COMMENTARY – 2nd SUPPLEMENT TO USP 31-NF 26

Revision proposals published in *Pharmacopeial Forum* often elicit public comments that are forwarded to the appropriate Expert Committee for review and response. In accordance with the Rules and Procedures of the 2005-2010 Council of Experts, revision proposals can advance to official status with minor modifications, as needed, without requiring further public review. In such cases a summary of comments received and the appropriate Expert Committee's responses are published in the *Commentary* section of the USP website at the time the revision becomes official. For those proposals that require further revision and republication in *Pharmacopeial Forum*, a summary of the comments and the Expert Committee's responses will be included in the briefing that accompanies each article.

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

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No comments received for the following proposals:

General Chapters
<741> Melting Range or Temperature
<797> Pharmaceutical Compounding – Sterile Preparations
<1196> Pharmacopeial Harmonization
<2030> Supplemental Information for Articles of Botanical Origin
<2750> Manufacturing Practices for Dietary Supplements

Monographs
Alprazolam
Alumina, Magnesia, Calcium Carbonate, and Simethicone Tablets
Alumina, Magnesia, Calcium Carbonate, and Simethicone Chewable Tablets
Alumina, Magnesia, and Simethicone Oral Suspension
Alumina, Magnesia, and Simethicone Tablets
Alumina, Magnesia, and Simethicone Chewable Tablets
Amiloride Hydrochloride and Hydrochlorothiazide Tablets
Atovaquone
Avobenzone
Bupropion hydrochloride
Calcitonin Salmon
Calcium Carbonate, Magnesia, and Simethicone Tablets

No comments received for the following proposals, continued

Monographs, continued

Calcium Carbonate, Magnesia, and Simethicone ChewableTablets
Calcium Silicate
Cefaclor Chewable Tablets
Chamomile
Ciclopirox
Ciclopirox Olamine
Clozapine
Colestipol Hydrochloride
Colestipol Hydrochloride for Oral Suspension
Colestipol Hydrochloride Tablets (new monograph)
Cupric Sulfate
Cyromazine
Dantrolene Sodium Capsules
Dehydroacetic Acid
Diltiazem Hydrochloride
Dinoprost Tromethamine Injection
Dimenhydrinate
Dimenhydrinate Injection
Estradiol and Norethindrone Acetate Tablets
Ethinyl Estradiol Tablets
Ethionamide
Famotidine Tablets
Formaldehyde Solution
Glucosamine Hydrochloride
Glucosamine Sulfate Potassium Chloride
Glucosamine Sulfate Sodium Chloride
Hydrocodone Bitartrate and Homatropine Methylbromide Tablets
Hydrophobic Colloidal Silica
Hyoscyamine Sulfate
Inositol
Isosorbide Mononitrate Extended-Release Tablets
Isotretinoin Capsules
Ivermectin and Clorsulon Injection
Ivermectin Injection
Ivermectin Paste
Ivermectin Tablets
Ivermectin Topical Solution
Magaldrate and Simethicone Oral Suspension
Magaldrate and Simethicone Tablets
Magaldrate and Simethicone Chewable Tablets
Mefloquine Hydrochloride
Naphazoline Hydrochloride Ophthalmic Solution
Nicotine transdermal system
Norethindrone Tablets

No comments received for the following proposals, continued

Monographs, continued
Octocrylene
Oxymetazoline Hydrochloride Nasal Solution
Paroxetine tablets
Povidone-Iodine
Powdered Bilberry Extract
Powdered Decaffeinated Green Tea Extract
Primaquine Phosphate
Primaquine Phosphate Tablets
Propylene Glycol Dicaprylate/Dicaprate
Pyrimethamine
Ritonavir
Saquinavir Mesylate
Silver Sulfadiazine
Simethicone Capsules
Simethicone Oral Suspension
Simethicone Tablets
Simvastatin
Stannous Chloride
Triclosan
Vecuronium Bromide
Verapamil Hydrochloride

General Chapters Commentary

General Chapter/Section(s): <525> Sulfur Dioxide/Multiple Sections
Expert Committee(s): EGC
No. of Commenters: 1
Comment Summary #1: Commenter indicated Methods I and II should not be considered as generally applicable methods based on the complexity of the apparatus and questionable accuracy. They indicated that it is difficult to qualify the consistent performance of the still apparatus and the accuracy of the Sulfur Dioxide value is unreliable due to the low recovery potential. In addition, it was noted that these methods can only be performed by highly qualified laboratory analysts. The commenter also suggested that all the methods in the chapter should have the same content format.
Response: Comment incorporated. The Committee deleted Methods I and II and reformatted the remaining methods.
Comment Summary #2: Commenter indicated that the Method III procedure for is not as specific as the individual monograph details for the filtration method and the solvents to be used in analysis.
Response: Comment incorporated. The committee revised the procedure to include the monograph specific details.
Expert Committee-initiated Change: The committee revised the numbering of proposed Methods III, IV, V to Methods I, II, III, respective because the original proposed Methods I and II have been deleted.

