Commentary – *First Supplement to USP 36–NF 31*

In accordance with USP's Rules and Procedures of the Council of Experts ("Rules"), USP publishes all 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 republished in *PF* for further notice and comment, in accordance with the Rules. In cases when proposals advance to official status without republication in *PF*, a summary of comments received and the appropriate Expert Committee's responses are published in the *Revisions and Commentary* section of the USP Website 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.

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

No comments were received for the following proposals:

General Chapters:
<467> Residual Solvents
<841> Specific Gravity
<1724> Semi-Solid Drug Products—Performance Tests
<2021> Microbial Enumeration Tests—Nutritional and Dietary Supplements
<2023> Microbiological Attributes of Nonsterile Nutritional and Dietary Supplements
<2232> Elemental Contaminants in Dietary Supplements

Monographs
Amikacin
Amikacin Sulfate
Amikacin Sulfate Injection

Ammonium Glycyrrhizate
Amoxicillin and Clavulanic Acid Extended-Release Tablets
Antipyrine
Atropine Sulfate Injection
Benzethonium Chloride Concentrate
Benzethonium Chloride Topical Solution
Benzoyl Peroxide Lotion
Butyl Palmitostearate
Butyl Stearate
Calcium Acetate
Ciprofloxacin Extended-Release Tablets
Clotrimazole Lozenges
Clotrimazole Topical Solution
Clotrimazole Vaginal Inserts
Cyclizine Hydrochloride
Cyclizine Hydrochloride Tablets
Cyclomethicone
Dapsone
Dibutyl Sebacate
Diphenhydramine Hydrochloride
Estradiol Pellets
Fluconazole for Oral Suspension
Gemfibrozil
Haloperidol
Hypromellose
Isobutane
Kanamycin Sulfate
Lorazepam Oral Concentrate
Maltitol
Maltose
Maprotiline Hydrochloride
Menotropins
Menotropins for Injection
Meprobamate
Methenamine Mandelate Delayed-Release Tablets
Methyl Salicylate
Mitomycin
Mitomycin for Injection
Octoxynol 9
Potassium Benzoate
Povidone
Praziquantel
Propanediol
Quinine Sulfate Capsules
Quinine Sulfate Tablets
Ribavirin Capsules

Rocuronium Bromide
Sodium Benzoate
Sterile Purified Water
Sterile Water for Inhalation
Sterile Water for Injection
Sterile Water for Irrigation
Sulfasalazine Delayed-Release Tablets
Temazepam
Thioridazine Hydrochloride Tabets
Triacetin
Valerian Tablets
Valproate Sodium Injection
Valproic Acid Oral solution

General Chapters

General Chapter/Section(s): <87> Biological Reactivity Tests, In Vitro
Expert Committee: Toxicology
No. of Commenters: 5
Comment Summary #1: The commenter requested deleting the proposed text that expands applicability of the tests in the General Chapter to other materials. Other materials (drug substance impurities and excipients for pharmaceutical products) are assessed using other guidelines, thus additional test requirements for drug substance impurities/excipients as defined with <87> *Biological Reactivity Tests, In Vitro and* <88> *Biological Reactivity Tests, In Vivo* do not offer further beneficial information.
Response: Comment incorporated.
Comment Summary #2: The commenter requested deleting the proposed text that requires determination that a leachable/ extractable is present in the extract before proceeding with the tests, and revert to original text. The term “leachable” is not appropriate for any of these General Chapters because the types of tests described in chapters <87>, <88>, and <1031> describe the forced extraction of chemicals under laboratory conditions from materials (test articles) that are not yet part of a final product.
Response: Comment incorporated.
Comment Summary #3: The commenter requested deleting the proposed text to quantify the leachable/ extractable, where appropriate.
Response: Comment incorporated.
Comment Summary #4: The commenter requested deleting the proposed text requiring quantification or determination of the dose-response of the extract, because the General Chapter is intended for initial screening
Response: Comment incorporated.
Comment Summary #5: The commenter requested clarifying the proposed text on use of alternate cell lines with the addition of a qualifier, “from a standard repository.”
Response: Comment incorporated.

Comment Summary #6: The commenter requested revising the proposed text, “In vitro tests that produce positive responses are candidates for the in vivo tests …” to “Materials that fail the in vitro tests are candidates for the in vivo tests …..”
Response: Comment incorporated.
Expert Committee-initiated Change #1: The Expert Committee clarified conditions of cells in culture (Table 2) by adding “greater than” for grade 2 (>20%) and grade 3 (>50%).

General Chapter/Section(s): General Chapter <88> *Biological Reactivity Tests*, *In Vivo*
Expert Committee: Toxicology
No. of Commenters: 5
Comment Summary #1: The commenter requested deleting the proposed revised text that requires to ascertain that a leachable/extractable is present in the extract before proceeding with the tests and revert to original text. The term “leachable” is not appropriate for any of these General Chapters because the types of tests described in General Chapters <87>, <88>, and <1031> describe the forced extraction of chemicals under laboratory conditions from materials (test articles) that are not yet part of a final product
Response: Comment incorporated.
Comment Summary #2: The commenter requested deleting the proposed text to quantify the leachable/ extractable, where appropriate.
Response: Comment incorporated.
Comment Summary #3: The commenter requested deleting the proposed text requiring quantification or determination of the dose-response of the extract, because the tests in the General Chapter are used for initial screening.
Response: Comment incorporated.
Comment Summary #4: The commenter requested revising the proposed change to systemic Injection in mouse to intraperitoneal from intravenous (i.v.) to overcome difficulties with i.v injection in mice and to allow alternate routes of injection, while retaining the intravenous route of injection. This is to allow users who currently use intravenous injection as the route of administration to continue to do so.
Response: Comment incorporated.
Comment Summary #5: The commenter requested revising the proposed revision to intracutaneous tests to replace rabbits with guinea pigs to overcome difficulties in doing an i.c injection into rabbits to allow guinea pig as an alternate test animal while retaining rabbit as one of the test animals. This is to allow users who currently use Rabbit as the test animal to continue to do so.
Response: Comment incorporated.

Monograph/Section(s): <208> *Anti-Factor Xa and Anti-Factor IIa Assays for Unfractionated and Low Molecular Weight Heparins/ Multiple Sections*
Expert Committee: Monographs—Biologics and Biotechnology 1
No. of Commenters: 1
Comment Summary #1: The commenter requested that the proposed potency range of 0.8-1.2 be removed or replaced with the correct range for all low molecular weight heparins.
Response: Comment incorporated. Potency range for each low molecular weight heparin will be included in individual product monograph instead.
Comment Summary #2: The commenter indicated that the proposed formula for calculation of anti-factor Xa activity is incorrect.
Response: Comment incorporated.
Comment Summary #3: The commenter requested removing the following system suitability requirement for potency ratios in the Anti-Factor IIa Assay for Low Molecular Weight Heparin section: "In the case of parallel-line analysis, all potency ratios must be in the range of 0.8-1.2. If this criterion is not met, the particular sample dilutions are not in the dose range of the standard dilutions. In this case, different sample dilutions must be prepared and assayed."
Response: Comment incorporated.

General Chapter/Section(s): <643> Total Organic Carbon/Sterile Water
Expert Committee(s): General Chapters—Chemical Analysis
Expert Committee-initiated Change #1: The Expert Committee revised the introductory paragraph of this new section and decided to remove the word "bulk" from the following sentence: "The following sections apply to tests for bulk *Sterile Water for Injection*, *Sterile Purified Water*, *Sterile Water for Irrigation*, and *Sterile Water for Inhalation*." because it was unintentionally included.

General Chapter/Section(s): <645> Water Conductivity/Sterile Water
Expert Committee(s): General Chapters—Chemical Analysis
No. of Commenters: **1**

Procedure
Comment Summary #1: The commenter requested keeping the acceptance criterion of conductivity as not greater than 25 µS/cm instead of the proposed value of 15 µS/cm for sterile waters in containers with a nominal volume of 10 mL or less. The data trending is well known and has shown that this limit is suitable. Containers are approved on the market and a clinical relevance of a lower limit is neither known nor to be expected.
Response: Comment incorporated.

General Chapter/Section(s): General Chapter <1031> The Biocompatibility of Materials Used in Drug Containers, Medical Device and Implants
Expert Committee: Toxicology
No. of Commenters: 2

Comment Summary #1: The commenter requested deleting the proposed revised text to ascertain that a leachable/extractable is present in the extract before proceeding with the tests **and** revert to original text. The term “leachable” is not appropriate for any of these General Chapters because the types of tests described in General Chapters <87>, <88>, and <1031> describe the forced extraction of chemicals under laboratory conditions from materials (test articles) that are not yet part of a final product
Response: Comment incorporated.

Comment Summary #2: The commenter requested deleting the proposed text to quantify the leachable/ extractable, where appropriate.
Response: Comment incorporated.

