

# Commentary

USP-NF 2021, Issue 3

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In accordance with USP's *Rules and Procedures of the Council of Experts ("Rules"*), and except as provided in Section 9.02 *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 republished in *PF* for further notice and comment, in accordance with the *Rules*. In cases when proposals advance to official status, a summary of comments received and the appropriate Expert Committee's responses, as well as Expert Committee-initiated changes, are published in the Proposal Status/Commentary section 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 or conflict between the contents of the *Commentary* and the official text, the official text prevails.

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# Comments were received for the following when they were proposed in PF:

## General Chapters

<17> Prescription Container Labeling

<1010>Analytical Data—Interpretation and Treatment

<1149> Guidelines for Assessing and Controlling the Physical Stability of Chemical and

Biological Pharmaceutical Raw Materials, Intermediates, and Dosage Forms

<1231> Water for Pharmaceutical Purposes

<1469> Nitrosamine Impurities

## **Monographs**

Alcohol

Azelastine Hydrochloride

Calcipotriene Cream

Choline C 11 Injection

Clonidine Transdermal System

Diphenoxylate Hydrochloride

Ethacrynic Acid

**Etoposide Phosphate** 

**Etoposide Phosphate for Injection** 

Fluorometholone Acetate

Gabapentin Compounded Oral Suspension

**Ketamine Compounded Oral Solution** 

Latanoprost Compounded Topical Solution

Lorazepam

Methyl Salicylate

Mupirocin Calcium

**Mupirocin Ointment** 

Naltrexone Hydrochloride Compounded Cream

Norethindrone Acetate and Ethinyl Estradiol Tablets

Oxacillin Injection

Oxycodone Hydrochloride Extended-Release Tablets

Phenobarbital Sodium for Injection

Pyrrologuinoline Quinone Disodium (PQQ)

Ringer's Injection

Riociguat

Scopolamine Hydrobromide

Sodium Lauroyl Sarcosinate

Sour Jujube Seed

Sour Jujube Seed Dry Extract

Sour Jujube Seed Powder

Thioguanine

Ursodiol Compounded Oral Suspension

Zoledronic Acid

## No comments were received for the following proposals:

## General Chapters

<89> Enzymes Used as Ancillary Materials in Pharmaceutical Manufacturing <130> Protein A Quality Attributes

