter from the apparatus and extract the drug from each component of the system into an aliquot of solvent and recover quantitatively the active ingredient from all inner surfaces." to read as follows for clarity: "Remove the induction port and mouthpiece/ nosepiece adapter from the apparatus and extract the drug from mouthpiece/nosepiece adapter and induction port into an aliquot of solvent and recover quantitatively the active ingredient from all inner surfaces."
Response: Comment not incorporated. The language in the chapter is more comprehensive than the language proposed in this comment.

Section C.5.2
Comment Summary #61: The commenter suggested revising the last sentence of the sixth paragraph in order to be more consistent with C.3.2 to read as follows: "After discharge of the last actuation, remove the product from the mouthpiece/nosepiece adapter, and switch off the vacuum pump."
Response: Comment incorporated.
Comment Summary #62: The commenter suggested revising the second line of the seventh paragraph as follows to specify which components are included: "Remove the induction port and mouthpiece/nosepiece adapter from the pre-separator and extract the drug from ~~each component of the system~~ mouthpiece/nosepiece adapter and induction port into an aliquot of appropriate solvent; remove the pre-separator from the impactor without spilling the solvent into the impactor; and recover quantitatively the active ingredient from all inner surfaces."
Response: Comment not incorporated. "Each component of the system" is not limited to the adapter and induction port. The language in the chapter is more comprehensive than the language proposed in this comment.

General Chapter: <631> *Color and Achromicity*

Expert Committee: General Chapters–Physical Analysis
No. of Commenters: 5

Introduction
Comment Summary #1: The commenter requested removing the typographical error "a" in the following sentence: "The purpose of this chapter is to provide a well-controlled methods for the assessment of color and achromicity of liquid samples."
Response: Comment incorporated.
Comment Summary #2: The commenter requested changing the following sentence from "Where a pair of objects exhibit a color match for one source of illumination and not another, they constitute a metameric pair." to "Where a pair of objects exhibit a color match for one source of illumination and not another, they constitute an 'illuminant metameric pair'."
Response: Comment not incorporated. A general search of terms found mostly the usage of "metameric pair" instead of "illuminant metameric pair." It is a well-accepted definition.

Color Attributes and Color Space Coordinates
Comment Summary #3: The commenter requested changing the following sentence: "Three attributes are commonly used to identify a color: 1) hue, or the quality by which one color family is distinguished from another, such as red, yellow, blue, green, and intermediate terms; 2) lightness, or the quality that distinguishes a light color from a dark one;" to "Three attributes are commonly used to identify a color: 1) hue, or the color dimension that is dominant in its purest form; 2) Luminance, or the quality that distinguishes a light color from a dark one;". Theoretically, all hues are basically a mixture of primary colors. However, one usually refers to the dominant or underlying color that is perceived or observed.
Response: Comment partially incorporated. The text was changed to: "Three attributes are commonly used to identify a color: 1) hue (angle), or the color dimension dominant in its purest form, such as red, yellow, blue, green, and intermediate terms; 2) lightness, or the quality that distinguishes a light color from a dark one;".
EC-Initiated Change #1: The term 'angle' was added after 'hue' throughout the chapter because 'hue' is necessarily an angle as a metric but may be described as a perceived color. Hence, the term in this chapter necessarily refers to an angle. To clarify, the chapter was updated to indicate 'hue (angle)' rather than using just the term 'hue' to avoid confusion.
Comment Summary #4: The commenter recommended replacing the term 'lightness' with 'luminance' throughout the chapter, because the term 'luminance' is used to describe the brightness or darkness of color and is more appropriate than 'lightness.'
Response: Comment not incorporated. Lightness is a well-accepted term when explaining tristimulus colorimetry in terms of CIELAB. Luminance is typically applied to illumination sources and the use of the term may lead to confusion.
Comment Summary #5: The commenter requested changing the following sentence from "and 3) chroma, or the quality that distinguishes a strong color from a weak one, such as the extent to which a color differs from a gray of the same lightness." to "and 3) chroma, or the quality that distinguishes an intense color from a weak one, such as the extent to which a color differs from a gray of the same luminance."
Response: Comment partially incorporated. The text was changed, except the replacement of 'lightness' as per response #4.
Comment Summary #6: The commenter suggested changing the following sentence from "For example, colorless or achromic water has an indeterminate hue angle, high lightness, and little to no chroma. If a colored solute is added, the water takes on a particular hue. As more is added, the color becomes darker, more intense, or deeper; that is, the chroma increases and lightness decreases." to "For example, colorless or achromic water has an indeterminate hue, luminance, and little to no chroma. If a colored solute is added, the water takes on a particular

hue. As more is added, the water becomes more hued, less luminous with increased chromaticity." to simplify the use of many similar terms to describe a singular phenomenon.
Response: Comment not incorporated. "Hue (angle)" will remain as per EC-Initiated Change #1, and lightness will remain instead of "luminance" as per response #4. The term "lightness decreases" is consistent in this chapter instead of "less luminous."
Comment Summary #7: The commenter requested reformatting the equation: "$C^*ab = [(a^*)2 + (b^*)2\ ]1/2$" because the variables "a*" and "b*" should be squared.
Response: Comment incorporated.
Comment Summary #8: The commenter requested reformatting the equation from "$\Delta E^* = \sqrt{\Delta L^{*2} + \Delta a^{*2} + \Delta b^2}$" to "$\Delta E^* = \sqrt{\Delta L^{*2} + \Delta a^{*2} + \Delta b^{*2}}$" because an asterisk is missing in the formula.
Response: Comment incorporated.

Color Determination and Standards
Comment Summary #9: The commenter recommended including a reference to other relevant chapters in addition to <1061> for color analysis of other samples (e.g., opaque solids, translucent solids, etc.).
Response: Comment not incorporated. There are no other relevant chapters with significant discussion of solids at this time. The scope of this revision has been limited to liquids to avoid confusion. A discussion of color measurement of solids may be added in future revisions if compendial applications require it.

Turbid and Opaque Samples
Comment Summary #10: The commenter recommended including an example case description for opaque sample testing.
Response: Comment partially incorporated. The sentence was changed to: "If the sample is turbid or opaque, the dispersed phase should be removed by centrifugation or filtration before evaluating the color."
Comment Summary #11: The commenter suggested adding exceptions to the use of centrifugation/filtration (e.g., when the progression of the test is marked by removal of color from the non-turbid solution). One recommendation included within this section is centrifugation to remove a dispersed phase in order to evaluate the color. However, in some instances, a solution's true coloration cannot be determined. For example, centrifuging a turbid antibody solution could result in removal of aggregates rendering it clearer than its evaluation at 'Time zero' as the dispersion medium is now closer to its formulation buffer than the product. This is evidenced by fluctuating values when using turbidimetry.
Response: Comment partially incorporated. The *Introduction* section of the chapter was updated to "uniform liquid samples" and a second sentence was added to clarify the scope of the chapter as follows: "The purpose of this chapter is to provide well-controlled methods for the assessment of color and achromicity of uniform liquid samples. The methods described in this chapter may be applied to the liquid phase of dispersed systems in cases where the dispersed phase can be removed prior to color measurements."

Method I: Organoleptic (Qualitative) Assessment of Color and Color Matches/Illuminant
Comment Summary #12: The commenter suggested allowing light boxes as an alternate, not a mandatory, means of measurement. That would allow for a gradual and longer transition period.
Response: Comment incorporated. The sentence was changed to: "Any additional illumination from room lighting or windows should be minimized (e.g., by use of a light box or light booth)."

Method I: Organoleptic (Qualitative) Assessment of Color and Color Matches/Observer

Comment Summary #13: The commenter recommended including an appropriate size range for the gap in the following sentence: “A small, discernible gap should exist between the sample and matching fluid.”
Response: Comment not incorporated. The physical size of a discernible gap will depend on the viewing conditions (i.e., viewing distance, angle, illumination, contrast with background). If a range is specified, then there will be no flexibility.

Method I: Organoleptic (Qualitative) Assessment of Color and Color Matches/Procedures
Comment Summary #14: The commenter requested clarifying that the brightness, saturation, and hue of the solutions should also be evaluated. A difference in brightness, saturation, or hue can be interpreted as a failure of the test.
Response: Comment incorporated. The section was changed to: “Evaluate the sample and at least one other matching fluid simultaneously. Evaluate the brightness, saturation, and hue (angle). Hue (angle) differences between the sample and the reference should be interpreted as a failure of the comparative test unless there are explicit instructions in the monograph to ignore hue (angle) differences.”

Table 2. Interpretation of Color Comparisons for Qualitative Color Evaluations
Comment Summary #15: The commenter suggested clarifying the acceptance criteria for “almost colorless” to allow some level of coloration to be less stringent than achromatic or B9 reference in the *European Pharmacopoeia*.
Response: Comment not incorporated. The current text requires that for a sample to be declared achromatic, it must not be discernably more colored than water as the colorless standard. There are two means to achieve this, either by being directly compared to the colorless standard (water) or by being shown to be less colored than a discernable standard (max color test). If a sample has discernable color, it may still be acceptable according to desired quality standards as defined in the monograph or by the user, but this condition should not be referred to as achromatic; rather, this condition is more accurately described as not discernably more colored than the maximum color standard.
Comment Summary #16: The commenter requested allowing similar levels of color for achromicity/colorless and almost colorless because the test requirement for "Almost Colorless" in this table is contradicting with what is included in the *Introduction*, where achromicity is considered to be equal to colorless. Moreover, it is stated there for practical purposes in case of achromicity, the observer is "unable to discern the difference between an almost colorless sample and a colorless reference."
Response: Comment incorporated. The next level in the table for “Sample Matches Reference” was changed to: “If used for achromicity, fails the test. Otherwise, passes the test.”

Method I: Instrumental (Quantitative) Assessment of Color and Color Matches/Instrumentation
Comment Summary #17: The commenter suggested clarifying that the spectrophotometer or colorimeter should be qualified for the operating range for visible wavelengths of 400-780 nm as described in <857>.
Response: Comment not incorporated. Many colorimeters available commercially have a more limited operating range. The only way to guarantee consistent results across platforms is to intentionally truncate the range for comparison, even if a specific apparatus can go beyond this range.

General

Comment Summary #18: The commenter suggested including an explanation of how to calculate CIELAB values or mention the mathematical software(s) available on the market able to do it.
Response: Comment partially incorporated. An additional cross reference to <1051> was introduced in the section for *Calculation of CIELAB Values*. Other sources of information are included in <1061>. Relevantly, this chapter includes a detailed example (in Tables 6 and 7) that provides the data and results that should be checked to verify/validate that the correct calculation method has been used.
Comment Summary #19: The commenter recommended allowing solvents other than water because it is possible that for certain materials the solvent of interest is not water.
Response: Comment not incorporated. The current text includes enough flexibility to enable use with non-aqueous samples. Any suitable reference standards may include non-aqueous reference standards. The use of purified water as a reference for achromicity should not affect the color measurements or comparisons for non-aqueous samples. Exceptions could be indicated in the individual monograph for other solvents other than water for comparison, if needed.
Comment Summary #20: The commenter requested replacing "distilled water" with "Purified Water" throughout the chapter because most of the compendial testing requires "Purified Water" and it is readily available (and mentioned in the *General Notices*, under the section 8.230.30 as the "default" type of water in compendial procedures).
Response: Comment incorporated.

General Chapter: <643> *Total Organic Carbon*
Expert Committee: General Chapters–Chemical Analysis
No. of Commenters: 3

Introduction
EC-Initiated Change #1: The title of the section *Introduction* was incorporated for style and consistency.

Procedures
EC-Initiated Change #2: A new numeric system was introduced for all procedural sections and subsections for clarity in cross references.

Bulk Water/Limit Response
Comment Summary #1: The commenter suggested revising the formula for calculating Limit response (r_L) from: "Result = r_S - r_W" to: ""$r_L = r_S - r_W$."
Response: Comment incorporated.

Bulk Water/System Suitability
EC-Initiated Change #3: The section was redesigned accordingly with the section *Sterile Water* for consistency.

Sterile Water/Apparatus Requirements
Comment Summary #2: The commenter requested adding text to clarify the upper limit value of r_{L2} as follows: "In addition to the Apparatus requirements in Bulk Water, the apparatus must have a manufacturer's specified dynamic range capability of at least 0.10 mg/L, up to the TOC limit for the container size under test (0.10 ppm to upper limit value under test of carbon). The upper limit value corresponds to the appropriate limit response 2 (r_{L2}) in Table 1."
Response: Comment partially incorporated. The sentence was simplified but further description of the limit response 2 (r_{L2}) was added to the section *Sterile Water*.

Sterile Water/Limit Response
Comment Summary #3: The commenters recommended clarifying the upper range for the apparatus requirements when using 5-mL containers.
Response: Comment incorporated. The complete section was redesigned for clarity about the multilevel specification based on container volume. The equivalent section under *Bulk Water* section was also redesigned for consistency.

Sterile Water/System Suitability Solution
Comment Summary #4: The commenter requested changing the specification for containers less than 5 mL in the *Sterile Water* system suitability testing requirements to 42 ppm because the proposed 48 ppm standard solution concentration is near the upper limit for many TOC analyzers, and the 85-115 tolerance puts the upper tolerance limit above the linear range of many TOC analyzers.
Response: Comment not incorporated. Most of the commercially available instruments for this analysis have an upper limit of 50 ppm.
Comment Summary #5: The commenter requested revising the concentrations of USP 1,4-Benzoquinone RS to be used for the system suitability solution for *Sterile Water*, based on the procedure for *Bulk Water*, as follows: “18.00 mg/L of 1,4-benzoquinone (12.00 mg/L of carbon) for containers >100 mL; 54.00 mg/L of 1,4-benzoquinone (36.00 mg/L of carbon) for containers >5 and ≤100 mL.”
Response: Comment incorporated.
EC-Initiated Change #4: The section was redesigned for clarity.

Sterile Water/Standard Solution
EC-Initiated Change #5: The section was redesigned for clarity in describing the preparation of Limits 1 and 2.

System Suitability
Comment Summary #6: The commenter recommended clarifying the system suitability calculation and the multiple standards.
Response: Comment incorporated. This section was completely redesigned for clarity.
EC-Initiated Change #6: The section was redesigned for consistency.

Procedure
Comment Summary #7: The commenter requested clarifying the use of r_{L2} currently in the footnote of Table 1 into the system suitability preparation instructions.
Response: Comment partially incorporated. The table was moved to the beginning of the section *Sterile Water* and additional information was introduced for clarification.
Comment Summary #8: The commenter suggested clarifying the statement “verified analytical procedures suitable for the intended use" because verification implies additional activities that are not necessarily needed for this application.
Response: Comment incorporated. The sentence was changed to “suitable analytical procedures appropriate for the intended use.”
EC-Initiated Change #7: The section was redesigned for consistency.

General
EC-Initiated Change #8: The term “apparatus” was replaced with “instrument” in the chapter.
Comment Summary #9: The commenter requested introducing in the chapter some background information about the new proposed specifications.

Response: Comment not incorporated. This is a procedural chapter. There are other sources of information readily available about contributions of organic impurities from the container, including two *Stimuli* articles published in *PF* 36(5), and numerous scientific articles.
Comment Summary #10: The commenter requested clarifying how the manufacturers are going to diagnose or detect out of trend results on the ppb scale and how the new specifications are going to affect predetermined alert and action levels.
Response: Comment not incorporated. It is out of the scope of this chapter.
Comment Summary #11: The commenter recommended adding information about the safety, health, and environmental impact of the 1,4-Benzoquinone at the described concentrations.
Response: Comment not incorporated. It is out of the scope. The USP website contains the Safety Data Sheet for this USP reference material, which includes stability and reactivity, toxicological information, ecological information, and disposal considerations. It is expected that all concentrations are handled properly as per the applicable GLP and regulatory requirements.

General Chapter: <915> *Measurement of Structural Strength of Semisolids by Penetrometry*
Expert Committee: General Chapters–Physical Analysis
No. of Commenters: 1

Apparatus
Comment Summary #1: The commenter suggested the introduction of the two penetrometer cone figures from ASTM-217-D2.
Response: Comment not incorporated. The two penetrometer cone figures were proposed in the first proposal of this chapter in *PF*. Based on public comments, it was decided to keep only the one equivalent in the *European Pharmacopoeia* and most widely used by pharmaceutical industry with the same definition, and introducing one new procedure using a needle for other future applications.

Procedure
Comment Summary #2: The commenter recommended using a single temperature range for both storage (currently 25.0° ± 0.5°) and testing (23.5° ± 2.0°).
Response: Comment not incorporated. The original testing temperature was proposed as the same for storage, but it was changed in its second proposal of this chapter in *PF* based on public comments in order to provide flexibility due to the complexity in controlling the temperature during testing.

General
Comment Summary #3: The commenter recommended transforming this chapter into an informational chapter (i.e., chapter number above 1000) because the discussion of the basis of the test and the description of the apparatus is not clear in the absence of specific acceptance criterion.
Response: Comment not incorporated. Four *USP-NF* monographs contain this test described completely and include the acceptance criteria. The *European Pharmacopoeia* has a similar chapter and two monographs containing this test are harmonized within the ICH PDG. The companion general chapter already provides complementary information.

General Chapter: <922> *Water Activity*
Expert Committee: General Chapters–Physical Analysis
No. of Commenters: 9

Introduction

Comment Summary #1: The commenter requested the removal of the following sentence: "However, water may be allocated in more than one compartment within these materials."
Response: Comment incorporated.
Comment Summary #2: The commenter suggested clarifying the meaning of water determination as it could loosely be described as the boundness of water, but not the bound water.
Response: Comment incorporated. The requested sentences were changed to: "Some of the water may be tightly bound and not available to participate in chemical, biochemical, or physicochemical reactions (e.g., as hydrate salts), whereas some of the water may be more freely available to participate in reactions such as hydrolysis or may provide an environment that can support microbiological growth. It is important to establish what fraction of the total water is available (active) and the determination of water activity (a_w) provides this information."
Comment Summary #3: The commenter recommended reducing the introduction content to be more concise or use reference paper(s) for the theory.
Response: Comment partially incorporated. Several edits were incorporated to make the chapter clearer and more concise.

Theoretical Background
Comment Summary #4: The commenter recommended clarifying the term "headspace" because it is unclear whether it is referring to a packaged product or if this is loosely being applied to all surrounding atmosphere.
Response: Comment incorporated. The usage of this term is clarified later in this section: "The relative humidity of the headspace of the instrument cell is defined as…."
Comment Summary #5: The commenter suggested prefacing each method description with the associated terminology: psychrometry, optical absorption, and dew point temperature to improve readability.
Response: Comment not incorporated. This mandatory chapter is not intended to provide exhaustive description of each method included.
Comment Summary #6: The commenter recommended incorporating the conventional expression for relative humidity (%RH) for clarification.
Response: Comment incorporated. An additional equation was included: "%RH = RH * 100."
Comment Summary #7: The commenters recommended incorporating additional concepts to define water activity in relation to relative humidity (%RH) for clarification and another mean of correction.
Response: Comment partially incorporated. The text was changed to: "Use this equation to determine the water activity of a sample from a relative humidity measurement of the headspace. If the air in the headspace is also in temperature equilibrium with the sample the saturation vapor pressures divide out so that a_w = RH. If the temperatures are not equal, and one assumes that water activity equals the air relative humidity, errors can be significant."
Comment Summary #8: The commenter requested revising the equation to include temperature of the measurement in both sides of the formula, for consistency with the equation for a_w.
Response: Comment incorporated.

Factors Affecting Water Activity
Comment Summary #9: The commenter recommended expanding that storage of material at higher humidity prior to testing can significantly influence the water activity results.
Response: Comment incorporated. Text added under *Sample Preparation*.

Application of Water Activity Measurements

Comment Summary #10: The commenter suggested clarifying that high-water activity, especially in formulations can result in increased reaction rates for a wide range of reactions, not to call out hydrolysis specifically.
Response: Comment incorporated.
Comment Summary #11: The commenter requested clarification on complementary methods that water activity provides information on water content, not in the same way that Karl Fischer is used.
Response: Comment incorporated.

Types of Water Activity Instruments
Comment Summary #12: The commenter recommended the inclusion of a summary table discussing possible applications of each technique, including advantages and disadvantages.
Response: Comment not incorporated. This is not an informational chapter and the suitability depends on the specific application.

Dew Point Temperature - Chilled Mirror
Comment Summary #13: The commenter requested clarifying that dew point instruments need calibration adjustment either routinely or yearly, and confirmation of accuracy.
Response: Comment incorporated. The following sentence has been removed: “therefore, evaluation of standard solutions is considered a confirmation of the accuracy of the instrument rather than a calibration of the instrument.”

Procedure for Standard Solutions
Comment Summary #14: The commenter requested to change the text from “Water activity meters should be calibrated (or verified for dew point instruments) using saturated or unsaturated salt standard solutions.” to “Water activity meters should be calibrated using either prepared or purchased standard solutions or using a calibrated humidity generator.” This is to clarify that humidity generators controlled by verified dew point instruments are a convenient method for calibration of water activity meters and may provide an acceptable alternative to saturated salt solutions depending on the given measurement task.
Response: Comment incorporated.

Calibration of Water Activity Meters
Comment Summary #15: The commenters requested removing the sentence “Dew point instruments do not require calibration and, therefore, instrument operation can be verified by proceeding to the Procedure for Calibration Check.” because it is misleading as a calibration adjustment is more than needed (e.g., first measurement often fails) or not needed at all. Vendor’s recommendations should be followed.
Response: Comment incorporated.

Procedure for Calibration Check
Comment Summary #16: The commenter requested to change the text from “A calibration check should be performed every day the instrument is used to perform measurements.” to “It is recommended that calibration check be performed every 24 hr the instrument is used to perform measurements.” for clarification.
Response: Comment partially incorporated. The text was changed to: “A calibration check should be performed each day the instrument is used to perform a_w measurements (e.g., every 24 h during continual use).”
Comment Summary #17: The commenters requested aligning reporting with conventional digits expectation, to two or three significant digits depending on the precision of the instrument.
Response: Comment incorporated.

Comment Summary #18: The commenter requested to change the text from “Perform the calibration check with the same number of replicates as will be performed on the samples.” to “It is recommended to perform the calibration check with the same number of replicates as will be performed on the samples.” because current standardized practice is to perform one calibration check and run samples in duplicate.
Response: Comment incorporated.

Procedure for Sample Preparation
Comment Summary #19: The commenter recommended addressing “sample handling” and “suitable sample types” in this or other sections.
Response: Comment not incorporated. This additional information would fit better in an informational chapter.

Sample Preparation
Comment Summary #20: The commenter suggested removing the reference to “water impermeable” containers for clarification and practicality purposes.
Response: Comment not incorporated. Permeable containers may result in incorrect values due to changes in a_w of sample.
Comment Summary #21: The commenter recommended removing the sentence “It is recommended that the sample containers have minimal headspace to avoid significant changes in water activity due to re-equilibration of the sample to the environment in the sampling container.” because this recommendation is not practical. It is highly dependent on the purpose of the study. Headspace generally does not contribute significantly to error as low mass does.
Response: Comment partially incorporated. The text was changed to: “It is recommended that the sample containers have minimal headspace or a larger sample mass to avoid significant changes in water activity due to re-equilibration of the sample to the environment in the sampling container.”
Comment Summary #22: The commenter requested changing the text from “Condensation of water on container walls can result from temperature gradients in containers when water activity is high; this could result in large measurement errors.” to “Large measurement errors can potentially result from: condensation of water on container walls due to temperature gradients in containers with samples containing high water activity, as well as permeable sample containers exposed to high relative humidity.” because sample containers that are permeable to the humidity in the environment where testing occurs is another potential cause for measurement errors.
Response: Comment incorporated.
Comment Summary #23: The commenter recommended providing other options that might be appropriate per method development for uniform powders or liquids.
Response: Comment partially incorporated. The text was changed to: “For uniform powders or liquids, it is recommended the sample material should cover the bottom surface of the sample container entirely unless alternate methods have been verified.”

