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

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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
<181> *Identification – Organic Nitrogenous Bases*
<698> *Deliverable Volume*

Monographs
Anagrelide Capsules
Bisacodyl
Conjugated Estrogens
Epinephrine
Estazolam Tablets

Esterified Estrogens
Esterified Estrogens Tablets
Estradiol Vaginal Inserts
Eugenol
Famotidine Injection
Famotidine Tablets
Famotidine for Oral Suspension
Felbamate
Felbamate Oral Suspension
Felbamate Tablets
Haloperidol Injection
Haloperidol Oral Solution
Homosalate
Itraconazole
Lactulose Solution
Mirtazapine Orally Disintegrating Tablets
Quinine Sulfate
Sincalide for Injection
Triazolam
Verapamil Hydrochloride Extended-Release Capsules

General Chapters

General Chapter/Sections:	<660> *Containers—Glass*/Multiple Sections
Expert Committee:	General Chapters–Packaging, Storage and Distribution
No. of Commenters:	4

Glass Grains Test
Comment Summary #1: The commenter requested defining Type I and II Glass in Table 1.
Response: Comment Incorporated.
Comment Summary #2: The commenter requested that USP keep the Powdered Glass Test.
Response: Comment not incorporated. There is no significant difference in the USP Powdered Glass Test and EP Glass Grains Test.
Comment Summary #3: The commenter requested adding the Ball Mill-Beaker as an alternative to the mortar and pestle.
Response: Comment incorporated.
Comment Summary #4: The commenter requested deleting “and, if required, its equivalent in alkali extracted, calculated as µg of sodium oxide per gram of glass grains: 1 mL of 0.02M hydrochloric acid is equivalent to 620 mg of sodium oxide” from the Titration section of the glass Grains Test because this statement can lead to a misunderstanding of the Flame Photometric Surface Test.
Response: Comment incorporated.

Surface Glass Test

Comment Summary #5: The commenter requested grandfathering existing Type III containers in the event that they do not meet the Surface Hydrolytic Test.

Response: Comment not incorporated. USP does not provide for grandfathering of any provision.

Comment Summary #6: The commenter requested removing the requirement to conduct the Surface Glass Test to qualify glass as Type III.

Response: Comment not incorporated. Without the Surface Glass Test, there is nothing to establish the quality of the inner surface of Type III glass. Glass surface quality is a combination of the glass formulation and the manufacturing conditions.

Comment Summary #7: The commenter questioned the accuracy and reliability of the Surface Glass Test.

Response: Comment not incorporated. Companies in the US have been performing the Ph. Eur. Surface Glass test for many years without any issues regarding the accuracy and reliability of the test.

Comment Summary #8: The commenter suggested that the test results show a disconnect between the Glass Grains Test and the Surface Glass Test.

Response: Comment not incorporated. This is the purpose of the Surface Glass Test. If the results were the same, one could rely solely on the Glass Grains Test to establish the inner surface quality. The quality of the inner surface produced depends not only on the glass composition, but also on control of the forming process. The drug contacts the inner surface, not the glass matrix.

Comment Summary #9: The commenter suggested that some glass containers may remain unused in customer inventory for several years, and asked if customers are required to re-test inventories with new standards.

Response: Comment not incorporated. All changes to the chapter have a date which indicates when it will become effective. Once effective, the glass containers must comply with all of the specifications in the chapter.

Comment Summary #10: The commenter suggested that the maximum volume of HCL listed in Table 4 under Type II is incorrect and should be: “express titration values of more than or equal to 1.0 ml to 1 decimal place.”

Response: Comment incorporated.

Surface Etching Testing

Comment Summary #11: The commenter requested adding the following warning about the hazardousness of hydrofluoric acid: “CAUTION — Hydrofluoric acid is extremely aggressive. Even tiny quantities can cause life threatening injuries.”

Response: Comment incorporated.

General Chapter/Section: <731> *Loss on Drying*
Expert Committee: General Chapters–Physical analysis
No. of Commenters: 1
Comment Summary #1: The commenter requested eliminating the reference to the General Notices in the new text. The information in this revised General Chapter takes precedence over the General Notices, so the reference may be confusing and unnecessary.
Response: Comment incorporated.

General Chapter/Section: <1032> *Design and Development of Biological Assays*/Multiple Sections
Expert Committee: Statistics
No. of Commenters: 13

General
Comment Summary #1: The commenter indicated that the statistical principles described in this General Chapter may not be always aligned with other compendial references (e.g. the European Pharmacopeia). Also, harmonization efforts should be undertaken.
Response: Comment not incorporated. The chapter acknowledges that a variety of sound scientific methods and perspectives exist, however, the intent of the authors is that publication of the chapters will contribute to further refinements and help diminish controversy regarding best bioassay practices.
Comment Summary #2: The commenter suggested it would be helpful if case study examples that illustrate the application of some of the complex concepts described in this chapter were posted on the USP website.
Response: USP intends to develop and post such a resource on the USP website. At this time, a 4PL bioassay simulator is available for use at: http://www.usp.org/uspnf/compendialtools.html.

Introduction
Comment Summary #3: The commenter indicated that the following statement in the chapter can be misconstrued because the assay does have to reach a range that ensures it meets system suitability and acts as a control: “Relative potency is determined by comparison of the Test to the Standard, which means that the assay does not need to achieve a specific observable response.”
Response: The statement in question was changed to delete the assertion that the assay does not need to achieve a specific observable response.

Bioassay Fitness for Use
Comment Summary #4: The commenter indicated that the following statement is incorrect because the full potency range should be evaluated: “For bioassays used to support stability…it may be useful to assess similarity using the asymptote of maximum response.”

Response: Chapter text was changed to support the assessment of similarity using the entire concentration-response curve, including the asymptotes.
Comment Summary #5: The commenter requested including more detailed guidance on significant figures.
Response: Comment incorporated. Detailed guidance on significant figures is included in a section of General Chapter <1033>.
Comment Summary #6: The commenter suggested that the text is too prescriptive in two parts: 1) the requirement of a bioassay to mimic a putative mechanism of action; and 2) the requirement of the bioassay to correlate with clinical efficacy.
Response: Pertinent chapter text was changed as follows: "To the extent possible, the assay should reflect or mimic the product's known or intended mechanism of action."
Comment Summary #7: The commenter indicated that the potency assay is not necessarily stability-indicating.
Response: Chapter text was modified to reflect that the potency assay *may* be used to assess stability.

