Commentary

USP 42–NF 37, Second Supplement

June 1, 2019

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

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

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

General Chapters

<3> Topical and Transdermal Drug Products—Product Quality Tests
<60> Microbiological Examination of Nonsterile Products—Tests for *Burkholderia cepacia* Complex
<81> Antibiotics—Microbial Assays
<509> Residual DNA Testing
<795> Pharmaceutical Compounding—Nonsterile Preparations (this commentary is contained in a separate document)
<797> Pharmaceutical Compounding—Sterile Preparations (this commentary is contained in a separate document)
<825> Radiopharmaceuticals—Preparation, Compounding, Dispensing, and Repackaging (this commentary is contained in a separate document)
<1071> Rapid Sterility Testing of Short-Life Products: A Risk-Based Approach
<1085> Guidelines on the Endotoxins Test
<1103> Immunological Test Methods—Enzyme-Linked Immunosorbent Assay (ELISA)
<1227> Validation of Microbial Recovery from Pharmacopeial Articles
<1229.16> Prion Sterilization
<1236> Solubility Measurements
<1430> Analytical Methodologies Based on Scattering Phenomena—General
<1430.1> Analytical Methodologies Based on Scattering Phenomena - Static Light Scattering
<1430.2> Analytical Methodologies Based on Scattering Phenomena- Light Diffraction Measurements of Particle Size
<1430.4> Analytical Methodologies Based on Scattering Phenomena- Electrophoretic Light Scattering (Determination of Zeta Potential)
<1430.5> Analytical Methodologies Based on Scattering Phenomena- Small Angle X-Ray Scattering and Small Angle Neutron Scattering

Monographs

Alosetron Hydrochloride
Alosetron Tablets
Amcinonide Cream
Amiodarone Hydrochloride Injection
Amiodarone Hydrochloride Tablets
Amlodipine and Olmesartan Medoxomil Tablets
Chinese Skullcap RootChinese Skullcap Root Dry Extract
Chinese Skullcap Root Powder
Cholecalciferol Chewable Gels
Desmopressin Acetate
Desoximetasone
Epinephrine

Fluoxetine Hydrochloride
Galantamine Hydrobromide
Glucagon
L-Alpha-Glycerylphosphorylcholine
Menaquinone-7 Preparation
Meropenem
Meropenem for Injection
Metaraminol Bitartrate
Neohesperidin Dihydrochalcone
Omega-3 Free Fatty Acids
Prazosin Hydrochloride Capsules
Ropinirole Tablets
Rotigotine
Saccharin
Saccharin Sodium
Sorbic Acid
Timolol Maleate

No comments were received for the following proposals:

General Chapters
<857> Ultraviolet-Visible Spectroscopy
<861> Sutures—Diameter
<871> Sutures—Needle Attachment
<881> Tensile Strength
<1226> Verification of Compendial Procedures
<1602> Spacers and Valved Holding Chambers Used with Inhalation Aerosols—Characterization Tests
<2091> Weight Variation of Dietary Supplements

Monographs
Absorbable Surgical Suture
Aluminum Monostearate
Aminobenzoate Potassium Tablets Ascorbic Acid Chewable Gels
Astemizole
Astemizole Tablets
Atropine Sulfate Tablets
Azithromycin Tablets
Captopril and Hydrochlorothiazide Tablets
Cobamamide
Cystine
Dehydrocholic Acid Tablets
Demeclocycline Hydrochloride Capsules
Demeclocycline Oral Suspension

Dexamethasone Sodium Phosphate Cream
Dexamethasone Sodium Phosphate Ophthalmic Ointment
Dextroamphetamine Sulfate Capsules
Diatrizoate Sodium
Diazepam Capsules
Diazepam Extended-Release Capsules
Dicloxacillin Sodium for Oral Suspension
Diethylstilbestrol Injection
Diethylstilbestrol Tablets
Enalapril Maleate
Ergoloid Mesylates Sublingual Tablets
Erythromycin
Erythromycin Ethylsuccinate
Erythromycin Stearate
Ezetimibe
Fenoldopam Mesylate Injection
Glycopyrrolate
Iodinated I 131 Albumin Aggregated Injection
Krypton Kr 81m
Levobunolol Hydrochloride Ophthalmic Solution
Levodopa Capsules
Levodopa Tablets
Loracarbef
Magaldrate Oral Suspension
Magaldrate Tablets
Mazindol Tablets
Menadiol Sodium Diphosphate Injection
Menadiol Sodium Diphosphate Tablets
Menadione Injection
Menaquinone-7
Metaproterenol Sulfate Inhalation Solution
Methylbenzethonium Chloride Ointment
Methylbenzethonium Chloride Topical Powder
Monobenzone Cream
Nonabsorbable Surgical Suture
Orlistat Capsules
Oxaprozin
Oxprenolol Hydrochloride Tablets
Oxtriphylline Oral Solution
Oxtriphylline Tablets
Oxytetracycline and Nystatin Capsules
Oxytetracycline and Nystatin for Oral Suspension
Oxytetracycline Calcium
Oxytetracycline Calcium Oral Suspension

Phensuximide
Phensuximide Capsules
Piperacillin Sodium
Potassium Perchlorate Capsules
Propyliodone Injectable Oil Suspension
Purified Bentonite
Tetracycline Hydrochloride Capsules
Thioridazine Oral Suspension
Triamterene and Hydrochlorothiazide Tablets
Trifluridine
Valproate Sodium Injection

General Chapters

General Chapter/Section(s): <3> *Topical and Transdermal Drug Products—Product Quality Tests*/Multiple Sections
Expert Committee(s): General Chapters–Dosage Forms
No. of Commenters: 4

Comment #1: In the section *Product Quality Tests for Topical and Transdermal Drug Products*, item 3, the commenter suggested increasing the sample quantity for analysis to avoid a quantity too low to be representative of the whole batch. The request was to remove "(for the assay test, typically NMT 2 actuations)" from the text.
Response: Comment not incorporated. The current language gives general guidance on sample collection.
Comment Summary #2: The commenter requested keeping the *Rolling Ball Method* in *Specific Tests for TDS*, *Tack Test*.
Response: Comment not incorporated. It is not a preferred method, inclusion would incorrectly indicate this is an appropriate test to perform as part of transdermal delivery systems (TDS) product development.
Comment Summary #3: The commenter suggested exempting solutions and lotions from the *Delivered-Dose Uniformity in Metered Dose Containers* as the drug substance(s) is/are fully dissolved in these dosage forms.
Response: Comment not incorporated. The purpose of this test is to demonstrate that the target-delivered dose is administered by actuation per labeling instructions. The main purpose of this test is to evaluate the reproducibility of the closure system.
Comment Summary #4: The commenter noted that discussion regarding acceptance criteria for all in vitro adhesion tests is included in the general test of *Specific Tests for TDS* as well as in all individual tests. The commenter suggested revising the text to avoid this repetition.
Response: Comment not incorporated. The Expert Committee (EC) determined that it was appropriate to keep the discussion on acceptance criteria in this section. The EC's position is that the *Specific Tests for TDS* is an introduction to specific tests and discussing that product acceptance criteria would need to be defined is appropriate.
Comment Summary #5: In the INTRODUCTION section, first paragraph, penultimate sentence, the commenter suggested adding "and topical delivery systems."

Response: Comment not incorporated. The INTRODUCTION section is not meant to provide an exhaustive list of topical dosage forms. Including topical delivery systems is not warranted, and it is not an official dosage form title.

Comment Summary #6: In the INTRODUCTION section, second paragraph, the commenter suggested including penetration enhancer content.

Response: Comment not incorporated. This test is already accounted for with the statement "other tests that may be product specific." This test may be added to the *Specific Tests for TDS* section in a future revision.

Comment Summary #7: The commenter suggested adding visual examination of the identifying label for TDS to the section *Universal Tests*, *Description*.

Response: Comment not incorporated. The tests outlined in <3> are specific to chemical and physical testing.

Comment Summary #8: Under the *Specific Tests*, *Crystal Formation* test, the commenter suggested deleting "using conditions of stress."

Response: Comment incorporated.

Comment Summary #9: In *Specific Tests for Topical Aerosols*, under *Delivered-Dose in Metered Dose Containers*, the commenter suggested adding a cross-reference to General Chapters <601> *Inhalation and Nasal Drug Products: Aerosols, Sprays, and Powders—Performance Quality Tests* and <905> *Uniformity of Dosage Units*.

Response: Comment not incorporated. There are several aspects of these two general chapters that are not applicable to topical dosage forms.

Comment Summary #10: In *Specific Tests for TDS*, third paragraph, the commenter suggested that the acceptance criteria for adhesion testing should be supported by results from clinical batches that demonstrate acceptable in vivo adhesion.

Response: Comment not incorporated. There is no clear in vivo/in vitro correlation for adhesion tests. Products that demonstrated good adhesion by in vitro testing would advance to clinical testing, but not the other way around.

Comment Summary #11: Under *Development of Peel Adhesion and Static Shear Test Methods*, second paragraph, the commenter suggested clarifying what constitutes a failure to the peel adhesion test.

Response: Comment incorporated.

Comment Summary #12: Under *Tack Test*, *Probe Tack Method*, the commenter suggested replacing "5 independent samples" with "5 individual samples" to be consistent with other specific test descriptions in the chapter.

Response: Comment incorporated.

Comment Summary #13: Under *Leak Test*, *In-Process Testing*, *Seal Integrity*, last bullet, the commenter suggested revising the text to read "The product fails if TDS leaks are detected."

Response: Comment not incorporated. The seal integrity test as written has acceptable limits for this test. This suggestion may be considered in a future revision of the chapter.

Comment Summary #14: Under *Leak Test*, *In-Process Testing*, *Packaged Product Testing*, last bullet, the commenter suggested revising the text to indicate that the product fails if TDS leaks are detected.

Response: Comment not incorporated. The *Packaged Product Testing* as written has acceptable limits for this test. This suggestion may be considered in a future revision of the chapter.

General Chapter/Sections:	General Chapter <60> *Microbiological Examination of Nonsterile Products—Tests for Burkholderia cepacia* Complex
Expert Committee:	General Chapters–Microbiology
No. of Commenters:	8

Comment Summary #1: The commenter suggested that the abbreviation "Bcc" be used in place of "BCC" for the members of the *Burkholderia cepacia* complex.
Response: Comment incorporated. Change made throughout the text.
Comment Summary #2: The commenter recommended revising the text to indicate that the tests for Bcc are applicable to not just aqueous products for oral, oromucosal, cutaneous, inhalation or nasal use meant for high-risk populations, but also to aqueous products for oral, oromucosal, cutaneous, inhalation or nasal use in general.
Response: Comment incorporated. Change made.
Comment Summary #3: The commenter recommended that it would be preferable to select a single, ideally worst-case, Bcc organism to confirm growth promotion and method suitability.
Response: Comment not incorporated. The test is required for all members of the Bcc; therefore, without the availability of extensive data for use of a single organism, the EC chose the three most frequently isolated Bcc members that cause infection as growth promotion and method suitability test organisms. When additional data is available, the EC would be willing, in the future, to reduce the number of challenge organisms.
Comment Summary #4: The commenter questioned the rationale for developing a method specific to Bcc because it is not the only Gram-negative bacterium of concern.
Response: Comment not incorporated. The USP acknowledges that other objectionable microorganisms, including members of the family Enterobacteriaceae, must also be excluded from non-sterile drug products. However, given the prominence of Bcc in U.S. product recalls, infection outbreaks, the advisory from the U.S. Food and Drug Administration (FDA), and the requests from stakeholders for a standard test for Bcc, adding the test is timely and fully justified.
Comment Summary #5: The commenter noted that the atmospheric conditions for growth of the listed microorganisms in the chapter are not indicated
Response: Comment not incorporated. Unless otherwise indicated, aerobic condition is the default requirement.
Comment Summary #6: The commenter noted that the incubation temperature recommendations are not consistent with clinical standards recommendations for *B. cepacia* growth (i.e., 35 ± 2º). To harmonize with currently recognized clinical standards, suggest changing the incubation temperature to 35 ± 2º.
Response: Comment not incorporated. The incubation temperature recommended is 30 to 35º in the harmonized General Chapters <61> *Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests* and <62> *Microbiological Examination of Nonsterile Products*: *Tests for Specified Microorganisms*. Therefore, USP believes this temperature will be best

suited for a quality control (QC) microbiology laboratory screening for Bcc in pharmaceutical products, in contrast to clinical samples in a hospital microbiology laboratory. From a practical point-of-view, this temperature selection would allow QC laboratories to use existing incubators and allow for the use of a common enrichment for multiple specified microorganisms. In practice, the incubators are set at 32.5º. The efficacy of the medium and incubation conditions will be demonstrated during growth promotion testing.

Comment Summary #7: The commenter noted that there is no mention of the growth promotion for the primary media (soybean casein digest broth [SCDB] or dilution of SCDB). This media would be growth promoted as outlined in <61>. However, if this media is used for Bcc testing, should Bcc organisms be included?

Response: Comment not incorporated. Any other media or dilution buffer used for the test should be either growth promoted using the indicated organisms in Table 1, or it should be tested for lack of inhibition or toxicity by default.

Comment Summary #8: The commenter recommended changing the phrase “small number (NMT 100 cfu)” to “inoculating each plate with NMT 100 cfu” because including “small number” in the phrase could be misleading.

Response: Comment not incorporated. Similar language exists in other chapters with a long history of use without confusion in terms of the challenge level.

Comment Summary #9: The commenter recommended substituting *Burkholderia contaminans* for *Burkholderia cenocepacia* to align with the most frequently isolated clinical species in the last decade

Response: Comment not incorporated. Review of literature did not confirm the statement that *B. contaminans* is the most frequently isolate member of the Bcc in the past decade.

Comment Summary #10: The commenter suggested also including a negative control to verify the testing conditions.

Response: Comment incorporated. Change made.

Comment Summary #11: The commenter noted that it is not clear whether the comparison should be made on paper based on the results of the test performed with the previously tested and approved batch of medium or the test should be performed in parallel on the current and previous batch of media.

Response: Comment not incorporated. This is identical to the requirement in <62> and is addressed in the frequently asked questions (FAQ).

Comment Summary #12: The commenter indicated that the chapter does not recognize that there could be growth of *Pseudomonas aeruginosa* on the selective agar. Some manufacturers of *Burkholderia cepacian* selective agar (BCSA) have noted that *P. aeruginosa* may be partially inhibited.

Response: Comment incorporated, and the definition of inhibition of growth on BCSA has been changed to address this and to include *Staphylococcus aureus* American Type Culture Collection (ATCC) 25923 as another inhibitory microorganism.

Comment Summary #13: The commenter suggested including a membrane filtration method in addition to the spread plate method and potential use of (Reasoner’s 2A) R2A agar.

Response: Comment not incorporated. Not all oral liquids are filterable, so the enrichment step as described in the chapter is generally more applicable. The point of using selective media is to make the method specific for Bcc. That would not be the case if R2A agar was employed.

Comment Summary #14: The commenter noted that acclimatizing of Bcc may be an issue and suggested including additional text on conditions for acclimatizing the cells in *Suitability of the Test Method*.
Response: Comment not incorporated. While conditions for testing microorganisms from water is indicated in the chapter, it is difficult to specify a standard condition for acclimatization (air, equipment surfaces, pharmaceutical-grade water, or products). All of the current harmonized microbial test methods, i.e., General Chapters <61>, <62>, <63> *Mycoplasma Tests* and <71> *Sterility Tests*, use standardized laboratory cultures to demonstrate that the methods are capable of recovering a range of representative microorganisms.
Comment Summary #15: The commenter suggested changing the shortest incubation time in Trypticase soy broth (TSB) and on BCSA to 48 hours to accommodate growth of slow-growing Bcc members.
Response: Comment incorporated. The pre-incubation of the enrichment broth and the incubation of the BCSA will be changed to at least 48 hours. Note: The shortest incubation times are verified during method suitability testing.
Comment Summary #16: The commenter recommended adding a statement that this test is not applicable for examination of pharmaceutical waters.
Response: Comment not incorporated. Unlike *P. aeruginosa*, Bcc members are frequently found in purified water and have been implicated in product recalls
Comment Summary #17: The commenter recommended adding text to indicate that the product to be examined should be mixed well in Soybean-Casein Digest Broth to ensure even distribution of organisms prior to inoculating BCSA.
Response: Comment not incorporated. An aerobic bacterium would grow throughout the broth, so such a requirement would not be necessary. Also, such a requirement is not found in other tests.
Comment Summary #18: The commenter noted that the pH range indicated for BCSA is 7.0 ± 0.1 and recommended a wider acceptable pH range of 6.8 ± 0.3 to align with more than one supplier of BCSA.
Response: Comment incorporated. Change made.
Comment Summary #19: The commenter recommended updating the interpretation regarding colony characteristics on BCSA to include all vendor specifications.
Response: Comment not incorporated. The description of colony color may vary by media manufacturer and may be subjective. Any growth on BCSA is confirmed by identification tests.
Comment Summary #20: The commenter asked whether all Bcc members have the same reaction on BCSA.
Response: Comment not incorporated. This is largely unknown. Clinical literature indicates BCSA is more reliable and selective, and that Bcc members grow more rapidly on BCSA than other selective media. This uncertainty motivated the EC to use the three most clinically significant strains as method suitability test organisms. Any growth on BCSA is confirmed by identification tests
Comment Summary #21: The commenter indicated that it is not clear if confirmatory identification tests are required in cases where colony growth on the on the BCSA plates do not exhibit the positive-indicative attributes. They suggested clarification on this requirement.