Procedure for Verification and Validation
Comment Summary #24: The commenter suggested removing this section because it is not applicable to an enforceable chapter.
Response: Comment not incorporated. Water activity measurements may be implemented for many different applications. The specific amount of validation and verification may not be the same for all applications of water activity. Therefore, a reference is made to <1058> and the chapter is written with intentional flexibility to enable the amount of validation and verification required to be driven by the intended use and intended operational range.

Comment Summary #25: The commenter requested clarifying that the testing laboratory is responsible to conduct the verification.
Response: Comment incorporated.
Comment Summary #26: The commenter requested establishing a wider limit for relative standard deviation criterion for repeatability and intermediate precision because the proposed values are neither achievable for dry and very dry samples (a_w = 0.3 and below).
Response: Comment incorporated. Acceptance criterion for precision (repeatability) was changed to: "NMT 5.0% for aw>0.4, NMT 15% for 0.15<aw≤0.4, and NMT 20% for aw≤0.15" and for intermediate precision to: "NMT 6.0% for aw>0.4, NMT 15% for 0.15<aw≤0.4, and NMT 20% for aw≤0.15."

Precision (Repeatability)
Comment Summary #27: The commenter recommended clarifying the use of a minimum of three separate sample aliquots for this type of test.
Response: Comment not incorporated. The standard method for assessing instrument and method repeatability requires more than three replicates. This is an assessment of the instrument and/or method performance and not representative of typical sample analysis replicates.

Intermediate Precision
Comment Summary #28: The commenter suggested removing this section because it is not an appropriate test for water activity. Water activity is a measure of the current state of the product. Since containers are permeable to water testing on different days can yield different results. This is not an issue with the technique or equipment but rather the consequence of moisture transfer and equilibration which is difficult to control.
Response: Comment not incorporated. This is just a specific example with a semi-permeable container where a_w may change over time due to moisture gain or loss by the package. This suggests that intermediate precision of the method is not a valid metric in that case because the method variability is not independent of the sample variability.

General
Comment Summary #29: The commenter recommended moving this chapter to an informational section because it is unclear how the chapter is intended to be implemented in monographs, and they also recommended adding a clear statement that the content of this chapter is informational guidance and any suitable validated method can be used without the necessity to show equivalence to the 'procedure for sample measurement' discussed in this chapter.
Response: Comment not incorporated. The chapter already states: "Any type of water activity instrument that is shown to be fit for the intended purpose, by meeting the qualification criteria, may be used to provide a_w results according to the guidelines of this chapter." This statement allows flexibility with most available water activity instruments without the need to demonstrate equivalence to specific instruments discussed within the chapter.
Comment Summary #30: The commenter recommended adding a glossary of terms to clarify focus and avoid confusion.
Response: Comment not incorporated. Glossaries are not acceptable in mandatory chapters as per USP style guide.

General Chapter: <1051> *Cleaning Glass Apparatus*
Expert Committee: General Chapters—Physical Analysis
No. of Commenters: 8

Cleaning Validation Best Practices

Comment Summary #1: The commenter requested changing the sentence "It is recommended that the validation of a cleaning process involve both a qualitative and a quantitative assessment of cleaning performance followed by specific assessments of cleanliness appropriate for the intended use," to "It is recommended that the validation of a cleaning process may involve both a qualitative and a quantitative assessment of the cleaning performance appropriate for the intended use."

Response: Comment partially incorporated. The sentence was changed to: "The validation of a cleaning process may involve both a qualitative and a quantitative assessment of cleaning performance and may be followed by specific assessments of cleanliness appropriate for the intended use. An established cleaning procedure may require revalidation when significant changes to the procedure are made or when the intended use of the glassware changes."

Comment Summary #2: The commenter requested changing the sentence "General Cleaning Validation Procedure" to "Cleaning validation procedure for general laboratory use" to match the text in the first line of Table 2.

Response: Comment incorporated.

Comment Summary #3: The commenter recommended changing the content of section "1. Qualitative assessment of cleaning process" to "A. Take a soiled worst-case load according to intended use or prepare a load by applying formulation with fluorescent indicator (see Table 1); B. Perform cleaning process; C. Inspect glassware visually (e.g., black light lamp, UV lamp) to evaluate cleanliness" to introduce the worst-case load, if available.

Response: Comment partially incorporated. The content of the section was changed to "A. Take a soiled worst-case load according to intended use or prepare a load by applying formulation with fluorescent indicator (see Table 1); B. Inspect glassware with UV lamp or black light to verify suitable coverage with fluorescent indicator; C. Perform cleaning with process to be validated; D. Inspect glassware with UV lamp or black light to qualitatively evaluate cleanliness."

Comment Summary #4: The commenter recommended changing the content of the section "1.C." from "C. Inspect glassware with UV lamp or black light to qualitatively evaluate cleanliness" to "C. Inspect glassware with UV lamp or black light to qualitatively evaluate the efficiency of the coverage i.e. all surface of items to be washed are reached by water after a certain time."

Response: Comment not incorporated. The introduction of the worst-case load and a comparison pre- and post- cleaning, based on a previous comment, confirms that all surfaces of items to be washed are reached by water after a certain time.

Comment Summary #5: The commenter recommended changing the content of the section "2. Quantitative assessment of cleaning process" to "A. Rinse the visually inspected glassware with purified water; B. Collect rinse water; C. Test rinse water per Total Organic Carbon <643> and Water Conductivity <645>, if needed pH <791> may be used." for clarity. They also recommended the removal of pH since this test does not add more value than conductivity.

Response: Comment partially incorporated. The testing of pH was removed because it is redundant with conductivity.

Comment Summary #6: The commenter suggested changing the content of section 3 from "3. Perform additional (chemical) validation evaluations as appropriate for the intended use" to "3. Perform additional validation evaluations as appropriate for intended use, if used for specific sensitive analyses, see table 2. The evaluation and eventually additional cleaning validation are a part of the analytical method verification." to allow this section to stand for itself.

Response: Comment partially incorporated. A cross reference to Table 2 was added to the sentence to point out additional evaluation recommended for specific use in sensitive analyses.

Quantitative Assessment of Cleaning Procedure

Comment Summary #7: The commenters recommended changing the content of this section: 1) to consider the use of different types of water chosen on the basis of a risk assessment and to consider the intended use and the analytical test involved, 2) to clarify that the amount of water utilized should be commensurate to the quantities described in the respective general chapters to avoid obtaining inconsistent/incorrect results, 3) to remove the requirement to remain compliant with Purified Water since the specifications for drinking water vary depending on the regulation of a particular region, and 4) to add a risk-based consideration for the intended use.
Response: Comment incorporated. The text was changed to: "For quantitative assessment of cleaning, the recommended approach is to follow the cleaning process by rinsing the glassware (or other laboratory equipment) with water of appropriate quality (e.g., Purified Water) and collecting the rinse water. The properties of this rinse water are evaluated to assess whether any contaminants are present at sufficient levels to significantly affect the properties of the rinse water and the involved analytical use of the glassware. The amount of rinse water utilized should be commensurate to the quantities described in the methods in chapters ⟨643⟩, and ⟨645⟩, which have been found to be good for assessing the cleanliness of the rinsed glassware. The results from these general chapter tests should show that the properties of the rinse water are not significantly changed after rinsing the glassware or remain compliant with the requested cleanliness level for the glassware. Determination of necessary cleanliness level should be risk-based and consider the intended use and the analytical test(s) involved."

Additional Cleaning Validation Analyses
Comment Summary #8: The commenter requested to remove this section because it does not provide enough latitude for the organizations to choose the process appropriate for their intended use.
Response: Comment not incorporated. The purpose of this general chapter is to provide guidelines. It is an informational chapter and the section describes additional evaluations recommended for specific uses in sensitive analyses.
Comment Summary #9: The commenter suggested revising this section to convey two concepts: 1) the general cleaning validation practices discussed in this chapter are suitable for all laboratory glassware. Without this clarification, it could be interpreted that all glassware must include additional validation experiments, regardless of intended use, and 2) the additional validation experiments are intended for glassware which is isolated for the specific use indicated.
Response: Comment not incorporated. The content is considered a general recommendation of validation practices. It is up to the users to evaluate the practices that are suitable for the intended specific use.

Table 2
Comment Summary #10: The commenter suggested changing the title of the table from "Additional Validated Experiments Recommended for Specific Uses" to "Additional Evaluation Recommended for Specific Use in Sensitive Analyses" as per response for Comment Summary #6.
Response: Comment incorporated.
Comment Summary #11: The commenter suggested changing the recommended experiment for "General laboratory use" from "Default evaluation (total organic carbon, pH, and conductivity of rinse water)" to "Default evaluation according to Cleaning Validation Best Practice 1 and 2."
Response: Comment incorporated.
Comment Summary #12: The commenters suggested changing the recommended experiment for "Micro-Samples" because water for injection is not available in API or oral dosage form

facilities. Also, certain machines do not function with water for injection quality. For micro-related samples, these items are sterilized before use.
Response: Comment partially incorporated. The row for “Micro-Samples” was removed because for microbial purposes, the cleaning portion does not require anything beyond the standard (default) cleaning evaluation and does not require the use of sterile water in the cleaning evaluation. The additional testing would be the sterilization or depyrogenation and it would be validation of these steps that would ensure that the cleaned glassware was suitable for microbial use.
EC-Initiated Change #1: The row for “Endotoxin Samples” was removed for the same reasons as per response for Comment Summary #12.

Validation of Automated Glassware Cleaning
Comment Summary #13: The commenters requested clarifying the relevance of conducting a suitable validation procedure and replacing the characteristics listed for a “suitable molecule” with some wording representing the worst case scenario for each laboratory. Additionally, not all quantitative testing is appropriate for the various suitable molecules chosen, so a clarification is requested.
Response: Comments incorporated. The text was changed to: “In laboratories that use automatic washers to clean glassware, it is important to conduct a validation procedure to demonstrate the effectiveness of the cleaning cycles by conducting a suitable validation procedure. One way this can be conducted is by first selecting a suitable molecule that is likely to be difficult to clean from soiled glassware. A suitable molecule is most relevant to the risks involved for each laboratory. It is recommended that laboratories choose a molecule which represents a worst-case scenario of the materials the glassware may be exposed to (e.g., poorly soluble molecules in common solvents). Next, items of glassware from a selection of different shapes and sizes (e.g., beakers, conical flasks, volumetric flasks) are spiked with known quantities of this analyte (i.e., analyte is dissolved into a good solvent and applied uniformly) and then allowed to dry. The spiked glassware is then distributed to selected positions in the glassware washer, which is then fully loaded with unspiked glassware so that all locations in the washer are populated. The wash cycle is then run, and all spiked items are extracted separately with a suitable solvent. Finally, the sample preparations are analyzed quantitatively to determine the residual contaminants in each item where application of the quantitative method is based on the chosen soil test case.”

Alternative Rinsing Procedures
Comment Summary #14: The commenter requested changing the sentence from “Generally, it is best to rinse glassware with purified or distilled water, and allow it to dry without blowing air into it to force it to dry.” to “Generally, it is best to rinse glassware with purified or distilled water, and allow it to dry with or without blowing air into it to force it to dry.” This is because when air is blown to dry the glassware, generally this air has been filtrated by a HEPA filter. The quality of the air filtrated is compliant with a Grade C quality. This is the common approach used in every GMP part washer for laboratories and product contact items (machine supplier standard).
Response: Comments incorporated.

General
Comment Summary #15: The commenters suggested including additional details regarding the use of more risk-based approaches that rely on validated cleaning processes and experimental controls, and the replacement of some general terms to highlight the fact that the content represents recommendations.
Response: Comments partially incorporated. Additional details and clarifications were introduced in the chapter based on comments. The chapter is not intended to be exhaustive of

all possible procedures and details because it provides general recommendations. It is the responsibility of the users of glassware to assess the effectiveness of cleaning procedures.
Comment Summary #16: The commenters suggested not adopting the proposed changes because some of them are too detailed and restrictive for laboratories where common glassware is used to test numerous products using many techniques.
Response: Comments not incorporated. The chapter has received numerous comments confirming its usefulness as a general guideline. It is an informational chapter and therefore laboratories are not required to strictly comply with it.

General Chapter: <1086> *Impurities in Drug Substances and Drug Products*
Expert Committee: General Chapters–Chemical Analysis
No. of Commenters: 6

Introduction
Comment Summary #1: The commenter suggested adding "reagents" to the following sentence: "…impurities in drug products classified as degradation products of the drug substance or reaction products of the drug substance with an excipient and/or immediate container–closure system." The reason is to include all materials that can interact with the drug substance or drug products leading to formation of impurities.
Response: Comment not incorporated. There are no reactions that are conducted during formulation work.
Comment Summary #2: The commenter recommended incorporating enantiomeric impurities in the explicit exclusions of this chapter to align with ICH Q3B guidelines.
Response: Comment not incorporated. This scope of this informational chapter is wider than the one in the ICH Q3B, including drug substances and drug products. Enantiomeric impurities could be by-products and therefore are covered under drug substances.
Comment Summary #3: The commenter recommended adding fermentation products as they are used for the semisynthetic peptides expressed in yeast.
Response: Comment not incorporated. The fermentation products are excluded in both ICH Q3A and Q3B.
Comment Summary #4: The commenter requested removing "inorganic/elemental impurities and residual solvents" from the exclusions because this chapter covers all impurities, not just organic impurities.
Response: Comment incorporated.
Comment Summary #5: The commenter suggested clarifying that resolution of inactive ingredients at low concentration from active ingredients is not an issue per se. The chapter should focus on impurities and the suitability of using chromatographic assays.
Response: Comment partially incorporated. Text was changed to: "Purity or impurity measurements for drug products using chromatographic methods could present a challenge to Pharmacopeial standards-setting due to their low concentration of the impurity and complexity of matrix. As a consequence, many monographs for Pharmacopeial preparations rely on chromatographic assays, where more significant impurities are known, and some monographs set forth specific tests for these impurities."

Drug Substance
Comment Summary #6: The commenter suggested replacing "e.g., geometric and stereoisomers" with "e.g., stereoisomers" because geometric isomers are a type of stereoisomers.
Response: Comment partially incorporated. Enantiomeric impurities are out of the scope and it is not relevant. The examples were removed.

Comment Summary #7: The commenter requested including genotoxic impurities in the list of organic impurities that can arise during the manufacturing process and/or storage of the drug substance.
Response: Comment not incorporated. Genotoxicity refers to the biological effect of the impurity; any of the impurities (e.g., a starting material, a by-product or an intermediate, etc.) could be genotoxic.
Comment Summary #8: The commenter suggested replacing “impurities include catalysts” with “impurities can include catalysts.”
Response: Comment incorporated.
Comment Summary #9: The commenter suggested including “drug product intermediate or drug product” into the following sentence: “Residual solvents are organic liquids used as vehicles in the synthesis of a drug substance.”
Response: Comment partially incorporated. The text was changed to: “Residual solvents are organic liquids used as vehicles in the synthesis of a drug substance, starting material or the intermediates involved in the synthesis.” Because this section is about drug substances, there is no need to include drug product related compounds.
Comment Summary #10: The commenter suggested including the following sentence: "Genotoxic impurities control is described in <476> Organic impurities in Drug Substances and Drug Products."
Response: Comment partially incorporated. Guidelines about control of impurities that are known or suspected to be highly toxic (e.g., genotoxic) or that produce undesired pharmacological effects are already provided in the chapter but the following sentence was added: “As described in <476>, unusually toxic impurities (for example mutagenic impurities) in drug substance and drug product require more stringent control compared to non-mutagenic impurities.”

Drug Product
Comment Summary #11: The commenter requested adding “excipients compatibility studies” to the strategies used to characterize the degradation profile.
Response: Comment partially incorporated. The text was changed to: “Stability studies, forced degradation studies, knowledge of degradation pathways, product development studies, compatibility studies and laboratory studies should be used to characterize the degradation profile.”
Comment Summary #12: The commenter requested changing the term “sound scientific judgment” because it is vague and open to interpretation. Setting degradation limits should be based on available data and as defined by guidance.
Response: Comment incorporated. The text was changed to: “For drug products, the concept for setting degradation product limits is based on scientific assessment as applied to available data on the safety and stability of the drug product.”
Comment Summary #13: The commenter requested replacing the term “predictive toxicology” with “predictive toxicology programs for mutagenicity assessments, and in vitro and in vivo toxicology studies.”
Response: Comment incorporated.
Comment Summary #14: The commenter requested clarifying that there are cases where impurities from the drug substance are controlled in the drug product and requested the reasoning for that.
Response: Comment incorporated. The following text was added: “In cases where the studies show that impurities from the drug substance can increase over time, i.e. they are also drug product degradation products, they should be controlled in the drug substance and also in the drug product.”

Organic Impurities in Drug Substances and Drug Products

Comment Summary #15: The commenter recommended clarifying for drug products the exclusion of impurities that are not degradation products (e.g., process impurities from the drug substance and impurities arising from excipients).

Response: Comment incorporated. The text was changed to: “Impurities that are not degradation products (such as drug substance process-related impurities) are often not controlled in the drug product, as they are typically controlled in the drug substance and these impurities are not expected to increase over time. In cases where the studies show that impurities from the drug substance can increase over time, i.e. they are also drug product degradation products, they should be controlled in the drug substance and also in the drug product.”

Comment Summary #16: The commenter suggested providing clarification whether drug substance process impurities should be included in the drug product specification in all cases.

Response: Comment partially incorporated. The text was changed to: “However, in some cases drug substance process impurities may be included in the drug product specifications, if appropriate, and limited by an appropriate acceptance criterion.”

Comment Summary #17: The commenter requested including drug products to the paragraph stating that when there are changes to the chemistry, manufacturing, and/or controls of the drug substance, it should be evaluated to determine if the differences affect the impurity profile listed in the existing monograph because changes to drug product CMC may also impact its impurity profile.

Response: Comment not incorporated. The paragraph is located under the section *Organic Impurities in Drug Substances and Drug Products* and therefore applies to both drug substances and drug products.

Comment Summary #18: The commenter suggested clarifying the sentence stating that the quantitation/detection limit of the analytical procedure should be commensurate with the acceptance criteria for impurities that are known or suspected to be highly toxic (e.g., genotoxic), or that produce undesired pharmacological effects, because this principle applies regardless.

Response: Comment incorporated.

Comment Summary #19: The commenter requested adding wording that significant metabolites are generally considered qualified.

Response: Comment incorporated.

Organic Impurities Decision Tree

Comment Summary #20: The commenter recommended deleting the first step of the decision tree “Approved NDA or ANDA” and revising the figure such that it refers to both NDA/ANDA and OTC monograph products, because the chapter also applies to OTC monograph drug substances and drug products, and such products might not be marketed under an approved NDA or ANDA.

Response: Comment incorporated.

Comment Summary #21: The commenter recommended simplifying the decision tree by not including the “impurities and thresholds defined in the registration” box, because stakeholders with an approved NDA or ANDA already know that impurities and thresholds are defined in the registration.

Response: Comment incorporated.

Comment Summary #22: The commenter requested changing the “drug substance or drug product” text at the end of the flow diagram to “adopt the impurities acceptance criteria per monograph requirements” for clarity.

Response: Comment incorporated.

Terminology Associated with Organic Impurities Used in Drug Substance and Drug Product Monographs
Comment Summary #23: The commenters requested changing the term "specified known impurity" to "specified identified impurity", and the term "specified unknown impurity" to "specified unidentified impurity" for consistency with ICH terminology.
Response: Comment incorporated.
Comment Summary #24: The commenter suggested replacing the term "minimum sensitivity" with "minimum response" when referring to the reporting threshold and the analytical system for a more accurate description.
Response: Comment not incorporated. In this context, the term "sensitivity" is better.
Comment Summary #25: The commenter suggested clarifying disregard peaks caused by solvents and reagents or arising from the mobile phase or the sample matrix.
Response: Comment partially incorporated in alignment with General Chapter <621> *Chromatography*.
Comment Summary #26: The commenter suggested changing the quantification limit as it should not be more than 50% of the specification limit or less or equal to the ICH reporting threshold.
Response: Comment incorporated. The text was changed to: "The quantitation limit for the analytical procedure should be not more than (≤) the reporting threshold" in alignment with ICH Q3B.

Appendix 1 - Glossary
Comment Summary #27: The commenter suggested removing the sentence stating the terms "disregard limit" and "reporting threshold" are considered synonyms. They are not synonymous scientifically but the terms do coincide most of the time.
Response: Comment incorporated.
Comment Summary #28: The commenter suggested changing "identified by relative retention times" to "specified by relative retention times" in part of the definition of "Total impurities/total degradation products" to align with ICH terminology.
Response: Comment partially incorporated. The text was changed to: "Drug product monographs may include a note that certain drug substance process-related impurities should not be included in the total degradation products."

Appendix 2 - Additional Sources of Information and Guidance
Comment Summary #29: The commenter recommended changing "International Council for Harmonisation" to "International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use."
Response: Comment incorporated.