Bioassay Fundamentals
Comment Summary #8: The commenter suggested the requirements for documenting the source of an assay's cell line were overly stringent.
Response: The text was modified as follows: "To the extent possible, information regarding functional and genetic characteristics of the bioassay's cell line should be documented, including details of the cell line's history from origin to banking."
Comment Summary #9: The commenter indicated that the cell banks require extensive characterization and monitoring of assay performance for purposes of quality assurance and longevity.
Response: The General Chapter was amended with the following statement: "Cell characterization and vigilance regarding aspects of assay performance that reflect on cell status are necessary to ensure the quality and longevity of cell banks for use in the QC environment."
Comment Summary #10: The commenter indicated that the word "clonal" should be deleted because most cell lines used for bioassays are not clonal, and there is no absolute need for clonality.
Response: Comment incorporated.

Linearity of Concentration-Response Data
Comment Summary #11: The commenter indicated that some usages of "linearity" and "nonlinearity" were not the appropriate terminology (e.g., Specify a measure of departure from nonlinearity…").
Response: Comment incorporated; chapter was reviewed for correct usage of terms.

Suitability Testing
Comment Summary #12: The commenter requested further elaboration of using RSSE in the evaluation of parallelism.
Response: RSSE is elaborated in Section 4.7, Suitability Testing.

Outliers
Comment Summary #13: The commenter suggested that further consideration of determining what constitutes the “rare” occurrence of an outlier and appropriate outlier investigation should be undertaken.
Response: The meaning of “rare” was elaborated in regard to distributional assumptions pertaining to the data, and associated investigations of possible outlying observations.

Fixed and Random Effects in Models of Bioassay Response
Comment Summary #14: The commenter indicated that there were few independent realizations of the random effects in the text addressing components of variation and specifying variance structure.
Response: Comment incorporated. Clarifying text added as appropriate.

[Bioassay] Development
Comment Summary #15: The commenter indicated that the Process Mapping and Risk Analysis section has value but it may not be easy to understand for non-QbD-trained biologists.
Response: Any sense of the chapter’s making prescriptive comments regarding utilization of process mapping and risk analysis was removed.

Data Analysis during Assay Development
Comment Summary #16: The commenter indicated that the requirement for constraining the curves before calculating the relative potency is missing.
Response: Comment not incorporated; this is addressed in both General Chapters <1032> and <1033>.

Bioassay Validation
Comment summary #17: The commenter requested that a stage-wise validation approach be considered.
Response: Comment incorporated. The chapter was amended to state that a stage-wise approach to validation may be considered.

General Chapter/Sections:	General Chapter <1033> *Biological Assay Validation/Multiple Sections*
Expert Committee:	Statistics
No. of Commenters:	2

General
Comments regarding phrasing and terminology were accepted when they were not in conflict with other chapters, or were noted below.

Introduction

Comment Summary #1: The commenter questioned staged validation, the timing of robustness studies, and readiness for validation in both the *Introduction* and throughout the chapter.

Response: Comment incorporated. Specific sections were modified to emphasize the need to address important assay operating characteristics throughout bioassay development.

Comment Summary #2: The commenter requested further distinctions between specificity and selectivity.

Response: Comment incorporated. The following text was added to section 2.4 on specificity: “Specificity may also refer to the capacity of the bioassay to distinguish between different but related biopharmaceutical molecules. An understanding of the molecule, its related forms, and other opportunities for related molecules to be introduced into the bioassay should be considered in assessing specificity of the method.”

Fundamentals of Bioassay Validation

Comment Summary #3: The commenter indicated that standards are assigned unitages other than 1.00.

Response: Comment incorporated. The chapter already indicates that sometimes the standard is assigned units based on some other property such as protein content. However, a statement is now included to convey that units of working standards might change with calibration.

Comment Summary #4: Comments were made in this section and others regarding the use of design of experiment (DOE).

Response: While not explicitly described, the application of best practices in the use of DOE is expected. Risk analysis should be utilized to identify key factors that are studied. Additionally, DOE is proposed in <1033> to organize the design by factors that change in the long term, not to identify significant factors. Thus, highly fractionated designs which lack “resolution” to identify interactions and the use of less structured designs using more than two levels of a factor are encouraged.

Bioassay Validation Protocol

Comment Summary #5: The commenter suggested that reassessment of run or sample failures should only be done under clearly defined conditions.

Response: Comment incorporated. The following text was included: “Run or sample failures may be reassessed according to criteria which have been defined in the validation protocol.”

Comment Summary #6: The commenter suggested that a validation failure should be followed by an investigation.

Response: Comment incorporated. The following text was included: “Steps should be taken upon failure to meet a target acceptance criterion should be specified in the validation protocol.”

Documentation of Bioassay Validation Results

Comment Summary #7: The commenter indicated that “Format” is only implicitly defined.

Response: Comment incorporated. The following text was included: “(such as *an increase in the replication strategy*).”

Comment Summary #8: The commenter requested that including raw validation data should not be mandatory.

Response: Comment incorporated. The following text was included: “The report could include the raw data and intermediate results (e.g., variance component estimates should be provided in addition to overall intermediate precision) which would facilitate reproduction of the bioassay validation analysis by an independent reviewer.”

Bioassay Validation Design

Comment Summary #9: The commenter suggested sources of variability from sampling should not be included in bioassay validation.

Response: Comment incorporated. The following text was excluded: “Validation samples should be randomly selected from the sources from which test articles will be obtained during routine use.”

Validation Strategies for Bioassay Performance Characteristics

Comment Summary #10: The commenter suggested that LOQ is important for vaccine potency testing.

Response: Comment incorporated. The following text was included: “These may be relevant, however, to the validation of an ancillary assay such as one used to score responders or measure response in conjunction with an in vivo potency assay.”

