



Commentary

USP 43–NF 38

November 1, 2019

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

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

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

General Chapters

[<203> High Performance Thin-Layer Chromatography Procedure for Identification of Articles of Botanical Origin](#)
[<591> Zinc Determination](#)
[<856> Near-Infrared Spectroscopy](#)
[<1010> Analytical Data -- Interpretation and Treatment](#)
[<1043> Ancillary Materials for Cell, Gene and Tissue Engineered Products](#)
[<1046> Cellular and Tissue-Based Products](#)
[<1047> Gene Therapy Products](#)
[<1119> Near-Infrared Spectroscopy \(now <1856>\)](#)
[<1850> Evaluation of Screening Technologies for Assessing Medicine Quality](#)

Monographs

[Allopurinol Compounded Oral Suspension](#)
[Arginine Hydrochloride Compounded Oral Solution](#)
[Azathioprine Tablets](#)
[Betaxolol Hydrochloride](#)
[Carboxymethylcellulose \[Intraperitoneal\] Compounded Solution, Veterinary](#)
[Chlorambucil Compounded Oral Suspension](#)
[Cholecalciferol](#)
[Clonidine Hydrochloride](#)
[Clonidine Hydrochloride Compounded Oral Suspension](#)
[Diclofenac Potassium for Oral Solution](#)
[Diflunisal Tablets](#)
[Diphenhydramine Oral Powder](#)
[Dobutamine Hydrochloride](#)
[Ergocalciferol](#)
[Fentanyl](#)
[Glyceryl Mono and Dicaprylate](#)
[Glyceryl Mono and Dicaprylocaprate](#)
[Glyceryl Monocaprylate](#)
[Glyceryl Monocaprylocaprate](#)
[Hexylene Glycol](#)
[Hydrochlorothiazide Compounded Oral Suspension](#)
[Indomethacin Extended-Release Capsules](#)
[Metformin Hydrochloride](#)
[Methacholine Chloride](#)
[Minoxidil](#)
[Oil- and Water-Soluble Vitamins with Minerals Tablets](#)
[Polypropylene Glycol 11 Stearyl Ether](#)
[Potassium Sorbate](#)
[Propranolol Hydrochloride](#)
[Rotigotine Transdermal System](#)
[Saccharin Calcium](#)
[Tetracycline Hydrochloride](#)
[Torsemide Compounded Oral Suspension](#)
[Vancomycin Compounded Oral Suspension](#)

[Water-Soluble Vitamins Tablets](#)
[Water-Soluble Vitamins with Minerals Tablets](#)

No comments were received for the following proposals:

Monographs

Alginic Acid
Amitriptyline Hydrochloride
Arginine Hydrochloride Compounded Oral Solution
Aurothioglucose Injectable Suspension
Azatadine Maleate
Azatadine Maleate Tablets
Betaxalol Tablets
Calcium with Vitamin D Tablets
Calcium and Vitamin D with Minerals Tablets
Chloramphenicol Compounded Oral Solution
Creatine
Demeclocycline Hydrochloride
Demeclocycline Hydrochloride Tablets
Deslanoside
Deslanoside Injection
Diazoxide Capsules
Diazoxide Injection
Doxycycline Compounded Oral Solution; Veterinary
Glyceryl Monostearate
Hydrocortisone Gel
Lecithin
Loperamide Hydrochloride
Low-Substituted Carboxymethylcellulose Sodium
Lysolecithin
Manganese Chloride for Oral Solution
Mazindol
Medium-Chain Triglycerides
Minocycline Hydrochloride Oral Suspension
Nicardipine Hydrochloride Injection
Oil- and Water-Soluble Vitamins Tablets
Oil-Soluble Vitamins Tablets
Oil-Soluble Vitamins with Minerals Tablets
Oxprenolol Hydrochloride Extended-Release Tablets
Oxycodone and Acetaminophen Capsules
Parachlorophenol
Phenytoin Compounded Topical Gel
Physostigmine Salicylate Ophthalmic Solution
Piperazine Citrate Tablets
Potassium Alginate
Prednisolone Cream
Primidone Oral Suspension
Procaine and Tetracaine Hydrochlorides and Levonordefrin Injection
Promazine Hydrochloride Syrup
Propoxycaine Hydrochloride
Propoxycaine and Procaine Hydrochlorides and Levonordefrin Injection

Propoxycaïne and Procaine Hydrochlorides and Norepinephrine Bitartrate Injection
Propylidone
Pyrvinium Pamoate
Pyrvinium Pamoate Oral Suspension
Risedronate Sodium
Ritodrine Hydrochloride
Ritodrine Hydrochloride Injection
Ritodrine Hydrochloride Tablets
Scopolamine Hydrobromide Injection
Scopolamine Hydrobromide Ophthalmic Solution
Scopolamine Hydrobromide Tablets
Secobarbital
Sodium Benzoate Compounded Oral Solution
Sodium Fluoride Gel
Sodium Fluoride Tablets
Thioridazine Hydrochloride Oral Solution
Vitamin A Tablets

General Chapters

Chapter/Section(s): <203> High Performance Thin-Layer Chromatography Procedure for Identification of Articles of Botanical Origin / EQUIPMENT/PROCEDURE

Expert Committee: Botanical Dietary Supplements and Herbal Medicines

EC-initiated Change #1: The description of the photographic system for documentation of chromatograms was simplified to remove outdated and self-evident language.

EC-initiated Change #2: Under *System Suitability*, the proposal to eliminate the reference to the USP Reference Standard extracts was not incorporated, and the original language retained.

EC-initiated Change #3: In *Table 1*, the title of the second column “Standard Parameter” was changed to “Standard” for better alignment with the title of the first column, “Parameter”.

General Chapter/Sections: <591> Zinc Determination

Expert Committee: General Chapters—Chemical Analysis

No. of Commenters: 7

GENERAL COMMENTS

Comment Summary #1: The commenter recommended removing specific details regarding preparation of zinc working standard solutions, which depends on, for example, instrument type and sample matrix.

Response: Comment incorporated.

Comment Summary #2: The commenter recommended removing specific instrumental conditions, which depends on, for example, instrument type and sample matrix.

Response: Comment incorporated.

Comment Summary #3: The commenter suggested to matrix match the standards, samples and blank.

Response: Comment incorporated.

Comment Summary #4: The commenter suggested allowing for following options:

- A qualitative test to determine zinc using the simple titration method

- An ICP-MS based method (General Chapter <233> can be referenced for test method and method validation) to quantify trace levels of zinc
- An electrochemical method for certain pharmaceutical preparations

Response: Comment not incorporated. USP *General Notices* 6.30. Alternative and Harmonized Methods and Procedures allows the user to use any method as long as it is appropriately validated. USP can consider adding the suggested methods in the chapter if an appropriate proposal is received.

Comment Summary #5: The commenter suggested including a method robustness study to justify the proposed acceptance criteria.

Response: Comment not incorporated. A robustness study is part of validation studies and since this chapter does not include a section on “Validation,” it therefore cannot be included.

Comment Summary #6: The commenter suggested adding a quality control standard solution with appropriate acceptance criteria to check the calibration curve against specific known concentrations.

Response: Comment not incorporated. A quality control standard is not needed since the system suitability requirement of the correlation coefficient of the standard curve provide the proposed assurance.

Comment Summary #7: The commenter recommended revising the Assay procedure in Zinc Oxide monograph to allow use of any of the three methods in <591>.

Response: Comment not incorporated. The Assay procedure in Zinc Oxide monograph is suitable for the intended use.

General Chapter/Sections: <856> Near-Infrared Spectroscopy/Multiple Sections

Expert Committee: General Chapters—Chemical Analysis

No. of Commenters: 8

GENERAL COMMENTS

Comment Summary #1: The commenter recommended including reference to 21 CFR Part 11 requirements when discussing various hardware and software throughout the General Chapter.

Response: Comment not incorporated. The regulatory requirements of Quality Systems are out of scope of the General Chapter.

Comment Summary #2: The commenter recommended including reference to FDA Draft Guidance for Industry: *Development and Submission of Near Infrared Analytical Procedures* in the General Chapter.

Response: Comment not incorporated. FDA guidance is currently being drafted and therefore cannot be referenced.

Comment Summary #3: The commenter suggested that General Chapters related to Mid-Infrared Spectroscopy and Near-Infrared Spectroscopy be consolidated into a single General Chapter.

Response: Comment not incorporated. The scope of spectroscopy General Chapters was discussed in the *Stimuli* article “*An Alignment of Concepts and Content across the Spectroscopy General Chapters in the United States Pharmacopeia–National Formulary (USP–NF)*” in *PF* 40(1).

Section 2. QUALIFICATION OF NIR SPECTROMETERS

Comment Summary #4: The commenter indicated that in order to execute spectrometer qualifications, equipment should be manufactured under Good Manufacturing Practice regulations and approved protocols based on design function specifications must be in place.

Response: Comment not incorporated. The scope of spectroscopy General Chapters are captured in *PF 40(1) An Alignment of Concepts and Content across the Spectroscopy General Chapters in the United States Pharmacopeia–National Formulary (USP–NF)*.

Comment Summary #5: The commenter recommended a note be included that the General Chapter pertains to conventional NIR instrumentation only.

Response: Comment not incorporated. The *Introduction* indicates qualification should consider the intended purpose, “The instrument qualification tests and acceptance criteria provided in this chapter may not be appropriate for some instrument configurations. In such cases, alternative instrument qualification and performance checks should be scientifically justified and documented before use.”

Comment Summary #6: The commenter suggested including additional factors in subsection *2.1 Installation Qualification*, including calibrations, design safety features, and recommended environmental/preventive maintenance measures by the manufacturer’s instructions.

Response: Comment not incorporated. These factors are dependent on the intended use of the spectrometer and the manufacturer’s application of Good Manufacturing Practices, which are out of scope of the General Chapter.

Comment Summary #7: The commenter recommended revision of the text describing frequency of performance testing in subsection *2.2.1 Characterizing Instrument Performance*.

Response: Comment incorporated. Text changed to: “The frequency at which each performance test is conducted must be assessed for risk, depending on the instrument type, application and its environment.”

Comment Summary #8: The commenter recommended that the General Chapter specify that wavelength accuracy be established for grating-based dispersion NIR spectrometers.

Response: Comment not incorporated. Grating-based dispersion NIR spectrometers are addressed in General Chapter <1856>.

Comment Summary #9: The commenter suggested the acquisition of the sample and/or reference standard spectrum for wavelength accuracy include an adjustment of instrument parameters, including slit width.

Response: Comment not incorporated. Adjustment of instrument parameters is out of scope of the General Chapter.

Comment Summary #10: The commenter suggested reference to NIST SRM 2034 for verification of wavelength scale.

Response: Comment not incorporated. NIST SRM 2034 is not used for the near-infrared range.

Comment Summary #11: The commenter suggested to correct an incorrect tolerance value of for wavelength/wavenumber standard value at ± 3 nm at 2500 nm (± 2 cm^{-1} at 4000 cm^{-1}).

Response: Comment not incorporated. The tolerance reported is correct.

Comment Summary #12: The commenter suggested that instrument componential noise, such as electrical and mechanical noise, can be determined, and circulating the system noise is highly important to eliminate spectral artifacts.

Response: Comment not incorporated. The comment is outside the scope of the General Chapter.

Comment Summary #13: The commenter suggested the tolerance of photometric noise can be determined from replicate measurements of a reference material, and the criteria should be zero.

Response: Comment not incorporated. The EC disagreed with the suggested tolerance, as zero noise cannot be achieved.

Comment Summary #14: The commenter suggested the objective stated for Performance Qualification (PQ) is not completely aligned with <1058>. The type of tests described in this section have more to do with instrument performance verification and performance checks and

are PQ tests, but not the full PQ, which would require additional activities to demonstrate that the instrument is suitable for the intended analytical application.

Response: Comment incorporated. The objective of PQ was changed to, “The objective of PQ is to ensure that the instrument is performing within specified limits with respect to critical operational parameters.”

Comment Summary #15: The commenter indicated subsection 2.3 *Performance Qualification* contains inconsistent terminology and is unclear, particularly as it applies to the use of the term “model”.

Response: Comment not incorporated. The use of the terminology is clear in context of the General Chapter and subsection.

Section 4. VALIDATION AND VERIFICATION

Comment Summary #16: The commenter indicated the criteria for validation parameters, particularly accuracy and precision, are not appropriate, as a method can be acceptable if the criteria are not met, but the method is shown to be fit for purpose.

Response: Comment not incorporated. The General Chapter may be revised when ICH Q2 and Q14 are finalized.

Comment Summary #17: The commenter suggested the objective to NIR procedure validation is ambiguous and uses non-standard terminology to refer to analytical method validation.

Response: Comment incorporated. The text was changed to: “The objection of NIR procedure validation, as is the case with validation of any analytical procedure, is to demonstrate that it is suitable for its intended purpose.”

Comment Summary #18: The commenter suggested other NIR test procedures may require sufficient validation to ensure suitability and validity of the results.

Response: Comment incorporated. The word “only” was removed, and the text was changed to: “The validation criteria described below are required when an NIR spectroscopic procedure is intended for use as an alternative to the monograph procedure for testing an official article.”

Comment Summary #19: The commenter indicated that when a chemometric model is used, other metrics other than standard error of prediction (SEP) can be used in estimating accuracy (e.g., RMSEP and mean bias).

Response: Comment incorporated. The text was changed to: “If a chemometric model is used, accuracy can be determined by methodologies in <1039>*Chemometrics*.”