## Monographs

Annatto Seed Oil Tocotrienols

Bendroflumethiazide

Bitter Orange Fruit Flavonoids Dry Extract

Chloral Hydrate Capsules

Chloral Hydrate Oral Solution

Chloroprocaine Hydrochloride Injection

Chloroquine Hydrochloride Injection

Chlorpromazine Suppositories

Chymotrypsin

Chymotrypsin for Ophthalmic solution

Cisplatin for Injection

Colistin Sulfate for Oral Suspension

Cyclosporine

Dapsone

**Dehydrated Alcohol** 

Demecarium Bromide Ophthalmic Solution

Dexamethasone Compounded Oral Suspension

**Dexpanthenol Preparation** 

Dextrose Injection

Didanosine Tablets for Oral Suspension

Dorzolamide Hydrochloride and Timolol Maleate Ophthalmic Solution

Dorzolamide Hydrochloride Ophthalmic Solution

Epitetracycline Hydrochloride

Ergocalciferol Oral Solution

Erythromycin Estolate

Erythromycin Estolate Capsules

Erythromycin Estolate for Oral Suspension

Erythromycin Estolate Oral Suspension

Erythromycin Estolate and Sulfisoxazole Acetyl Oral Suspension

**Erythromycin Estolate Tablets** 

Ferrous Fumarate Tablets

Fludrocortisone Acetate Compounded Oral Suspension

Fludrocortisone Acetate Compounded Oral Suspension, Veterinary

Gadoversetamide

Gadoversetamide Injection

Gluconolactone

Hydroxyamphetamine Hydrobromide Ophthalmic Solution

**lodoquinol Tablets** 

Iohexol

Iron Sorbitex Injection

Kanamycin Sulfate Capsules

Levocarnitine

Lime

Mafenide Acetate

Methacycline Hydrochloride Oral Suspension

Neomycin and Polymyxin B Sulfates and Hydrocortisone Acetate Ophthalmic

Suspension

Penicillamine Capsules

Poloxamer

Propofol Injectable Emulsion

Propylene Glycol Mono and Dicaprylate

Propylene Glycol Monocaprylate

Quinidine Sulfate Capsules

Red Asian Ginseng Root and Rhizome

Red Asian Ginseng Root and Rhizome Powder

Reserpine and Chlorothiazide Tablets

Sodium Monofluorophosphate

Sulfacetamide Sodium

Sulfadiazine

Sulfadiazine Sodium

Teriparatide

Timolol Maleate and Hydrochlorothiazide Tablets

Tolbutamide for Injection

Triclosan

**Trimeprazine Tartrate Tablets** 

White Peony Root

White Peony Root Dry Extract

White Peony Root Powder

#### General Chapters

**General Chapter/Section(s):** <17> Prescription Container Labeling

Commentary/Multiple Sections

**Expert Committee(s):** Healthcare Safety & Quality Expert Committee

No. of Commenters: 3

#### Introduction

**Comment Summary #1:** The commenter suggested adding a reference for the statement "Medication misuse has resulted in more than 1 million adverse drug events per year in the United States."

**Response:** Comment incorporated.

**Comment Summary #2:** The commenter suggested changing the "best" source of information to "main" source because in some instances, patients have access to

additional sources of drug information, and the prescription container label may not always be the "best" source of information.

**Response:** Comment partially incorporated. Sentence changed to, "...patients' primary source of information regarding the medications they have been prescribed is on the prescription container label."

**Comment Summary #3** The commenter suggested using a single "auxiliary" term since there were multiple terms (i.e., auxiliary information, auxiliary warnings, auxiliary statements, and auxiliary label information).

**Response:** Comment incorporated. Terms were standardized to "auxiliary label," as this is the common term used by pharmacists. A definition was added to provide further clarity.

**Comment Summary #4:** The commenter suggested further clarity of the term "supplemental instructional information" since it was unclear whether it is additional information on the prescription container label, or a separate sheet(s) of information provided with the prescription container.

**Response:** Comment incorporated. Text was included to clarify "supplemental instructional information."

**Comment Summary #5:** The commenter suggested clarity on the term "prescription medication instructions" and suggested revising to "prescription container label medication instructions" to be more specific.

Response: Comment incorporated.

## Emphasize Instructions and Other Information Important to Patients

**Comment Summary #6:** The commenter suggested a reference change for the definition of a "pill" from the USP Nomenclature Guidelines to USP general chapter <1151>, which includes a definition for "pill" in the Glossary.

**Response:** Comment incorporated.

## Oral Liquid Medication Dosing Tools

**Comment Summary #7:** The commenter suggested creating a subheading (e.g., Oral Liquid Dosage Forms) to bring prominence to the important topic discussed.

Response: Comment incorporated.

## Opioid Warning Label Development

**Comment Summary #8:** One commenter suggested that a USP requirement regarding opioid warning labels would not be necessary.

**Response:** Comment not incorporated. This section is not a prescriptive requirements but a recommendation.

**Comment Summary #9:** One commenter suggested that selection of an auxiliary opioid warning label should be determined by the pharmacist providing the opioid medication.

**Response:** Comment incorporated.

**Comment Summary #10:** One commenter suggested USP draw from existing warning label principles for opioid warning label principles.

**Response:** Comment incorporated.

**Comment Summary #11:** One commenter suggested USP avoid overly detailed principles that dictate a specific color, style, or location for opioid warning labels.