Comment Summary #11: The commenter indicated that “R” is required for linearity (trend in bias) in ICH Q2.

Response: Comment not incorporated. “R” is not an accurate measurement of linearity. The chapter attempts to introduce more relevant measures of bioassay performance.

Comment Summary #12: Several commenters indicated that the equations for the CV of a log-normal distribution are incorrect.

Response: Comment incorporated and addressed with a change in notation and appendix. The measure of precision was changed to percent geometric coefficient of variation (%GCV) with origins in the literature. In addition, an appendix was added to discuss the differences between %CV and %GCV.

Validation Target Acceptance Criteria

Comment Summary #13: The commenter indicated that process capability analysis is difficult to perform during development.

Response: Comment not incorporated. This is suggested as a possible basis for setting target acceptance criteria. Methods used by practitioners will vary depending upon availability of relevant information.

Comment Summary #14: The commenter indicated that the process capability index is incorrect.

Response: Comment incorporated. The process capability index Cpk has been replaced by the more appropriate index Cpm. The inclusion of the relative bias term is a commonly accepted statistical practice.

Statistical Considerations

Comment Summary #15: Several commenters suggested that the number of significant digits be expanded.

Response: Comment incorporated. The section on significant digits was modified to de-emphasize the impact on specifications. The example data was expanded to 4 decimal places, and calculations were appropriately revised to capture the information in the validation data.

Comment Summary #16: Several comments were made regarding the sample size calculation as it relates to uses other than validation and to appropriate error rates.

Response: Comment not incorporated. Comments regarding method transfer (paired results) and statistical error rates are beyond the scope of General Chapter <1033>.

Comment Summary #17: The commenter suggested that the interpretation of the confidence interval is statistically incorrect.

Response: Comment not incorporated. The 90% CI is used in the context of equivalence testing. The interpretation is commonly accepted in this context.

Comment Summary #18: The commenter indicated that the sample size formula does not account for within-run replication.

Response: Comment incorporated. The following text was included: “Note that the calculation of sample size assumes that a single replication set of the validation samples will be performed in each validation run. The use of multiple replication sets will provide valuable information regarding intra-run and inter-run variability, and will decrease the risk of failing to meet the validation target acceptance criteria.”

Comment Summary #19: The commenter requested that consideration of bias should not be included in the sample size formula.

Response: Comment not incorporated. Inclusion of “bias” in the sample size formula is protection related to the “measured bias” during the validation. It is not related to “offsetting” the impact of bias during normal application of the bioassay.

Bioassay Validation Example

Comment Summary #20: The commenter indicated that Cpk and sample size using logs is confusing, and should instead use unlogged data.

Response: Comment not incorporated. The arithmetic should be performed in the log scale due to the log-normal nature of the data and the specifications.

Comment Summary #21: The commenter indicated that process variability cannot be equal to zero, and that this is not part of bioassay validation.

Response: Comment not incorporated. The term for process variability is appropriate to assess the overall manufacturing variability. While the example uses 0 for simplicity, the user is encouraged to seek sources of information which will make the calculation more accurate for their application.

Comment Summary #22: Several comments were received on the basis of two titrations of the test material and one of the standard.

Response: Comment incorporated. The following text was included: “A run consists of a full dilution series of the Standard as described in the bioassay operating procedure, together with two independent dilution series of each Test sample.”

Intermediate Precision
Comment Summary #23: The commenter requested that the method for obtaining the upper bound on %GCV be described.
Response: Comment not incorporated. A description of this calculation is beyond the scope of the chapter. A reference is given for Confidence Intervals for Variance Components.
Comment Summary #24: The commenter requested that a method for determining an acceptance criterion on trend in relative bias be given.
Response: Comment not incorporated. Examples of approaches for establishing acceptance criterion on trend in relative bias are beyond the scope of the chapter.

General Chapter/Section(s):	<1034> *Analysis of Biological Assays*/Multiple Sections
Expert Committee:	Statistics
No. of Commenters:	11

General
Comment Summary #1: The commenter indicated there is overlap between General Chapter <1034> *Analysis of Biological Assays* and General Chapter <1032> *Design and Development of Biological Assays*, therefore, there is a need to ensure the two chapters are consistent.
Response: Comment incorporated. The chapters were reviewed for unnecessary reiteration, and material was deleted where it was fully developed elsewhere. Some material does remain in multiple sections within the chapters where this is warranted by the bioassay contexts. Some overlap is intended so the chapters can be read separately. Prior to publication in *PF* 36(4) for public comment, the authors of these General Chapters reviewed the two chapters for consistency and made edits accordingly.
Comment Summary #2: The commenter indicated that <1034> (and <1032> and <1033>) require additional efforts, resources, and time that exceed their benefit. In particular, the chapter recommends modeling effects that can be eliminated by sound bioassay practice. The modeling could require individual software solutions rather than the use of commercially-available software.
Response: Comment not incorporated. General Chapters <1034> (and <1032> and <1033>) reference current best practices. They are all above <1000> chapters, so they are not mandatory. It is understood that companies will not immediately switch where these chapters are inconsistent with the company’s current practices. Also, sound bioassay practice leads to design elements that should be included in the model. These elements can be ignored in favor of simpler models, but the assay may be less precise than it could be.

Overview of analysis of bioassay data
Comment Summary #3: The commenter indicated that a constrained model (constrained to be parallel) needs to be fit prior to estimating relative potency.
Response: Further text was added requiring this to be done.
Comment Summary #4: The commenter indicated that using the term “fails” for assays that do not satisfy system suitability is inappropriate. It is better to use “fails system suitability”.
Response: Comment incorporated.

Analysis Models
Comment Summary #5: The commenter indicated that the language on choice of parameters for assessing parallelism is too restrictive. Additional references should be added.
Response: Comment incorporated. The text was changed to be less restrictive, however, references to a single method were not added because it could appear as an endorsement. The language, as changed, permits all options.
Comment Summary #6: The commenter requested that more time be spent on describing the choice of a five-parameter sigmoidal model and, in particular, assessing whether the additional parameter (vs. a 4PL model) was needed.
Response: Comment not incorporated. The language used was reviewed to ensure that the use of the 5PL model was not precluded.