Comment Summary #20: The commenter indicated redundancy in subsection 4.1.1 *Accuracy Validation Criteria*.

Response: Comment incorporated. Text revised for clarity.

Comment Summary #21: The commenter suggested that testing effects of at least two factors may not be feasible in an intermediate precision study.

Response: Comment not incorporated. The purpose of an intermediate precision study is to establish an expected routine precision of the procedure under normal operating conditions (factors) within a laboratory (e.g., time, instrument, or operator). The only circumstance where less than two factors can be varied is unlikely. For example, in a circumstance where only one instrument is available, both time and operator are two factors that can be varied in an intermediate precision study.

Comment Summary #22: The commenter suggested the static validation criteria may not apply to many applications, and the flexibility of adjusting the criteria based on sound scientific justification should be included.

Response: Comment not incorporated. Introductory text in section 4.1 *Validation* includes a disclaimer on alternative validation criteria for analytical procedures.

Comment Summary #23: The commenter recommended mentioning that the precision validation criteria in the General Chapter is for guidance only and should not be mandatory to demonstrate better precision than the reference method.

Response: Comment not incorporated. Introductory text in section 4.1 *Validation* includes a disclaimer on alternative validation criteria for analytical procedures. In addition, *General Notices*, 6.30 “Alternative and Harmonized Methods and Procedures” states “an alternative method or procedure must be fully validated (see <1225> *Validation of Compendial Procedures*) and must produce comparable results to the compendial method or procedure within allowable limits established on a case-by-case basis.”

Comment Summary #24: The commenter indicated that NIR models are instrument-specific, and one would need to carry out a transfer protocol and equivalence testing to evaluate instrument variation.

Response: Comment not incorporated. The criteria for Intermediate Precision does not preclude transfer protocols and instrument equivalence testing.

Comment Summary #25: The commenter requested the inclusion of Hotelling’s T² and DmodX in demonstrating specificity.

Response: Comment not incorporated. The list of examples in demonstrating specificity is not exhaustive but may include those provided. The requested information is not relevant for below 1000 general chapters.

Comment Summary #26: The commenter suggested it is unclear how to demonstrate the quantitation limit for Limit Tests.

Response: Comment not incorporated. In accordance with General Chapter <1225>, the quantitation limit is not required for Limit Tests.

Comment Summary #27: The commenter suggested that it may be necessary to determine the quantitation limit of quantitative procedures for impurities.

Response: Comment not incorporated. Additional wording was added in section 7. *Procedure Validation* in General Chapter <1856> for clarity.

Comment Summary #28: The commenter requested additional clarification on the meaning of NIR spectral response in subsection 4.1.5 *Linearity*.

Response: Comment incorporated. Text revised for clarity.

Comment Summary #29: The commenter recommended that linearity validation criteria should be rephrased to state that the residual plot should not show a pattern or trend that compromises the assessment of linearity.

Response: Comment not incorporated. Subsection 4.1.5 *Linearity* already states “Visual inspection of the residual plots should reveal no significant pattern. For further guidance on multivariate procedures, see <1039>.”

Comment Summary #30: The commenter suggested that the range of the procedure should be established with an independent test set.

Response: Comment not incorporated. However, text was changed to, “The range typically is established by confirming suitable measurement capability (accuracy and precision) over the proposed operational range.”

Comment Summary #31: The commenter recommended the General Chapter include the possibility to validate an alternate range.

Response: Comment not incorporated. Text in section 4.1 *Validation* includes a disclaimer on alternative validation criteria for analytical procedures.

Comment Summary #32: The commenter suggested that a robustness experiment could be designed such that it systematically varies the parameters of interest in few experiments.

Response: Comment not incorporated. This is outside of the scope of the General Chapter.

General Chapter/Sections: <1010> Analytical Data – Interpretation and Treatment/Multiple Sections

Expert Committee: General Chapters–Statistics

No. of Commenters: 9

Section 1. Introduction

Comment Summary #1: The commenter recommended the use of “product” instead of “formulation” in describing process and formulation design for the assurance of pharmaceuticals.

Response: Comment not incorporated. Both the drug substance and drug product are used synonymously within the scope of process and formulation design.

Comment Summary #2: The commenter indicated there is currently no guidance on Analytical Target Profile (ATP) within the *USP-NF*, or within the current General Chapter, although the term is introduced within the scope of this section.

Response: Comment not incorporated. However, the USP Validation and Verification Expert Panel are undertaking the development of a General Information chapter for the Analytical Target Profile (ATP). A reference has been included for the ATP, where the following text has been included in *Appendix 3*, “The option of minimum performance requirements has evolved into the concept of the analytical target profile (ATP) which has been introduced in Pharmacopeial Forum (Barnett et al. 2016).”

Comment Summary #3: The commenter indicated that metrological principles are new concepts to industry and additional discussion is needed within the scope of the General Chapter.

Response: Comment incorporated. Discussion of metrological principles specific to measurement uncertainty is provided in *Appendix 4*.

Comment Summary #4: The commenter recommended expounding upon the definitions of “investigational studies” and “confirmatory studies” within the scope of analytical procedure measurements and empirical studies.

Response: Comment not incorporated. The definitions for both terms are adequately defined.

Comment Summary #5: The commenter recommended that the use of the term “parameter” of a pharmaceutical study may be misunderstood to mean method parameter or control variable (e.g., temperature, flow rate).

Response: Comment incorporated. The term “parameter” is replaced with “population parameter”.

Comment Summary #6: The commenter suggested that additional clarification may be warranted as it is common practice to explore statistical outliers at various stages of data analysis, including after the fitting of a statistical model.

Response: Comment incorporated. Additional text added to expand upon outlier exploration.

Section 2. Prerequisite Laboratory Practices and Principles

Comment Summary #7: The commenter suggested that text addressing the handling of significant figures and decimal places in data reporting is inconsistent with USP *General Notices 7.20 Rounding Rules*.

Response: Comment incorporated. Text within the General Chapter was changed to be consistent with USP *General Notices 7.20 Rounding Rules*. Within this section, the text was changed to, “Rounding of results from uses of analytical data should occur only after final calculations are completed as per the General Notices and Requirements.”

Comment Summary #8: The commenter recommended the section expand upon its relationship to USP General Chapter <1226>, ensuring consistency of concepts.

Response: Comment incorporated. Reference to USP General Chapter <1226> is included for analytical procedure verification.

Comment Summary #9: The commenter recommended that the section clarify that an investigation is required prior to retesting of a sample when it fails to meet the performance requirement.

Response: Comment incorporated. The text was changed to, “A failure to meet a sample performance requirement can result in a retest of the sample after an appropriate investigation, versus a complete repeat of an analytical procedure run.”

Section 3. Basic Statistical Principles and Uncertainty

Comment Summary #10: The commenter requested a definition be included for “producers and consumers risk” from the sentence within the *Uncertainty* subsection stating, “in most cases these are components of producers and consumers risks respectively.”

Response: Comment incorporated. The sentence in question was removed.

Comment Summary #11: The commenter requested clarification and suggested that the decision to report an average result would be at the discretion of the regulatory authorities. The text in question is captured under subsection *Averaging* and states, “There may be instances when one might consider the use of averaging because the variability associated with the average value better meets the target measurement uncertainty requirement for its use. Thus, the choice of whether to use individual measurements or averages will depend upon the use of the measurement and the risks associated with making decisions from the measurement.”

Response: Comment not incorporated. Regulatory authorities are inconsistent and unclear on this point.

Comment Summary #12: The commenter suggested alternative methods for reporting individual measurements in lieu of reporting the average value.

Response: Comment not incorporated. However, the text was changed for clarification: “...it is generally advisable to average the individual values to represent the sample value. This should be supported by some routine suitability check on the variability amongst the individual measures.”

Comment Summary #13: The commenter suggested that additional metrics, such as range, may be used as a decision rule to report the average value of individual measures.

Response: Comment incorporated. The text was changed to include range: “A decision rule, which defines and describes how a decision will be made, should be explicit to the population parameter of interest. ... When this is variability amongst the individual measurements, then it should be the standard deviation, %CV, or range.”

Comment Summary #14: The commenter suggested equation (2) applies when $n > 2$ and is a difference equation when $n = 2$.

Response: Comment not incorporated. Equation (2) applies for $n > 2$ and $n = 2$.

Comment Summary #15: The commenter suggested that the subsection *Averaging* may be contradictory to regulatory authorities and guidance documents, including reference to 21 CFR 211.192, “Any unexplained discrepancy (including a percentage of theoretical yield exceeding the maximum or minimum percentages established in master production and control records) or the failure of a batch or any of its components to meet any of its specifications shall be thoroughly investigated, whether or not the batch has already been distributed.”

Response: Comment not incorporated. Regulatory guidance documents and recommendations are inconsistent on this point.

Comment Summary #16: The commenter suggested revisions to <1210> in order to ensure consistency between General Chapters <1210> and <1010> equations.

Response: Comment not incorporated into current General Chapter, and revisions to General Chapter <1210> are not being considered.

Comment Summary #17: The commenter recommended use of %RSD in lieu of %CV throughout the General Chapter.

Response: Comment incorporated. The first instance of coefficient of variation (%CV) in the text includes relationship to percent relative standard deviation (%RSD) as follows, “Statistical measures used to estimate the center and dispersion of a population include the mean,

standard deviation, and expressions derived there from, such as the percent coefficient of variation (%CV), sometimes referred to as percent relative standard deviation (%RSD).”

Comment Summary #18: The commenter indicated that %CV should not be reported for measurands in percent units and suggested including additional text to achieve normality by using a logarithmic transformation.

Response: Comment not incorporated. Text captured in *Appendix 2*, subsection *Transformation* includes a discussion on logarithmic transformations.

Comment Summary #19: The commenter indicated that variability of percentage measurands can be reported as standard deviation.

Response: Comment incorporated. Text changed to, “It is incorrect to report %CV for measurands reported as a percentage (e.g., percent purity) or which are in log units (e.g., pH). In such a case, the appropriate measure of variability is the standard deviation. The same is true of measurands which are log-normally distributed, and are log transformed. See Appendix 2 on Data Considerations for recommendations on log transformed data.”

Comment Summary #20: The commenter suggested including guidance on when prediction intervals, tolerance intervals, and confidence intervals should be used. For example, the commenter indicated that confidence intervals are typically used to bound a single value (e.g., mean), tolerance intervals bound a range of data with a degree of confidence, and prediction intervals determine the probability of the next results based on previous observations. In addition, the commenter suggested aligning text to General Chapter <1210>.

Response: Comment not incorporated. Definition of confidence intervals is expounded upon in subsequent paragraphs in the *Statistical Intervals* subsection. Reference to General Chapter <1210> is included for discussion on prediction and tolerance intervals.

Comment Summary #21: The commenter indicated that a two-sided interval is composed of a lower bound (LB) and an upper bound (UB).

Response: Comment incorporated. Text changed to include, “A two-sided interval is composed of a lower bound LB and an upper bound UB.”

Section 4. Study Considerations

Comment Summary #22: The commenter indicated the discussion of difference versus equivalence tests is heavy in statistical language such as “unknown parameter value” and “unknown parameter value equivalent to some expected value.”

Response: Comment incorporated. The section was rewritten with definitions and examples.

Comment Summary #23: The commenter indicated that the hypotheses do not change when blocking is used, only the calculations change, and thus the sentence, “The hypotheses expressed thus far are associated with comparing two independent groups” should be rephrased.

Response: Comment incorporated. The section was rewritten.

Comment Summary #24: The commenter requested additional explanation and examples on the following text, “where the factor k should be justified on the basis of ensuring fitness for use of the new procedure.”

Response: Comment partially incorporated. The sentence was deleted, and the discussion was moved from Section 4 to Section 5 of the General Chapter, subsection *Determination of d and k* .

Comment Summary #25: The commenter indicated that the term “blocking” was mentioned several times throughout the Section. They further suggested the Section expand upon pairing and blocking of datasets.

Response: Comment not incorporated. References to “blocking” were removed in the rewriting of this section, and further explanation is provided in Section 5.

Comment Summary #26: The commenter indicated that the half width of the 95% confidence interval is known as the margin of error and is an important concept in estimating parameters.

Response: Comment not incorporated. References to half width of the 95% confidence interval were removed in the rewriting of this section.

Comment Summary #27: The commenter indicated that the solution for n in equation (9) cannot be done by the formula as it is contained within the t-distribution quantile.

Response: Comment incorporated. Following equation (9), text was changed to: “Since the degrees of freedom of the t-value are a function of n, one must either solve equation (9) iteratively, or use an approximation by replacing the t-value with the associated Z-value.”

Comment Summary #28: The commenter indicated that ASTM E2935-15 provides additional guidance on sample size calculations for estimation, tests of differences, and tests of equivalence.

Response: Comment not incorporated. The EC recognizes that there are other useful standards on this topic.

Comment Summary #29: The commenter suggested that sampling lots or multiple levels of a material and collecting measurements with two analytical procedures may be contradictory to the prior statement in the Section which states “procedure comparison should address accuracy and precision across the range of the assay.”

Response: Comment partially incorporated. The discussion was moved from Section 4 to Section 5 of the General Chapter.

Comment Summary #30: The commenter indicated that transformations are often decided during analysis, and not prior to analysis, as the determination of data normality must first be evaluated.

Response: Comment incorporated. The consideration of transformation was moved to the end of the paragraph under subsection *Study Analysis*, and the text was changed to: “Transformations based on either scientific information or empirical evidence can be considered, and screening for outlying values and subsequent investigations completed (see *Appendix 2: Models and Data Considerations*).”