General Chapter/Section(s): <645> Water Conductivity/Multiple Sections
Expert Committee(s): PW
No. of Commenters: 8
Comment Summary #1: Commenter recommended that the phrases "…because of the high purity of the water tested, with ionic and organic impurities in the sub-mg/L range, off-line measurements of water may be adversely affected by the sampling method, the sampling container, and environmental factors such as ambient carbon dioxide concentration and organic vapors. Except for packaged water, on-line measurements may be preferred…" be deleted, citing that all kinds of measurements (microbiological, chemical or physical) could be affected during the sampling process and that "under appropriate controls, off-line measurement of conductivity is perfectly acceptable" be included in the text.
Response: Comment incorporated. The Expert Committee agreed that (except for packaged water) on-line measurement may be more representative of the water sample conductivity and to modified the proposal to clarify the informative aspect of the text. The new text is "Precaution should be taken while collecting water samples for off-line conductivity measurements. The sample may be affected by the sampling method, the sampling container, and environmental factors such as ambient carbon dioxide concentration and organic vapors." The last sentence "Except for packaged water, on-line measurements may be preferred" was removed from the chapter.
Comment Summary #2: Commenters recommended that the sentences "Stage 1 is intended for on-line testing. Proceed to stage 2 if off-line testing is intended." be deleted and the sentence "The measurement may be performed in a suitable container or as an on-line measurement" be re-inserted. The rationale was to consider that in a case in which a successful stage 1 uses off-line measurement, there is no need to conduct stage 2, and companies should have the "flexibility" to choose between the 2 methods.
Response: Comment incorporated and the new sentence is "Stage 1 is intended for on-line measurement or may be performed off-line in a suitable container."
Comment Summary #3: Commenter recommended removing the tests for chloride, sulfate and ammonia if a conductivity requirement is added to the monograph for packaged water (sterile purified water).
Response: Comment not incorporated. The Sterile Purified Water monograph does not require chloride, sulfate and ammonia tests, so the current text proposed in the PF remains appropriate.
Comment Summary #4: Commenter suggested an alternative method for the determination of the cell constant value within 2% accuracy. The rationale of this proposal was based on the difficulty of obtaining such a value (with an acceptable Test Article Ratio) from material available on the market.
Response: Comment not incorporated. Alternate methods may be used as explained in the "TEST AND ASSAYS" section of the USP General Notices. The definition, choice, development and validation of an alternative method are the responsibility of the company deciding to use the alternate method.
Comment Summary # 5: Commenter recommended replacing the sentence "It is suggested that verification of the entire equipment be performed" with "It is suggested that periodic verification of the entire equipment be performed." This comment aims to clarify the frequency required for such a test.
Response: Comment incorporated.

Comment Summary #6: Commenter considered that the "entire equipment verification" description does not indicate if it is meant for on-line, off-line or both measurements. It suggested considering that "it is much more critical to use a conductivity probe that is designed to read at the low conductivities seen on compendial-grade water samples, and to have an established cell constant that is consistently met, than to use a second meter."
Response: Comment not incorporated. The equipment verification section is intended to assure that all the equipment used in water testing is checked before use so accurate results are obtained.
Comment Summary #7: Commenter considered the sentence "The selected sampling instrument location(s) must reflect the quality of the water used during its application" would appear to rule out the opportunity to replace "grab sampling" with on-line instruments since the on-line instrument would not be capable of determining the quality of the water after it exits the system through the point of use.
Response: Comment incorporated. The phrase "during its application" will be deleted since this could imply on-line vs. use point verification with every use of the water.
Comment Summary #8: Commenter proposed replacing "…must be known within ± 2%" with "… must be known within 2% of measured value".
Response: Comment not incorporated.
Comment Summary #9: The commenter proposed replacing "…solution of known or traceable conductivity" by "solution of known and traceable conductivity". In addition, it was suggested to replace "…conductivity sensor of known or traceable cell constant" by "…conductivity sensor of known and traceable cell constant."
Response: Comment not incorporated. The Expert Committee decided the proposed text restricts the conditions for the performance of the test
Comment Summary #10: Commenter proposed to describe "the calibration of the conductivity meter…" before "the verification of the cell constant." This proposal is made on the basis that a calibrated meter is required for the determination of the cell constant.
Response: Comment not incorporated.
Comment Summary #11: Commenter proposed to "emphasize that a verification of the entire equipment should be performed before initial use to ensure that the cell constant can be considered constant in the measuring range and temperature interval relevant for the measurement situation." Then it is suggested that "once this is done, it will be sufficient to calibrate the meter and the full measurement system" as described in a text proposed. But also, that "if the reading of the measured conductivity is performed elsewhere than on the meter display, this reading should also be used during calibration …".
Response: Comment not incorporated. The general chapter aims to provide general guidance on the calibration approaches of conductivity and specific procedures should be developed by individual users.
Comment Summary #12: Commenter proposed "to allow the option of either a system accuracy test or a cell constant accuracy test" considering that "if the cell is tested as system with the meter, there is minimal benefit from a separate cell accuracy test."
Response: Comment not incorporated. The proposed suggested text does not help assure the accuracy of the testing results.

Comment Summary #13: Commenter proposed replacing "The conductivity cell constant … must be known within ±2%" with "The conductivity cell constant… must be known within ±10%" and replacing "Excluding the conductivity sensor cell constant accuracy, the instrument accuracy must be ± 0.1 µS/cm" with "Excluding the conductivity sensor cell constant accuracy, the instrument accuracy must be ± 0.1 for readings below 5 µS/cm."
Response: Comment not incorporated. The rationale for use of the current instrument and cell constant accuracy was discussed in PF Nov-Dec 1991 p2673 Vol 17(6) and PF Nov-Dec 1992 p4390 Vol 18(16)
Comment Summary #14: Commenter proposed adding "typically" in the sentence reading "This is typically done using a temperature sensor embedded in the conductivity cell probe sensor and …circuitry".
Response: Comment incorporated.
Comment Summary #15: Commenter proposed removing the sentence: "An external temperature sensor is also acceptable". In addition they suggested adding the following sentences: "This temperature compensation algorithm may not be accurate. Conductivity values used in this method are non-temperature compensated measurements. If temperature compensated measurements are used, the accuracy of the thermocompensation algorithm must be verified. The standard curve should be based on pure water with neutral salt such as defined in ASTM, Table 3. Temperature measurements may be made using the temperature sensor embedded in the conductivity cell sensor. An external temperature sensor positioned near the conductivity sensor is also acceptable. Accuracy of the temperature measurement must be ±2°." The rationale of this proposal is to clarify the text and allow the use of compensated temperature measurements.
Response: Comment incorporated.
Comment Summary #16: Commenter proposed replacing the sentence "water packaged in bulk but manufactured elsewhere" with "water packaged in bulk".
Response: Comment not incorporated.