General Chapter: <1088> *In Vitro and In Vivo Evaluation of Dosage Forms*
Expert Committee: General Chapters–Dosage Forms
No. of Commenters: 2

Comment Summary #1: In the *Technical Requirements* section, the commenter recommended modifying the sentence: "Ideally, the dissolution method used to establish the IVIVC should be identical to the regulatory dissolution method used for routine quality control testing."
Response: Comment not incorporated. The EC believes that this chapter may be more up to date than the guidance. In addition, there are references to the FDA guidance in this chapter.
Comment Summary #2: The commenter recommended adding a paragraph to point out that the development of IVIVC should be risk-based and to keep the line of sight (i.e., what the future use of the IVIVC would be) as the requirement for inclusion of more batches in the development

of IVIVC would be necessary if the IVIVC is to be used to support higher levels of post-approval changes.
Response: Comment not incorporated. However, a reference to the SUPAC Guidelines is provided. In addition, the EC will consider adding a risk-based approach in the next revision.
Comment Summary #3: The commenter recommended adding a paragraph somewhere in the chapter to describe IVIVR and how it differs from an IVIVC.
Response: Comment not incorporated. The EC thought this is sufficiently addressed in this chapter and defined in the glossary.
Comment Summary #4: In the *Purpose* section, the commenter recommended revising the sentence to read as follows: “This chapter focuses on the in vitro and in vivo performance of oral dosage forms and provides an overview of the methodology for characterizing the properties of a drug substance as well as its associated oral dosage forms that are critical to establish the relationship to the pharmacokinetic properties of the drug product.”
Response: Comment incorporated. The text is modified as suggested.
Comment Summary #5: In the *Purpose* section, the commenter recommended revising the final sentence to read as follows: “Establishing an IVIVC may enable waiver of an in vivo bioequivalence study requirements as well as support scale-up and post-approval changes.”
Response: Comment incorporated. The text is modified as suggested.
Comment Summary #6: In the *Scope* section, the commenter recommended revising the sentence to read as follows: “An IVIVC is linked to the in vitro test conditions and the product critical quality attributes (CQAs) controlling the in vivo and in vitro release characteristics. If either is changed, the relationship may be compromised.”
Response: Comment incorporated. The text is modified as suggested.
Comment Summary #7: The commenter recommended that the second sentence in the *In Vitro Characterization* section should also include the drug product, in addition to the drug substance. The revision to the sentence should be as follows: “In order to best characterize the performance of the dosage form, an understanding of the physicochemical properties of the drug substance and drug product is needed.”
Response: Comment not incorporated. Mostly, the drug substance properties (e.g., solubility, pKa, etc.) dictate the performance of a dosage form.
Comment Summary #8: In the *Drug Product Properties* section, the commenter recommended revising the fifth sentence to read as follows: “In addition to factors critical to the in vivo performance of immediate release formulations, key variables of importance for delayed-release are onset of the dissolution and pH dependence.”
Response: Comment incorporated. The text is modified as suggested.
Comment Summary #9: In the *Experimental Variables* section, the commenter recommended revising the first sentence as follows: “Experimental variables of the dissolution method to consider when characterizing the dosage form include the media pH, volume of the dissolution medium, composition of the dissolution medium, and agitation (hydrodynamic).”
Response: Comment incorporated. The text is modified to include volume and composition.
Comment Summary #10: In the *Experimental Variables* section, the commenter recommended modifying the sentence by not grouping organic solvents with others. The second paragraph does include organic solvents. According to the regulatory agencies, use of organic solvents is discouraged.
Response: Comment incorporated. The organic solvents was removed from the first sentence and an additional sentence was added to read: “Organic solvents may be added to the dissolution medium with appropriate justification.”
Comment Summary #11: In the *Experimental Design* section, the commenter recommended revising the first sentence to read: “Experimental design should be reflective of the physiological conditions prevailing within the gastrointestinal (GI) tract.”

Response: Comment incorporated. The text is modified as suggested.
Comment Summary #12: In the *Experimental Design* section, the commenter recommended revising the fourth sentence to read as follows: “One should consider the combinations of experimental variables in the gastrointestinal tract such as pH and composition as they would occur in human (or veterinary) GI physiology.”
Response: Comment incorporated. The text is modified as suggested.
Comment Summary #13: In the *Technical Requirements* section, the commenter recommended revising the first sentence of the second paragraph to read as follows: “The in vitro characterization should include a sufficient number of data points to support pivotal phases of dissolution kinetics and a duration that provides a full profile with nearly if not complete dissolution (100% release).”
Response: Comment not incorporated. Data points come with duration.
Comment Summary #14: In the *Technical Requirements* section, since critical material attribute and manufacturing process variables play an important role, the commenter recommended revising the first sentence of the third paragraph to read: “The selected dosage form will be varied, such as by composition**,** by critical material attributes (e.g., API particle size) and by manufacturing process, so there are variant formulations that represent different levels of drug release in vitro and in vivo.”
Response: Comment incorporated. The text is modified as suggested.
Comment Summary #15: In the *Technical Requirements* section, the commenter recommended revising the fourth sentence of the third paragraph to read: “Ideally, the dissolution method used to establish the IVIVC should be identical to the regulatory dissolution method used for routine quality control testing, even if the IVIVC method utilizes sequential changes in the pH of the dissolution media.”
Response: Comment not incorporated. The EC thought the original sentence is more appropriate.
Comment Summary #16: In the *Technical Requirements* section, the commenter recommended revising the second to final sentence of the third paragraph (“An IVIVC method is based on differences in in vivo performance*.”)* for clarity as it is unclear and incomplete.
Response: Comment not incorporated. It will be discussed for a future revision.
Comment Summary #17: In the *Technical Requirements* section, the commenter noted that the word “a” is missing in the final sentence of the third paragraph.
Response: Comment incorporated. The word “a” is inserted in the text as suggested.
Comment Summary #18: In the *In Vivo Evaluation of Dosage Forms* section, the commenter recommended revising the final sentence of the second paragraph to read: “Although these guidelines focus on oral drug delivery systems, the principles may be applicable to other routes of administration (e.g., transdermal, subcutaneous, intramuscular). It should be noted that while in vitro dissolution studies can serve as a surrogate for in vivo dissolution drug release, it remains essential to confirm the absence of excipients that can impact in vivo effects (e.g., altered GI transit time, permeability enhancement, or changes in enterocyte drug metabolism and transporter activity).”
Response: Comment not incorporated. It will be discussed for a future revision.
Comment Summary #19: In the *Biopharmaceutics Classification System* section, the commenter recommended that the section also reference the guidance: “M9 Biopharmaceutics Classification System-Based Biowaivers, Oct 2018.”
Response: Comment incorporated. An additional sentence is added to the requested reference.
Comment Summary #20: In the *Biopharmaceutics Classification System* section, the commenter recommended adding the following sentence to the last sentence of this section: “Please note that the BCS system is based upon the physiology of the human GI tract. Due to

species differences in GI physiology, a compound's BCS classification is frequently not applicable to the GI tract of many veterinary species."
Response: Comment not incorporated. This chapter does not cover veterinary products but this will be considered for a future revision.
Comment Summary #21: In the *Pharmacokinetic Profiling* section, the commenter noted that the word "a**"** is missing from the first sentence.
Response: Comment incorporated. The word "a" is inserted into the sentence.
Comment Summary #22: In the *Pharmacokinetic Profiling* section, the commenter recommended revising the second and third sentences to include this information: "An intravenous solution provides instantaneous and complete bioavailability as is required by the Loo-Riegelman model for level A correlations in order to establish the drug depletion characteristics. The oral aqueous solution is used as a reference for assessing drug absorption characteristics in the absence of constraints associated with in vivo product dissolution. The in vivo data from the oral solution and intravenous administration are then used to evaluate the input profile of the modified-release dosage form."
Response: Comment not incorporated. Oral aqueous solution may not be used for IVIVC.
Comment Summary #23: In the *Pharmacokinetic Profiling* section, the commenter recommended adding a sentence to the final sentence to include information on additional factors that need to be accounted for in the IVIVC model, as follows: "Furthermore, efforts to establish an IVIVC can be negatively impacted by presystemic factors (e.g., segment-specific location of metabolizing enzymes or transporter activity) if these are not accounted for in the model used to establish the IVIVC."
Response: Comment not incorporated. This is too detailed for this chapter and does not help to explain systemic rates.
Comment Summary #24: In the *Pharmacokinetic Profiling* section, the commenter recommended adding the following item to the list: "10. Presystemic drug processing occurring with the segment-specific enterocyte (e.g., drug metabolism, influx or efflux transporter activity). Of particular concern is the segmental-specific differences in each of these activities and how it may impact the extent of movement of the drug from the gut to the portal vein."
Response: Comment not incorporated. This is not for IVIVC.
Comment Summary #25: In the *Pharmacokinetic Properties: Immediate-Release Products* section, the commenter recommended revising the first sentence as follows: "The types of pharmacokinetic studies that should be conducted are based on how much is known about the drug, its clinical pharmacokinetics, and its BCS class for an FDA-approved drug product that undergoes changes in the manufacturing after its approval."
Response: Comment not incorporated. The EC thought the suggested sentence lacks clarity.
Comment Summary #26: In the *Pharmacokinetic Properties: Modified-Release Products* section, the commenter recommended revising the first sentence as follows: "A study to evaluate the potential for food effects including robustness of the dosage form (including dose dumping) from extended-release dosage forms also is required as a separate study or is included as an arm of a crossover study."
Response: Comment incorporated. The text is modified as suggested.
Comment Summary #27: In the *Pharmacokinetic Properties: Modified-Release Products* section, for the fifth and sixth sentences, the commenter recommended adding more information about first-pass metabolism as follows: "If the drug exhibits saturable first-pass hepatic metabolism from the small intestine, a reduction in system availability could result after oral administration if the input rate is decreased, if more drug is delivered to an intestinal segment associated with active influx transport (i.e., upper small intestine), or if more drug is available at an intestinal segment associated with enterocyte-associated metabolism or active efflux mechanisms. An increase in system availability could be observed if a drug is absorbed from

the colon from a delayed-release dosage form that targets the colon, thus avoiding a first-pass effect or the converse of any of the above potential sources of decreased oral bioavailability."
Response: Comment not incorporated. This requires further discussion and will be considered for a future revision.
Comment Summary #28: In the section *In Vitro – In Vivo Correlations (IVIVC)*, the commenter suggested that the definition of IVIVC should be expanded to include any drug formulation for which in vivo dissolution is the rate limiting factor governing the rate and extent of drug absorption, in addition to the extended release formulations.
Response: Comment not incorporated. It is discussed in the immediate release section.
Comment Summary #29: In the *General Considerations* section, the commenter recommended revising the first sentence as follows: "In an ideal case, correlations should be **generated** by using the entire profiles of both in vitro dissolution testing and plasma concentrations from bioavailability studies."
Response: Comment incorporated. The text is modified as suggested.
Comment Summary #30: In the *General Considerations* section, the commenter suggested that further clarification is needed for the second sentence that reads as follows: "Alternatively, a reduced number of summary parameters can be used but with a lower predictive capability. A point-to-point data analysis allows establishment of a functional relationship, which does not imply a full correlation." The commenter inquired the following: Does this mean going from Level A to C, or can a Level A still be made but now there is a greater risk of error when applying the IVIVC to new dosage forms?
Response: Comment not incorporated. This may be considered for a future revision. In addition, the following sentence was deleted: "Alternatively, a reduced number of summary parameters can be used but with a lower predictive capability."
Comment Summary #31: In the *General Considerations* section, the seventh sentence reads as follows: "Each correlation level displays important differences in the quality of the correlation." The commenter noted that the statement was unclear and recommended the word "quality" be clarified.
Response: Comment not incorporated. The EC thought the sentence and surrounding sentences accurately described the levels of correlation that could be determined.
Comment Summary #32: In the *General Considerations* section, the commenter recommended revising the eighth and ninth sentences to read as follows: "This chapter provides a discussion of each type of correlation with respect to when each may be the most appropriate type of relationship to establish and then to describe their potential utility within the framework of product development, the development of release specifications, and their regulatory utility in supporting biowaivers. Typically, one target formulation and one or two alternative formulations with expected higher and/or lower in vivo performance are included in the IVIVC study protocol."
Response: Comment incorporated. Text added with a minor change of "in vivo performance" to "drug release."
Comment Summary #33: In the *General Considerations* section, the commenter suggested that the ninth sentence, "In general one target formulation and one or two alternative formulations with expected higher and/or lower in vivo performance are included in the IVIVC study protocol," is unclear and needs revision.
Response: Comment incorporated. Text added with a minor change of "in vivo performance" to "drug release."
Comment Summary #34: In the *General Considerations* section, the tenth sentence, "If feasible an oral solution is administered to a selected number of subjects in order to compute the relative oral bioavailability and to perform a model free numerical deconvolution procedure,*"* lacks specificity and the commenter recommended this statement be revised specifying to use aqueous and not non-aqueous solutions.

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

Comment Summary #35: In the *General Considerations* section, the commenter recommended revising the tenth sentence into two sentences as follows: “This allows the task of developing an IVIVC to occur early enough in product development so that it helps in predicting the in vivo developing an IVIVC to occur early enough in product development so that it helps in predicting the in vivo linkage and minimizes bio studies. It also has a role in specification selection.”

Response: Comment incorporated. Text added with a typo corrections.

Comment Summary #36: In the *Correlations Levels* section, the commenter recommended adding the following statements to the beginning of the section: “For any of these correlations to be appropriate, the rate and extent of product absorption must be controlled by the in vivo rate and extent of product dissolution. **If permeability rather than dissolution is rate limiting**, or if there is solubility-limited absorption, **the development of an IVIVC/R should be attempted.**”

Response: Comment partially incorporated. Bolded text above added to the section.

Comment Summary #37: In the *Correlations Levels* section, the commenter recommended revising the fifth sentence to read as follows: “The model-dependent mass balance approaches do not allow for prediction of oral bioavailability, whereas the numerical deconvolution is based on the assumption of **absorption and elimination processes** being invariant over time.”

Response: Comment partially incorporated. Bolded text above is added to the section. The term “linear pharmacokinetics” also remains in the original sentence.

Comment Summary #38: In the *Correlations Levels* section under the Level A subsection, the commenter recommended revising the final sentence to read as follows: “Interpolation of specifications from the so-called side batches is a commonly accepted way, whereas extrapolation necessitates verification of additional assumptions regarding in vivo product performance, that in vivo drug release is governed by the same CQAs, and the adequacy of the in vitro dissolution test to characterize the change in that CQA.”

Response: Comment not incorporated. The suggested sentence is not well understood.

Comment Summary #39: In the *Correlations Levels* section under the Level B subsection, the commenter recommended revising the fourth sentence to read as follows: “It does not correlate the actual in vivo plasma profiles but rather parameters that result from analysis of the second statistical moment (e.g., mean residence time).”

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

Comment Summary #40: In the *Correlations Levels* section under Level C subsection, the commenter suggested revising the fourth sentence to read as follows: “Because of this type of correlation is not predictive of the full rate and extent of in vivo product dissolution characteristics, it generally serves primarily as a guide in formulation development or as a production quality control procedure.”

Response: Comment incorporated. The text is modified as suggested.

Comment Summary #41: In the *Correlations Levels* section under the Level C subsection, the commenter suggested revising the sixth sentence to read as follows: “The advantage of a Level C correlation is that it provides an opportunity to relate the IVIVC to some targeted clinical performance attribute.”

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

Comment Summary #42: In the *Developing Correlation* section, the commenter noted that it is unclear if there is a minimum percent dissolved that must be achieved by all formulations used for establishing the IVIVC. It is recommended that this be specified.

Response: Comment not incorporated. It is based on the type of compound/molecule being used. It is clarified in the guidance.

Comment Summary #43: In the *Developing Correlation* section, the commenter recommended deleting the first sentence of Point 2, “Different dissolution profiles of a formulation should be obtained,” as a similar statement is made in the next sentence.
Response: Comment incorporated. The sentence is deleted.
Comment Summary #44: In the *Developing Correlation* section, the commenter recommended revising the second sentence of Point 2 to read as follows: “The formulation should be modified to produce different dissolution profiles, by having the same excipients in all the formulations that will be tested, but may differ in terms of excipient grade, amount per tablet, and/or some physicochemical characteristic such as hardness. Importantly, the in vivo and in vitro dissolution of the various formulations need to all be a function of the same CQA.”
Response: Comment not incorporated. The EC thought this is the ideal case, which is sometimes hard to reach.
Comment Summary #45: In the *Developing Correlation* section, the commenter recommended revising the first paragraph of Point 3 to read as follows: “The plasma levels obtained in the definitive bioavailability study of the modified-release dosage forms are analyzed using a deconvolution procedure. The resulting data may represent the apparent drug input rate of the dosage form. The deconvolution represents in vivo dissolution when the rate-controlling step for oral drug absorption is its dissolution rate (i.e., drug absorption after dissolution is considered to be instantaneous). Any deconvolution procedure (e.g., mass balance or mathematical deconvolution) will produce acceptable results if properly validated. However, the results of mass balance algorithms versus numerical deconvolution are not comparable. Figure 3 illustrates the results of numerical deconvolution of the plasma profiles obtained for the formulation in Figure 2.”
Response: Comment is accepted. The text is modified as suggested.
Comment Summary #46: In the *Developing Correlation* section, the commenter recommended revising the fifth sentence of the first paragraph of Point 3, “However, the results of mass balance algorithms versus numerical deconvolution are not comparable.”, to reflect why this is the case (e.g., the mass balance does not distinguish parent metabolite, and this can confound the assessment of parent drug absorption per unit time).
Response: Comment not incorporated. The “numerical deconvolution” reaches asymptotically the point estimate of relative bioavailability. Mass balance always reaches 100%.
Comment Summary #47: In the *Developing Correlation* section, the commenter recommended revising the final two sentences to read as follows: “The intercept may or may not be zero depending on whether there is a lag time between administration and drug absorption (such as that which may occur due to delays in gastric transit). In either case, it is considered to be a point-to-point or a Level A correlation when the least-squares fit of the line approaches a coefficient of determination, R2, of 1.”
Response: Comment partially incorporated to incude, “the intercept may or may not be zero depending on whether there is a lag time.” Also, the “R2” is changed to “r2.”
Comment Summary #48: In the *Developing Correlation* section, the commenter recommended revising the fourth point to read as follows: “A discriminative in vitro method establishes that in vitro behavior is predictive of in vivo dissolution. This is demonstrated by preparing at least two formulations that have significantly different in vitro behavior. One should demonstrate a more rapid release while the other should be a slower release than the clinical bioavailability batch (or biobatch). A pilot BA-BE study should be performed with these formulations, and the previously established IVIVC/R should be confirmed. The modifications of these formulations should be based on factors that are expected to share the same CQA that determines the rate and extent of in vivo and in vitro dissolution.”
Response: Comment not incorporated. In vivo absorption differences are important.

General Chapter: <1102> *Immunological Test Methods—General Considerations*
Expert Committee: General Chapters–Biological Analysis
No. of Commenters: 1

General Comments
Comment Summary #1: The commenter requested additional concentration expression in units for describing the quantitative ITM data.
Response: Comment partially incorporated. Added statement that data reporting might also depend on units of the reference standard.

General Chapter: <1151> *Pharmaceutical Dosage Forms*
Expert Committee: General Chapters–Dosage Forms
No. of Commenters: 1

Comment Summary #1: In the *Dosage Forms* section, under the *Powders* subsection, the commenter recommended changing the following text to clarify the term "concentrate":
"In veterinary medicine, a powder that needs to be reconstituted prior to administration has been called a concentrate (e.g., drug products administered via drinking water). Such use of the term "concentrate" is no longer preferred."
Response: Comment incorporated. The text is modified to read "In veterinary medicine, a powder that needs to be reconstituted prior to administration previously has been called a concentrate. The term "concentrate" is no longer preferred."
Comment Summary #2: In the *Product Quality Tests, General* section, in the *Impurities* subsection, the commenter recommended that the text be revised to refer to <232> *Elemental Impurities*.
Response: Comment incorporated. The text is revised to include reference to <232>.
Comment Summary #3: In the *Dosage Forms* section, the commenter recommended the text be revised to include reference to chewable bar as there is an approved chewable bar drug product.
Response: Comment not incorporated. The EC will consider this comment for the next revision.
Comment Summary #4: In the *Foams* subsection, the commenter recommended the text be revised to include a reference to injectable foams as there is an approved injectable foam drug product, Polidocanol Injectable Foam.
Response: Comment incorporated. An additional sentence is included as "Foams can also be delivered by the injection route."
Comment Summary #5: In the *Injections* subsection, the commenter recommended adding "Foams" to the list of dosage forms.
Response: Comment incorporated. "Foams" is added to the dosage form list.
Comment Summary #6: In the *Pastes* subsection, the commenter suggested the text in this section be revised to recognize that rarely, pastes may also be orally administered to humans.
Response: Comment incorporated. A sentence was added to read "Although rare, pastes can be administered orally, for example, to evaluate pharyngeal function."
Comment Summary #7: In the *Plasters* subsection, the commenter recommended referring the reader to "System" or "Systems," rather than referring to "Transdermal Systems."
Response: Comment incorporated. The text was modified to include "Systems."
Comment Summary #8: In the *Systems* subsection, the commenter recommended including information about topical systems in the text as there are approved marketed topical systems.
Response: Comment not incorporated. The EC will consider this comment for the next revision.

Comment Summary #9: The commenter suggested that the <1151> subcommittee begin working on developing text about microneedle drug delivery systems.
Response: Comment not incorporated. The EC will consider this comment for the next revision.
Comment Summary #10: The commenter recommended that the <1151> subcommittee work with the Nomenclature and Labeling EC to revise and reflect minor changes that are in the process in the definitions for the Injectable dosage forms.
Response: Comment not incorporated. The EC will consider this comment for the next revision.
Comment Summary #11: The commenter recommended that the <1151> subcommittee work with the Nomenclature and Labeling EC in developing definitions for Chewable Bar, Injectable Foam, and Extended Release Injection.
Response: Comment not incorporated. The EC will consider this comment for the next revision.

General Chapter <1153> *Drug Products Containing Nanomaterials*
Expert Committee: Dosage Forms
No. of Commenters: 3

Introduction
Comment Summary #1: The commenter suggested defining the "dendrimers" in Table 1 as "highly branched star-shaped macromolecules" instead of "branching structures consisting of polymers" because dendrimers are generally used to describe types of molecules, rather than type of structures.
Response: Comment incorporated.
Comment Summary #2: The commenter recommended defining "drug nanoparticles" and "nanocrystals" as separate items in Table 1 for clarity and accuracy. Nanocrystals are simply nano-scaled crystalline solids and therefore exclude amorphous nanoparticles. Drug nanoparticle should also be revised to state: "nanoparticles that consist of crystalline or amorphous form of pure drug substance."
Response: Comment incorporated.
Comment Summary #3: The commenter suggested revising the second sentence under "Drug nanoparticles/Nanocrystals" as follows to complete the explanation of why nanoparticles have increased bioavailability: "Nanocrystals are used as a formulation strategy to enhance bioavailability by increasing drug solubility as described by the Kelvin equation and dissolution rate as described by the Noyes-Whitney equation (A.S. Narang, R.K. Chang and M.A. Hussain, "Pharmaceutical Development and Regulatory Considerations for Nanoparticles and Nanoparticulate Drug Delivery Systems", J.Pharm. Sci., DOI:10.1002/jps.23691 (August 23, 2013))."
Response: Comment incorporated.
Comment Summary #4: The commenter recommended modifying the third sentence as follows since Fenofibrate is typically used in the treatment of dyslipidemia: "Examples of nanocrystal products include those used for cancer (megestrol acetate), organ rejection (sirolimus), and emesis (aprepitant) as well as **dyslipidemia** (fenofibrate)."
Response: Comment incorporated.
Comment Summary #5: The commenter suggested revising the second sentence of the liposome definition as follows for clarity: "Liposomes have been employed to formulate both water-soluble and -insoluble ***~~lipophilic~~*** drug substances." The word "lipophilic" may lead to confusion as it seems to suggest that both water-soluble and water insoluble drug substances are lipophilic.
Response: Comment incorporated.