Section 5. Comparison of Analytical Procedures

Comment Summary #31: The commenter requested an example be provided to clarify the following text, with cross references to General Chapters <1224> and <1010> : “It is often necessary to compare two analytical procedures to determine if differences in accuracy and precision are less than an amount deemed practically important.”

Response: Comment incorporated. For clarification, text was changed to: “For example, General Notices 6.30 describes the need to produce comparable results to the compendial method. Transfer of analytical procedures as described in USP <1224> *Transfer of analytical procedures* allows for comparative testing as an acceptable process. A change in a procedure includes a change in technology, a change in laboratory (called transfer), or a change in the reference standard in the procedure.”

Comment Summary #32: The commenter suggested additional text detailing the study design approaches to method comparisons. The first approach is described in the General Chapter using legacy data (with large amounts of data) being compared to a new method (with limited data). The second approach suggested is where both methods have limited data.

Response: Comment partially incorporated. For clarity, the text under subsection *Accuracy* was changed to: “In some cases there exists a large amount of legacy data that may inform the decision, while in other cases there may be only limited data.”

Comment Summary #33: The commenter suggested the subsection *Precision* was incomplete and of limited use without a direct reference to Kringle et al. (2001).

Response: Comment incorporated. Additional text was added to this section to improve clarity.

Comment Summary #34: The commenter suggested that any new method would meet the requirements specified in the ATP, and a comparison study design is not used to determine the ATP, but rather demonstrates the new method provides equivalent or superior quality of data.

Response: Comment incorporated. The subsection *Study Objective Using a Lifecycle Approach* has been removed.

Comment Summary #35: The commenter suggested the subsection *Study Design* may be contradictory to the following previous statement in the General Chapter, “procedure comparison should address accuracy and precision across the range of the assay.”

Response: Comment not incorporated. No contradiction identified.

Comment Summary #36: The commenter requested that additional equations be included for the unequal sample size adjustments for equation (18), as opposed to the textbook reference provided.

Response: Comment incorporated.

Comment Summary #37: The commenter requested equation (20) be moved to after its following paragraph, as the hypotheses only apply if $\sigma_L^2 = 0$. Whereas, prior to the next paragraph it appears to be a general hypothesis statement regardless if $\sigma_L^2 = 0$.

Response: Comment partially incorporated. The section was reorganized, and the subsection was removed.

Comment Summary #38: The commenter suggested to include the formula to estimate confidence intervals of the variability for a new method in equation (23) for when $\sigma_L^2 > 0$ and no lot replicates are available. The commenter requested clarification on whether the guidance includes confidence intervals along with a variance estimate for a new method.

Response: Comment partially incorporated. Equation (23) has been removed.

Comment Summary #39: The commenter suggested clarification related to replication of lots in a paired design used to obtain separate estimates of σ_N^2 and σ_O^2 .

Response: Comment partially incorporated. The section was reorganized.

Comment Summary #40: The commenter requested the equation for calculation of sample size when testing for population precision difference be included, as equation (25) is only for sample size calculation when testing the population mean (accuracy) difference.

Response: Comment incorporated. The equation was added.

Comment Summary #41: The commenter requested clarity on the preference of the sample size calculation formula, equation (25), in the proposed revision compared with the currently official General Chapter equation.

Response: Comment not incorporated. The equation included in the proposed revision is a general formula, and examples are provided for clarity.

Comment Summary #42: The commenter requested clarity on how k is defined based on the risk assessment and indicated the assumption of equal standard deviation of the old method to the new method in determining the value of d is incorrect.

Response: Comment incorporated. The General Chapter proposes a solution by determining values of d and k simultaneously.

Comment Summary #43: The commenter requested a comment be added to the beginning of the General Chapter indicating that the information within is applicable for normal distribution data.

Response: Comment not incorporated. Refer to Section 3, *Statistical Assumptions*.

Comment Summary #44: The commenter requested a reference or equation deduction details for equation (31).

Response: Comment incorporated. The subsection *Study Design and Analysis Using a Lifecycle Approach* has been removed.

Comment Summary #45: The commenter suggested that there are inconsistencies between equations (31) and (32).

Response: Comment incorporated. The subsection *Study Design and Analysis Using a Lifecycle Approach* has been removed.

Appendix 1. Control Charts

Comment Summary #46: The commenter recommended replacing the term “attribute” with “variable” because the term “attribute” is often used for cases when data is “pass/fail”, for which p-charts would apply and not I-MR, which could be confusing.

Response: Comment incorporated. The term “attribute” was replaced with “variable” throughout.

Comment Summary #47: The commenter suggested that the moving range statistic (MR) is a measure of short-term variability compared to “overall long-term” variability, and better describes the “expected variability” behavior within the system when the desired control chart goal is to flag any shift in the means.

Response: Comment incorporated. The text was changed to include the following statement and definition of MR: “The standard deviation can be estimated in a couple of ways, but for an I-chart, best practice is to base the estimate on the moving range statistic (MR). This estimator considers the ‘short term’ variability of the process and guards against limits that are too wide if an unexpected trend exists in the data.”

Comment Summary #48: The commenter indicated the Figure A-1 chart is an I-chart, and the MR part is not shown.

Response: Comment incorporated. Figure 1 is now an I-chart for example data set.

Comment Summary #49: The commenter suggested that Table A-1 Nelson Rules could all be applied, and the I-MR chart does in fact use three standard deviation limits as the moving range calculation is an estimate of three standard deviations.

Response: Comment partially incorporated. The text was changed to: “The Nelson rules are provided in Table 10. The relevance of these rules depends on the type of control chart. All eight rules can be applied to an I-chart, and selection of the particular rules depends on the desired sensitivity of the control process.”

Comment Summary #50: The commenter indicated that the column labeled “Indication” in Table A-1 is not generally applicable to all charts when applying Nelson rules.

Response: Comment not incorporated. The Nelson rules listed in the Table are for I-charts only.

Comment Summary #51: The commenter indicated that the sample standard deviation should not be used for the creation of the control chart limits.

Response: Comment not incorporated. However, the subsection *Detection of Out-Of-Control Results* was rewritten, and the example provided was removed. ASTM E2587 (2016), Montgomery (2013), and Wheeler (2012) references were provided for example applications.

Appendix 2. Models and Data Considerations

Comment Summary #52: The commenter indicated Figure A-3 and Figure A-4 had reversed references in the body of the text.

Response: Comment incorporated. The section has been rewritten to incorporate all necessary information into one figure (Figure 3).

Comment Summary #53: The commenter suggested that an example should be provided for determining normality.

Response: Comment incorporated. The text was changed to include the following: “Statistical tests of normality are described in Section 1.3.5 of the previously referenced NIST handbook and available in statistical software packages.”

Comment Summary #54: The commenter requested that an example should be provided to further clarify the term “fold-variation” in the sentence, “Because S_T is non-negative, $GSD \geq 1$ and represents a fold-variation in the original scale”.

Response: Comment incorporated. Fold-variation is not intended to be used as a statistical term. However, the text was changed to: “Because S_T is non-negative, $GSD \geq 1$ and represents a fold-variation in the response scale. While a summary for arithmetically scaled responses can

be written as $\bar{Y} \pm S$, this might be summarized as GM \times/\div GSD, or GM/GSD to GM \times GSD for geometrically scaled responses. If for example GSD = 1.25 and GM = 1.0, a range might be summarized as $1.0/1.25 = 0.80$ to $1.0 \times 1.25 = 1.25$. It should be noted that this represents a 1-standard deviation range. A more appropriate range might be calculated in the log transformed scale (see below)."

Comment Summary #55: The commenter indicated that inverting the transformation in equation A9 does not provide a confidence interval for the untransformed mean, but instead a confidence interval for the geometric mean.

Response: Comment incorporated. Equation (46) is described as the confidence interval on the geometric mean in the original scale.

Comment Summary #56: The commenter requested clarity on what is considered a large number of observations when detecting normality.

Response: Comment partially incorporated. The text was changed to: "Statistical tests of normality are described in Section 1.3.5 of the previously referenced NIST handbook and available in statistical software packages." Reference to the number of observations has been removed.

Comment Summary #57: The commenter requested additional information on alternative approaches for assessing outliers, including examination of standardized residuals.

Response: Comment incorporated. The text was changed to: "'Outlier labeling' is informal recognition of outlying results that should be further investigated with more formal methods. Outlier labeling is most often performed visually with graphical techniques such as residual plots, standardized residual plots, or box and whisker plots. 'Outlier identification' is the use of statistical significance tests to confirm that the values are inconsistent with the known or assumed data distribution. The selection of the correct outlier identification technique often depends on the initial recognition of the number and location of the values."

Appendix 4. The Principle of Uncertainty

Comment Summary #58: The commenter indicated there are inconsistencies in the symbols of Equation 3 in *Appendix 4*, and β_N does not appear anywhere in the equation.

Response: Comment incorporated. The equation has been removed.

General Comments

Comment Summary #59: The commenters suggested several editorial changes, including a number of equation and variable definition edits, sentence structure edits, and typographical errors.

Response: Comments incorporated. Editorial changes provided by several commenters were addressed appropriately and incorporated as necessary.

Comment Summary #60: The commenter suggested the flow of topics and examples in the General Chapter could be improved, and it is not always clear how to implement and compare current approaches to the analytical QbD approach.

Response: Comment incorporated. The chapter was reorganized and parts were rewritten for clarity. In addition, reference to QbD has been removed from the General Chapter. A reference has been included for the Analytical Target Profile (ATP), where the following text has been included in *Appendix 3*, "The option of minimum performance requirements has evolved into the concept of the analytical target profile (ATP) which has been introduced in Pharmacopeial Forum (Barnett et al. 2016)."

Comment Summary #61: The commenter recommended a Table of Contents may be helpful to the reader.

Response: Comment not incorporated. A summary of the contents of the General Chapter is discussed in the Introduction.

Comment Summary #62: The commenter suggested that the paragraph on “precision” should be positioned before the paragraph on “accuracy” as the decision of whether equal variances in the evaluation of accuracy can be assumed or not is based on the result of the precision comparison.

Response: Comment not incorporated. The EC concludes that “accuracy” should proceed “precision”.

Comment Summary #63: The commenter suggested the subsection *Study Objective Using a Lifecycle Approach* may not be appropriate in the *Comparison of Analytical Procedures* section.

Response: Comment incorporated. The subsection has been removed.

Comment Summary #64: The commenter suggested that outliers could also be used to support laboratory investigations.

Response: Comment not incorporated. The wording of the text in subsection *Outliers* does not preclude the support of a laboratory investigation.

Comment Summary #65: The commenter recommended noting in the General Chapter that care is needed to ensure an analytical procedure is operated in similar fashion as it will be in routine operation, as quite often automated DoEs artificially reduce the typical variability observed.

Response: Comment not incorporated. There may exist a reason for non-routine operations.

Comment Summary #66: The commenter suggested information related to process and analytical variability is confounded (e.g., in the analysis of tablets or blisters).

Response: Comment not incorporated. The comment is outside the scope of the General Chapter.

Comment Summary #67: The commenter suggested a glossary of terms would be helpful to the reader.

Response: Comment not incorporated. Terms have been adequately defined in the text.

Comment Summary #68: The commenter recommended improving upon sections of the General Chapter that discuss the concepts of population and sample, including method validation and method comparison.

Response: Comment incorporated throughout text. Text within the *Introduction* and Section 5, *Comparison of Analytical Procedures*, were improved upon.

Comment Summary #69: The commenter recommended including guidance on who the intended audience is of the General Chapter, the statistician or analytical chemist who has basic statistics training.

Response: Comment incorporated. The text of the *Introduction* was changed to: “This chapter has been written for the laboratory scientist and the statistician alike. The laboratory scientist is primarily skilled in the analytical procedures and the uses made of those procedures and should be aware of the value of statistical design and analysis in their practices. The statistician is primarily skilled in the design of empirical studies and the analysis which will return reliable decisions and should appreciate the science and constraints within the laboratories. While variously knowledgeable in their understanding across specialties, both disciplines should value the essential components that comprise uses of analytical data.”

Comment Summary #70: The commenter suggested the General Chapter is far too expansive and statistically dense for the analytical chemist and recommends that additional details are captured for practical applications, while referencing statistical methods and equations for further reading.

Response: Comment incorporated. Additional references were included for statistical methods and equations. In addition, the appendices were rewritten to provide additional detail.

Comment Summary #71: The commenter suggested that some of the material in the Appendices is not connected to the main text and/or proper context, an example being *Appendix 1. Control Charts*.

Response: Comment incorporated. *Appendix 1* was referenced throughout the text as appropriate.

Comment Summary #72: The commenter suggested the removal of *Appendix 5*, as Bayesian statistics may not be appropriate for this General Chapter.

Response: Comment not incorporated. However, *Appendix 5* was rewritten for clarity.

Comment Summary #73: The commenter suggested additional detail throughout the chapter would benefit the reader, particularly in sections related to sample size, study design, and reporting.

Response: Comment incorporated. The General Chapter was redrafted in many sections to improve the overall clarity and writing.

General Chapters/Sections: <1043> *Ancillary Materials for Cell, Gene, and Tissue-Engineered Products/ Multiple Sections*

Expert Committee: Biologics Monographs 3 – Complex Biologics

No. of Commenters: 2

Introduction

Comment Summary #1: The commenter suggested that the phrase, “final CGT product final CGT product” should differentiate between materials used in processing from materials used in QC assays.

