Commentary – *Second Supplement to USP 35-NF 30*

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 pertinent 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 Web site 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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No comments were received for the following proposals:

General Chapters
<913> Rolling Ball Viscometer Method

Monographs
Atracurium Besylate
Atracurium Besylate Injection
Azeotropic Isopropyl Alcohol
Beta Carotene
Beta Glucan
Carisoprodol
Carisoprodol Tablets
Copovidone
Diosmin

Estradiol Cypionate
Estradiol Cypionate Injection
Glucagon
Glucagon for Injection
Goserelin Acetate
Hydrocortisone
Hydrocortisone Acetate
Meclizine Hydrochloride
Melatonin
Methylbenzethonium Chloride
Nystatin Vaginal Inserts
Omeprazole Delayed-Release Capsules
Oxycodone HydrochlorideTablets
Oxycodone and Acetaminophen Capsules
Oxycodone and Acetaminophen Tablets
Pregelatinized Hydroxypropyl Corn Starch
Pregelatinized Hydroxypropyl Pea Starch
Pregelatinized Hydroxypropyl Potato Starch
Ribavirin Tablets
Sulfaquinoxaline
Valsartan and Hydrochlorothiazide Tablets
Xylitol

General Chapters

General Chapter/Section:	General Chapter <123> Glucagon Bioidentity Tests/Multiple Sections
Expert Committee:	Monographs-Biologics & Biotechnology 1
No. of Commenters:	2

Procedure
Comment Summary #1: The commenter recommended that the language in the *Procedure* section be modified to describe the surgical procedure as: “Insert an angiocatheter and tie into the portal vein at the general location of the lineal branch and then connect to a perfusion pump.”
Response: Comment incorporated.

System Suitability of Cell Preparation
Comment Summary #2: The commenter requested changing the title “System Suitability” to “System Suitability of Cell Preparation” in order to differentiate it from the *System Suitability* section for the glucose quantitation.
Response: Comment incorporated.

Glucose Determination
Comment Summary #3: The commenter requested that serial or point dilutions be allowed for preparation of the *Standard* and *Assay Preparations*.
Response: Comment incorporated.
Comment Summary #4: The commenter requested that the curve range and number of standards be extended.
Response: Comment not incorporated. Validation data support the curve values shown, not other values. If a manufacturer wishes to extend and validate an alternative curve range, this may be allowed per *USP General Notices 6.30. Alternative and Harmonized Methods and Procedures.*

System Suitability
Comment Summary #5: The commenter requested editorial changes in the *System Suitability* section for the glucose quantitation.
Response: Comment incorporated.

Calculations
Comment Summary #6: The commenter requested that the F-test be set at 2.5% because it appears that language in the *Calculations* section of the previously official Glucagon monograph's bioassay had changed.
Response: Comment not incorporated, but language modified for clarity. Laboratories should use appropriate statistical methods for parallel-line assays. Also, the F-test is not required in this chapter's calculation for bioidentity.
Comment Summary #7: The commenter indicated that the statement regarding the test being invalid if the L value of 0.1938 is not attained after 4 assays is not appropriate if further testing could improve results that are due to technical difficulties. The commenter considered the 95% *Confidence Interval* requirement as a system suitability requirement and a basis for retest. Therefore, the commenter suggested that the sentence be modified to reflect this approach.
Response: Comment incorporated.

General Chapter/Section: <232> Elemental Impurities – Limits/Multiple Sections
Expert Committee: General Chapters–Chemical Analysis
No. of Commenters: 18
Comment Summary #1: The commenter suggested alignment of this chapter with ICH Q3D (pending) and EMA guidelines to avoid confusion.
Response: Comment incorporated. To the extent possible, the chapter has been aligned with the pending ICH Q3D document and the current EMEA guideline.
Comment Summary #2: The commenter requested that USP provide five years following publication of the final, official chapters for implementation of the new requirements because these new requirements will not only impact the pharmaceutical industry, but also impact external manufacturers of active ingredients, excipient manufacturers, instrument manufacturers, contract laboratories, and the FDA.
Response: Comment not incorporated. Notifications that the heavy metals chapter would be changing began more than five years ago, with the publication of proposed General Chapters <232> and <233> for public comment. There will be a delayed

implementation date and an additional period of time between when the chapters are posted on the USP Web site and the time that they are published as official, giving the industry an additional period of time during which to prepare. Given the globalization of the supply chain and a series of recent issues regarding elemental impurity contamination in drugs and dietary supplements, patient safety dictates the setting of acceptable levels for the elements specified, presentation of sensitive and specific methodology to allow the appropriate quantification, and a timely implementation period.
Comment Summary #3: The commenter requested clearly stating the intent of the chapter because the first and last sentences in the first paragraph (*Introduction*) clearly indicate that the limits in the chapter apply to drug products, yet the second sentence in the second paragraph implies that there is also a responsibility to detect and report impurities levels in components.
Response: Comment not incorporated. No change to the text was deemed necessary. The text is consistent in that compliance to the limits indicated in the chapter is only expected for a drug product, but it is important that the presence and the amount of each elemental impurity is known to the manufacturer and customers of a component of a drug product.
Comment Summary #4: The commenter requested clarifying that General Chapter <232> is only intended to apply to drug products, so that other industries should not extrapolate these requirements to their own products.
Response: Comment not incorporated. This chapter indicates the application to drug products and the exclusion of dietary supplements. Additionally, the General Notices of the *USP-NF* indicates the scope of the Pharmacopeia.
Comment Summary #5: The commenter requested clarifying the text under *Drug Substance and Excipients* section that states that the presence of elemental impurities in drug substances and excipients must be reported to indicate where and to whom this should be reported.
Response: Comment not incorporated. A more complete description is not possible due to variable customer needs and regulatory requirements.
Comment Summary #6: The commenter requested adding the following footnote after the *Large Volume Parenterals* subsection heading to reference the ICH definition. This footnote will link this chapter with the other USP General Chapter ~1/ *Injections*:

> Footnote: *ICH Q3D defines a large volume parenteral as an injection for which the total daily dose is greater than 100 mL.

Response: Comment not incorporated because the chapter already contains this definition.
Comment Summary #7: The commenter requested including text similar to the statement in USP General Chapter <467> *Residual Solvents*, Table 2 because the average adult weight exceeds 50 kg in United States.
Response: Comment not incorporated. Average weight is a fixed number that is used by Toxicologists to arrive at a uniform Permissible Daily Exposure.
Comment Summary #8: The commenter requested allowing higher PDEs and concentration limits in cases of short-term use (30 days or less), or for products for life-

saving indications. ICH Q3C Guideline for Residual Solvents considers this approach as well. Such higher PDE's and concentration limits are justified on a case by case basis.
Response: Comment not incorporated. USP monographs do not indicate nor do they consider typical dosing strengths, intervals, or durations. Such considerations may be discussed with the appropriate regulatory body as a rationale for an exception from this standard.
Comment Summary #9: The commenter suggested differentiating between chronic and short term use because this would result in PDEs and concentration limits based on a safer and sounder scientific ground and make implementation of the monograph easier. Products for chronic use and/or large quantities administered (e.g., solutions for parenteral nutrition) make compliance with limits based on toxicological considerations unfeasible due to limitations of the technologies.
Response: Comment not incorporated—see the answer to Comment #8 above. Note also that solutions for parenteral nutrition are specifically addressed by the large volume parenteral section of the chapter and the limits are well within the capabilities of current measurement technologies.
Comment Summary #10: The commenter requested assigning an exposure factor for Topicals and Dermals of greater than 1 because this route of administration has a much lower potential for exposure than do Oral and Mucosal routes.
Response: Comment not incorporated. Exposure factors have been removed from General Chapter <232>, but the discussion surrounding the appropriate limits for topical administration has been extensive and continues in the Expert Panel. If changes are indicated at a later date, then a revision will be considered.
Comment Summary #11: The commenter indicated concerns with the inclusion of the additional routes of administration in the chapter, beyond "Oral" and "Parenteral" and requested that further details be provided regarding inclusion of "Inhalation", "Mucosal", and "Topicals and Dermals", and the rationale for the proposed "Exposure Factor."
Response: See the response to Comment #10 above.
Comment Summary #12: The commenter requested changing the title of Table 3 from "default limits" to "suggested minimum limit" as the intention of this listing is to aid in discussions between drug product and drug substance/excipient manufacturers,
Response: Comment not incorporated. Table 3 has been revised and renumbered as Table 2. Limits listed in Table 2 are based on the assumption of 10 g daily dose and can vary depending on the daily dose. Most drug products have a maximum daily exposure much lower than these values. The table is intended to serve as a starting point for further discussions between drug substance / excipient manufacturers and the drug product manufacturer. This table was added in response to the comments received from the drug substance/excipient manufacturers.
Comment Summary #13: The commenter requested deleting Table 3 because its inclusion will give suppliers of these materials a false sense of the true requirements.
Response: Comment not incorporated—see the response to Comment #12 above.
Comment Summary #14: The commenter requested that USP harmonize with the Ph. Eur. and ICH Q3D in relation to EMA cumulative sub-class limit for group 1B (Ir, Os, Rh, Ru – the total parenteral PDE not to exceed 10 µg/day). If conducted as a limit test, the testing limits for each of the four members of the sub-class would need to be 25% of the additive class limit, in order to determine if the required cumulative limit was being met.