Confidence Intervals
Comment Summary #7: The commenter questioned the accuracy of text regarding heterogeneity tests and the assertion that lack of statistical significance is not evidence for homogeneity.
Response: Comment not incorporated. The assertion that lack of statistical significance is not evidence for homogeneity arises from discussions in the chapters pertaining to the fundamental bases of difference and equivalence testing. Tests of homogeneity and normality, like tests for parallelism, are similarly subject to these considerations. The Panel developed arguments in support of the merits of equivalence testing throughout the chapters.

General Chapter/Sections:	General Chapter <1105> *Surface Plasmon Resonance*/Multiple Sections
Expert Committee:	General Chapters–Biological Analysis
No. of Commenters:	2

General
Comment Summary #1: The commenter requested expanding the qualitative studies section to include more assay troubleshooting and background, with comparisons to other assays.
Response: Comment not incorporated. The chapter’s scope is focused on quantitative methods for the target audience and includes sufficient information for qualitative methods.

Introduction

Comment Summary #2: The commenter requested adding information regarding screening for immobilization conditions that assure proper preconcentration of molecules on the chip surface.

Response: Comment not incorporated. Conditions are often chip dependent and manufacturers' suggestions should be followed.

Comment Summary #3: The commenter requested that the chapter should allow suitable flexibility for modern testing applications, giving an example that an Rmax range of 5-50 RU seemed low.

Response: Comment not incorporated. Because of the capabilities of modern commercial SPR biosensors (baseline noise < 1 RU), an Rmax of <50 RU is a reasonable recommendation. Note also that this chapter is an informational chapter providing guidance and does not contain mandatory requirements.

Immunogenicity Assessment

Comment Summary #4: The commenter requested that this section be expanded to include vaccines.

Response: Comment not incorporated. This section describes one example application of the technique, for unwanted immunogenicity of biotechnology products. The Expert Panel and Committee selected the three most common uses of this method and users should be able to apply some of the principles to their particular application. It is not intended to provide every possible example for use.

Comment Summary #5: The commenter requested changing text regarding assay cut-point determination to be aligned with wording in 2009 FDA Draft Guidance for Industry Assay Development for Immunogenicity Testing of Therapeutic Proteins.

Response: Comment incorporated. The text was changed to read as follows: "… and set the cut-point at 95% (equivalent to the mean plus 1.645 times the standard deviation for a normal distribution)."

Comment Summary #6: The commenter requested that truncation analysis to map epitopes should not be recommended because it can lead to inconclusive results.

Response: Comment incorporated. The following text was included: "It should be kept in mind that point mutations and truncations not only influence the primary sequence of a protein, but can also influence the tertiary structure (i.e. folding, conformation) of a protein."

Concentration Analysis

Comment Summary #7: The commenter requested including a separate discussion on competition/inhibition assays.

Response: Comment incorporated.

Comment Summary #8: The commenter requested adding more guidance regarding the choice of signal (i.e., rate of binding vs. amount bound) for the reference standard curve.

Response: Comment incorporated.

Kinetic and Affinity Analysis
Comment Summary #9: The commenter requested adding more information on other complex kinetic and single-cycle kinetic models.
Response: Comment not incorporated. Current data fitting discussion meets the needs of the majority of SPR users and more complex kinetic models are outside of the scope of this General Chapter.

Use of SPR in a Regulated Environment
Comment Summary #10: The commenter requested including definitions of EC_{50}, asymptotes, and parallelism in the context of SPR.
Response: Comment incorporated.

General Chapter/Section: <1231> *Water for Pharmaceutical Purposes*/Multiple Sections
Expert Committee: General Chapters–Chemical Analysis
No. of Commenters: 3

General
Comment Summary #1: The commenter suggested that the subject matter in the chapter is too broad. The commenter requested including: requirements for each type of water within the monograph and deletion of multiple general chapters related to water; nonmonographed water in a different chapter or section; and transference of some specific sections into a different chapter.
Response: Comment not incorporated in this revision. Proposals were deferred to the Expert Panel tasked with the revision of General Chapter <1231>.

Nonmonographed Waters – LAL Reagent Water
Comment Summary #2: The commenter requested replacing the current title “LAL Reagent Water” with “Water for BET” in order to be consistent with the terminology used in the harmonized General Chapter <85> *Bacterial Endotoxins Tests* published in USP 33.
Response: Comment incorporated.
Comment Summary #3: The commenter requested retaining the name “LAL Reagent Water” within the description of this water instead of “endotoxin-free water” because it is widely used in the endotoxin testing community and water of that name is distributed by LAL manufacturers. Also, it is not feasible to demonstrate the absolute absence of any analyte.
Response: Comment incorporated.
Comment Summary #4: The commenter requested replacing the description of “This is usually Water for Injection” with “This is often Water for Injection” because LAL reagent manufacturers provide LAL reagent water that does not claim to be Water for Injection.
Response: Comment incorporated.

Nonmonographed Waters – High Purity Water
Comment Summary #5: The commenter indicated that there is a missing relation sign in the description of this water.
Response: Comment incorporated.
Comment Summary #6: The commenter indicated that there is a typographical error in the description of this water, and suggested changing “Megohm” to “Megaohm.”
Response: Comment not incorporated. Megohm (or Mohm) is the correct expression as a compound word.

General Chapter/Section(s): <1644> *Theory and Practice of Electrical Conductivity Measurements of Solutions*/Multiple Sections
Expert Committee: General Chapters—Chemical Analysis
No. of Commenters: 1

General
Comment Summary #1: The commenter requested a number of editorial changes throughout in order to clarify the text.
Response: Comment incorporated with modifications. There is no substantive change in content.
Expert Committee-initiated Change #1: Additional editorial changes were incorporated to clarify some redundancies and the organization of the information.

Calibration
Comment Summary #2: The commenter requested the inclusion of the statement: “A conductivity measuring system can be calibrated as a system or by separate calibration of its components”.
Response: Comment not incorporated because a conductivity system cannot be properly calibrated as a system. A properly calibrated conductivity system must be calibrated by its components.