Comment Summary #3: The commenter requested deleting the proposed text requiring quantification or determination of the dose-response of the extract, because the General Chapter is intended for initial screening.
Response: Comment incorporated.

Comment Summary #4: The commenter requested revising the proposed change to systemic Injection in mouse to intraperitoneal from intravenous (i.v) to overcome difficulties with i.v injection in mice and to allow alternate routes of injection, while retaining the intravenous route of injection. This is to allow users who currently use intravenous injection as the route of administration to continue to do so.
Response: Comment incorporated.

Comment Summary #5: The commenter requested revising the proposed revision to replace rabbits with guinea pigs for intracutaneous (i.c.) to overcome difficulties to do an i.c. injection into rabbits and to allow guinea pig as an alternate test animal while retaining rabbit as one of the test animals. This is to allow users who currently use rabbits as the test animal to continue to do so.
Response: Comment incorporated.

Expert Committee-initiated Change #1: The Expert Committee replaced the inappropriate term Subacute Toxicity in Tables 3, 4 and 5 with “Repeat dose up to 90 days” in the text.

General Chapter/Section(s): General Chapter <1106> Immunogenicity Assays—Design and Validation of Assays to Measure Anti-Drug Antibodies
Expert Committee: General Chapters—Biological Analysis
No. of Commenters: 4

General Comments
Comment Summary #1: The commenter requested alignment with FDA and EMA guidances and adding detailed literature references where appropriate.
Response: Comment partially incorporated. The 2012 EMA's "Guideline on immunogenicity assessment of monoclonal antibodies intended for in vivo clinical use" that the commenter recommended was added. All other guidances mentioned were already in the forum proposal and appropriate references are already included. USP General Chapters do not normally provide an exhaustive list of literature references.
Comment Summary #2: The commenter asked USP to review all occurrences of the words "must" and "should."
Response: Comment incorporated.
Comment Summary #3: The commenter stated that measurement of neutralizing antibody (Nab) activity is required in all clinical studies and not only in high risk situations.
Response: Comment not incorporated because Nab measurement is not always an FDA requirement.
Comment Summary #4: The commenter requested that "bioanalytical" be changed to "analytical" or "antibody analytical" so that it is not confused with PK assays.
Response: Comment not incorporated because the term "bioanalytical" can apply to more than only PK assays.

Introduction and Scope
Comment Summary #5: The commenter requested that "how the assay is executed" in the first sentence of the second paragraph be clarified and that selection of time points be added as an important factor.
Response: Comment incorporated.
Comment Summary #6: The commenter requested that the third paragraph be broken into two sentences.
Response: Comment incorporated.
Comment Summary #7: The commenter requested that the second sentence of the fourth paragraph begin with, "If an endogenous counterpart of a drug exists, ADA that...".
Response: Comment incorporated.
Comment Summary #8: The commenter requested that the guidance regarding biosimilars and pediatric studies be added to the chapter section.
Response: Comment not incorporated because this is outside the scope of the General Chapter.
Comment Summary #9: The commenter requested that the first sentence of the fifth paragraph be broken into two sentences.
Response: Comment incorporated.

Factors that Affect the Immunogenic Potential of a Therapeutic Protein
Comment Summary #10: The commenter requested that "variant" in the first sentence include drug formulation as one of the factors which can influence the immune response against a drug.
Response: Comment incorporated.

Determination of Preclinical and Clinical Immunogenicity
Comment Summary #11: The commenter requested that text be added to the end of the second paragraph regarding statistical powering of studies and genetic diversity considerations.
Response: Comment incorporated.
Comment Summary #12: The commenter requested that text be added after the first sentence of the third paragraph of this section stating that anti-drug antibodies (ADA) can increase the half life of short lived drugs and therefore the exposure to a bioactive complex.
Response: Comment incorporated.
Comment Summary #13: The commenter requested addition of text to the last sentence in the third paragraph indicating that lack of effect on PK if the assay represents the mechanism of action (MOA) can also be informative.
Response: Comment incorporated with modification because a PK assay does not have to reflect the MOA to still be informative. Instead, the sentence now reads "Therefore, lack of an effect on a PD marker and/or on PK also should be considered..."
Comment Summary #14: The commenter indicated that the text "In fact, most nonclinical toxicology studies do not evaluate the kinetics of ADA development, and samples for the assessment of ADA usually are taken at baseline, end of treatment, and end of recovery periods" include reference to nonclinical studies containing high dose cohorts and that current methods are sensitive to the presence of circulating drug.
Response: Comment not incorporated. This comment does not reflect all testing cases.
Comment Summary #15: The commenter requested that text be added after the first sentence of the fifth paragraph of this section stating that analysis of samples during this dosing phase is complicated by drug interference and it is important to sample at appropriate times.
Response: Comment incorporated except that the sentence says "may be complicated" rather than "is complicated" because therapeutics with short half lives are not a problem for these studies.
Comment Summary #16: The commenter requested that "relative mass units" be added to the titer units in the last sentence of the fifth paragraph of this section.
Response: Comment incorporated.
Comment Summary #17: The commenter requested that the first sentence of the sixth paragraph of this section say "A case by case approach..." rather than "A risk based approach" because this is not necessary for a preclinical study.
Response: Comment not incorporated. Under some circumstances it is good practice to run animal studies for a high-risk molecule differently than for a low-risk molecule and it is still related to a clinical study.

Comment Summary #18: Regarding the third sentence of the sixth paragraph of this section, the commenter stated that typically Nab assays are not performed in nonclinical studies due to high circulating levels of drug and it might be helpful to provide an example.
Response: Comment not incorporated. This would be redundant because the sentence already states "If data from a neutralizing antibody assay..."
Comment Summary #19: The commenter requested that the sentence "However it should be noted that the transfer of immunogenicity data across animals/cohorts can be limited." be added to the end of the sixth paragraph of this section.
Response: Comment not incorporated. The concept is sufficiently covered as written.
Comment Summary #20: The commenter requested that the first sentence of the Clinical subsection of this section be modified to include the bold text, "In clinical studies, ADA **detection and** characterization..."
Response: Comment incorporated.
Comment Summary #21: The commenter requested that the first sentence of the last paragraph of this section not state that the further characterization is "routinely" done.
Response: Comment incorporated.
Comment Summary #22: The commenter requested that "profile" be deleted from the last sentence of the last paragraph of this section because there are sensitivity and other technical limitations that limit the significance of subclass data.
Response: Comment partially incorporated by removing "profile" and clarifying language but technical limitations are not true across labs and subclass remains.

Risk-based Approach to Assessing Immunogenicity and its Consequences
Comment Summary #23: Two commenters asked for clarification of the term “Risk” in Table 1.
Response: Comments incorporated.
Comment Summary #24: Two commenters requested changes to "Patient Disease State" in Table 2, either deletion, further explanation, or revision to "Patient's immune status."
Response: Comments not incorporated. This is a broad category capturing more than the immune status of the patient.
Comment Summary #25: The commenter requested that "Limited number of multiple doses or" be removed from Table 2 to keep only "Episodic dosing."
Response: Comment incorporated.
Comment Summary #26: The commenter requested that the last sentence in the second paragraph after Table 2 be modified to include immune complexes in the example.
Response: Comment incorporated by changing the example to "...(e.g., the reactivity of ADA with aggregated vs. nonaggregated drug)."
Comment Summary #27: One commenter requested deletion of the two sentences in Step 2 of this section starting with "In their absence..." and add instead "As the actual drug tolerance of a study sample cannot be predicted, samples containing drug should always be reported together with the statement of drug interference." Two other commenters asked for clarity regarding these sentences.

Response: Comment not incorporated. However, the reference to *Relative Sensitivity* section added for greater clarity of this section.
Comment Summary #28: Two commenters requested removal of "relative mass units" in the last sentence of Step 2 of this section because they are not usually used and that the FDA guidance document strongly argues against expressing ADA levels in mass units.
Response: Comment incorporated.
Comment Summary #29: The commenter suggested adding a sentence to Step 3 regarding MOA of a therapeutic.
Response: Comment incorporated.
Comment Summary #30: The commenter requested that the next sentence in Step 3 be modified because it is the correlation of antibody data to pharmacodynamic (PD) markers that shows whether antibodies have a neutralizing effect in vivo whereas the Nab assay only determines a potential neutralizing effect in vitro under the conditions used in the assay.
Response: Comment incorporated.