Response: Comment incorporated—see the response to Comment #1 above.
Comment Summary #15: The commenter requested that the Chromium in Table 2 be footnoted to specify the limit as Chromium (+6), and *Speciation* section be updated to include a discussion of the oxidation states of Chromium.
Response: Comment not incorporated. The oxidation state of Chromium was thoroughly discussed by the Expert Panel and the need for speciation of Chromium was considered to be unnecessary due to the extremely rapid conversion rate of Chromium (VI) to Chromium (III) *in vivo.* The USP Expert Committee is willing to consider a future revision if data support tighter limits.
Comment Summary #16: The commenter requested removing the following text: ”Exceptions for pediatric or special populations that lower the PDE should be reflected in the limits in the appropriate monographs." The interpretation and application of this caveat is unclear, and will introduce the analytical challenges unique to LVP’s.
Response: Comment incorporated.
Comment Summary # 17: The commenter requested that the *Drug Product Analysis* option also be permitted for parenterals with an intended maximum dose of greater than 10 mL and not more than 100 mL.
Response: Comment not incorporated. The Expert Committee incorporated this approach to reduce the testing burden on the parenterals manufacturing industry. As volumes of injections increase, the limit concentrations associated with the PDE become increasingly lower and more difficult to meet. To further aid the industry, USP will include a limit of elemental impurities in either the *Water for Injection* or the *Sterile Water for Injection* general chapters. With these limits, a manufacturer can be assured that the water will not contribute a significant amount of impurities to the total, which would then be discounted. A user would therefore only be expected to ensure control of the active and other inactive ingredients that would be present.
Comment Summary # 18: The commenter requested clarifying the *Speciation* section by adding the word “specific” to the last sentence right before monograph to clarify that this statement is referring to a specific article.
Response: Comment not incorporated. Adding the word “specific” would not add additional clarity.
Comment Summary #19: The commenter requested removing the reference to special or pediatric populations because the statement is not specific and could lead to compliance issues due to differences in opinions of what products the statement would apply to and what an acceptable limit(s) would be.
Response: Comment incorporated.
Comment Summary #20: The commenter requested adding PDEs for children and neonates to the chapter.
Response: Comment not incorporated because special populations are not addressed in <232>.
Comment Summary #21: The commenter requested replacing “validated processes" with “process monitoring” in the *Analytical testing* section.
Response: Comment incorporated.
Comment Summary #22: The commenter requested using the Institute of Medicines (IOM) published guidelines on Tolerable Upper Intake Level (UL) as the oral daily dose

PDE, and calculating the parenteral daily dose PDE by multiplying the UL for each element by the IOM estimates of the lowest oral absorption of that element.
Response: Comment not incorporated. Limits were established by a team of toxicologists, who considered a variety of information in making their determinations. The IOM guidelines were one of the sources used in their deliberations.
Comment Summary #23: The commenter requested adding other elements such as aluminum, fluoride, and iodine to the Tables.
Response: Comment not incorporated. Attempts were made to harmonize with the EMA and ICH, wherever possible. Additional metals are currently in discussion in several forums. As a consensus is formed, the USP will reconsider their inclusion in General Chapter <232>. An informational chapter, <1232>, is contemplated to provide recommended limits for other, less-toxic elemental impurities.
Comment Summary #24: The commenter requested mentioning that individuals with organ system dysfunction, especially liver and kidney, can experience toxicity with exposures significantly below the stated PDEs.
Response: Comment not incorporated. Not every special population can be accommodated with a general standard and therefore, special populations are not delineated in General Chapter <232>.
Comment Summary #25: The commenter requested including the elemental impurities classification back in the chapter and adjusting the testing requirements accordingly.
Response: Comment not incorporated. These classifications were deemed unnecessary in a quality-focused chapter.
Comment Summary #26: The commenter requested an elaboration of the statement "risk-based control strategy may be appropriate when analysts determine how to assure compliance with this standard" to allow development of not-likely-to-be-present arguments (and no routine release testing), and skip testing for present metals that are shown to be adequately controlled.
Response: Comment not incorporated. Discussions regarding appropriate risk-based strategies must be conducted with the appropriate regulatory body. All drug products should comply with the requirements when tested.
Comment Summary #27: The commenter indicated that the limit of 0.50 ppm for Cadmium in Calcium Carbonate is much lower than the levels found in the natural carbonate deposits. The introduction of this proposed limit would eliminate the ability to supply this mineral ingredient to the pharmaceutical and dietary supplements market worldwide. Therefore, it is suggested changing the individual monographs to allow for higher limits of impurities found in some mineral excipients/dietary supplements.
Response: The specific limit included in General Chapter <232> is 25 µg/day for oral delivery, 2.5 µg/day for parenteral delivery, and 1.5 µg/day for inhalation delivery. The PDE limits must be adjusted by the maximum daily dose to determine the limit in terms of concentration (ppm). When considered in this manner, it is likely that the drug product in question would be found to be in compliance. However, exceptions to monograph requirements can be made via the appropriate regulatory channels.
Comment Summary # 28: The commenter requested replacing the language addressing veterinary products in the chapter with the following: "Articles intended for veterinary use are exempt from complying with the requirements in this Chapter, unless specific safety concerns are identified by the appropriate regulatory Agency."

Response: Comment incorporated.
Comment Summary #29: The commenter requested that USP exclude natural mineral excipients that conform to *USP* and *NF* monographs from calculations of total elemental impurities in drug products because trace metals inherent in mineral structures are not process residues, and are not subject to control or removal in the way that residues would be. In addition, these trace elements in natural mineral excipients do not pose any risk to human health.
Response: Comment not incorporated. The source of a given Elemental Impurity does not change its toxicity. Because these limits are directly linked to safety, material-specific limits will not be included in the general chapter, but monograph specific exemptions or variations may be considered by the appropriate Expert Committees.
Comment Summary # 30: The commenter requested that USP justify the elemental impurity limits proposed in this Chapter, and their application to natural mineral excipients, with health and safety data and a subsequent risk-based analysis that shows such application is warranted.
Response: Comment not incorporated. Limits were established by a team of toxicologists, who used a variety of data to make their determinations. The justification for the various limits was provided in a Stimuli to the Revision Process article and will be further elaborated through the ICH Q3D process.
Comment Summary #31: The commenter requested that USP provide guidance on how to reconcile the requirements in this chapter with existing specifications for As and Pb in current NF monographs.
Response: Comment not incorporated. The USP will work to reconcile requirements on a case-by-case basis. Monograph-specific acceptance criteria supersede the general chapter requirements.
Comment Summary #32: The commenter requested limiting the application of General Chapters <232> and <233> to new drug products only to avoid significant turmoil in the pharmaceutical industry.
Response: Comment not incorporated. USP standards are applicable to all monographs to which they apply independent of the date of regulatory approval.
Comment Summary #33: The commenter requested adding the component option for demonstrating compliance back in the chapter.
Response: Comment not incorporated. In earlier presentations of the chapter, the level of confusion caused by the inclusion of the component option led to its removal. However, the limits provided in Table 2 are consistent with the Component Option limits.
Comment Summary #34: The commenter requested allowing the flexibility to use any of the three options: 1) drug product, 2) summation, or 3) individual component options, to demonstrate compliance for all routes of administration to align with the precedent set in General Chapter <467> *Residual Solvents* and reflect the current EMEA guidance.
Response: Comment not incorporated—see comment #33 above.
Comment Summary #35: The commenter requested to better align the “Acceptance Criteria” in this chapter with the intention of the text and ICH Q6A terminology.
Response: Comment not incorporated. Acceptance Criteria are not provided in General Chapter <232>. Instead, PDE that are used to calculate the acceptance criteria are presented.

Comment Summary #36: The commenter requested reevaluating the flow of the information and use illustrative means to guide the user through the requirements, such as flow diagrams and decision trees.
Response: Comment not incorporated. The broad scope of this chapter makes the inclusion of a comprehensive decision tree very difficult. It is anticipated that subsequent documents will be developed either by USP or external parties. These documents will provide step-by-step instructions for users that need guidance.
Comment Summary #37: The use of Exposure Factor listed in table 1 and Daily Dose PDE from table 2 will not yield the same limits as listed in EMEA Guideline.
Response: Comment incorporated. Exposure factors were removed from General Chapter <232>. See also the response to Comment #1.
Comment Summary #38: The commenter requested replacing the word "validate" with "ensure" in the following sentence (summation Option): "…Before products can be evaluated using this option, the manufacturer must validate that additional elemental impurities cannot be inadvertently added through the manufacturing process."
Response: Comment incorporated.
Comment Summary #39: The commenter requested the following revision in the section on "Analytical Testing": "If, by validated processes and supply chain control, manufacturers can demonstrate ensure the absence of impurities, then further testing is not needed." This is to allow flexibility for the manufacturers and the agency to determine the optimal way to ensure compliance and not limit the choices to validation and supply chain controls.
Response: Comment not incorporated. USP does not specify when or how often to test. However, when tested, the article must pass. The ability to ensure compliance through control strategies and the extent of testing should be discussed with the appropriate regulatory body.

General Chapter/Section: <233> Elemental Impurities – Procedures/Multiple Sections
Expert Committee: General Chapters–Chemical Analysis
No. of Commenters: 16
Comment Summary #1: The commenter requested removing the fourth sentence that states, "In addition, system standardization and suitability..." because it seems out of place in the introduction.
Response: Comment incorporated.
Comment Summary #2: The commenter indicated that under *Target Elements*, the statement that target elements *must include* lead, mercury, arsenic and cadmium does not agree with the concept in the first sentence that addresses elements *potentially being present* nor with the concept in the introduction of General Chapter <232> that discusses elements *known to be present.* It should be acceptable to utilize a risk based control strategy.
Response: This wording has been changed to indicate that lead, mercury, arsenic and cadmium must be considered as "*potentially being present"* in any control strategy, but that testing is not always indicated. A risk-based control strategy is included in General Chapter <232> but not General Chapter <233> where the use is broader than just General Chapter <232>.