General Chapter/Section(s): <1119> Near-Infrared Spectroscopy/Multiple Sections
Expert Committee(s): GC
No. of Commenters: 10
Comment Summary #1: Commenter suggested removing the terms Herschel or silicon region and lead sulfide region from the chapter because these terms are not commonly used in the industry.
Response: Comment not incorporated because the terms are still widely used within the NIR community.
Comment Summary #2: Commenter suggested including a description on the dependence of powder bulk density on the penetration of light into powder materials.
Response: Comment not incorporated because a detailed description of interactions between primary particles and light in the context of depth penetration is beyond the scope of this chapter.
Comment Summary #3: Commenter suggested adopting the European Pharmacopoeia description of transflectance, which is written more like an instruction set for conducting the experiment than a general description.
Response: Comment incorporated. The expert committee made revisions to the text to improve the description of transflectance but the detailed instruction set approach used in the European Pharmacopoeia was not adopted.

Comment Summary #4: Commenter suggested changing the section entitled "Factors that Affect Spectral Response" to "Factors that Affect Quantitation".
Response: Comment not incorporated. The Expert Committee did change the title to Factors that Affect NIR Spectra because the current title meets the concerns of the stakeholders and eliminates the need to define spectral response.
Comment Summary #5: Commenter suggested requiring only a single peak for wavelength accuracy rather than 3 peaks for FT-NIR instruments.
Response: Comment not incorporated because the procedure cited is described as a "typical" procedure and alternate standards and acceptance criteria can be used with appropriate justification per the General Notices and Requirements.
Comment Summary #6: Commenter suggested revising typical tolerances for wavelength uncertainty. The tolerances for FT-NIR spectrometers appear to be tighter than the corresponding tolerances for dispersive NIR spectrometers.
Response: Comment not incorporated because the stated tolerances were developed in a round-robin study, are commonly used by the NIR community, and instrument manufactures have incorporated the tolerances into their software algorithms.
Comment Summary #7: Commenter suggested defining tolerances for long-term stability on photometric linearity.
Response: Comment not incorporated because the typical tolerances for long-term stability are integrated into the tolerances for photometric linearity currently in the chapter in combination with statements made in the IQ, OQ, and PQ parts of the chapter.
Comment Summary #8: Commenter suggested removing "low flux noise" as an instrument test from the chapter.
Response: Comment not incorporated because no justification was provided to support its removal.
Comment Summary #9: Commenter suggested adding an expanded discussion on the relationship between SEC, SEL, and SEP.
Response: Comment not incorporated because the Expert Committee felt the current discussion was adequate.
Comment Summary #10: Commenter suggested changing the title of the Method Transfer section to Model Transfer.
Response: Comment not incorporated because Model Transfer is a subset of Method Transfer.

General Chapter/Section(s): <1125> Nucleic Acid-Based Techniques-General/Multiple Sections
Expert Committee(s): BB-VV
No. of Commenters: 3
Comments on Scope:
Comment Summary #1: Commenter suggested that NAT does not refer to target amplification as indicated in the chapter but that common target amplification methods such as PCR, Rolling Circle, TMA, LCR, 3SR, NASBA, should be referred to as PCR instead of NAT.
Response: Comment not incorporated. NAT is the generic term for amplification technologies, which include PCR, Rolling Circle, TMA, LCR, 3SR, NASBA
Comment Summary #2: Commenter suggested that the definition of "NAT" does not refer to amplification technologies but rather nucleic acid testing.
Response: Comment not incorporated. The correct definition of NAT is Nucleic Acid Amplification Technologies.

Comment Summary #3: Commenter suggested referencing the ICH and NCCLS guidelines.
Response: Comments incorporated. An Appendix has been created to include existing guidance documents and reference standards for NAT tests.
Comments on Glossary:
Comment Summary #4: Commenters indicated that the terms "polymerase chain reaction", "complementary DNA nucleotides", "allele", "deoxyribonucleic acid (DNA)", "deoxyribonucleotide triphosphate (dNTP)" and "ribonucleic acid (RNA)" were either confusing or incorrectly defined. The commentators provided corrections.
Response: Comment and corrections incorporated.

General Chapter/Section(s): <1126> Nucleic Acid-Based Techniques-Extraction, Detection and Sequencing/Multiple Sections
Expert Committee(s): BB-VV
No. of Commenters: 3
Comments on Acid Extraction and Cesium Chloride Density Gradient Centrifugation:
Comment Summary #1: Commenter suggested that some chemicals and procedures specified in the chapter may pose safety concerns, and USP should suggest alternate chemicals and include safety statements, respectively.
Response: Comment incorporated: 1) Safety concerns for diethylpyrocarbonate (DEPC) are now stated in the chapter along with commercially available alternatives; 2) A safety concern for use of mortar, pestle and liquid nitrogen on a routine basis in a laboratory has been addressed; 3) A safety concern in regard to high quantity of EtBr has been addressed.
Comments on Silica Technology:
Comment Summary #2: Commenter pointed out that the various silica methods have lower MW limits also.
Response: Comment not incorporated. Limitations for smaller NA sizes apply for some commercial methods but not in general. There are even silica-based kits available that are specifically optimized to purify small NA molecules.
Comments on Specific Applications for Hard-to-Extract Materials:
Comment Summary #3: Commenter asked if RNA purified from FFPE samples could be used in downstream applications if the length and integrity of the RNA could be verified.
Response: Comment not incorporated.
Comments on Sample Handling and Long-term Storage:
Comment Summary #4: Commenter indicated that the DNA storage temperature is not adapted for residual DNA testing where DNA is in small amounts.
Response: Comment incorporated and a sentence was added to include storage temperature for small quantities of DNA.
Comment on Absorbance Spectroscopy:
Comment Summary #5: Commenter indicated that this section could be improved by reorganization.
Response: Comment incorporated and the section was reorganized for clarity.
Comments on Detection by Size-Agarose Gel Electrophoresis:
Comment Summary #6: Commenter suggested the chapter address RNA preparations from both eukaryotic and prokaryotic organisms.
Response: Comment incorporated.