**Response:** Comment not incorporated. This section is not a prescriptive requirements but a recommendation.

**Comment Summary #12:** The commenter suggested adding the word "misuse" to a sentence to align with a phrase used in regulation, "Opioids are a class of drugs with a high risk of dependence, abuse, misuse, and addiction."

**Response:** Comment incorporated.

**Comment Summary #13:** One commenter suggested an alternative example regarding a warning labeling statement for opioid prescriptions to inform patients the medication contains an opioid rather than asking the pharmacist about naloxone.

Response: Comment incorporated.

## Improve Readability

**Comment Summary #14:** The commenter provided publications which support the use of serif versus sans serif and suggested USP support this font type for legibility.

**Response:** Comment incorporated. Sentence added to describe availability of guidance that support the use of sans serif.

**General Chapter/Sections**: <1010> Analytical Data—Interpretation and

Treatment/Multiple Sections

**Expert Committee:** General Chapters–Statistics

No. of Commenters: 5

#### Introduction

**Comment Summary #1**: The commenter suggested a change to the following sentence in the Introduction section, under the Study Conduct subsection: "Effective use of randomization should be considered to minimize the impact of systematic variability or bias." Randomization should be completed before sample collection and data analysis. To clarify this point, the commenter recommended revising the sentence to "Effective use of randomization should be considered during the study design to minimize the impact of systematic variability or bias."

**Response**: Comment not incorporated. The topic is addressed in Section 4.0.

### **Prerequisite Laboratory Practices and Principles**

**Comment Summary #2**: The commenter suggested a change in the Prerequisite Laboratory Practices and Principles section, under the Analytical Procedure and Sample Performance Verification subsection, noting that the section begins with a brief description of "system suitability." They recommended expanding this description to clarify system suitability requirements and to be consistent with <621>.

**Response**: Comment not incorporated. The chapter does not elaborate on the assay protocol.

## Basic Statistical Principles and Uncertainty

**Comment Summary #3**: A commenter suggested Equation 4 seems to be a general definition of a confidence interval; the calculations that presume a simple case are given

in Equation 5. Also, the typesetting of Equation 5 seems confusing, since it appears to give two different formulas that are both labeled "UB," when the first formula is in fact identical to the preceding formula line that is labeled "LB." The chapter needs to highlight somewhere that all presented calculations are for the simplest possible univariate case only; for all other cases, random-effects or mixed-effects models need to be considered and the help of a statistician is absolutely required.

**Response:** Comment not incorporated. Equation 5 was corrected in *PF* 46(4). Equation 5 provides the general form of a confidence interval. More complex estimates of variance are outside the scope of this chapter.

**Comment Summary #4**: A commenter asked if the central limit theorem is enough for a normality assumption or if normality check is required every time with data transformations.

**Response:** Comment not incorporated. Query is outside of the chapter scope.

**Comment Summary #5**: Several commenters noted inconsistency in the use of colon and semicolon in Equation 5.

**Response:** Comment incorporated. Colons are now used in all formulas.

## Study Considerations

**Comment Summary #6**: A commenter asked how to evaluate the sample size using Equation 9 with prior maximum allowable value of %RSD.

**Response**: Comment not incorporated. Converting %RSD to standard deviation is mentioned in references and statistical textbooks.

# Comparison of Analytical Procedures

**Comment Summary #7**: A commenter suggested that this could be an opportunity to clarify terminology and contrast with ICH and/or IEEE terminology for the terms "accuracy" and "trueness."

**Response**: Comment not incorporated. Reader is referred to <1225>, where these terms are defined.

**Comment Summary #8**: Several commenters noted that in Equation 14, there should be a subtraction sign between the two cumulative functions.

**Response**: Comment incorporated.

Comment Summary #9: Several commenters noted confusion in Equations 17 and 18. The paragraph immediately preceding Equation 18 begins with the following sentence: "The information provided earlier to select d=1 and k=2 is now used to determine sample size for the study." Though "and k=2" has been stricken, several examples throughout the chapter continue to refer to results with this value in place. For consistency, we recommend either retaining "k=2" (and updating Equation 18 for consistency) or updating all subsequent references and examples where the value "k=2" is assumed.