Comment Summary #3: The commenter requested including a statement about adding a suitable stabilizer for mercury analyses prior to digestion in the closed-vessel digestion section.
Response: Comment incorporated.
Comment Summary #4: The commenter requested defining the “indicated levels” in the *Precision for Instrumental Methods* section.
Response: Comment incorporated.
Comment Summary #5: The commenter requested clarifying the meaning of “unequivocally assess” in the specificity section with specific acceptance criteria to prevent differences in interpretation.
Response: Comment incorporated via reference to General Chapter <1225>.
Comment Summary #6: The commenter requested that Aqua Regia should have its own definition as mixture of ultrapure HCl and ultrapure $HN0_3$ at a ratio of 3:1or 4:1.
Response: Comment incorporated.
Comment Summary #7: The commenter requested adding the formula for the calculation of drift.
Response: Comment not incorporated, as the suggested text belongs in General Chapter <730> Plasma Spectrochemistry.
Comment Summary #8: The commenter requested defining “concentrated acid, ultra-pure acid and ultra-high purity.”
Response: Comment not incorporated. These terms are often used interchangeably or may be defined differently depending upon the application. The user should determine the appropriate purity during method development.
Comment Summary #9: The commenter requested adding a reference to USP General Chapter <730> Plasma Spectrochemistry.
Response: Comment incorporated.
Comment Summary #10: The commenter requested adding a statement in the *Analysis* section of Procedure 1 similar to that in Procedure 2 indicating that appropriate measures must be taken to correct for matrix-induced interferences (e.g., wavelength overlaps).
Response: Comment incorporated.
Comment Summary #11: The commenter questioned the need for six replicate samples in the “Repeatability” portion of “Precision” (Quantitative Procedures), as ICH allows either six replicates at the indicated level or three replicates at each of three levels, which is already specified in the *Accuracy* subsection.
Response: Comment not incorporated. From a statistical standpoint, the additional degrees of freedom are necessary to adequately determine the acceptability of the procedure.
Comment Summary #12: The commenter suggested that the “Note” in the mode section of Procedure 2 should also include “collision cell or reaction cell.”
Response: Comment incorporated.
Comment Summary #13: The commenter requested the addition of details in the *Specificity* subsection of *Quantitative Procedures* to properly conduct the experiments.
Response: Comment incorporated via General Chapter <1225>.
Comment Summary #14: The commenter requested to clarify the *Sample Preparation* subsection because the purpose of this sentence is not clear: “Samples and blanks may

be spiked with Target Elements where an analyte has limited solubility in the solvent system of choice."
Response: Comment incorporated.
Comment Summary #15: The commenter requested a Relative Standard Deviation of NMT 10% in the *Precision* subsection of the *Quantitative Procedures* section because the methods typically used for determination of elemental impurities (e.g., AA and ICP) have higher precision as compared to HPLC methods for which Relative Standard Deviation of 10-15% is generally acceptable.
Response: Comment not incorporated. The allowance of alternative technologies and the range of concentrations and elements that may need to be measured warrant the broader acceptance criterion.
Comment Summary #16: The commenter requested that the acceptance criteria for non-instrumental Procedures (*Detectability* section) state that the criteria must be met for each target element. For example, "Spike Sample Solution 1 provides a signal or intensity equivalent or greater than that of the Standard Solution for each Target Element."
Response: Comment incorporated.
Comment Summary #17: The commenter requested removing the bracketed "Note" to weigh all liquid samples within *Sample Preparation* because this is too much detail for this document.
Response: Comment not incorporated. The additional guidance was deemed necessary.
Comment Summary #18: The commenter requested providing clarification of the meaning of the term "unsolvated samples."
Response: Comment incorporated.
Comment Summary #19: The commenter considered the Closed Vessel Digestion procedure too specific.
Response: Comment not incorporated. Only closed-vessel digestion was deemed acceptable for the compendial procedure.
Comment Summary #20: The commenter requested removing the Detector listed in Procedure 1, ICP-AES, as it is incorrect.
Response: Comment not incorporated. The particular detector used in an ICP-AES may differ by instrument; however, the intention here is to differentiate between different techniques that may employ an inductively coupled plasma front end.
Comment Summary #21: The commenter requested not specifying the Rinse in Procedure 1 ICP-AES, as flexibility is needed.
Response: Comment not incorporated, as this level of detail was deemed necessary.
Comment Summary #22: The commenter indicated that the Mode recommendation in Procedure 2 ICP-MS is too detailed.
Response: Comment not incorporated, as this level of detail was deemed necessary.
Comment Summary #23: The commenter indicated that the Detector listed in Procedure 2 ICP-MS is incorrect, as mass spectrometer is a mass analyzer, not a detector.
Response: Comment not incorporated. In the case of these analyses, the mass spectromenter serves as a detector for the ions of interest.

Comment Summary #24: The commenter requested revising the title of the section on "Compendial Procedures 1 and 2" to "General Procedures 1 and 2."
Response: Comment not incorporated. The terminology used better expresses the Expert Committee's intent.
Comment Summary #25: The commenter requested revising the title of the section "Alternative Procedure Validation" to "Validation of Other Suitable Procedures."
Response: Comment not incorporated. The term "alternative procedure" has a specific meaning as discussed in Section 6.30 of the General Notices.
Comment Summary #26: The commenter requested including an example of the calculation of J in the chapter.
Response: Comment incorporated.
Comment Summary #27: The commenter requested allowing the use of standards from 1J - 10J.
Response: Comment not incorporated. Extending the calibration range upwards may increase the correlation coefficient without necessarily improving accuracy at the concentration of interest at J. It also may increase issues with elements that can be difficult to rinse out (memory effects) such as mercury. If there is a case where a sample solution has a concentration higher than 2J, an additional dilution can be applied to keep the concentration within range.

Chapter/Section: <911> Viscosity – Capillary Viscometer Methods/Multiple Sections
Expert Committee: General Chapters–Physical Analysis
No. of Commenters: 2
Comment Summary #1: In the *Method I. Ubbelohde-Type Capillary Viscometer* section, the commenter recommended adding an additional table that lists slightly different viscometer sizes because the specifications listed in Table 1 differ from the specifications listed in *ASTM D446* and in *Certification of Calibration* from several of the commenter's Ubbelohde viscometers.
Response: Comment incorporated.
Comment Summary #2: In the *Method II. Ostwald-Type Capillary Viscometer* section, the commenter recommended changing operation order because this will provide consistency between the outlined procedure in the In-Process Revision and the one recommended by the viscometer manufacturer.
Response: Comment incorporated.
Comment Summary #3: The commenter requested information on how the limit of flow time is established.
Response: Comment not incorporated. The Expert Committee is working on General Chapter <1911> *Rheometry*, which will include the requested information.

Chapter/Section: <912> Rotational Rheometer Methods/Multiple Sections
Expert Committee: General Chapters – Physical Analysis
No. of Commenters: 1
Comment Summary #1: The commenter requested guidance on running viscosity at different temperatures and a discussion regarding potential apparatus issues.

Response: Comment not incorporated. The Expert Committee is working on General Chapter <1911> *Rheometry*, which will include the requested information.
Comment Summary #2: The commenter suggested including a section on parallel plate viscometer.
Response: Comment not incorporated. The Expert Committee plans to add a test section for parallel plate viscometer once the procedure and related performance data are received.
Comment Summary #3: The commenter requested information on how to handle volatile solvents.
Response: Comment not incorporated. The Expert Committee is working on General Chapter <1911> Rheometry, which will include the requested information.

General Chapter/Section(s):	<1079> Good Storage and Shipping Practices
Expert Committee:	General Chapters–Packaging, Storage and Distribution
No. of Commenters:	12

General
Comment Summary #1: The commenter requested adding other ICH guidelines that are referenced in the chapter.
Response: Comment incorporated.

Introduction
Comment Summary #2: The commenter requested that the *Introduction* be revised to exclude clinical trial materials.
Response: Comment incorporated.

General Definitions
Comment Summary #3: The commenter requested revising the definition of "Distribution" so it reflects current industry terminology.
Response: Comment incorporated.
Comment Summary #4: The commenter requested deleting the parenthetical statement in the Drug Product definition that clinical material is defined as "investigational medicine/IND" because IND refers to the investigational new drug application that is submitted to FDA.
Response: Comment incorporated.
Comment Summary #5: The commenter requested revising the definition of "Drug Products" because it goes beyond the current industry definition.
Response: Comment incorporated.
Comment Summary #6: The commenter requested revising the "end user" definition and replacing "practitioner" with "healthcare specialist."
Response: Comment incorporated.
Comment Summary #7: The commenter requested revising the "Environmental Management" definition, because as written, it applies to an environmental monitoring program rather than a management program.
Response: Comment incorporated.

Comment Summary #8: The commenter requested the inclusion of a “hazardous drug” definition.
Response: Comment not incorporated. Such a definition is beyond the scope of this chapter.
Comment Summary #9: The commenter requested changing “Preventative Measures” to “Preventative Action” because this term is used internationally as part of CAPA.
Response: Comment incorporated.
Comment Summary #10: The commenter requested revising the “Transport Vehicles” definition so that “emergency medical service vehicles” and “industry representatives’ automobiles” are not recognized as transport vehicles.
Response: Comment incorporated.

Scope
Comment Summary #11: The commenter requested removing reference to “Manufacturers of combination products” because they are drug products and already covered.
Response: Comment incorporated.
Comment Summary #12: The commenter requested including “drug product compounders” to the scope.
Response: Comment incorporated.
Comment Summary #13: The commenter requested removing “Laboratory operations” from the scope of the chapter
Response: Comment not incorporated. Laboratory operations are required to follow the principles of good storage and distribution practices and regulations.
Comment Summary #14: The commenter requested removing “Clinical Trial Drug Products” from the scope of the chapter.
Response: Comment incorporated.
Comment Summary #15: The commenter requested adding “Pharmacies, including but not limited to community, mail order ...” to the eighth bullet.
Response: Comment incorporated.
Comment Summary #16: The commenter requested adding specialty pharmacies among the entities that should adhere to the recommendations set forth in the chapter.
Response: Comment incorporated.
Comment Summary #17: The commenter requested including more discussion about insight and guidance on what distributors can do to minimize loss as products clear customs.
Response: Comment not incorporated. The requested discussion is beyond the scope of this chapter.
Comment Summary #18: The commenter requested that the inclusion of the phrase “Mail distributors including the U.S. Postal Service (USPS) and other shipping services” may not be appropriate because these services may not have all the information necessary to ensure proper storage during shipping.
Response: Comment not incorporated. It is important to communicate all information related to the proper storage and distribution of drug products to supply chain members, including the USPS and other shipping services.

Comment Summary #19: The commenter requested greater discussion on temperature-sensitive products.
Response: Comment not incorporated. All drug products should be stored and distributed properly. Calling out temperature-sensitive products may send the message that these products are more important than others.
Comment Summary #20: The commenter requested deleting the example that mentions European Medicines Agency's Good Distribution Practices document, because the content should focus on FDA guidance.
Response: Comment incorporated.

Responsibilities
Comment Summary #21: The commenter requested adding a "Responsibility Assignment Matrix" such as a RACI (Responsible Accountable Consulted Informed) for assigning responsibilities.
Response: Comment not incorporated. Adding such a matrix is beyond the scope of this chapter.
Comment Summary #22: The commenter requested adding language that indicates the Authorization Holder should be contacted to evaluate the potential impact to product quality when excursions occur.
Response: Comment incorporated.
Comment Summary #23: The commenter requested using another word in place of "adulterated" in the sixth bullet.
Response: Comment not incorporated. Current use of the word "adulterated" is appropriate.