Design of Immunoassay-based Test Methods
Comment Summary #31: The commenter requested modification of the sentence "By ensuring a defined false positive rate, analysts help ensure that the false negative rate essentially is zero" because no one can ensure this or know what the false negative rate actually is.
Response: Comment incorporated.
Comment Summary #32: The commenter requested that the solution phase assay in the *Screening Assays* subsection state that the labeled drugs are incubated simultaneously rather than sequentially and the description should be modified.
Response: Comment not incorporated. Multiple formats are possible and these are examples.
Comment Summary #33: The commenter requested addition of a Design of Experiments discussion to the sentence with "various technology platforms" in the *Screening Assays* subsection because it can save time, reagents, and resources.
Response: Comment not incorporated. Design of Experiments does not eliminate the shortcomings of platforms which is the focus of the sentence.
Comment Summary #34: The commenter requested that the first sentence of the third paragraph in the *Screening Assays* subsection be deleted because it is nearly impossible to "confirm" that the binding epitopes are not blocked with the tags or by coating on plates or beads.
Response: Comment incorporated.
Comment Summary #35: The commenter requested that the sentence in the *Screening Assays* subsection regarding solution phase ECL versus ELISA assays be modified because it is possible to perform solution phase ELISAs too.
Response: Comment incorporated.
Comment Summary #36: The commenter requested that the sentence "Assay performance typically is optimized..." in the *Screening Assays* subsection be modified because they usually test specificity, drug tolerance and selectivity in the development

phase with minimal precision and then the stability and robustness are tested in validation.
Response: Comment not incorporated because the sentence contains recommendations and the word "typically" to indicate that they are not required if justified.
Comment Summary #37: The commenter requested deletion of the sentence before Table 3 because there are no requirements to validate more than one assay format if the initial assay cannot meet the performance goals.
Response: Comment incorporated by modifying the sentence rather than deleting it.
Comment Summary #38: The commenter requested modification of the bridging assay advantages listed in Table 3 because it is not highly specific.
Response: Comment not incorporated. Bridging assays can often be more specific because they require two binding events.
Comment Summary #39: The commenter requested that "low sensitivity" be added to the SPR disadvantages listed in Table 3.
Response: Comment not incorporated. SPR can actually detect more antibodies because it also detects low affinity binders that other methods may miss and that may not be reflective of a typical positive control. The commenter can learn more details about this in USP General Chapter <1105>.
Comment Summary #40: The commenter requested modification of the "orthogonal methods" use for the *Confirmatory Assay* subsection because the same screening assay could be used for confirmation.
Response: Comment not incorporated because options already are described and not prohibited.
Comment Summary #41: The commenter requested deletion of the sentence "However, when analysts express ADA data in terms of titer values, they also should..." in the *Characterization Assays* subsection because linearity is not relevant for quasi-quantitative assays.
Response: Comment not incorporated. One still needs to demonstrate linearity of dilution to show the titer has some relevance and the response is not just a matrix effect.
Comment Summary #42: The commenter requested addition of the bold words to the sentence "In addition to performing titration, analysts routinely characterize positive ADA samples in neutralization assays to determine the **in vitro** effect of ADA..." in the *Characterization Assays* subsection.
Response: Comment incorporated.

Validation of Immunoassays
Comment Summary #43: The commenter requested addition of information about positive controls and how you choose, prepare, and store them, to the sentence starting "Pre-study validation therefore..." in the second paragraph of this section.
Response: Comment not incorporated because information about positive controls is found later in the General Chapter.
Comment Summary #44: The commenter requested deletion of the entire *Minimum Required Dilution* subsection.

Response: Comment not incorporated because no reason was provided for the request and this information is important to the General Chapter.
Comment Summary #45: The commenter requested deletion of the Z-factor discussion in the *Minimum Required Dilution* (MRD) subsection because it is more appropriate for high throughput screening.
Response: Comment not incorporated because Z-factor is appropriate for these purposes too and is not unique to high throughput screening.
Comment Summary #46: Two commenters requested modification of the MRD definition and better definition of the background sample (e.g., is it really a "reagent blank sample"?).
Response: Comments incorporated.
Comment Summary #47: The commenter requested adding to the *Pre-study Validation* subsection that pre-study validation is carried out using controls prepared by spiking a fixed concentration of positive control into target matrix and the concentration of QC's are determined during development.
Response: Comment not incorporated because "pre-study" means all the components necessary to test study samples (vs. "in-study," which is discussed later in the General Chapter). In addition, the use of controls is already discussed in this section's *Defining System Suitability* subsection.
Comment Summary #48: The commenter requested deletion of "or potential positive" in the first paragraph of the *Screening Cut-points* subsection.
Response: Comment not incorporated because the samples have not been confirmed here yet so the language as written is correct.
Comment Summary #49: The commenter requested recommending more than 50 drug-naive individuals in the second paragraph of the *Screening Cut-points* subsection.
Response: Comment not incorporated. The sentence already says "at least 50."
Comment Summary #50: The commenter requested recommending more than 20 drug-naive individuals per indication in the second paragraph of the *Screening Cut-points* subsection.
Response: Comment incorporated.
Comment Summary #51: The commenter requested changing the recommendation of 25 drug-naive individuals to 15 for nonclinical applications in the second paragraph of the *Screening Cut-points* subsection.
Response: Comment not incorporated because 25 is the number of drug-naive individuals supported by peer-reviewed literature.
Comment Summary #52: The commenter requested that the words "plate orientations" be modified to "plate layouts" in the second paragraph of the *Screening Cut-points* subsection.
Response: Comment incorporated.
Comment Summary #53: The commenter requested a clarification of the phrase "sample results empirically" because both parametric and non-parametric methods can be considered empirical *Fixed Cut-points* subsection.
Response: Comment incorporated.
Comment Summary #54: The commenter requested addition of the text "However, in preclinical trials it is also considered adequate to use a cut-point at the 99th or 99.9th percentile as immunogenicity of a protein normally results in high antibody titers. This

approach ensures an acceptable sensitivity for preclinical trials and omits the need of a confirmatory assay as no false positive results are expected." to the *Fixed Cut-points* subsection.
Response: Comment partially accepted by adding the first sentence with the modification in bold "**However, in preclinical trials it may be considered adequate**..." but not the second sentence because a confirmatory assay may still be needed.
Comment Summary #55: The commenter requested correction of the text "by adding (if data were not transformed) or multiplying" in the *Floating Cut-point* subsection because the multiplication factor can be used not only for log-transformed data. In addition if normalized intensity data is normally distributed, then no log-transformation is required and the cut-point F-factor will be multiplied by the background and not added to the background.
Response: Comment incorporated by revising the text for greater clarity. "A floating cut-point is a cut-point calculated by applying an additive or multiplicative normalization factor, determined from the pre-study validation data, to the biological background obtained during the in-study phase (see Appendix G of Shankar et al, 2008, for details)."
Comment Summary #56: The commenter suggested, regarding the *Dynamic Cut-point* subsection, that a pre- vs. post-dose cut-point may be a more practical solution than a dynamic cut-point in some assays and that it is worth mentioning here if someone can't use a fixed or floating cut-point.
Response: Comment incorporated.
Comment Summary #57: Two commenters suggested that more than 25 individuals may be needed (gave an example of 60) and a 0.1% false positive rate may not be possible with only 25 individuals for the *Dynamic Cut-point* evaluation.
Response: Comment incorporated.
Comment Summary #58: The commenter suggested that "when the signal from the assay buffer" in the *Titration method Cut-point* subsection does not make sense because titration samples should be diluted in negative control matrix.
Response: Comment incorporated.
Comment Summary #59: The commenter requested removing or revising the recommendations in the statement "define the titration cut point..." in the *Titration method Cut-point* subsection because it may cause significant issues because some borderline confirmed ADA-positive samples selected in the screening assay using the 5% false positive rate may suddenly become negative when the 0.1% false positive rate titration cut point is applied.
Response: Comment not incorporated. This approach is only for the purpose of reporting titers and the chapter further clarifies that the MRD is reported if confirmed samples fall between the two cut-points.
Comment Summary #60: The commenter suggested, regarding "assigned a titer value equal to the MRD" in the *Titration method Cut-point* subsection, that the samples should be diluted in the negative control matrix and tested at fixed MRD and the titers should be reported in neat samples irrelevant of which MRDs are used in the assay; otherwise, accounting for MRDs in determining values will make these values assay-dependent and not comparable to the data sets performed in different assays.