Comment Summary #6: The commenter pointed that the description of “Micelles” as written is restricted to polymeric micelle. Both surfactants and block copolymers can also self-assemble into micelles; therefore, they suggested revising the first sentence of the definition as follows: “Nano-scaled colloidal structures are formed by self-assembly of amphiphilic molecules. The constituents of the micelles can be either surfactants or block copolymers.”
Response: Comment incorporated.
Comment Summary #7: The commenter suggested deleting the following sentence from the micelle description: “These are constructs in which the polymers employed differ in their hydrophobic blocks [e.g. poly(propylene oxide), poly(L-amino acids), or poly(esters) such as polylactide-polyethylene glycol (PLA-PEG) deblock polymers].” This sentence could be confusing as it describes block copolymers and not micelles.
Response: Comment incorporated.
Comment Summary #8: The commenter suggested modifying the first sentence in the description of “nanobubbles“ as follows to form a complete sentence: “**The nanobubbles are** created using oscillating vibration sources to disperse air in water, usually in the presence of surfactant.”
Response: Comment incorporated.
Comment Summary #9: The commenter indicated that the nanoemulsion definition as given seems to suggest that nanoemulsions include thermodynamically stable microemulsions and kinetically stable nanoemulsions, which are both submicron sized. Since there is considerable confusion on the terminology of nanoemulsions and microemulsions in the literature, commenter suggested including a footnote discussion about these two different formulations if the definition includes both microemulsions and nanoemulsions.
Response: Comment partially incorporated. Definition revised for clarity by including droplet size information.
Comment Summary #10: The commenter suggested revising the last two sentences of nanoemulsion defintions as follows: “Nanoemulsions are used in ophthalmic and oral products, for example, to deliver cyclosporin for dry eyes and for prophylaxis of organ rejection and immune regulation.” This is because there are no approved nanoemulsion products for avermectin and cyclosporin microemulsion are indicated for prevention of organ rejection following transplant and immune regulation, but not for psoriasis treatment. Cyclosporin nanoemulsions are also used in the treatment of dry eyes.
Response: Comment incorporated.

General Quality Tests of Drug Products Containing Nanomaterials
Comment Summary #11: The commenter suggested that the following methods of analysis are applicable to this chapter, but are not included in the chapter:

- SLS (static light scattering)
- AFFF (asymmetrical field flow fractionation)
- NTA (nano particle tracking analysis)
- Fluorescence activated particle sorting (FAPS)
- Disk centrifugation

Therefore, Figure 2 from the journal publication “Particles in Therapeutic Protein Formulations, Part 1: Overview of Analytical Methods," S Zölls, R Tantipolphan, M Wiggenhorn, G Winter, W Jiskoot, W Friess, and A Hawe, Journal of Pharmaceutical Sciences, March 2012, Volume 101, Issue 3, pp 914–935” should be added to this chapter.
Response: Comment partially incorporated. Relevant information was extracted from Figure 2 and added to the chapter.

Composition and Structure

Comment Summary #12: The commenter recommended adding atomic emission spectroscopy in the second sentence under *Composition and Structure* to read as follows as it is also used for elemental analysis of nanomaterials: “For example, for inorganic molecules, elemental analysis by atomic absorption spectroscopy **and atomic emission spectroscopy** with flame ionization or inductively coupled **plasma** mass spectrometry can be employed.”
Response: Comment incorporated.
Comment Summary #13: The commenter indicated that the correct terminology for gel chromatography should be, “gel permeation chromatography/size exclusion chromatography” and MALS detector can be used to determine the absolute molar mass of the molecules. Therefore, they recommended revising the third sentence as follows: “For organic polymeric systems, **gel permeation chromatography/size exclusion chromatography** with refractive index detection may be supplemented with viscosity determinations and application of the Mark-Houwink equation to estimate the molecular weight (20). **If a multi-angle light scattering detector (MALS) is added the absolute molecular weight can be determined.**”
Response: Comment incorporated.
Comment Summary #14: The commenter requested removing the fourth sentence of the paragraph which reads, “Photon correlation spectroscopy (dynamic light scattering) also may be used in this context.”, as this method does not give structural or compositional information about a material.
Response: Comment not incorporated. Photon correlation spectroscopy does give structural information, molecular weight, or molecular size.
Comment Summary #15: The commenter suggested revising the sixth sentence as follows to indicate that liposomal size and morphology can be gleaned from this method: “Electron microscopy techniques such as **cryogenic transmission electron microscopy** may be used for liposome/lipid-based nanoparticle formulations **to determine their size and morphology (e.g. lamellarity)**”.
Response: Comment incorporated.

Encapsulation Efficiency
Comment Summary #16: The commenter suggested revising the second sentence as follows into small sentences as it is long and confusing: “This can be achieved by separating the drug substance in the nanomaterial from the free drug substance, typically using centrifugal filter devices. Size-exclusion spin columns or solid phase extraction (SPE) columns are used to separate free from encapsulated or carrier associated drugs, performing an appropriate quantitative assay of free drug versus encapsulated drug as a proportion of the total drug present.”
Response: Comment incorporated.

Particle Size Distribution
Comment Summary #17: The commenter indicated that the dynamic light scattering is also appropriate for the measurement of particle size as well as particle size distribution; therefore, it should be added under *Particle Size Distribution*.
Response: Comment incorporated.

Shape
Comment Summary #18: The commenter recommended including multiangle light scattering (MALS) as a method for determining shape, as it can also give information on the conformation (e.g., sphere, coil and rod) of the molecules when coupled with separation techniques.
Response: Comment incorporated.

Solubility

Comment Summary #19: The commenter recommended revising the second sentence as follows because the qualifier used is unnecessary and potentially confusing: “Methods to assess the solubility of nanomaterials ~~**that dissolve**~~ (i.e., nanoparticles or nanocrystals) sometimes use characterization of the particle size distribution and changes in the particle size distribution as a function of time as a surrogate or complementary data to dissolution data.”
Response: Comment incorporated.

Surface Properties
Comment Summary #20: The commenter suggested completing the first sentence under *Surface Properties* as it is incomplete as written.
Response: Comment incorporated. Sentence is reworded for completion.

General Quality Tests
Table 2
Comment Summary #21: The commenter suggested adding some explanation in the *Introduction* section to explain why recommendation of using “all general quality tests identified in General Quality Tests of Drug Products Containing Nanomaterials” apply to some, but not all, of the materials listed in Table 2.
Response: Comment not incorporated. The EC determined that the reason behind this recommendation is well understood by those who work with the materials identified; therefore, no explanation is provided.
Comment Summary #22: The commenter suggested replacing the terms “dissolution” and “in vitro release” with “dissolution/in vitro release” as it currently appears on Page 8. In some cases (e.g., nanoemulsions), the drug is in the molecular state and dissolution is not a correct term for the case, as the term suggests the extent and rate the solid drug dissolved in an appropriate medium.
Response: Comment incorporated.
Comment Summary #23: The commenter suggested adding some information on the characterization of nanomaterial surfaces in case of PEGylation on liposomes.
Response: Comment not incorporated. Although PEGylation is the most obvious one, the particles can be decorated with other things as well. Introducing PEGylation at this point may require consideration of adding all the other decorations. The EC will consider this comment in the next revision of this chapter.
Comment Summary #24: The commenter requested adding clarification on why the test for encapsulation efficiency is not listed as a recommended method for liposomes. They noted that adding this information would align this chapter with the FDA final liposome guidance.
Response: Comment not incorporated. This test is part of development and will not be covered in this chapter at this time.

Description of Product Quality Tests
Comment Summary #25: The commenter suggested adding the test “Density” to this chapter as density of nanoparticles is important for certain routes of drug administration, such as inhalation.
Response: Comment not incorporated. Density and shape factors are intrinsic to aerodynamic measurements. Density is not measured independently. Nanoparticles themselves are a subset of a delivered particle in aerosol products (this is mentioned in the chapter).
Comment Summary #26: The commenter suggested adding the test for “Crystallinity” as a nanoparticulate drug can be crystalline or amorphous.
Response: Comment incorporated**.**

Comment Summary #27: The commenter suggested adding the test for "pH" as the pH test is a quality test for many drug products containing nanomaterials (e.g., internal pH for liposome preparations).
Response: Comment not incorporated. All other tests included are specific to the particle structure and this is a general product/formulation specific test. The EC decided to not include text as suggested.

General Chapter/Sections:	<1195> *Significant Change for Bulk Pharmaceutical Excipients*/Multiple
Expert Committee:	Excipients Monographs 1
No. of Commenters:	2

Comment Summary #1: In subsection *Packaging, Labeling, and Documentation* of section *5.1 Changes to the Site, Infrastructure Used to Manufacture, and Distribution of the Excipient*, the commenter recommended revising the phrase "any changes to seals that are intended to be tamper evident is level 2" to make that a "Risk Assessment". The commenter states that in their case all seals are labeled with company information, and a similar seal containing company information would not need customer notification as long as the seal is present, secure, and able to maintain its integrity for its purpose.
Response: Comment not incorporated. Unique and tamper-evident seals discourage intentional substitution with counterfeit products during transportation activities. Combined with acceptance testing and other receiving controls, they give drug product manufacturers confidence that the quality of the excipients they have received has not been compromised during storage or transit. The EC believes that any change to a tamper-evident seal without customer notification would reduce the integrity of this control and undermine confidence in the security of the supply chain.
Comment Summary #2: In subsection *Packaging, Labeling, and Documentation* of section *5.1 Changes to the Site, Infrastructure Used to Manufacture, and Distribution of the Excipient*, the commenter requested removing the word "testing" from the sentence "Any change to labeling or documentation pertaining to the company name, product name, batch/lot number scheme, site of manufacture or testing, species origin, additives, or storage and handling conditions is a Level 2 change" and instead be a risk assessment. The commenter states that contract laboratories are already being approved for their intended use, and a risk assessment would be better suited to evaluate if the testing being done is for information only or for critical parameters and thereby allowing the risk-assessment to determine whether notification is required. This would reduce unnecessary qualification activities for the manufacturer and the customers.
Response: Comment not incorporated. In Section *5.1 Changes to the Site*. . .", the bulleted item "Site Change" describes how to determine the significance of a change in a testing lab. The bulleted item referred to by the commenter, "Packaging, Labeling and Documentation" is not describing the significance of the change in the testing site, but the significance of the change to labeling, where the previous testing site was stated on such documentation. If the testing site was previously stated on the labeling, and this information will be removed, or another testing site will be listed in its place, customers need to be able to prepare for this change so that they do not encounter delays in their receipt and approval of purchased excipients.
Comment Summary #3: The commenter recommended adding a definition for 'Starting Material' to the glossary.
Response: Comment incorporated.
Comment Summary #4: The commenter recommended changing "Level 2" in the diagram branch "Raw Materials for the Manufacture of the Excipient – Origin – Country of Origin" of Figure 2 to "Risk Assessment." In certain cases, the country of origin is not going to

be significant for highly purified materials. A notification in these circumstances would not be required and would create arduous qualification activities where there is no potential for the origin to have any impact on the finished product.
Response: Comment not incorporated. The EC agrees that changes to raw material country of origin are not always Level 2. However, the text in the chapter (section 5.2.7) indicates that only changes in the country of origin of the raw materials which may impact regulatory status are a Level 2 change, and therefore not all changes are Level 2. Therefore, the commenter could justify only using a risk assessment in cases where there may be no impact on regulatory status from change of country of origin.
Comment Summary #5: In *Introduction*, section *1.3 Principles Adopted*, the commenter suggested changing "the drug manufacturer(s)" to "the drug product manufacturer(s)" in the sentence "However, the excipient manufacturer has a responsibility to follow the principles and guidance provided herein and to inform (notify) the drug manufacturer(s) of any significant change…."
Response: Comment incorporated.
Comment Summary #6: The commenter pointed out that two sections *Introduction,* subsection *1.3 Principles Adopted* and *3. Determination of Significance/Risk Assessment*, subsection, *3.1 General,* contain sentences that state that "all changes should be regarded (assumed) to be level 2 and thus notifiable unless otherwise scientifically justified and documented." However, the sentence in section *3. Determination of Significance/Risk Assessment*, subsection *3.1 General* continues as "or defined in this chapter to be level." The commenter recommended that the sentence in section *3. Determination of Significance/Risk Assessment*, subsection *3.1 General* be changed to read the same as in section *Introduction,* subsection *1.3 Principles Adopted.*
Response: Comment incorporated.
Comment Summary #7: The commenter recommended replacing "risk analysis" with "risk assessment" in the sentence "Judgment, based on risk analysis and a thorough knowledge of the process and intended application…." in *Introduction*, subsection *1.5 General Considerations, GMP*.
Response: Comment incorporated.
Comment Summary #8: In subsection *3.4 Justification for Level 1 Change*, the commenter suggested changing "medicinal product quality" to "medicinal drug product quality" in the sentence "the change does not pose a significant risk to the medicinal product quality."
Response: Comment incorporated.
Comment Summary #9: In subsection *5.2 Determination of Impact of Changes on Excipient Quality and Performance, Physical Properties,* the commenter recommended adding the sentence "The number of batches chosen for evaluation should be justified" after "Physical properties should be considered based upon the physical form of the excipient" and moving the last sentence in *Physical Properties* after the newly added sentence.
Response: Comment incorporated.
Comment Summary #10: In subsection *5.2 Determination of Impact of Changes on Excipient Quality and Performance, Change in the Distribution of the Excipient,* the commenter requested changing the third sentence to read "For example, storage and transportation conditions may affect excipient *quality*, stability, or the potential to become contaminated."
Response: Comment incorporated.
Comment Summary #11: In subsection *5.2 Determination of Impact of Changes on Excipient Quality and Performance, Change in the Distribution of the Excipient,* the commenter suggested revising the last sentence to read "…the excipient manufacturer must evaluate any known carrier changes to be assured that there will be no changes in storage *and*/or transportation conditions," so that both storage and transportation is covered.

Response: Comment incorporated.
Comment Summary #12: In *Glossary,* the commenter recommended revising the definition for residual solvents from "Organic chemicals that are used or produced in the manufacture…" to "Organic chemical solvents that are used or produced in the manufacture…"
Response: Comment incorporated.

General Chapter:	<1235> *Vaccines for Human Use—General Considerations*
Expert Committee:	General Chapters–Biological Analysis
No. of Commenters:	5

General Comments
Comment Summary #1: The commenter stated that a sterility test of each lot of each product is conducted according to procedures described in <71> and 21 CFR §610.12 for both bulk and final container material. Either <71> or 21 CFR 610.12 requires a bulk sterility test.
Response: Comment partially incorporated. Text added with edits since bulk sterility is acceptable in some cases. The text has been modified to be clear when and where the test must be applied.
Comment Summary #2: The commenter had several proposals on GMP, facilities, quality systems, BLA/CTD application content, requirements for testing, and raw materials. The commenter proposed that the Code of Federal Regulations (CFR) references should be reviewed for accuracy and applicability to information in the chapter.
Response: Comment partially incorporated. Revisions added to sections that address the comment. All CFR references have been reviewed for accuracy and applicability.
Comment Summary #3: The commenter stated that the section on permissible combinations should have reference to the FDA guidance document as they may be controversial or misinterpreted. On alternative tests, the text refers to FDA license change requirements which seemed out of place for this chapter.
Response: Comment partially incorporated. Stakeholders can refer to USP General Notice 6.30 and Appendix to the GC 1235 for applicable regulations and definitions.

Comment Summary #4: The commenter stated that since this is an informational general chapter, perhaps the addition of an Appendix with relevant additional sources of information can be added as is done with other USP General Chapters numbered >1000.
Response: Comment not incorporated. The EC will consider addition of an Appendix in the vaccine product class chapters, since the methods used tend to be common across product classes.
Comment Summary #5: The commenter recommended adding value to the chapter by improving the accuracy regarding US regulatory requirements, re-structuring the content to improve the information flow and with less verbiage, supporting directive statements by scientific references or other explanation where appropriate, and by adding an Appendix with appropriate references in addition to the section containing the relevant selected US regulatory documents.
Response: Comment not incorporated. USP General Chapters numbered above 1000 chapters are informational per *General Notices*. These chapters give guidance and not specific directive action. The EC will consider addition of an Appendix in the vaccine product class chapters, since the methods used tend to be common across product classes.
Comment Summary #6: The commenter stated that the chapter has little forward-looking guidance, and it would be very helpful to include some forward-looking statements or content like increased use of state-of-the-art analytical methods offers the potential to improve or replace obsolete methods and technologies, including-older animal-based methods. Some

advice towards these ends could be incorporated into the text.
Response: Comment not incorporated. The EC determined that forward-looking statements and speculation on the future state should not be included in the chapter.
Comment Summary #7: The commenter stated that the recombinant proteins by CHO were missing in this *Introduction* section and should be included.
Response: Comment partially incorporated. Text revised to include recombinant protein expressed in genetically engineered cell line. Listing examples were however not included.
Comment Summary #8: The commenter suggested including live attenuated bacterial vaccines to Table 1.
Response: Comment incorporated. Revised Table 1.
Comment Summary #9: The commenter suggested that the production of intermediates should be applicable to all production steps and not only specifically for intermediates.
Response: Comment has been incorporated. The first paragraph under *Intermediates* was combined with the paragraph under *Production of Intermediates* to address the comment.
Comment Summary #10: The commenter stated that drug substance bulk may be manufactured either as low-bioburden bulk or sterile bulk. The paragraph title should include both manufacturing practices, considering that low-bioburden bulks are subject to final sterilizing filtration prior to filling.
Response: Comment incorporated. A revision has been added to the sections between lines 367-386 that address the comment.
Comment Summary #11: The commenter stated that if the objective of the filter is to reduce the bioburden to obtain a low bioburden drug substance, it is not required to validate it with an EFA of $Ax10^7$CFU.
Response: Comment incorporated. In the section on *Filtered Bulk or Drug Substance*, the mention of drug product has been removed.
Comment Summary #12: One commenter stated that through the application of USP General Chapter <1031>, the vials and syringes would be considered as non-direct body contact and hence would not need a container biocompatibility check. Another commenter stated that through the new proposals of USP General Chapters <87> and <88>, it's clearly mentioned that material can be claimed compliant to biocompatibility requirements if USP <87> testing passes. The commenter enquired regarding compliance to Class VI in vivo in view of the need to perform other characterization tests on the final container material through the <381> and <661> series, including physicochemical, extractable, and leachables testing. The third commenter stated that classification of material through USP <88> testing is not applicable to elastomer or oral products.
Response: Comment incorporated. The second comment has been incorporated in lines 635-639 to accept the proposed change. The style has been aligned with other USP chapters to ensure consistency and that informational chapters are not made a requirement.
Comment Summary #13: The commenter stated that if filtration takes place at the point of filling, the final bulk is considered low bioburden. For low bioburden final bulk, the sterility test is not pertinent, it should be a bioburden test. The commenter also suggested revising to 0.2 µm filtration for sterility tests.
Response: Comment not incorporated**.** FDA guidance states the 0.2 and 0.22 µm filters are equivalent, therefore no change was made to the test.
Comment Summary #14: The commenter stated that a new section on *Filtered Bulk or Drug Substance* has been introduced in this revised general chapter. The commenter suggested that removal of manufacturing residuals may be performed also at drug substance level and not always at drug product level.
Response: Comment incorporated. A revision has been drafted to the section between lines 367-376 that address the comment.
Comment Summary #15: The commenter stated that in *Table 2, Vaccine Components*, there

was no mention of the containers and hence all components of the vaccine were not included.
Response: Comment incorporated. A line for containers was added to the Table.
Comment Summary #16: In reference to the *Final Bulk* section, the commenter suggested that the addition of diluents, excipients, etc., can happen before the bulk is sterile filtered, provided that the formulated bulk is then sterile filtered before filling. The current wording gave the perception that the sterile filtered bulk steps came before the production of final bulk which was not always the case.
Response: Comment incorporated. Texted added between lines 383-391 to address the comment.
Comment Summary #17: The commenter stated that there are some potentially novel adjuvants discussed in the adjuvants section on DP and suggested including regulatory reference(s).
Response: The adjuvant listed in Table 2 has been updated by limiting the chapter to adjuvants licensed in the United States.
Comment Summary #18: The commenter stated that gelatin or processed gelatin is used as a vaccine stabilizer. The gelatin source may be either bovine or porcine and suggested moving it to the *Materials of Animal Origin*.
Response: Comment has been incorporated. Text added between lines 282-300 to accept the proposed change.
Comment Summary #19: The commenter suggested adding "Another use of stability data/rate is to determine release potency specifications to ensure that Drug Product will meet end-expiry potency specifications, i.e. development of a release model." in the *Stability Protocols* section.
Response: Comment not incorporated. The sentence in lines 578-579 stating that "These latter studies define the product end–expiry specifications that allow definitions of acceptable and unacceptable product" already covers this concept.
Comment Summary #20: The commenter stated that the sentence "treated to prevent delamination (spalling)" appeared to specify treated glass to prevent delamination. The commenter suggested removing this sentence as they are no longer using treated glass.
Response: Comment incorporated. Text was deleted.
Comment Summary #21: The commenter suggested to remove the definition of "Component" and add the definitions for the following words instead: Ancillary raw material, Excipient, Residual impurity.
Response: Comment not incorporated. Instead, definitions for Ancillary raw material, Excipient, and Residual impurity have been added to the text under *Glossary*.
Comment Summary #22: The commenter asked why materials of animal origin are under manufacturing residuals but not mentioned under protein stabilizers (there is a whole section on animal derived stabilizers later in the document).
Response: Comment incorporated. Text added between lines 282-300 and as in described in response to Comment Summary #18.

General Chapter: <1238> *Vaccines for Human Use—Bacterial Vaccines*
Expert Committee: General Chapters–Biological Analysis
No. of Commenters: 2

General Comments
Comment Summary #1: The commenter stated that the purpose and the intended use of this general chapter on bacterial vaccines for human use is unclear. The level of detail is not consistent among chapters and depending on the prior knowledge of the reader, it might be confusing. The intended purpose of this chapter as well as the target audience with respect to the USP role should be expressed.

Response: Comment not incorporated. The purpose and scope of the connected chapters are defined in the *General Notices*.
Comment Summary #2: The commenter stated that a new section *Sterile Filtered Bulk* has been introduced in this revised general chapter. For some vaccines (e.g., live viral vaccines), it is not feasible to perform a sterile filtration. In other cases, the manufacturing bulk process is fully performed under aseptic conditions ensuring the sterility of the process, thus the sterile filtration of the bulk is not necessary. When a bulk sterile filtration is not feasible or necessary, sterility testing should be replaced by low bio burden strategy. Extractables and leachables testing should be performed following a risk-based approach. Definition of process steps/locations where endotoxin and bioburden testing need to be performed should be based on a risk assessment.
Response: Comment incorporated. Text added to the new section on *Filtered Bulk (Drug Substance).*

Other Vaccine Components and Vaccine Properties
Comment Summary #3: The commenter stated that it is not clearly specified at which process steps the mentioned tests should be performed. It should be considered that excipients testing on final bulk/finished product may not be applicable depending on vaccine matrix and the excipients nature itself.
Response: Comment incorporated. Text added to the section since some products in biologics require excipient testing. Polysorbate concentration testing is often required by the regulators.

General Chapter	<1239> *Vaccines for Human Use—Viral Vaccines*
Expert Committee:	General Chapters–Biological Analysis
No. of Commenters:	2

General Comments
Comment Summary #1: The commenter requested clarification of intended purpose of this chapter as well as the target audience.
Response: Comment not incorporated. The chapter aligns with USP *General Notices* and the *Briefing* provides relevant information regarding intent.
Comment Summary #2: The commenter mentioned that some flu vaccines are split vaccines and not always subunit vaccines as mentioned in Table 1.
Response: Comment incorporated.
Comment Summary #3: The commenter suggested including additional challenge of reverting to a virulent strain to Table 2.
Response: Comment not incorporated. This is covered in the stability of attenuation point.
Comment Summary #4: The commenter suggested altering purification of split influenza vaccine to remove references to neuramidase as it is principally driven by hemagglutinin.
Response: Comment incorporated.
Comment Summary #5: The commenter requested clarifying requirements in vaccine purification as some vaccines like yellow fever are not purified.
Response: Comment not incorporated. There is a purification step requiring filtration after homogenization of embryo during production of the yellow fever vaccine.
Comment Summary #6: The commenter recommended adding a better introduction of the problem of vaccine virus impairing the detection of contaminant before the viral seeds are tested for adventitious agents.
Response: Comment not incorporated. It is not feasible to detect whether an antibody would neutralize an unknown adventitious virus.
Comment Summary #7: The commenter suggested removing the redundancy pertaining to the two phases vs a biphasic process in the cell culture/virus culture section.