Response: Comment not incorporated. Comment is beyond the scope of the chapter, which covers materials used in the product manufacturing.

Comment Summary #2: In the definition of an ancillary material, which includes materials that come into contact with the cellular starting material, the commenter suggested that some starting materials are not intended to be present in the final product and can be considered an impurity, for example undifferentiated cells in an induced Pluripotent Stem Cell (iPS) product.

Response: Comment not incorporated. Undifferentiated cells are not considered ancillary materials.

Comment Summary #3: In reference to this text in the *Introduction*, “Excipients, which are intended to be present in the final product, are therefore not AMs”, the commenter indicated that excipients are an example of a constituent material.

Response: Comment not incorporated. There was no actionable text change suggested.

Comment Summary #4: In reference to this sentence in the *Introduction* of the chapter, “However, ‘helper’ viruses and ‘helper’ plasmids may be considered AMs if they are not intended to be part of the final product”, the commenter indicated that “helper” viruses usually provide “trans” factors such as packaging components & accessory protein and are not intended to incorporate genetic material.

Response: Comment not incorporated. The statement in the chapter is correct and addresses the comment as is.

Comment Summary #5: The commenter suggested that statements in the introduction that describe examples of ancillary materials may overly generalize as some of the examples could be considered excipients or even final products.

Response: Comment not incorporated. The chapter defines reagents that are specifically used as ancillary materials.

Comment Summary #6: The commenter suggested adding a reference to the text that describes specific requirements for cell and virus bank certification and regulatory approval.

Response: Comment incorporated. A reference to ICH Q5D was added.

Comment Summary #7: The commenter recommended changing the order of sentences of this text because the sentences do not logically flow: “Because CGT products are not usually amenable to extensive purification, filtration, and terminal sterilization procedures, reagents and material qualification are critically important to ensuring CGT product quality. The purpose of

this chapter is to provide guidance on the development of appropriate material qualification programs for CGT products.”

Response: Comment incorporated.

Comment Summary #8: In reference to this sentence in the chapter, “Cell banks and virus banks are also not considered AMs; guidance documents describe specific requirements for cell and virus bank certification and regulatory approval,” the commenter suggested revising, as a feeder layer would be considered an ancillary material.

Response: Comment incorporated. The text was changed to include that feeder layer cells that are not intended to be incorporated in the final product may be considered an AM or an impurity.

Comment Summary #9: The commenter indicated that the regulatory status of a scaffold would have to be reviewed as it is not necessarily a device and not necessarily a combination product. It is possible that the scaffold could be considered an ancillary material, such as beads used to grow adherent cells in suspension.

Response: Comment partially incorporated. The text was changed to clearly define when scaffolds or delivery devices are not an AM.

Regulatory Considerations

Comment Summary #10: The commenter indicated that 21CFR 876.5885 is regulation provided to device manufacturers.

Response: Comment not incorporated. The 21 CFR 876.5885 is regulation for device manufacturers; however, it provides some information to cell therapy manufacturers for tissue media.

Impact of Ancillary Material Quality on Product Quality, Sourcing of Ancillary Materials

Comment Summary #11: In reference to this sentence in the chapter, “The most direct way to achieve this goal is to eliminate AMs containing materials of human or animal origin,” the commenter indicated that eliminating AMs containing materials of human or animal origin is a good goal but may be challenging to eliminate all sources of these proteins because many serum-free mediums contain insulin, transferrin, and albumin.

Response: Comment not incorporated. The commenter provided an observation, but no actionable change was requested.

Comment Summary #12: In reference to this sentence in the chapter, “The most direct way to achieve this goal is to eliminate AMs containing materials of human or animal origin,” the commenter indicated that serum-free culture medium can be contaminated with mycoplasma through cross-contamination.

Response: Comment not incorporated. The commenter provided an observation, but no actionable change was requested.

Comment Summary #13: In reference to the sentence from the chapter, “Specific safeguards are required in order to minimize or eliminate the risk of transmitting adventitious agents (viruses, bacteria, mycoplasma, protozoa, fungi, prions, etc.) when sourcing AMs using human- or animal-derived components such as sera, antibodies, or growth factors,” the commenter suggested changing the word “required” to “necessary”.

Response: Comment incorporated.

Comment Summary #14: The commenter suggested adding “and traceability” to this sentence from the chapter, “Screening and qualifying (e.g., through bacterial or viral testing) and documenting (e.g., through herd certification) the sources of human- or animal-derived components as being free of suspected adventitious agents.”

Response: Comment incorporated.

Qualification of Ancillary Materials

Comment Summary #15: The commenter indicated that requirements for licensure may also vary by country.

Response: Comment not incorporated. Regardless of where the product is licensed, it may still require qualification as an AM.

Comment Summary #16: The commenter indicated that inappropriate materials used in the generation of a cell bank might raise serious safety concerns, and potentially necessitate the generation of a new bank.

Response: Comment not incorporated. The commenter provided an observation, but no actionable change was requested.

Comment Summary #17: The commenter suggested adding the phrase “used in manufacturing” to the end of this sentence in the chapter: “AM qualification is the process of acquiring and evaluating data to establish the source, identity, purity, safety, and overall suitability of a specific AM.”

Response: Comment incorporated.

Comment Summary #18: The commenter suggested adding the phrase, “establishing and continuously re-evaluating the adequacy” to this sentence in the chapter, “CGT product developers and manufacturers are responsible for establishing rational and scientifically sound AM qualification programs.”

Response: Comment partially incorporated. The phrase, “and periodically reevaluating as necessary” was added to the end of the sentence.

Comment Summary #19: The commenter suggested citing ICH Q9.

Response: Comment partially incorporated. ICH Q9 is already cited in the chapter and the reference will be added to the reference list at the end of the chapter.

Risk Management

Comment Summary #20: The commenter indicated that an adventitious agent introduced through an AM upstream could also result in a high risk to the patient.

Response: Comment not incorporated. The commenter provided an observation, but no actionable change was requested.

Comment Summary #21: The commenter indicated that for a licensed AM there is not a greater emphasis placed on lot-to-lot variability as it is a concern for all AM. Research grade would have the additional safety concerns. Variability would be appropriate similarly, regardless of grade.

Response: Comment not incorporated. AM qualification should be comprehensive irrespective of the source.

Comment Summary #22: In reference to this sentence in the chapter, “Validation of the CGT product manufacturing process to demonstrate removal or inactivation of adventitious agents or specific contaminants,” the commenter indicated that there are very few cases where inactivation or clearance can be applied to CGT products.

Response: Comment not incorporated. The chapter provides a list of options for CGT product manufacturers.

Comment Summary #23: The commenter indicated that “Confirm certificate of analysis test results” and “certificate of analysis verification testing” might be synonymous and requested clarification.

Response: Comment partially incorporated. The two phrases are not synonymous, but related. The phrase, “Confirm certificate of analysis test results” was removed from *Table 2*, as this phrase was redundant in *Table 2*. *Table 3* was revised to include the phrase “and/or testing” after “Upgrade manufacturing process”. These revisions provided clarification and removed the redundancy.

General Chapters/Sections: <1046> *Cell-Based Advanced Therapies and Tissue-based Products*

Expert Committee: Biologics Monographs 3 – Complex Biologics

No. of Commenters: 4

Introduction

Comment Summary #1: The commenter requested that a sentence be added to the last paragraph to note that the regulatory path will depend on the specifics of the product.

Response: Comment not incorporated as this chapter gives general guidance, and specific information would be provided by the regulator.

Comment Summary #2: The commenter suggested that in the text, “For tissue-based grafts that contain non-autologous cells, the cells are derived from the same cadaveric donor”, the donor does not have to be cadaveric.

Response: Comment incorporated. The word “cadaveric” was removed from the text.

Comment Summary #3: The commenter indicated that there are examples of cell therapy products that do not involve cells; therefore, good tissue practices (GTPs) are not always required, although for most products they are required.

Response: Comment incorporated. The word, “most” was added to the text, “Additionally, most cellular therapy products must comply with both good tissue practices (GTPs)”.

Comment Summary #4: The commenter indicated that the term HCT/Ps (human cells, tissues, and tissue-based products) does not include cell-based advanced therapies.

Response: Comment incorporated. The term “cell-based advanced therapies” was removed from the sentence.

Components Used in Cell-Based Advanced Therapies And Tissue-Based Product Manufacturing, Introduction

Comment Summary #5: The commenter indicated that rational and scientifically sound programs must be developed for each component is also true for non-cell therapies.

Response: Comment not incorporated. Non-cell therapies are out of scope of the chapter.

Components Used in Cell-Based Advanced Therapies and Tissue-Based Product Manufacturing, Qualification of Source Cells and Tissues

Comment Summary #6: The commenter indicated that autologous might also be more specific to the patient, and potentially more efficacious for that reason.

Response: Comment not incorporated. No change to the text was requested.

Comment Summary #7: The commenter indicated that allogeneic material source is often chosen because it could potentially be an off-the-shelf product.

Response: Comment not incorporated. Differences between autologous and allogeneic are adequately described in the section of the General Chapter.

Comment Summary #8: The commenter indicated that the phrase, “and place in the product life cycle” should be clarified.

Response: Comment incorporated. The phrase was deleted to avoid confusion, and because it is not needed.

Comment Summary #9: The commenter indicated that the statement, “Despite the potential complications of using allogeneic donor cells or tissues, in the absence of other alternatives the risk to-benefit ratio is often favorable” was a statement of judgement that should not be included in the General Chapter.

Response: Comment partially incorporated. The phrase, “is often favorable” was changed to “may be acceptable”.

Components Used in Cell-Based Advanced Therapies and Tissue-Based Product Manufacturing, Donor Eligibility

Comment Summary #10: The commenter indicated that the term “physical examination” implies more than is conducted.

Response: Comment incorporated. The sentence was changed to include, “could include performing a physical assessment” instead of a “physical examination”.

Comment Summary #11: The commenter indicated that some assays are supplied as test kits, some are listed as tests.

Response: Comment incorporated. The phrase, “test kits” was added to the text.

Components Used in Cell-Based Advanced Therapies and Tissue-Based Product Manufacturing, Animal Sources Of Cells And Tissues

Comment Summary #12: The commenter indicated that the “The FDA guidance Source Animal, Product, Preclinical, and Clinical Issues Concerning the Use of Xenotransplantation Products in Humans (April 2003)” was updated in 2016.

Response: Comment incorporated.

Comment Summary #13: The commenter suggested to revise the last sentence of the second paragraph in this section by adding the word, “generally” to reflect the fact that the information in this chapter on the regulatory path is general information.

Response: Comment incorporated.

Components Used in Cell-Based Advanced Therapies and Tissue-Based Product Manufacturing, Cell Bank System

Comment Summary #14: The commenter indicated that in addition to identity, sterility, purity, viability, and the presence of viruses and mycoplasma, the MCB and the WCB could also be tested for endotoxin, although it is not always performed.

Response: Comment not incorporated. The chapter describes the tests that are “at a minimum” performed, and do not need to include tests that are not always performed.

Comment Summary #15: The commenter suggested that “minimally” be changed to “at a minimum” in this sentence, “The MCB and WCB should be minimally tested for identity, sterility, purity, viability, and the presence of viruses and mycoplasma.”

Response: Comment incorporated.

Comment Summary #16: The commenter indicated that the statement, “Decellularized (i.e., nonviable) xenograft tissue-based products are not subject to the PHS guideline and FDA guidance mentioned above and are regulated in the US as medical devices and must follow the applicable regulatory pathway [e.g., 510(k)] and all related requirements.” does not apply in all cases.

Response: Comment incorporated. The phrase, “In most cases” was added to the beginning of the sentence.

Comment Summary #17: The commenter indicated that a Master Cell Bank may be the only bank used to produce a licensed biologic.

Response: Comment incorporated. The phrase “in early trials” was deleted to clarify that the “The WCB, or MCB becomes the source of cells for every batch produced for human use”.

Components Used in Cell-Based Advanced Therapies and Tissue-Based Product Manufacturing, Cell Bank Qualification

Comment Summary #18: The commenter indicated that although Q5A is cited, Q5D also applies and should be cited.

Response: Comment not incorporated. Q5A gives specific recommendations for testing, while Q5D gives recommendations for characterization. Q5D mentions viral testing, but does not give specifics, so it does apply, but not in this context.

Components Used in Cell-Based Advanced Therapies and Tissue-Based Product Manufacturing, Characterization of MCB and WCB

Comment Summary #19: The commenter indicated that if the same sponsor is using multiple human cell lines as source material, identity testing will require an assay that can distinguish each one.

Response: Comment not incorporated. The list of testing is adequate. Sponsors with mixed cell lines would know to sort and test using the list of tests provided in the General Chapter.

Comment Summary #20: The commenter indicated that other parameters, such as cell counts, should be evaluated before and after freezing and that stability studies could further evaluate morphology and growth kinetics.

Response: Comment not incorporated. The use of the phrase, “such as” indicates that a list of examples is included in the General Chapter and does not include all possible requirements.

Components Used in Cell-Based Advanced Therapies and Tissue-Based Product Manufacturing, Biocompatible Scaffold Materials

Comment Summary #21: The commenter indicated that the breakdown products of scaffold materials should not be toxic or interfere with the function of the product.

Response: Comment not incorporated. The material used must be biocompatible, and a safety assessment would be part of early product development.

Comment Summary #22: The commenter suggested to change the word “possible” to “suitable” in the phrase, “When possible, use scaffolds that have previously been approved for other clinical uses”.

Response: Comment incorporated.