Comments on Detection by Size-pulsed Field Electrophoresis:
Comment Summary #7: Commenter indicated that interpretation of pulsed-field electrophoresis is difficult if the length is less than 50,000 base pairs.
Response: Comment incorporated and the resolution was modified from 10,000 to 50,000 base pairs.
Comments on Detection by Size- Polyacrylamide Gel Electrophoresis (PAGE):
Comment Summary #8: Commenter indicated that staining with silver nitrate is laborious and time consuming. Another commenter indicated that silver nitrate is not a widely used staining solution for DNA/RNA but it is used extensively for protein staining. Thus, USP should consider not recommending silver nitrate solution for DNA/RNA staining.
Response: Comment incorporated to include the drawbacks of silver nitrate staining and the potential interference of protein contaminants.
Comments on Sequence Integrity:
Comment Summary #9: Commenter suggested that DNA sequences should be read several times, using different primers as starting points, to guarantee the accuracy of the developed consensus sequence.
Response: Comment incorporated to include the suggestion while allowing other methods of sequence verification that may come up in the future.

General Chapter/Section(s): <1127> Nucleic Acid-Based Techniques-Amplification/Multiple Sections
Expert Committee(s): BB-VV
No. of Commenters: 3
Comments on Introduction:
Comment Summary #1: Commenter suggested that “Rolling Circle Amplification” might be included in the discussion.
Response: Comment not incorporated. The Expert Committee considers PCR and TMA as the two major current NAT techniques representative of current industry practice.
Comments on Assay Components-Assay Optimization:
Comment Summary #2: Commenter suggested including annealing temperature, primers and probes concentration, cycle number and matrix effect.
Response: Comment incorporated.
Comments on NAT ASSAYS-PCR:
Comment Summary #3: Commenter indicated that cycles above >45 are considered by most PCR experts to be excessive and indicative of a poorly optimized assay. Assays requiring excessive cycles should have full justification for the need.
Response: Comment incorporated. The number of cycles was modified to a range of 30 to 45 times while including assays that may require extra sensitivity gained from excessive cycles.
Comments on Quantitation:
Comment Summary #4: Commenter stated the use of an internal control is an important part for the validation of the PCR results and hence it should be treated in a separate chapter.
Response: Comment incorporated. The internal control is discussed in the QA and QC for NAT section. Also, the text was modified to remove the term “internal control” to avoid confusion since, in the text, the reference was to an exogenous target molecule (control) used for quantitation.

Comments on Quantitation-Real-time PCR and Real-time RT-PCR:
Comment Summary #5: Commenter noted that shorter amplicons are much better for an efficient real-time assay, and that optimal length of amplicons should be optimized for each assay.
Response: Comment incorporated and the text was modified to reflect this suggestion.
Comment Summary #6: Commenter asked for the reference method for the quantification of DNA.
Response: Comment not incorporated. General information chapters typically do not incorporate single reference methods with fixed system suitability and acceptance criteria. The method specifics would be included in a general test chapter or a product monograph.
Comments on Quantitation-Real-time PCR Probes:
Comment Summary #7: Commenter disagreed with the introduction to this section that began by describing the early simply labeled probes and the inherent problems. Commenter suggested that the common probes used (hydrolysis) incorporate both a fluorophore and a quencher molecule that overcomes this issue.
Response: Comment incorporated and the start of this section has been modified to clearly indicate that the comment on simply labeled probes is for historical purposes. Quenched probes, which are now commonly used, are subsequently described in detail.
Comments on Normalization of Assay Results:
Comment Summary #8: Commenter noted that the efficiency of conversion of target RNA to cDNA is not necessarily consistent, even within a single-tube reaction. It is a function of primer design, target sequence, etc.
Response: Comment incorporated and the text modified to reflect this suggestion.
Comments on Equipment QC/QA-Carry-Over Prevention with UNG:
Comment Summary #9: Commenter suggested that the level of contamination "sterilization" by UNG should be evaluated within the context of each assay, as UNG has concentration limits above it does not fully remove PCR carry-over products.
Response: Comment incorporated.
Comments on Equipment QC/QA-Validation of NAT Systems:
Comment Summary #10: Commenter suggested the need to clearly define terms such as LOD, LOQ and Sensitivity.
Response: Comment incorporated. These terms will be defined in the GLOSSARY section.
Comment Summary #11: Commenter asked for guidance on development & characterization of new reagents for validation.
Response: Comment not incorporated, as this sort of guidance is not offered in a general information chapter.
Comments on Quality Control of Reagents-Primers:
Comment Summary #12: Commenter asked if purity of primers could be assessed by manufacturers' CofA coupled with in-house comparison to previous lots.
Response: Comment not incorporated. The Expert Committee recommends using the CoA together with an in-house comparison to determine the purity of primers but this assessment is the responsibility of the company.
Comments on Run Control:
Comment Summary #13: Commenter suggested modifying the statement "Controls should be non-infectious and validation of viral inactivation should be provided" to include in-house-use-only assays, in which viral inactivation may not be necessary or desirable.
Response: Comment incorporated.

Comment Summary #14: Commenter asked if the addition of internal control to each specimen could be made optional.
Response: Comment not incorporated. Since this is a validation section, the inclusion of an internal control in every test is critical.

General Chapter/Section(s): <1129> Nucleic Acid-Based Techniques-Genotyping /Introduction
Expert Committee(s): BB-VV
No. of Commenters: 2
Comments on Introduction:
Comment Summary #1: Commenter suggested including reference to NCBI data base of Single Nucleotide Polymorphism (dbSNP).
Response: Comment incorporated as a footnote.