Response: Comment incorporated.
Comment Summary #8: The commenter suggested removal of “conditions of the production cell culture” in testing of other extraneous agents in indicator cell lines as the condition of cell culture needs to correspond to the indicator cell line when performing tests for extraneous agents on control cell supernatant (not the production condition that does not correspond to indicator cells).
Response: Comment not incorporated. Text is in alignment with international guidance.
Comment Summary #9: The commenter requested clarification of storage conditions for viral seed lots at cryogenic temperatures and multiple locations.
Response: Comment partially incorporated. Viral seed lots are to be stored at temperatures to ensure stability as temperatures can vary from product to product.
Comment Summary #10: The commenter suggested indicating characteristics of seed stock and/or viral production process (egg or cell line), or suggested adding a risk-based approach.
Response: Comment incorporated. Text added to align with regulatory guidance.
Comment Summary #11: The commenter requested clarification on several sentences concerning which tests should be performed on Master Viral Seed Lots as regulatory requirements are different across the world.
Response: Comment incorporated. Added clarifying sentence on differences in regulatory requirements.
Comment Summary #12: The commenter recommended adding additional information to factors that affect in ovo virus propagation.
Response: Comment not incorporated. Text mirrors FDA guidance.
Comment Summary #13: The commenter suggested keeping the text high level in control of cell production where requirements are mandatory.
Response: Comment not incorporated. Text is high level and mirrors regulatory guidance.
Comment Summary #14: The commenter suggested removal of testing requirements of control eggs for extraneous viruses in the *Control Cells During Production* section to better align with CBER and *Ph. Eur* guidance.
Response: Comment incorporated.
Comment Summary #15: The commenter recommended that tests on controlled eggs should not be mandatory as other measures for viral safety are in place by risk-based approach.
Response: Comment incorporated. Added risk-based approach to the chapter.
Comment Summary #16: The commenter suggested removing test for adventitious agents from *Table 3 Examples* or tests for unprocessed bulk harvest, as it better fits cell line production section.
Response: Comment not incorporated. The table is a general example and not mandatory.
Comment Summary #17: The commenter suggested removing **“**The drug substance is the final bulk antigen that will be combined with adjuvants and excipients that will be packaged in the final container–closure” from the *Drug Substances* section as it is more suitable for the *Drug Product* section.
Response: Comment incorporated.
Comment Summary #18: The commenter recommended adding a general statement in the *Lot Release Tests* section for tests chosen to assure control of process related critical quality attributes.
Response: Comment incorporated
Comment Summary #19: The commenter requested clarifications on clearly differentiating the requirements for different kind of viral vaccines.
Response: Comment incorporated. Added examples to the chapter.
Comment Summary #20: The commenter requested general harmonization throughout the chapter with CBER, EMA guidance, and *Ph. Eur.* monographs.
Response: Comment incorporated. Aligned text with regulatory guidance.

General Chapter/Sections: <1711> *Oral Dosage Forms—Performance Tests*/Multiple Sections
Expert Committee: General Chapters–Dosage Forms
No. of Commenters: 8

Comment Summary #1: The commenter suggested specifying if a dissolution test can replace a disintegration test for effervescent tablets that result in a suspension. If not, they suggested including that the dissolution test is in addition to the disintegration test.
Response: Comment not incorporated. A dissolution test always needs to be developed. It can be replaced by a disintegration test with appropriate justification.
Comment Summary #2: The commenter suggested that for effervescent and chewable tablets, when the paddle height is adjusted to a position greater than 2.5 cm, to add the recommendation to adjust the paddle speed to 50 rpm.
Response: Comment not incorporated. The rotation speed is selected in a case-by-case approach, supported by data obtained with the samples under evaluation.
Comment Summary #3: The commenter suggested including a statement that the dissolution test must account for the sustained release of the drug in the case of gastroretentive tablets.
Response: Comment not incorporated. The dissolution test conditions should be selected in a case-by-case approach.
Comment Summary #4: The hyperlink to the FDA guidance on high solubility products is incorrect.
Response: Comment incorporated.
Comment Summary #5: In Reference 2, the date is incorrect. This FDA guidance is from 1997.
Response: Comment incorporated.
Comment Summary #6: The title of the section *Dissolution Procedure Development* should be consistent with the changes in the chapter title.
Response: Comment incorporated.
Comment Summary #7: The commenter suggested clarifying that the performance test should be discriminative for the critical quality attributes that affect product performance.
Response: Comment not incorporated. It is included in the definition of critical quality attributes.
Comment Summary #8: The commenter questioned the need of developing a dissolution or a disintegration test for lozenges with topical/local action.
Response: Comment not incorporated. The text does not make any distinction between lozenges with topical/local and systemic actions, and the quality requirements are irrespective of the way of action.
Comment Summary #9: The commenter suggested including under *Suspensions,* the option of introducing the sample to the dissolution equipment by volume.
Response: Comment incorporated.
Comment Summary #10: The commenter questioned the need of having two separate sections for suspensions.
Response: Comment not incorporated. The chapter discusses the conditions for *Suspensions* and for *Powders for Oral Suspension, Granules for Oral Suspension, and Tablets for Oral Suspension* because of the differences on the dosage forms and on the dissolution conditions.
Comment Summary #11: In the section *Animal Feed and Animal Pre-mix Type A Medicated Articles and Type B and Type C Medicated Feeds*, there is a cross-reference to USP General Chapter <1152>. If the latter covers dissolution, the commenter is suggesting that this section could be removed from the proposed new General Chapter <1711>.

Response: Comment not incorporated. The USP General Chapter <1152> does not address dissolution of this type of veterinary products.
Comment Summary #12: The text states that for effervescent tablets it may be necessary to increase the distance between the paddle and the bottom of the vessel to accommodate bigger products. However, if that is done, the stirring hydrodynamics may not be adequate. Most effervescent products cease effervescence within a period of two to three minutes. The commenter suggested that an alternative may be to add the tablets without stirring and start the stirrer when all six tablets have ceased effervescence. This would maintain the hydrodynamics of the system.
Response: Comment not incorporated. The chapter allows the use of any conditions with appropriate justification.
Comment Summary #13: The commenter recommended including a calibration procedure when the paddle height is changed.
Response: Comment not incorporated. The *Performance Verification Test* for USP Apparatus 2 was developed only for the paddle height of 2.5 cm.
Comment Summary #14: The text states that for "Chewable tablets," the dissolution test should be conducted using intact tablets. The commenter suggested that the dissolution test should be conducted using both the intact and deformed tablets.
Response: Comment not incorporated. The test is done with intact tablets to simulate the worst case where the patient swallows the tablet without chewing it. The dissolution of deformed tablets may be investigated in a one time study.
Comment Summary #15: The commenter suggested adding that care should be taken to avoid having dosage forms with sustained release coating being hit by paddle or basket. For example, it is not appropriate to choose Apparatus 1 for the dissolution test of pellets, tablets, or capsules with sustained release coating.
Response: Comment not incorporated. No dosage form should be hit by the paddle, otherwise the test is considered not valid. The sample should be added to the vessel with the paddle not in motion.

General Chapter:	<1788> *Methods for the Determination of Subvisible Particulate Matter*
Expert Committee:	General Chapters–Dosage Form
No. of Commenters:	8

General
Comment Summary #1: The commenter suggested adding specific details on light obscuration, membrane microscopy and flow imaging to <1788>.
Response: Comment not incorporated. The chapter would be too long and difficult to navigate, plus specific details have been added to the subsequent chapters on the topics.
Comment Summary #2: The commenter recommended adding the flow imaging method to <788> *Particulate Matter in Injections*.
Response: Comment not incorporated. General Chapter <788> is a harmonized chapter and discussion and agreement would have to occur within the Pharmacopeial Discussion Group.

Introduction
Comment Summary #3: The commenter recommended giving more context around the position of intrinsic and extrinsic matter, visible and subvisible particles, and the purpose of subvisible particle testing.
Response: Comment incorporated.

Background

Comment Summary #4: The commenter suggested revising this section to focus more on the technical background of the methods, as opposed to historical developments.
Response: Comment incorporated.

Testing Considerations
Comment Summary #5: The commenter recommended adding text that vaccines are a type of protein-based pharmaceutical for which inherent particles are not a safety concern, but rather a desirable product quality attribute.
Response: Comment incorporated.
Comment Summary #6: The commenter recommended changing text to make ≥150 µm the upper threshold instead of ≥100 µm.
Response: Comment not incorporated. The ≥100 µm is the upper limit that is referenced in other USP chapters.
Comment Summary #7: The commenter recommended consolidating *Section 3.1 Testing Considerations* and *3.2 The Nature of Particulate Matter*.
Response: Comment not incorporated. The EC felt there was value in not consolidating.

Detection and Enumeration of Particles in Different Size Ranges
Comment Summary #8: The commenter recommended clarifying the chapter's guidance on adjuvanted vaccines.
Response: Comment incorporated.
Comment Summary #9: The commenter suggested adding clarity as to whether there is a need to justify choice of methods and to run an orthogonal method.
Response: Comment incorporated.

Applicability of Methods (Table 1)
Comment Summary #10: The commenter recommended adding Shlieren lines to the list of flow imaging artifacts.
Response: Comment incorporated.

USP Subvisible Particulate Matter Limits (Table 2)
Comment Summary #11: The commenter suggested that the table is difficult to interpret and should be reviewed.
Response: Comment incorporated.

Development
Comment Summary #12: The commenter suggested that choosing the appropriate particulate matter method/technique should also include some consideration of the particulates' shape/morphology.
Response: Comment incorporated.

Statistical Sampling Plan
Comment Summary #13: The commenter suggested revising the section for clarity and readability.
Response: Comment incorporated.

Elements of Measurement Quality Control
Comment Summary #14: The commenter suggested that the bulleted list is missing linearity/range and should be added.
Response: Comment incorporated.

Sample Handling (Degassing)
Comment Summary #15: The commenter suggests expanding the recommendations for degassing.
Response: Comment incorporated.

Pooled Samples (Formulae)
Comment Summary #16: The commenter recommended reviewing the formulae to ensure accuracy.
Response: Comment incorporated.

General Chapter: <1788.1> *Light Obscuration Method for the Determination of Subvisible Particulate Matter*
Expert Committee: General Chapters–Dosage Form
No. of Commenters: 3

Principles of Operation
Comment Summary #1: The commenter suggested changing “polystyrene latex microspheres” to "polystyrene microspheres" and "PSL" to "PS."
Response: Comment incorporated.

Mixing
Comment Summary #2: The commenter recommended including some discussion on the appropriate mixing method for biologics.
Response: Comment incorporated.

General Chapter: <1788.2> *Membrane Microscope Method for the Determination of Subvisible Particulate Matter*
Expert Committee: General Chapters–Dosage Form
No. of Commenters: 4

General
Comment Summary #1: The commenter suggested adding a discussion on modern analytical methods for counting particle loads, including the use of digital microscopes and the availability of particle analysis/image processing software.
Response: Comment not incorporated. General Chapter <1788.2> is meant to support <788> which includes manual based methods.

Introduction
Comment Summary #2: The commenter recommended removing the discussion of the membrane microscopy method from the *Introduction*.
Response: Comment not incorporated. The EC felt that it is appropriate to include a discussion of the membrane microscopy method in the *Introduction*.

Instrument Dynamic Range
Comment Summary #3: The commenter recommended clarifying the size threshold requirements for the dynamic range.
Response: Comment incorporated.

Sample Preparation
Comment Summary #4: The commenter recommended removing the details from <1788> and adding it into <1788.2>.

Response: Comment not incorporated. The EC felt the current organization of the chapters are appropriate.

Particle Enumeration
Comment Summary #5: The commenter recommended reviewing the section to ensuring consistency of symbols and how they are used.
Response: Comment incorporated.

Automated Approach
Comment Summary #6: The commenter recommended expanding the discussion of modern analytical methods in this chapter.
Response: Comment not incorporated. The first section describes the issues associated with human operations in order to set up the advantages of automated systems. It also describes the elements of assay control that automated systems must control.

General Chapter: <1788.3> *Flow Imaging Method for the Determination of Subvisible Particulate Matter*
Expert Committee: General Chapters–Dosage Form
No. of Commenters: 4

Introduction
Comment Summary #1: The commenter suggested using “Micro-flow Imaging” (“MFI” instead of “Flow Imaging (FI)”).
Response: Comment not incorporated. Micro-flow Imaging is a brand name.
Comment Summary #2: Commenter recommended stating that flow imaging is a useful orthogonal method to light obscuration and membrane microscopy.
Response: Comment incorporated.

Principles of Operation
Comment Summary #3: The commenter recommended clarifying that the process of assigning particle types is manual.
Response: Comment incorporated.
Comment Summary #4: The commenter suggested that the optical configuration is most important for obtaining high quality images and this should be reflected in the text.
Response: Comment not incorporated. There are other important imaging attributes that contributes to image quality.
Comment Summary #5: The commenter recommended adding more specific instruction regarding a specific instrument.
Response: Comment not incorporated. The EC determined that the chapter should not include specific instructions for a given instrument.
Comment Summary #6: The commenter recommended adding text around particle libraries.
Response: Comment incorporated.

Sample Flow Rate
Comment Summary #7: The commenter suggested that flow rate on some instruments are fixed and should be noted.
Response: Comment incorporated.

Qualification Consideration
Comment Summary #8: The commenter suggested including text that daily operational checks are normally not required or only performed if the instrument is not operated every day.

Response: Comment incorporated.
Comment Summary #9: The commenter recommended changing "polystyrene latex microspheres" to "polystyrene microspheres" and “PSL” to “PS.”
Response: Comment incorporated.
Comment Summary #10: Commenter suggested that highly opalescent sample that use Polysorbate 20 may be obscured.
Response: Comment not incorporated. Although the EC agreed with the comment, the EC determined that there was no need to edit any text.
Comment Summary #11: Commenter suggested that not all systems have software recognition, and this should be stated in the chapter.
Response: Comment incorporated.
Comment Summary #12: The commenter suggested clarifying that size range may depend on the system manufacturer and the optical configuration.
Response: Comment incorporated.
Comment Summary #13: The commenter suggested that particle size should be associated with the count for system suitability.
Response: Comment incorporated.

Particle Counting Accuracy (System Suitability)
Comment Summary #14: Commenter suggested that larger particle count standard sizes are available, and sizes used for the assay should cover the measurement range.
Response: Comment not incorporated. The size range was not changed, but clarifying text was added.
Comment Summary #15: Commenter suggested adding flexibility to the sample counts for suspensions.
Response: Comment incorporated.
Comment Summary #16: The commenter recommends adding guidance on viscosity modifiers, such as sucrose.
Response: Comment incorporated.
Comment Summary #17: The commenter suggests removing the statement about existing particles, because it is not clear what particles are being referenced.
Response: Comment incorporated.

Flow Imaging Calculations
Comment Summary #18: The commenter suggested including the equation for calculating particle load.
Response: Comment incorporated.

Appendix
Comment Summary #19: The commenter recommended that for identifying a range of particle bins that are symmetric, a sample equation should be given.
Response: Comment incorporated.
Comment Summary #20: Commenter recommended removing the following statement, “Filter the data to remove any particles with circularity < 0.85 and then generate a PSD with bin sizes not more than 0.25 µm.”
Response: Comment incorporated.
Comment Summary #21: The commenter suggested adding clarity as to whether automated methods can only be used if vendors supply written certification.
Response: Comment incorporated.
Comment Summary #22: Commenter suggested adding text describing the nature of field technicians vs. factory settings during the instrument verification process.

Response: Comment incorporated.

General Chapter: <1912> *Measurement of Hardness of Semisolids*
Expert Committee: General Chapters–Physical Analysis
No. of Commenters: 1

Oscillation Amplitude Sweep Measurements
Comment Summary #1: The commenter requested the introduction of units used earlier in the chapter "rad/s" in the following sentence for consistency: "Most amplitude sweep experiments will use 1 Hz or 10 radian/s as a default frequency."
Response: Comment incorporated.

Penetrometry Measurements
Comment Summary #2: The commenter recommended stating the same temperature range for testing stated in <915> for consistency.
Response: Comment not incorporated. The testing temperature was adjusted per previous public comments received during the first proposal published in *PF*.
Comment Summary #3: The commenter suggested the introduction of the two penetrometer cone figures from ASTM-217-D2.
Response: Comment not incorporated. The two penetrometer cone figures were proposed in the first proposal of this chapter in *PF*. Based on public comments, it was decided to keep only the one equivalent in the *European Pharmacopoeia* most widely used by pharmaceutical industry with the same definition, and introducing one new procedure using a needle for other future applications.

Monographs

Monograph/Sections: Abacacvir Lamivudine and Zidovudine Tablets/Multiple Sections
Expert Committee: Chemical Medicines Monographs 1
No. of Commenters: 1

Comment Summary #1: The commenter commented that the dissolution tolerance is tighter for their approved product in the *Dissolution* test.
Response: Comment not incorporated. The EC determined that the proposed tolerances are consistent with FDA-approved application.
Comment Summary #2: The commenter recommended replacing the UV procedure with the modern HPLC procedure for *Dissolution*.
Response: Comment not incorporated. The EC will consider future revisions to the monograph upon receipt of additional supporting data.
Comment Summary #3: The commenter commented that the specification and method in the test for *Organic Impurities* are different for their product.
Response: Comment not incorporated. The EC determined that the proposed procedure is consistent with the sponsor's FDA-approved application. The EC will consider a future revision to the monograph upon receipt of the supporting data.
Comment Summary #4: The commenter requested clarifying the footnote "b" in Table 2 in the test for *Organic Impurities*.
Response: Comment incorporated. The footnote "b" is updated to remove the statement "not included in the total impurities content."

Monograph/Section: Albuterol Inhalation Solution/*Organic Impurities*
Expert Committee: Chemical Medicines Monographs 4
No. of Commenters: 3

Comment Summary #1: Commenter indicated that the limit of *Any unspecified degradation product* is not consistent with ICH Q3B identification threshold and recommended revising the limit to match ICH Q3B.
Response: Comment incorporated. The limit for *Any unspecified degradation product* was widened from 0.10% to 0.1% for consistency with what has been approved.
Comment Summary #2: Commenter requested changing the degradation product specifications to values which are not part of FDA-approved applications.
Response: Comment not incorporated. The requested changes are not suitable for inclusion in the *USP-NF*.
EC-Initiated Change #1: The preparation of *Solution A* in the *Assay* is clarified.
EC-Initiated Change #2: The chemical name of the specified impurity deshydroxy albuterol is updated to be consistent with IUPAC nomenclature guidelines.

Monograph/Section: Amlodipine Besylate Tablets/*Organic Impurities*
Expert Committee: Chemical Medicines Monographs 2
No. of Commenters: 2

Comment Summary #1: The commenter indicated that the acceptance criterion for *Total Impurities* is different from what has been approved by the FDA.
Response: Comment not incorporated. The acceptance criterion is consistent with the FDA-approved applications and the EC will consider a future revision upon receipt of supporting data.
EC-Initiated Change #1: The “besylate” is removed from “Amlodipine besylate” in Table 1 because the chemical name refers to the analyte.

Monograph/Sections: Atomoxetine Hydrochloride/Multiple Sections
Expert Committee: Chemical Medicines Monographs 4
No. of Commenters: 0

EC-Initiated Change #1: One of the chemical names for atomoxetine hydrochloride and a chemical name for atomoxetine related compound C are updated for consistency with current USP style.
EC-Initiated Change #2: The information provided in the USP Reference Standards <11> section has been updated to acknowledge that USP Atomoxetine Related Compound B RS may be available as the *R*-isomer or as a racemic mixture. The chemical names of USP Atomoxetine Related Compound B RS and USP Atomoxetine *S*-Isomer RS has been updated for consistency with current USP style.

Monograph/Sections: Azithromycin for Oral Suspension/Multiple Sections
Expert Committee: Chemical Medicines Monographs 1
No. of Commenters: 2

Comment Summary #1: The commenter recommended elaborating the type of sodium phosphate buffer used in the preparation of dissolution medium in the *Dissolution* test.
Response: Comment incorporated. The preparation of sodium phosphate buffer is updated to include disodium hydrogen orthophosphate anhydrous in water.

Comment Summary #2: The commenter recommended revising limits for “Azithromycin N-oxide, N-Demethylazithromycin, “3’- De(dimethylamino)-3’-oxoazithromycin”, and total degradation products in the test for *Organic Impurities*.
Response: Comment not incorporated. The EC will consider a future revision to the monograph upon receipt of supporting data.
Comment Summary #3: The commenter recommended removal of the statement of “Disregard any peaks at relative retention times before 0.29 and after 1.31” in the test for *Organic Impurities*.
Response: Comment not incorporated. The EC determined that it is consistent with the validation data and will consider a future revision to the monograph upon receipt of supporting data.

Monograph/Sections: Baclofen Injection/Multiple Sections
Expert Committee: Chemical Medicines Monographs 4
No. of Commenters: 1

Comment Summary #1: The commenter requested revising the acceptance criteria for the *Assay*, *pH*, *Osmolality,* and baclofen related compound A within the test for *Organic Impurities* to be consistent with what has been approved.
Response: Comment not incorporated. The acceptance criteria reflect the specifications of a company with an approved application. 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 the test for *Organic Impurities*.
Response: Comment not incorporated. Based on comments received on a proposed policy change 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.

Monograph/Sections: Benazepril Hydrochloride and Hydrochlorothiazide Tablets / /Multiple Sections
Expert Committee: Chemical Medicines Monographs 2
No. of Commenters: 2

Comment Summary #1: The commenter indicated that their approved tolerances for the *Dissolution* test are different from the ones in the proposal and requested to add a new *Dissolution* test based on their FDA-approved application.
Response: Comment not incorporated. The EC decided to add the *Dissolution Test 2* via the revision bulletin process to reflect the approved dissolution tolerances.
Comment Summary #2: The commenter requested widening the acceptance criterion for total degradation products by excluding benzothiadiazine related compound A, in addition to benazepril related compound C.
Response: Comment incorporated.

Monograph/Section: Benztropine Mesylate/*Organic Impurities*
Expert Committee: Chemical Medicines Monographs 4
No. of Commenters: 2

Comment Summary #1: The commenters requested revising the acceptance criterion for all specified, unspecified, and total impurities for consistency with what has been approved.

Response: Comment not incorporated. The acceptance criteria reflect the specifications of an approved application. The EC will consider future revisions to the monograph upon receipt of supporting data.
EC-Initiated Change #1: The chemical information in the USP Reference Standards <11> section is updated.

Monograph/Sections: Bifidobacterium Bifidum/Multiple Sections
Expert Committee: Non-Botanical Dietary Supplements and Herbal Medicines
No. of Commenters: 0

Definition
EC-Initiated Change #1: Changes were incorporated into the *Definition* to describe both species and individual strain characteristics.