Response: Comment not incorporated. The chapter clearly indicates “The product complies with the test if colonies of the type described are not present or if the confirmatory identification tests are negative.”

Comment Summary #22: The commenter noted that clarification is needed regarding the level of identification.

Response: Comment not incorporated. It is expected that depending on the non-sterile, aqueous drug product, any Bcc member would be considered objectionable unless proven otherwise.

Comment Summary #23: The commenter noted that it is stated in the chapter that other media may be used provided that their suitability can be demonstrated. Will it be expected to perform alternative method validation if the user substitutes proposed media with Cetrimide or Violet Red Bile Glucose (VRBG) Agar?

Response: Comment not incorporated. The two media cited would be unsuitable for the selective isolation of Bcc members.

Comment Summary #24: The commenter noted that BCSA that is indicated for clinical use contains crystal violet, polymyxin B, gentamycin, and vancomycin that inhibit/suppress microorganisms found in clinical samples, i.e., respiratory samples. Non-sterile liquid pharmaceutical products would not harbor these types of clinical sample microorganisms, so the antimicrobials included are not necessary for suppression of overgrowth. In addition, any residual antimicrobials on glassware/equipment from the proposed media could result in false negatives in other testing. Therefore, use of subculture media not intended for clinical use, e.g., Bcc Chromogenic agar, is recommended

Response: Comment not incorporated. Crystal violet suppresses Gram-positive bacteria, while polymyxin B, gentamycin, and vancomycin suppress respiratory pathogens such as *P. aeruginosa* and *S. aureus*. We are aware of the need to use clean glassware. General Chapter <1117> *Microbiological Best Laboratory Practice*s emphasizes the necessity of using clean glassware when testing for *P*. *aeruginosa* and *B. cepacia* in non-sterile drug products. The indicated medium is a single-supplier, proprietary product that cannot be include in a USP test chapter.

Comment Summary #25: The commenter noted that BCSA is a highly selective agar with five selective ingredients. It might be beneficial to use a less selective agar in parallel.

Response: Comment not incorporated. The test chapter is specially written as an official test for Bcc. It represents a minimum requirement, and companies may add additional testing or strategy for testing depending on the risk involved.

Comment Summary #26: The commenter questioned the need to use a medium such as BCSA when Cetrimide Agar used for *P.aeruginosa* can also recover Bcc members.

Response: Comment not incorporated. Just as growth on Cetrimide Agar is selective for *P. aeruginosa*, growth on BCSA is selective for Bcc. With general microbiological growth media, *P. aeruginosa* may outgrow Bcc members.

Comment Summary #27: The commenter noted that there are a number of variants of BCSA, and it would be useful to specify the names of the original developers of the medium.

Response: Comment not incorporated. The BCSA formulation indicated in the chapter is representative of multiple suppliers.

Comment Summary #28: The commenter noted that according to the instructions provided in the chapter, on preparation of BCSA, all the ingredients can be mixed together and sterilized. Typically, antibiotics are added after media is sterilized and cooled down to 45–50º. The commenter therefore suggested changes to media preparation
Response: Comment incorporated. Changes made accordingly.

General Chapter/Section(s): <81> *Antibiotics—Microbial Assays*/Multiple Sections
Expert Committee(s): Biologics Monographs 4
No. of Commenters: 3
Comment Summary #1: The commenter suggested omitting the reference for Vancomycin in *Table 1* through *Table 4* and *Table 6* based on the proposed deletion of the Vancomycin monograph published in *PF* 44 (5).
Response: Comment not incorporated. The vancomycin monograph will not be omitted as proposed in *PF* 44(5) due to public comments received.
Comment Summary #2: The commenter suggested that the triplicates or more assay runs can be performed independently within a day or on different days.
Response: Comment incorporated. The requirement for performing additional assays on a different day was removed from <81>.
Comment Summary #3: The commenter requested flexibility for the base layer volume for Nystatin and Amphotericin B.
Response: Comment not incorporated. USP provides the base layer volume that has been validated. Refer to *General Notices* 6.30 *Alternative and Harmonized Methods and Procedures* for using methods different from compendial methods.

General Chapter/Section(s): <509> *Residual DNA Testing*
Expert Committee: General Chapters–Biological Analysis (GCBA)
No. of Commenters: 8
Comment Summary #1: The commenter recommended including the information for isolating DNA in General Chapter <1130> *Nucleic Acid-Based Techniques—Approaches for Detecting Trace Nucleic Acids (Residual DNA Testing)* rather than in <509>.
Response: Comment not incorporated. Chapter <1130> is a guidance chapter and is not in revision, but these comments will be considered in the future. Chapter <509> contains validated procedures with system suitability criteria and RSs, so that users can more rapidly adopt a procedure and verify that it is suitable for their particular purpose. It is not appropriate to add a test chapter method to a general chapter, e.g., <1130>.
Comment Summary #2: Commenters recommended either clarifying the purpose of the chapter if no monographs cite it or noting that residual DNA measurement and extraction methods do not necessarily have to be followed as outlined, and that similar methods are equally acceptable if properly validated and shown to be fit-for-purpose.
Response: Comment not incorporated. There is no requirement to use the <509> procedure unless a monograph cites it and even then, per USP *General Notices* section 6.30 *Alternative and Harmonized Methods and Procedures*, users can use their validated methods if they give equivalent or better results than the compendial method.

Comment Summary #3: The commenter recommended aligning <509> with <1130> and clarifying that when sample characteristics (e.g., matrix effects or sample preparation method) make achieving a recovery acceptance criterion of 50%–150% impractical, other approaches may be possible.
Response: Comment not incorporated. Chapter <509> is intended for release testing, not in-process testing. It is common industry practice to not accept results with less than 50% recovery.
Comment Summary #4: The commenter recommended aligning the chapter with the World Health Organization (WHO) guidance and clarifying in the Briefing that the removal of residual DNA may be demonstrated during process development so that the testing of individual lots may not be required at release.
Response: Comment not incorporated. The Briefing is deleted in the official publication.
Comment Summary #5: The commenter recommended removing "optional" from the description of the extraction procedure. Instead, the commenter recommended that the extraction procedure is made a default approach.
Response: Comment incorporated.
Comment Summary #6: The commenter recommended deleting the Note in the *Sample Preparation* section that states that "Other sample preparation techniques may be used with the qPCR-based method, if validated" because USP *General Notices* section 6.30 *Alternative and Harmonized Methods and Procedures* already allows the use of validated methods if they give equivalent or better results than the compendial method.
Response: Comment incorporated.
Comment Summary #7: The commenter recommended clarifying the preparation of the resuspension solution to: "Dissolve tris(hydroxymethyl)aminomethane hydrochloride (Tris-HCl) and ethylenediaminetetraacetic acid (EDTA) to obtain a solution of 10 mM and 1.0 mM, respectively. Add hydrochloric acid or sodium hydroxide to adjust to pH 8.0."
Response: Comment incorporated.
Comment Summary #8: The commenter recommended specifying that the "Tris-HCl" used in the preparation of the resuspension solution should be prepared with nuclease free water.
Response: Comment not incorporated. The EC determined that this is a well-known practice in a molecular biology laboratory and the positive control will fail if nucleases are present.
Comment Summary #9: The commenter recommended referencing the sample preparation "as described in the monograph."
Response: Comment not incorporated. There is no requirement to use a procedure in <509> unless a monograph cites the chapter and procedure. In addition, per USP *General Notices* section 6.30 *Alternative and Harmonized Methods and Procedures,* users can use their validated methods if they give equivalent or better results than the compendial method.
Comment Summary #10: The commenter recommended preparing the reference standard in 10 mM Tris (pH 8.0) or 10 mM Tris-1mM EDTA (pH 8.0) rather than with nuclease free water.
Response: Comment not incorporated. The method was validated as written, and as described above, USP *General Notices* 6.30 allows suitable alternatives.
Comment Summary #11: The commenter recommended adding instructions on handling, aliquoting, and storage procedures of in-house preparation of the genomic DNA reference standard.

Response: Comment not incorporated. USP does not provide users with information on the preparation or storage of in-house reagents. USP recommends the users refer to the http://www.usp.org/frequently-asked-questions/reference-standards for further information.
Comment Summary #12: The commenter asked if the stock reference standard DNA at 1 µg/mL could be stored for future use and recommended adding stability information and storage instructions.
Response: Comment not incorporated. USP does not have information to support this type of use.
Comment Summary #13: The commenter suggested providing additional guidance on matrix interference.
Response: Comment not incorporated. The EC determined that this information is beyond the scope of <509> and would belong in an informational general chapter.
Comment Summary #14: The commenter suggested adding more internal controls, clearly discernable from the target sequence.
Response: Comment not incorporated. The method was validated as written with the most important target control.
Comment Summary #15: The commenter suggested clarifying the preparation of the proteinase K solution.
Response: Comment not incorporated. The EC determined that the method was written to allow flexibility where possible, and additional clarifications would not provide added value.
Comment Summary #16: The commenter suggested allowing flexibility on the number of replicates to be performed for the preparation of the Proteinase K solution in the extraction procedure, depending on the precision of the method.
Response: Comment not incorporated. The method was validated as written, and the Expert Panel and EC believe it is suitable for most laboratories performing these types of measurements.
Comment Summary #17: The commenter suggested including the sample storage conditions, including time and temperature, in the extraction procedure.
Response: Comment not incorporated. Long-term sample storage conditions were not evaluated in the method validation.
Comment Summary #18: The commenter suggested adding a note in the extraction procedure before “Add 50 µL of Proteinase K solution to 450 µL of triplicate samples each…” The note would state “Equivalent commercially available extraction kits may be used” in the extraction procedure.
Response: Comment not incorporated. The EC determined that the method provides sufficient flexibility as written and further clarifications are not needed.
Comment Summary #19: The commenter suggested deleting the ambiguous note: “[Note—Centrifugation at colder temperatures may be helpful to improve DNA recovery.]”
Response: Comment partially incorporated. The note will be revised to “Note—Centrifugation at 2–8º temperatures may be helpful to improve DNA recovery.”
Comment Summary #20: The commenter suggested adding “to ensure total ethanol removal” to the extraction procedure after the pellet air drying instruction.
Response: Comment not incorporated. The EC determined that the text was clear as written.

Comment Summary #21: Commenters suggested clarifying the text about recording the actual sample recovery in the extraction procedure that is used for the final calculations.
Response: Comments incorporated. The text will be revised to “Resuspend the pellet and record the volume of water or resuspension solution used that may be needed when reporting…”
Comment Summary #22: The commenter suggested adding that other suitable primer pairs and probe sequences could be used in the DNA stock primers and probes sections.
Response: Comment not incorporated. The method was validated as written.
Comment Summary #23: The commenter suggested deleting the word “swirling” to allow for other methods of mixing the 2X master mix.
Response: Comment accepted. The text was edited to read “Mix well immediately before use.”
Comment Summary #24: The commenter suggested adding recommendations for freeze/thaw and storage conditions for the primers and probes.
Response: Comment not incorporated. The chapter method was validated as written, and longer-term storage or freeze/thaw conditions were not evaluated during validation.
Comment Summary #25: For clarity, the commenter recommended adding to the Table 1 footnote “6-FAM” and “6-TAMRA” after 6-carboxyfluorescein and 6-carboxytetramethylrhodamine, respectively.
Response: Comment not incorporated. These abbreviations are not used later in the chapter.
Comment Summary #26: The commenter recommended removing either the footnote a or b in Table 1 as they are identical.
Response: Comment accepted. Footnote b will be removed.
Comment Summary #27: The commenter recommended adding a note to the standard solution preparation stating: “[Note: if a product monograph or other established specification for residual DNA justifies, the concentration range can be adapted accordingly].
Response: Comment not incorporated. The method was validated as written, and the preparation of the Standard solutions already allows some suitable flexibility.
Comment Summary #28: Two commenters recommended clarifying that alternative software and instruments can be used.
Response: Comment not incorporated. The method already states that the user can use the alternative instruments and software.
Comment Summary #29: The commenter recommended using a similar criterion for system suitability as for the negative control No Template Control (NTC).
Response: Comment accepted. The text will be edited to state: “Negative control solution: The Ct corresponding to the Negative control solution, if any, is NLT the Ct of all of the lowest concentration of the Standard solutions.”
Comment Summary #30: The commenter recommended adding that mean recovery of the three replicates must be within 50% and 150% of the observed residual DNA plus the spiked-in amount in the Positive control solution, for the particular test sample.
Response: Comment partially incorporated. The Accuracy requirements will be revised to state “The mean **spike** recovery of three replicates of Positive control solution is between 50% and 150%.”
Comment Summary #31: The commenter recommended using the mean recovery of two replicates rather than three to determine the Accuracy for system suitability.

Response: Comment not incorporated. The method was validated as written, and the EC believes that the use of three replicates is suitable for this method.
Comment Summary #32: The commenter recommended editing the Suitability requirements for the Relative standard deviation to "NMT than 30% for the three replicates of the Sample solutions and Positive control solutions should be determined and implemented based on method development and later method validation."
Response: Comment not incorporated. The method was validated as written.
Comment Summary #33: The commenter recommended changing the slope specification of the linearity system suitability specifications to 3.00–3.75 (85–115% PCR efficiency) instead of 3.1–3.8 (83–110% PCR efficiency).
Response: Comment not incorporated. The method was validated as written, and multiple laboratories easily passed this requirement during collaborative testing. The proposed change may be too low and indicate that the method accuracy is not adequate.

General Chapter/Sections:	General Chapter <1071> *Rapid Sterility Testing of Short-Life Products: A Risk-Based Approach*
Expert Committee:	General Chapters—Microbiology
No. of Commenters:	8

Comment Summary #1: The commenter recommended changing the title to *Rapid Microbial Tests for Release of Sterile Short Life Product*s since testing whether rapid or classical does not measure or indicate sterility.
Response: Comment incorporated. Title was changed in addition to any text that indicates "rapid sterility tests."
Comment Summary #2: The commenter recommended adding a statement indicating that <71> is the referee test for any drug product when there is a dispute of sterility.
Response: Comment incorporated. Change made.
Comment Summary #3: The commenter recommended deleting references to the use of rapid sterility testing (RST) for compounded products. Provisions for RST of compounded products are already included in General Chapter <797> *Pharmaceutical Compounding—Sterile Preparations*. Given the variation of the expertise between compounding pharmacies and firms performing cutting-edge gene therapy, the chapter should be written for the appropriate audience, considering both the need of use and the expertise.
Response: Comment not incorporated. Several sterile compounding pharmacies are already using rapid sterility tests as alternatives to <71>, after appropriate validation; therefore, they have expertise in this area.
Comment Summary #4: The commenter noted that not all cell and gene therapies need new test methods. Those based on large cell banks and that are cryopreserved can use traditional test methods such as <71>. Although there may be sample volume limitations that might necessitate alternative methods, rapidity is not always a requirement.
Response: Comment not incorporated. The EC agrees that some allogeneic cell therapies are derived from cell banks, expanded in bioreactors, filled in large batches, tested using <71>, and stored frozen. However, with patients in dire need of these products, rapidity may be a requirement. Furthermore, facilities prefer to get sterility test results prior to freezing the cells.

Comment Summary #5: The commenter noted that the term “risk-based” is used throughout the chapter, but it is not well-defined and recommended adding a section that describes the concept of risk in the context of this chapter. The commenter also suggested dividing the chapter into separate sections for cell and gene therapy products, positron emission tomographic (PET) drugs, and other products because the considerations and test methods for these products are largely different.
Response: Comment not incorporated. The section entitled *The Concept of Risk-Based Microbiological Monitoring and Release Testing* addresses the issue of risk. Also, as many considerations are common, it would not be useful to subdivide the sections
Comment Summary #6: The commenter recommended defining “rapid” in the chapter introduction. Almost any test could be considered “rapid” compared to the compendial method, which has a 14-day incubation period.
Response: Comment incorporated. Change made.
Comment Summary #7: The commenter recommended that any reference to compounding be deleted from the chapter.
Response: Comment not incorporated. Several sterile compounding pharmacies are using rapid sterility tests as alternatives to <71>, after appropriate validation, and they have expertise in this area.
Comment Summary #8: The commenter noted the alternate sterility test method should be demonstrated to be comparable to the reference test (<71>). As written, this is not necessarily clear to the reader.
Response: Comment not incorporated. The Introduction to the chapter clearly states “It should be noted that as with alternate test methods, the referee test in the event of a dispute <71>.” USP intends on developing rapid microbial detection tests for the release of sterile products in a future chapter.
Comment Summary #9: The commenter recommended replacing “ability to detect, preferably less than 100 colony-forming units (cfu)” with “detection limit” in the section on user requirement specifications (URS).
Response: Comment incorporated. Text changed to clarify detection in the test sample.
Comment Summary #10: The commenter recommended changing “a wide range of viable microorganisms” to “a wide range of microorganisms” in the section on URS.
Response: Comment not incorporated. The distinction between viable and non-viable microorganisms is clinically important, and the technology employed may require modification to avoid detecting dead microorganisms
Comment Summary #11: The commenter recommended identifying the detected microorganism (or allowing a subsequent identification) in the section on the addition of a URS.
Response: Comment incorporated. Change made.
Comment Summary #12: The commenter suggested the addition of the following requirement to the URS section: “When feasible, manufacturers should consider assay requirements during process design.”
Response: Comment incorporated.
Comment Summary #13: The commenter recommended adding “And a possibility to identify false positive and false negative rates (i.e., control reactions)” to the URS.