Comment Summary #23: The commenter indicated that the properties a scaffold should have would depend on the intended purpose and the necessary function in vitro and in vivo.

Response: Comment incorporated. The text was changed to include, “Depending on the intended use,” and “should” was used instead of “must” to describe the properties of the scaffold material.

Comment Summary #24: The commenter suggested to remove the quotations from the word “regulated” in the first sentence of this section.

Response: Comment incorporated.

Comment Summary #25: The commenter suggested to replace PCL with polycaprolactone.

Response: Comment incorporated.

Comment Summary #26: The commenter suggested to add the word, “some” to the beginning of the following text, “wound healing or skin substitute products contain cells seeded on a scaffold.”

Response: Comment incorporated.

Comment Summary #27: The commenter suggested to delete the word, “dermis” as “dermis demineralized cortical bone particles” does not exist.

Response: Comment incorporated.

Comment Summary #28: The commenter indicated that ISO 10993 is a series of standards. ISO 10993-1 should be the correct reference as ISO 10993-1 provides guideline on biological evaluation and testing of medical device within a risk management process and suggested revising the references to ISO standard (ISO 10993-1) and the FDA guidances.

Response: Comment partially incorporated. The reference to FDA Blue Book G95-1 was updated to FDA Guidance: Use of International Standard ISO 10993-1.

Components Used in Cell-Based Advanced Therapies and Tissue-Based Product Manufacturing, Qualification of Ancillary Materials

Comment Summary #29: The commenter recommended rewording to clarify the fact that there are currently no cGMPs covering the manufacture of AMs. The exception is ancillary materials that are marketed medicinal products, which are manufactured according to cGMP.

Response: Comment not incorporated. The statement describes the ideal situation but does not imply that cGMP is a regulatory requirement.

Comment Summary #30: The commenter indicated that clinical protocols and informed consent forms should consider the risk of possible antigenic materials.

Response: Comment not incorporated. Requirements for clinical trials are beyond the scope of the chapter. The limits could be included in inclusion/exclusion criteria for a trial.

Comment Summary #31: The commenter agreed with the statement from the General Chapter that, “Ideally, each ancillary material should be produced under conditions that are in compliance with cGMP”, but also noted that the risk of materials goes beyond where it was manufactured. Materials with inherent risk will still be risky even if manufactured under full cGMP compliance.

Response: Comment not incorporated as no change was recommended by the commenter.

Comment Summary #32: The commenter suggested adding “including full traceability of the ancillary material and raw materials used to make it.”

Response: Comment not incorporated. The overall qualification program covers what is suggested to be added, so no additional text is needed.

Comment Summary #33: The commenter suggested to add, “Human cellular material should have traceability back to donor (1271.290)”.

Response: Comment not incorporated. The comment is out of scope of the content of the General Chapter.

Comment Summary #34: The commenter indicated that cell separation devices such as flow sorters or Clinimacs are considered manufacturing equipment, not ancillary materials. Paramagnetic beads could be considered ancillary materials.

Response: Comment incorporated. “Cell separation devices” was changed to “components of cell separation systems.”

Components Used in Cell-Based Advanced Therapies and Tissue-Based Product Manufacturing, Qualification of Excipients

Comment Summary #35: The commenter indicated that profreeze may not be considered a novel excipient.

Response: Comment not incorporated as no change was requested.

Comment Summary #36: The commenter suggested that it would be more accurate to say that preclinical studies should include product formulated the same way as intended for clinical use, rather than a separate study.

Response: Comment incorporated. This sentence was added to end of the paragraph, “In addition, preclinical studies should include product formulated the same way as intended for clinical use.”

Manufacturing of Cell-Based Advanced Therapies or Tissue-Based Products, Cell Isolation and Selection

Comment Summary #37: The commenter suggested that “quality” is the term that should be used instead of “viability” in this phrase, “processing area under controlled conditions optimized to maintain viability.”

Response: Comment incorporated.

Comment Summary #38: The commenter indicated that the use of “blood products” was unclear as it could refer to PBMC-based source material, blood components for use as a reagent, or something regulated as a blood product.

Response: Comment incorporated. “Blood products” was changed to “blood-derived materials” for clarification.

Manufacturing of Cell-Based Advanced Therapies or Tissue-Based Products, Cell Ex Vivo Expansion and Differentiation, Ex Vivo Expansion

Comment Summary #39: The commenter suggested that software should be validated and mentioned in the General Chapter.

Response: Comment not incorporated. Quality control personnel would know whether software needs to be validated.

Comment Summary #40: The commenter indicated that this General Chapter uses the terms “must” and “required” often. Unless there is no manufacturing alternative, or there is a specific regulatory requirement, it would be best to say “typically”, “normally”.

Response: Comment not incorporated. The EC determined that the terms “must” and “required” have been used when appropriate.

Comment Summary #41: The commenter suggested changing the word, “only” to “typically”.

Response: Comment incorporated.

Comment Summary #42: The commenter suggested adding “and consistency” to the end of this sentence, “In all cases standard cell culture parameters should be optimized for maximum process efficiency.”

Response: Comment incorporated.

Comment Summary #43: The commenter suggested changing the phrase “are required” to “may be needed” in the following text, “Bioreactors: Specialized bioreactors and devices are required for manufacturing three-dimensional combination products.”

Response: Comment incorporated.

Comment Summary #44: The commenter suggested changing the words, “must be fully characterized” to “should be appropriately characterized”.

Response: Comment incorporated.

Comment Summary #45: The commenter suggested changing the text from, “to inhibit endogenous gene expression” to “to elevate existing genes”.

Response: Comment partially incorporated. The text was changed to, “to change endogenous gene expression” because the expression can be reduced or elevated.

Comment Summary #46: The commenter suggested to add the phrase, “and end of production cells” to the sentence about issues associated with cell banking and stability.

Response: Comment partially incorporated. The text was changed to, “Specialized equipment and processes for introduction of genetic material must be validated and monitored. Issues associated with cell banking and stability apply to cell lines used in cell therapy product manufacturing.” The phrase, “in MCBs and WCBs” was deleted, and the end of production cells would be included in the cell therapy product manufacturing.

Comment Summary #47: The commenter suggested that elements of Critical Process Parameters (CPP) be mentioned.

Response: Comment not incorporated. The *Risk Assessment* section of the General Chapter contains information on Critical Process Parameters (CPP).

Manufacturing of Cell-Based Advanced Therapies or Tissue-Based Products, Analytical Methods, General Considerations

Comment Summary #48: The commenter indicated that autologous products can vary tremendously from lot-to-lot. A single reference lot may be useful, but not fully representative.

Response: Comment not incorporated. Reference standards are often used for assay performance that are not lot-specific.

Comment Summary #49: The commenter indicated that for many CTG products, the criteria are set very wide. The fact that a lot meets all criteria does not necessarily guarantee it would be an appropriate lot to use as a reference.

Response: Comment not incorporated. The reference standard should at minimum meet the release criteria.

Comment Summary #50: The commenter indicated that it might cause complications if a product is not cryopreserved, but a cryopreserved reference is used.

Response: Comment not incorporated. The reference standard has been qualified for its use, which would include stability.

Comment Summary #51: The commenter indicated that a reference standard can be extremely helpful, but not easy in the case of CTG products, and suggested adding the phrase, “when available”.

Response: Comment incorporated. The text was changed to say, “ideally” should be anchored using a reference standard or reference material.

Comment Summary #52: The commenter requested that “working standard” be defined.

Response: Comment incorporated. A definition of a “working standard” was added to the *Glossary*.

Comment Summary #53: The commenter indicated that for combination products that include cells and biomaterials, the stability of all components should be considered, and the stability of the components combined should be considered as there may be synergistic effects.

Response: Comment incorporated. Text revised to “For combination products that include cells and biomaterials, the stability of all components, when combined, must be considered.”

Manufacturing of Cell-Based Advanced Therapies or Tissue-Based Products, In-Process Controls

Comment Summary #54: The commenter suggested that it would be useful to distinguish in-process acceptance criteria for the product versus Critical Process Parameters (CPP) for the process.

Response: Comment partially incorporated. A reference to the *Risk Assessment* section of the General Chapter for information on Critical Process Parameters (CPP) was added.

Manufacturing of Cell-Based Advanced Therapies or Tissue-Based Products, Storage

Comment Summary #55: The commenter suggested adding “in some cases” to the following text in the General Chapter, “though the expiration date may be extended by increasing the volume of the storage medium, or by adjusting the storage temperature”.

Response: Comment not incorporated. The language in the General Chapter already allows flexibility.

Manufacturing of Cell-Based Advanced Therapies or Tissue-Based Products, Shipping

Comment Summary #56: The commenter suggested that the statement that a product would be “maintained under conditions of actual use” depends on the development stage of the product.

Response: Comment not incorporated. The product conditions of actual use should be maintained at any stage of product development.

Comment Summary #57: The commenter suggested to add the text “and maintain final container closure integrity” to the description of packaging systems for cell-based therapies and tissue-based products.

Response: Comment incorporated.

Comment Summary #58: The commenter indicated that final container closures are typically transparent/translucent to allow visual inspection. Shipping containers are typically opaque.

Response: Comment partially incorporated. The text was changed to specify the product in its “final container closure” to be more specific about the container used for shipping.

Isolation

Comment Summary #59: Because the examples currently provided are from organ-derived cells and tissues, the commenter suggested adding cell examples such as iPSC or embryonic stem cells.

Response: Comment not incorporated. The *Isolation* section of the General Chapter describes organ-derived and tissue-derived cells. The cell-based examples that the commenter requested to include would be outside the scope of this section of the General Chapter.

Safety Testing of MCB and WCB

Comment Summary #60: The commenter suggested inclusion of new sensitive molecular techniques with broad detection capabilities that are available and may be used as an alternative to *in vivo* or specific nucleic acid technique tests, or as supplement/alternative to *in vitro* culture tests in agreement with the competent authority.

Response: Comment partially incorporated. The text was changed to reflect that freedom from adventitious viruses should be demonstrated using *in vitro* and/or *in vivo* test systems, and a few examples of test methods were added.

Comment Summary #61: The commenter requested to add Celsius to the temperature.

Response: Comment not incorporated. Celsius is understood, and the “C” is not added as per USP style and *General Notices section 8.180. Temperatures* that states, “Temperatures are expressed in centigrade (Celsius) degrees, and all measurements are made at 25° unless otherwise indicated.”

Expert Committee-initiated Change #1: Changed the phrase “that cells are not subjected to temperatures above -130°” to “cells are stored at an appropriately low temperature” because not all cells are stored at -130°.

Sterility

Comment Summary #62: The commenter recommended to delete sections that are outdated including the FDA Guidance for industry that has been officially cancelled and recommended citing the USP General Chapter <1071> for the testing of short-lived products such as cell therapies.

Response: Comment incorporated. USP General Chapter <1071> is referenced, and the outdated text, including the reference to the cancelled FDA guidance, was deleted.

Considerations for Incorporating Quality System Concepts Early in Cellular Cell-Based Advanced Therapies and Tissue-Based Product Development

Comment Summary #63: The commenter indicated that future regulations have not been issued, so it is difficult to predict what the requirements will be.

Response: Comment not incorporated. The text, “robust quality attributes early in the design phase to ensure a focus on patient safety by means of a high degree of process understanding” will not be changed because robust quality attributes will be required early in design phase.

Comment Summary #64: The commenter suggested that the phrase “developers of cell-based advanced therapies and tissue-based products” implies that only cell-based therapies are advanced therapies which is not an accurate statement.

Response: Comment not incorporated. The use of cell-based advanced therapies describes cell-therapies but does not indicate that the cell-based are the only advanced therapies.

Comment Summary #65: The commenter indicated that terms had been mixed as “quality systems” is not the same thing as “quality standards” or process understanding.

Response: Comment not incorporated. Quality systems are open to continual improvement, and the use of “quality standards” has been removed.

Comment Summary #66: The commenter requested to cite references for tools that provide a quantifiable means of prioritizing risk so that higher-risk elements of a process can be identified and corrected.

Response: Comment not incorporated. References have been provided in the previous sentence and can be easily accessed online.

Comment Summary #67: The commenter indicated that although numerous common risk analysis tools were listed, there was no description supplied to explain their differences or where one might be more useful than another. Although FMEA is the most commonly used, it should be explained why this is used as an example.

Response: Comment not incorporated. Describing the difference of the tools and where one might be more useful than another is out of scope of the chapter. A manufacturer should be able to evaluate which tools are appropriate.

Comment Summary #68: The commenter indicated that regulations, guidances, and guidelines are not really standards in most cases. Regulations are requirements; guidances and guidelines are advice.

Response: Comment incorporated. The phrase “recognized as the new global standards” was replaced with “for ensuring quality”.

Comment Summary #69: The commenter suggested adding the phrase “and medical”.

Response: Comment incorporated. Text was revised to “The level of effort, formality, and documentation of the risk management process should be commensurate with the level of risk, should be based on scientific and medical knowledge, and ultimately should be linked to patient protection.”

Comment Summary #70: The commenter suggested changing the phrase, “can be readily accessed” to “are described”.

Response: Comment incorporated. Text revised to “The elements of risk management have become an accepted paradigm; these are described in FDA and international regulatory guidance documents, especially ICH Q9.”

Comment Summary #71: The commenter indicated that and “formalized” is not clear in the sentence, “A more formalized risk assessment system is necessary for process or product development.” An out of specification deviation is a serious issue that must be properly investigated, documented, closed out, with appropriate corrective actions and change control as necessary.