Identification
EC-Initiated Change #2: To align the *Definition* with test requirements in relation to microscopic features of individual strains, a new *Identification* test (*Identification* test *A. Microscopic test*), was incorporated.
EC-Initiated Change #3: In the *Identification* test *B. Nucleic Acid-Based Identification*, a new PCR positive control was incorporated proposing the use of either the genomic DNA of the reference strain or species-specific universal primers for *Bifidobacterium bifidum*.

Assay
EC-Initiated Change #4: The *Assay (Enumeration)* section has been referenced to General Chapter <64> *Probiotic Tests*.

Contaminants
EC-Initiated Change #5: The *Contaminants* section has been referenced to General Chapter <64> *Probiotic Tests* (except for *Listeria,* which is still referenced to the *Food Chemicals Codex*, Appendix XV).

Monograph/Sections: Bifidobacterium longum subsp. longum/Multiple Sections
Expert Committee: Non-Botanical Dietary Supplements and Herbal Medicines
No. of Commenters: 1

Definition
EC-Initiated Change #1: Changes were incorporated into the *Definition* to describe both species and individual strain characteristics.

Identification
EC-Initiated Change #2: To align the *Definition* with test requirements in relation to microscopic features of individual strains, a new *Identification* test (*Identification* test *A. Microscopic test*) was incorporated.
EC-Initiated Change #3: In the *Identification* test *B. Nucleic Acid-Based Identification,* a new PCR positive control was incorporated proposing the use of either the genomic DNA of the reference strain or species-specific universal primers for *Bifidobacterium longum* subsp. *longum*.
Comment summary #1: In relation to the acceptance criteria (amplification product of 164 base pairs) proposed in *Identification* test *A. Nucleic Acid Based Identification,* the commenter indicated:

- The proposed nucleic acid-based PCR identification without further data is only applicable for the monographed strain *B. longum* subsp. *longum* BI-05, and it is also not a reliable identification method.
- Since the proof (or reference) that the DNA interface used is congruent with other strains of *B. longum* subsp. *longum* is missing, the taxonomic justification of the identity is not clarified and therefore cannot be generally transferred to other strains of the species mentioned.
- In addition, not even the proof of the strain affiliation to the subspecies (subsp. *longum*) and the identity of the strain (BI-05) can be inferred beyond doubt, since data on biochemical and physiological characteristics are missing (e.g., "colorful series").

Response: Comment partially incorporated. The PCR method proposed in *Identification* test A. *Nucleic Acid-Based Identification* was designed specifically for the identification of *Bifidobacterium longum* subsp. *longum*. BL-05, which is currently the only strain covered by the monograph. Primers were screened against all public and available strains including BL-05. Cross testing was performed on 3 strains of the same subspecies that are the most closely related ones. Method validation information is not typically a part of the monograph and is proprietary. In addition, in the *Identification* test *B. Nucleic Acid-Based Identification,* a new PCR positive control was incorporated proposing the use either the genomic DNA of the reference strain or species-specific universal primers *for Bifidobacterium longum* subsp. *longum*. USP will incorporate other strains of *Bifidobacterium longum* subsp. *longum*. into this monograph upon the receipt of the corresponding supporting information.

Assay
EC-Initiated Change #4: The *Assay (Enumeration)* section has been referenced to General Chapter <64> *Probiotic Tests*.

Contaminants
EC-Initiated Change #5: The *Contaminants* section has been referenced to General Chapter <64> *Probiotic Tests* (except for *Listeria,* which is still referenced to the *Food Chemicals Codex*, Appendix XV).

Monograph/Sections: Calcipotriene/Multiple Sections
Expert Committee: Chemical Medicines Monographs 3
No. of Commenters: 1

Comment Summary #1: The commenter requested removing the ‘reporting threshold’ from the test for *Organic Impurities, Procedure 1*.
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 the correction of the chemical name of impurity A for *Organic Impurities, Procedure 2*.
Response: Comment incorporated.
EC-Initiated Change #1: The chemical name of impurity B in *Organic Impurities, Procedure 1* is corrected and the name of precalcipotriene in *Organic Impurities, Procedure 2* is revised.

Monograph/Sections: Calcium Magnesium Citrate/Multiple Sections
Expert Committee: Non-Botanical Dietary Supplements
No. of Commenters: 0

EC-Initiated Change #1: The EC suggested a change to the chromatographic column temperature in the *Content of Calcium and Magnesium* procedure from 30° to 35°. It is also suggested to change the acceptance criteria for tailing factor from 2.0 to 2.
Response: Comment incorporated.
EC-Initiated Change #2: The EC suggested removing the USP Calcium Magnesium Citrate RS from the USP Reference Standards section of the monograph and the respective sections where it is used.
Response: Comment incorporated.

Monograph/Section: Carbidopa and Levodopa Tablets/*Organic Impurities*
Expert Committee: Chemical Medicines Monographs 4
No. of Commenters: 1

Comment Summary #1: The commenter requested widening the acceptance criteria for dihydroxyphenylacetone from NMT 1.0% to NMT 1%.
Response: Comment not incorporated. The EC has decided that an acceptance criteria of NMT 1.0% for dihydroxyphenylacetone is appropriate for inclusion in the public standard.
Comment Summary #1: The commenter requested removing the reference to methyldopa from the test for *Organic Impurities*.
Response: Comment not incorporated. The EC has decided that the current reference to methyldopa is appropriate for inclusion in the public standard. The EC will consider future revisions to the monograph upon receipt of supporting data.

Monograph/Sections: Carbomer Copolymer/Multiple Sections
Expert Committee: Excipients Monographs 1
No. of Commenters: 1

Comment Summary #1: The commenter recommended changing the units of one of the equivalency factor (F) in the equation for the *Carboxylic Acid Content* test from “mEq/mg” to “mg/mEq.”
Response: Comment incorporated.
Comment Summary #2: The commenter recommended removing “on the dried basis” from the acceptance criteria of the *Carboxyl Acid Content* test because it is unnecessary since the sample must be “previously dried under vacuum at 80° for 1 h.”
Response: Comment incorporated.
Comment Summary #3: The commenter recommended adding the column pore size (5 micron) into the column description in the *Limit of Acrylic Acid* test.
Response: Comment incorporated.
Comment Summary #4: The commenter recommended changing the calculation in the *Limit of Acrylic Acid* test from “Result (wt%) = (r / RF) × C × F × 100” to “Result (wt%) = (r / RF) / C × F × 100.”
Response: Comment incorporated.

Monograph/Sections: Carbomer Homopolymer/Multiple Sections
Expert Committee: Excipients Monographs 1
No. of Commenters: 1

Comment Summary #1: The commenter recommended changing the units of one of the equivalency factor (F) in the equation for the *Carboxylic Acid Content* test from “mEq/mg” to “mg/mEq.”
Response: Comment incorporated.
Comment Summary #2: The commenter recommended removing “on the dried basis” from the acceptance criteria of the *Carboxyl Acid Content* test because it is unnecessary since the sample must be “previously dried under vacuum at 80° for 1 h.”
Response: Comment incorporated.
Comment Summary #3: The commenter recommended adding the column pore size (5 micron) into the column description in the *Limit of Acrylic Acid* test.
Response: Comment incorporated.
Comment Summary #4: The commenter recommended changing the calculation in *the Limit of Acrylic Acid* test from “Result (wt%) = (r /RF) × C × F × 100” to “Result (wt%) = (r /RF) / C × F × 100.”
Response: Comment incorporated.

Monograph/Sections: Carbomer Interpolymer/Multiple Sections
Expert Committee: Excipients Monographs 1
No. of Commenters: 1

Comment Summary #1: The commenter recommended changing the units of one of the equivalency factor (F) in the equation for the *Carboxylic Acid Content* test from “mEq/mg” to “mg/mEq.”
Response: Comment incorporated.
Comment Summary #2: The commenter recommended removing “on the dried basis” from the acceptance criteria of the *Carboxyl Acid Content* test because it is unnecessary since the sample must be “previously dried under vacuum at 80° for 1 h.”
Response: Comment incorporated.
Comment Summary #3: The commenter recommended adding the column pore size (5 micron) into the column description in the *Limit of Acrylic Acid* test.
Response: Comment incorporated.
Comment Summary #4: The commenter recommended changing the calculation in the Limit of Acrylic Acid test from “Result (wt%) = (r /RF) × C × F × 100” to “Result (wt%) = (r /RF) / C × F × 100.”
Response: Comment incorporated.

Monograph/Section: Cefepime for Injection/*Organic Impurities*
Expert Committee: Chemical Medicines Monographs 1
No. of Commenters: 1

Comment Summary #1: The commenter commented to include acceptance criterion for Cefepime Related Compound B (Cefepime Dioxime) impurity to be consistent with FDA-approved application in test for *Organic Impurities*.
Response: Comment not incorporated. The EC determined that Cefepime Dioxime is a process impurity controlled in the drug substance monograph and should not be included in the drug product monograph.
Comment Summary #2: The commenter recommended not to replace the statement for reporting level with reporting threshold in the test for *Organic Impurities.*
Response: Comment incorporated. The EC removed the proposed changes to the reporting level in Table 2 in the test for *Organic Impurities*.

EC-Initiated Change #1: In the *Assay*, the calculation has been updated to account for the potency of the USP Cefepime Hydrochloride RS in terms of cefepime.

Monograph/Sections: Cetirizine Hydrochloride/Multiple Sections
Expert Committee: Chemical Medicines Monographs 5
No. of Commenters: 1

Comment Summary #1: The commenter requested removing the reporting threshold from *Organic Impurities, Procedure 1* and *Organic Impurities, Procedure 2*.
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 chemical name for Cetirizine Related Compound A in Table 1, footnote d will be removed to be consistent with current USP style and subsequent footnotes in the same table will be renumbered. The chemical information (chemical name and molecular weight) for Cetirizine Related Compound A in Reference Standards <11> will be revised to include an alternate chemical name, Ethyl 2-[2-{4-[(4-chlorophenyl)(phenyl)methyl]piperazin-1-yl}ethoxy]acetate oxalate salt, in order to be consistent with the current USP naming convention. The molecular weight will be changed from 506.98 to 506.97 to be consistent with information available in the International Union of Pure and Applied Chemistry (IUPAC).

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

Comment Summary #1: The commenter indicated that the acceptance criterion for total degradation products is different from what has been approved by the FDA.
Response: Comment not incorporated. The proposed acceptance criterion is consistent with the sponsor's FDA-approved application. The EC will consider future revisions to the monograph upon receipt of supporting data.
Comment Summary #2: The commenter requested removing cilostazol related compound A and cilostazol related compound B from the *Acceptance Criteria* section, which are not controlled as impurities to provide the flexibility to allow the control of these impurities in other FDA approved applications.
Response: Comment incorporated. Cilostazol related compound A and cilostazol related compound B were removed from the *Acceptance Criteria* section and their relative retention times were added in the *System Suitability* section, below *Samples.*

Monograph/Sections: Clarithromycin Extended-Release Tablets/Multiple Sections
Expert Committee: Chemical Medicines Monographs 1
No. of Commenters: 3

Comment Summary #1: The commenter recommended adding an orthogonal test for *Identification*.
Response: Comment not incorporated. The EC will consider a future revision to the monograph upon receipt of supporting data.
Comment Summary #2: The commenter recommended removing the statements "Not more than four impurities exceed 0.4%" and "Disregard the peaks eluting before impurity I and after impurity H" from Table 7 in the test for *Organic Impurities*.

Response: Comment not incorporated. The EC determined that it is consistent with the validation data and will consider a future revision to the monograph upon receipt of supporting data.
Comment Summary #3: The commenter recommended removing process impurities, Clarithromycin impurity A, Clarithromycin impurity F, Clarithromycin impurity H from the table in the test for *Organic Impurities*.
Response: Comment not incorporated. The EC recommended to include process impurities in the table to aid the manufacturers in identifying them based on retention time. USP intends to do further stakeholder engagement on the topic.
Comment Summary #4: The commenter requested removing the "reporting threshold" from the test for *Organic Impurities*.
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 #5: The commenter recommended including additional specified impurity or degradation impurities in the test for *Organic Impurities*.
Response: Comment not incorporated. The EC will consider a future revision to the monograph upon receipt of supporting data.
Comment Summary #6: The commenter requested widening the limit for any individual unspecified impurity from 0.20% to 0.2% in the test for *Organic Impurities*.
Response: Comment incorporated.

Monograph/Section: Clobetasol Propionate Ointment/*Organic Impurities*
Expert Committee: Chemical Medicines Monographs 5
No. of Commenters: 1

Comment Summary #1: The commenter recommended revising the impurity profile and acceptance criteria to include additional degradation products to be consistent with FDA-approved products.
Response: Comment not incorporated. The proposed impurity profile and *Acceptance criteria* are consistent with the sponsor's FDA-approved application. The EC will consider a future revision upon receipt of supporting data.
Comment Summary #2: The commenter recommended revising the limit for total degradation products to be consistent with FDA-approved products.
Response: Comment not incorporated. The proposed *Acceptance criteria* for total degradation products is consistent with the sponsor's FDA-approved application. The EC will consider a future revision upon receipt of supporting data.
Comment Summary #3: 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. USP intends to do further stakeholder engagement on the topic.

Monograph/Sections: Clonazepam Tablets/Multiple Sections
Expert Committee: Chemical Medicines Monographs 4
No. of Commenters: 2

Comment Summary #1: The commenter requested retaining the *Relative Standard Deviation* requirement of NMT 2.0% in the *Assay* to be aligned with the corresponding requirement test for *Organic Impurities*.
Response: Comment not incorporated. The *Relative Standard Deviation* of NMT 1.0% is appropriate for use in the *Assay*.
Comment Summary #2: The commenter requested removing the *Tailing factor* requirement from the test for *Organic Impurities* as it is not necessary.
Response: Comment not incorporated. The *Tailing factor* requirement is appropriate for inclusion in the test for *Organic Impurities*.
Comment Summary #3: The commenter requested adding a chemical name to the unknown impurity with a relative retention time of 0.7 and a relative response factor of 0.41.
Response: Comment not incorporated. No revision to this portion of the monograph was proposed. The EC will consider future revisions to the monograph upon receipt of supporting data.
Comment Summary #4: The commenter requested removing the "reporting threshold" from the test for *Organic Impurities*.
Response: Comment not incorporated. Based on comments received on a proposed policy change 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.

Monograph/Sections:	Clonidine Hydrochloride Extended-Released Tablets /Multiple Sections
Expert Committee:	Chemical Medicines Monographs 2
No. of Commenters:	5

Comment Summary #1: Commenter suggested replacing the TLC-based method in *Identification A* with UV spectra agreement obtained from *Assay*.
Response: Comment is not incorporated. There is no distinct UV spectrum profile for clonidine at the concentration used in the *Assay*. The EC determined the proposed TLC-based method is more suitable for its intended use.
Comment Summary #2: The commenter indicated that dissolution conditions and tolerances for the *Dissolution* test are different from what has been approved by the FDA, and the *Dissolution* test may not be suitable for some other approved products.
Response: Comment not incorporated. The proposed dissolution test is consistent with the sponsor's approved application. The EC decided to add dissolution tests for other approved manufacturers' products via revision bulletin process.
Comment Summary #3: The commenter indicated that the acceptance criteria for "Any unspecified degradation product "Total degradation products" in *Organic Impurities* test are different from what has been approved by the FDA. The commenter recommended revising the acceptance criteria to be consistent with what has been approved by the FDA.
Response: Comment incorporated. The acceptance criteria for "Any unspecified degradation product" and "Total degradation products" are widened from NMT 0.5% and 1.0% to 1.0% and 3.0%, respectively.
Comment Summary #4: The commenter suggested their method be adopted for the *Organic Impurities* test.
Response: Comment not incorporated. The EC determined that the proposed *Organic Impurities* method is suitable for intended use and the manufacturer can use alternative procedures as described in *USP General Notices* 6.30. *Alternative and Harmonized Methods and Procedures*.

Monograph/Section: Clozapine/*Organic Impurities*
Expert Committee: Chemical Medicines Monographs 4
No. of Commenters: 2

Comment Summary #1: The commenter requested removing "clozapine *N*-oxide" and "2-amino-4-chlorofenamic acid" from the monograph.
Response: Comment incorporated.
Comment Summary #2: The commenter requested retaining the currently official test for *Organic Impurities* as the proposed procedure does not provide significant improvement and is not sufficiently robust.
Response: Comment incorporated. The text was updated to reflect current USP style, but the scientific content was retained.
EC-Initiated Change #1: The relative retention time for benzoyl methylpiperazine analog is updated for consistency with the currently official text.
EC-Initiated Change #2: The chemical information for USP Clozapine Resolution Mixture RS was updated for consistency with the current USP style.

Monograph/Section: Clozapine Tablets/*Organic Impurities*
Expert Committee: Chemical Medicines Monographs 4
No. of Commenters: 3

Comment Summary #1: The commenter requested removing "2-amino-4-chlorofenamic acid" from the monograph.
Response: Comment incorporated.
Comment Summary #2: The commenter requested removing the references to demethyl clozapine from the monograph as it is known to be a process impurity.
Response: Comment not incorporated. Under certain circumstances, this compound can be a photodegradation product.
Comment Summary #3: The commenters requested removing the references to didiazepinyl piperazine from the monograph as it is known to be a process impurity.
Response: Comment incorporated. The compound was removed from the table and the relative retention time is provided within a Note in the *System suitability* subsection.
Comment Summary #4: The commenters requested widening the acceptance criterion for total impurities for consistency with what has been approved.
Response: Comment incorporated.
Comment Summary #5: The commenter requested removing the 'reporting threshold' from the test for *Organic Impurities*.
Response: Comment not incorporated. Based on comments received on a proposed policy change 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 chemical information for USP Clozapine Resolution Mixture RS was updated for consistency with the current USP style.

Monograph/Section: Codeine Phosphate/*Organic Impurities*
Expert Committee: Chemical Medicine Monographs 2
No. of Commenters: 2

Comment Summary #1: The commenter indicated that the acceptance criterion for codeine methyl ester is different from that in the FDA-approved applications.

Response: Comment not incorporated. The acceptance criterion for codeine methyl ester is consistent with the FDA approved sponsor's application. The EC will consider future revisions upon receipt of supporting data.
EC-Initiated Change #1: The percentage specified for each component in USP Codeine System Suitability Mixture RS was removed to be consistent with the USP Certificate.

Monograph/Section: Dacarbazine/USP Reference Standards
Expert Committee: Chemical Medicines Monographs 3
No. of Commenters: 0

EC-Initiated Change #1: The chemical information for USP Dacarbazine Related Compound B RS is updated by including monohydrate to be consistent with the Reference Standard label.
EC-Initiated Change #2: The molecular weight is updated for USP Dimethylamine Solution RS from 45.08 to 45.09 to be consistent with the Reference Standard label.

Monograph/Section: Dacarbazine for Injection/*Organic Impurities*
Expert Committee: Chemical Medicines Monographs 3
No. of Commenters: 2

Comment Summary #1: The commenter requested removing the "reporting threshold" from the test for *Organic Impurities.*
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 chemical information for USP Dacarbazine Related Compound B RS is updated by including monohydrate to be consistent with the Reference Standard label.

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

Comment Summary #1: The commenter requested removing the "reporting threshold" from the test for *Organic Impurities.*
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 on the topic.

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

Comment Summary #1: The commenter requested revising the relative response factor for doxepin related compound A to be more consistent with their correction factor of 0.79.
Response: Comment incorporated. The relative response factor was revised from 1.2 to 1.26.
EC-Initiated Change #1: The chemical name for doxepin related compound C is corrected.

Monograph: Edetate Disodium Compounded Ophthalmic Solution
Expert Committee: Compounding
No. of Commenters: 1

Comment Summary #1: The commenter noted that there is an inconsistency between the proposed pH specification 6.1-7.1 and the information in the compounding section of the monograph which indicates that the pH is to be adjusted between 6.5 and 7.5. Without additional information, that commenter stated that it is not possible to provide a recommendation on how to modify the monograph. However, they recommended that the supportive information be reviewed and appropriate changes be incorporated in the monograph.
Response: Comment Incorporated. The pH range was adjusted to 6.1 – 7.1.
Comment Summary #2: The commenter noted that the *Specific Tests - Particulate Matter in Ophthalmic Solutions* may not be appropriate since Edetate Disodium Compounded Ophthalmic Solution is used topically. Topical solutions should reference General Chapter <788> *Particulate Matter in Injections*. General Chapter <789> *Particulate Matter in Ophthalmic Solutions* is to be referenced when testing for particulate matter in intraocular solutions.
Response: Comment partially incorporated. The EC removed the specification for the requirement for particulate matter testing.
Comment Summary #3: The commenter noted that under the *Packaging and Storage* section that the product should be packaged in a "10-mL sterile single-dose dropper." The commenter noted that they are not aware of any sterile single-dose "droppers" for ophthalmic products and are concerned that the proposed phrasing will encourage compounders to package the product in a syringe. Therefore, depending on whether the intent is to package the product in an ophthalmic dropper bottle or a syringe, the commenter recommended that the phrasing be revised to read: "sterile single-dose ophthalmic dropper bottle" or "sterile single-dose syringe." The commenter noted that these variations of both options appear in currently official monographs for compounded ophthalmic drug products.
Response: Comment incorporated. The EC clarified the packaging and storage statement to read "Package in sterile plastic ophthalmic single-unit container for use in one patient only."
Comment Summary #4: The commenter recommended adding a statement to the labeling section to indicate that this product is for topical use only or for topical application to the eye. The commenter also recommended adding a statement to indicate that the product is not for injection.
Response: Comment partially incorporated. The EC clarified the labeling statement to read "Label it to indicate that it is for ophthalmic use only."

Monograph/Section: Epinephrine Bitartrate/*Organic Impurities*
Expert Committee: Chemical Medicines Monographs 6
No. of Commenters: 1

Comment Summary: The commenter indicated that the proposed acceptance criterion for norepinephrine is not consistent with the FDA approved limits.
Response: Comment incorporated. The acceptance criterion for norepinephrine is widened from NMT 0.10% to NMT 0.15% to be consistent with the FDA approved application.

Monograph/Section: Escitalopram Oral Solution/*Organic Impurities*
Expert Committee: Chemical Medicines Monographs 4
No. of Commenters: 1

Comment Summary #1: The commenter requested removing the "reporting threshold" from the test for *Organic Impurities*.
Response: Comment not incorporated. Based on comments received on a proposed policy change 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.

Monograph/Sections: Esomeprazole Magnesium/Multiple Sections
Expert Committee: Chemical Medicines Monographs 3
No. of Commenters: 3

Comment Summary #1: The commenter recommended retaining either both tests of *Identification B* and *Content of Magnesium* by atomic absorption spectrophotometry or, at least, the test of *Identification B* for the specificity of the method.
Response: Comment incorporated. Both tests are retained.
Comment Summary #2: The commenter recommended retaining the current acceptance criteria of 3.30– 3.55% for the *Content of Magnesium*.
Response: Comment incorporated. The EC will consider future revisions to the monograph upon receipt of the supporting data.
Comment Summary #3: The commenter recommended retaining the test for *Color of Solution* for the degradation products that can't be determined by the test for *Organic Impurities*.
Response: Comment incorporated.