Response: Comment partially incorporated. It is unclear if one can identify a rate but measuring a rate may be possible. The ability to evaluate a result in terms of the controls, both positive and negative, is critical. Change made to the list to add that URS.

Comment Summary #14: The commenter recommended changing the URS "method suitability" to "method validation." Companies would be expected to validate the method in the presence of product.

Response: All validated test methods are required to meet the requirements of method suitability to demonstrate the recovery of the analyte in the presence of the product. When rapid microbial tests become official USP test methods, they will be considered validated, and the only requirement with be method suitability.

Comment Summary #15: The commenter recommended adding the following to the list of URS: "Established methods preferred over unproven technologies."

Response: Comment partially incorporated. The candidate technologies highlighted in this chapter are proven technologies with a well-established history of use in detecting microbial contamination. The only exception to this is Isothermal Microcalorimetry, and a sentence has been added to indicate this under the technology overview.

Comment Summary #16: The commenter noted that use of the phrase "LOD above 1 cfu" is vague and potentially misleading, given the variation in sample volumes used for different types of sterility tests and the fact that the compendial sterility test (<71>) is not a quantitative test. Therefore, the commenter recommended removing the reference to a 1 cfu detection limit. The commenter also recommended emphasizing the need to consider both the time to result and the limit of detection (LOD) when performing a risk assessment for choosing an appropriate sterility test.

Response: Comment incorporated. Change made.

Comment Summary #17: The commenter noted the chapter stated that one advantages of non-growth-based RST methods is "the inability to be affected by antibiotics in the test sample." However, there are antibiotics noted in the literature that inhibit polymerase chain reaction (PCR).

Response: Comment incorporated. Change made to indicate this.

Comment Summary #18: The commenter indicated that because "risk-based" is not well-defined in this chapter, Table 2 (now Table 1) lacks context. Therefore, the commenter recommended a discussion of the concept of risk and suggested noting that relative risk is complicated by the fact that bacteria in the sample could multiply.

Response: Comment not incorporated. The paragraph above the table provides the context. The risk of the administered parenteral product in terms of adverse reaction, pyrogenic response, and infection are all related to the volume and route of injection of the drug product.

Comment Summary #19: The commenter recommended changing "intramuscular, i.e., forearm" to "intramuscular" in Table 2 (now Table 1)

Response: Comment incorporated. Change made.

Comment Summary #20: The commenter noted that the chapter discusses some of the challenges, parameters, and possible sensitivities of alternate test methods, but does not discuss validation of these methods. The commenter acknowledged that validation is beyond

the scope of this chapter and recommended adding “validated” to this phrase to remind stakeholders that alternate test methods would need to be validated.
Response: Comment not incorporated. The proposed <1071> is not about alternate test methods. Rather, it introduces a new generation of microbial test methods that the USP plans to develop. Validation of alternate microbial test methods is discussed in General Chapter <1223> *Validation of Alternative Microbial Methods*.
Comment Summary #21: The commenter suggested adding the qualifier “sensitive” to differentiate the approved Chapter’s Table 2 methods from traditional methods such as Gram staining that are rapid but not sensitive.
Response: Comment not incorporated. The table indicates that the Gram stain is for comparative purposes only. The columns in the table already address the limit of detection, time to result, and the sample.
Comment Summary #22: The commenter asked why Table 2 omits the baseline (<71> parameters) that RST proposes to improve, and they recommended adding conventional sterility testing as a comparison.
Response: Comment incorporated. Change made.
Comment Summary #23: The commenter noted that it is not clear whether the limits of detection shown in Table 3 are cfu/sample or cfu/mL.
Response: Comment not incorporated. It is per test sample as evident from the table.
Comment Summary #24: The commenter noted that for nucleic acid-based methods, the LOD should be in terms of genomic units.
Response: Comment incorporated. Change made via a footnote.
Comment Summary #25: The commenter noted that the chapter incorrectly references only Table 2 for the sampling plan for <71> sterility testing.
Response: Comment incorporated. Change made to indicate Tables 2 and 3 of <71>.
Comment Summary #26: The commenter noted that although there may be some flexibility in the sampling point for cell and gene therapies, the final container material should be tested unless another sampling point can be justified.
Response: Comment incorporated. Change made.
Comment Summary #27: The commenter recommended deleting the statement “… for a cell preparation less than 1 mL, the preparation would not be tested.” This statement is incompatible with 21 Code of Federal Regulations (CFR) 211.165(a), 211.165(b), and 211.167(a) and is not justified.
Response: Comment not incorporated. The referenced statement in the chapter is from the recently developed *European Pharmacopoeia* (*Ph.Eur.*) chapter 2.6.27 that is specifically intended for cell therapies. Furthermore, <1071> is an informational chapter and does not state requirements with which compendial users must comply. Compendial users are responsible for following applicable regulatory requirements in their jurisdiction.
Comment Summary #28: The commenter noted that it is inappropriate to conclude that non-growth-based RSTs, or any type of RST, cannot attain single cell detection. If the technology supplier has designed and demonstrated an LOD of a single cell, then that method is capable of attaining this level of detection in the hands of the stakeholder. Therefore, Limit of Detection should be revised, or the latter section deleted, to reflect the current state of available technologies. To be clear, it is acceptable to state that the required LOD should be determined

by the stakeholder based on a risk assessment and the capability of the method being employed.
Response: Comment partially incorporated. The statement is too broad a generalization. Solid phase fluorescence cytometry is capable of detecting 1 cfu, while technologies do exist for concentrating a test sample into the range of the LOD for other candidate testing methods. However, flow cytometry and PCR cannot detect 1 cfu with concentration or microbial growth.
Comment Summary #29: The commenter noted that the statements about infectious dose in Limit of Detection are already discussed in the *Stimuli* article (see reference #1 in the *References* section of the General Chapter) that was published earlier and may not add value to the chapter.
Response: Comment incorporated. The statements about infectious dose have been deleted.
Comment Summary #30: The commenter suggested adding a reference to <1223>.
Response: Comment not incorporated. The proposed chapter is not about alternate methods.
Comment Summary #31: The commenter suggested adding continuously monitored culture-based methods to the list of technologies recommended.
Response: The ability to progressively monitor detection methods based on respiration is already included.
Comment Summary #32: The commenter suggested adding the following text to the paragraph on flow cytometry: “Bacteria are very small and may be hard to distinguish from cell debris.”
Response: Comment incorporated. Change made.
Comment Summary #33: The commenter noted there is no mention of the ability to detect a wide range of microorganisms. Even if in some real applications, the universality of test is not mandatory, it is important to detect a wide number of microorganisms to control patient risk. And for nucleic acid amplification technology, the need to develop many different probes must be considered as a critical parameter as well.
Response: Comment partially incorporated. Change made. In user requirements, the ability to detect a wide range of microorganisms is clearly stated. There are universal probes and primers for both bacteria and fungi described in the literature. A statement about pan bacterial and pan fungal probes has been added.
Comment Summary #34: The commenter noted that a convenient and easy method to remove free microbial DNA would be a centrifugation/washing step at the beginning of the sample preparation. Free DNA would stay in the supernatant, and the pellet could be used for further analysis.
Response: Comment incorporated. Change made.
Comment Summary #35: The commenter noted direct comparison between growth-based and nucleic acid amplification-based assays is complicated by the fact that nucleic acid amplification-based assays also detect non-viable organisms and are a measure of microbial genome copy number, not cfu.
Response: Comment incorporated. Change made.
Comment Summary #36: The commenter recommended deleting the statement “a test method with the demonstrated sensitivity of 10–100 cfu/mL would be suitable to detect clinically significant bacterial contamination.”
Response: Comment not incorporated. This conclusion was reached by the authors of the cited publication.

Comment Summary #37: The commenter noted that in some situations, even a non-growth-based test may not necessarily be completed before a short-life product needs to be administered to a patient. For example, some cell therapies are given within 30 minutes of product formulation. The commenter also noted that for any method, GMPs require quality assurance (QA) sign-off and written records. (The test results may be available, but additional time is required to complete the process of product release.) Therefore, the commenter recommended changing "the test will be completed" to "the test may be completed and reviewed."
Response: Comment not incorporated. A pharmaceutical GMP model is not necessarily appropriate to cell therapies that are clinician driven and time sensitive.
Comment Summary #38: The commenter noted that nucleic acid amplification-based tests detect microorganisms, but they do not isolate microorganisms. Therefore, they recommended changing "isolation" to "detection."
Response: Comment incorporated. Change made.
Comment Summary #39: The commenter noted that most cell therapy products cannot be filtered and suggested including this in the discussion on solid phase cytometry.
Response: Comment incorporated. Change made.
Comment Summary #40: The commenter recommended deleting Figure 1. The purpose of the figure and the accompanying text is unclear.
Response: Comment incorporated. Change made.

General Chapter/Sections: General Chapter <1085> *Guidelines on Endotoxins Test*
Expert Committee: General Chapters–Microbiology
No. of Commenters: 8
Comment Summary #1: The commenter disagreed with the statement "If GNB [Gram-negative bacteria] cannot grow, endotoxins cannot be generated." Growth of GNB before the manufacturing process can lead to the presence of endotoxins. Prior to introduction to the manufacturing facility, materials could be contaminated with bacteria that have died, but the endotoxins would remain. Whether or not bacteria are actively growing, persisting, or dead is irrelevant. Bacterial contamination from any source could introduce endotoxins.
Response: Comment not incorporated. The paragraph already addresses the issue. Generally, people are not great sources of endotoxins because they generally do not shed GNB.
Comment Summary #2: The commenter recommended removing discussion of outer membrane vesicles (OMVs) from the entire chapter. The mechanisms of how lipopolysaccharide (LPS) and endotoxins are released from the Gram-negative membrane is a complex and evolving area of research
Response: Comment not incorporated. Sufficient references to peer reviewed research on OMV have been provided, and additional references to current research have been included.
Comment Summary #3: The commenter noted naturally occurring endotoxins are being debated and should not be included at this time in the guidance.
Response: Comment not incorporated. This is a statement on the composition of the current standard and the fact that LPS is not found in nature by itself. It cannot contaminate parenterals and therefore while control standard endotoxin (CSE)/Endotoxin Reference Standard (RSE)

may be good choices for calibration, they may not be representative of what is actually in the product

Comment Summary #4: The commenter recommended that USP expand on the discussion of endotoxin recovery studies.

Response: Comment not incorporated. This is out of scope of the compendial test.

Comment Summary #5: The commenter suggested deleting information presented on the preparation and formulations of various endotoxin preparations since it does not add value to the chapter.

Response: Comment not incorporated. This information is meant only to remind all that the endotoxins found in products are different in many respects from the *Escherichia coli* RSE/CSE calibration standard. Reference to the *Guidance for Industry: Pyrogen and Endotoxins Testing: Questions and Answers* is important in that it confirms an acknowledgement by FDA that the two preparations may not react the same. Neither <1085> nor <85> directly reference sample storage or hold time studies.

Comment Summary #6: The commenter suggested referencing General Chapter <1058> *Analytical Instrument Qualification* for instrument qualification

Response: Comment incorporated. Change made.

Comment Summary #7: The commenter suggested referencing <85> for the definition of maximum valid dilution and keeping only additional information (not provided in chapter <85>).

Response: Comment not incorporated. The EC feels it is appropriate enough to repeat the definition here because of its importance and place in the sequence of testing events.

Comment Summary #8: The commenter indicated that the *Japanese Pharmacopoeia* (*JP*) RSE is made from a different bulk of LPS preparation than the USP and WHO RSE.

Response: Comment incorporated. Change made.

Comment Summary #9: The commenter recommended including additional details regarding potency determination of CSE because it is so critical to the assay.

Response: Comment incorporated. Change made.

Comment Summary #10: The commenter noted that clarification is needed as to which liquid endotoxin standard the text is referring.

Response: Comment incorporated. Change made.

Comment Summary #11: The commenter suggested providing additional flexibility and clarification such that testing/verifying vendor supplied plastic disposables are not construed as a requirement.

Response: Comment not incorporated. This is a requirement per the current <85>. While an in-house screen is possible, at least during the qualification of vendors and periodically thereafter, these results must be experimentally determined.

Comment Summary #12: The commenter recommended deleting the sentence that the plastic apparatus used “does not interfere in the test” as consumables will indirectly be tested for interference by the assay controls.

Response: Comment not incorporated. While consumables can be indirectly tested by controls, if a control does not work, one cannot rule out the consumables unless they are tested. This is a requirement per the current <85>.

Comment Summary #14: The commenter noted the sentence indicating that depyrogenated consumables have a low risk of recontamination if stored properly implies that the risk of

recontamination is low without any understanding of manufacturing and storage conditions. Instead, the manufacturer should be urged to consider control measures to ensure appropriate storage conditions and to avoid contact with potentially contaminating substances. Therefore, the commenter recommended deleting the sentence.
Response: Comment partially incorporated. Clarification added. The statement cited is intended for laboratory-use disposables, not manufacturing disposables. For manufacturing disposables, there may be additional safeguards required.
Comment Summary #15: The commenter recommended that in reference to consumables, the vendor should provide on the certificate of analysis (CoA) the sensitivity of the limulus amebocyte lysate (LAL) method and specify the technique used to conduct the test.
Response: Comment partially incorporated. Clarification added.
Comment Summary #16: The commenter suggested adding guidance on calculating log/log linear correlation for analyst and reagent qualifications, either that individual reaction time values must be calculated or that the average of all replicates is acceptable.
Response: Comment incorporated. Guidance added.
Comment Summary #17: The commenter recommended revising the section on Analyst Qualification by writing the list of items in a consistent style such that each item reads as an issue to be emphasized during training.
Response: Comment not incorporated, in the absence of a specific suggestion.
Comment Summary #18: The commenter recommended adding “hands-on” or “on the job” training category to the section on Analyst Qualification.
Response: Comment incorporated. Change made.
Comment Summary #19: The commenter noted that the ability to achieve the requirements outlined in <85> for photometric methods, i.e., r value of -0.980 or better, does not demonstrate the competency of performance or accuracy of the analyst. An analyst can make significant dilution errors in the construction of the standard curve and still meet the criteria set out in <85>. To truly test the competency and accuracy of the analyst, known concentrations of RSE should be tested as unknowns alongside the curve, with proficiency and accuracy determined by the proximity of the calculated values to the known values.
Response: Comment partially incorporated. While this is not the only way to demonstrate the competency of the analyst, it does require that the analyst meet some pre-determined benchmark to determine accuracy.
Comment Summary #20: The commenter noted that preparing RSE dilutions may bear no resemblance to normal sample preparation techniques. It seems, from the suggestion to make and test RSE dilutions, what is really being proposed is a challenge of the cartridges’ archived standard curve range. As the archived standard curve for every batch of cartridges produced has already been challenged, using multiple known concentrations of RSE, by the manufacturer as part of their QC program, and that data is submitted to the competent authority for batch release approval, a further challenge by an analyst as part of their qualification/training seems excessive. It would also require USP/*Ph.Eur.*/WHO to keep up with the increased demand for RSE should this proposal remain in the guidance.
Response: Comment partially incorporated. There are many ways to demonstrate analyst capability. This is not done, of course, for each analyst and each cartridge lot. It is a one-time

thing, just as confirming lambda or making a linear standard curve is the norm for analyst qualification in gel or kinetic. Nothing here is prescriptive, it is only a recommendation.
Comment Summary #21: The commenter recommended providing a better description of "Standard laboratory aseptic technique." Depending on the laboratory performing the assay, the "standard" can vary greatly. Perhaps using the term "appropriate" rather than "standard" would provide clarity
Response: Comment incorporated. Change made.
Comment Summary #22: The commenter recommended including the use of an ultrasonicated bath as an alternative to vortex mixer for the dilution of the sample and dilution of the standard (but not reconstitution of CSE or RSE).
Response: Comment incorporated. Change made.
Comment Summary #23: The commenter suggested including the possibility that the vendor has performed validations of the stability and used RSE and/or CSE. If this is the case, these should be followed.
Response: Comment not incorporated. Conditions between vendors and the laboratory can vary (e.g., storage conditions, volumes, tube composition).
Comment Summary #24: The commenter noted that while the contents of the tubes should not be jostled, the requirement to only pick up one tube at a time may be too restrictive since a skilled analyst may be able to pick up two or more tubes without jostling.
Response: Comment not incorporated. Historically, the "rule" is one at a time to avoid the possibility of jostling. If you want skilled analysts to do more than one at a time, that is part of analyst training.
Comment Summary #25: The commenter recommended deleting information on instrument qualification, operational qualification, performance qualification, software 21 CFR part 11, etc., since this is a global requirement on current GMP testing and not specific to endotoxin by LAL.
Response: Comment not incorporated. This is to ensure users understand that LAL testing is not a special case. Unlike chemistry laboratories, there is relatively little in the microbiology laboratory that requires validation of instruments and software.
Comment Summary #26: The commenter noted that gloves are not mandatory for performance of bacterial endotoxins test (BET).
Response: Comment partially incorporated. Clarification added. Gloves may be required to protect the analyst from any effects of the material under test. In this case, if gloves are used, they should be talc free.
Comment Summary #27: The commenter suggested including clarification on whether sampling holding times are required and addressing how these types of studies would be performed.
Response: Comment not incorporated. The specifics of hold time testing are process- and product-specific and are beyond the scope of the chapter. GMP and risk analysis per International Conference on Harmonisation (ICH) Q9 requires that companies need to construct studies accordingly if/when hold time studies are determined pertinent.
Comment Summary #28: The commenter suggested deleting some redundancies with <85> regarding the section on calculating endotoxin limits and adding some information for products with inherent pyrogenic effect for specifications.