Response: Comment not incorporated. This approach is only for the purpose of reporting titers and the chapter further clarifies that the MRD is reported if confirmed samples fall between the two cut-points.
Comment Summary #61: The commenter requested adding tracking of controls over time to the *Defining System Suitability* subsection.
Response: Comment incorporated.
Comment Summary #62: The commenter stated that the sentences in the second paragraph of the *Defining System Suitability* subsection that begin with "For example, a 1% rejection rate…" do not add value because minor changes in reagents or assay drift can be problematic and too many good assays may be rejected.
Response: Comment not incorporated because the sentences do add value, although the sentence was modified to clarify the intent using the bold words: "As an example and in order to understand if the low positive control is sufficiently low, a 1% rejection rate may…".
Comment Summary #63: The commenter requested clarification of the phrase "ratio of the high positive control to the low…" in the *Defining System Suitability* subsection.
Response: Comment incorporated.
Comment Summary #64: The commenter requested adding an example of excluding robustness runs that did not have technical errors but are not acceptable and such conditions will be disallowed during normal sample testing in the *Defining System Suitability* subsection.
Response: Comment not incorporated. The chapter can't cover every possibility and sufficient examples are given.
Comment Summary #65: The commenter requested that it may be worth mentioning that the second case (in the presence of a drug) is also often referred to as drug tolerance rather than sensitivity in the phrase "not as a single value, but as a set of at least 2 values" in the *Relative Sensitivity* subsection.
Response: Comment not incorporated because the additional language is not necessary.
Comment Summary #66: The commenter suggested that 250 ng/mL for clinical assays and 500 ng/mL for preclinical assays should be targeted rather than the "of at least 500 ng/mL" stated in the *Relative Sensitivity* subsection.
Response: Comment not incorporated because the statement "of at least 500" is in the immunogenicity white papers and "at least" does not contradict a 250 ng/mL value.
Comment Summary #67: The commenter requested addition of the sentence, "The relevant assay sensitivity for nonclinical studies should take the drug concentration during treatment into consideration by estimating the amount of drug that can be neutralized by ADA." after the sentence in the first paragraph of the *Relative Sensitivity* subsection that ends with "…should be justified on a case-by-case basis."
Response: Comment not incorporated because the statement differs from the white papers.
Comment Summary #68: The commenter suggested that titration should occur on a case by case basis and not routinely proposed in the first sentence of the last paragraph in the *Relative Sensitivity* subsection.
Response: Comment incorporated by changing the word "should" to "could".

Comment Summary #69: The commenter suggested that it is not clear if multiple or a single positive control concentration is recommended in the phrase "set concentrations of a positive control" in the first sentence of the last paragraph in the *Relative Sensitivity* subsection.
Response: Comment not incorporated because text is clear that multiple positive controls are used based on reading the first and second sentences.
Comment Summary #70: The commenter suggested that the concept using "anticipated drug trough concentrations" in the second sentence of the last paragraph in the *Relative Sensitivity* subsection is complicated and may potentially cause confusion of how to report, interpret, or apply this information to understand study sample results. The commenter suggested that the highest concentrations of drug should be conservatively estimated at given timepoints of immunogenicity samples to achieve the projected drug tolerance of the assay at appropriate fixed positive control levels.
Response: Comment partially incorporated by deleting the last sentence of the paragraph which could lead to the complexity of the concept.
Comment Summary #71: The commenter stated that the definition of specificity in the *Specificity* subsection differs from that in the 2009 FDA draft guideline.
Response: Comment not incorporated because in its simplest form specificity provides information on how likely a positive result is due to an antibody against the drug and should not be too complicated.
Comment Summary #72: The commenter stated that tighter criteria may be possible for ELISAs because ECL assays tend to be more variable particularly due to plate effects so this point should be changed in the *Precision* subsection.
Response: Comment incorporated by deleting the example in parentheses, "…(e.g., tighter criteria may be possible…").
Comment Summary #73: The commenter stated that %CV of intensities should be explicitly stated rather than just %CV in the *Precision* subsection.
Response: Comment incorporated by adding the bold words, "These are expressed as %CV **of** ADA signals."
Comment Summary #74: The commenter requested, regarding the sentence "A recommended but more rigorous approach…" in the *Precision* subsection, that a caution be added to try not to be too quantitative or over interpret the titer data.
Response: Comment not incorporated. This approach allows a user to better determine differences and variability in titer levels and does not over interpret or make titration more quantitative.
Comment Summary #75: The commenter requested adding more guidance on robustness in the *Robustness* subsection.
Response: Comment incorporated.
Comment Summary #76: The commenter requested consistency in uses of the words "ruggedness" and "reproducibility."
Response: Comment incorporated.
Comment Summary #77: The commenter suggested that it is dangerous to mix together reagent stability and sample stability in the *Stability* subsection.
Response: Comment not incorporated. Reagent stability is addressed in this section and sample stability is addressed later in the General Chapter when discussing sample archiving.

Comment Summary #78: Two commenters suggested that antibodies are known to be stable at -20°, so the *Stability* subsection should be modified to be consistent with this and the 2008 Shankar reference that supports two years stability.
Response: Comments incorporated.

Life Cycle Management
Comment Summary #79: The commenter suggested that it is generally not feasible to archive analyte-spiked samples and blinded patient samples as recommended in this section due to ethical considerations.
Response: Comment not incorporated because one can use pooled patient samples which are de-identified, but the sentence was modified by replacing the word "necessary" with "useful" in the following: "In addition, archiving of analyte-spiked samples as well as blinded patient samples is useful to bridge between reagent lots and methods in order to…".
Comment Summary #80: The commenter requested changing the sentence "Quality controls that ensure assay equivalence include %CV, tolerance limits, EC_{50} values of slope, titer level, and signal-to-noise ratio" to "Quality controls that ensure assay equivalence include %CV, acceptance limits, and titer levels."
Response: Comment not incorporated because it is useful to highlight various parameters that can be used to demonstrate equivalence in reagent qualification.
Comment Summary #81: The commenter requested deletion or a better explanation of the statement that it may be prudent to also archive patient samples to demonstrate the long-term consistency of the polyclonal ADA response in actual patient samples (last sentence of this section).
Response: Comment incorporated by changing the word "consistency" to "stability" for better clarity.

Appendix
Comment Summary #82: The commenter requested addition of the 2012 EMA Guideline on immunogenicity assessment of monoclonal antibodies intended for in vivo clinical use.
Response: Comment incorporated.

General Chapter/Sections: <1118> Monitoring Devices—Time, Temperature, and Humidity
Expert Committee(s): General Chapters–Packaging, Storage and Distribution
No. of Commenters: 2

Introduction
Comment Summary #1:
The commenter requested that a differentiation be made concerning the distribution conditions that might differ from storage conditions during transportation.
Response: Comment incorporated.

Calibration of Temperature—Monitoring Device
Comment Summary #2: The commenter requested deleting the text discussing measurement responsiveness and time accuracy, because these parameters are not critical.
Response: Comment incorporated.
Comment Summary #3: The commenter requested that the text stating, “Different levels of responsiveness are needed” be revised to better fit with the remainder of the sentence that addresses time interval
Response: Comment incorporated.

The Use of Historical Temperature Data
Comment Summary #4: The commenter requested that text recommending lane-specific temperature monitoring include a statement on risk based approaches, taking the product’s stability, distribution route and mode of transportation, and the potential risk to compromise the quality of the product into consideration.
Response: Comment incorporated.
Comment Summary #5: The commenter requested that text recommending temperature monitoring also include a statement on risk based approaches, taking the product’s stability, the distribution route and mode of transportation and the potential risk to compromise the quality of the product into consideration to come to a more general profile instead of focusing on specific lanes which can change.
Response: Comment incorporated.
Comment Summary #6: The commenter suggested that when a drug product is sufficiently protected by the primary container proven by sound stability studies, humidity monitoring can be omitted. Humidity monitoring should be required only if special environmental conditions concerning the humidity are defined for the drug product.
Response: Comment incorporated.

General Chapter/Section(s): General Chapter <1229> Sterilization of Compendial Articles
Expert Committee(s): General Chapters—Microbiology
No. of Commenters: 6
Comment Summary #1: The commenter suggested inserting “≤” before 10^{-6} in the definition of *Probability of a Non-sterile Unit* (PNSU).
Response: Comment incorporated.
Comment Summary #2: The commenter requested adding “$\leq 10^{-6}$” to figure 1
Response: Comment incorporated.
Comment Summary #3: The commenter requested revising the definition of D-value for steam and dry heat to read, "For dry heat, the D-value is a function of temperature while for moist heat, the D-value is a function of moisture saturation level and temperature."
Response: Comment not incorporated. This effort speaks specifically to saturated steam, thus the moisture saturation level is 100%. The only variable for D-value in steam sterilization is temperature.

Comment Summary #4: The commenter requested changing “Biological Indicator” to "Microbial" in Figure 2.
Response: Comment incorporated.
Comment Summary #5: The commenter requested deferring to ISO and removing use of PNSU from this chapter and use SAL instead.
Response: Comment not incorporated. SAL has no independent meaning; it can only be understood in relation to PNSU. This set of General Information Chapters is restricted to sterilization, and thus PNSU applies. Aseptic processing is outside the scope of the <1229> series. During the transition to these new General Chapters there may be some confusion, it will be alleviated when the revised Aseptic Processing content (to appear in General Chapter <1211>) is provided.
Comment Summary #6: The commenter requested revising the definition of D-value by replacing “1 $\log_{10}$ cycle” with “1 $\log_{10}$ base 10 logarithm.”
Response: Comment incorporated.
Comment Summary #7: The commenter requested inclusion of Parametric Release content.
Response: Comment incorporated.
Expert Committee-initiated Change #1: The Expert Committee added a new figure (Figure 3) to describe a typical death curve for microorganisms subjected to a sterilization process.
Expert Committee-initiated Change #2: The Expert Committee added a sub-section on Training.