Monograph/Section: Exemestane Tablets/*Organic Impurities*
Expert Committee: Chemical Medicines Monographs 3
No. of Commenters: 4

Comment Summary #1: The commenter requested revising the limits for several impurities and total degradation products in the *Organic Impurities* test to be consistent with the FDA-approved specifications.
Response: Comments incorporated. The acceptance criterion for the following impurities are changed as below:

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Exemestane related compound B	0.41	0.4
6-Oxo Boldione	0.42	0.7
Exemestane methanesulfonate analog	0.49	—
Exemestane oxide 1	0.53	1.0
Exemestane oxide 2	0.60	1.0
Exemestane methoxy ether	0.77	—
Exemestane related compound C	0.80	—
Exemestane	1.0	—
Exemestane related compound A	1.12	0.4
Any unspecified degradation product	—	0.2
Total degradation products	—	2.0

Comment Summary #2: The commenter requested to delete the footnote reference indicating it is a process impurity in the *Acceptance Criteria* table in order to be consistent with the FDA-approved specifications.

Response: Comment not incorporated. The EC has decided that the identified process impurities do not need to be reported or included in the total degradation products.
Comment Summary #3: The commenter requested to replace the "Any unspecified impurity" with "Any unspecified degradation product" and the "Total unspecified impurities" with "Total degradation products" in the *Acceptance Criteria* table as only degradation products are monitored by this monograph.
Response: Comment incorporated.
Comment Summary #4: The commenter requested to tighten the limits for impurities in the *Acceptance Criteria* table based on their FDA-approved specification.
Response: Comment not incorporated. The proposed limits are consistent with the FDA-approved specifications.

Monograph/Section: Felodipine/USP Reference Standards <11>
Expert Committee: Chemical Medicines Monographs 2
No. of Commenters: 0

EC-Initiated Change #1: The chemical name of "Ethyl 3-Aminocrotonate RS" is revised from "Ethyl 3-aminobut-2-enoate to Ethyl (Z)-3-aminobut-2-enoate" to reflect the Z configuration of the RS.

Monograph/Section: Fentanyl Citrate/*Organic Impurities*
Expert Committee: Chemical Medicines Monographs 2
No. of Commenters: 2

Comment Summary #1: The commenter recommended 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. USP intends to do further stakeholder engagement on the topic.
Comment Summary #2: The commenter indicated that the specified impurity of fentanyl pyruvyl analog is not controlled as specified impurity in their approved specification.
Response: Comment not incorporated. Fentanyl pyruvyl analog can be controlled as any unspecified impurity at the limit of NMT 0.10% from the commenter's specifications which is within the proposed limit for fentanyl pyruvyl analog at NMT 0.15%.

Monograph/Sections: Ferumoxides Injection/Multiple Sections
Expert Committee: Chemical Medicines Monographs 4
No. of Commenters: 1

Comment Summary #1: Commenter requested proceeding with the omission only if this drug product is no longer actively marketed in the U.S.
Response: Comment incorporated. The omission was delayed until confirming that this drug product is no longer actively marketed in the U.S.

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

Comment Summary #1: The commenter recommended removal of the reporting threshold in the test for *Organic Impurities*.

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.

Monograph/Sections: Gadoterate Meglumine Injection/Multiple Sections
Expert Committee: Chemical Medicines Monographs 4
No. of Commenters: 3

Comment Summary #1: Commenter requested revising the chemical structure of gadoterate meglumine complex to be consistent with approved labeling.
Response: Comment incorporated.
EC-Initiated Change #1: The name of the general chapter referenced in *Identification A* is updated for consistency with its revised name.
EC-Initiated Change #2: The concentration of *Buffer 1* in the *Assay* is updated so the procedure will be more robust.
EC-Initiated Change #3: The *Tailing Factor* requirement in the *Assay* is widened from NMT 2.0 to NMT 2.
EC-Initiated Change #4: The calculations within the tests for the *Content of Meglumine, Limit of Free Gadolinium,* and *Limit of Free Tetraxetan* are updated.
EC-Initiated Change #5: The *Blank* preparation in the test for the *Limit of Free Tetraxetan* is updated.

Monograph/Sections: Galantamine Tablets/Multiple Sections
Expert Committee: Chemical Medicines Monographs 4
No. of Commenters: 1

Comment Summary #1: The commenter requested removing the “reporting threshold” from the test for *Organic Impurities*.
Response: Comment not incorporated. Based on comments received on a proposed policy change 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 chemical information for USP Galantamine Hydrobromide Related Compound Mixture RS is updated to be consistent with the current USP style.

Monograph/Section: Granisetron Hydrochloride Injection/*Organic Impurities*
Expert Committee: Chemical Medicines Monographs 3
No. of Commenters: 1

Comment Summary #1: The commenter recommended to include acceptance criteria for “Granisetron related compound B” and “Granisetron related compound D” and remove the footnote for these two impurities in *Table 1*.
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 the supporting data.
Comment Summary #2: The commenter requested removing the “reporting threshold” from the test for *Organic Impurities*.
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 on the topic.

Monograph/Section: Granisetron Hydrochloride Tablets/*Organic Impurities*
Expert Committee: Chemical Medicines Monographs 3
No. of Commenters: 1

Comment Summary #1: The commenter requested to include acceptance criteria for "Granisetron related compound B" and "Granisetron related compound D" and remove the footnote for these two impurities in *Table 1*.
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 the supporting data.
Comment Summary #2: The commenter requested removing the "reporting threshold" from the test for *Organic Impurities*.
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 on the topic.

Monograph/Sections: Haloperidol/Multiple Sections
Expert Committee: Chemical Medicines Monographs 4
No. of Commenters: 2

Comment Summary #1: The commenter requested removing the "reporting threshold" from the test for *Organic Impurities*.
Response: Comment not incorporated. Based on comments received on a proposed policy change 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 #2: The commenter requested revising the *Assay* in order to reduce peak fronting.
Response: Comment not incorporated. The EC will consider future revisions to the monograph upon receipt of the necessary supporting data.

Monograph/Section: Haloperidol Tablets/*Organic Impurities*
Expert Committee: Chemical Medicines Monographs 4
No. of Commenters: 1

Comment Summary #1: Commenter requested changing "Haloperidol *trans N*-oxide" to "Haloperidol *N*-oxide."
Response: Comment incorporated.

Monograph/Sections: Hydroxychloroquine Sulfate Tablets/Multiple Sections
Expert Committee: Chemical Medicines Monographs 1
No. of Commenters: 1

Comment Summary #1: The commenter commented that desethyl hydroxychloroquine is a known degradation product and recommended to update the table in the test for *Organic Impurities* with the degradation products of hydroxychloroquine that are controlled in the FDA-approved products.
Response: Comment incorporated. The footnote for desethyl hydroxychloroquine as process impurity has been removed. The EC determined to add a limit of NMT 0.5% for this impurity based on the limit proposed in the hydroxychloroquine API monograph.

Comment Summary #2: The commenter indicated that the acceptance criteria for "Total Impurities" is different from what has been approved by the FDA in the test for *Organic Impurities*.
Response: Comment incorporated. The limit for "Total impurities" is widened from NMT 1.0% to NMT 2.0%.
Comment Summary #3: The commenter recommended removal of the reporting threshold in the test for *Organic Impurities* for the drug product monograph.
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: In the test for *Organic Impurities*, the reporting threshold is revised from 0.05% to 0.1% to be consistent with ICH Q3B guidelines.
EC-Initiated Change #2: The official date for the proposed revision is extended from May 1, 2021, to Nov 1, 2021, due to the COVID-19 public health crisis and to help manufacturers adapt to the changes.

Monograph/Sections: Ipratropium Bromide/Multiple Sections
Expert Committee: Chemical Medicines Monographs 4
No. of Commenters: 1

Comment Summary #1: The commenter requested clarifying that the *Acceptance criteria* in the test for the *Limit of Ipratropium Related Compound A* applies to any spot from the *Sample solution* corresponding to ipratropium related compound A.
Response: Comment incorporated.
EC-Initiated Change #1: The word 'anhydrous' is removed throughout the monograph when describing the concentrations of solutions containing USP Ipratropium Bromide RS. The note describing the form of USP Ipratropium Bromide RS is also removed.

Monograph/Sections: Ipratropium Bromide and Albuterol Sulfate Inhalation Solution/Multiple Sections
Expert Committee: Chemical Medicines Monographs 4
No. of Commenters: 0

EC-Initiated Change #1: The word "anhydrous" is removed throughout the monograph when describing the concentrations of solutions containing USP Ipratropium Bromide RS. The note describing the form of USP Ipratropium Bromide RS is also removed.

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

Comment Summary #1: Commenter indicated that the proposed specifications for ipratropium related compound C and total degradations products are not consistent with approved limits.
Response: Comment incorporated. The limit for ipratropium related compound C was widened from NMT 0.2% to NMT 1.0% and the total impurities was widened from NMT 0.8% to NMT 1.5% to be consistent with approved limits.
Comment Summary #2: Commenter recommended not including process impurities in the impurity profile.

Response: Comment not incorporated. The inclusion of process impurities with a corresponding footnote is consistent with current USP practice.
Comment Summary #3: The commenter requested removing the "reporting threshold" from the test for *Organic Impurities*.
Response: Comment not incorporated. Based on comments received on a proposed policy change 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 word "anhydrous" is removed throughout the monograph when describing the concentrations of solutions containing USP Ipratropium Bromide RS. The note describing the form of USP Ipratropium Bromide RS is also removed.

Monograph/Sections: Lacosamide/Multiple Sections
Expert Committee: Chemical Medicines Monographs 4
No. of Commenters: 3

Comment Summary #1: The commenter requested removing the "reporting threshold" from the test for *Organic Impurities*.
Response: Comment not incorporated. Based on comments received on a proposed policy change 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 replacing the test for *Organic Impurities* with a procedure which includes a degradation product that is not part of the FDA-approved applications.
Response: Comment not incorporated. The EC has decided that the test for *Organic Impurities* is suitable for inclusion in the public standard.
Comment Summary #3: The commenter requested widening the specifications in the tests for *Water Content* and *Organic Impurities* to include values which are not part of the FDA-approved applications.
Response: Comment not incorporated. The EC will consider future revisions to the monograph upon receipt of the necessary supporting data.

Monograph/Section: Lacosamide Injection/*Assay*
Expert Committee: Chemical Medicines Monographs 4
No. of Commenters: 1

Comment Summary #1: The commenter requested revising the acceptance criteria for the *Assay* to be consistent with what has been approved.
Response: Comment incorporated. The acceptance criteria are widened from NLT 95.0% and NMT 105.0% to NLT 90.0% and NMT 105.0%. The *Definition* is also revised accordingly.
Comment Summary #2: The commenter requested removing the "reporting threshold" from the test for *Organic Impurities*.
Response: Comment not incorporated. Based on comments received on a proposed policy change 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.

Monograph/Section: Lacosamide Oral Solution/*Assay*
Expert Committee: Chemical Medicines Monographs 4

No. of Commenters: 1

Comment Summary #1: The commenter requested revising the acceptance criteria for the *Assay* to be consistent with what has been approved.
Response: Comment incorporated. The acceptance criteria are widened from NLT 95.0% and NMT 105.0% to NLT 90.0% and NMT 105.0%. The *Definition* is also revised accordingly.
Comment Summary #2: The commenter requested removing the "reporting threshold" from the test for *Organic Impurities*.
Response: Comment not incorporated. Based on comments received on a proposed policy change 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.

Monograph/Section: Lacosamide Tablets/*Assay*
Expert Committee: Chemical Medicines Monographs 4
No. of Commenters: 1

Comment Summary #1: The commenter requested revising the acceptance criteria for the *Assay* to be consistent with what has been approved.
Response: Comment incorporated. The acceptance criteria are widened from NLT 95.0% and NMT 105.0% to NLT 90.0% and NMT 105.0%. The *Definition* is also revised accordingly.
Comment Summary #2: The commenter requested removing the "reporting threshold" from the test for *Organic Impurities*.
Response: Comment not incorporated. Based on comments received on a proposed policy change 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.

Monograph/Sections: Lactobacillus Reuteri/Multiple Sections
Expert Committee: Non-Botanical Dietary Supplements and Herbal Medicines
No. of Commenters: 0

Definition
EC-Initiated Change #1. Changes were incorporated into the *Definition* to describe both species and individual strains characteristics.

Identification
EC-Initiated Change #2. To align the *Definition* with test requirements in relation to microscopic features of individual strains, a new *Identification* test (*Identification* test *A. Microscopic Test*) was incorporated.
EC-Initiated Change #3. In the *Identification* test *B. Nucleic Acid-Based Identification,* a new PCR positive control was incorporated proposing the use of either the genomic DNA of the reference strain or species-specific universal primers *for Lactobacillus reuteri.*

Assay
EC-Initiated Change #4. The *Assay (Enumeration)* section has been referenced to General Chapter <64> *Probiotic Tests*.

Contaminants

EC-Initiated Change #5. The *Contaminants* section has been referenced to General Chapter <64> *Probiotic Tests* (except for *Listeria*, which is still referenced to the *Food Chemicals Codex*, Appendix XV).

Monograph/Sections: Lactobacillus Rhamnosus/Multiple Sections
Expert Committee: Non-Botanical Dietary Supplements and Herbal Medicines
No. of Commenters: 0

Definition
EC-Initiated Change #1. Changes were incorporated into the *Definition* to describe both species and individual strains characteristics.

Identification
EC-Initiated Change #2. To align the *Definition* with test requirements in relation to microscopic features of individual strains, a new *Identification* test (*Identification* test *A. Microscopic Test*) was incorporated.
EC-Initiated Change #3. In the *Identification* test *B. Nucleic Acid-Based Identification,* a new PCR positive control was incorporated proposing the use of either the genomic DNA of the reference strain or species-specific universal primers *for Lactobacillus rhamnosus.*
EC-Initiated Change #4. In the *Identification* test *B. Nucleic Acid-Based Identification,* a recommendation to use Sanger sequencing for the sequencing of SNP in the *Acceptance criteria* for Primer sets 2 and 3 for *Lactobacillus rhamnosus* strain GG (Table 1) has been incorporated.

Assay
EC-Initiated Change #5. The *Assay (Enumeration)* section has been referenced to General Chapter <64> *Probiotic Tests*.

Contaminants
EC-Initiated Change #6. The *Contaminants* section has been referenced to General Chapter <64> *Probiotic Tests* (except for *Listeria*, which is still referenced to the *Food Chemicals Codex*, Appendix XV).

Monograph/Section: Lamotrigine Orally Disintegrating Tablets/*Organic Impurities*
Expert Committee: Chemical Medicines Monographs 4
No. of Commenters: 1

Comment Summary #1: The commenter requested removing the “reporting threshold” from the test for *Organic Impurities*.
Response: Comment not incorporated. Based on comments received on a proposed policy change 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.

Monograph/Sections: Levofloxacin Tablets/Multiple Sections
Expert Committee: Chemical Medicines Monographs 1
No. of Commenters: 2

Comment Summary #1: The commenter commented to include a separate UV procedure than the UV-PDA spectra match from the *Assay* for *Identification B*.
Response: Comment not incorporated. The EC determined that the proposed procedure is suitable for compendial use with one procedure for *Assay* and *Identification*.
Comment Summary #2: The commenter commented that the detrofloxacin impurity is included in their product approval but it is listed as a process impurity in the proposal.
Response: Comment not incorporated. The EC determined that the process impurities are controlled in the drug substance and the limit for process impurity is not included in drug product monographs.
Comment Summary #3: The commenter commented that their in-house method is superior than the *PF* proposed method in the test for *Organic Impurities*.
Response: Comment not incorporated. The EC determined that the proposed method is suitable for its intended use
EC-Initiated Change #1: In the test for *Organic Impurities,* the trivial name for detrofloxacin is updated to include D-isomer in the table to be consistent with the family of monographs.

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

Comment Summary #1: The commenter requested that the quantitative procedure for *Sodium Content* be retained.
Response: Comment not incorporated. The EC determined that the monograph already includes *Identification Tests—General ⟨191⟩ Sodium,* which is sufficient for counter ion confirmation.
Comment Summary #2: The commenter requested removing the “reporting threshold” from the test for *Organic Impurities*.
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.

Monograph/Section: Loratadine Capsules/*Assay*
Expert Committee: Chemical Medicines Monographs 6
No. of Commenters: 1

Comment Summary: The commenter recommended revising the acceptance criteria for *Assay* to be consistent with what has been approved by the FDA.
Response: Comment incorporated. The acceptance criteria are widened from NLT 95.0% and NMT 105.0% to NLT 90.0% and NMT 110.0% to be consistent with the FDA approved limits. The *Definition* is also revised accordingly.

Monograph/Section: Maltitol/*Limit of Nickel*
Expert Committee: Excipients Monographs 1
No. of Commenters: 2

Comment Summary #1: To avoid contradiction with ICH Q3D guidelines, <232> *Elemental Impurities—Limits,* and <233> *Elemental Impurities—Procedures*, the commenter recommended that the *Limit of Nickel* test be deleted from the monograph. The commenter believes that

deletion of the test from the monograph will not only modernize the monograph to ICH Q3D, but also it will allow manufacturers to establish appropriate limits based on application.
Response: Comment not incorporated. Neither ICH Q3D guideline nor <232> *Elemental Impurities—Limits* applies to excipients. Additionally, the EC followed recommendations put forward by the Element-Specific General Chapters Joint Subcommittee to keep the test and the acceptance criteria in the monograph.

Monograph/Section: Maltitol Solution/*Limit of Nickel*
Expert Committee: Excipients Monographs 1
No. of Commenters: 2

Comment Summary #1: The commenter recommended replacing the proposed inductively coupled plasma-optical emission spectroscopy (ICP-OES) procedure with a reference to <233> *Elemental Impurities—Procedures*.
Response: Comment not incorporated. The commenter was asked to provide supporting data that analysis of Sorbitol Solution can be done exactly as it is written in <233>. The EC will consider a future revision to the monograph upon receipt of supporting data.
Comment Summary #2: To avoid contradiction with ICH Q3D guidelines, <232> *Elemental Impurities—Limits,* and <233> *Elemental Impurities—Procedures*, the commenter recommended that the *Limit of Nickel* test be deleted from the monograph. The commenter believes that deletion of the test from the monograph will not only modernize the monograph to ICH Q3D, but also it will allow manufacturers to establish appropriate limits based on application.
Response: Comment not incorporated. Neither ICH Q3D guideline nor <232> *Elemental Impurities—Limits* applies to excipients. Additionally, the EC followed recommendations put forward by the Element-Specific General Chapters Joint Subcommittee to keep the test and the acceptance criteria in the monograph.

Monograph/Section: Methylphenidate Hydrochloride/*Organic Impurities, Procedure 2*
Expert Committee: Chemical Medicines Monographs 4
No. of Commenters: 2

Comment Summary #1: The commenter recommended revising the acceptance criterion for "any individual unspecified impurity" in *Organic Impurities, Procedure 2* to be consistent with the criterion in the test for *Organic Impurities, Procedure 1* and with ICH Q3A.
Response: Comment not incorporated. The proposed *Acceptance criteria* is consistent with the sponsor's FDA-approved application. The EC will consider future revisions to this monograph upon receipt of the necessary supporting data.
Comment Summary #2: The commenter requested changes to the buffer strength in the *Mobile phase*, concentration of the components of the *System suitability solution*, *Flow rate*, and *Relative standard deviation* requirement in *Organic Impurities, Procedure 2*.
Response: Comment not incorporated. The requested changes are outside of the scope of the proposed changes to the monograph listed in the *Briefing*. The EC will consider future revisions to this monograph upon receipt of the necessary supporting data.

Monograph/Section: Minoxidil Tablets
Expert Committee: Chemical Medicines Monographs 2
No. of Commenters: 1

Comment Summary #1: The commenter requested removing the “reporting threshold” from the test for *Organic Impurities*.
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.

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

Comment Summary #1: The commenter requested removing the “reporting threshold” from the test for *Organic Impurities*.
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.

Monograph/Section: Modafinil Tablets/*Organic Impurities*
Expert Committee: Chemical Medicines Monographs 5
No. of Commenters: 1

Comment Summary #1: The commenter requested removing the “reporting threshold” from the test for *Organic Impurities*.
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.

Monograph/Section: Nefazodone Hydrochloride/*Organic Impurities*
Expert Committee: Chemical Medicines Monographs 4
No. of Commenters: 1

Comment Summary #1: The commenter requested renaming “Any individual unidentified impurity” as “Any unspecified impurity” to be consistent with ICH Q3A.
Response: Comment incorporated.

Monograph/Section: Noncrystallizing Sorbitol sorbitan solution Solution/*Limit of Nickel*
Expert Committees: Excipients Monographs 1
No. of Commenters: 3

Comment Summary #1: The commenter suggested using inductively coupled plasma–mass spectrometry (ICP-MS) instead of inductively coupled plasma-optical emission spectroscopy (ICP-OES), or suggested adding ICP-MS as an option similar to the way ICP-MS and ICP-EOS options are listed in <233> *Elemental Impurities—Procedures.*
Response: Comment not incorporated. The commenter was asked to provide supporting data for ICP-MS. The EC will consider a future revision to the monograph upon receipt of supporting data.
Comment Summary #2: The commenter recommended replacing the proposed ICP-OES procedure with a reference to <233>.

Response: Comment not incorporated. The commenter was asked to provide supporting data that analysis of Sorbitol Solution can be done exactly as it is written in <233>. The EC will consider a future revision to the monograph upon receipt of supporting data.
Comment Summary #3: To avoid contradiction with ICH Q3D guidelines, <232> *Elemental Impurities—Limits,* and <233> *Elemental Impurities—Procedures,* and to keep in line with the *European Pharmacopeia* approach, the commenter recommended that the *Limit of Nickel* test be deleted from the monograph. The commenter believes that deletion of the test from the monograph will not only modernize the monograph to ICH Q3D, but also it will allow manufacturers to establish appropriate limits based on application.
Response: Comment not incorporated. Neither ICH Q3D guideline nor <232> *Elemental Impurities—Limits* applies to excipients. Additionally, the EC followed recommendations put forward by the Element-Specific General Chapters Joint Subcommittee to keep the test and the acceptance criteria in the monograph. This recommendation was based on the evaluation of nickel content in multiple lots/batches of Noncrystallizing Sorbitol Solution.

Monograph: Oil-and Water-Soluble Vitamins with Minerals Chewable Gels
Expert Committee: Non-Botanical Dietary Supplements
No. of Commenters: 3

Comments Summary #1: The commenters recommended increasing the proposed upper limits for Vitamins A, D, E, C, B12, folic acid, and biotin; and for calcium, magnesium, phosphorus, and zinc minerals to cover instability of the ingredients and give more flexibility in variation between batches.
Response: Comments incorporated. The acceptance criteria for the upper limits of Vitamins A, D, and E were changed from NMT 165.0% to NMT 170.0%. The upper limit for Vitamin C was changed from NMT 150.0% to NMT 250.0%. The upper limits for Vitamin B12 and biotin were changed from NMT 150.0% to NMT 170.0%. The upper limit for folic acid was changed from NMT 150.0% to NMT 245.0%. The upper limits for calcium, magnesium, phosphorus, and zinc were changed from NMT 125.0% to NMT 130.0%.
Comments Summary #2: The commenters reported high instability of pantothenic acid and recommended increasing its upper limit up to 550%.
Response: Comments not incorporated. The EC decided that a chewable gel is not a suitable delivery vehicle for pantothenic acid and recommended that pantothenic acid be excluded from the *Definition* of the monograph.
EC-Initiated Change #1: A note was added to the *Definition* that any overage of folic acid should not exceed the Tolerable Upper Intake Level.
EC-Initiated Change #2: The statement to the *Definition* was added to indicate that the Oil-and Water-Soluble Vitamins with Minerals Chewable Gel products do not contain any additional vitamins or minerals for which nutritional value is claimed.