Response: Comment not incorporated. These are examples, meant to clarify and expand on <85>, especially since numerical limits are now omitted from product monographs and companies are required to calculate endotoxin limits using <85>.

Comment Summary #29: The commenter suggested including an example to illustrate that the specification for a product dosed on a per mg basis ultimately ends up in endotoxin unit (EU)/mg.

Response: Comment incorporated. Change made.

Comment Summary #30: The commenter suggested omitting the reference to administration time and providing the possibility of expressing the specification as EU per dose.

Response: Comment not incorporated. The compendial requirement is dose/kg/hr.

Comment Summary #31: The commenter noted that calculating endotoxin limits based upon a 30 kg body weight pediatric dosage instead of the normal 70 kg body weight is a new concept that has not been prescribed previously in any regulatory guidance. This change may indicate unnecessarily tightening endotoxin limits for many product lines.

Response: Comment not incorporated. There is no differentiation in <85> between adult and pediatric: it is dose/kg. Chapter <85> no longer refers to 70 kg. Therefore, going through the product insert, one would have to take the highest dose/kg. If the pediatric dose is higher, then that is the dose that should be used.

Comment Summary #32: The commenter noted that in Table 2, injection routes other than intravenous (IV) (intramuscular [IM], subcutaneous [SC]) are specified. This is inconsistent with alternate guidelines. For example, the JP (Monographs for Preparations) excludes BET testing for products that are exclusively for intracutaneous, subcutaneous, or intramuscular administration. Please remove IM and SC designations from the informational chapter. The commenter also recommended that USP consider a Pharmacopeial Discussion Group (PDG) working group discussion on harmonizing the requirements to test IM/SC injections for bacterial endotoxins.

Response: Comment not incorporated. The requirements for testing depend on a firm's submission and approvals.

Comment Summary #33: The commenter recommended adding General Chapter <771> *Ophthalmic Products—Quality Tests* K value reference of NMT 2 EU/eye/day for injected or implanted ophthalmic drug product and K value reference for irrigation solution.

Response: Comment incorporated. Change made.

Comment Summary #34: The commenter suggested that the calculation of the endotoxin limit should always be done based on the product package insert, even if there is a compendial monograph limit. The discussion should recommend that the most stringent limit should be applied.

Response: Comment not incorporated. Current text already indicates this.

Comment Summary #35: The commenter suggested that for clarity, changing the sentence “care must be taken to avoid the addition of endotoxins to the preparations” to “care must be taken to avoid contaminating the preparations with endotoxin.”

Response: Comment incorporated. Change made.

Comment Summary #36: The commenter suggested providing an example for calculating endotoxin limits for non-compendial articles.

Response: Comment incorporated. Change made.

Comment Summary #37: The commenter noted that while the recommended approach in the chapter to calculate limits for non-compendial articles is probably "lowest risk," it may be impractical for many products.
Response: Comment partially incorporated. Text was added to address some of the issues raised. Ultimately, it is up to the company to justify what they do, but finished product testing alone will not make up for a lack of raw material testing.
Comment Summary #38: The commenter suggested providing specific instruction for drug/device combination products where drug is solid.
Response: Comment not incorporated. This information is available elsewhere.
Comment Summary #39: The commenter suggested clarifying whether a combination product/kit would be specific to a single manufacturer.
Response: Comment not incorporated. Kit components do not have to be from one manufacturer.
Comment Summary #40: The commenter suggested revising “the endotoxin limit for the drug product prevails” to “the more conservative endotoxin limit should prevail” for combination products.
Response: Comment not incorporated. The syringe is allowed 20 EU. The drug product is added—just like it is added to a vial. A prefilled syringe should not default to 20 EU.
Comment Summary #41: The commenter noted that IV and IM are the only other routes of injection.
Response: Comment incorporated. Change made.
Comment Summary #42: The commenter noted that there is a lack of guidance for determining endotoxin limits for components used in for the drug product (e.g., vials, stoppers). Such components are not considered medical devices, and the 20 EU/device would not be an applicable limit for the component of a drug product. Therefore, the commenter recommended clarifying that components are excluded from the scope of this section.
Response: Comment incorporated. Change made.
Comment Summary #43: The commenter noted that the section on endotoxin limits for devices does not address devices that contact the anterior segment of the eye. The commenter recommended inserting the following sentence after the first sentence of the first paragraph: “Devices that contact the anterior segment of the eye, including intraocular fluids and solid devices, should have a limit of 0.2 EU/mL and 0.2 EU/device, respectively.”
Response: Comment incorporated. Change made.
Comment Summary #44: The commenter recommended separating the Maximum Valid Dilution section into two sections: “Maximum Valid Dilution for Products” and “Maximum Valid Dilution for Medical Devices”
Response: Comment not incorporated. The text is clear enough.
Comment Summary #45: The commenter suggested providing clarification on the number of lots required for suitability testing.
Response: Comment incorporated. Clarification provided.
Comment Summary #46: The commenter noted that there was no mention or discussion of a standard methodology for low endotoxin recovery (LER) detection.
Response: Comment not incorporated. No sufficient data exists to support LER as a special interference. If such data is generated and presented, this section can be revised in the future.

#47: The commenter recommended including in Table 3 the use of a dispersing agent supplied by a lysate vendor to resolve interference issues.
Response: Comment incorporated. Change made.
Comment Summary #48: The commenter suggested clarifying what is considered “simple dilution” and “neutralization.”
Response: Comment incorporated. Change made.
Comment Summary #49: The commenter recommended adding the word “always” as follows: “Just as bacteria are not always homogeneously distributed in a product, so are endotoxins not **always** homogenous.”
Response: Comment incorporated. Change made.
Comment Summary #50: The commenter recommended clarifying the discussion to ensure pooling (as an acceptable practice) remains as an option
Response: Comment incorporated. Change made.
Comment Summary #51: The commenter recommended clarifying whether a pooling approach is applicable only for drug products or also for raw materials.
Response: Comment incorporated. Change made.
Comment Summary #52: The commenter recommended including an example to illustrate that the specification for a product dosed on a per mg basis ultimately ends up in EU/mg.
Response: Comment not incorporated. Comment has already been addressed (see Comment Summary #28).
Comment Summary #53: The commenter recommended including only specific information related to BET and not including discussion on out of specification and retesting.
Response: Comment not incorporated. BET is a compendial quality test, and quality tests sometimes have results that exceed the endotoxin limit. This is an informational general chapter with suggestions for how to think about failures with respect to BET.
Comment Summary #54: The commenter recommended deleting the term native endotoxin. There is currently no standard scientific definition of native endotoxins and no peer-reviewed studies to support this.
Response: Comment not incorporated. The term has been used in the past in several publications.
Comment Summary #55: The commenter recommended deleting the sections on Use of Risk Assessments, Centrality of GNB proliferation, and Basics of Risk Identification since they are out of scope for this chapter.
Response: Comment incorporated. Changes made.

General Chapter:	<1103> Immunological Test Methods—Enzyme-Linked Immunosorbent Assay (ELISA)
Expert Committee:	General Chapters–Biological Analysis
No. of Commenters:	2

Comment Summary #1: The commenter recommended including the topic of orientation of the molecule when coated, or sterics in the *Solid Phase* section where Microtiter Plates are discussed.
Response: Comment not incorporated. The use of streptavidin and intermediate proteins is discussed in the chapter providing relevant information.

Comment Summary #2: The commenter recommended adding discussion on sample linearity and hook effect.
Response: Comment incorporated. Hook effect is defined as “Inadequate blocking can result in a hook effect, which will negatively impact assay performance.”

General Chapter: <1227> *Validation of Microbial Recovery from Pharmacopeial Articles*
Expert Committee: General Chapters–Microbiology
No. of Commenters: 5
Comment Summary #1: The commenter recommended clarifying that compendial methods require only method suitability.
Response: Comment incorporated. Text revised.
Comment Summary #2: The commenter recommended clarifying how to handle a situation when the product has intrinsic microbial properties and no neutralization can be achieved.
Response: Comment incorporated. Change made.
Comment Summary #3: The commenter suggested replacing the term "chemical inhibition" with the term "chemical neutralization.”
Response: Comment incorporated. Change made throughout the text wherever the term chemical inhibition is used.
Comment Summary #4: The commenter suggested replacing the term "direct transfer" with the term "direct inoculation," consistent with text in <71>.
Response: Comment incorporated. Change made throughout the text wherever appropriate.
Comment Summary #5: The commenter recommended replacing the terms "biocide" and "bactericide" with the term "antimicrobial" for consistency with rest of the chapter and other USP microbiology chapters.
Response: Comment incorporated. Change made throughout the text wherever appropriate.
Comment Summary #6: The commenter suggested referring the reader to <61>/<62> for diluents to be used for membrane filtration for nonsterile products whenever <1227> mentions Fluid A.
Response: Comment not incorporated. It is clearly indicated in the section on Membrane Filtration that Fluid is an example of a non-toxic fluid that may be used for dilution or rinsing membrane filters in general.
Comment Summary #7: The commenter suggested adding an alternate method that would involve only validating neutralizer efficacy once a lack of toxicity has been established.
Response: Comment not incorporated. The approach in the current text is a recommendation, not a requirement and is flexible enough to allow alternate approaches that address neutralizer efficacy and toxicity.
Comment Summary #8: The commenter suggested clarifying the difference between groups 2 (peptone control) and 3 (inoculum control).
Response: Comment not incorporated. Current text is clear enough.
Comment Summary #9: The commenter suggested adding a reference to the maximum number of rinses for routine testing for consistency with <71> requirements.
Response: Comment incorporated. Text revised.

Comment Summary #10: The commenter suggested rewording the text that describes inoculation of the challenge organism to the final (third) rinse for routine testing.
Response: Comment not incorporated. Current text is clear enough.
Comment Summary #11: The commenter suggested adding a consideration for the need to solubilize test preparations prior to plating on solid (agar) medium, as well.
Response: Comment incorporated. Text revised.
Comment Summary #12: The commenter noted that the process of demonstrating that the media provides for both neutralization and growth of all organisms is also applicable to <62>, not just <71>.
Response: Comment not incorporated. The current text, while referencing <71> as an example, does not preclude such a use in other tests where appropriate. It would be applicable wherever liquid medium serves as a neutralizer and supports growth.
Comment Summary #13: The commenter suggested replacing the text "clearly visible growth within the indicated time period in <71>" with "clearly visible growth, visually comparable to that in the control vessel without product" for consistency with <71> requirements.
Response: Comment incorporated. Text revised.
Comment Summary #14: The commenter noted the section on *Recovery of Injured Microorganisms* is unclear regarding the context or the method to prepare injured microorganisms.
Response: Comment not incorporated. The section clearly states that recovery of injured microorganisms may be considered when using alternate media for recovery of microorganisms, especially in the context of preserved products.
Comment Summary #15: The commenter noted that in the section *Estimating the Number of Colony-Forming Unit*s, it states that lower counting thresholds for the greatest dilution plating in the series must be justified, but the section does not give any guidance on how this can be done.
Response: Comment not incorporated. The section clearly indicates the increased error associated with lower counts, and this should be considered.

General Chapter/Sections: General Chapter <1229.16> *Prion Sterilization*
Expert Committee: General Chapters–Microbiology
No. of Commenters: 5
Comment Summary #1: The commenter recommended changing the title of the chapter to *Prion Inactivation* since there are no sterilization processes validated for complete destruction of prions on medical devices or for elimination of infectivity.
Response: Comment incorporated. Title changed.
Comment Summary #2: The commenter suggested adding a brief discussion of where in the manufacturing process one might find prion contamination.
Response: Comment incorporated. Text added.
Comment Summary #3: The commenter recommended adding a table within the chapter that delineates the varying degrees of effectiveness (ineffective/variable) of the chemical, gaseous, and physical methods for the inactivation of prions.

Response: Comment not incorporated since this would be too prescriptive in an informational general chapter.
Comment Summary #4: The commenter noted that empirical confirmation should be recommended for all prion inactivation methods.
Response: Comment incorporated. Change made.
Comment Summary #5: The commenter recommended clarifying the discrepancy regarding effectiveness of phenolic compounds and guanidine thiocyanate between <1229.16> and the WHO document referenced herein.
Response: Comment incorporated. Change made throughout the text wherever appropriate.
Comment Summary #6: The commenter noted that the chapter does not include information on guidelines for prion disinfection and prion sterilization of equipment and suggested referencing appropriate Centers for Disease Control and Prevention (CDC) and WHO guidelines.
Response: Comment incorporated. References added.
Comment Summary #7: The commenter suggested including information on the agents/conditions that are most commonly used by the pharmaceutical industry for prion decontamination. Additionally, the commenter also recommend stating that instruments and equipment surfaces should not be allowed to dry prior to prion decontamination/sterilization treatment.
Response: Comment incorporated. Changes made.
Comment Summary #8: The commenter noted that the chapter provides a temperature range for prion destruction by moist heat but does not include the exposure time. The commenter recommended adding a time/duration component for these temperatures. A time component would allow the reader to understand where to begin when attempting to “empirically confirm” their heating process.
Response: Comment incorporated. Changes made.
Comment Summary #9 The commenter suggested adding applicability of the inactivating agents to raw materials and equipment as well as appropriate reference to these.
Response: Comment incorporated. Text revised.
Comment Summary #10 The commenter suggested emphasizing that the whole process and the products used for prion sterilization should be considered to ensure patient safety and as part of the risk assessment during product manufacturing and any reprocessing.
Response: Comment incorporated. Suggested text added.
Comment Summary #11 The commenter recommended that the chapter should not imply that the combination of chemical and thermal inactivation methods provide the greatest confidence in prion titer reduction because it is unknown which method is truly effective in prion inactivation.
Response: Comment incorporated. Text revised to clarify the statement.
Comment Summary #12 The commenter noted that due to the varied success of decontamination methods, the safest method for ensuring no risk of residual prion infectivity is to discard and destroy contaminated materials by incineration. The commenter recommended adding a statement indicating this.
Response: Comment incorporated. Statement added.

Comment Summary #13: The commenter suggested removing the statement on use of commercially available disinfectant solutions for consistency since it is unclear in relation to the rest of the section on Methods that are not effective.
Response: Comment incorporated. Text revised.

General Chapter/Section(s): <1236> *Solubility Measurements* / Multiple Sections
Expert Committee(s): General Chapters–Physical Analysis
No. of Commenters: 14

General

Comment Summary #1: The commenter recommended adding the testing conditions for Aqueous Relative Solubility to align with applicable FDA guidances, as a complement to the saturation approach currently included in the *Equilibrium Solubility* section. Specifically, that the highest strength of drug substance in a drug product should be used in the solubility study.
Response: Comment not incorporated because the purpose of this chapter is not to help define a biopharmaceutics classification system solubility classification of a drug but rather to provide information on how to evaluate solubility. Categorizing the results of a solubility test and a primer on what controls drug solubility (and how to test the solubility of a molecule) are two very different purposes.

Title

Comment Summary #2: The commenter suggested that the chapter name be changed to *Biopharmaceutical Solubility Measurements* or similar because the chapter deals primarily with solubility measurements relevant to biopharmaceutics, distinguishable from solubility measurements relevant to other aspects of drug development (e.g., crystallization, isolation).
Response: Comment not incorporated because although there is significant discussion in the chapter about biorelevant solubility, the methods described are useful for solubility measurements in general.