General Chapter/Section(s): <1130> Nucleic Acid-Based Techniques-Approaches for Detecting Trace Nucleic Acids (Residual DNA Testing)/Multiple Sections
Expert Committee(s): BB-VV
No. of Commenters: 2
Comments on Introduction:
Comment Summary #1: Commenter noted that the three described methods are limited and should be expanded to include other appropriate methods.
Response: Comment not incorporated. The methods indicated typically meet the general needs of the pharmaceutical industry. There may be situations where lower sensitivities are needed because the dose is so large (e.g., recombinant hemoglobin). A phrase “other DNA amplification methods” was added to a previous sentence to indicate that there are other techniques beyond these three, but these three are the most predominant.
Comments on Sample Pre-treatment:
Comment Summary #2: Commenter suggested replacing “SDS” with “a detergent”.
Response: Comment incorporated.
Comment Summary #3: Commenter suggested deleting the reference to DNA Extractor Kit and replacing with the following “Many commercial kits are available for recovery of nucleic acid for samples of various complexity. These commercial kits and any of a number of traditional extraction and recovery protocols can be used to prepare the nucleic acid for a downstream analytical detection method.”
Response: Comment not incorporated. Not all commercial kits are acceptable for this analysis because their specific manufacturing process may introduce residual DNA. This is not a problem if using a specific assay (hybridization or PCR) but is a problem if using DNA binding protein assay.
Comment Summary #4: Commenter noted that a recovery over 80% is very challenging taking into account the whole process: DNA extraction, qPCR efficiency, matrix effects, etc. This criterion could be less, if the measured DNA quantity in the sample is corrected by the load recovery percentage.
Response: Comment incorporated to state that it is guidance and not a requirement. The chapter was edited to include load recovery percentage as an option.
Comment Summary #5: Commenter suggested deleting the sentence “During the qualification of a residual DNA assay, some scientists treat the samples with DNase I to degrade the DNA in the sample in order to demonstrate that the assay response was due to DNA and not some other sample component.”

Response: Comment not incorporated. This is a routine part of assay validation for many of these assays.

Comments on Hybridization-Based Residual DNA Assay:

Comment Summary #6: Commenter suggested including DNA probes generated synthetically, or through amplification (PCR) methods.

Response: Comment not incorporated. The sentence reads "The first residual DNA assays". The "first assays" did not use synthetic probes.

Comment Summary #7: Commenter noted that host cell DNA probe can consist of a specific sequence that is targeted to a given region of the residual nucleic acid target; label can also be a tag molecule (like biotin or digoxigenin or others) that can be detected via affinity and chromogenic substrates or chemiluminescence.

Response: Comment not incorporated. The "host cell" probe is not specific. The purpose of this sentence is to inform the reader of the pitfalls of using certain techniques. There are most likely still older products on the market tested this way so it helps readers to understand older products.

Comments on DNA-Binding Protein-Based Residual DNA Assay:

Comment Summary #8: Commenter suggested the phrase in the first sentence reading "quantitation of residual DNA" should be replaced with "non-specific quantitation of total DNA".

Response: Comment not incorporated. The instrument does quantitate DNA specifically.

Comments on Quantitative PCR-Based Residual DNA Assay:

Comment Summary #9: A commenter suggested replacing "Real-time q-PCR" with "amplification".

Response: Comment not incorporated. This general suggestion has been addressed in the Introduction by adding a statement acknowledging that other amplification methods exist.

Comments on Practical Applications of Residual DNA Testing:

Comment Summary #10: Commenter suggested stating that densitometer results of hybridization assays may be semi-quantitative, not quantitative.

Response: Comment not incorporated. Use of the densitometer makes the analysis quantitative.

Comment Summary #11: Commenter recommended adding a synthesized probe to render specificity to the DNA hybridization assay.

Response: Comment incorporated. A statement "A synthesized probe, specific for a specific sequence, can be prepared and used in the hybridization assay if this level of specificity is desirable" has been added.

Comment Summary #12: Conflicting opinions from commenters were received regarding the lower limit of DNA detection by a hybridization method. One commenter pointed out that the hybridization assay could underestimate dramatically the DNA content for biological products containing small DNA fragments, thus it is not true to say that the hybridization assay detects fragments up to 50 bp. Other commenter noted that the hybridization may be able to detect with fewer minimum, q-PCR can certainly detect with fewer, other new methods can detect with fewer.

Response: The Expert Committee put these values in as "guidance". Users are encouraged to demonstrate through validation other values that are relevant to their system and what they should use.

Monograph Commentary

Monograph/Section(s): Aztreonam/Definition
Expert Committee(s): MD-ANT
No. of Commenters: 1
Comment Summary #1: Commenter recommended that the *Definition* be revised to provide a single *Assay* requirement of requirement of NLT 92.0% to NMT 105.0% for both forms (anhydrous and hydrated).
Response: Comment not incorporated. The Expert Committee is willing to consider future changes to the monograph upon receipt of supporting data.

Monograph/Section(s): Bacitracin/Multiple Sections
Expert Committee(s): MD-ANT
No. of Commenters: 1
Comment Summary #1: Commenter suggested that the *Definition* be revised to indicate that bacitracin is a mixture of polypeptides rather than a single polypeptide. The commenter also recommended indicating that the main components are bacitracins A, B1, B2 and B3. This revision explains the need for the Composition test.
Response: Comment incorporated.
Comment Summary #2: Commenter suggested that the text of the *Composition* test be revised to indicate that the limit of early-eluting peptides refers to the peptides eluting before bacitracin B1.
Response: Comment incorporated.
Comment Summary #3: Commenter recommended that the text of the *Composition* test be revised to indicate that bacitracin F is a known impurity. This revision would distinguish between the other peptides specified in the test and the known impurity.
Response: Comment incorporated.
Expert Committee-initiated change: The committee revised the preparation of the *System suitability solution* in the test for *Composition* was revised to correct the volume of dilute hydrochloric acid added to make the preparation universally applicable regardless of the final volume of solution.