Labeling Considerations for Drug Products
Comment Summary #24: The commenter requested deleting the hazardous materials section because the information is not relevant.
Response: Comment not incorporated. The information is relevant and should be maintained in the chapter.
Comment Summary #25: The commenter requested revising the language dealing with the use of other storage conditions because it is vague and open to interpretation.
Response: Comment incorporated.
Comment Summary #26: The commenter requested adding the reference to PDA Technical Report 53 to support the discussion.
Response: Comment not incorporated because the reference is not appropriate.
Comment Summary #27: The commenter requested adding a reference to ICH Q1A Stability Testing of New Drug Substances and Products.
Response: Comment incorporated

Quality Management Systems
Comment Summary #28: The commenter requested adding information on a deviation management system because it is a critical quality component.
Response: Comment incorporated.
Comment Summary #29: The commenter requested adding Joint SOPs as a valid alternative to written agreement.

Response: Comment not incorporated. More than Joint SOPs are needed to ensure a clear understanding of expectation by all parties participating in the supply chain.

Good Documentation Practices

Comment Summary #30: The commenter requested replacing “assessments” with “investigations” throughout the section in order to encompass minor events controlled by trending and more significant issues managed through investigations.
Response: Comment not incorporated. The current word choice is appropriate.
Comment Summary #31: The commenter requested deleting the reference to temperature deviations because it is ambiguous (i.e., is it referring to ambient profile or the product itself and does not fit in this section).
Response: Comment incorporated.
Comment Summary #32: The commenter requested deleting the following text because it is too prescriptive: “Manufacturers should develop written procedures for security records that confirm container– closure integrity (e.g., security seals, narcotic controls) and for returned and salvaged goods.”
Response: Comment not incorporated. However, the text was revised to clarify the Expert Committee’s intent and eliminate prescriptive text.
Comment Summary #33: The commenter requested replacing “narcotic” with “controlled substance.”
Response: Comment incorporated.
Comment Summary #34: The commenter requested deleting the following sentence because the chapter’s scope is not intended to cover e-pedigree: “These records should ensure the traceability from the manufacturer to the end user so that the pedigree of the drug product can be followed throughout its life cycle.”
Response: Comment incorporated.

Storage Management System—Receiving and Transferring Drug Products

Comment Summary #35: The commenter requested including a more precise definition of storage.
Response: Comment incorporated.

Storage Management System—Refrigerators and Freezers

Comment Summary #36: The commenter requested revising the introduction paragraph to allow for a variety of freezer conditions and using an example to illustrate.
Response: Comment incorporated.
Comment Summary #37: The commenter requested revising the first bullet to clarify the requirement (i.e., what is “proper” airflow?).
Response: Comment incorporated.
Comment Summary #38: The commenter requested revising the third bullet to state that one temperature monitor is not enough, and there should be a minimum of two to determine hot and cold spots.
Response: Comment incorporated.

Distribution Management System—Validation and Thermal Performance Qualification

Comment Summary #39: The commenter requested adding text that specifies the use of calibrated electronic monitors.

Response: Comment not incorporated because the proposed change is too prescriptive.

Comment Summary #40: The commenter requested revising the section so that it includes a “formal qualification protocol” that uses both controlled environments and actual field testing.

Response: Comment not incorporated. The current language expresses the Expert Committee’s intent.

Comment Summary #41: The commenter requested deleting the following sentence: “A transport container/vehicle, or transport packaging system as well as the transport process may be qualified in accordance with current good distribution practices, thereby providing the assurance for environmental control without other temperature monitors.”

Response: Comment incorporated.

Comment Summary #42: The commenter requested deleting the sentence: “The validation or qualification program for a vehicle or storage area should represent a statistically high proportion of the environmental conditions to which a drug product may be exposed.”

Response: Comment incorporated.

Comment Summary #43: The commenter requested deleting the following sentence because it is not technically correct: “Storage facilities themselves, unless thermostatically controlled, cannot be validated because of their unpredictability and the influence of external temperature; however, they can be qualified via a mapping process. The generator back-up power supply should be validated.”

Response: Comment incorporated.

***Environmental Management System*—Temperature Monitoring**

Comment Summary #44: The commenter requested reintroducing the following text that appeared in Pharmacopoeial Forum 36(1): “Chemical temperature indicators may be used as appropriate.”

Response: Comment incorporated.

Comment Summary #45: The commenter requested clarifying temperatures can only be controlled with active systems, and indicated that the focus should be on tracking.

Response: Comment incorporated.

Comment Summary #46: The commenter requested adding a definition of accuracy in the third bullet.

Response: Comment incorporated. A reference to General Chapter <1118> *Monitoring Device* was added where accuracy is discussed.

***Environmental Management System*—Temperature Mapping**

Comment Summary #47: The commenter requested deleting diagrams because they are confusing and add little value.

Response: Comment incorporated.

Comment Summary #48: The commenter requested changing the temperature mapping time from two weeks to one, because one week is sufficient.
Response: Comment incorporated.
Comment Summary #49: The commenter requested deleting the statement that an OQ performance should be done on trucks, for there are too many extreme scenarios to make this a feasible or practical activity.
Response: Comment incorporated.

***Environmental Management System*—Mean Kinetic Temperature**
Comment Summary #50: The commenter requested that USP re-assess the discussion of the application of Mean Kinetic Temperature (MKT). There are differing opinions with the application (long term vs. short term; room temperature storage vs. cold chain applications). The chapter should be clear and consistent within the document and supporting references.
Response: Comment incorporated.

***Environmental Management* System—Mail Delivery Distribution**
Comment Summary #51: The commenter indicated that the proposals given in this section are correct, but not practical. The commenter requested revising or deleting this section.
Response: Comment incorporated. This section was revised to focus on “Mail Order Pharmacy Distribution.”

General Chapter/Section: <1088> In Vitro and In Vivo Evaluation of Dosage Forms/Multiple Sections
Expert Committee: General Chapters–Dosage Forms
No. of Commenters: 2
Comment Summary #1: The commenter requested that the word “product” be replaced by the word “substance” in the *In Vitro Evaluation, Physicochemical Properties—Drug Product* section to be consistent with terminology from the Biopharmaceutics Classification System (BCS).
Response: Comment incorporated.
Comment Summary #2: The commenter requested that topics such as sink conditions and discriminatory power of the dissolution method be included under *In Vitro Evaluation, Dissolution Testing*.
Response: Comment not incorporated. *General Chapter <1092> The Dissolution Procedure: Development and Validation* contains discussion of these topics.
Comment Summary #3: The commenter indicated that the sentence starting with the phrase “Knowledge of drug properties” should read: “Knowledge of drug substance properties.”
Response: Comment incorporated.
Comment Summary #4: The commenter requested replacing the phrase “three test times” with “three time points” where it appears under *In Vitro Evaluation Extended—Release Dosage Forms*.
Response: Comment incorporated.

Comment Summary #5: The commenter requested including, in the *In Vivo Evaluations of Dosage Forms* section, examples where bioequivalence can sometimes be replaced by in vitro studies.
Response: Comment incorporated. The chapter now includes a footnote giving a citation to 21 CFR 320.22.
Comment Summary #6: The commenter requested that, under the *In Vitro—In Vivo Correlations, Level A Correlations* section, a reference be made to the FDA guidance document, *SUPAC–MR: Modified Release Solid Oral Dosage Forms Scale up and Postapproval Changes: Chemistry, Manufacturing, and Controls and Extended Release Solid Oral Dosage Forms Development, Evaluation, and Application of In Vitro/In Vivo Correlations*.
Response: Comment incorporated.
Comment Summary #7: The commenter indicated that the correlation shown in figure 5 would be improved if a time scale factor was applied to the pH 4.5 dissolution profiles.
Response: Comment not incorporated. The demonstration that a Level A correlation need not be linear was a purpose of the section.

General Chapter/Section: General Chapter <1102> Immunological Test Methods – General Considerations
Expert Committee: General Chapters–Biological Analysis
No. of Commenters: 1
Comment Summary #1: The commenter requested that other methods similar to ELISA, such as multiplex bead-based assays, should be included.
Response: Comment not incorporated. This chapter serves as a general introduction to immunological test methods. ELISA-type methods, including bead-based methods, are discussed in *General Chapter <1103> Immunological Test Methods – Enzyme-Linked Immunosorbent Assay*; however, multiplex assays are not discussed in detail because they are difficult to validate and not used for compendial purposes.
Comment Summary #2: The commenter requested removing the disadvantage “works only with cells and particles” for flow cytometry because cytokines and other factors in solution can be quantitated via flow cytometry using bead-based methods.
Response: Comment incorporated. Table 1 text was modified to read: “Use limited to cells, particles, and samples bound to beads.”

General Chapter/Section: General Chapter <1103> Immunological Test Methods – Enzyme-Linked Immunosorbent Assay (ELISA)
Expert Committee: General Chapters–Biological Analysis
No. of Commenters: 3

Introduction
Comment Summary #1: The commenter requested clarifying the definition of a “reporter substrate” to include “…or is directly labeled with an enzyme)…”
Response: Comment incorporated.
Comment Summary #2: The commenter requested editorial changes for the definition of “quantitative assays” in the fifth and sixth sentences of the *Definition* section.

Response: Comment incorporated with exception of changing “assay” to “plate” in the fifth sentence. It is possible to validate an ELISA to demonstrate that it is legitimate to run more than one plate and quantitate from another plate as long as the assay is stable and the appropriate controls are present.
Comment Summary #3: The commenter requested including text that indicates a capture reagent can bind to a plate in addition to a solid surface.
Response: Comment not incorporated because a plate is a solid surface.