Introduction

Comment Summary #3: The commenter suggested removing the use of “apparent solubility,” or providing a clearer definition because the discussion and use of the term in the chapter is confusing and counterproductive.
Response: Comment not incorporated because the chapter is not contradictory but rather stating that within the framework of assessing solubility, one can do this from one of two perspectives: 1) absolute, which is the classical definition as described in the equations provided in this chapter, or 2) relative, where we are generating a solubility comparison.
Comment Summary #4: The commenter requested adding “molarity” to the sentence “Solubility may be stated in units of concentration such as molality, mole fraction, mole ratio, weight/volume, or weight/weight.” because “molarity” is one of the most commonly used units and referred to throughout the document as “molar concentration.
Response: Comment incorporated.
Comment Summary #5: Several commenters recommended adding discussion from available FDA guidance and ICH M9 biowaver about the “highest dose strength” and its solubility over the entire pH range at a temperature of 37°. Although harmonization is still currently ongoing, and

the term is defined differently by the FDA and by the European Medicines Agency (EMEA). Alignment with veterinary guidance (VICH GL39) is also suggested.
Response: Comment partially incorporated. The entire sentence was omitted because the differences in definition of highly soluble can add unnecessary disagreement and controversy that does not add value to the objective of this chapter.
Comment Summary #6: The commenter suggested modifying the following sentence: "The aqueous solubility (see the Glossary) of a material is affected by the physicochemical properties of the material (e.g., surface area, particle size, crystal form), the properties of the solubility media (e.g., pH, polarity, surface tension, added surfactants, co-solvents, salts), and the control of the solubility measurement parameters (e.g., temperature, time, agitation method)." to remove surface area and particle size because they impact dissolution rate. Additionally, the mixing time would impact the level of influence the agitation method would have on the experiment, which is why studies are carried out to equilibrium solubility to mitigate the influence of dissolution rate on solubility results.
Response: Comment partially incorporated, replacing “aqueous solubility” with “apparent solubility” to provide the relevant approach to solubility. The factors were not removed because the point is to illustrate those factors that should be considered important to understand and control in the measurement.
Expert Committee-Initiated Change #1: The word “experimental” was added to the following statement: “Control of these **experimental** factors during solubility measurements is key to obtaining accurate, reliable values for the equilibrium solubility of a material.”

Background
Comment Summary #7: The commenter requested providing definitions for each character/term used in the equations. The current section is dependent on scientific interpretation, but as a general chapter, all information should be clear to all readers.
Response: Comment incorporated.

Background/Thermodynamic Equilibrium and Solubility
Expert Committee-Initiated Change #2: The following statement was added for clarification: “Dissolution of a crystalline solid solute can be modeled by the two-step process of melting the crystal into a pure liquid solute followed by mixing the liquid solute into the solvent.”
Comment Summary #8: The commenter suggested revising the definition of “T” as follows “T = absolute temperature in degrees Kelvin.” for specificity.
Response: Comment not incorporated because the proposed sentence is redundant. The current definition has the same meaning.
Comment Summary #9: Several commenters suggested revising or removing the equations of this section to more accurate equations for entropy of mixing without “ideal.”
Response: Comment partially incorporated. The section explaining the changes on free energy of mixing, enthalpy of mixing, and entropy of mixing was rewritten.
Comment Summary #10: The commenter requested removing one section of the discussion of Kirchhoff’s law because it is related to aqueous solubility estimation in special cases, and they suggested moving the revised equation to the next section.

Response: Comment partially incorporated. This equation was replaced with Yalkowsky's general solubility equation.
Comment Summary #11: The commenter requested correcting or removing the description to the derivation of the equation for log (Xu,ideal) because it is incomplete. The text implies that the equation can simply be derived using Kirchhoff's law. In reality, other assumptions are necessary to derive this equation, including Walden's rule.
Response: Comment partially incorporated. The equation and explanation were replaced.

Background/Methods of Estimating Aqueous Solubility
Comment Summary #12: The commenter recommended adding more information concerning the accuracy (and frequency of accuracy) of this technique. Also, the purity of material will impact melting point data. Compounds that decompose prior to melt will be less likely to "fit" this model, and error in the partition coefficient value could be perpetuated with this simplified equation.
Response: Comment not incorporated. This section clearly indicates general solubility equation (GSE) is for estimating solubility. The recommendations are out of the scope of this chapter.
Comment Summary #13: The commenter suggested clarifying the term "intrinsic solubility" and including some language in the chapter to note that for weak acids and bases, the intrinsic solubility is the solubility of the uncharged moiety (i.e., the free acid or base).
Response: Comment incorporated in the Introduction.
Comment Summary #14: The commenter suggested revising the equation to read: "log S_w^{solid} = 0.5 – 0.01 (*MP* – 25) – log K_{ow}" for consistency with previous equations.
Response: Comment not incorporated because the current equation is consistent with the revised equations in the *Background*.

Background/Factors that Affect Solubility and Solubility Measurements/Effect of pH
Comment Summary #15: The commenter suggested revising the first paragraph because it is unclear, particularly regarding the resulting equation beneath the text.
Response: Comment incorporated partially. The following phrase was added: "The total solubility of the ionizable acid or base is the sum of the intrinsic solubility and the amount of ionized solute present at that pH."
Comment Summary #16: Two commenters requested adding definitions for S_{tot} and S_0 for clarity.
Response: Comment incorporated.
Expert Committee-Initiated Change #3: The word "will" was replaced with "may" in the following sentence: "The formation of a salt **may** limit the solubility at a low or high pH (see Figure 1)."
Comment Summary #17: Several commenters requested updating Figure 1 to correct the "Salt Solubility," "Common Ion-Effect," "Intrinsic Solubility, S_0," "pK_a (basic)," "pK_a (acidic)," and the shape of the salt solubility.
Response: Comment incorporated.

Background/Factors that Affect Solubility and Solubility Measurements/Effects of Salts and Counter-Ions

Comment Summary #18: The commenter recommended rewording the first paragraph to: "…in the presence of the charged counter-ion, the solubility product describes this equilibrium reaction as follows:" because the term "solubility of the charged molecule" is used incorrectly. Solubility is a property of the solid state, not the species in solution.
Response: Comment incorporated.

Background/Factors that Affect Solubility and Solubility Measurements/Effect of Co-solvents
Comment Summary #19: The commenter suggested removing the numbers from the axes in Figure 2 because it is an illustration of the log-linear model of Yalkowsky et al., and it represents a general scheme and not a specific example.
Response: Comment incorporated.

Background/Factors that Affect Solubility and Solubility Measurements/Effect of Surfactants
Comment Summary #20: The commenter requested including language to define the terms "surfactant" and "micelle." A suggested text was provided.
Response: Comment partially incorporated. The suggested text was added with changes.
Comment Summary #21: The commenter suggested adding background to this section.
Response: Comment incorporated.
Expert Committee-Initiated Change #4: The following text regarding micellar partitioning coefficient was added: "The solubilization of a molecule by a surfactant can be evaluated based on two descriptors: the molar solubilization capacity, and the micelle-water partition coefficient. The micelle-water partition coefficient is the ratio of drug concentration in the micelle to the drug concentration in water for a particular surfactant concentration." [J Pharm Pharmaceut Sci (www.cspscanada.org) 8(2):147-163, 2005 Micellar solubilization of drugs. Carlota Oliveira Rangel-Yagui, Adalberto Pessoa Junior, Leoberto Costa Tavares].
Comment Summary #22: The commenter recommended revising a sentence to read: "The CMC for surfactants is dependent on several factors including temperature, ionic strength and pH." based on the information found in reference 2 (Yalkowsky, et al.).
Response: Comment incorporated.
Comment Summary #23: The commenter suggested removing the numbers from the axes in Figure 3 because it is a general scheme to show solubility above and below the critical micelle concentration (CMC). Also, the including the definition/discussion of micellar partition coefficient is recommended.
Response: Comment incorporated.
Comment Summary #24: The commenter requested revising the label of the slope to "Solubilization Capacity" instead of "Micellar Partition Coefficient" because "Solubilization Capacity" is the generally preferred term in the literature.
Response: Comment incorporated.

Background/Factors that Affect Solubility and Solubility Measurements/Effect of Complexing Agents

Comment Summary #25: The commenter suggested revising the following sentence: "Complexing agents may form complexes with low-solubility materials and enhance the solubility." to "Complexing agents may form intermolecular association (complexation) with low-solubility materials and enhance the solubility." for clarity.
Response: Comment partially incorporated. The sentence was revised to "Complexing agents may form intermolecular complexes with low-solubility materials and enhance the solubility."
Comment Summary #26: The commenter requested including some discussion of the reasons for the improvement of aqueous solubility. The following text was suggested: "Aqueous solubility of nonpolar molecules in the presence of complexing agents is improved as the nonpolar molecules and the nonpolar region of the complexing agent are sequestered out of water. When this occurs, the aqueous solution can accommodate more of the nonpolar molecules."
Response: Comment incorporated.
Comment Summary #27: The commenter suggested removing the hyphen in the following sentence to avoid misleading: "Complexes with high-stability constants may bind solutes strongly enough to enhance aqueous stability."
Response: Comment incorporated.

Background/Factors that Affect Solubility and Solubility Measurements/Effect of Surface Area (Dissolution Rate)
Comment Summary #28: The commenter indicated that the paragraph explaining the Noyes–Whitney equation implies that h is a constant initially but then mentions that good mixing can be used to reduce h. A sentence at the end of the paragraph should be inserted, indicating that h can be reduced through good mixing.
Response: Comment incorporated.
Comment Summary #29: The commenter recommended removing the equation for spherical particles and its description from the section because it does not add value and is not needed.
Response: Comment not incorporated because spherical shape is relevant to surface area and dissolution rate.

Background/Factors that Affect Solubility and Solubility Measurements/Effect of Surface Energy
Comment Summary #30: The commenter recommended introducing the topic in more general terms before reaching the conclusion that we find later in the paragraph, instead of the section beginning with the conclusion.
Response: Comment incorporated.
Comment Summary #31: The commenter suggested removing the first reference to 1 micron particle size and moving the last sentence to just before the equation for clarity.
Response: Comment incorporated.

Experimental Methods/Methods for Determination of Equilibrium Solubility/Saturation Shake-Flask Method
Comment Summary #32: The commenter suggested including some discussion on which media/buffer should be used for research purposes vs dissolution testing, solubility measurements, etc., for clarity.

Response: Comment not incorporated because it is not the intention to provide comprehensive guidelines. The suggested media are based upon their biorelevance.

Experimental Methods/Methods for Determination of Equilibrium Solubility/Sample preparation

Expert Committee-Initiated Change #5: The following statement: “The surface area of the solid may be increased by grinding (e.g., in a mortar and pestle) prior to addition or by sonication of the sample after addition of the solid to the medium.” was revised to say: “The surface area of the solid may be increased by grinding (e.g., in a mortar and pestle) of the sample prior to addition to the medium or by sonication of the sample after addition to the medium.”

Experimental Methods/Methods for Determination of Equilibrium Solubility/Equilibration of solution

Comment Summary #33: The commenter recommended adding additional wording to incorporate best practices.

Response: Comment not incorporated at this time. Additional best practices will be discussed during next revision.

Comment Summary #34: The commenter suggested revising the second sentence as follows: “As a good initial time of incubation, 24 h is recommended; however, the suitability of the selected equilibration time must be verified.” for clarity.

Response: Comment incorporated.

Comment Summary #35: The commenter recommended replacing the criteria of solubility (e.g., change by less than 5% over 24 h, or less than 0.2%/h) to align it with the next section. Additionally, it is unclear what purpose the additional 24 hours of mixing serves, as solubility for both the apparent and equilibrium solubilities are conducted to the point at which saturation is reached.

Response: Comment partially incorporated. Non-binding example changed to “(e.g., change by less than 5% over 24 h, or less than 0.2%/h).”

Experimental Methods/Methods for Determination of Equilibrium Solubility/Analysis of solution

Comment Summary #36: The commenter recommended revising the second paragraph to “It is recommended that the excess solid in the suspension be analyzed at the end of the solubility measurement only if a new solid form is expected.” because the excess solid should only be analyzed if the material is expected to change (known route).

Response: Comment not incorporated because the statement currently says "recommended," which is generally true and is non-binding.

Experimental Methods/Methods for Determination of Equilibrium Solubility/Reporting of solubility results

Comment Summary #37: The commenter requested clarifying that further evaluation of form change would be warranted before reporting the result for the new solid form. If a form change

occurs, the relevance of the measurement should be evaluated on a case-by-case basis and not based on the assumption that the soluble portion is the new form.
Response: Comment incorporated. Statement edited and moved to the previous section.

Methods for Determination of Apparent Solubility/Physical Assessment of Solubility
Comment Summary #38: The commenter requested correcting a typographical error from "principal" to "principle."
Response: Comment incorporated.

Solubility Measurements in Biorelevant Media/Human Fasted-State Simulated Gastric Fluid (FaSSGF)/Table 1
Comment Summary #39: The commenter suggested revising the Sodium Taurocholate Concentration (mM) against Concentration (g/L) due to discrepancies.
Response: Comment incorporated.

Solubility Measurements in Biorelevant Media/Human Fed-State Simulated Gastric Fluid (FeSSGF) /Table 2
Comment Summary #40: The commenter suggested revising the Sodium Acetate Concentration (mM) against Concentration (g/L) due to discrepancies.
Response: Comment incorporated.

Solubility Measurements in Biorelevant Media/Human Fasted-State Simulated Intestinal Fluid (FaSSIF-V2/Table 3
Comment Summary #41: The commenter suggested revising the Sodium Hydroxide, Sodium Taurocholate, and Lecithin Concentration (mM) against Concentration (g/L) due to discrepancies.
Response: Comment incorporated. Other concentrations were revised and corrected.

Solubility Measurements in Biorelevant Media/Human Fed-State Simulated Intestinal Fluid (FeSSIF-V2)/Table 4
Comment Summary #42: The commenter suggested revising the Maleic Acid, Sodium Hydroxide, and Sodium Oleate Concentration (mM) against Concentration (g/L) due to discrepancies.
Response: Comment incorporated. Other concentrations were revised and corrected.

Solubility Measurements in Biorelevant Media/Human Simulated Colonic Fluid—Proximal Colon (SCoF2)/Table 5
Comment Summary #43: The commenter requested correcting a typographical error from "proimal" to "proximal"
Response: Comment incorporated.

Solubility Measurements in Biorelevant Media/Canine Fasted-State Simulated Intestinal Fluid (FaSSIFc)/Table 9

Comment Summary #44: The commenter suggested revising the Sodium Hydroxide Concentration (mM) against Concentration (mg/L) due to discrepancies.
Response: Comment incorporated.

Glossary/Equilibrium solubility
Comment Summary #45: The commenter recommended removing the statement "Practically, solubility measurements may never truly be at equilibrium" because in most cases, dynamic equilibrium may be attained with sufficient agitation and time, within reasonable experimental setups and conditions.
Response: Comment incorporated. Introduction was edited to be consistent.

General Chapter/Sections: <1430> *Analytical Methodologies Based on Scattering Phenomena—General*
Expert Committee: General Chapters—Chemical Analysis
No. of Commenters: 3
General
Comment Summary #1: Commenter suggested adding "This chapter summarizes the general chapters based on scattering phenomena giving general principles of scattering".
Response: Comment not incorporated. The EC determined that the existing text was suitable.

Title
Comment Summary # 2: Commenter suggested revising the chapter title to replace "based on scattering" with "based on elastic scattering" reasoning that the chapters included are all related to elastic scattering.
Response: Comments not incorporated. The EC determined that the existing title is suitable and clearly conveys the scope.

Section 1 Overview
Comment Summary # 3: Commenter suggested revising the section title to include "elastic" to highlight the fact that the overview is discussing elastic scattering.
Response: Comment not incorporated. The EC determined that there is no need to change the section title. The overview and introduction clarifies the scope.
Comment Summary #4: The commenter recommended revising the text to highlight that the inelastic scattering (e.g. Raman Spectroscopy) is covered under General Chapter <1120> and not in this suite of chapters.
Response: Comment not incorporated. The EC determined that the existing text was suitable there is no need for additional clarification. The overview and introduction makes clear what is the scope.
Comment Summary #5: The commenter requested revising the X-ray range entry to replace 0.15 nm with 0.07-0.15 nm.
Response: Comment partially incorporated. The EC determined to revise the X-Ray range with 0.06-0.33 nm to cover the range of all working X-ray instrumentation (Laboratory SAXS and Synchrotron SAXS).
Comment Summary #6: The commenter requested revising the "Primary Purpose: entry for the X-Ray in Table 1 to change the length scale from 1-500 nm to <1nm -500 nm and to include "porosity, crystallinity, and molecular weight after ordering".
Response: Comment partially incorporated. The EC determined revising the length scale to include: "scales from 0.1–2500 nm for SAXS and 0.2–1000 + nm for SANS. Also properties of condensated phases (e.g. porosity and crystallinity) can be determined".

Taxonomy
Comment Summary #7: The commenter requested adding Wide Angle X-ray Scattering (WAXS) and Transmission Imaging in the box of Small-Angle X-Ray Scattering (SAXS).
Response: Comment partially incorporated. The Expert Committee revised the entry of this box to state Small-angle and Wide-angle X-ray Scattering (SAXS and WAXS).
Comment Summary #8: The commenter requested changing the X-ray range from 0.15 nm to 0.15 nm – 0.07 nm.
Response: Comment partially incorporated. See EC response for Comment 5.