Monograph/Section(s): Bacitracin Zinc/Multiple Sections
Expert Committee(s): MD-ANT
No. of Commenters: 1
Comment Summary #1: Commenter suggested that the *Definition* be revised to indicate that bacitracin zinc contains salts of a mixture of polypeptides rather than a single polypeptide. The commenter also recommended indicating that the main components are bacitracins A, B1, B2 and B3. This revision explains the need for a *Composition* test.
Response: Comment incorporated.
Comment Summary #2: Commenter suggested that the text of the *Composition* test be revised to indicate that the limit of early-eluting peptides refers to the peptides eluting before bacitracin B1.
Response: Comment incorporated.
Comment Summary #3: Commenter recommended that the text of the *Composition* test be revised to indicate that bacitracin F is a known impurity.
Response: Comment incorporated.

Monograph/Section(s): Bicalutamide/Multiple Sections
Expert Committee(s): MD-OOD
No. of Commenters: 1
Comment Summary #1: Commenter suggested replacing the isocratic HPLC method with a gradient HPLC method for the *Related compounds* and *Assay* tests.
Response: Comment not incorporated. The Expert Committee concluded that the isocratic HPLC method is suitable for the *Related compounds* and *Assay* tests.
Comment Summary #2: Commenter requested a revision of the impurity limits.
Response: Comment not incorporated because the proposed limits are not FDA approved. The Expert Committee is willing to consider future changes to the monograph upon FDA approval and receipt of supporting data.
Comment Summary #3: Commenter requested that the limit of the *Heavy metals* be increased.
Response: Comment not incorporated because the proposed limit is not FDA approved. The Expert Committee is willing to consider future changes to the monograph upon FDA approval and receipt of supporting data.

Monograph/Section(s): Bismuth Subsalicylate Magma/Packaging and storage
Expert Committee(s): MD-CCA
No. of Commenters: 1
Comment Summary: Commenter requested that the *Packaging and storage* section be revised to include the description "light resistant" to be consistent with the drug substance monograph.
Response: Comment incorporated.

Monograph/Section(s): Bovine Acellular Dermal Matrix/new monograph/Multiple Sections
Expert Committee(s): BB-CGT, NOM
No. of Commenters: 2
Comment Summary #1: Commenters requested that *Acellular Dermal Matrix* change to *Bovine Acellular Dermal Matrix* because the product is of bovine origin and this aspect needs to be reflected in the title of the monograph as well as in the different sections of the monograph.
Response: Comment incorporated.
Comment Summary #2: Commenter suggested clarifying the statement that calls for the official uses for the Authentic Visual Reference standards within the text of the monograph, under the *Histological Evaluation Section*. The text needs to be amended to essentially require the end user to use the Photomicrographs as reference standard.
Response: Comment incorporated.

Monographs/Section(s): Colestipol Hydrochloride and Colestipol Hydrochloride for Oral Suspension/Water-soluble substances
Expert Committee(s): MD-GRE
No. of Commenters: 1
Comment summary: Commenter requested to revise the filtering step of this test and to replace the fine porosity fritted-glass funnel currently described in the monographs by a 0.45-um nylon membrane filter, combined with the use of a 0.45-um PVDF filter. Commenter indicated that this change will improve the accuracy of the test by assuring that only water-soluble substances are passed through. This proposed modification also

makes use of more modern and up-to-date equipment and allows the use of a fresh filter each time the test is conducted.
Response: Comment incorporated.

Monograph/ Section(s): Didanosine Tablets for Oral Suspension/Labeling
Expert Committee(s): MD-AA and NOM
No. of Commenters: 1
Comment Summary #1: Commenter proposed that the dispersion solvent for the product should be water because didanosine is an acid labile substance. Didanosine drug products approved by FDA should be formulated to include buffering substances to prevent gastric degradation of the drug substance. Dispersing this drug product in an acidic medium would negate the purpose of including buffering substances in formulation thus the solvent should be specified as water.
Response: Comment incorporated

Monograph/Section(s): Enoxaparin Sodium/Multiple Sections
Expert Committee(s): BB-BBP
No. of Commenters: 3
Comments on Potency Unit:
Comment Summary #1: Commenter suggested that USP adopt International Unit (IU) for Enoxaparin Sodium potency assays. The drug product, currently sold in the United States, labels potency values in IU instead of USP Unit. The option of IU will achieve not only harmonization with EP but could avoid potential dosage errors due to different potency units.
Response: Comment incorporated:
Comments on Molecular Weight Distribution and Weight-average Molecular Weight:
Comment Summary #2: Commenter suggested to rename *USP LMWH RS* to *USP Enoxaparin Sodium Molecular Weight Calibrant A RS* and *USP Enoxaparin Sodium Molecular Weight Calibrant B RS*. In addition, reconstitution step for these RS should be added under the "Procedure" in the Identification D.
Response: Comment incorporated.
Comments on Assay (anti-factor Xa activity):
Comment Summary #3: Commenter asked if the "Calculations" section could be revised to render clarity. Specifically, the combination of the four independent dilution estimates is not clear.
Response: Comment incorporated. The sentence has been modified to read "The four independent log relative potency estimates are then combined to obtain the final geometric mean."

Monograph/Section(s): Enoxaparin Sodium Injection/Multiple Sections
Expert Committee(s): BB-BBP
No. of Commenter: 1
Comments on Potency Unit:
Comment Summary #1: Commenter suggested that USP adopt International Unit (IU) for Enoxaparin Sodium potency assays. The drug product, currently sold in the United States, labels potency values in IU instead of USP Unit. The option of IU will achieve not only harmonization with EP but could avoid potential dosage errors due to different potency units.
Response: Comment incorporated.

Monograph/Section(s): Fulvestrant/Multiple Sections
Expert Committee(s): MD-PS
No. of Commenters: 2
Comment Summary #1: Commenter requested that the *Specific rotation* test should be removed because the more definitive Diastereoisomer ratio test is included in the monograph.
Response: Comment not incorporated because the Expert Committee concluded that the Specific rotation test still adds value to the monograph.
Comment Summary #2: Commenter proposed a normal phase HPLC method for the Diastereoisomer ratio test. The proposed procedure is comparable to the current procedure, uses readily available solvents and a less expensive, more durable column that is more easily sourced than the current chiral column.
Response: Comment not incorporated because no supporting data was provided. The Expert Committee is willing to consider future changes to this monograph upon receipt of supporting data.
Comment Summary #3: Commenter requested that the "L" designation of the column used in the Diastereoisomer ratio test be corrected from L40 to L51 to correspond to information provided in the *Briefing* accompanying the PF proposal.
Response: Comment incorporated.
Expert committee-initiated change: The committee revised the chemical names of the impurities listed as footnotes in the impurity table under the *Related compounds* test to make the names consistent with the chemical name provided for the parent compound, fulvestrant.