General Chapter/Section(s): General Chapter <1229.1> Steam Sterilization by Direct Contact
Expert Committee: General Chapters—Microbiology
No. of Commenters: 6
Comment Summary #1: The commenter requested changing the title from “steam” to “moist heat.”
Response: Comment not incorporated. The Expert Committee determined “steam” was the more appropriate term to use. There may be some confusion because <1229.2> was not in the same issue of *Pharmacopeial Forum* (*PF*). The suggestion to change title from 'steam' to 'moist heat' is more appropriate for General Chapter <1229.2> and will be incorporated there.
Comment Summary #2: The commenter requested adding content on Bioburden method.
Response: Comment not incorporated. This content is included in General Chapters <1229> and <1229.2>.
Comment Summary #3: The commenter suggested revising format of equation.
Response: Comment incorporated.
Expert Committee-initiated Change #1: The Expert Committee added appropriate references at the end of the General Chapter.

General Chapter/Section(s): General Chapter <1229.2> Steam Sterilization of Aqueous Liquids
Expert Committee: General Chapters—Microbiology

No. of Commenters: 6
Comment Summary #1: The commenter requested changing the title from "steam" to "moist heat" because many aqueous liquids are sterilized with superheated water and not steam.
Response: Comment incorporated.
Comment Summary #2: The commenter requested deleting the reference to air as one of the components used to heat to the liquid filled containers.
Response: Comment not incorporated. Air is present in the sterilizer in many thermal sterilization processes. Air is present for container integrity and must be mentioned.
Comment Summary #3: The commenter requested inclusion of Parametric Release content.
Response: Comment incorporated.
Comment Summary #4: The commenter requested revising the format of equation 2.
Response: Comment incorporated.
Comment Summary #5: The commenter requested inserting "≤" before 10^{-6} in the definition of *Probability of a Non-sterile Unit* (PNSU).
Response: Comment incorporated.
Comment Summary #6: The commenter requested adding a reference for Bioburden-Biological Indicator method D-value (Table 1, Routine Usage).
Response: Comment not incorporated. This is intended to be illustrative of relative D-values and does not represent any real system.
Expert Committee-initiated Change #1: The Expert Committee added appropriate references at the end of the General Chapter.

General Chapter/Section(s): <1231> Water for Pharmaceutical Purposes/Multiple Sections
Expert Committee(s): General Chapters—Chemical Analysis
No. of Commenters: 1

General
Comment Summary #1: The commenter requested clarifying the terms "parenteral dosage forms" and "nonparenteral dosage forms" when used to describe type of water to be used for each preparation.
Response: Comment not incorporated because parenteral and other routes of administration are clearly defined in revised General Chapter <1151>. *Pharmaceutical Dosage Forms*

Nonmonographed Analytical Waters
Expert Committee-initiated Change #1: The Expert Committee updated the definition of "High Purity Water" because it is no longer available in the General Chapter <660> *Container-Glass* and it contained other out-of-date references (for instance, copper stills are no longer used).

Monographs

Monograph/Section(s): Acetaminophen/Multiple Sections

Expert Committee: Monographs—Small Molecules 2
No. of Commenters: 2
Comment Summary #1: The commenter indicated that the use of methanol as a *Diluent* resulted in difficulty meeting the requirement for relative standard deviation in the *Assay* procedure, and requested to use the initial *Mobile phase* as a *Diluent* instead of methanol.

Response: Comment not incorporated. The proposed solution preparations are consistent with the validation data and were found to be suitable for analysis.
Comment Summary #2: The commenter indicated that the *Assay* procedure should be revised because the acetaminophen peak shape deteriorated over time. The commenter reported observing peak broadening and splitting.
Response: Comment not incorporated. The Expert Committee will consider future revisions to this monograph upon the receipt of the necessary supporting data.
Comment Summary #3: The commenter indicated that the *Limit of Free p-Aminophenol* procedure should be revised because they have observed poor peak shape for 4-aminophenol.
Response: Comment not incorporated. The Expert Committee will consider future revisions to this monograph upon the receipt of the necessary supporting data.
Comment Summary #4: The commenter requested providing additional information in the test for *Loss on Drying*.
Response: Comment incorporated. The text is updated to specify that the material should be dried to constant weight for consistency with the procedure that was adopted from the *European Pharmacopeia*.
Comment Summary #5: The commenter requested removal of the requirement to use low-actinic glassware for the preparation of the *Sample solution* in the *Assay* procedure.
Response: Comment not incorporated. The use of low-actinic glassware is consistent with the validation data and was determined necessary for analysis.
Comment Summary #6: The commenter requested widening the relative standard deviation requirements for the *Assay* from NMT 1.0% to NMT 2.0% and the procedure for *Limit of p-Aminophenol* from NMT 5.0% to NMT 10.0%.
Response: Comment not incorporated. The relative standard deviation requirements are consistent with the validation data and were found to be suitable for analysis.
Comment Summary #7: The commenter requested widening of the relative standard deviation requirement for acetaminophen related compound D in the *Organic Impurities* procedure.
Response: Comment incorporated. The relative standard deviation requirement for acetaminophen related compound D is revised from NMT 2.0% to NMT 5.0% based on supporting data.

Monograph/Section(s): Amiloride Hydrochloride Tablets/Organic Impurities
Expert Committee: Monographs—Small Molecules 2
No. of Commenters: 1
Comment Summary #1: The commenter requested specification of a column temperature.

Response: Comment not incorporated**.** The Expert Committee will consider future revisions to the monograph upon the receipt of the necessary supporting data.
Comment Summary #2: The commenter requested revision of the composition of the diluent used to prepare the *Sample solution.*
Response: Comment not incorporated. The preparation of the *Sample solution* is consistent with the validation data*.*

Monograph/ Section(s): Amlodipine and Benazepril Hydrochloride Capsules/Multiple Sections
Expert Committee: Monographs—Small Molecules 2
No. of Commenters: 4
Comment Summary #1: The commenters requested revision of the preparation of the *Standard solution* and *Sample solution* in the *Assay* and of the *Standard solution* in the test for *Dissolution* to accommodate additional capsule strengths.
Response: Comment incorporated.
Comment Summary #2: The commenter requested inclusion of a different procedure with relevant acceptance criteria for *Organic Impurities* because it is not specific for a degradation product.
Response: Comment not incorporated. The Expert Committee will consider future revisions to the monograph upon the receipt of the necessary supporting information.
Comment Summary #3: The commenters requested revision of the acceptance criteria in *Organic Impurities, Table 5* from NMT 0.15% to NMT 1.0% for amlodipine related compound A, from NMT 0.5% to NMT 3.0% for benazepril related compound C, and from NMT 1.5% to NMT 5.0% for total impurities, to be consistent with the FDA approved specifications
Response: Comment incorporated.

Monograph/Section(s): Amoxapine Tablets/Dissolution
Expert Committee: Monographs—Small Molecules 4
Expert Committee-initiated Change: The calculation formula was updated for consistency with current USP style.

Monograph/Section(s): Ampicillin/Multiple Sections
Expert Committee: Monographs—Small Molecules 1
No. of Commenters: 1
Comment Summary #1: The commenter requested revision of the limits in *Organic Impurities Procedures 1, 3,* and *4* to have the same acceptance criteria for impurities that are seen in several procedures.
Response: Comment not incorporated. The procedures and limits reflect FDA-approved specifications with different impurity profiles or intended uses of the drug substance.

Monograph/Sections(s): Aripiprazole/Multiple Sections
Expert Committee: Monographs—Small Molecules 4
No. of Commenters: 3

Comment Summary #1: The commenter indicated that their material contains process-related impurities which coelute with other peaks using the *Organic Impurities* procedure.
Response: Comment not incorporated. The Expert Committee will consider future revisions to the monograph when appropriate and upon the receipt of the necessary supporting data.
Comment Summary #2: The commenters requested widening of the acceptance criteria for aripiprazole related compound G and unspecified impurity in the *Organic Impurities* procedure. The commenters also indicated that the aripiprazole 4,4'-dimer is not relevant to their synthetic route.
Response: Comment not incorporated. The Expert Committee will consider future revisions to the monograph when appropriate and upon the receipt of the necessary supporting data.
Comment Summary #3: The commenter requested an increase in the *Sample solution* concentration within the *Organic Impurities* procedure.
Response: Comment not incorporated. The Expert Committee will consider future revisions to the monograph upon the receipt of the necessary supporting data.
Comment Summary #4: The commenter requested the use of USP Aripiprazole Related Compound G RS instead of USP Aripiprazole Related Compound F RS to meet the resolution requirement for system suitability in the *Assay* and *Organic Impurities* procedures.
Response: Comment not incorporated. The resolution requirement is consistent with the validation data and was found to be suitable for analysis.
Comment Summary #5: The commenters requested inclusion of flexible requirements in the test for *Loss on Drying* to accommodate different polymorphs.
Response: Comment not incorporated. The Expert Committee will consider future revisions to the monograph upon the receipt of the necessary supporting data.
Expert Committee-initiated Change: The redundant chemical information in *Table 2* was removed and the footnotes were renumbered accordingly.