Introduction
Comment Summary #9: The commenter recommended revising the entry for the Small-angle X-ray scattering in the introduction to add " With SAXS and WAXS measurements you receive information about shape, size (in contrast to the hydrodynamic radius from DLS the radius of gyration is received from SAXS), inter- and intraparticle interferences, molecular weight, correlation length, lattice parameter, preferential orientation, porosity, fractal structure, specific surface, Pore Volume, specific inner volume, crystallinity, core shell".
Response: Comment partially incorporated. The EC revised the text to include some of the suggestion to state "Like SLS, these techniques also measure size, shape and interactions but on much shorter length scales; typically ranging from around one nanometer to several hundred nanometers. Very/ultra small-angle (VSAXS/VSANS, USAXS/USANS) and wide-angle (WAXS/WANS) analogues extend these length scales to the micrometer and sub-nanometer regimes, respectively. These applications are discussed in Genera Chapter 1430.5.*Analytical Methodologies Based on Scattering Phenomena—Small-Angle X-Ray Scattering and Small-Angle Neutron Scattering.*

General Chapter/Sections: <1430.1> *Analytical Methodologies Based on Scattering Phenomena-Static Light Scattering*
Expert Committee: General Chapters—Chemical Analysis
No. of Commenters: 1
Comment Summary #1: Commenter recommended revising the text of the second bulleted paragraph in *Section 6. Practical Considerations* to highlight the impact that the colored samples have on the results.
Response: Comment incorporated. The EC revised the paragraph to add "If the samples are colored more advanced data analysis techniques are required. Otherwise the results will be unreliable".

General Chapter/Sections: <1430.2> *Analytical Methodologies Based on Scattering Phenomena—Light Diffraction Measurements of Particle Size*
Expert Committee: General Chapters—Chemical Analysis
No. of Commenters: 2
Theory
Comment Summary #1: Commenter recommended changing the phrase "several micrometers" to "greater than 1-10 µm".
Response: Comment not incorporated. The EC determined that the existing text was suitable.
Comment Summary #2: Commenter discussed the entry for the refractive index reasoning that "In some equipment, the residual (which is a "goodness of fit parameter") provides information

on how appropriate a particular optical model is, the lower the residual the more likely it is to be appropriate."
Response: Comment not incorporated. The EC determined that the existing text is sufficient and clearly conveys the information. In addition, no alternative was suggested. The EC stated: "Though the residual is a useful guideline, the minimization of this measure should not be used as the major criterion for optimization of the refractive index parameters, as it will often lead to unrealistic conditions".

Section 4 Applications
Comment Summary #3: Commenter suggested revising the following paragraph: "It also offers the advantage of being able to sample the dispersion for observation by microscopy" to read: "It also offers the advantage of being able to sample the particle dispersion in the liquid dispersant taken from the instrument for observation by microscopy (after stirring, ultrasound)."
Response: Comment partially incorporated. The EC revised the paragraph to read: "It also offers the advantage of being able to sample the dispersion's particles from the instrument dispersion outflow for observation by microscopy."
Comment Summary #4: The commenter recommended revising the text to add: "Another advantage is the use of less amount of material in comparison with dry dispersion."
Response: Comment not incorporated. The EC determined that it is already mentioned under dry dispersion that it uses more material.
Comment Summary #5: The commenter recommended revising the text to add: "Furthermore, broken particles may occur due to use of excessive air pressure in dry powder sample preparation".
Response: Comment not incorporated. The EC determined that the text already says "fracture" which has the same meaning.

Section 5. Method Development
Comment Summary #6: The commenter requested adding that: "the vibrational feed rate of the sample tray may also be adjusted".
Response: Comment incorporated. The EC revised the entry to state: "For dry dispersions, analyses using different shear air pressures and feed rates are done."
Comment Summary #7: The commenter recommended revising the paragraph: "The amount of incident light scattered or absorbed by the sample, expressed in terms of obscuration or transmittance" to "The amount of incident light scattered or absorbed by the sample, expressed in terms of laser obscuration, laser transmittance or optical concentration of the sample….".
Response: Comment partially incorporated. The EC revised the text to include part of the recommendation to read: "The amount of incident light scattered or absorbed by the sample, expressed in terms of obscuration, transmittance, or optical concentration range of the sample…"

Section 6. Method Validation Strategy
Comment Summary #8: The commenter recommended revising the paragraph starting with: "Sample concentration, as indicated by obscuration, is an important factor" to add "Sonication time and power should also be included in a robustness assessment."
Response: Comment partially incorporated. The EC revised the text to add dispersion energy after stir rate.
Comment Summary #9: The commenter recommended revising the information to add also the vibrational tray feed rate for dry dispersion parameters.
Response: Comment partially incorporated. The EC revised the text to state: "For dry dispersion, measurement time, sample amount, air pressure, and feed rate to achieve target obscuration may be most important."

Comment Summary #10: The commenter recommended revising the information to add "feed rate or gap opening are also important to assess as robustness parameters for dry dispersions."
Response: Comment partially incorporated. The Expert Committee revised the text to state: "For dry dispersion, measurement time, sample amount, air pressure, and feed rate to achieve target obscuration may be most important."

General Chapter/Sections: <1430.4> *Analytical Methodologies Based on Scattering Phenomena—Electrophoretic Light Scattering (Determination of Zeta Potential)*
Expert Committee: General Chapters—Chemical Analysis
No. of Commenters: 2

General

Comment Summary #1: The commenter suggested adding information regarding the sample preparation.
Response: Comment not incorporated. The EC determined that the existing text was suitable. Sample preparation factors are addressed in proposed chapter <432>
Comment Summary #2: The commenter suggested adding a validation section.
Response: Comment not incorporated. The EC determined that the existing text was suitable for the scope of this chapter. The validation is addressed in proposed chapter <432>.

Introduction

Comment Summary #3: The commenter suggested adding the definition of Zeta Potential and the definition include detailed information.
Response: Comment not incorporated. The EC determined that the existing text was suitable. The definition is given in proposed chapter <432> and the theory is known to users.
Comment Summary #4: The commenter recommended revising the sentence: "Electrophoretic light scattering (ELS) is the most general and common way to determine zeta potential" to add "...zeta potential of particles".
Response: Comment partially incorporated. The EC revised the sentence to say: "...to determine the zeta potential of colloidal systems".

Instrumentation

Comment Summary #5: The commenter stating that the first paragraph and Figure 1 present the example of a small angle light scattering arrangement which appear to be out of context and recommended adding text and an explanation for the small-angle light scattering arrangement.
Response: Comment partially incorporated. The EC revised the text to state: "Electrophoretic light scattering Zeta potential instruments are light scattering instruments which have either a reference beam optics alignment (most common) or a cross-beam optics alignment (less common)".
Comment Summary #6: The commenter suggested revising the paragraph: "Another advantage of PALS is that it can eliminate the effects of electroosmosis in aqueous suspensions" adding: "... because it makes it possible to frequently reverse the orientation of the electric field during the measurement."
Response: Comment not incorporated. The EC determined that the current text is suitable. Adding the recommended text would add confusion. All ELS instruments alternate the field at a certain frequency.

Applications

Comment Summary #7: The commenter, noting that a suspension and an emulsion are special cases of dispersion, recommended replacing "…and stability of suspensions, dispersions and emulsions" with "…stability of dispersions."
Response: Comment partially incorporated. The EC revised the text to say "…and stability of suspensions and emulsions", and noted that dispersions include also aerosols, mist and dust.

Data Analysis
Comment Summary #8: The commenter noted that the definition of the reference beam alignment for Equation 1 and cross-beam alignment for equation 2 was missing and recommended adding it.
Response: Comment incorporated. The EC revised the text to add definitions under *Instrumentation* section.

Data Interpretation
Comment Summary #9: The commenter recommended to replace "…physical stability of a suspension" with "…physical stability of a dispersion".
Response: Comment partially incorporated. The EC revised the text to state "…stability of a suspension/emulsion".

General Chapter/Sections:	<1430.5> *Analytical Methodologies Based on Scattering Phenomena—Small-Angle X-Ray Scattering and Small-Angle Neutron Scattering*
Expert Committee:	General Chapters–Chemical Analysis
No. of Commenters:	2

Section 2. Type of SAS
Comment Summary #1: The commenter recommended the following change in Table 1: Replacing "Large facility" in the Synchrotron-SAXS and SANS columns with "Synchrotron source" and "Neutron source," respectively.
Response: Comment incorporated. The EC revised the entries as recommended.
Comment Summary #2: The commenter requested changing the X-Rays wavelength range for the Lab SAXS in Table 1 and provided the rationale for the change.
Response: Comment incorporated. The EC revised the entries for the X-rays wavelength range for Lab SAXS from 0.07–0.15 nm to 0.07–0.23 nm.
Comment Summary #3: The commenter requested changing the length scale probed for the Lab SAXS in Table 1 and provided the rationale for the change.
Response: Comment incorporated. The EC revised the entry for the length scale probed for Lab SAXS from 1–250 nm to <1–300 nm.
Comment Summary #4: The commenter, stating that the small-angle X-ray scattering (SAXS) measurement is in principle non-destructive, requested changing the radiation damage entry for the Lab SAXS in Table 1 from "Likely" to "Negligible."
Response: Comment partly incorporated. The EC revised the entry from "Likely" to "Possible." The EC reasoned that the intended readership of this chapter are people specifically working in the pharmaceutical arena and in life sciences more generally. It would be misleading to suggest to this community that X-rays are non-destructive and/or do not cause radiation damage. Whilst the degree of damage will indeed vary from lab-SAXS to lab-SAXS, the reality is that ever more

powerful lab-SAXS instruments are being developed and are becoming available, so these are what will be used, increasingly.
Comment Summary #5: The commenter requested changing the Sample volumes range entry for the Lab SAXS in Table 1 from 0.007–0.03 mL to 0.007–0.1 mL
Response: Comment incorporated. The EC revised the entry as requested.
Comment Summary #6: The commenter discussed the "Use quartz sample containers" entry in Table 1 and commented that this should not be restricted to quartz sample containers only, since, as examples, holders with capton or beryllium windows are often used for solids and pasteous samples, and holders with special SiN windows are often used for weakly scattering samples, and various x-ray transparent polymers are also used.
Response: Comment partially incorporated. The EC revised the raw heading entry to read "Typical container material" and deleted the raw with heading "Use metallic sample containers." Specific text was added to the respective columns for the "Typical container material" row: 1) glass, quartz under SALS; 2) Lab-SAXS and Synchrotron SAXS—see comment 7; and 3) silicon, silica/quartz, aluminium, titanium, vanadium, copper small-angle neutron scattering (SANS).
Comment Summary #7: The commenter requested putting a note for the "Use quartz sample containers" raw under the Lab-SAXS column in Table 1 to say that depending on the sample, other dedicated sample holders (i.e., sample containers) made from a polymer (e.g., disposable polymer capillaries) or equipped with e.g., capton, SiN, or beryllium windows are feasible as well.
Response: Comment partially incorporated. The EC revised the row heading as in comment #6 and the entry under Lab-SAXS column for the row to read "polyimide (Kapton), polycarbonate, beryllium, silica/quartz, silicon nitride."

Section 3. Basic Theory
Comment Summary #8: The commenter noted that "In commercially available SAXS systems, often a combination of SAXS and wide-angle X-ray scattering (WAXS) is available, which extends the experimental range to > 10° 2 Θ (WAXS). This is beneficial to analyze smaller structures such as crystal lattice on the atomic level."
Response: Comment partially incorporated. The EC revised the text to state "In a typical SAS experiment, $0.01° < \Theta < 10°$; this value of Θ is different from that in a wide-angle and classical crystallographic diffraction experiments, where $\Theta > 10°$. On some instruments it may be possible to record the small- and wide-angle data concurrently.

Section 4. Contrast Matching
Comment Summary #9: The commenter stating that under Contrast Matching for SAXS, the first sentence is misleading and the meaning of the second was not correct. They suggested revising the text to "Contrast matching is required if two or more …" and "contrast matching a molecule with a heavy atom is difficult and may change the pristine characteristics of the analyte and its chemical environment." The commenter also recommended deleting the third sentence.
Response: Comment partially incorporated. The EC revised the third sentence to state "However, this course of action may change the pristine characteristics of the analyte and its chemical environment." The EC determined that the other entries needed no change, stating

that while the recommendation “contrast matching a molecule with a heavy atom is difficult” is correct, the existing text makes that clear and is more descriptive for the intended readership of this chapter.

Section 5. Instrumentation

Comment Summary #10: The commenter discussed the entry regarding how the wavelength of monochromatic radiation is determined noting that “Nowadays modern laboratory SAXS systems are equipped with high-flux microfocus X-ray sources providing a highly brilliant X-ray beam at low power and being almost maintenance-free, or high-performance Metal Jet microfocus X-ray sources with a liquid anode material and with highest X-ray flux for a laboratory SAXS system.”

Response: Comment partially incorporated. The EC revised the text to accommodate the essence of the commenter’s discussion to state “The wavelength of monochromatic radiation is determined by the choice of source (replacing one type of anode material with another), but may also be varied by changing optical filters, or adjusting the synchrotron monochromator.”

Comment Summary #11: The commenter requested correcting the paragraph ending with “In these fixed-wavelength measurements, altering…” noting that “especially for lab systems in SAXS, two proofed set-ups are available in the markets.” They requested inserting “two system setups for laboratory SAXS are available either to move the sample stage in respect to the detector or vice versa.”

Response: Comment partially incorporated. The EC revised the text to: “In these fixed-wavelength measurements, altering the dynamic range in q of the instrument requires changing the sample-to-detector distance (either along the incident beam direction or off-axis) in order to change the range of scattering angles subtended to the sample.”

Comment Summary #12: The commenter requested revising the phrase “A state-of-the-art SAXS detector for laboratory applications may have 300 thousand to 1 million pixels, and more for large-facility instruments.” to “A state-of-the-art SAXS detector for laboratory applications may have 300 thousand to more than 1 million pix, and more for large-facility instruments.”

Response: Comment partially incorporated. The EC revised the sentence to “A state-of-the-art SAXS detector for laboratory applications may have 1 thousand (for 1D detectors) to more than 1 million pixels (for 2D detectors), and more for large-facility instruments.”

Comment Summary #13: The commenter, referencing the entry “A state-of-the-art SAXS detector for laboratory applications may have 300 thousand to 1 million pixels, and more for large-facility instruments” commented that “Modern laboratory SAXS systems are also equipped with synchotron-proven detectors based on hybrid photon-counting (HPC) technology, ensuring highest spatial resolution and best signal-to-noise ratio. There are 1D and 2D detectors in use, where the pixel range for 1D detectors is between a few hundred up to more than 1000 pixels.”

Response: Comment partially incorporated. See the revised text under Comment #12.

Section 6. Experimental Considerations

Comment Summary #14: The commenter noted, under the Incident Flux subsection, that “Modern laboratory SAXS systems equipped with microfocus X-ray sources or MetalJet X-ray sources achieve a maximum flux at sample of > 1 x 108 photons/s (Cu microfocus source) and > 1 x 109 photons/s (MetalJet). These X-ray sources, combined with advanced optics, result in

outstanding X-ray flux in a high spectral purity and bring laboratory SAXS systems even closer to the synchotron level" without any specific suggestion or recommendation to revise the text.
Response: Comment not incorporated. The EC determined that the existing text is suitable and while the information in the commenter's discussion is correct, it is too specific and outside the scope.
Comment Summary #15: The commenter requested correcting the equations in the section 6.2.1 Size resolution to delete the number 2 in the numerators of both equations.
Response: Comment incorporated. The EC revised the equations.
Comment Summary #16: The commenter, questioning the clarity of the paragraph starting with "Laser light sources and X-ray sources have…" requested a more precise explanation and differentiation between beamlines and laboratory SAXS systems, as the latter are equipped with different X-ray sources and mirror. The commenter provided a literature reference and rationale for the request.
Response: Comment partially incorporated. The EC revised the text to "Conventional light sources depend on the use of a bandpass filter for which $\Delta\lambda/\lambda$ may be ~1%. Whilst good wavelength resolution is an intrinsic property of a laser, in the case of X-rays it is determined by the monochromator in use" and added "In most instances, better wavelength resolution can always be traded for reduced flux, and vice versa." The EC determined that the level of details in the commenter's discussion and the provided reference are beyond the scope of the chapter.
Comment Summary #17: The commenter, noting that it is unclear how the statement under Figure 5 ("Only the scattering from the R = 50 nm particle is fully within the measurement window of this simulated instrument") should be interpreted with the figure, requested adding detail to the figure or modifying the statement to clarify what part of the figure shows this to be true.
Response: Comment incorporated. The EC revised the Figure 5 note to read "Only the scattering from the R = 50 nm particle is fully within the measurement window of this simulated instrument, as shown by the limiting behavior of the form factor at low-Q and multiple interference fringes at intermediate-Q."
Comment Summary #18: The commenter, referencing the entry "Pre-screening for aggregation in biological samples destined for SAXS or SANS instruments, for example by DLS, should be considered *de rigour*" commented that "One can follow the building of aggregates in dependence of time and temperature during SAXS experiments. Also, ab-initio modelling of the received scattering data can give a hint of the molecule or molecule aggregate. With measuring the transmittance via standard SAXS, possible degeneration can be followed in situ, even if the shape is preserved."
Response: Comment partially incorporated. The EC revised the text to read "Prescreening for unintended aggregation…" instead of "Prescreening for aggregation." The EC determined that while the information in the comment is true, this section is on Sample Quality.
Comment Summary #19: The commenter, referencing the paragraph starting "However, as an illustration, most SAXS/SANS instruments can handle …" in section 6.5. Sample Concentration, commented that "In principle one should know that with SAXS there is almost no limit regarding concentration, since the interparticle interference (repulsive/attractive interactions) can be assessed and the structure factor can be separated from the form factor contribution, which results in a scattering curve with eliminated interaction influence. This is most beneficial,