Monographs

Monograph/Section: Allantoin/Optical Rotation
Expert Committee: Monographs–Small Molecules 3
Expert Committee-initiated Change #1: The test for *Optical Rotation* is deleted. The Expert Committee decided that this test does not add value to the monograph because Allantoin is only available as a racemic mixture. The *Sample solution* under *Acidity and Alkalinity* is revised to remove the cross-reference to the test for *Optical Rotation*.

Monograph/Section: Amiloxate/Assay
Expert Committee: Monographs–Small Molecules 3
Expert Committee-initiated Change #1: In the *Assay,* the solvent for the *Sample solution* is changed from acetone to *tert*-butyl methyl ether to be consistent with the solvent for the *Standard solution*.

Monograph/Section: Anagrelide Hydrochloride/Multiple Sections
Expert Committee: Monographs– Small Molecules 2
No. of Commenters: 4
Comment Summary #1: The commenter indicated that one of the impurities increases in the presence of 0.1*N* hydrochloric acid, and requested to use dimethyl formamide as a diluent in preparation of *Sample solution* in the *Organic impurities* section.
Response: Comment not incorporated. The solution stability data indicate that the sample is stable in presence of small quantities of 0.1N hydrochloric acid. In addition, the use of dimethyl formamide may cause interference at the wavelength specified in the method.
Comment Summary #2: The commenter requested to revise the pH of *Mobile Phase* from 2.5 to 3.0.
Response: Comment not incorporated because the solution stability data indicate that the sample is stable at pH 2.5.
Comment Summary #3: The commenter requested to revise the storage conditions from “store at room temperature” to “store in a cold place.”
Response: Comment incorporated.
Comment Summary #4: The commenter requested to revise the relative standard deviation, under *Organic impurities*, from NMT 2.0% to NMT 10.0%.
Response: Comment incorporated.
Comment Summary #5: The commenter requested to correct the requirement for column efficiency under *Assay* and *Organic impurities* from NMT 3000 theoretical plates to NLT 3000 theoretical plates.
Response: Comment incorporated.

Monograph/Section: Betadex Sulfobutyl Ether Sodium/Average Degree of Substitution
Expert Committee: Monographs–Excipients
No. of Commenters: 1
Comment Summary #1: The commenter requested specifying capillary electrophoresis method at pH 8.1.
Response: Comments not incorporated. It is necessary to adjust the pH because it allows the user to meet system suitability requirements depending on the system in use.

Monograph: Cefamandole Nafate
Expert Committee: Monographs–Small Molecules 1
No. of Commenters: 1
Comment Summary #1: The commenter indicated that products containing Cefamandole Nafate are no longer marketed in the US.
Response: No action required. There is value in maintaining an official public standard for Cefamandole Nafate.

Monograph: Cefamandole Nafate for Injection
Expert Committee: Monographs–Small Molecules 1
No. of Commenters: 1
Comment Summary #1: The commenter indicated that Cefamandole Nafate for Injection is no longer marketed in the US.
Response: No action required. There is value in maintaining an official public standard for Cefamandole Nafate for Injection.

Monograph: Cefpiramide
Expert Committee: Monographs–Small Molecules 1
No. of Commenters: 1
Comment Summary #1: The commenter indicated that products containing Cefpiramide are no longer marketed in the US.
Response: No action required. There is value in maintaining an official public standard for Cefpiramide.

Monograph: Cefpiramide for Injection
Expert Committee: Monographs–Small Molecules 1
No. of Commenters: 1
Comment Summary #1: The commenter indicated that Cefpiramide for Injection is no longer marketed in the US.
Response: No action required. There is value in maintaining an official public standard for Cefpiramide for Injection.

Monograph/Section: Celecoxib/Multiple Sections
Expert Committee: Monographs–Small Molecules 2
No. of Commenters: 2
Comment Summary #1: The commenter requested changing the resolution criterion under *Organic Impurities* and *Assay* from NLT 1.8 to NLT 1.5.
Response: Comment not incorporated. The resolution requirement of NLT 1.8 is supported by the validation data and is suitable for the analysis.
Comment Summary #2: The commenter requested revising the pH range of the *Buffer* under *Organic Impurities* and *Assay* from "± 0.1" to "± 0.2", to make it consistent with the *European Pharmacopoeia* monograph.
Response: Comment incorporated.
Comment Summary #3: The commenter requested that sonication be deleted from the *Sample solution* preparation under *Organic Impurities* and *Assay* to make them consistent with the *European Pharmacopoeia* monograph.
Response: Comment incorporated.

Monograph/Section: Cetirizine Hydrochloride Tablets/Multiple Sections
Expert Committee: Monographs–Small Molecules 4
No. of Commenters: 5
Comment Summary #1: Several commenters requested the limit for cetirizine lactose ester be widened from NMT 0.2% to NMT 0.40% to be consistent with FDA-approved specifications.

Response: Comments incorporated.
Comment Summary #2: The commenter requested the limit for cetirizine lactose ester be widened to NMT 0.5%.
Response: Comments not incorporated. The Expert Committee will consider revising the limit once the drug product under FDA review receives full approval.
Comment Summary #3: The commenter requested the limit for total degradation products be widened from NMT 0.5% to NMT 0.8% to be consistent with FDA-approved specifications.
Response: Comment incorporated.
Comment Summary #4: The commenter requested that a second *Identification* test be added 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.
Comment Summary #5: The commenter requested that a test for *Water Determination* be added to the monograph.
Response: Comment not incorporated. The tests for water content are generally not included in the dosage form monographs as these specifications are formulation-specific.
Comment Summary #6: The commenter requested that term “orthophosphoric acid” be replaced with “phosphoric acid” throughout the monograph.
Response: Comment incorporated.
Comment Summary #7: The commenter requested that the chromatographic procedures under *Assay*, *Organic impurities* and *Dissolution* be replaced with the commenter’s single chromatographic procedure.
Response: Comment not incorporated. The Expert Committee will consider addressing this comment in a future revision.
Comment Summary #8: The commenter requested inclusion of the *Dissolution* test for their product.
Response: Comment not incorporated. The Expert Committee will consider addressing this comment in a future revision upon receipt of the necessary supporting data.