Response: Comment incorporated. Reference to non-conformance was removed. The sentence, “Preliminary, less formal risk analysis comes into play when a risk assessment needs to be expedited, as in the resolution of a manufacturing nonconformance” was deleted from the General Chapter.

Quality Systems

Comment Summary #72: The commenter requested to revise the sentence in the General Chapter to, “and 820 apply to the manufacturing of cell-based therapies and tissue-based products that are subject to PMA or are regulated as a device or a combination product with a device constituent part.”

Response: Comment not incorporated. Defining how products are regulated is out of the scope of the chapter.

General Chapters/Sections: <1047> *Gene Therapy Products*/ Multiple Sections

Expert Committee: Biologics Monographs 3 – Complex Biologics

No. of Commenters: 3

Manufacturing Overview Introduction

Comment Summary #1: The commenter suggested adding clarification to this section with the risk-based approach that is explained in USP <1043>.

Response: Comment not incorporated. Adding the risk-based approach to <1047> is out of scope of the chapter, but a new above 1000 chapter on risk-based approaches for biotherapeutics and gene therapy vectors could be considered.

Comment Summary #2: The commenter suggested changing “quality assurance testing” to “quality control testing”.

Response: Comment incorporated.

Comment Summary #3: The commenter suggested adding text to describe that new, sensitive molecular methods with broad detection capabilities are available for detection of adventitious agents.

Response: Comment not incorporated. It is not necessary to describe specific methods used for analysis as the methods and technology may change over time.

Qualification

Comment Summary #4: The commenter suggested adding “if *in vivo*” to the end of this sentence for clarification, “All the raw materials required for production of the banks, media, sera, trypsin and similar substances must also be tested for adventitious agents.”

Response: Comment not incorporated. The statement is also true if *ex vivo*.

Qualifying the Master Cell Bank

Comment Summary #5: The commenter suggested removing the requirement for freedom from adventitious viruses during *in vivo* testing in order to enhance the harmonization between the *European Pharmacopeia* and USP, and also to give the manufacturer more time to develop the assay.

Response: Comment not incorporated. Public safety and the requirement for freedom from adventitious viruses are required at all stages of manufacturing.

Production and Processing of Nonviral Vectors

Comment Summary #6: Since plasmids can be further processed in cell culture, the commenter suggested to remove the Endotoxin limit of <10 EU/mg DNA, and replace with this text, “Suitable criteria based on the final manufacturing process.”

Response: Comment incorporated.

Comment Summary #7: The commenter recommended adding an “e” to “Molony” to change to correct spelling, Moloney.

Response: Comment incorporated.

Vector Design Criteria

Comment Summary #8: The commenter recommended removing the word, “adenoviral” before “Coxsackie virus B”.

Response: Comment incorporated.

Comment Summary #9: The commenter recommended adding Celsius after degree.

Response: Comment not incorporated. Celsius is understood, and the “C” is not added as per USP style and *General Notices section 8.180. Temperatures* that states “Temperatures are expressed in centigrade (Celsius) degrees, and all measurements are made at 25° unless otherwise indicated.”

Analytical Methods

Comment Summary #10: The commenter suggested removing pyrogen from the safety under the columns for viral and nonviral gene therapy products.

Response: Comment not incorporated. This suggested change was outside the scope of the revision and can be addressed in a future revision of the chapter.

Comment Summary #11: The commenter suggested removing General Safety test from *Table 5*, as this test has been revoked and should not be considered anymore.

Response: Comment incorporated.

Nonviral Gene Therapy Products, Purity

Comment Summary #12: The commenter suggested removing residual moisture from the examples of process-related impurities associated with gene therapy products.

Response: Comment not incorporated. Residual moisture may be considered an impurity.

Accelerated and Most Appropriate Challenge Conditions

Comment Summary #13: The commenter recommended adding Celsius after degree.

Response: Comment not incorporated. Celsius is understood, and the “C” is not added as per USP style and *General Notices section 8.180. Temperatures* that states “Temperatures are expressed in centigrade (Celsius) degrees, and all measurements are made at 25° unless otherwise indicated.”

Formulation of Gene Therapy Products

Comment Summary #13: Commenter suggested replacing “Organic carbohydrates such as mannitol, sorbitol, sucrose, and trehalose” with “Cryoprotectants such as mannitol, sorbitol, sucrose, and trehalose.”

Response: Comment not incorporated. Cryoprotectants can be excipients in some products and ancillary materials in others. This comment can be revisited in a future revision.

Glossary

Comment Summary #14: The commenter suggested replacing the definition of liposome with the following: “Vesicles composed of a bilayer (uni-lamellar) and/or a concentric series of multiple bilayers (multi-lamellar) separated by aqueous compartments form by amphipathic molecules such as phospholipids that enclose a central aqueous compartment.”

Response: Comment partially incorporated. The text was changed to include one or more aqueous compartments.

General Chapter/Section(s): <1850> Evaluation of Screening Technologies for Assessing Medicine Quality/Multiple Sections

Expert Committee(s): Council of Experts

No. of Commenters: 2

Comment Summary #1: The commenter proposed avoiding the word “screening” and replacing with “testing”.

Response: Comment not incorporated. The word “screening” is commonly used, including usage in the title of existing General Chapters. The EC requested adding the definition for “screening” to the *Glossary* section.

Comment Summary #2: The commenter suggested changing “screening technologies” to “portable technologies”.

Response: Comment not incorporated. The EC noted that the word “portable” does not imply screening.

Comment Summary #3: The commenter requested clarification on if “supply chain” includes the warehouse.

Response: Comment incorporated. This was clarified in a definition for “supply chain” added to the *Glossary*.

Comment Summary #4: The commenter indicated *Tables 1 and 2* should be aligned with ICH Q2 (R1) requirements.

Response: Comment incorporated. The EC noted that the General Chapter is about validating a tool, not validating an analytical procedure and proceeded to make the appropriate revisions to the Tables to be consistent with ICH Q2 (R1).

Comment Summary #5: The commenter requested addition of “intrinsically safe” as one of the considerations for the technologies under the *Durability and Use* subsection in the *Durability* subheading.

Response: Comment incorporated.

Comment Summary #6: The commenter requested including the following question, “Can models/methods developed on a master instrument be remotely transferred to field units as needed?” under the *Durability and Use* subsection in the USE subheading.

Response: Comment incorporated.

Comment Summary #7: The commenter requested adding a reference to General Chapter <1039> under the *Protocol and Statistics* subsection, in the *Statistics* subheading.

Response: Comment incorporated.

EC-initiated Change #1: A sentence was added to the *Introduction* section to indicate that the chapter’s application is not limited to the WHO essential medicines.

EC-initiated Change #2: Under the *Specifications, Relative Cost, and Data* subsection in the *Relative Cost* subtopic, consumables and maintenance costs are provided as examples of recurring costs.

EC-initiated Change #3: Under the *Durability and Use* subsection in the *Durability* subtopic, Electrical variability (e.g., voltage, surge, frequency) is provided as an example of operational environment change.

EC-initiated Change #4: Under the *Technology Applications and Analytical Performance Characteristics to Evaluate* section in the *Quantitative Applications* subtopic, the word “adulterants” is included in the description of *Application V*. A definition of “adulterant” is also added to the *Glossary* section.

General Chapter/Sections: <1856> *Near-Infrared Spectroscopy – Theory and Practice*/Multiple Sections

Expert Committee: General Chapters–Chemical Analysis

No. of Commenters: 6

GENERAL COMMENTS

Comment Summary #1: The commenter suggested including reference to FDA Draft Guidance for Industry, *Development and Submission of Near Infrared Analytical Procedures*, and that calibration considerations per this guidance be included in the General Chapter.

Response: Comment not incorporated. FDA Guidance is currently being drafted and therefore cannot be referenced at this stage. The EC may revise the chapter when guidance is finalized.

Section 1. THEORY

Comment Summary #2: The commenter recommended including the list of techniques and principles that would be considered “other spectroscopic techniques.”

Response: Comment not incorporated. The term “vibrational spectroscopy” specifies the other techniques described within the text.

Comment Summary #3: The commenter indicated an incorrect reference of wavelength as the y-axis.

Response: Comment incorporated. The term was corrected to “x-axis.”

Section 2. TRANSMISSION, REFLECTION, AND TRANSFLECTION MODES

Comment Summary #4: The commenter suggested the definition of variables provided following the equation for transmittance may be omitted as it is defined in the text.

Response: Comment not incorporated. The variable definition is consistent with USP General Chapter style.

Comment Summary #5: The commenter indicated that the following text is not specific to reflectance measurements, but applies to general NIR theory, “For such materials, NIR radiation can penetrate a substantial distance into the sample, where it can be absorbed when the wavelength of the radiation corresponds to a transition between the ground vibrational state of the analyte and either a harmonic of a given vibrational mode (an overtone) or the sum of two or more different modes (a combination band).”

Response: Comment incorporated. Text changed to, “For such materials, NIR radiation can penetrate a substantial distance into the sample, where it can be absorbed.”

Section 3. FACTORS THAT AFFECT NIR SPECTRA

Comment Summary #6: The commenter indicated that the text in the chapter does not clearly state the NIR spectrum contains information related to both overtone and combination bands.

Response: Comment incorporated. Text changed to, “The NIR spectrum contains information on overtone resonances and combination of fundamental vibrational modes of the sample that can yield both sample and process understanding.”

Comment Summary #7: The commenter requested additional information on the methodology or approach in demonstrating that the background reference sample/measurement is reliable, reproducible, and stable over time.

Response: Comment not incorporated. The approach is indicated in the text as written.

Comment Summary #8: The commenter suggested the following sampling factor should be removed, “Where multiple crystalline forms are present, care must be taken to ensure that the model calibration samples have a distribution of forms relevant to the intended application.”

Response: Comment not incorporated. This is one of the sampling factors that can be easily overlooked therefore should be listed.

Comment Summary #9: The commenter requested to clarify that aging samples may also lose solvent content, and impurities may form.

Response: Comment incorporated. Text changed to, “Depending on the storage conditions, solid samples may either absorb or desorb water/solvent, and portions of amorphous materials may crystallize.”

Section 4. PRETREATMENT OF NIR SPECTRAL DATA

Comment Summary #10: The commenter requested section 4. *Pretreatment of NIR Spectra Data* be revised for clarity.

Response: Comment not incorporated. Reference to <1039> is provided for additional information.

Section 5. INSTRUMENTATION

Comment Summary #11: The commenter suggested including a reference to the following publication in the General Chapter: Agelet, L. & Hurburgh, C. (2010). A Tutorial on Near Infrared Spectroscopy and Its Calibration. *Critical Reviews in Analytical Chemistry*. 40(4):246-260

Response: Comment not incorporated. The chapter does not include a reference section.

Comment Summary #12: The commenter suggested further discussion on other specialized NIR-based techniques be included in section 5.2 *Specialized Techniques*.

Response: Comment not incorporated. Section title renamed to “5.2 Imaging Techniques” with general information, without referencing any techniques.

Comment Summary #13: The commenter suggested a simplification and clarification of content in section 5.2.1 *Imaging Techniques*.

Response: Comment not incorporated. However, text was added to the section to provide additional information and clarity related to imaging techniques.

Comment Summary #14: The commenter suggested aligning section 5.3 *Instrument Calibration Considerations* with ISO standard 12099.

Response: Comment not incorporated. ISO standard 12099 describes the calibration of a model, not the calibration of the instrument.

Comment Summary #15: The commenter suggested to include section 5.3.1 *Photometric Noise* into section 5.3.3 *Photometric Linearity and Response Stability (Y-Axis)*.

Response: Comment not incorporated. Photometric noise is already included in the table in 5.3.3.

Comment Summary #16: The commenter recommended that the General Chapter specify that wavelength accuracy be established for grating-based dispersion NIR spectrometers.

Response: Comment incorporated. Text in section 5.3.2 *Wavelength Accuracy and Uncertainty (X-axis)* was changed to, "NIR spectra collected by the conventional grating based instrument from sample and/or reference standard materials can be used to demonstrate an instrument's suitable wavelength-dispersion performance against target specifications."

Comment Summary #17: The commenter suggested reference to NIST SRM 2034 for verification of wavelength scale.

Response: Comment partially incorporated. Text was changed to, "Certified traceable standards are available from the National Institute of Standards and Technology (NIST) for transmittance measurements (SRM 2035a) and reflectance (SRM 2036) and can be used for wavelength verification." Other suitable standards were also referenced and may be used for verification of the wavelength scale for transmission measurements, including NIST SRM 2065, Polystyrene 65 μm , and TS5 liquid.

Comment Summary #18: The commenter recommended a correction to the row "verification of wavelength repeatability" in *Table 1*, as some of the content should be moved to the row labeled "verification of wavelength scale."

Response: Comment incorporated. The following text was moved to the "verification of wavelength scale" row, "For FT instruments the calibration of the wavenumber scale may be performed using a narrow, isolated water-vapor line (for example, the line at 7306.74 cm^{-1} , 7299.45 cm^{-1} , or 7299.81 cm^{-1})."

Section 6. APPLICATIONS

Comment Summary #19: The commenter recommended adding another physical analysis application: "Analysis of intact pharmaceutical dosage forms: Tablets, Capsules, Lyophilized products and implants (e.g. polymeric and microspheres)."

Response: Comment incorporated. The additional application was added.

Comment Summary #20: The commenter suggested revising applications of "process analysis" to "process monitoring and process control analysis" to be consistent with current literature.