especially for all biological samples, as there is no need for concentration matching (e.g., multiple scattering)."
Response: Comment partially incorporated. The EC revised the text to add "For investigations of S(q) relevantly higher concentrations are used" at the end of the section. The EC noted that SAXS is as governed by the same physics of scattering as SALS or SANS. There are approaches, both experimental and computational, that can be used to separate the contributions of P(q) and S(q), but they are not exact. Whether this is an issue depends on the sample under study and the intended method of data analysis. This section is meant to provide guidance/best practice on the sort of concentration envelope one might employ in a SAS experiment.
Comment Summary #20: The commenter, referencing the entry "Poly(amides) (nylons) are not suitable because they are semi-crystalline. All hydrogenous polymers are wholly unsuitable for use as SANS sample containers." commented that "For SAXS, also special containers equipped with beryllium, capton or SiN windows are available. One should check depending on the type of sample (liquid, solid, semi-solid), which is the most suitable one."
Response: Comment partially incorporated. The EC revised the text to read "For SAXS, it is possible to use sample containers constructed from amorphous engineering polymers such as poly(carbonate) (PC), poly(etheretherketone) (PEEK), or poly(imide) (Kapton)" and added the following sentence "Beryllium, being of low atomic number, is however a practical choice for SAXS." at the end of the paragraph.
Comment Summary #21: The commenter, referencing the entry "The use of cryostats, furnaces, pressure cells, rheometers, and stop-flow cells is very common with large-facility SAXS/SANS instruments." commented that "Also for laboratory SAXS systems, special sample holders and stages are available for non-ambient conditions like temperature-controlled, humidity, and tensile stages, etc."
Response: Comment partially incorporated. EC revised the text to read "The use of cryostats, furnaces, pressure cells, rheometers, tensile stages and stop-flow cells with SAXS/SANS instruments is very common."
Comment Summary #22: The commenter requested correcting the range of the sample containers path length for SAXS from 0.1–0.5 mm to 0.1–1 mm to include the semi-solids and solid biological sample containers.
Response: Comment incorporated. The EC revised text as requested.
Comment Summary #23: The commenter, referencing the entry "The essence of the problem is that the history of multiply scattered photons/neutrons is unknown, and thus one cannot know whether or not to use them." in section 6.10 Multiple scattering, commented "However, SAXS is well suitable for highly concentrated as well as turbid samples since the interparticle interference (repulsive/attractive interactions) can be assessed and the structure factor can be separated from the form factor contribution, which results in a scattering curve with eliminated interaction influence."
Response: Comment not incorporated. The EC determined that the comment is related to inter-particle interactions and not the multiple scattering.
Comment Summary #24: The commenter requested revising the entry "An important consideration during SAXS experiments is that the X-ray beam can be extremely destructive to

the sample if mitigating strategies are not deployed, such as the use of flow-through cells or cryogenic cooling" in section 6.11 Radiation damage to add "synchrotron" before SAXS.
Response: Comment partially incorporated. EC revised the text to read "An important consideration during SAXS, particularly synchrotron-SAXS, experiments is that the X-ray beam can be extremely destructive to some samples."
See also the EC response for Radiation damage in Table 1.
Comment Summary #25: The commenter, referencing the entry "(for example, the C–C bond energy is just 4 eV), and hydrogen bonds are weaker still." in section 6.11 Radiation damage, commented that "this general information is a bit misleading, since this only applies for proteins and other biological single crystals, especially cryogenic cooled ones. In general, laboratory SAXS is a non-destructive and non-invasive technique. However, if sensitive samples are probed, degradation can be followed via in-situ transmittance measurement in the SAXS system..."
Response: Comment partially incorporated. EC revised the text to read "An important consideration during SAXS, particularly synchrotron-SAXS, experiments is that the X-ray beam can be extremely destructive to some samples."
See also the EC response for Radiation damage in Table 1.

Data Processing
Comment Summary #26: The commenter recommended considering rearrangement of the steps under Section 7.1. Data Reduction to follow the true sequence for laboratory SAXS systems
Response: Comment incorporated. The EC revised text as requested.
Comment Summary #27: The commenter, noting that in section 7.2. Data Analysis, the Ab initio and simulation methods sections are not clearly delineated. Readers may not be able to distinguish the different methods. The commenter recommended separating the Ab initio and simulation methods sections to make sure that the bullet point statements underneath each are clearly referring to the different methods."
Response: Comment incorporated. The EC determined that the format error was introduced unintentionally during the publication process.
Comment Summary #28: The commenter recommended adding the following text at the end of section 7.2: "One should always check for the state-of-the art evaluation and analysis techniques, since many elusive properties can be obtained with the proper model."
Response: Comment partially incorporated. The EC revised the text to add the following paragraph at the end of the section "As SAS data analysis procedures become ever more sophisticated, so too does the degree of detail about the sample that they can return. However, one must never take this information in isolation; always look to cross-validate it with information derived from alternative techniques or the scientific literature. For example, model-fitting a large number of parameters without a priori information can result in 'local' rather than 'global' solutions. And PDDF, ab-initio and simulation methods work best when they can be constrained (e.g., to a known radius-of-gyration)."
Comment Summary #29: The commenter offered to provide additional illustrations that would be useful on what can be determined from SAXS

Response: Comment not incorporated. EC determined that, while correct and valuable, it would add too much detail for the scope of this chapter, and similar information can be found in the references included in the chapter.

Monographs

Monograph/Section: Alosetron Hydrochloride/Multiple Sections
Expert Committee: Chemical Medicines Monographs 3
No. of Commenters: 3
Comment Summary #1: The commenters noted that in the test for *Organic impurities*, the acceptance criterion for specified impurity, Dealkyl alosetron is tighter and different from what has been approved by the FDA.
Response: Comment incorporated. The acceptance criterion for Dealkyl alosetron is widened from NMT 0.07% to 0.15% to be consistent with FDA approval.
Comment Summary #2: The commenter noted that in the test for *Organic impurities*, the acceptance criterion for *Total impurities* is different from what has been approved by the FDA.
Response: Comment incorporated. The acceptance criterion for *Total impurities* is widened from NMT 0.4% to NMT 0.8% to be consistent with FDA approval.
Comment Summary #3: The commenter noted that the acceptance criterion for *Residue on Ignition* is different from what has been approved by FDA.
Response: Comment incorporated. The acceptance criterion for *Residue on Ignition* is widened from NMT 0.1% to 0.2%.
Comment Summary #4: The commenter suggested changing the resolution parameter between Alosetron and Alosetron Related Compound A from NLT 7 to NLT 3 to be consistent with the validation data in the test for *Organic impurities*.
Response: Comment incorporated. The resolution between Alosetron and Alosetron Related Compound A is revised from NLT 7 to NLT 3.

Monograph/Section: Alosetron Tablets/Multiple sections
Expert Committee: Chemical Medicines Monographs 3
No. of Commenters: 3
Comment Summary #1: The commenter noted that in the Assay, the acceptance criterion is different from what has been approved by the FDA.
Response: Comment incorporated. The acceptance criterion for Assay is revised from NLT 93.0% and NMT 105.0% to NLT 90.0% and NMT 110.0% based on input from FDA approved manufacturers.
Comment Summary #2: The commenters noted that the acceptance criterion for the Dealkyl alosetron impurity in the test for *Organic impurities* is different from what has been approved by the FDA.
Response: Comment incorporated. The acceptance criterion for Dealkyl Alosetron impurity is revised from NMT 0.1% to NMT 0.3%.
Comment Summary #3: The commenters noted that the acceptance criterion for any individual impurity and *Total impurities* in the test for *Organic impurities* is different from what has been approved by the FDA.

Response: Comment incorporated. The acceptance criterion for any other individual impurities is revised from NMT 0.2% to NMT 0.5% and *Total impurities* is revised from NMT 0.5% to NMT 2.5%.
Comment Summary #4: The commenter suggested including information on the chemical name, structure, and availability of the reference standard for Alosetron Related Compound A.
Response: Comment not incorporated. The EC determined that the necessary information is provided in the proposal.
Comment Summary #5: The commenter requested clarification on dissolution conditions for different tablet strengths in the *Dissolution* test.
Response: Comment not incorporated. The proposed acceptance criterion is based on the sponsor's FDA approved specifications. The EC will consider a future revision to the monograph upon receipt of supporting data.
Comment Summary #6: The commenter noted the diluents used for Standard solution and Sample solution preparations are different in the *Assay*.
Response: Comment incorporated. The diluent for the Standard solution is revised from water to phosphoric acid.
Comment Summary #7: The commenter noted that their in-house *Assay* method provides more precise results than the *PF* proposed method.
Response: Comment not incorporated. The EC determined that the proposed method is suitable for its intended use.

Monograph/Section: Amcinonide Cream/Multiple Sections
Expert Committee: Chemical Medicines Monographs 5
No. of Commenters: 1
Comment Summary #1: The commenter recommended adding a second orthogonal identification test.
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 revising the *Acceptance criteria* for total yeast and mold count in <*61*> and <*62*> for consistency with what has been approved.
Response: Comment not incorporated. The *Acceptance criteria* are consistent with a manufacturer's FDA-approved application and are also consistent with the recommended *Acceptance criteria* in <*1111*> *Microbiological Examination of Nonsterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use*.

Monograph/Sections: Amiodarone Hydrochloride Injection /Organic Impurities
Expert Committees: Chemical Medicines Monographs 2
No. of Commenters: 1
Comment Summary: The commenter suggested retaining the currently official limit of 0.20% for any unspecified degradation product.
Response: Comment incorporated.

Monograph/Sections: Amiodarone Hydrochloride Tablets/Multiple Sections
Expert Committees: Chemical Medicines Monographs 2

No. of Commenters: 1
Comment: The commenter indicated that the proposed *Dissolution* test may not be suitable for some FDA-approved products.
Response: Comment not incorporated. The EC will consider a future revision to the monograph upon receipt of supporting data.
Expert Committee-initiated Change #1: The relative standard deviation requirement in the *Organic impurities* is corrected from NLT 10.0% to NMT 10.0%.

Monograph/Sections: Amlodipine and Olmesartan Medoxomil Tablets/Multiple Sections
Expert Committees: Chemical Medicines Monographs 2
No. of Commenters: 2
Comment Summary #1: The commenter indicated that the proposed *Dissolution* test may not be suitable for some FDA-approved products.
Response: Comment not incorporated. The EC will consider a future revision to the monograph upon receipt of supporting data.
Comment Summary #2: The commenter indicated that the proposed acceptance criteria for Olmesartan and Amlodipine Related Compound A in *Organic Impurities* are not consistent with the FDA-approved products.
Response: Comment not incorporated. The acceptance criteria are consistent with the sponsor's FDA-approved application, and the EC will consider future revisions to the monograph upon receipt of supporting data.
Comment Summary #3: The commenter suggested including all process related impurities, at least the ones listed in the individual drug substance monographs, in the proposed *Organic impurities* test, to assist in the identification and quantitation process.
Response: Comment not incorporated. The EC determined that the proposal is consistent with the sponsor's FDA-approved application.
Comment Summary #4: The commenter indicated that the limit for individual process impurities is usually NMT 0.1%. Based on the sample concentration from the proposal, spiking process impurities may not result in detection and quantitation of the impurities.
Response: Comment not incorporated. The EC determined that the Sample solution concentration in the proposal is suitable for its intended purpose. A future revision will be considered upon receipt of supporting data.
Comment Summary #5: The commenter suggested including the potential impurities that are identified by the FDA in the *Organic Impurities* test even though they are not a part of the process-related impurities in the drug substance.
Response: Comment not incorporated. The EC determined that the proposal as written is consistent with the sponsor's FDA-approved product, and future revisions will be considered upon receipt of the supporting data.

Monograph/Section(s): Chinese Skullcap Root/Multiple Sections
Expert Committee: Botanical Dietary Supplements and Herbal Medicines
No. of Commenters: 0 (Initiated by EC)

IDENTIFICATION

Expert Committee Initiated Change #1: In the high-performance thin layer chromatography (HPTLC) system suitability requirements, the statement “a yellow band immediately below baicalein” was removed

COMPOSITION

Expert Committee Initiated Change #2:

The HPLC column re-equilibration time was increased from 5 min to 10 min by increasing the final step from 55 min to 60 min.

ADDITIONAL REQUIREMENTS/*Labeling*

Expert Committee Initiated Change #3: The following caution statement was added to the label: “Dosage forms prepared with this article should bear the following statement: Discontinue use and consult a healthcare practitioner if you develop symptoms of liver trouble, such as abdominal pain, dark urine, or jaundice (yellowing of the eyes or skin).”

Monograph/Section(s):	Chinese Skullcap Root Dry Extract/Multiple Sections
Expert Committee:	Botanical Dietary Supplements and Herbal Medicines
No. of Commenters:	0 (Initiated by EC)

IDENTIFICATION

Expert Committee Initiated Change #1: In the HPTLC system suitability requirements, the statement “a yellow band immediately below baicalein” was removed

COMPOSITION

Expert Committee Initiated Change #2:

The HPLC column re-equilibration time was increased from 5 min to 10 min by increasing the final step from 55 min to 60 min.

ADDITIONAL REQUIREMENTS/*Labeling*

Expert Committee Initiated Change #3: The following caution statement was added to the label: “Dosage forms prepared with this article should bear the following statement: Discontinue use and consult a healthcare practitioner if you develop symptoms of liver trouble, such as abdominal pain, dark urine, or jaundice (yellowing of the eyes or skin).”

Monograph/Section(s):	Chinese Skullcap Root Powder/Multiple Sections
Expert Committee:	Botanical Dietary Supplements and Herbal Medicines
No. of Commenters:	0 (Initiated by EC)

IDENTIFICATION

Expert Committee Initiated Change #1: In the HPTLC system suitability requirements, the statement “a yellow band immediately below baicalein” was removed

COMPOSITION

Expert Committee Initiated Change #2: The HPLC column re-equilibration time was increased from 5 min to 10 min by increasing the final step from 55 min to 60 min.

ADDITIONAL REQUIREMENTS/*Labeling*

Expert Committee Initiated Change #3: The following caution statement was added to the label: "Dosage forms prepared with this article should bear the following statement: Discontinue use and consult a healthcare practitioner if you develop symptoms of liver trouble, such as abdominal pain, dark urine, or jaundice (yellowing of the eyes or skin)."

Monograph/Section(s): Cholecalciferol Chewable Gels/Weight Variation
Expert Committee: Non-Botanical Dietary Supplements
No. of Commenters: 0 (initiated by EC)
Expert Committee Initiated Change: The LABELING section has been changed to be consistent with Cholecalciferol Tablets and Capsules monographs, specifically to add the option for strength to be expressed in terms of USP or International Units, in parentheses, after the declaration of the amount of cholecalciferol in mcg, and to introduce a footnote with the relationship between USP Units or International Units and mass.

Monograph/Section(s): Desmopressin Acetate/Identification Test A
Expert Committee: Biologics Monographs 1–Peptides and Insulins
No. of Commenters: 1
Comment Summary # 1: The commenter recommended revising the acceptance criteria for the Identification Test A, "The monoisotopic mass by Mass spectrometry <736> is 1068.4 +0.5 mass units" to 1069.4 +0.5 mass units.
Response: Comment not incorporated. The monoisotopic mass of Desmopressin is 1068.4.

Monograph/Section: Desoximetasone/Multiple Sections
Expert Committee: Chemical Medicines Monographs 5
No. of Commenters: 2
Comment Summary #1: The commenter requested revising the *Acceptance criteria* for total impurities in the test for *Organic Impurities* for consistency with what has been approved.
Response: Comment not incorporated. The *Acceptance criteria* are consistent with the sponsor's FDA-approved application. The EC will consider future revisions to the monograph upon receipt of the supporting data.
Comment Summary #2: The commenter requested retaining the *Acceptance criteria* of NMT 0.2% in the test for *Residue on Ignition* for consistency with what has been approved.
Response: Comment incorporated.
Comment Summary #3: The commenter requested replacing the resolution requirement of NLT 1.5 between desoximetasone and desoximetasone acid with a peak-to-valley factor of ≥ 0.5 between the same two peaks in *System suitability* in the test for *Organic Impurities*.
Response: Comment not incorporated. The EC determined the proposal is suitable for its intended use.

Monograph/Sections: Epinephrine / Multiple

Expert Committee: Chemical Medicines Monographs 6
No. of Commenters: 3
Comment Summary #1: The commenter requested including the addition of known amount of 0.1N hydrochloric acid in the preparation of Standard solution and Sample solution under Assay, and Sensitivity solution under *Enantiomeric purity test*, for complete dissolution of epinephrine.
Response: Comment incorporated.
Comment Summary #2: The commenter requested revising the acceptance criteria for N-Benzyl epinephrine and N-Benzyl adrenalone from NMT 0.10% to NMT 0.1% and the Loss on Drying limit from NMT 0.5% to NMT 1.0% to be consistent with the FDA-approved specifications.
Response: Comment incorporated.
Comment Summary #3: The commenter recommended harmonizing the acceptance criteria for N-Benzyl epinephrine and N-Benzyl adrenalone from two decimal points to one decimal to be consistent with the limits proposed in *Ph.Eur.*
Response: Comment not incorporated. The EC revised the acceptance criteria for N-Benzyl epinephrine and N-Benzyl adrenalone from NMT 0.10% to NMT 0.1% to be consistent with the FDA-approved specifications.