Monograph/Section: Diphenhydramine Hydrochloride/Multiple Sections
Expert Committee: Monographs–Small Molecules 4
No. of Commenters: 3
Comment Summary #1: The commenter requested the limit for any unspecified impurity be tightened from NMT 0.3% to NMT 0.10% to make it consistent with the ICH Q3A guidelines.
Response: The proposed procedure for *Organic Impurities* is deferred from becoming official in the *First Supplement to USP 35–NF 30*. A revised procedure will be republished in a future issue of PF.
Comment Summary #2: The commenters requested that the proposal to replace the HPLC-based Assay with the titration procedure be canceled because titration is not specific for diphenhydramine hydrochloride. The commenters requested that an HPLC procedure similar to that in the *Organic Impurities* be used for the *Assay*.
Response: The proposed revision to the *Assay* procedure is canceled. The HPLC-based Assay procedure will be presented in a future issue of PF.

Monograph/Section: Esomeprazole Magnesium Delayed-Release Capsules/Multiple Sections
Expert Committee: Monographs–Small Molecules 3
No. of Commenters: 1
Comment Summary #1: The commenter requested adding an *Identification* test for magnesium using atomic absorption spectroscopy.
Response: Comment not incorporated. One of the excipients in the Capsules is magnesium stearate which will interfere with the test.
Comment Summary #2: The commenter requested tightening the limit for any individual unknown impurity under *Organic impurities*.
Response: Comment not incorporated. The proposed limit is consistent with ICH Q3B. According to the information received from the sponsor, there are no safety issues to justify the tighter limit.
Expert Committee-initiated Change #1: Under *Identification–A*, the resolution requirement between the two enantiomers is changed from "NLT 1" to "NLT 1.0."
Expert Committee-initiated Change #2: In the preparation of the *Standard solution* under *Dissolution*, the volumes of USP Omeprazole RS solution and 0.25 M NaOH are specified to 0.1 mL to be consistent with the preparation of the *Sample solution*.

Monograph/Section: Estazolam/Organic Impurities
Expert Committee: Monographs–Small Molecules 4
No. of Commenters: 1
Comment Summary #1: The commenter indicated that the *Organic impurities* procedure does not separate the impurities generated by their manufacturing process, and proposed to replace it with the validated modified method which is able to separate all impurities.
Response: Comment incorporated. The proposed *Organic impurities* procedure is canceled. The commenter's proposal will be presented in a future issue of *PF*.

Monograph/Section: Estradiol Transdermal System/Drug Release
Expert Committee: Monographs–Small Molecules 4
No. of Commenters: 1
Comment Summary #1: The commenter requested that the *Medium* composition for *Drug Release Test 3* be corrected from "1% Polysorbate 40 in water" to "1% (v/v) Polysorbate 40 in water."
Response: Comment incorporated.
Comment Summary #2: The commenter requested that the preparation of the Standard *solution* under *Drug Release Test 3* be corrected so that the final concentration of Polysorbate 40 is 1% (v/v).
Response: Comment incorporated.
Comment Summary #3: The commenter requested that the duplicate version of Table L1 in *Drug Release Test 3* be deleted.
Response: Comment incorporated.
Comment Summary #4: The commenter requested that a formula for calculating the release rate of estradiol be added to the *Drug Release Test 3*.
Response: Comment incorporated.

Comment Summary #5: The commenter requested that the *Labeling* statement be changed to: “The label states the total amount of estradiol in the Transdermal System and the release rate, in mg per day, for the duration of application of one system, and states with which Drug Release Test the product complies.”
Response: Comment not incorporated. The *Labeling* statement is consistent with the USP style regarding multiple *Dissolution* and *Drug Release* tests.

Monograph/Section: Ethinyl Estradiol/Optical Rotation
Expert Committee: Monographs–Small Molecules 4
No. of Commenters: 1
Comment Summary #1: The commenter requested that sonication be added to the sample preparation procedure to ensure the complete dissolution of the sample.
Response: Comments incorporated.

Monograph/Section: Eucalyptol/Assay
Expert Committee: Monographs–Small Molecules 2
Expert Committee-initiated Change #1: The *System suitability solution* under *Assay* is revised to specify the use of USP Eucalyptol RS.

Monograph/Section: Famotidine/Multiple Sections
Expert Committee: Monographs–Small Molecules 3
No. of Commenters: 3
Comment Summary #1: The commenter requested that the proposal to replace the titration *Assay* with the HPLC procedure be canceled. The commenter indicated that the long gradient procedure is not a feasible approach for an *Assay*, and the existing titration *Assay*, although nonspecific, is acceptable when coupled with a specific procedure for *Organic impurities*.
Response: Comment incorporated. The titration-based Assay procedure is retained.
Comment summary #2: The commenter requested removing specific directions for preparing the electrode system under the *Assay*, to allow flexibility for the user.
Response: Comment incorporated.
Comment Summary #3: The commenter requested deleting the lower limit for vacuum in the *Loss on drying* test, to make it consistent with the *European Pharmacopoeia* monograph for Famotidine.
Response: Comment incorporated

Monograph/Section: Lamotrigine Tablets for Oral Suspension/Reference Standards
Expert Committee: Monographs–Small Molecules 4
No. of Commenters: 1
Comment Summary #1: The commenter indicated that USP Lamotrigine Related Compound B RS can be removed from the *Reference Standards <11>* section because it is not used in the preparation of any solution in the monograph.
Response: Comment incorporated.

Monograph/Section: Leflunomide Tablets/Dissolution
Expert Committee: Monographs–Small Molecules 2
No. of Commenters: 1
Comment Summary #1: The commenter requested to correct the name of the reagent used to prepare the *Medium* in the *Dissolution Test 1*.
Response: Comment incorporated.