Monograph/Section(s): Atomoxetine Hydrochloride/Multiple Sections
Expert Committee: Monographs—Small Molecules 4
No. of Commenters: 1
Comment Summary #1: The commenter requested increasing the system suitability requirement for relative standard deviation from NMT 0.73% to NMT 1.0% in the *Assay*.
Response: Comment not incorporated. The relative standard deviation requirement is consistent with the repeatability requirement from General Chapter <621> *Chromatography* and is supported by validation data.
Comment Summary #2: The commenter requested including a procedure from the Authorized USP Pending Monograph v.1 for Atomoxetine Hydrochloride because the *Organic Impurities, Procedure 2* is not suitable for their impurity profile.
Response: Comment not incorporated. The Expert Committee will consider future revisions to the monograph when appropriate and upon the receipt of the necessary supporting data.
Expert Committee-initiated Change#1: The redundant chemical information in Tables 1 and 2 was removed and the footnotes were renumbered accordingly.

Expert Committee-initiated Change #2: The units of the *Standard solution* concentration in *Organic Impurities, Procedure 1* were revised for consistency with the equation.

Monograph/Section(s): Atropine Sulfate/Organic Impurities
Expert Committee: Monographs—Small Molecules 4
Expert Committee-initiated Change#1: The redundant chemical information in Table 2 was removed and the footnotes were renumbered accordingly.

Monograph/Section(s): Baclofen/Multiple Sections
Expert Committee: Monographs—Small Molecules 4
No. of Commenters: 1
Comment Summary #1: The commenter requested correction of the acceptance criteria in the *Definition* to NLT 98.0% and NMT 102.0% for consistency with the acceptance criteria in the *Assay* procedure.
Response: Comment incorporated.
Comment Summary #2: The commenter requested specifying that the tailing factor requirement applies only to the baclofen peak in the *Organic Impurities* procedure.
Response: Comment incorporated.
Comment Summary #3: The commenter requested widening of the relative standard deviation requirement in the *Organic Impurities* procedure from NMT 1.0% to NMT 5.0%.
Response: Comment incorporated.
Expert Committee-initiated Change: The chemical information for USP Baclofen Related Compound A RS is added to the USP Reference Standards <11> section for consistency with current USP style.

Monograph/Section(s): Baclofen Tablets/Dissolution
Expert Committee: Monographs—Small Molecules 4
No. of Commenters: 1
Comment Summary #1: The commenter requested replacing the “Procedure for a pooled sample” with a procedure which tests individual units.
Response: Comment not incorporated. The Expert Committee will consider future revisions to the monograph upon the receipt of the necessary supporting data.

Monograph/Section(s): Cefprozil/Multiple Sections
Expert Committee: Monographs—Small Molecules 1
No. of Commenters: 4
Comment Summary #1: The commenter requested correction of the chemical names of *Z*-cefprozil open ring and *E*-cefprozil open ring in *Organic Impurities Procedure 1*.
Response: Comment incorporated.
Comment Summary #2: The commenter requested widening of the limit of cefprozil dimer in *Organic Impurities Procedure 2* from NMT 0.15% to NMT 0.2% to reflect the FDA-approved limit.
Response: Comment incorporated.

Comment Summary #3: The commenter requested revising the limits in *Organic Impurities Procedures 1* and *2* to have the same acceptance criteria for impurities that are seen in both procedures.
Response: Comment not incorporated. The two procedures represent two different impurity profiles; the limits in each procedure reflect FDA-approved limits.
Expert Committee Initiated Change #1: The dimensions of the column specified for the *Assay* were revised to reflect those of columns that are commercially available.

Monograph/Section(s): Dinoprostone/Organic Impurities
Expert Committee: Monographs—Small Molecules 4
No. of Commenters: 1
Comment Summary #1: The commenter requested retention of the current relative standard deviation requirement of NMT 2.0% unless supporting data have been provided for the proposed requirement of NMT 10.0%.
Response: Comment not incorporated. The Expert Committee determined that NMT 10.0% is a suitable criterion because the concentration of the *Standard solution* is being significantly decreased (from 2.5 mg/mL to 0.025 mg/mL).

Monograph/Section(s): Diphenhydramine Citrate and Ibuprofen Tablets/USP Reference Standards <11>
Expert Committee: Monographs—Small Molecules 4
Expert Committee-initiated Change: The chemical information for USP Diphenhydramine Related Compound A RS was corrected and also updated to reflect that the material is available as a hydrochloride salt.

Monograph/Section(s): Dorzolamide Hydrochloride Ophthalmic Solution/pH
Expert Committee: Monographs—Small Molecules 3
No. of Commenters: 2
Comment Summary #1: The commenter requested widening the pH acceptance criteria from “5.5–5.8” to “5.4–5.9” to be consistent with the FDA-approved specification.
Response: Comment incorporated.
Comment Summary #2: The commenter requested widening the pH acceptance criteria from “5.5–5.8” to “5.0–6.0” to be consistent with the monograph for Dorzolamide Eye Drops in *British Pharmacopoeia*.
Response: Comment not incorporated. The acceptance criteria for pH were revised to “5.4–5.9” to be consistent with the FDA-approved specification.

Monograph/Section(s): Estazolam/Organic Impurities
Expert Committee: Monographs—Small Molecules 4
Expert Committee-initiated Change: The redundant chemical information in Table 2 and in the USP Reference Standards <11> section was removed.

Monograph/Section(s): Galantamine Hydrobromide/Multiple Sections
Expert Committee: Monographs—Small Molecules 4
Expert Committee-initiated Change #1: In the *Assay*, the word “hydrobromide” in the requirement for the tailing factor was removed.

Expert Committee-initiated Change #2: In Table 2, the chemical information for galantamine and galantamine impurities was updated for consistency with current USP style.
Expert Committee-initiated Change #3: In *Enantiomeric Purity, Procedure 1*, the equation was updated to reference USP Galantamine Hydrobromide Racemic RS for consistency with the *Standard solution* preparation.

Monograph/Section(s): Gentamicin Sulfate/Content of Gentamicins
Expert Committee: Monographs—Small Molecules 1
No. of Commenters: 5
Comment Summary #1: The commenter requested correction of the concentration of sodium hydroxide in the *Post-column reagent* from 20 mg/L to 20 g/L, to be consistent with the validated procedure.
Response: Comment incorporated.
Comment Summary #2: The commenter requested revision of the calculation to include all gentamicins.
Response: Comment incorporated.
Comment Summary #3: The commenter requested correction of the volume of 12.5 M sodium hydroxide in the *Mobile phase* preparation from 5 mL to 4 mL to be consistent with the validated procedure.
Response: Comment incorporated.
Comment Summary #4: The commenter requested revision of the acceptance criteria to reflect the limits in the *European Pharmacopoeia* monograph.
Response: Comment not incorporated. The proposed acceptance criteria reflect the FDA-approved limits, which are wider than those in the *European Pharmacopoeia* monograph.
Comment Summary #5: The commenter requested inclusion of additional information regarding the electrode used in the validated procedure.
Response: Comment not incorporated. The information requested is to identify a particular brand of electrode rather than a type of electrode. Brand information is not suitable for inclusion in the public standard.
Comment Summary #6: The commenter requested revision of the section of the waveform used to clean the surface of the electrode to reflect the validated procedure.
Response: Comment not incorporated. The requested change does not pertain to the section of the waveform used to report analytical results.
Comment Summary #7: The commenter requested revision of the relative retention time of gentamicin C1 from 2.9 to 3.0 to reflect their validated procedure.
Response: Comment not incorporated. Relative retention times are provided for guidance only.
Comment Summary #8: The commenter requested use of the flexible monograph approach to allow manufacturers to use either the currently official derivatization procedure or the proposed electrochemical detection procedure.
Response: Comment not incorporated. The electrochemical detection procedure is more modern and provides more reproducible results.

Monograph/Section(s): Gymnema
Expert Committee: Monographs—Dietary Supplements
Expert Committee-initiated Change #1: Include an additional identification test

Monograph/Section(s): Irinotecan Hydrochloride Injection/Packaging and Storage
Expert Committee: Monographs—Small Molecules 3
No. of Commenters: 1
Comment Summary #1: The commenter requested removal of the requirement to use vials made of glass for consistency with their FDA-approved product label.
Response: Comment incorporated.
Expert Committee-initiated Change #1: The word “amber” was removed because there already is a requirement to store the product protected from light.