Monograph/Sections: Fluoxetine Hydrochloride/Packaging and Storage
Expert Committee: Chemical Medicines Monographs 4
No. of Commenters: 1
Comment Summary #1: The commenter requested the addition of a temperature requirement in the *Packaging and Storage* section.
Response: Comment not incorporated. The EC will consider future revisions to the monograph upon the receipt of supporting data.

Monograph/Sections: Galantamine Hydrobromide/Multiple sections
Expert Committee: Chemical Medicines Monographs 4
No. of Commenters: 1
Comment Summary #1: The commenter requested revising the references within the test for *Enantiomeric Purity* to provide clarification that the isomer being quantitated is the 4*R*,6*S*,8*R* isomer.
Response: Comment incorporated.
EC-Initiated Change #1: The references to 4*S*,8*S* stereoisomer and 4*R*,8*R* stereoisomer were replaced with 4*S*,6*R*,8*S* isomer and 4*R*,6*S*,8*R* isomer, respectively, throughout the monograph.
EC-Initiated Change #2: The test for *Enantiomeric Purity* was renamed the *Limit of the 4R,6S,8R Isomer* to provide clarity, and all references to the test name throughout the monograph were updated for consistency.
EC-Initiated Change #3: The reference to sodium acetate was corrected to anhydrous sodium acetate in the *Buffer* preparation description within the *Limit of the 4R,6S,8R Isomer, Procedure 2.*

EC-Initiated Change #4: The chemical information and formatting within the descriptions of USP Galantamine Hydrobromide Racemic RS and USP Galantamine Hydrobromide Related Compounds Mixture RS were updated for consistency with current USP style.

Monograph/Section(s): Glucagon
Expert Committee: Biologics Monographs 1–Peptides and Insulins
No. of Commenters: 2
Comment Summary #1: The commenter recommended clarifying in the DEFINITION that host cell-derived protein content and/or the host cell-derived or vector-derived DNA content apply to Glucagon produced by microbial processes by adding the word "only" before "when produced by microbial processes."
Response: Comment not incorporated. The EC noted that the text was clear as written.
Comment Summary #2: The commenter recommended revising the *Identification* test section to include additional tests such as amino acid analysis or electrospray ionization mass spectrometry (ESI-MS) that may be more common for synthetic products.
Response: Comment not incorporated. The EC decided that the two identification methods currently in the monograph, HPLC and peptide mapping, are suitable for both synthetic and recombinant glucagon.
Comment Summary #3: The commenter recommended updating the acceptance criteria for the HPLC identification test and introducing a criterion for co-elution.
Response: Comment not incorporated but will be considered for future revisions.
Comment Summary #4: Two commenters recommended shortening or removing the isocratic step at the end of the *Assay* run.
Response: Comment incorporated. Table 2 was revised to change 70 minutes to 45 minutes based on submitted data.
Comment Summary #5: The commenter recommended developing a new reference standard for the synthetic glucagon.
Response: Comment not incorporated. The EC determined that a separate RS for synthetic glucagon is not needed.
Comment Summary #6: The commenter recommended updating the acceptance criteria for glucagon impurities and related compounds/substances.
Response: Comment not incorporated but will be implemented in a future revision when all supporting materials are available and laboratory studies are completed.

Monograph/Section(s): L-alpha-Glycerylphosphorylcholine/Multiple Sections
Expert Committee: Non-Botanical Dietary Supplements
No. of Commenters: 3
Comment Summary #1: The commenter recommended replacing the titration method for the *Assay* procedure with a chromatographic method.
Response: The comment not incorporated. The commenter has agreed to work on the development of an HPLC Assay based on the current method for organic impurities and will propose the new HPLC assay method for a future revision.

Comment Summary #2: The commenter recommended removing the correction factor in the test for Limit of glycerol due to the fact that response factors of glycerol in the *Sample solution* and *Standard solution* are equal.
Response: Comment incorporated. The correction factor was removed.
Comment Summary #3: The commenter suggested that, based on laboratory test results for the identification test, the Potasium Bromide (KBr) IR procedure should be changed to an attenuated total reflection (ATR)-IR procedure.
Response: Comment incorporated. The KBr-IR procedure has been replaced with ATR-IR procedure for the identification test.

Monograph/Section(s): Menaquinone-7 Preparation/Multiple Sections
Expert Committee: Non-Botanical Dietary Supplements
No. of Commenters: 1
Comment Summary #1: The commenter raised concerns that increasing the limit of Menaquinone-6 (MK-6) in the Menaquinone-7 Preparation monograph would lead to low quality products, and it would affect the assay value of the Menaquinone-7 (MK-7) ingredient.
Response: Comment not incorporated. This is the Preparation monograph, and the preparation ingredient can be produced either from pure (or highly purified) MK-7 ingredient or directly from the fermentation extract as the definition denotes. With regard to the assay value, the content of MK-6 is calculated separately from the content of MK-7 and, therefore, its presence even at 10% should not diminish the potency of MK-7 in the preparation monograph.

Monograph/Section: Meropenem/Multiple Sections
Expert Committee: Chemical Medicines Monographs 1
No. of Commenters: 2
Comment Summary #1: The commenter recommended including a statement in the *Total Impurities* in the test for *Organic Impurities*: “Total impurities, excluding meropenem open ring and meropenem dimer’ at NMT 0.3%.”
Response: Comment incorporated. The statement “Total unspecified Impurities” is changed to “Total impurities, excluding meropenem open ring and meropenem dimer” in the monograph.
Comment Summary #2: The commenter recommended revising the *Assay* and *pH* acceptance criteria to be consistent with approved products.
Response: Comment not incorporated. The EC will consider a future revision to the monograph upon receipt of supporting data.
Comment Summary #3: The commenter requested providing the flexibility to use either a ultraviolet (UV) spectrophotometer or photodiode array (PDA) for the Identification test.
Response: Comment not incorporated. The EC determined that the proposed method is suitable for its intended use and consistent with the drug product monograph.
Comment Summary #4: The commenter suggested including the alternative column L42 and relative retention time range for the meropenem dimer impurity when using the L42 column in the test for *Organic Impurities*.
Response: Comment not incorporated. The EC determined that the currently official L1 column for the *Organic Impurities* test is suitable for its intended use.

Monograph/Section: Meropenem for Injection/Multiple Sections
Expert Committee: Chemical Medicines Monographs 1
No. of Commenters: 1
Comment Summary #1: The commenter requested providing the flexibility to use either a UV spectrophotometer or PDA for the Identification test.
Response: Comment not incorporated. The EC determined that the proposed method is suitable for its intended use.
Comment Summary #2: The commenter suggested including the alternative column L42 and relative retention time range for the meropenem dimer impurity when using the L42 column in the test for *Organic Impurities*.
Response: Comment not incorporated. The EC determined that the currently official L1 column for the *Organic Impurities* test is suitable for its intended use.

Monograph/Sections: Metaraminol Bitartrate/Organic Impurities
Expert Committee: Chemical Medicines Monographs 2
No. of Commenters: 1
Comment Summary #1: The commenter recommended revising the concentration of the sensitivity solution in accordance with the ICH reporting threshold.
Response: Comment not incorporated. The EC determined that the proposal is consistent with the FDA-approved sponsor's data and will consider a future revision upon receiving the supporting information.

Monograph/Section(s): Neohesperidin Dihydrochalcone/Multiple Sections
Expert Committee(s): Excipients Monographs 1
Number of Commenters: 0 (Initiated by EC)
Expert Committee-initiated Change #1: The names of six impurities, including Neohesperidin Related compound A and C to G, were corrected to Neohesperidin Dihydrochalcone related compound A and C to G in *Assay* and in *Organic Impurities*.
Expert Committee-initiated Change #2: Run time was changed from "NLT 5 times the retention time of neohesperidin dihydrochalcone" to "5 times the retention time of neohesperidin dihydrochalcone" in *Assay* and in *Organic Impurities*.

Monograph/Section(s): Omega-3 Free Fatty Acids / Multiple Sections
Expert Committee: Non-Botanical Dietary Supplements
No. of Commenters: 1
Comment Summary #1: The commenter recommended updating the Relative retention time (RRT) of Moroctic acid from 0.700 to 0.592 and correcting the RRTs listed in Table 2 to be in accordance with those in Table 4.
Response: Comment incorporated, and the RRTs are corrected.

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

Comment Summary #1: The commenter recommended revising the impurity profile in the *Organic Impurities* test to include all impurities and the corresponding acceptance criteria to be consistent with the FDA-approved applications.
Response: Comment not incorporated. The proposed impurity profile and the corresponding acceptance criteria are consistent with the sponsor's FDA-approved application. The EC will consider a future revision to the monograph upon receipt of supporting data.
Comment #2: The commenter recommended revising the preparation of Sample stock solution in the Assay from "Transfer the contents of NLT 20 Capsules" to "Transfer a portion of the contents of NLT 20 Capsules" for clarification.
Response: Comment incorporated.
Comment #3: The commenter requested clarification for the difference between the proposed relative response factor of prazosin related compound D in *Organic Impurities* and the validation.
Response: Comment not incorporated. The EC determined that the proposed relative response factor is suitable for the intended purpose.

Monograph/Sections: Ropinirole Tablets/Dissolution
Expert Committee: Chemical Medicines Monographs 4
No. of Commenters: 1
Comment #1: The commenter stated that the proposed run time of NLT 1.3 should be increased.
Response: Comment not incorporated. The minimum run time is consistent with supporting validation data for the *Dissolution* test. Manufacturers are able to select longer run times as needed for their product.

Monograph/Sections: Rotigotine/Multiple sections
Expert Committee: Chemical Medicines Monographs 4
No. of Commenters: 1
Comment #1: The commenter requested revising the acceptance criteria for each specified impurity and total impurities in the test for *Organic Impurities* for consistency with what has been approved.
Response: Comment incorporated as follows: several acceptance criteria were widened, an acceptance criterion was added for acetyl rotigotine, and all references to rotigotine *N*-oxide were removed.
Comment #2: The commenter requested adding a footnote to identify rotigotine O-tosylate as a potential genotoxic impurity and adding additional comments in the test for *Organic Impurities*.
Response: Comment not incorporated. The acceptance criterion for rotigotine O-tosylate has been revised to make it consistent with the approved limit.
Comment #3: The commenter requested increasing the concentration of *R*-rotigotine in the System suitability solution in the test for the *Limit of Rotigotine R Enantiomer* to ensure that *R*-rotigotine is above the reporting threshold and can be detected.
Response: Comment not incorporated. The EC will consider a future revision upon receipt of supporting data.

Comment #4: The commenter recommended clarifying the preparation of Sample solution in *Organic Impurities* and revising the proposed statement from “Transfer a suitable portion of the contents from NLT 20 capsules to a suitable volumetric flask” to “Transfer a suitable portion of the contents from NLT 20 capsules to a suitable volumetric flask that doubles the volume of the Diluent used” to be consistent with the sponsor’s procedure.
Response: Comment incorporated.

Monograph/Section(s): Saccharin/Assay
Expert Committee(s): Excipients Monographs 2
No. of Commenters: 3
Comment #1: The commenter recommended changing the Assay acceptance criteria from 98.0–102.0% to 99.0–101.0%.
Response: Comment not incorporated. The liquid chromatography method replaces the non-specific titration method for Assay. Generally, the chromatographic procedures use one or more external standards, the variability of results is higher than that of results obtained by titration procedures, and the specificity is substantially greater, so the EC decided to keep the Assay acceptance criteria at “98.0–102.0%.”
Comment #2: The commenter recommended changing the HPLC column temperature from 20° to 30° because many factories may not have the capability to control the temperature to the lower value.
Response: Comment partially incorporated. The EC reviewed the robustness study results, which demonstrated that the Saccharin main peak overlapped with the Phthalic Anhydride (PAn) impurity peak when the column temperature was at 30°. However, the resolution between Saccharin and PAn were able to meet the acceptance criteria NLT 1.5 when the column temperature was below 25°. Therefore, the column temperature is changed to “20 ± 5°,” and the resolution requirement is changed to “NLT 1.5 between Saccharin and PAn.”
Comment #3: The commenter recommended changing the system suitability requirement (% RSD) from “NMT 0.5%” to “NMT 0.73%” to align with the General Chapter <621> *Chromatography.*
Response: Comment incorporated.
Comment #4: The commenter requested all impurities from different manufacturing processes be included in the monograph.
Response: The EC responded that the impurity method is under development by using instrumental analysis. Stakeholders are encouraged to assist USP for the method development and validation.
Comment #5: The commenter recommended updating the flame test for sodium identification. In addition, they recommended applying the retention time of the principal peak from *Assay* for the IDENTIFICATION test.
Response: The EC responded that these recommendations will be considered in the upcoming revisions to this monograph, so the revisions can be commented by all stakeholders.
Comment #6: The commenter requested more details about the harmonization process for the Saccharin monograph since it was recently suppressed from the PDG workplan.

Response: The EC responded that the monograph will be harmonized through bilateral harmonization with the *JP* and/or other pharmacopeias. In addition, the suppressed monograph might return to the PDG harmonization workplan if needed in the future.

Monograph/Section(s): Saccharin Sodium/Assay
Expert Committee(s): Excipients Monographs 2
No. of Commenters: 3
Comment #1: The commenter recommended changing the Assay acceptance criteria from 98.0–102.0% to 99.0–101.0%.
Response: Comment not incorporated. The liquid chromatography method replaces the non-specific titration method for Assay. Generally, the chromatographic procedures use one or more external standards, the variability of results is higher than that of results obtained by titration procedures, and the specificity is substantially greater, so the EC decided to keep the Assay acceptance criteria at "98.0-102.0%."
Comment #2: The commenter recommended changing the HPLC column temperature from 20° to 30° because many factories may not have the capability to control the temperature to the lower value.
Response: Comment partially incorporated. The EC reviewed the robustness study results, which demonstrated that the Saccharin main peak overlapped with the Phthalic Anhydride (PAn) impurity peak when the column temperature was at 30°. However, the resolution between Saccharin and PAn were able to meet the acceptance criteria NLT 1.5 when the column temperature was below 25°. Therefore, the column temperature is changed to "20 ± 5°," and the resolution requirement is changed to "NLT 1.5 between Saccharin and PAn."
Comment #3: The commenter recommended changing the system suitability requirement (% RSD) from "NMT 0.5%" to "NMT 0.73%" to align with <621>.
Response: Comment incorporated.
Comment #4: The commenter requested all impurities from different manufacturing processes be included in the monograph.
Response: The EC responded that the impurity method is under development by using instrumental analysis. Stakeholders are encouraged to assist USP for the method development and validation.
Comment #5: The commenter recommended updating the flame test for sodium identification. In addition, they recommended applying the retention time of the principal peak from Assay for the identification test.
Response: The EC responded that these recommendations will be considered in the upcoming revisions to this monograph, so the revisions can be commented by all stakeholders.
Comment #6: The commenter requested more details about the harmonization process for the Saccharin monograph since it was recently suppressed from the PDG workplan.
Response: The EC responded that the monograph will be harmonized through bilateral harmonization with the *JP* and/or other pharmacopeias. In addition, the suppressed monograph might return to the PDG harmonization workplan if needed in the future.

Monograph/Section(s): Sorbic Acid/Multiple Sections
Expert Committee(s): Excipients Monographs 1

Number of Commenters: 0 (Initiated by EC)
Expert Committee-initiated Change#1: The system suitability solution preparation condition was revised from “0.1 mg/mL of USP Sorbic Acid RS in diluent with UV irradiation for 2 h” to “Prepare 0.1 mg/mL of USP Sorbic Acid RS in diluent first and then treat the solution with UV irradiation to generate ~1% degradation of sorbic acid (based on area%)” in *ASSAY.* Irradiation time to achieve ~1% degradation depends on type of lamp used. The requirement “to achieve ~1% degradation of the potassium sorbate (based on area %)” that was mentioned in the note should be moved to the main body.
Expert Committee-initiated Change#2: Information was added to supply a sensitivity test to determine whether the Decolorized Fuchsin solution is stable and suitable for use and to give solution storage conditions in *LIMIT OF ALDEHYDE*. This added information is beneficial to users.

Monograph/Section(s): Timolol Maleate/ Enantiomeric Purity
Expert Committee: Chemical Medicines Monographs 2
No. of Commenters: 1
Comment #1: The commenter recommended using the accelerated revision process for processing the proposal because the proposed changes are relatively minor and allow manufacturers to comply quickly.
Response: Comment not incorporated. The EC determined that the revision vehicle used is appropriate for the proposal.
Comment #2: The commenter recommended replacing the resolution requirement between Timolol and Timolol related compound A to the resolution between the critical pair of Timolol and Timolol related compound B.
Response: Comment not incorporated. The EC determined that the proposal as written is suitable for the intended purpose.