Monograph/Section: Montelukast Sodium/Multiple Sections
Expert Committee: Monographs–Small Molecules 4
No. of Commenters: 12
Comment Summary #1: The commenter indicated that the *Assay* acceptance criteria are different than those approved by the FDA.
Response: Comment not incorporated. The Montelukast Sodium monograph was developed in conjunction with the *European Pharmacopoeia* as part of a prospective harmonization pilot study. The acceptance criteria are consistent with those in the *European Pharmacopoeia* monograph, and are typical for drug substance assays that employ chromatographic procedures.
Comment Summary #2: Several 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 drug products under FDA review receive full approval.
Comment Summary #3: Several commenters requested including additional specified impurities with appropriate limits, and widening the limits for organic impurities specified in the monograph.
Response: Comment not incorporated. The limits in the test for *Organic Impurities* in the monograph are consistent with the specifications approved by FDA. The Expert Committee will consider revising the specification in the future when the drug products under FDA review receive full approval.
Comment Summary #4: Two commenters requested that the trivial names for the impurities listed under *Organic impurities* be harmonized with those in the *European Pharmacopoeia* monograph for Montelukast Sodium, and that the chemical structures be provided.
Response: Comment not incorporated. The complete chemical names provided as footnotes in *Table 2* are consistent with those in the *European Pharmacopoeia* monograph. USP currently does not include the chemical structures for impurities in the monograph.
Comment Summary #5: Two commenters requested widening the specification for *Water* from NMT 4.0% to NMT 5.0%.
Response: Comment not incorporated. The Expert Committee will consider revising the specification when the drug products under FDA review receive full approval.
Comment Summary #6: The commenter indicated that the ignition step is not necessary in the *Identification–B* test for *Sodium*.
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: Three commenters requested revising the solubility in alcohol from “very soluble” to “freely soluble.”
Response: Comment incorporated. The *Description and Solubility* entry was revised to read: “freely soluble to very soluble in alcohol.”
Comment Summary #8: The commenter indicated that two impurities in their drug substance partially co-elute with the *S*-enantiomer peak in the test for *Enantiomeric purity*.
Response: No action required. The Expert Committee will consider future changes to the monograph when the drug product under FDA review receives full approval and upon receipt of the necessary supporting data.
Comment Summary #9: The commenter indicated that the *Heavy Metals* test in the monograph was not suitable for their drug substance, and requested replacing the procedure with *USP Heavy Metals <231> Method II*, or with *Heavy Metals 2.4.8, Method C* in the *European Pharmacopoeia*.
Response: Comment not incorporated. The procedure in the monograph is consistent with that in the *European Pharmacopoeia* monograph for Montelukast Sodium.
Expert Committee-initiated Change #1: The instruction to avoid exposure of the samples to moisture in the *Note* in the *Organic Impurities* test was removed.
Expert Committee-initiated Change #2: The chemical name for the sulfoxide impurity was changed from “[1-[[(*RS*)[1-[3-[(*E*)-2-(7-chloroquinolin-2-yl)ethenyl]phenyl]-3-[2-(1-hydroxy-1-methylethyl)phenyl]propyl]sulfinyl]methyl]cyclopropyl]acetic acid” to “[1-[[[1-[3-[(*E*)-2-(7-chloroquinolin-2-yl)ethenyl]phenyl]-3-[2-(1-hydroxy-1-methylethyl)phenyl]propyl]sulfinyl]methyl]cyclopropyl]acetic acid” to be consistent with the chemical name of *Impurity C* in the *European Pharmacopoeia* monograph.

Monograph: Omega-3-Acid Ethyl Esters Capsules
Expert Committee: Monographs–Dietary Supplements
No. of Commenters: 1
Comment Summary #1: The commenter requested that the requirements for absence of Staphylococcus aureus be eliminated from the monograph because this testing is typically performed for topical, not oral dosage forms
Response: Comment incorporated

Monograph/Section: Oxcarbazepine Oral Suspension/Dissolution
Expert Committee: Monographs–Small Molecules 4
No. of Commenters: 1
Comment Summary #1: The commenter indicated that the *Dissolution* method is different from those approved by the FDA.
Response: No action required. The *Dissolution* method in the proposed monograph is consistent with FDA-approved specifications.

Monograph/Section: Piperacillin for Injection/Identification
Expert Committee: Monographs–Small Molecules 1
No. of Commenters: 1
Comment Summary #1: The commenter requested revising the infrared absorption *Identification–A* because the infrared spectrum of piperacillin sodium, which is the active ingredient of the product, does not match that of USP Piperacillin RS.
Response: Comment incorporated. A sample preparation procedure was added to convert piperacillin sodium to piperacillin.

Monograph/Section: Tacrolimus/Multiple Sections
Expert Committee: Monographs–Small Molecules 1
No. of Commenters: 4
Comment Summary #1: The commenter requested revising the infrared absorption-based *Identification–A* test to specify the use of a mineral oil suspension rather than a potassium bromide pellet.
Response: Comment not incorporated. The proposed *Identification* procedure is consistent with FDA-approved specifications and is suitable for the analysis.
Comment Summary #2: The commenter requested adding a test for Identification by X-ray diffraction to the monograph.
Response: Comment not incorporated. Identification tests by X-Ray diffraction are generally not included in the USP monographs. However, if this specification is required to address a known bioavailability issue for tacrolimus drug products, the Expert Committee will consider adding this test in the future upon receipt of the necessary supporting data.
Comment Summary #3: The commenter requested retaining the *Assay* procedure previously proposed in PF 35(2) [Mar-Apr 2009].
Response: No action required. The updated Assay procedure is able to resolve tacrolimus from tacrolimus 8-epimer, a specified impurity in some impurity profiles.
Comment Summary #4: The commenter requested replacing the *Assay* procedure with a validated procedure that is able to resolve impurities in commenter's impurity profile.
Response: Comment not incorporated at this time. The Expert Committee may consider future revisions upon receipt of supporting data.
Comment Summary #5: The commenter requested deleting the 3-hour waiting period for the *Standard* and *Sample solutions* in the *Assay*.
Response: Comment not incorporated. The 3-hour waiting period prior to analysis is shown to be necessary to achieve equilibrium between tacrolimus, tacrolimus open ring, and tacrolimus 19-epimer.
Comment Summary #6: The commenter requested replacing the acetonitrile-water *Diluent* in the *Assay* with acetonitrile.
Response: Comment not incorporated because the proposed procedure is supported by validation data. The Expert Committee may consider future revisions upon receipt of supporting data.
Comment Summary #7: The commenter requested replacing *Organic Impurities Procedure 2* with the commenter's validated procedure.