Monograph/Section(s): Latanoprost/Multiple Sections
Expert Committee: Monographs—Small Molecules 3
No. of Commenters: 6
Comment Summary #1: The commenter requested revision of the reagent reference from “Hexane” to “Chromatographic solvent Hexane” in *Mobile phase* under *Assay***.**
Response: Comment incorporated.
Comment Summary #2: The commenter requested deletion of the test for *Residue on Ignition*.
Response: Comment not incorporated. The limit is widened from NMT 0.3% to NMT 0.50% to be consistent with the FDA-approved specification.
Comment Summary #3: The commenter requested deletion of the test for *Heavy Metals* to be consistent with the FDA- approved specification.
Response: Comment incorporated.
Comment Summary #4: The commenter requested widening of the limits in the test for *Organic impurities* for isopropyl diphenylphosphorylpentanoate, latanoprost related compound B and unspecified impurity to NMT 0.1%, NMT 0.5% and NMT 0.1% respectively to be consistent with the FDA-approved specifications.
Response: Comment incorporated.
Comment Summary #5: The commenter requested widening of the limit for total impurities from NMT 0.30% to NMT 0.5% to be consistent with the FDA-approved specifications, and clarification of the definition of impurities included in the total impurities.
Response: Comment incorporated.
Comment Summary #6: The commenter requested widening the limit for latanoprost related compound E in the test for *Limit of Latanoprost Related Compound E* to NMT 0.2% to be consistent with the FDA-approved specification.
Response: Comment incorporated.
Comment Summary #7: The commenter requested widening of the limit for *Water Determination* from NMT 0.5% to NMT 5.0%.
Response: Comment not incorporated. The Expert Committee will consider future revisions to the monograph when appropriate and upon the receipt of the necessary supporting data.

Comment Summary #8: The commenter requested widening of the limit for *Water Determination* from NMT 0.5% to NMT 2.0% to be consistent with the FDA- approved specification.
Response: Comment incorporated.
Comment Summary #9: The commenter requested to allow the use of General Chapter <921> Method *1a* for *Water Determination*.
Response: Comment incorporated.
Comment Summary #10: The commenters requested the replacement of the tests for *Organic impurities* and *Limit for Latanoprost Related Compound E* with other procedures.
Response: Comment not incorporated. The Expert Committee has determined that the current procedures are suitable.
Comment Summary #11: The commenter requested revision of the storage condition to allow storage in a freezer or a refrigerator.
Response: Comment incorporated.

Monograph/Section(s): Lopinavir and Ritonavir Tablets/Multiple Sections
Expert Committee: Monographs—Small Molecules 1
No. of Commenters: 2
Comment Summary #1: The commenter requested that the filter pore size in *Sample solutions* under *Dissolution* be removed to provide flexibility.
Response: Comment incorporated.
Comment Summary #2: The commenter requested correcting the column particle size from 3-µm to 5-µm in the *Assay.*
Response: Comment incorporated.
Comment Summary #3: The commenter requested that the impurity profile/limits for a tentatively approved product be incorporated in the monograph.
Response: Comment not incorporated. The Expert Committee will consider future revisions to the monograph when appropriate and upon the receipt of the necessary supporting data.

Monograph/Section(s): Meprobamate Tablets/Multiple Sections
Expert Committee: Monographs—Small Molecules 4
No. of Commenters: 2
Comment Summary #1: The commenter requested correction of the solvent composition in the *Standard solution* preparation within the *Assay* procedure.
Response: Comment incorporated.
Comment Summary #2: The commenter requested the inclusion of two additional impurities in the *Organic Impurities* test.
Response: Comment not incorporated. The Expert Committee will consider future changes to the monograph upon receipt of the necessary supporting data.
Comment Summary #3: The commenter requested the replacement of the “Procedure for a pooled sample” in the *Dissolution* test with a procedure which tests individual units.
Response: Comment not incorporated. The Expert Committee will consider future revisions to the monograph upon the receipt of the necessary supporting data.
Monograph/Sections(s): Metacresol/Multiple Sections

Expert Committee: Monographs—Small Molecules 3
No. of Commenters: 2
Comment Summary #1: The commenter requested adoption of the HPLC *Organic impurities* procedure as the *Assay* procedure.
Response: Comment not incorporated. The Expert Committee has determined that the current *Assay* procedure is suitable.
Comment Summary #2: The commenter requested use of USP Metacresol RS instead of metacresol reagent in the *Sensitivity solution* in the test for *Organic impurities***.**
Response: Comment incorporated.

Monograph/Section(s): Methacholine chloride/Limit of Acetylchloine Chloride
Expert Committee: Monographs—Small Molecules 4
Expert Committee-initiated Change #1: Renamed the *Limit of Acetylchloine Chloride* test to *Organic Impurities.*

Monograph/Section(s): Mitotane/Water Determination
Expert Committee: Monographs—Small Molecules 3
No. of Commenters: 1
Comment Summary #1: The commenter requested retaining the test for *Loss on Drying*.
Response: Comment not incorporated because of sublimation of mitotane under the *Loss on Drying* conditions.

Monograph/Section(s): Native Gymnema Extract
Expert Committee: Monographs—Dietary Supplements
Expert Committee-initiated Change #1: Inclusion of an additional identification test.

Monograph/ Section(s): Nicardipine Hydrochloride/Multiple sections
Expert Committee: Monographs—Small Molecules 2
No. of Commenters: 2
Comment Summary #1: The commenters requested revision of the titration-based *Assay* procedure to an HPLC-based *Assay* procedure and adding an *Identification* test based on the retention time agreement using the HPLC procedure.
Response: Comment not incorporated. The Expert Committee will consider future revision to the monograph upon the receipt of the necessary supporting data.
Comment Summary #2: The commenters requested addition of a test for *Melting Range or Temperature*.
Response: Comment not incorporated. The Expert Committee will consider future revision to the monograph upon the receipt of the necessary supporting data.
Comment Summary #3: The commenter requested that the specification limit for Total impurities be revised to reflect the FDA-approved specification of NMT 1.0%.
Response: Comment incorporated.
Comment Summary #4: The commenter requested specification of additional process impurities in the *Organic Impurities* procedure.

Response: Comment not incorporated. The Expert Committee will consider future revision to the monograph when appropriate and upon the receipt of the necessary supporting data.
Comment Summary #5: The commenter requested revision of the limit in the test for *Loss on Drying* from NMT 0.5% to NMT 1.0%.
Response: Comment not incorporated. The Expert Committee will consider future revision to the monograph when appropriate and upon the receipt of the necessary supporting data.

Monograph/Section(s): Nortriptyline Hydrochloride/<11> USP Reference Standards
Expert Committee: Monographs—Small Molecules 4
Expert Committee-initiated Change #1: Revised the chemical name of USP Cyclobenzaprine Related Compound B RS to indicate the correct salt form.

Monograph/Section(s): Oxaliplatin/Organic Impurities, Procedure 3
Expert Committee: Monographs—Small Molecules 3
No. of Commenters: 1
Comment Summary #1: The commenter requested the use of peak heights instead of peak areas for the calibration curve.
Response: Comment incorporated.

Monograph/Section(s): Oxcarbazepine/Organic Impurities, Procedure 1
Expert Committee**:** Monographs—Small Molecules 4
No. of Commenters: 2
Comment Summary #1: The commenter requested widening of the limit of carbamazepine from NMT 0.15% to NMT 0.5% to be consistent with the FDA-approved limit.
Response: Comment incorporated.
Comment Summary #2: The commenter requested increasing the limit of Total Impurities from NMT 0.5% to NMT 1.0% to be consistent with the FDA-approved limit.
Response: Comment incorporated.

Monograph/Section(s): Powdered Gymnema
Expert Committee: Monographs - Dietary Supplements
Expert Committee-initiated Change #1: To include an additional Identification test

Monograph/Section(s): Purified Gymnema Extract
Expert Committee: Monographs - Dietary Supplements
Expert Committee-initiated Change #1: To include an additional Identification test

Monograph/Section(s): Quinapril and Hydrochlorothiazide Tablets/Organic Impurities
Expert Committee: Monographs—Small Molecules 2
No. of Commenters: 1
Comment Summary #1: The commenter requested widening of the acceptance criteria for quinapril related compound B from NMT 0.5% to NMT 3.0% and for

benzothiadiazine related compound A from NMT 0.5% to 1.0% to be consistent with their FDA-approved limits.
Response: Comment incorporated.
Comment Summary #2: The commenter requested replacement of the specification for *Total impurities* as the "sum of all specified and unspecified degradation products" with a limit of NMT 2.5% and a specification for *Total Impurities* excluding quinapril related compound B and benzothiadiazine related compound A with a limit of NMT 2.0% to be consistent with their FDA-approved limits.
Response: Comment incorporated.

Expert Committee-initiated Change: The acceptance criterion for any other individual unspecified impurity was widened from NMT 0.10% to NMT 0.2% to be consistent with the ICH guidelines.