Monograph/Section(s): Gamma Cyclodextrin/Assay
Expert Committee(s): EM2
Expert Committee-initiated Change: The committee revised the *Assay stock preparation* to change the corresponding calculation formula to subtract the water content from the weight of Gamma Cyclodextrin.

Monograph/Section(s): Light Mineral Oil/Multiple Sections
Expert Committee(s): EM2
No. of Commenter: 5
Comment Summary #1: Commenters noted there is no method or test procedure for *Viscosity* and the specification only has an upper limit. The specification with both upper and lower limits was suggested.
Response: Comment incorporated and the details for the *Viscosity* test has been added to the monograph as follows: Perform the test at 40.0 ± 0.1° using a suitable capillary viscometer. The suggestion to revise the specification to include both upper and lower limits was accepted.
Comment Summary #2: Commenter suggested the test for *Limit of sulfur compounds* is not necessary.
Response: Comment not incorporated.

Monograph/Section(s): Mineral Oil/Multiple Sections
Expert Committee(s): EM2
No. of Commenters: 6
Comment Summary #1: Commenter wanted confirmation that this monograph belongs under Dietary Supplements Monographs.
Response: Comment incorporated. The monograph will be listed as a USP monograph.
Comment Summary #2: Commenters noted there is no method or test procedure for *Viscosity* and the specification only has a lower limit. The specification with both upper and lower limits was suggested.
Response: Comment incorporated and the details for the *Viscosity* test has been added to the monographs as follows: Perform the test at 40.0 ± 0.1° using a suitable capillary viscometer. The suggestion to revise the specification to include both upper and lower limits was accepted.
Comment Summary # 3: Commenter requested that White Mineral Oil [8042-47-5] be listed under Mineral Oil monograph.
Response: Comment not incorporated. This Issue is unable to be resolved at this time and CAS number [8012-95-1] proposed in the *Pharmacopeial Forum* is deleted from the Mineral Oil monograph.
Comment Summary # 4: Commenter suggested the test for *Limit of sulfur compounds* is not necessary.
Response: Comment not incorporated.

Monograph/Section(s): Mycophenolate Mofetil/Related compounds
Expert Committee(s): MD-OOD
Expert committee-initiated change: The committee initiated a change to the *Related compounds* test. Impurity A was deleted from the table because the chemical identity of Impurity A is not known and it is considered as an individual unknown impurity.

Monograph/Section(s): Oxandrolone Tablets/Assay
Expert Committee(s): MD-PS
Expert committee-initiated change: The committee revised the mobile phase composition ratio from 620:380 to 62:38 because the former ratio suggests users are required to prepare 1000 mL of mobile phase.

Monograph/Section(s): Paraffin/Infrared Absorption
Expert Committee(s): EM2
No. of Commenters: 1
Comment Summary # 1: A commenter noted in the *IR identification* test, doublet peaks were occasionally observed at about 1460 cm^{-1} and 730 cm^{-1}.
Response: Comment incorporated. The committee found that the doublet peaks may be caused by not completely melting Paraffin Wax. A note was was added stating " Ensure complete melting to avoid doublet peaks that may be observed at wavenumbers at about 1460 cm^{-1} and 730 cm^{-1}.]"

Monograph/Section(s): Paroxetine Hydrochloride/Related compounds
Expert Committee(s): MD-PP
No. of Commenters: 1
Comment Summary: Commenter requested that the limits for Paroxetine Related compound B be revised in both Test 1 and Test 2 so that they are identical.
Response: Comment not incorporated because both Test 1 and Test 2 are used to monitor the impurity profiles of different synthetic processes. The Expert Committee is willing to consider future changes to the monograph upon receipt of supporting data.

Monograph/Section(s): Poloxamer/IR Identification Test
Expert Committee(s): EM2
No. of Commenters: 2
Comment Summary #1: Commenter noted the identification procedure requires using a thin film of melted test specimen, however, the detailed melting procedure to obtain the specimen is not provided in the monograph. In addition, they noted the USP poloxamer Solid RS is not available so they were not able to perform the necessary verification of compendial procedure as written. They requested the proposal be re-published with the detailed melting procedure included and that RS be made available prior to the implementation to allow time for appropriate verification and comment on the method.
Response: Comment not incorporated. The committee does not think modification of the description of the IR method is necessary. The monograph procedure refers to <197F> which is the thin film method. The thin film method is for liquid samples and the higher melting Poloxamers can be made liquid through melting. The Reference Standards were available in March 2008.

Monograph/Section(s): Pullulan/Identification B
Expert Committee(s): EM2
Expert Committee-initiated Change: The committee revised *Identification B*. The phrase "a significant loss of viscosity is observed" was changed to read "a substantial loss of viscosity is observed".

Monograph/Section(s): Raloxifene Hydrochloride/Multiple Sections
Expert Committee(s): MD-PS
No. of Commenters: 3
Comment Summary #1: Commenter requested the *Assay* acceptance criteria be changed from 97.0-102.0% on the as-is basis to 97.5-102.0% on the dried basis, to reflect assay variability and reporting results on the dried basis.
Response: Comment incorporated.
Comment Summary #2: Commenter requested the removal of raloxifene 7-isomer and raloxifene N-oxide as specified impurities in the *Related compounds* test because the 7-isomer is a process related impurity that is observed at very low levels and the N-oxide is not typically observed in the drug substance. The two impurities will be controlled at the 0.10% limit for unspecified impurities.
Response: Comment incorporated.
Comment Summary #3: Commenter requested additional details be provided for the preparation of the *System suitability stock solution* under the *Related compounds* test because the procedure yielded very low quantity of the raloxifene N-oxide impurity.
Response: Comment incorporated. Detailed information is added to the procedure.