Assay Design
Comment Summary #4: The commenter requested removing the discussion of a bridging ELISA from this chapter because it is a subset of sandwich ELISAs.
Response: Comment not incorporated. The bridging ELISA was moved within the sandwich ELISA section, however, because it is a subset of sandwich ELISAs.
Comment Summary #5: The commenter requested that “Format difficult to troubleshoot” and “Limited dynamic range” be included as disadvantages for a competitive ELISA format.
Response: Comment incorporated.
Comment Summary #6: The commenter requested that “Impact of matrix and adjuvants” be included as a disadvantage for a direct detection ELISA format.
Response: Comment incorporated by adding the following text: “Sensitive to matrix and adjuvant components.”
Comment Summary #7: The commenter suggested reformatting Table 1 and Table 2 (Procedures) because they are difficult to read.
Response: Comment incorporated.
Comment Summary #8: The commenter indicated that the analyte can be directly attached to a plate for Direct Detection and Indirect Detection.
Response: Comment not incorporated. Analyte directly attached to plate is shown as Indirect in Table 1. The table focuses on the detection aspects of the format.
Comment Summary #9: The commenter requested that “May modify the conformation of the analyte” be included as a disadvantage for Indirect Detection.
Response: Comment not incorporated. Analyte is unlabeled in this example.
Comment Summary #10: The commenter requested that “Difficult to adapt to quantitative formats” be removed from Table 1 as a disadvantage for Competitive Format.
Response: Comment incorporated.
Comment Summary #11: The commenter requested that “Longer because of more incubation steps” be added to the same section of Table 1 mentioined in comment #10.
Response: Comment not incorporated because more incubation steps do not always apply.
Comment Summary #12: The commenter requested that “…or a few closely spaced epitopes” be added to the last disadvantage in the Table 1 Sandwich format.
Response: Comment incorporated.
Comment Summary #13: The commenter requested including text that mentions blocking unbound reactive sites for a Direct ELISA.
Response: Comment incorporated.

Comment Summary #14: The commenter indicated that the traditional small molecule inhibition assay was omitted and should be included.
Response: Comment incorporated.
Comment Summary #15: Three commenters requested editorial changes for Direct Antigen Competitive ELISA, Indirect Antigen Competitive ELISA, and Sandwich ELISA.
Response: Comment incorporated.

Choice of Assay
Comment Summary #16: The commenter requested clarifiying that when small proteins or peptides are being evaluated as analytes, coating the solid phase with the analyte is not recommended due to steric hindrance/epitope inaccessibility.
Response: Comment incorporated.
Comment Summary #17: The commenter requested editorial changes in the second paragraph of this section.
Response: Comment incorporated
Comment Summary #18: Two commenters requested that text be modified or removed stating that replicates should not be in adjacent wells because many commercial kits do not offer this as an option, and it can be addressed in validation.
Response: Comment incorporated.
Comment Summary #19: The commenter requested clarification regarding imprecision in assays with steep dose-response curves.
Response: Comment incorporated.

Procedures
Comment Summary #20: The commenter requested editorial changes in the section on *Immobilization of Capture Reagent*.
Response: Comment incorporated.
Comment Summary #21: The commenter requested that text regarding optimum coating concentration be changed from "*µg/mL*" to "*µg/well.*"
Response: Comment incorporated.
Comment Summary #22: The commenter requested that additional text be included to indicate what steps should be taken if plates are precoated with Protein A or Protein G.
Response: Comment incorporated.
Comment Summary #23: The commenter requested including examples from different manufacturers with regards to different coating options.
Response: Comment not incorporated. USP does not provide specific manufacturer information.
Comment Summary #24: Two commenters requested editorial changes in the Adding Samples and Reagents section and the Coating Temperature section.
Response: Comment incorporated.
Comment Summary #25: The commenter requested that "… and acidic buffers" be added to the *Coating Buffer* section.
Response: Comment not incorporated. The list is intended to provide examples. The reader can try other buffers (e.g. acidic buffers which are not commonly used for this purpose).

Comment Summary #26: The commenter indicated that there were redundant statements in the *Blocking Agents and Buffers* and *Blocking Conditions and Non-Specific Reactions* sections, and requested merging the statements.
Response: Comment incorporated.
Comment Summary #27: The commenter requested that “calf” (in fetal calf serum) be replaced with “bovine”, and to add the word “empirically” before “determine” in the next sentence in the *Blocking Reagents and Buffers* section.
Response: Comment incorporated.
Comment Summary #28: The commenter requested editorial changes regarding changing “automatic” to “electronic” pipets and “automated” liquid handlers (not automatic) in the *Adding Samples and Reagents* section.
Response: Comment incorporated.
Comment Summary #29: The commenter requested that not only murine capture antibodies should be mentioned, but also murine detection antibodies.
Response: Comment incorporated.
Comment Summary #30: The commenter requested adding the following text to the *Blocking Conditions and Non-Specific Reactions* section: “Cross reactivity with other assay reagents should be considered, for example endogenous biotin is found in milk and serum and serum may contain antibody to viral or bacterial proteins. Therefore screening of serum lots may be necessary.”
Response: Comment incorporated.
Comment Summary #31: The commenter requested editorial changes in Pretreatment of Samples section.
Response: Comment incorporated.
Comment Summary #32: The commenter requested removing the example at the end of the sentence that discusses the linear range of a plate reader in the *Detector Antibodies* section.
Response: Comment incorporated.
Comment Summary #33: The commenter requested removing “time consuming” as a disadvantage of Colorimetric readout in Table 2.
Response: Comment incorporated.
Comment Summary #34: The commenter requested adding a safety statement regarding substrates at the end of the *Detector Antibodies* section.
Response: Comment not incorporated because investigator safety should always be considered, and is not specific to just this procedure.

Assay Development and Validation
Comment Summary #35: The commenter requested minor editorial changes in the Critical Reagent Developments section.
Response: Comment incorporated.
Comment Summary #36: The commenter indicated that any changes of critical biological reagents should be evaluated according to *General Chapter <1032> Design and Development of Biological Assays*.
Response: Comment incorporated.
Comment Summary #37: The commenter requested additional details for steps by which an ELISA is developed, validated, and used in routine sample analysis.

Response: Comment incorporated.
Comment Summary #38: The commenter requested including the evaluation of any prozone effects during development/validation.
Response: Comment not incorporated. This level of detail is outside of the scope of this chapter.
Comment Summary #39: The commenter suggested clarification in the *Basic Statistical Analysis* section regarding whether ELISAs are considered biological assays.
Response: Comment not incorporated. The chapter's *Introduction* states that General Chapter <1103> is related to the general information chapters for bioassays (<1032>, <1033>, and <1034>), but most ELISAs are not used for that purpose.

General Chapter/Section: General Chapter <1150> Pharmaceutical Stability
Expert Committee: General Chapters–Packaging, Storage and Distribution/General
No. of Commenters: 2
Comment Summary #1: The commenter requested retaining the basic information in this chapter including the discussion on Mean Kinetic Temperature (MKT) because MKT is a basic concept in the performance of isothermal stability studies.
Response: Comment Incorporated, and the information was also added to *General Chapter <1079> Good Storage and Shipping Practices*.

General Chapter/Section: General Chapter <1238> Vaccines for Human Use – Bacterial Vaccines/Multiple Sections
Expert Committee: General Chapters–Biological Analysis
No. of Commenters: 2

Introduction
Comment Summary #1: The commenters requested expanding the language describing carrier proteins as well as the composition of subunit vaccines.
Response: Comment incorporated.
Comment Summary #2: The commenter suggested removing the sentence "To be effective, protein or glycoprotein conjugate immunogens are non covalently adsorbed onto the surface of the adjuvant particles."
Response: Comment incorporated.
Comment Summary #3: The commenter indicated that the text over-emphasized the importance of vaccines from recombinant sources
Response: Comment not incorporated. The description is balanced.

Cell Banks
Comment Summary #4: The commenter requested replacing the term "validated banks" with "released GMP banks."
Response: Comment not incorporated. While GMP applies to the entire development process through and post licensure, "validated" is the appropriate term in the scope of process validation

Comment Summary #5: The commenters requested removing language describing the freedom from adventitious cellular contaminants, and qualifying the language regarding mycoplasma and virus testing with “as applicable.”
Response: Comment incorporated
Comment Summary #6: The commenter requested replacing the term “cells” with “microorganisms.”
Response: Comment not incorporated in order to maintain consistency in terminology within this section of the chapter.
Comment Summary #7: The commenter proposed language that implied that Master Cell Banks (MCBs) did not require the same amount of stability monitoring as Working Cell Banks.
Response: Comment not incorporated because stability monitoring applies with equal importance to MCBs.

Fermentation
Comment Summary #8: The commenter requested several minor editorial changes.
Response: Comment incorporated.
Comment Summary #9: The commenter requested additional language regarding the use of physicochemical characterization in the comparability exercises for scale changes.
Response: Comment incorporated.

Purification
Comment Summary #10: The commenter indicated that raw materials for phase I/II materials do not necessarily have to be made under cGMPs.
Response: Comment not incorporated. The chapter now includes clarifying language that raw materials used for late clinical stage and commercial materials should be made under cGMPs.
Comment Summary #11: The commenter requested widening the scope of drug substances to include peptide and protein conjugates.
Response: Comment incorporated
Comment Summary #12: The commenter requested deleting ion exchange chromatography from the section on fractional precipitation.
Response: Comment not incorporated because ion exchange resins are used for this purpose.
Process Controls
Comment Summary #13: The commenter requested the clarification of language regarding process targets for process parameters and tolerances.
Response: Comment incorporated.
Comment Summary #14: The commenter requested revisions to the section that discusses parameters influencing polysaccharide size and how it is measured. The commenter also requested the inclusion of a statement regarding the use of alternative analytical procedures.
Response: Comment incorporated.
Comment Summary #15: The commenter requested the inclusion of bacterial endotoxin and exclusion of lipids in the scope of residuals testing.

Response: Comment incorporated.
Comment Summary #16: The commenter requested clarification regarding the type of antitoxin standard to be used (USP or other).
Response: Comment incorporated.
Comment Summary #17: Several commenters focused on the uneven level of detail and the examples used in the section (relevance of examples to products marketed in the US).
Response: Comment not incorporated, however, the examples that do not apply to marketed products were removed.

Intermediates
Comment Summary #18: The commenter requested the inclusion of microfluidisation and mechanical treatment as methods for depolymerization/size reduction.
Response: Comment incorporated.
Comment Summary #19: Several commenters requested clarification edits to the analytical descriptions of the intermediates section, focusing on different instrumentation and procedure approaches and linking appropriate analytical approaches with the chosen production process.
Response: Comment incorporated.
Comment Summary #20: The commenter requested clarifying “stability testing.”
Response: Comment incorporated.