Monograph/Section(s): Salicylic Acid Plaster/Assay
Expert Committee: Monographs—Small Molecules 3
Expert Committee-initiated Change #1: The preparation of *Sample solution* was modified to provide more flexibility for the users.

Monograph/Sections: Valerian/Contaminants, Elemental Impurities—Procedures <233>
Expert Committee: Monographs—Dietary Supplements and Herbal Medicines
No. of Commenters: 1
Comment Summary #1: The commenter requested that the specific requirements for elemental impurities be removed from this monograph and be included only in the product monograph.
Response: Comment not incorporated. Given the literature suggesting that the elemental impurities may accumulate when this article is derived from soil in contact with environmental contaminants, the Expert Committee found it necessary to include limits for elemental contaminants in this monograph. The inclusion of limits for contaminants is important to define the pharmacopeial quality of this ingredient.
Comment Summary #2: The commenter indicated that the monograph should reference General Chapter <2232> *Elemental Contaminants in Dietary Supplements* and include a reference to the delayed implementation of this General Chapter, because the specifications in the product monograph would negate the need for specifications of the ingredients.
Response: Comment not incorporated. General Chapter <2232> *Elemental Contaminants in Dietary Supplements* states, "This general chapter is not intended to set limits for dietary ingredients. Those limits are set in the corresponding individual monographs." Thus, it applies only to finished dietary supplement dosage forms and therefore will not be applicable to this dietary ingredient. The need for specifications in this ingredient monograph is explained in the response to Comment #1.
Comment Summary #3: The commenter indicated that there is no justification for lower limits for mercury compared to the limits in General Chapter <2232> or ICH criteria.

Response: Comment not incorporated. The Expert Committee determined that the available literature on the typical content of mercury in Valerian justified lower limits for mercury in this ingredient. This also is in line with *European Pharmacopoeia* standards for herbal drugs. The difference in elemental impurities limits from those specified in General Chapter <2232> and from ICH limits are not relevant because the General Chapter <2232> applies only to finished dosage forms and the ICH Q3D Step 2b guideline under development specifies that it does not apply to herbal products.
Comment Summary #4: The commenter indicated that the monograph content for elemental impurities should follow the delayed implementation of General Chapters <232> *Elemental Impurities—Limits* and <233> *Elemental Impurities—Methods*.
Response: Comment not incorporated. The implementation of General Chapters <232> *Elemental Impurities—Limits* and <233> *Elemental Impurities—Procedures* through General Notices provision 5.60.30 relates to drug product monographs. It is not applicable to dietary supplements monographs, and thus its deferral does not apply to dietary supplement monographs.

Monograph/Sections: Powdered Valerian/Contaminants, Elemental Impurities—Procedures <233>
Expert Committee: Monographs—Dietary Supplements and Herbal Medicines
No. of Commenters: 1
Comment Summary #1: The commenter requested that the specific requirements for elemental impurities be removed from this monograph and be included only in the product monograph.
Response: Comment not incorporated. Given the literature suggesting that the elemental impurities may accumulate when this article is derived from soil in contact with environmental contaminants, the Expert Committee found it necessary to include limits for elemental contaminants in this monograph. The inclusion of limits for contaminants is important to define the pharmacopeial quality of this ingredient.
Comment Summary #2: The commenter indicated that the monograph should reference General Chapter <2232> *Elemental Contaminants in Dietary Supplements* and include a reference to the delayed implementation of this General Chapter, because the specifications in the product monograph would negate the need for specifications of the ingredients.
Response: Comment not incorporated. General Chapter <2232> *Elemental Contaminants in Dietary Supplements* states, “This general chapter is not intended to set limits for dietary ingredients. Those limits are set in the corresponding individual monographs.” Thus, it applies only to finished dietary supplement dosage forms and therefore will not be applicable to this dietary ingredient. The need for specifications in this ingredient monograph is explained in the response to Comment #1.
Comment Summary #3: The commenter indicated that there is no justification for lower limits for mercury compared to the limits in General Chapter <2232> or ICH criteria.
Response: Comment not incorporated. The Expert Committee determined that the available literature on the typical content of mercury in Valerian justified lower limits for mercury in this ingredient. This also is in line with *European Pharmacopoeia* standards for herbal drugs. The difference in elemental impurities limits from those specified in

General Chapter <2232> and from ICH limits are not relevant because the General Chapter <2232> applies only to finished dosage forms and the ICH Q3D Step 2b guideline under development specifies that it does not apply to herbal products.
Comment Summary #4: The commenter indicated that the monograph content for elemental impurities should follow the delayed implementation of General Chapters <232> *Elemental Impurities—Limits* and <233> *Elemental Impurities—Methods*.
Response: Comment not incorporated. The implementation of General Chapters <232> *Elemental Impurities—Limits* and <233> *Elemental Impurities—Procedures* through General Notices provision 5.60.30 relates to drug product monographs. It is not applicable to dietary supplements monographs, and thus its deferral does not apply to dietary supplement monographs.

Monograph/Sections: Powdered Valerian Extract/Contaminants, Elemental Impurities—Procedures <233>
Expert Committee: Monographs—Dietary Supplements and Herbal Medicines
No. of Commenters: 1
Comment Summary #1: The commenter requested that the specific requirements for elemental impurities be removed from this monograph and be included only in the product monograph.
Response: Comment not incorporated. Given the literature suggesting that the elemental impurities may accumulate when this article is derived from soil in contact with environmental contaminants, the Expert Committee found it necessary to include limits for elemental contaminants in this monograph. The inclusion of limits for contaminants is important to define the pharmacopeial quality of this ingredient.
Comment Summary #2: The commenter indicated that the monograph should reference General Chapter <2232> *Elemental Contaminants in Dietary Supplements* and include a reference to the delayed implementation of this General Chapter, because the specifications in the product monograph would negate the need for specifications of the ingredients.
Response: Comment not incorporated. General Chapter <2232> *Elemental Contaminants in Dietary Supplements* states, “This general chapter is not intended to set limits for dietary ingredients. Those limits are set in the corresponding individual monographs.” Thus, it applies only to finished dietary supplement dosage forms and therefore will not be applicable to this dietary ingredient. The need for specifications in this ingredient monograph is explained in the response to Comment #1.
Comment Summary #3: The commenter indicated that there is no justification for lower limits for mercury compared to the limits in General Chapter <2232> or ICH criteria.
Response: Comment not incorporated. The Expert Committee determined that the available literature on the typical content of mercury in Valerian justified lower limits for mercury in this ingredient. This also is in line with *European Pharmacopoeia* standards for herbal drugs. The difference in elemental impurities limits from those specified in General Chapter <2232> and from ICH limits are not relevant because the General Chapter <2232> applies only to finished dosage forms and the ICH Q3D Step 2b guideline under development specifies that it does not apply to herbal products.

Comment Summary #4: The commenter indicated that the monograph content for elemental impurities should follow the delayed implementation of General Chapters <232> *Elemental Impurities—Limits* and <233> *Elemental Impurities—Methods*.
Response: Comment not incorporated. The implementation of General Chapters <232> *Elemental Impurities—Limits* and <233> *Elemental Impurities—Procedures* through General Notices provision 5.60.30 relates to drug product monographs. It is not applicable to dietary supplements monographs, and thus its deferral does not apply to dietary supplement monographs.

Monograph/Section(s): Valproic Acid/ Multiple sections
Expert Committee: Monographs–Small Molecules 4
No. of Commenters: 6
Comment Summary #1: The commenters requested retention of the existing capillary GC procedure for *Organic Impurities* because it is better at separating the process impurities than the proposed HPLC procedure.
Response: Comment incorporated.
Comment Summary #2: The commenter requested adaptation of the existing capillary GC procedure for *Organic Impurities* for use as the *Assay* procedure.
Response: Comment not incorporated. The proposed HPLC procedure replaces the existing packed column GC procedure which is consistent with USP monograph modernization initiative.
Comment summary #3: The commenter requested harmonizing the *Organic impurities* procedure with the *European Pharmacopeia.*
Response: Comment not incorporated. The Expert committee may consider harmonization with *European Pharmacopeia* as part of a future revision.

Monograph/Section(s): Valproic Acid Capsules/Assay
Expert Committee: Monographs–Small Molecules 4
No. of Commenters: 1
Comment Summary #1: The commenter requested revision of the *Sample solution* preparation to allow using 1 hour of stirring to ensure complete dissolution of the capsules as an alternative to 5 minutes of sonication.
Response: Comment incorporated.

Monograph/Section(s): Vigabatrin/Assay
Expert Committee: Monographs–Small Molecules 4
No. of Commenters: 1
Comment Summary #1: The commenter requested replacing the proposed HPLC procedure with the titration procedure from the *European Pharmacopeia.*
Response: Comment not incorporated. The use of an HPLC procedure is consistent with USP monograph modernization initiative.