Response: Comment incorporated. The description of the application was also changed to, "Monitoring of unit operations such as synthesis, crystallization, blending (e.g. powder), pelletization, tableting, capsule filling, drying, granulation, and coating (e.g. film), and packaging, for the purpose of process control."

Comment Summary #21: The commenter suggested including a discussion on NIR imaging applications in section 6. *Applications*.

Response: Comment incorporated. Section 5.2 *Imaging Techniques* was changed to include the text, "NIR imaging is a combination of NIR spectroscopy with digital image processing. A NIR imaging system is basically composed of an illumination source, an imaging optic, a spectral encoder selecting the wavelengths, and a focal plane array. NIR imaging in particular has a huge potential for gaining rapid information about the chemical structure and related

physical or biopharmaceutical properties of all types of pharmaceutical dosage forms, thus improving product quality and enhancing production speed.”

Comment Summary #22: The commenter suggested that it may be necessary to determine the Quantitation Limit of quantitative procedures for impurities.

Response: Comment partially incorporated. Reference to ISO 12099 was added in section 6.3, and the following text was added to section 7. *Procedure Validation*, “It may be necessary to determine QL for methods of detection and quantification of an impurity or polymorphic form.”

Comment Summary #23: The commenter recommended including range as a model validation parameter.

Response: Comment incorporated. Text changed to, “Specific acceptance criteria for each validation parameter must be consistent with the intended use of the method. Validation parameters for quantitative methods are accuracy, linearity over the operational range, precision (repeatability and intermediate precision), robustness, and specificity.”

Section 7. PROCEDURE VALIDATION

Comment Summary #24: The commenter requested additional discussion for section 7.1 *Ongoing Method Evaluation*.

Response: Comment not incorporated. Additional information can be found in <1039>.

Comment Summary #25: The commenter suggested that any change to the instrument may require model revalidation, not only “major changes”.

Response: Comment incorporated. Text changed to, “Revalidation of qualitative models may be necessary as a result of changes in instrument hardware.”

GLOSSARY

Comment Summary #26: The commenter recommended including definitions for Standard Error of Prediction (SEP), Root-mean-square (RMS), Bias (d), and Ratio of performance of deviation (RPD) from literature cited in Comment Summary #11.

Response: Comment not incorporated. A reference to <1039> was included for additional information.

Comment Summary #27: The commenter suggested the equation for transfection should be included in the *Glossary*.

Response: Comment not incorporated. Transfection is a mode not practically different from transmittance.

Comment Summary #28: The commenter suggested the definition for “infinite thickness” should be included in the *Glossary*.

Response: Comment not incorporated. The term “infinite thickness” is described in subsection 3.2.4 *Sample Thickness*.

Comment Summary #29: The commenter indicated that some terms in the *Glossary* were not contained in the text, including Root-mean-square (RMS), Standard error of calibration (SEC), Standard error of the laboratory (SEL), and Standard error of prediction (SEP).

Response: Comment not incorporated. The glossary terms were included for additional information, and reference to <1039> was provided.

Comment Summary #30: The commenter suggested definitions for “Diffuse Reflectance” and “Reflectance” be concordant with section 2.2 *Reflection Modes*.

Response: Comment not incorporated. Section 2.2 can be referenced for additional information.

Comment Summary #31: The commenter indicated an incorrect definition for the intensity of incident radiation in the equation for Transmittance.

Response: Comment incorporated. Text changed to, “where *I* is the intensity of the radiation transmitted through the sample and includes losses due to solvent absorption, refraction, and

scattering I_0 is the intensity of the radiant energy incident on the sample; and A is the absorbance.”

Monographs

Monograph/Section(s): Allopurinol Compounded Oral Suspension
Expert Committee(s): Compounding
No. of Commenters: 1

Commentary Summary #1: A commenter suggested specifying whether the pH of the new formula needed to be adjusted, and stating what solution should be used to adjust the pH.

Response: Comment partially incorporated. The pH range of the new formula was specified based on data provided by the donor.

Monograph/Section(s): Arginine Hydrochloride Compounded Oral Solution/Compounding instructions
Expert Committee(s): Compounding
No. of Commenters: 1

Commentary Summary #1: A commenter suggested adding clarification whether the paraben solution needs to be cooled before the addition of the arginine hydrochloride powder.

Response: Comment incorporated. The compounding instructions were revised to add a cooling step after preparing the paraben solution.

Monograph/Section: Azathioprine Tablets/Multiple sections
Expert Committee: Chemical Medicines Monographs 3
No. of Commenters: 2

Comment Summary #1: The commenter requested revising the limits in the test for *Organic Impurities* to be consistent with the FDA-approved specifications.

Response: Comment incorporated. The acceptance criteria for mercaptopurine, any individual unspecified degradation product, and total degradation products in *Table 1* are widened as listed below:

Impurity Name	Acceptance Criteria, NMT (%)
Mercaptopurine	Revised from 0.50 to 0.5
Any individual unspecified degradation product	Revised from 0.10 to 0.2
Total degradation products	Revised from 1.5 to 2.0

Comment Summary #2: The commenter indicated the impurities in the test for *Organic Impurities* of the drug product monograph are not aligned with those in the drug substance monograph.

Response: Comment not incorporated. The EC determined that the process impurities may vary depending on the route of synthesis and they are monitored in the drug substance monograph either as specified or unspecified impurities.

EC-initiated Change #1: In the test for *Organic Impurities*, the “Total impurities” in footnote (a) is changed to “Total degradation products” to be consistent with the naming in *Table 1*.

EC-initiated Change #2: The column particle size of 10 μm is added in *Assay* for clarity.

Monograph/Section: Betaxolol Hydrochloride/ Organic Impurities

Expert Committee: Chemical Medicines Monographs 3

No. of Commenters: 2

Comment Summary #1: The commenter noted that in the test for *Organic impurities*, the acceptance criterion for individual impurities is different from what has been approved by the FDA.

Response: Comment incorporated. The acceptance criterion for individual impurities is widened from NMT 0.3% to NMT 0.5% to be consistent with FDA approval.

Comment Summary #2: The commenter recommended revising the name for “Betaxolol dicyclopropyl analog” to “Betaxolol oxirane analog”.

Response: Comment incorporated.

Comment Summary #3: The commenter suggested harmonizing the test for *Organic Impurities* with the *European Pharmacopeia* based on the statement in the briefing.

Response: Comment not incorporated. The EC determined that the proposed method is suitable for its intended use.

Monograph/Section(s): Carboxymethylcellulose Compounded Solution, Veterinary/
Title

Expert Committee(s): Compounding

No. of Commenters: 1

Commentary Summary #1: A commenter suggested adding “intraperitoneal” to the title to indicate the route of administration of the formulation, in line with the requirements in <1121>.

Response: Comment incorporated. The new name of the monograph is Carboxymethylcellulose Compounded Intraperitoneal Solution, Veterinary.

Monograph/Section(s): Chlorambucil Compounded Oral Suspension/ Labeling and
Definition

Expert Committee(s): Compounding

No. of Commenters: 1

Commentary Summary #1: A commenter suggested adding a requirement to label the formulation as “carcinogenic and probably mutagenic and teratogenic”, in line with the warnings contained on the approved label for chlorambucil tablets.

Response: Comment not incorporated. General Chapter <795> contains precautions to be followed when handling conventionally manufactured hazardous drugs in compounding. The monograph requires compounders to follow requirements in <795>.

Commentary Summary #2: A commenter suggested adding a caution statement in the definition to state, “Great care should be taken to prevent inhaling particles of Chlorambucil and exposing the skin to it.”

Response: Comment not incorporated. General Chapter <795> contains precautions to be followed when handling conventionally manufactured hazardous drugs in compounding. The monograph requires compounders to follow requirements in <795>.

Monograph/Section(s): Cholecalciferol / Assay

Expert Committee: Non-Botanical Dietary Supplements

No. of Commenters: 1

Comment Summary: Based on the available data the commenter suggested providing “1.5 mL/min” as the specific value for flow rate instead of the proposed “1.0 - 2.0 mL/min” to the Chromatographic system in the Assay.

Response: Comment incorporated.

Monograph/Sections: Clonidine Hydrochloride / Multiple Sections
Expert Committees: Chemical Medicines Monographs 2
No. of Commenters: 1

Comment Summary #1: The commenter recommended removing the filtration step in the preparation of the *Standard solution* and the *Sample solution* under both *Assay and Organic Impurities*.

Response: Comment incorporated.

Monograph/Section(s): Clonidine Hydrochloride Compounded Oral Suspension/
Assay

Expert Committee(s): Compounding

No. of Commenters: 1

Commentary Summary #1: A commenter suggested clarifying whether the limit of the tailing factor parameter for the evaluation of system suitability was NMT 2 or NMT3.

Response: Comment incorporated. Clarification was added to indicate that the limit of the tailing factor parameter for system suitability is NMT 3.

Monograph/Section: Diclofenac Potassium for Oral Solution/Dissolution

Expert Committee: Chemical Medicines Monographs 2

No. of Commenters: 1

Comment Summary#1: The commenter recommended revising the tolerances for *Dissolution* to be consistent with the FDA-approved application.

Response: Comment not incorporated. The proposed tolerances are consistent with the sponsor's FDA-approved application. The EC will consider a future revision to the monograph upon receipt of supporting data.

Monograph/Section: Diflunisal Tablets/Organic Impurities

Expert Committee: Chemical Medicines Monographs 2

No. of Commenters: 1

Comment Summary #1: The commenter recommended revising the acceptance criterion for any unspecified degradation product to be consistent with the identification threshold in the International Conference on Harmonisation (ICH) Q3B guidelines.

Response: Comment not incorporated. The acceptance criterion is consistent with the identification threshold in ICH Q3B guidelines.

Monograph/Sections: Diphenhydramine Oral Powder / Organic Impurities

Expert Committees: Chemical Medicines Monographs 6

No. of Commenters: 0

EC-initiated Change: The EC widened the limit of diphenhydramine related compound A from NMT 0.2% to NMT 0.5% to be consistent with the drug substance monograph.

Monograph/Sections: Dobutamine Hydrochloride /Organic Impurities

Expert Committees: Chemical Medicines Monographs 2

No. of Commenters: 1

Comment Summary: The commenter requested to align the acceptance criterion for Dobutamine related compound C with the corresponding name in *Table 2*.

Response: Comment incorporated.

Monograph/Section(s): Ergocalciferol / Assay

Expert Committee: Non-Botanical Dietary Supplements

No. of Commenters: 1

Comment Summary: Based on the existing data the commenter suggested providing “1.5 mL/min” as the specific value for flow rate instead of the proposed “1.0 - 2.0 mL/min” to the Chromatographic system in the Assay.

Response: Comment incorporated

Monograph/Sections: Fentanyl / Organic Impurities

Expert Committees: Chemical Medicines Monographs 2

No. of Commenters: 2

Comment Summary #1: The commenter indicated that the acceptance criterion for *Total impurities* is different from the limit in the FDA-approved applications.

Response: Comment not incorporated. The acceptance criterion for *Total impurities* is consistent with the FDA-approved sponsor’s application. The EC will consider future revisions upon receipt of supporting data.

Comment Summary #2: The commenter indicated that each of the other impurities with similar structure to that of Fentanyl Related Compound E might be significantly overestimated due to its higher peak response compared to that of Fentanyl related compound G, which is used to quantitate other impurities.

Response: Comment not incorporated. The EC determined that the procedure for quantitating the other impurities is suitable for the intended use and is consistent with the FDA approved sponsor’s application.

Comment Summary #3: The commenter indicated that the detector wavelength of 240 nm is not the maximum absorbance wavelength and might not be adequate to detect the unspecified impurities.

Response: Comment not incorporated. The proposed wavelength of 240 nm is based on the validation data and is consistent with the FDA approved sponsor’s application. The EC determined the procedure is suitable for the intended use.

Monograph/Section(s): Glyceryl Monocaprylate/ Title note

Expert Committee(s): Excipients Monographs 1

EC-initiated Change#1: The official date of any article currently titled Glyceryl Monocaprylate Type I as Glyceryl Mono and Dicaprylate and any article currently titled Glyceryl Monocaprylate Type II as Glyceryl Monocaprylate was changed from “Dec 1, 2024” to “May 1, 2025” to reflect the change of the official date of this monograph revision.

Monograph/Section(s): Glyceryl Mono and Dicaprylate/ Title note

Expert Committee(s): Excipients Monographs 1

EC-initiated Change#1: The 60-month extension period for the article with the name Glyceryl Monocaprylate Type I was changed from “Dec 1, 2019–Dec 1, 2024” to “May 1, 2010–May 1, 2025” to reflect the change of the official date of this new monograph.

Monograph/Section(s): Glyceryl Mono and Dicaprylocaprate/ Multiple Sections

Expert Committee(s): Excipients Monographs 1

No. of Commenters: 1

Comment Summary #1: The commenter recommended removing CAS number [85536-07-8] from the monograph because a product containing the higher amount of triglycerides would not work with the CAS number published in the proposed monograph, and most monographs do not include CAS numbers.

Response: Comment not incorporated. EC determined that the CAS number was fully supported by data and documents.

EC-initiated Change#1: The 60-month extension period for the article with the name Glycerol Monocaprylocaprate Type I was changed from “Dec 1, 2019–Dec 1, 2024” to “May 1, 2010–May 1, 2025” in the title note to reflect the change of the official date of this new monograph.

EC-initiated Change#2: A note of “May also be labeled as ‘USP Glycerol Monocaprylocaprate RS (Type I)’ until May 1, 2025.” was added to USP Glycerol Mono and Dicaprylocaprate RS to reflect the 60-month extension for implementation of the new monograph.