Drug Substance
Comment Summary #21: The commenters requested clarification of the language regarding the appropriate scope of stability testing for bulk.
Response: Comment incorporated.

Drug Product and Lot Release
Comment Summary #22: The commenter requested modifying the discussion of adjuvants to include the evaluation of alternative adjuvant systems.
Response: Comment incorporated.
Comment Summary #23: Several commenters requested revising and correcting CFR references.
Response: Comment incorporated.

Monographs

Monograph/Section: Amoxapine/Multiple Sections
Expert Committee: Monographs–Small Molecules 4
No. of Commenters: 1
Comment Summary #1: The commenter requested to retain the *Assay* procedure based on titration.
Response: Comment not incorporated. The use of a specific HPLC procedure is consistent with USP’s modernization efforts.

Comment Summary #2: The commenter indicated that their material has a process impurity which coelutes with amoxapine and proposed a replacement *Organic Impurities* procedure that is capable of separating the peaks.
Response: The proposed procedure for *Organic Impurities* from *PF* 37(5)[Sept.-Oct. 2011] is deferred from becoming official in the *Second Supplement to USP 35–NF 30*. A revised procedure will be republished in a future issue of PF.

Monograph/Section: Articaine Hydrochloride and Epinephrine Injection/Multiple Sections
Expert Committee: Monographs–Small Molecules 4
No. of Commenters: 2
Comment Summary #1: The commenter requested the test for *Assay-Epinephrine* be revised to include the type of electrodes used for electrochemical detection.
Response: Comment incorporated.
Comment Summary #2: The commenter noted that the proposed limit for total articaine impurities under *Organic Impurities, Limit of Articaine Related Compounds* (NMT 0.5%) may be exceeded if the limits for impurity B (NMT 0.5%) and any unspecified impurity (NMT 0.1%) are at their respective upper limits.
Response: Comment not incorporated**.** The proposed limits for individual and total articaine impurities are consistent with the specifications approved by the FDA.
Comment Summary #3: The commenter requested that the limit for any other individual impurity under *Organic Impurities, Limit of Articaine Related Compounds* be widened from NMT 0.1% to NMT 0.2% to be consistent with their FDA-approved specifications.
Response: Comment incorporated.
Comment Summary #4: The commenter noted that the proposed limit for total epinephrine impurities under *Organic Impurities, Limit of Epinephrine Related Compounds* (NMT 10%) may be exceeded if the limits for epinephrine sulfonate (NMT 5%), any specified impurity (NMT 8%), and any unspecified impurity (NMT 1%) are at their respective upper limits.
Response: Comment not incorporated. The proposed limits for individual and total epinephrine impurities are consistent with the specifications approved by the FDA.
Comment Summary #5: The commenter requested widening the limit for the epinephrine sulfonate under *Organic Impurities, Limit of Epinephrine Related Compounds* from NMT 5% to NMT 7.5% to be consistent with their FDA-approved specifications.
Response: Comment incorporated.
Comment Summary #6: The commenter requested that a second HPLC procedure that uses UV detection be added to monitor epinephrine related impurities that are not observed by electrochemical detection.
Response: Comment not incorporated. The Expert Committee noted that electrochemical detection is sufficient for establishing the purity of the formulation.
Comment Summary #7: The commenter requested that a colorimetric test be added as a qualitative test for the presence of oxidative degradation products of epinephrine, such as adrenochrome.

Response: Comment not incorporated. The Expert Committee will consider addressing this comment in a future revision.
Comment Summary #8: The commenter requested that a test for *Limit of iron* be added to the monograph because iron is known to cause degradation of epinephrine.
Response: Comment not incorporated. The Expert Committee will consider addressing this comment in a future revision.
Comment Summary #9: The commenter requested that the range for *pH* be widened from 2.8–5.2 to 2.7–5.2 to be consistent with their FDA-approved specifications.
Response: Comment incorporated.

Monograph/Section(s): Azithromycin for Injection/Organic Impurities
Expert Committee: Monographs–Small Molecules 1
No. of Commenters: 4
Comment Summary #1: The commenter requested revising the *Sample solution* in the test for *Limit of Azithromycin N-Oxide, Desosaminylazithromycin and N-Demethylazithromycin* to specify the number of vials to be used.
Response: Comment not incorporated. The requested change is not consistent with the sponsor's validation data.
Comment Summary #2: The commenter requested deleting the resolution requirement in the test for *Limit of Aminoazithromycin, Formamido analog, Methylformamido analog and 3'-De(dimethylamino)-3'-oxoazithromycin*.
Response: Comment not incorporated. The resolution requirement is needed to establish system suitability.
Comment Summary #3: The commenter requested revising the tests for *Limit of Azithromycin N-Oxide, Desosaminylazithromycin and N-Demethylazithromycin* and the *Limit of Aminoazithromycin, Formamido analog, Methylformamido analog and 3'-De(dimethylamino)-3'-oxoazithromycin* to use UV detection rather than electrochemical detection.
Response: Comment not incorporated. The Expert Committee is willing to consider future changes to the monograph upon receipt of the necessary supporting data.
Comment Summary #4: The commenter requested tightening the limit for azithromycin *N*-oxide in the test for *Limit of Azithromycin N-Oxide, Desosaminylazithromycin and N-Demethylazithromycin*.
Response: Comment not incorporated. The proposed limits are consistent with the specifications approved by FDA.
Comment Summary #5: The commenter requested correcting the calculation formulas in the tests for *Limit of Azithromycin N-Oxide, Desosaminylazithromycin and N-Demethylazithromycin* and the *Limit of Aminoazithromycin, Formamido analog, Methylformamido analog and 3'-De(dimethylamino)-3'-oxoazithromycin*.
Response: Comment incorporated.

Monographs: Beta Carotene Capsules and Beta Carotene Preparation
Expert Committee: Monographs–Dietary Supplements
No. of Commenters: 1

Comment Summary #1: The commenter indicated that the proposed monographs for Beta Carotene Preparation and Beta Carotene Capsules contain a specification of 95% trans beta-carotene in the total beta-carotene present that many beta-carotene products on the market would not be able to meet. The commenter requested deferring these monographs from becoming official until additional data is acquired.
Response: Comment not incorporated. When the additional data is acquired and a new specification for the percentage of trans beta-carotene is set, the Expert Committee will consider incorporating the changes in an Accelerated Revision.

Monograph/Section: Biotin/ Multiple Sections
Expert Committee: Monographs–Dietary Supplements
No. of Commenters: 1
Comment Summary #1: The commentator indicated that the dissolution of the analyte in the *Sample solution* is not always complete and that leads to inconsistent results.
Response: Comment incorporated by decreasing the concentration of the *Sample solution* by half of that proposed.
Comment Summary #2: The commentator requested increasing the limit of the individual impurity requirement based on their historical data, which show that some impurities are as high as 0.7%.
Response: Comment incorporated.

Monograph/Section: Cefepime Hydrochloride/Multiple Sections
Expert Committee: Monographs–Small Molecules 1
No. of Commenters: 1
Comment Summary #1: The commenter requested tightening the limit of any individual unspecified impurity in the test for *Organic Impurities Procedure 2*.
Response: Comment not incorporated. The proposed limits are consistent with the specifications approved by the FDA.
Expert Committee-initiated Change #1: The *USP Reference Standards* section was updated to replace USP Cefepime Hydrochloride System Suitability RS, which was difficult to procure, with two individual reference standards, USP Cefepime Related Compound D RS and USP Cefepime Related Compound E RS. The *System suitability solution* in the test for *Organic Impurities Procedure 2* was updated to reflect the change in the *USP Reference Standards* section.

Monograph/Section: Cefepime for Injection/Multiple Sections
Expert Committee: Monographs–Small Molecules 1
Expert Committee-initiated Change #1: The *USP Reference Standards* section was updated to replace USP Cefepime Hydrochloride System Suitability RS, which was difficult to procure, with two individual reference standards, USP Cefepime Related Compound D RS and USP Cefepime Related Compound E RS. The *System suitability solution* in the test for *Organic Impurities Procedure 2* was updated to reflect the change in the *USP Reference Standards* section.
Expert Committee-initiated Change #2: In the *Packaging and Storage* section, the term “reconstituted powder” was replaced with “reconstituted solution.”

Monograph/Section: Ciclopirox Topical Solution**/**Multiple Sections
Expert Committee: Monographs–Small Molecules 1
No. of Commenters: 3
Comment Summary #1: The commenter requested widening the acceptance criteria for the *Assay* from 95.0%-105.0% to 90.0%-110.0% to be consistent with the FDA-approved specification.
Response: Comment incorporated.
Comment Summary #2: The commenter requested revising the *Packaging and storage* section from "Preserve in well-closed containers…" to "Preserve in well-closed clear glass containers…" because there is a possibility of leaching of alkaline earth metals if a colored glass is used.
Response: Comment not incorporated. The color of a container for packaging/storage is based on product's light sensitivity and not on extractables and leachables. In addition, it is the responsibility of the manufacturers to have an appropriate container closure system for their formulation.
Comment Summary #3: The commenter requested shortening the run time under the test for *Organic impurities* from about 50 min (5 times the retention time of the major peak) to about 30 min.
Response: Comment not incorporated because of a potential late-eluting impurity which may be present in the drug product.
Comment Summary #4: The commenter requested including a second identification test based on UV absorption.
Response: Comment not incorporated. The Expert Committee is willing to consider future changes to the monograph upon receipt of the necessary supporting data.
Comment Summary #5: The commenter requested including additional specified impurities with their corresponding limits under the test for *Organic Impurities*.
Response: Comment not incorporated. The Expert Committee is willing to consider future changes to the monograph upon receipt of the necessary supporting data.
Comment Summary #6: The commenter requested adding a test for alcohol content to the monograph.
Response: Comment not incorporated. The Expert Committee is willing to consider future changes to the monograph upon receipt of the necessary supporting data.

Monograph/Section: Clozapine/Multiple Sections
Expert Committee: Monographs–Small Molecules 4
No. of Commenters: 2
Comment Summary #1: The commenter requested the inclusion of a run time of about 3 times the retention time of clozapine to prevent carryover for successive injections in the *Assay.*
Response: Comment incorporated.
Comment Summary #2: The commenters requested correcting the requirement for relative standard deviation in the *Assay* from NLT 1.0% to NMT 1.0%.
Response: Comment incorporated.
Comment Summary #3: The commenter requested retaining the test for *Melting range,* to be consistent with ICH Q6A – Physicochemical properties.