Comment Summary #4: Commenter requested that the following potential impurities be specified in the related compounds test and at the limits provided.

- 4-(2-Piperidinoethoxy) benzoic acid HCl (NMT 0.15%)
- Methyl 4-(2-Piperidinoethoxy) benzoate HCl (NMT 0.15%)
- [4-Hydroxy-2-(4-hydroxy-phenyl)benzo[b]thien-3-yl]-[4-[2-(1-piperidinyl)-ethoxy]phenyl]methanone.HCl (isomer) (NMT 0.15%)

Response: Comment not incorporated because no supporting validation data was provided. The Expert Committee is willing to consider future changes to this monograph upon receipt of supporting data.
Expert committee-initiated change: The committee changed the name of the impurity "raloxifene diacylated 1" to "raloxifene impurity 1" in the Related compounds test. The chemical name of this impurity was also revised to make it consistent with the chemical name provided for the parent compound, raloxifene.

Monograph/Section(s): Raloxifene Hydrochloride Tablets/Multiple Sections
Expert Committee(s): MD-PS
No. of Commenters: 1
Comment Summary #1: Commenter suggested adding a test for Water to control the total water content at NMT 6%.
Response: Comment not incorporated because total water content is dependent upon the identity of the excipients and it would be difficult to establish meaningful criteria that would apply to all formulations. The drug product manufacturer should establish the limits for their product based on scientific evaluation of their own formulation performance and stability data.
Comment Summary #2: Commenter requested a correction in the injection volume from 10 µL to 50 µL in the *Dissolution* test.
Response: Comment incorporated.
Comment Summary #3: Commenter requested the reporting threshold included in the test for *Related compounds* be deleted because a reporting threshold has not been applied to this test for this monograph.
Response: Comment incorporated.
Comment Summary #4: Commenter requested additional details be provided for the preparation of the *System suitability stock solution* under the *Related compounds* test because the procedure yielded very low quantity of the raloxifene N-oxide impurity.
Response: Comment incorporated. Detailed information was added to the procedure.
Expert committee-initiated change: The committee revised the chemical name of raloxifene N-oxide in the *Related compounds* test to make it consistent with the chemical name provided for the parent compound, raloxifene.

Monograph/Section(s): Rectal Mineral Oil/Multiple Sections
Expert Committee(s): EM2
No. of Commenters: 6
Comment Summary #1: Commenter wanted confirmation that these monographs belong under Dietary Supplements Monographs.
Response: Comment incorporated. The monograph will be listed as a USP monograph.
Comment Summary #2: Commenters noted there is no method or test procedure for *Viscosity* although test specification is given.

Response: Comment incorporated and the details for the *Viscosity* test has been added to the monographs as follows: Perform the test at 40.0 ± 0.1° using a suitable capillary viscometer.
Comment Summary # 4: Commenter suggested the test for *Limit of sulfur compounds* is not necessary.
Response: Comment is not incorporated.

Monograph/Section(s): Sevoflurane/Related compounds
Expert Committee(s): MD-PS
No. of Commenters: 1
Comment Summary #1: Commenter requested the impurity limits provided in the *Related compounds* be revised to the following limits which are consistent with limits approved for the commenting company's product: not more than 25 µg per g of sevoflurane related compound A, not more than 100 µg per g of any other single impurity; and not more than 300 µg per g of total impurities.
Response: Comment incorporated.
Comment Summary #2: Commenter requested that the "G" designation of the column used in the related compounds test be corrected from G19 to G43.
Response: Comment incorporated.
Comment Summary #3: Commenter recommended that USP revert to the earlier related compounds test published in PF 30(1) because the solvent ethylene dichloride that is used in the current related compounds procedure is hazardous.
Response: Comment not incorporated because the related compounds test published in PF 30(1) received several negative comments. The Expert Committee is willing to consider future changes to this monograph upon receipt of a proposal that uses a less toxic solvent.

Monograph/Section(s): Topical Light Mineral Oil/Multiple Sections
Expert Committee(s): EM2
No. of Commenters: 6
Comment Summary #1: A commenter wanted confirmation that these monographs belong under Dietary Supplements Monographs.
Response: Comment incorporated. The monograph will be listed as a USP monograph.
Comment Summary #2: Commenters noted there is no method or test procedure for *Viscosity* although test specification is given.
Response: Comment incorporated and the details for the *Viscosity* test has been added to the monographs as follows: Perform the test at 40.0 ± 0.1° using a suitable capillary viscometer.
Comment Summary # 3: Commenter suggested the test for *Limit of sulfur compounds* is not necessary.
Response: Comment is not incorporated.

Monograph/Section(s): Topiramate/Related Compounds by TLC
Expert Committee(s): MD-PP
No. of Commenters: 1
Comment Summary: Commenter requested the total impurities should include the impurities quantified by TLC and HPLC.
Response: Comment not incorporated because the Expert Committee did not have enough information to assess the specificity of related compounds by TLC relative to the

Related Compounds by HPLC test. The Expert Committee is willing to consider future changes to the monograph upon receipt of supporting data.
Expert Committee-initiated Changes: The committee added the note at the beginning of the related compounds by TLC section to indicate the test is optional since it applies to a specific synthetic process. The Expert Committee modified the note at the end of the related compounds by TLC so that it is consistent with note at the beginning of the test.

Monograph/ Section(s): Valganciclovir Hydrochloride/Multiple Sections
Expert Committee(s): MD-AA
No. of Commenters: 1
Comment Summary: Commenter proposed the use of existing USP Methoxymethlyguanine and D-Valganciclovir Reference Standards in the tests for *Assay* and *Enantiomeric purity of valganciclovir* due to limited commercial availability of these substances as reagents.
Response: Comment incorporated.