Monograph/Section(s): Glycerol Monocaprylocaprate/ Multiple Sections

Expert Committee(s): Excipients Monographs 1

EC-initiated Change#1: The official date to title any article currently titled Glycerol Monocaprylocaprate Type I as Glycerol Mono and Dicaprylocaprate and any article currently titled Glycerol Monocaprylocaprate Type II as Glycerol Monocaprylocaprate was changed from “Dec 1, 2024” to “May 1, 2025” in the title note to reflect the change of the official date of this monograph revision.

EC-initiated Change#2: A note of “May also be labeled as ‘USP Glycerol Monocaprylocaprate RS (Type I)’ until May 1, 2025.” was added to USP Glycerol Mono and Dicaprylocaprate RS to reflect the 60-month extension for implementation of the revised monograph.

Monograph/Section(s): Hexylene Glycol/Assay

Expert Committee(s): Excipients Monographs 1

EC-initiated Change#1: The missing *System suitability solution* as a sample in *System Suitability* section in the *PF* publication was added. Information of the solutions used in each suitability test was added. The added information will prevent confusion from users.

Monograph/Section(s): Hydrochlorothiazide Compounded Oral Suspension

Expert Committee(s): Compounding

No. of Commenters: 1

Commentary Summary #1: A commenter suggested deleting the word “containing” from the subheading “For Hydrochlorothiazide Compounded Oral Suspension containing 2.5 mg/mL” to be consistent with the current style of USP monographs.

Response: Comment incorporated.

Commentary Summary #2: A commenter suggested specifying, in the compounding instructions, how much of the vehicle has to be added to the calibrated container to bring to final volume.

Response: Comment incorporated. The sentence, “Add sufficient Ora-Blend to bring to final volume” was added to the compounding instructions.

Monograph/Section: Indomethacin Extended-Release Capsules/Organic Impurities

Expert Committee: Chemical Medicines Monographs 2

No. of Commenters: 1

Comment Summary: The commenter recommended revising the acceptance criterion of indomethacin related compound A to be consistent with the FDA approved application.

Response: Comment not incorporated. The acceptance criterion is consistent with the sponsor's FDA-approved application. The EC will consider future revision to the monograph upon receipt of supporting data.

Monograph/Section: Metformin Hydrochloride /Assay
Expert Committee: Chemical Medicines Monographs 3
No. of Commenters: 2

Comment Summary #1: The commenter commented that, in the Assay, the retention time for metformin was different from what was stated in the *PF* briefing.

Response: Comment not incorporated. It was confirmed that the retention time listed in the briefing was consistent with validation data. The EC determined that the difference in retention time will not impact suitability of the method.

Comment Summary #2: The commenter requested to retain the titration test for Assay.

Response: Comment not incorporated. It was noted that *FDA Compliance Policy Guide 420.400 Performance of Tests for Compendial Requirements on Compendial Products* provides guidance for such testing requirements.

Monograph/Section: Methacholine Chloride/Multiple Sections
Expert Committee: Chemical Medicines Monographs 4
No. of Commenters: 0

EC-initiated Change #1: The resolution requirement between acetylcholine and methylcholine in the Assay and the test for *Organic Impurities* was widened from NLT 2 to NLT 1.5.

Monograph/Sections: Minoxidil/Multiple sections
Expert Committee: Chemical Medicines Monographs 2
No. of Commenters: 2

Comment Summary #1: The commenter recommended revising the acceptance criterion for *Total impurities* in the *Organic Impurities Table 1* to be consistent with the FDA approved applications.

Response: Comment not incorporated. The proposed acceptance criterion for the *Total impurities* in the *Organic Impurities, Table 1* is consistent with the FDA-approved products. The EC will consider a future revision to the monograph upon receipt of supporting data.

Comment Summary #2: The commenter requested revising the chemical name of Pyrimidine oxide analog to 4-Chloropyrimidine-2,6-diamine-1-oxide in the *Organic Impurities, Table 1 footnote A*.

Response: Comment incorporated.

Comment Summary #3: The commenter recommended including a storage temperature requirement under *Packaging and Storage*.

Response: Comment not incorporated. The EC will consider a future revision to the monograph upon receipt of supporting data.

Comment Summary #4: The commenter requested harmonizing the test procedures and the acceptance criteria in the USP monograph with the corresponding procedures and acceptance criteria in the *European Pharmacopeia* monograph.

Response: Comment not incorporated. The *European Pharmacopeia* monograph test methods and acceptance criteria are not consistent with the FDA-approved products.

Monograph/Section(s): Oil- and Water-Soluble Vitamins Tablets /Multiple
Expert Committee: Non-Botanical Dietary Supplements
No. of Commenters: 2

Comment Summary #1: The commenter recommended deleting the text, “previously dried and stored in the dark over phosphorus pentoxide and protected from absorption of moisture while weighing” in the *Strength* section, under Calcium Pantothenate, Method 2, Standard stock solution, to eliminate the discrepancy between the new Calcium Pantothenate RS label information, which states, “use as is and correct for water content”.

Response: Comment incorporated.

Comment Summary #2: The commenter reported that the USP Ascorbic Acid RS is missing from the USP Reference Standards <11> section and recommended its inclusion.

Response: Comment incorporated.

Monograph/Section(s): Oil- and Water-Soluble Vitamins with Minerals Tablets/
Multiple

Expert Committee: Non-Botanical Dietary Supplements

No. of Commenters: 2

Comment Summary #1: The commenter recommended deleting the text, “previously dried and stored in the dark over phosphorus pentoxide and protected from absorption of moisture while weighing” in the *Strength* section, under Calcium Pantothenate, Method 2, Standard stock solution, to eliminate the discrepancy between the new Calcium Pantothenate RS label information, which states, “use as is and correct for water content”.

Response: Comment incorporated.

Comment Summary #2: The commenter reported that the USP Ascorbic Acid RS is missing from the USP Reference Standards <11> section and recommended its inclusion.

Response: Comment incorporated.

Monograph/Section(s): Polypropylene Glycol 11 Stearyl Ether/Hydroxyl value

Expert Committee(s): Excipients Monographs 1

EC-initiated Change #1: A note of, “The sand bath temperature must be set such that the sample reflux temperature is between 85-100°” was added. A footnote of, “Other types of heating devices may also be used if suitable for the intended use” was also added.

Monograph/Section(s): Potassium Sorbate/Multiple Sections

Expert Committee(s): Excipients Monographs 1

No. of Commenters: 2

Comment Summary #1: The commenter recommended removing the test of *Content of Potassium* because the HPLC assay is sufficient for quantitation.

Response: Comment not incorporated. The EC determines the content of potassium test using AA is necessary to avoid sodium sorbate contamination.

Comment Summary #2: The commenter recommended changing the system suitability solution preparation condition in the test of *Content of Potassium Sorbate* from “with UV irradiation for 2 h” to “with UV irradiation to achieve ~1% degradation of the potassium sorbate (based on area %)”. Irradiation time to achieve ~1% degradation depends on type of lamp used. The “to achieve ~1% degradation of the potassium sorbate (based on area %)” requirement that was mentioned in the note should be moved to the main body. The recommendation is supported by data.

Response: Comment incorporated.

Comment Summary #3: The commenter recommended supplying the Fuchsin solution stability information in *Limit of Aldehyde*.

Response: Comment incorporated. Information was added to supply a sensitivity test to determine whether the Fuchsin solution is stable and suitable for use and provide solution storage conditions.

Comment Summary #4: The commenter recommended including a more specific test for aldehydes in the section of *Limit of Aldehyde*. The proposed method relies on the intensity of color in solution compared to the standard solution, which is subjective.

Response: Comment not incorporated. The EC will consider future revisions to the monograph upon receipt of supporting data.

Monograph/Sections: Propranolol Hydrochloride
Expert Committee: Chemical Medicines Monographs 2
No. of Commenters: 1

Comment Summary #1: The commenter commented that the Organic Impurities procedure is not suitable for their products.

Response: Comment not incorporated. The EC will consider a future revision to the monograph upon receipt of supporting data.

Monograph/Section: Rotigotine Transdermal System / Assay
Expert Committee: Chemical Medicines Monographs 4
No. of Commenters: 1

Comment Summary #1: The commenter requested revising the acceptance criteria to be consistent with what has been approved by FDA.

Response: Comment not incorporated. The EC has determined that the acceptance criteria should be based on the label claim. This approach is consistent with other transdermal system monographs.

Monograph/Section(s): Saccharin Calcium/ Assay
Expert Committee(s): Excipients Monographs 2
No. of Commenters: 3

Comment Summary #1: The commenter recommended changing the Assay acceptance criteria from 98.0–102.0% to 99.0–101.0%.

Response: Comment not incorporated. The liquid chromatography method replaces the non-specific titration method for Assay. Generally, the chromatographic procedures use one or more external standards, the variability of results is higher than that of results obtained by titration procedures, and the specificity is substantially greater. The EC decided to keep the Assay acceptance criteria “98.0-102.0%”.

Comment Summary #2: The commenter recommended changing the HPLC column temperature from 20 °C to 30 °C because many factories may not have the capability to control the temperature to the lower value.

Response: Comment partially incorporated. The EC reviewed the robustness study results which demonstrated that the Saccharin main peak overlapped with the Phthalic Anhydride (PAn) impurity peak when the column temperature was at 30 °C. However, the resolution between Saccharin and PAn were able to meet the acceptance criteria of NLT 1.5 when the column temperature was below 25 °C. Therefore, the column temperature is changed to “20 ± 5°”, and the resolution requirement is changed to “NLT 1.5 between Saccharin and PAn”.

Comment Summary #3: The commenter recommended changing the system suitability requirement - %RSD from “NMT 0.5%” to “NMT 0.73%” to align with the General Chapter <621>.

Response: Comment incorporated.

Comment Summary #4: The commenter requested all impurities from different manufacturing processes be included in the monograph.

Response: The EC responded that the impurity method is under development by using instrumental analysis. Stakeholders are encouraged to assist USP for the method development and validation.

Comment Summary #5: The commenter recommended updating the flame test for sodium identification in the Saccharin Sodium monograph. Additionally, they recommended applying the retention time of the principal peak from Assay for the identification test. These comments apply to the Saccharin Calcium monograph as well.

Response: The EC responded that these recommendations will be considered in the upcoming revisions to this monograph so the revisions can be commented on by all stakeholders.

Comment Summary #6: The commenter requested more details about the harmonization process for the monographs of Saccharins since they were recently suppressed from the Pharmacopeial Discussion Group (PDG) workplan.

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

Monograph/Section: Tetracycline Hydrochloride/ Multiple Sections

Expert Committee: Chemical Medicines Monographs 1

No. of Commenters: 1

Comment Summary #1: The commenter recommended revising the limit for any individual unidentified impurity in the test for *Organic Impurities*.

Response: Comment not incorporated. The EC will consider a future revision to the monograph upon receipt of supporting data as no responses were received from manufacturers.

Comment Summary #2: The commenter recommended including the temperature requirement under *Packaging and Storage* section.

Response: Comments not incorporated. The EC will consider a future revision to the monograph upon receipt of supporting data.

Monograph/Section(s): Torsemide Compounded Oral Suspension/ formula

Expert Committee(s): Compounding

No. of Commenters: 1

Commentary Summary #1: A commenter suggested switching the order of the ingredients in the formula table to match the order in which they are used in the compounding instructions.

Response: Comment not incorporated. The order in which ingredients are used is not related to the order in which they are listed in the formula. <795> required compounders to create and maintain a compounding record to document the compounding process.

Monograph/Section(s): Vancomycin Compounded Oral Suspension

Expert Committee(s): Compounding

No. of Commenters: 1

Commentary Summary #1: A commenter suggested omitting the monograph because there is a commercially available product.

Response: Comment not incorporated. The EC resolved to continue development of the monograph to cater for situations when the commercial product is out of stock. Also, the compounded preparation is used in other countries where the commercial product may not be available. In addition, the availability of a standard for compounders will help compounders make a pharmaceutically elegant preparation when compounding is required.

Monograph/Section(s): Water-Soluble Vitamins Tablets/ Various

Expert Committee: Non-Botanical Dietary Supplements

No. of Commenters: 2

Comment Summary #1: The commenter recommended deleting the text, “previously dried and stored in the dark over phosphorus pentoxide and protected from absorption of moisture while weighing” in the *Strength* section, under Calcium Pantothenate, Method 2, Standard stock solution, to eliminate the discrepancy between the new Calcium Pantothenate RS label information, which states, “use as is and correct for water content”.

Response: Comment incorporated.

Comment Summary #2: The commenter reported that the USP Ascorbic Acid RS is missing from the USP Reference Standards <11> section and recommended its inclusion.

Response: Comment incorporated.

Monograph/Section(s): Water-Soluble Vitamins with Minerals Tablets/ Various

Expert Committee: Non-Botanical Dietary Supplements

No. of Commenters: 2

Comment Summary #1: The commenter recommended deleting the text, “previously dried and stored in the dark over phosphorus pentoxide and protected from absorption of moisture while weighing” in the *Strength* section, under Calcium Pantothenate, Method 2, Standard stock solution, to eliminate the discrepancy between the new Calcium Pantothenate RS label information, which states, “use as is and correct for water content”.

Response: Comment incorporated.

Comment Summary #2: The commenter reported that the USP Ascorbic Acid RS is missing from the USP Reference Standards <11> section and recommended its inclusion.

Response: Comment incorporated.