Response: Comment not incorporated. The Expert Committee believes that this test does not add value to the monograph because there are no known polymorphs of clozapine. The deletion of this test is consistent with USP's modernization efforts.

Monograph/Section: Cyanocobalamin/ Multiple Sections.
Expert Committee: Monographs–Dietary Supplements
No. of Commenters: 1
Comment Summary #1: The commentator requested decreasing the resolution requirement between cyanocobalamin and 8-lactocyanocobalamin peaks from 2.5 to 2.0 because they could not meet the requirement.
Response: Comment not incorporated. A small impurity peak has been observed between the cyanocobalamin and 8-lactocyanocobalamin peaks. This peak may be overlapped by either cyanocobalamin or 8-lactocyanocobalamin peak if the resolution is allowed to be 2 or less. In addition, data from the monograph sponsor and USP lab have shown an average resolution of 3 or higher.

Monograph/Section: Duloxetine Hydrochloride/Multiple Sections
Expert Committee: Monographs–Small Molecules 4
No. of Commenters: 6
Comment Summary #1: The commenters requested specifying the use of methanol as the solvent for the Sample solution in the *Identification* test for chloride.
Response: Comment incorporated by adding a Sample solution to *Identification* test *C.*
Comment Summary #2: The commenter requested deleting the resolution requirement in the *Assay* and the *Organic Impurities* procedure.
Response: Comment not incorporated. The resolution requirement is supported by the validation data and is suitable for analysis.
Comment Summary #3: The commenter indicated that the preparation of the *System suitability solution* in the *Assay* and the *Organic Impurities* procedures may require heating a solution for a longer period of time or using a temperature higher than 40°, and requested to allow the flexibility in the preparation.
Response: Comment incorporated.
Comment Summary #4: The commenters requested increasing the concentration or the injection volume of the System suitability solution in the *Limit of Duloxetine Related Compound A* procedure, so that the required signal-to-noise ratio could be met.
Response: Comment not incorporated. The Expert Committee is willing to consider future changes to the monograph upon receipt of the necessary supporting data.
Comment Summary #5: The commenter requested lowering acceptance criteria of the *Limit of Duloxetine Related Compound A* procedure to NMT 0.15% for pediatric use.
Response: Comment not incorporated. The limit in this test is consistent with the specifications approved by FDA.
Comment Summary #6: The commenter indicated that duloxetine impurity G has a low response and requested the use of a different wavelength in the *Organic Impurities* procedure.
Response: Comment not incorporated. The Expert Committee is willing to consider future changes to the monograph upon receipt of the necessary supporting data.

Comment Summary #7: The commenter requested that the word “hydrochloride” be deleted from the chemical name associated with duloxetine related compound F in Table 1.
Response: Comment incorporated.
Comment Summary #8: The commenter indicated that their material contains two process impurities which coelute with other peaks in the *Organic Impurities* procedure.
Response: Comment not incorporated. The Expert Committee is willing to consider future changes to the monograph when the commenter’s product receives full FDA approval and upon receipt of the necessary supporting data.

Monograph/Section: Drospirenone and Ethinyl Estradiol Tablets/Multiple Sections
Expert Committee: Monographs–Small Molecules 4
No. of Commenters: 4
Comment Summary #1: The commenter requested that the acceptance criteria for the Assay be widened to “NLT 90.0 and NMT 110.0%” for both drospirenone and ethinyl estradiol, to be consistent with their FDA-approved specifications.
Response: Comment incorporated.
Comment Summary #2: The commenter requested inclusion of the *Dissolution* test for their product.
Response: Comment not incorporated. The Expert Committee is willing to consider addressing this comment in a future revision to the monograph when the commenter’s product receives full FDA approval.
Comment Summary #3: The commenter requested that the impurity limits for individual and total impurities be the same for both dosage strengths.
Response: Comment not incorporated. The proposed limits for individual and total impurities for both strengths are consistent with the FDA-approved specifications.
Comment Summary #4: The commenter requested that the requirement for the relative standard deviation for the peak response from the *Standard solution* in the *Organic impurities* test be widened from NMT 3.0% to NMT 5.0%.
Response: Comment incorporated.
Comment Summary #5: The commenter requested that the ratio of drospirenone to 17-epidrospirenone ratio in the *System suitability solution* in the Organic impurities test be changed to “between 3:1 and 7:1.”
Response: Comment incorporated.
Comment Summary #6: The commenter requested that a column temperature of 25° be specified in the test for *Assay*.
Response: Comment incorporated. Based on the robustness data, the Expert Committee decided that a temperature range of 25 ± 3° is appropriate.
Comment Summary #7: The commenter requested that the preparation of the *System suitability stock solution, Standard solution, Sensitivity solution* and *Sample solution* be revised to accommodate different dosage strengths.
Response: Comment incorporated.
Comment Summary #8: The commenter observed high column backpressure when performing the *Organic impurities* procedure, and requested to defer the monograph from becoming official until this issue is addressed.

Response: Comment not incorporated. The Expert Committee noted that other laboratories have successfully performed the procedure.

Monograph/Section: Duloxetine Delayed-Release Capsules/Multiple Sections
Expert Committee: Monographs–Small Molecules 4
No. of Commenters: 4
Comment Summary #1: The commenter indicated that the concentrations of the *Standard solution* and *Sample solution* are dissimilar in the *Assay*.
Response: Comment not incorporated because the validation data supports the use of dissimilar concentrations.
Comment Summary #2: The commenter requested to indicate that the variable C_S in the *Dissolution* procedure refers to the concentration of duloxetine hydrochloride.
Response: Comment incorporated.
Comment Summary #3: The commenter requested inclusion of the *Dissolution* test for their product.
Response: Comment not incorporated. The Expert Committee is willing to consider future changes to the monograph when the commenter's product receives full FDA approval and upon receipt of the necessary supporting data.
Comment Summary #4: The commenter requested the inclusion of a sensitivity solution using N-succinoyl duloxetine in the *Organic Impurities* procedure.
Response: Comment not incorporated. The Expert Committee is willing to consider future changes to the monograph upon receipt of the necessary supporting data.
Comment Summary #5: The commenter indicated that the chromatographic column identified in the Briefing is available only with 3.5 µm particle size and not with a 3 µm particle size.
Response: Comment incorporated. The revised text for the *Organic Impurities* procedure allows the use of 3 or 3.5 µm particle size.
Comment Summary #6: The commenter requested that a second *Organic impurities* procedure be added to the monograph, to accommodate the impurity profile generated by their manufacturing process.
Response: Comment not incorporated. The Expert Committee is willing to consider future changes to the monograph when the commenter's product receives full FDA approval.

Monograph/Section: Esmolol Hydrochloride/Organic Impurities
Expert Committee: Monographs–Small Molecules 2
No. of Commenters: 2
Comment Summary #1: The commenter requested to correct the typographical error in the relative retention time for esmolol dimer and change it from 0.65 to 6.5.
Response: Comment incorporated.
Comment Summary #2: The commenter requested to include a process specific impurity, *N*-ethyl esmolol, with a relative retention time of 0.88 with a limit of NMT 0.15%.
Response: Comment incorporated.

Monograph/Section: Fenofibrate Tablets/Organic Impurities
Expert Committee: Monographs–Small Molecules 3
No. of Commenters: 2
Comment Summary #1: The commenter requested the limit for any unspecified impurity be widened from NMT 0.1% to NMT 0.2% to be consistent with their FDA-approved specifications.
Response: Comment incorporated.
Comment Summary #2: The commenter requested the limit for fenofibrate related compound B be widened from NMT 0.2% to NMT 0.4%, and the limit of total impurities be widened from NMT 0.3% to NMT 0.9%.
Response: Comment not incorporated. These limits in the proposed monograph are consistent with the FDA-approved specifications.

Monograph/Section: Ferrosoferric Oxide/Multiple Sections
Expert Committee: Monographs–Excipients
No. of Commenters: 2
Comment Summary #1: In the test for *Organic Colors and Lakes*, the commenters recommended revising the specification from “No peak greater than three times the noise level is found” to “Absorbance in the range of 350–750 nm is NMT 0.01 AU” because the data are in support of the latter specification.
Response: Comment incorporated.
Expert Committee-initiated Change #1: The Expert Committee deleted the specification for Antimony (Sb) because this element is not listed in the *General Chapter proposal <232> Elemental Impurities—Limits* in *PF* 37(3) and is not a specification required in 21 CFR 73.1200 which describes the requirements for synthetic iron oxide for use in drug products in the United States.

Monograph/Section: Fosfomycin Tromethamine***/***Organic Impurities
Expert Committee: Monographs–Small Molecules 1
No. of Commenters: 1
Comment Summary #1: The commenter requested including additional specified impurities with their corresponding limits under the test for *Organic Impurities*.
Response: Comment not incorporated. The Expert Committee is willing to consider future changes to the monograph upon receipt of the necessary supporting data.

Monograph/Section: Levetiracetam Oral Solution/Multiple Sections
Expert Committee: Monographs–Small Molecules 4
No. of Commenters: 4
Comment Summary #1: The commenter requested the acceptance criteria for *pH* be widened from 5.0-6.0 to 5.0-6.3 to be consistent with the FDA-approved specifications.
Response: Comment incorporated.
Comment Summary #2: The commenter requested the limit for total impurities in the *Organic impurities* test be widened from NMT 0.6% to NMT 1.0% to be consistent with FDA-approved specifications.
Response: Comment incorporated.

Comment Summary #3: The commenter informed that a process impurity, levetiracetam related compound B elutes at the void volume and hence cannot be quantitated.
Response: Comment not incorporated. Levetiracetam related compound B is a process impurity and is not monitored in the monograph.
Comment Summary #4: The commenter requested *Organic impurities* not be implemented because chromatographic injections of the *System suitability solution* failed to show the proper number of analyte peaks.
Response: Comment not incorporated. The proposed procedure is supported by the sponsor's validation data.
Comment Summary #5: The commenter requested to correct the chemical formula and molecular weight for USP Levetiracetam Related Compound A RS in the *USP Reference Standards* section.
Response: Comment incorporated.