Monograph/Sections: Omeprazole Magnesium/Multiple Sections
Expert Committee: Chemical Medicines Monographs 3
No. of Commenters: 3

Comment Summary #1: The commenter recommended retaining either both tests of *Identification B* and *Content of Magnesium* by atomic absorption spectrophotometry or, at least, the test of *Identification B* for the specificity of the method.
Response: Comment incorporated. Both tests are retained.
Comment Summary #2: The commenter recommended retaining the current acceptance criteria of 3.30–3.55% for the *Content of Magnesium*.

Response: Comment incorporated. The EC will consider future revisions to the monograph upon receipt of the supporting data.
Comment Summary #3: The commenter recommended retaining the test for *Color of Solution* for the degradation products that can't be determined by the test for *Organic Impurities*.
Response: Comment incorporated. The test is retained.
Comment # Summary 4: The commenter requested widening the tailing factor requirement in the system suitability for *Assay*.
Response: Comment not incorporated. The EC determined that the proposed requirement is consistent with the performance of chromatographic procedures.

Monograph/Sections: Oxcarbazepine Tablets/Multiple Sections
Expert Committee: Chemical Medicines Monographs 4
No. of Commenters: 1

Comment Summary #1: The commenter requested specifying that the mobile phase and/or its components need to be filtered in the *Assay*, test for *Organic Impurities Procedure 1* and test for *Organic Impurities, Procedure* 2.
Response: Comment not incorporated. The text reflects current USP style which does not include statements describing expected analytical practices such as mixing solutions or weighing accurately.
Comment Summary #2: The commenter requested revising the *System suitability solution* and *Sensitivity solution* as well as the system suitability requirements in both tests for *Organic Impurities*.
Response: Comment not incorporated. The EC will consider future revisions to the monograph upon the receipt of supporting data.

Monograph/Section: Oxycodone Hydrochloride Oral Solution/*Organic Impurities*
Expert Committee: Chemical Medicines Monographs 2
No. of Commenters: 5

Comment Summary #1: The commenters indicated that the acceptance criterion for total degradation products is different from what has been approved FDA.
Response: Comment incorporated. The acceptance criterion was revised from NMT 0.3% to NMT 2.0% to accommodate the additional approved specifications.
Comment Summary #2: The commenter indicated that the acceptance criterion for oxycodone related compound B should be revised from NMT 0.2% to NMT 1.0% based on their FDA-approved application.
Response: Comment incorporated.
Comment Summary #3: The commenter recommended removing the process impurities oxycodone related compound A and 7-Methyloxycodone, which are listed as not-controlled, from Table 2 to provide the flexibility to allow the control of these process impurities in other ANDA applications.
Response: Comment incorporated. Oxycodone related compound A and 7-Methloxycodone and the corresponding footnotes a and b were removed from Table 2 to accommodate the additional approved specifications. The relative retention times of these two impurities were moved from Table 2 to a Note in the *System suitability* section.
Comment Summary #4: The commenter indicated that they could not meet the system suitability requirement for the signal-to-noise ratio.
Response: Comment not incorporated. USP lab could meet this requirement and no adverse comments on signal-to-noise ratio requirement from other manufacturers were received.

Comment Summary #5: The commenter indicated that they control 10-hydroxyoxycodone as a specified impurity at NMT 0.2%.
Response: Comment not incorporated. The EC determined that since 10-hydroxyoxycodone is controlled by the commenter at the same level as the proposed acceptance criterion for 'Any unspecified degradation product', it is not necessary to list this impurity as a specified impurity in the monograph as a public standard.

Monograph: Pindolol
Expert Committee: Chemical Medicines Monographs 2
No. of Commenters: 1

Comment Summary #1: The commenter requested removing the "reporting threshold" from the test for *Organic Impurities*.
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.

Monograph: Prazosil Hydrochloride
Expert Committee: Chemical Medicines Monographs 2
No. of Commenters: 1

Comment Summary #1: The commenter requested removing the "reporting threshold" from the test for *Organic Impurities*.
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.

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

Comment Summary #1: The commenter recommended providing flexibility by adding <197K> to *Identification A*.
Response: Comment not incorporated. The EC will consider a future revision to the monograph upon receipt of supporting data.

Monograph/Sections: Quinapril Tablets/Multiple Sections
Expert Committee: Chemical Medicines Monographs 2
No. of Commenters: 1

Comment Summary #1: The commenter requested removing the "reporting threshold" from the test for *Organic Impurities*.
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.

Monograph/Section: Quinine Sulfate Capsules/*Organic Impurities*

Expert Committee: Chemical Medicines Monographs 1
No. of Commenters: 3

Comment Summary #1: The commenter commented to remove the "reporting threshold" from the test for *Organic Impurities*.
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 to revise the Quinine Sulfate Reference Standard to the Quinine Sulfate dihydrate salt in the test for *Organic Impurities*.
Response: Comment not incorporated. The EC determined that the current USP Quinine Sulfate Reference Standard is suitable for compendial use.
Comment Summary #3: The commenter requested widening the limit for any individual unspecified impurity from 0.20% to 0.2% in the test for *Organic Impurities*.
Response: Comment incorporated.

Monograph/Sections: Regorafenib/Multiple Sections
Expert Committee: Chemical Medicines Monographs 3
No. of Commenters: 1

Comment Summary #1: The commenter recommended revising the acceptance criteria for the *Limit of Regorafenib Related Compound A* test to be in line with ICH Q3A.
Response: Comment incorporated. Acceptance criterion for regorafenib related compound A is updated from NMT 0.01% to 0.15% and the *Standard solution* concentration is updated from 5.0 µg/mL to 0.075 mg/mL.
Comment Summary #2: The commenter requested clarifying the hydrate form of Regorafenib for the acceptance criteria of the *Water Determination* test.
Response: Comment incorporated. The monohydrate form is added to acceptance criteria of *Water Determination* test as per sponsor's FDA-approved application.

Monograph/Sections: Rifabutin/Multiple Sections
Expert Committee: Chemical Medicines Monographs 1
No. of Commenters: 1

Comment Summary #1: The commenter indicated that the acceptance criteria for 16-desacetylrifabutin, didehydrorifabutin, and specified unknown impurity is not consistent with the FDA-approved limits in the test for *Organic Impurities*.
Response: Comments incorporated. The limits for 16-desacetylrifabutin, didehydrorifabutin and specified unknown impurity are widened from 0.75%, 0.75% and 0.25% to 1.0%, 1.0% and 0.50%, respectively.
Comment Summary #2: The commenter recommended including the temperature requirement under the *Packaging and Storage* section.
Response: Comments incorporated. The *Packaging and Storage* section is updated to include that the storage temperature is "not to exceed 25°C."

Monograph/Section: Rifabutin Capsules/*Organic Impurities*
Expert Committee: Chemical Medicines Monographs 1
No. of Commenters: 1

Comment Summary #1: The commenter requested including "3-Aminorifamycin S" impurity in the table as a process impurity, and requested including a Note in the footnote that this impurity is a process impurity and is not included in the total impurities.
Response: Comments incorporated.

Monograph/Section: Risperidone Oral Solution/*Organic Impurities*
Expert Committee: Chemical Medicines Monographs 4
No. of Commenters: 0

EC-Initiated Change #1: The word "unspecified" is removed from the phrase "each unspecified degradation product" to clarify that the equation should be used to calculate both specified and unspecified degradation products.

Monograph/Section: Sodium Phenylbutyrate Oral Powder/*Organic Impurities*
Expert Committee: Chemical Medicines Monographs 3
No. of Commenters: 1

Comment Summary #1: The commenter recommended revising the acceptance criterion for *Total Impurities* to be consistent with the FDA-approved products.
Response: Comment incorporated. The acceptance criterion for *Total impurities* is widened from 0.3% to 0.5%.
Comment Summary #2: The commenter requested removing the "reporting threshold" from the test for *Organic Impurities*.
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.

Monograph/Sections: Sodium Phenylbutyrate Tablets/Multiple Sections
Expert Committee: Chemical Medicines Monographs 3
No. of Commenters: 1

Comment Summary #1: The commenter recommended revising the acceptance criterion for "Phenylbutyrate related compound A" in the *Organic Impurities Table 1* to be consistent with the FDA-approved products.
Response: Comment not incorporated. The EC will consider future revisions to the monograph upon receipt of the supporting data.
Comment Summary #2: The commenter requested removing the "reporting threshold" from the test for *Organic Impurities*.
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: Commenter commented that the acceptance criterion in the *Dissolution* test is different from FDA-approved products.
Response: Comment not incorporated. The EC will consider future revisions to the monograph upon receipt of the supporting data.
EC-Initiated Change #1: The text "The reporting threshold is 0.05%" is changed to "The reporting threshold is 0.05% except for Phenylbutyrate related compound B."

Monograph/Sections: Sorafenib Tablets/Multiple Sections

Expert Committee: Chemical Medicines Monographs 3
No. of Commenters: 3

Comment Summary #1: The commenter requested removing the "reporting threshold" from the test for *Organic Impurities.*
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 correcting the length of both columns A and B from 50 cm to 5 cm in the *Chromatographic System* for the *Dissolution* test.
Response: Comment incorporated.

Monograph/Sections: Sorafenib Tosylate/Multiple Sections
Expert Committee: Chemical Medicines Monographs 3
No. of Commenters: 4

Comment Summary #1: The commenter requested changing the test for *Organic Impurities* to include two additional process related impurities.
Response: Comment not incorporated. The EC will consider future revisions to this monograph upon receipt of the necessary supporting data.
Comment Summary #2: The commenter requested changing the column temperature from 75° to 60° in the *Organic Impurities* and *Assay* tests.
Response: Comment not incorporated. The EC determined that the method has been validated and tested without any issue. The chromatographic parameters can be adjusted according to General Chapter <*621*>.
Comment Summary #3: The commenter requested decreasing standards and samples concentrations in *Organic Impurities* and *Assay* for better spectral uniformity.
Response: Comment not incorporated. The EC determined that the method has been validated and tested without any issue.
Comment Summary #4: The commenter proposed to include determination of methyl-p-toluenesulfonate and ethyl-p-toluenesulfonate tests in monograph.
Response: Comment not incorporated. The EC will consider future revisions to this monograph upon receipt of the necessary supporting data.
Comment Summary #5: The commenter observed interference from diluent at retention time of sorafenib, sorafenib impurity F and sorafenib related compound H.
Response: Comment not incorporated. The EC determined that the procedure has been tested at USP laboratory and no issues have been reported.
Comment Summary #6: The commenter requested to relax the requirement for *Signal-to-noise ratio* in system suitability of *Organic Impurities* test.
Response: Comment not incorporated. The EC determined that the requirement has been achieved without any issue.
Comment Summary #7: The commenter requested changing injection volume from 3µL to 5µL in *Organic Impurities* and *Assay* tests.
Response: Comment not incorporated. The injection volume can be adjusted according to General Chapter *<621> Chromatography*.
Comment Summary #8: The commenter informed that the obtained RRF values are different from the RRF values published in *PF*.
Response: Comment not incorporated. The RRF values were determined based on a validated method. The EC will consider future revisions to the monograph upon receipt of the supporting data.

Monograph/Section: Sorbitol/*Limit of Nickel*
Expert Committee: Excipients Monographs 1
No. of Commenters: 3

Comment Summary #1: To avoid contradiction with ICH Q3D guidelines, <232> *Elemental Impurities—Limits,* and <233> *Elemental Impurities—Procedures*, and to keep in line with *European Pharmacopeia* approach, the commenter recommended that the *Limit of Nickel* test be deleted from the monograph. The commenter believes that deletion of the test from the monograph will not only modernize the monograph to ICH Q3D, but also it will allow manufacturers to establish appropriate limits based on application.
Response: Comment not incorporated. Neither ICH Q3D guideline nor <232> *Elemental Impurities—Limits* applies to excipients. Additionally, the EC followed recommendations put forward by the Element-Specific Chapters Joint Subcommittee to keep the test and the acceptance criteria in the monograph. This recommendation was based on the evaluation of nickel content in multiple lots/batches of Sorbitol.
Comment Summary #2: The commenter would like to petition USP to retain the current atomic absorption procedure.
Response: Comment not incorporated. USP received complaints from multiple stakeholders that the procedure does not perform as written. The current atomic absorption procedure utilizes a flammable organic solvent that creates a hazardous safety issue.

Monograph/Section: Sorbitol Solution/*Limit of Nickel*
Expert Committee: Excipients Monographs 1
No. of Commenters: 8

Comment Summary #1: The commenter recommended that the current methodology utilizing atomic absorption be retained in the new procedure. This is based on the inductively coupled plasma-optical emission spectroscopy (ICP-OES) method being added to the *Limit of Nickel* test. The commenter believes that this would allow laboratories that do not have advanced instrumentation like ICP-OES, to continue analyzing Sorbitol Solution without the added expense for either outsourcing the testing or investing in additional equipment.
Response: Comment not incorporated. USP received complaints from multiple stakeholders that the current atomic absorption procedure does not perform as written. Additionally, the current atomic absorption procedure utilizes a flammable organic solvent that creates a hazardous safety issue. USP policy only allows monographs to have multiple procedures for the same test for official substances that come from different sources, or manufacturing processes constituting different impurities profiles that may require two different analytical procedures. It does not apply to tests for elemental impurities.
Comment Summary #2: The commenter reported that the new ICP-OES appears to be very difficult and confusing from a preparation perspective and may potentially cause a significant increase in lab errors.
Response: Comment not incorporated. The commenter was asked to clarify the statement and provide supporting data. The EC will consider a future revision to the monograph upon receipt of supporting data.
Comment Summary #3: The commenter recommended removing the *Limit of Nickel* test from the monograph because most manufacturers of Sorbitol Solution have nickel levels controlled during a manufacturing process and have historical data to support this.
Response: Comment not incorporated. The commenter was asked to provide supporting data. The EC will consider a future revision to the monograph upon receipt of supporting data.

Comment Summary #4: The commenter suggested using inductively coupled plasma–mass spectrometry (ICP-MS) instead of ICP-OES, or suggested adding ICP-MS as an option similar to the way ICP-MS and ICP-EOS options are listed in <233> *Elemental Impurities—Procedures.*
Response: Comment not incorporated. The commenter was asked to provide supporting data for ICP-MS. The EC will consider a future revision to the monograph upon receipt of supporting data.
Comment Summary #5: The commenter recommended replacing the proposed ICP-OES procedure with a reference to <233>.
Response: Comment not incorporated. The commenter was asked to provide supporting data that analysis of Sorbitol Solution can be done exactly as it is written in <233>. The EC will consider a future revision to the monograph upon receipt of supporting data.
Comment Summary #6: To avoid contradiction with ICH Q3D guidelines, <232> *Elemental Impurities—Limits,* and <233> *Elemental Impurities—Procedures,* and to keep in line with *European Pharmacopeia* approach, the commenter recommended that the *Limit of Nickel* test be deleted from the monograph. The commenter believes that deletion of the test from the monograph will not only modernize the monograph to ICH Q3D, but also it will allow manufacturers to establish appropriate limits based on application.
Response: Comment not incorporated. Neither ICH Q3D guidelines nor <232> *Elemental Impurities—Limits* apply to excipients. Additionally, the EC followed recommendations put forward by the Element-Specific General Chapters Joint Subcommittee to keep the test and the acceptance criteria in the monograph. This recommendation was based on the evaluation of nickel content in multiple lots/batches of Sorbitol Solution.
Comment Summary #7: The commenter recommended including an option to introduce the internal standard solution manually rather than by an in-line mixing chamber.
Response: Comment not incorporated. A note in the procedure allows using a different type of instrument, which may require a different way of internal standard introduction into the instrument.
Comment Summary #8: The commenter would like to petition USP to retain the current atomic absorption procedure.
Response: Comment not incorporated. USP received complaints from multiple stakeholders that the procedure does not perform as written. The current atomic absorption procedure utilizes a flammable organic solvent that creates a hazardous safety issue.

Monograph/Section: Sorbitol Sorbitan Solution/*Limit of Nickel*
Expert Committee: Excipients Monographs 1
No. of Commenters: 2

Comment Summary #1: The commenter recommended replacing the proposed inductively coupled plasma-optical emission spectroscopy (ICP-OES) procedure with a reference to <233> *Elemental Impurities—Procedures*.
Response: Comment not incorporated. The commenter was asked to provide supporting data that analysis of Sorbitol Solution can be done exactly as it is written in <233>. The EC will consider a future revision to the monograph upon receipt of supporting data.
Comment Summary #2: To keep in line with *European Pharmacopeia* approach, the commenter recommended that the *Limit of Nickel* test be deleted from the monograph.
Response: Comment not incorporated. The EC followed recommendations put forward by the Element-Specific General Chapters Joint Subcommittee to keep the test and the acceptance criteria in the monograph.

Monograph: Spironolactone Compounded Oral Suspension
Expert Committees: Compounding
No. of Commenters: 1

Comment Summary #1: The commenter expressed concern with USP creating a compounding monograph for a preparation that may produce a drug product that is essentially a copy of an FDA approved product, as described in the FDA final guidance entitled "Compounded Drug Products That Are Essentially Copies of a Commercially Available Drug Product Under Section 503A of the Federal Food, Drug, and Cosmetic Act." The commenter recommended that this monograph be deleted from the *USP-NF*. The commenter recommended using only FDA-approved drug products unless the patient has a specific medical need (e.g., an allergy) that cannot be met by the approved drug products.
Response: Comment not incorporated. The FDA approved product is banana flavored and this may not be suitable for some human and animal patients. Also, the monograph is required for compounders to have a standard to follow when they need to compound it during drug shortages.

Monograph: Sterile Purified Water
Expert Committee: General Chapters–Chemical Analysis
No. of Commenters: 0

EC-Initiated Change #1: Replacement of the following text "[Note—For microbiological guidance, see *Water for Pharmaceutical Purposes* ⟨1231⟩.]" with "[Note—For additional information, see *Water for Pharmaceutical Purposes* ⟨1231⟩.]" because the referenced general information chapter contains useful information beyond microbiological.

Monograph Sterile Water for Inhalation
Expert Committee: General Chapters–Chemical Analysis
No. of Commenters: 0

EC-Initiated Change #1: Replacement of the following text "[Note—For microbiological guidance, see *Water for Pharmaceutical Purposes* ⟨1231⟩.]" with "[Note—For additional information, see *Water for Pharmaceutical Purposes* ⟨1231⟩.]" because the referenced general information chapter contains useful information beyond microbiological.

Monograph: Sterile Water for Injection
Expert Committee: General Chapters–Chemical Analysis
No. of Commenters: 0

EC-Initiated Change #1: Replacement of the following text "[Note—For microbiological guidance, see *Water for Pharmaceutical Purposes* ⟨1231⟩.]" with "[Note—For additional information, see *Water for Pharmaceutical Purposes* ⟨1231⟩.]" because the referenced general information chapter contains useful information beyond microbiological.

Monograph: Sterile Water for Irrigation
Expert Committee: General Chapters–Chemical Analysis
No. of Commenters: 0

EC-Initiated Change #1: Replacement of the following text "[Note—For microbiological guidance, see *Water for Pharmaceutical Purposes* ⟨1231⟩.]" with "[Note—For additional

information, see *Water for Pharmaceutical Purposes* ⟨1231⟩.]" because the referenced general information chapter contains useful information beyond microbiological.

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

Comment Summary #1: The commenter requested providing the justification for the upper limit change of *Assay* from NMT 101.0% to 102.0%.
Response: Comment not incorporated. The EC determined that the upper limit of 102.0% for the *Assay* is appropriate based on the proposed change to the *Assay* procedure from titration to HPLC
Comment Summary #2: The commenter recommended increasing the injection volume as it's challenging to meet the RSD requirement of NMT 0.73% for *Assay* with an injection volume of 2 µL.
Response: Comment not incorporated. Based on the available supporting information, the EC determined that the injection volume of 2 µL is consistent with the validation data and is suitable for the intended use.
Comment Summary #3: The commenter indicated that they could not meet the system suitability requirement of RSD at NMT 0.73% for the *Assay* and recommended that USP adopt their in-house *Assay* and *Organic Impurities* procedures.
Response: Comment not incorporated. Based on the available supporting information, the EC determined that the proposed procedures for *Assay* and *Organic Impurities* are suitable for public standards.

Monograph/Sections: Tetraxetan/Multiple Sections
Expert Committee: Chemical Medicines Monographs 4
No. of Commenters: 2

Comment Summary #1: Commenter indicated that there is no need to include a monograph for this article in the *USP-NF* as this is a chelating agent.
Response: Comment not incorporated. This is an excipient which qualifies for a monograph in *USP-NF* to ensure identity, purity, and quality.
Comment Summary #2: Commenter requested the correction of the incorrect equivalency factor for tetraxetan from 20.22 to 202.2.
Response: Comment incorporated.
EC-Initiated change #1: The name of the general chapter referenced in *Identification A* is updated for consistency with its revised name.

Monograph/Section: Tranexamic Acid/*Organic Impurities*
Expert Committee: Chemical Medicines Monographs 2
No. of Commenters: 2

Comment Summary #1: The commenter indicated that impurity name at RRT 2.1 in Table 1 is not correct.
Response: Comment incorporated. Publication error for *Ditranexamic Acid Amine* in Table 1 was corrected.
Comment Summary #2: The commenter recommended removing the "reporting threshold" from the test for *Organic Impurities*.
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 recommended revising the acceptance criterion for any individual unspecified impurity from 0.05% to 0.10%
Response: Comment not incorporated. The EC determined that the acceptance criterion of NMT 0.05% for any individual unspecified impurity is consistent with what has been approved by the FDA.
Comment Summary #4: The commenter suggested using the related compound names of tranexamic acid related compound A, tranexamic acid related compound B, and tranexamic acid related compound D instead of the short names in Table 1.
Response: Comment not incorporated. The names of these three impurities, which USP doesn't carry the corresponding reference standards, are consistent with current USP's practice of naming impurities.

Monograph/Section: Urea C13/*Isotopic Purity*
Expert Committee: Chemical Medicines Monographs 4
No. of Commenters: 0

EC-Initiated Change #1: Updated the style of the *System suitability* requirements for *Most abundant ion.*

Monograph/Section: Vecuronium Bromide/*Organic Impurities*
Expert Committee: Chemical Medicines Monographs 4
No. of Commenters: 0

EC-Initiated Change #1: The *Sensitivity solution*, *Signal-to-noise ratio* requirement, and reporting threshold were removed as the procedure is not suitably sensitive to support the *Signal-to-noise ratio* requirement of NLT 10 as proposed.

Monograph: Water-Soluble Vitamins Preparation
Expert Committee: Non-Botanical Dietary Supplements
No. of Commenters: 0

EC-Initiated Change #1: After reviewing the available stability data, the acceptance criteria for the upper limits were changed from NMT 110% to NMT 125%.
EC-Initiated Change #2: The labelling section was revised to indicate the name and content of any carries and antioxidants added.