Response: Comment not incorporated. The Expert Committee may consider future revisions upon receipt of supporting data.
Comment Summary #8: The commenter requested widening the limit of ascomycin in *Organic Impurities Procedure 2* from NMT 0.1% to NMT 0.50% to reflect FDA-approved specifications.
Response: Comment incorporated.
Comment Summary #9: The commenter requested adding limits for tacrolimus 19-epimer and tacrolimus open ring to *Organic Impurities Procedure 2*.
Response: Comment not incorporated. Based on the information that tacrolimus 19-epimer and tacrolimus open ring are formed in the *Sample solution* in the presence of water, the Expert Committee decided these limits are not suitable for inclusion in the public standard. Manufacturers are not precluded from having internal limits for these impurities.
Comment Summary #10: The commenter requested revising the calculation formula in *Organic Impurities Procedure 2* to delete references to tacrolimus open ring, which is not observed in the chromatograms.
Response: Comment incorporated.
Comment Summary #11: The commenter requested revising the specifications in the *Optical rotation* test from "-110° to -115° in *N*,*N*-dimethylformamide" to "-83.0° to -93.0° in chloroform."
Response: Comment not incorporated. The specifications in the proposed monograph are consistent with the sponsor's FDA-approved specifications.
Expert Committee-initiated Change #1: The limits for tacrolimus 19-epimer and tacrolimus open ring were deleted from *Organic Impurities Procedure 1*. Based on the information that tacrolimus 19-epimer and tacrolimus open ring are formed in the *Sample solution* in the presence of water, the Expert Committee decided these limits are not suitable for inclusion in the public standard. Manufacturers are not precluded from having internal limits for these impurities.
Expert Committee-initiated Change #2: The name of USP Tacrolimus System Suitability RS was revised to USP Tacrolimus System Suitability Mixture RS to indicate that the material is a mixture of tacrolimus and several related compounds.

Monograph/Section: Tacrolimus Capsules/Multiple Sections
Expert Committee: Monographs–Small Molecules 1
No. of Commenters: 4
Comment Summary #1: The commenter requested replacing the wet chemical test with a second orthogonal *Identification* procedure.
Response: Comment not incorporated. The Expert Committee will consider future revisions upon receipt of supporting data.
Comment Summary #2: The commenter requested revising the *Assay* acceptance criteria to make them symmetrical.
Response: Comment not incorporated. The *Assay* acceptance criteria in the proposed monograph are consistent with FDA-approved specifications.
Comment Summary #3: The commenter requested revising the calculation formula in the *Assay* to indicate that the sum of peaks includes tacrolimus open ring.

Response: Comment not incorporated. The proposed procedure is consistent with FDA-approved specifications and is suitable for the analysis. The Expert Committee may consider future revisions upon receipt of supporting data.
Comment Summary #4: The commenter requested retaining the *Assay* procedure previously proposed in PF 35(2) [Mar-Apr 2009].
Response: No action required. The updated Assay procedure is able to resolve tacrolimus from tacrolimus 8-epimer, a specified impurity in some impurity profiles.
Comment Summary #5: The commenter requested replacing the *Medium* in *Dissolution Tests 1* and *3* with phosphate buffer.
Response: Comment not incorporated. The *Dissolution* parameters in the proposed monograph are consistent with FDA-approved specifications.
Comment Summary #6: The commenter requested deleting the use of glass filters for the *Sample solution* in *Dissolution Test 1*.
Response: Comment not incorporated. The proposed procedure is supported by the sponsor's validation data.
Comment Summary #7: The commenter requested deleting acetonitrile from the *Sample solution* in *Dissolution Test 1*.
Response: Comment not incorporated. The proposed procedure is supported by the sponsor's validation data.
Comment Summary #8: The commenter requested revising the calculation formula in *Dissolution Test 1* to indicate that the sum of tacrolimus, tacrolimus 19-epimer and tacrolimus open ring are used to calculate the result.
Response: Comment not incorporated. The proposed procedure is supported by the sponsor's validation data.
Comment Summary #9: The commenter requested including relative retention times for the peaks in *Dissolution Tests 2* and *3*.
Response: Comment incorporated.
Comment Summary #10: The commenter requested deleting the statement in *Organic Impurities Procedure 1* about using the *Sample solution* within 30 minutes of preparation.
Response: Comment incorporated. Manufacturers can establish appropriate solution storage conditions based on data acquired during method verification.
Comment Summary #11: The commenter requested deleting the limits for tacrolimus 19-epimer and tacrolimus open ring from *Organic Impurities Procedure 1* because these impurities are formed in the *Sample solution* in the presence of water.
Response: Comment incorporated. This change does not preclude manufacturers from having internal limits for these impurities.
Expert Committee-initiated Change #1: The name of USP Tacrolimus System Suitability RS was revised to USP Tacrolimus System Suitability Mixture RS to indicate that the material is a mixture of tacrolimus and several related compounds.

Monograph/Section: Terbinafine Tablets/Organic Impurities
Expert Committee: Monographs–Small Molecules 1
No. of Commenters: 1
Comment Summary #1: The commenter requested that the acceptance criteria for any single unspecified degradation product be widened from NMT 0.1% to NMT 0.2% to be consistent with FDA-approved specifications.
Response: Comment incorporated.

Monograph/Section: Valsartan Tablets/Dissolution
Expert Committee: Monographs–Small Molecules 2
No. of Commenters: 1
Comment Summary #1: The commenter requested revising the *Standard solution* and *Sample solution* preparations to accommodate different strengths of the tablets.
Response: Comment incorporated by adding a note stating “dilute with *Medium* as needed.”