Monograph/Section : Metacresol/Organic Impurities
Expert Committee: Monographs–Small Molecules 3
No. of Commenters: 1
Comment Summary #1: The commenter requested the diluent for solution preparations be changed from methanol to ethanol.
Response: Comment not incorporated because the use of methanol is supported by the validation data and is suitable for the analysis.

Monograph/Section: Morphine Sulfate Injection/Multiple Sections
Expert Committee: Monographs–Small Molecules 2
No. of Commenters: 1
Comment Summary #1: The commenter requested retaining the text in the *Labeling* section stating "Injection containing antioxidant or antimicrobial agents includes in its labeling its routes of administration and the statement that it is not for intrathecal or epidural use." The commenter also requested deleting the proposed text stating "For intravenous use only. Fatal if given by other routes" because it does not reflect subcutaneous or intramuscular routes of administration which are not fatal when the recommended dose is administered.
Response: Comment incorporated.
Comment Summary #2: The commenter requested retaining the text under the *Bacterial Endotoxins Test* stating "if labeled for intrathecal use it contains NMT 14.29 USP Endtoxin Units/mg of morphine sulfate" because several morphine sulfate drug products in the *USP-NF* are approved for intrathecal use.
Response: Comment incorporated.

Monograph/Section: Niacin Extended-Release Tablets/Performance Tests, Dissolution <711>
Expert Committee: Monographs–Dietary Supplements
No. of Commenters: 1

Comment Summary #1: Since the dissolution has multiple time points (1, 3, 6, 9, 12, and 20 hrs), volume correction has to be considered in calculation for respective time points.
Response: Comment incorporated

Monograph/Section: Olmesartan Medoxomil/Multiple Sections
Expert Committee: Monographs–Small Molecules 2
No. of Commenters: 3
Comment Summary #1: The commenters reported that the resolution between olmesartan medoxomil and olmesartan medoxomil related compound A in the test for *Organic Impurities* may vary depending on the pH of the mobile phase, and requested to revise the resolution requirement from NLT 5 to NLT 3.
Response: Comment not incorporated because the proposed system suitability requirements are consistent with the sponsor's validation data and are suitable for analysis.
Comment Summary #2: The commenter requested to replace the current procedure for the *Assay* with the HPLC procedure used for *Organic impurities*.
Response: Comment not incorporated. The Expert Committee is willing to consider future changes to the monograph upon receipt of the necessary supporting data.
Comment Summary #3: The commenter reported poor peak shape and reproducibility due to the use of acetonitrile as a diluent in sample preparation. The commenter also indicated that the high ratio of acetonitrile in the *Mobile phase B* may cause precipitation of the phosphate.
Response: Comment not incorporated. The proposed sample preparation and mobile phase are consistent with the sponsor's validation data and are suitable for analysis.
Comment Summary #4: The commenter requested USP to consider developing reference standard(s) for the identification of impurities.
Response: Comment not incorporated. The Expert Committee is willing to consider future changes to the monograph when the new reference materials become available.
Expert Committee-initiated Change #1: The specification for total unidentified impurities is deleted. The Expert Committee decided that this specification is not suitable for inclusion in the public standard. Manufacturers are not precluded from having internal specification for total unidentified impurities.

Monograph/Section: Polyoxyl Stearate/Melting Range or Temperature <741>
Expert Committee: Monographs–Excipients
No. of Commenters: 1
Comment Summary #1: The commenter requested changing the specification for melting range or temperature for Polyoxyl 75 Stearate from "56–59°" to "53–59°" because the data support the specification "53–59°".
Response: Comment incorporated.

Monograph/Section: Polysorbate 20/Fats and Fixed Oils, Peroxide Value <401>
Expert Committee: Monographs–Excipients

No. of Commenters: 1
Comment Summary #1: The commenter recommended harmonizing the text of the *Peroxide Value* test with the presentation in the Polysorbate 80 monograph because this will provide consistency, clarity, and correct the solution preparation (in carbon dioxide-free water).
Response: Comment incorporated.

Monograph/Section: Polysorbate 40/Fats and Fixed Oils, Peroxide Value <401>
Expert Committee: Monographs–Excipients
No. of Commenters: 1
Comment Summary #1: The commenter recommended harmonizing the text of the *Peroxide Value* test with the presentation in the Polysorbate 80 monograph because this will provide consistency, clarity and correct the solution preparation (in carbon dioxide-free water).
Response: Comment incorporated.

Monograph/Section: Polysorbate 60/Fats and Fixed Oils, Peroxide Value <401>
Expert Committee: Monographs–Excipients
No. of Commenters: 1
Comment Summary #1: The commenter recommended harmonizing the text of the *Peroxide Value* test with the presentation in the Polysorbate 80 monograph because this will provide consistency, clarity and correct the solution preparation (in carbon dioxide-free water).
Response: Comment incorporated.

Monograph/Section: Ritonavir/Assay
Expert Committee: Monographs–Small Molecules 1
No. of Commenters: 1
Comment Summary #1: The commenter requested deleting *Solution C* because it is no longer used as a component in the mobile phase gradient table.
Response: Comment incorporated.

Monograph/Section: Sildenafil Citrate/Multiple Sections
Expert Committee: Monographs–Small Molecules 4
No. of Commenters: 4
Comment Summary #1: The commenter requested using USP Sildenafil Citrate RS instead of the sample to prepare all solutions used to establish system suitability, in order to avoid confusion when performing multi-lot analyses.
Response: Comment not incorporated. The Sildenafil Citrate monograph was developed in conjunction with the European Directorate for the Quality of Medicines (EDQM) as part of a prospective harmonization pilot study. The solution preparations are consistent with those in the *European Pharmacopoeia* monograph.

Comment Summary #2: Two commenters indicated that the *Organic impurities* procedure was not suitable for all impurities in their drug substance, or needed modification to improve specificity.
Response: No action required. USP will work with EDQM to consider future changes to the monograph when the commenters' products receive full FDA approval.
Comment Summary #3: Two commenters requested including additional specified impurities with appropriate limits.
Response: Comment not incorporated. The specified impurities and limits in the test for *Organic Impurities* in the monograph are consistent with the specifications approved by FDA. The Expert Committee is willing to consider including additional specified impurities and appropriate limits in the future when the commenters' drug products receive full FDA approval.
Comment Summary #4: The commenter indicated that 10 minutes was sufficient time to generate the sildenafil *N*-oxide impurity in the *System suitability solution* for the *Organic impurities* procedure.
Response: Comment incorporated.
Comment Summary #5: The commenter requested revising the description of the adsorbent used for the *Limit of imidazole* TLC test to clearly specify the use of HPTLC plates.
Response: Comment incorporated.
Expert Committee-initiated Change #1: The *Residue on Ignition* test was moved from the *Specific Tests* category to the *Impurities* category in the monograph, and a sample size of NLT 0.5 g was specified.
Expert Committee-initiated Change #2: The chemical name for USP Sildenafil Related Compound A RS was changed from "5-[2-Ethoxy-5-[(4-methylpiperazin-1-yl)sulfonyl]phenyl]-1-methyl-3-(2-methylpropyl)-6,7-dihydro-1*H*-pyrazolo[4,3-*d*]pyrimidin-7-one" to "5-[2-Ethoxy-5-[(4-methylpiperazin-1-yl)sulfonyl]phenyl]-1-methyl-3-(2-methylpropyl)-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one" to be consistent with the chemical name of Impurity A in the *European Pharmacopoeia* monograph.

Monograph/Section: Sumatriptan Injection/Multiple Sections
Expert Committee: Monographs–Small Molecules 4
No. of Commenters: 1
Comment Summary #1: The commenter indicated that the *Organic impurities* procedure was not suitable for all impurities in their drug product, and proposed a replacement *Organic Impurities* procedure. In addition, the commenter requested widening the limits for unspecified degradation product organic impurities and for total impurities, to make them consistent with their FDA-approved specifications.
Response: The proposed procedure for *Organic Impurities* from *PF* 37(5) [Sept.-Oct. 2011] is deferred from becoming official in the *Second Supplement to USP 35–NF 30*. A revised procedure will be republished in a future issue of *PF*.
Comment Summary #2: The commenter requested the limit for *Bacterial Endotoxins* test be widened from NMT 20 to NMT 29.2 USP endotoxin units/mg to be consistent with FDA-approved specifications.
Response: Comment incorporated.

Monograph/Section Vitamin E/Multiple Sections.
Expert Committee: Monographs–Dietary Supplements
No. of Commenters: 2
Comment Summary #1: The commenter requested adding the system suitability requirements (including the relative standard deviation) to the alpha tocopheryl acetate and alpha tocopheryl acid succinate tests with a cross reference to that in the alpha tocopherol test.
Response: Comment incorporated.
Comment Summary #2: The commenter requested that in order to optimize the chromatographic analysis, the *Standard solution* and *Sample solution* in the *Assay* for alpha tocopheryl acid succinate must be derivatized, similar to those described in the *European Pharmacopoeia's* (*EP*) dl-Alpha tocopheryl hydrogen succinate monograph.
Response: Comment incorporated by using the derivatization procedure described in the *EP* monograph for dl-Alpha tocopheryl hydrogen succinate.

Monograph/Section: Voriconazole/Multiple Sections
Expert Committee: Monographs–Small Molecules 1
No. of Commenters: 1
Comment Summary #1: The commenter requested to use *System suitability solution A* instead of the *Standard solution* to establish the retention time agreement under *Identification–B* because it has the same concentration of the analyte as the *Sample solution*.
Response: Comment incorporated.
Comment Summary #2: The commenter requested replacing USP Sodium Chloride RS with a reagent grade sodium chloride in the test for *Voriconazole Related Compound F* because it is not used for quantitation but only to establish resolution requirement for system suitability.
Response: Comment incorporated.
Comment Summary #3: The commenter requested specifying that the relative retention time of acetate ion peak is provided for information only and is not a part of system suitability requirements in the test for *Voriconazole Related Compound F*.
Response: Comment incorporated.
Comment Summary #4: The commenter requested revising the preparation of the standard and sample solutions in the test for *Voriconazole Related Compound B*, to replace sonication with dissolving the material first in a small amount of acetonitrile.
Response: Comment incorporated.
Comment Summary #5: The commenter requested correcting the molecular weight of USP Voriconazole Related Compound B RS from 331.32 to 349.31 in <11> *Reference Standards.*
Response: Comment incorporated.