**Response**: Comment incorporated with the following changes: removed Equation 17 and references to k=2.

**Comment Summary #10**: A commenter suggested that an equal sign (=) be added before the bracket solution in Equations 24 and 28.

**Response**: Comment incorporated.

#### **Control Charts**

**Comment Summary #11**: A commenter asked if control charts can be used in R&D procedures.

**Response**: Comment not incorporated. The comment is outside the scope of the chapter. References are provided for the application of control charts.

### Models and Data Considerations

**Comment Summary #12**: A commenter indicated that the geometric CV is Equation 44 and not Equation 43. The text refers to Kirkwood (17), where the geometric CV is defined as Equation 43, which is incorrect, but as this paper has been disseminated widely, this confusion has propagated in the literature.

**Response**: Not incorporated. The reference is to Kirkwood. The geometric CV as stated in Equation 43 (Equation 42 in final text) is taken from the Kirkwood reference (17). The expert committee believes that the reference is correct and should be left in the chapter as written in Kirkwood.

Comment Summary #13: A commenter suggested in the APPENDIX 2: MODELS AND DATA CONSIDERATIONS section, the OUTLIERS subsection contains the following: "A first defense against obtaining an outlying analytical result is application of an appropriate set of system suitability and control rules..." System suitability is respective to the analytical instrument; if an analytical result is obtained, then the system suitability has passed and any outlying results should be contributed to the control rules. For clarity, the commenter suggested revising this text as follows: "A first defense against obtaining an outlying analytical result is application of an appropriate set of control rules..."

**Response**: Comment not incorporated. The suggested change is context specific. **Comment Summary #14**: A commenter suggested that outlier testing should be 2-sided tests not the 1-sided tables shown in <1010> and <111>.

**Response**: Comment not incorporated. It will be reviewed for future revisions.

**Comment Summary #15**: A commenter noted that Equation 52 should contain a minus sign in  $H_0$ .

**Response:** Comment incorporated. Equation 52 is  $\mu_N - \mu_0 = 0$ .

**General Chapter/Section(s):** <1149> Guidelines for Assessing and Controlling the

Physical Stability of Chemical and Biological

Pharmaceutical Raw Materials, Intermediates, and

Dosage Forms

**Expert Committee(s):** General Chapters—Chemical Analysis

No. of Commenters: 6

#### General

**Comment Summary #1:** The commenter suggested a more prescriptive, granular, and perhaps more concise description of when specific tests may be applicable to determine the physical stability of raw materials and products.

**Response:** Comment not incorporated. This informational general chapter is intended to provide guidelines. It is not intended to describe practical information for performing stability studies. The comment is out of the scope for this chapter.

#### Introduction

**Comment Summary #2:** The commenter recommended revising the text related to recalls for readability and clarity. Most recalls related to polymorphic conversion are due to variations in performance and efficacy of the drug product as a result of phase conversion of the active pharmaceutical ingredient(s).

**Response:** Comment incorporated. The sentence was changed to: "Recalls have occurred for a drug product from the US marketplace due to changes in the unexpected appearance of a more stable and less soluble crystal form and for a transdermal system after crystals formed unexpectedly and compromised its efficacy."

## Definition of Physical Stability

**Comment Summary #3:** The commenter recommended adding the following text to the definition of physical stability: "(i.e., the physical variation is not significant enough to affect the drug product's performance)."

**Response:** Comment not incorporated. The definition states the materials remain physically unchanged over time. This section provides clarification and examples.

**Comment Summary #4:** The commenter requested clarifying that the commonly accepted physical forces of interaction are the van der Waals forces (such as the London dispersion force, Debye force, and Keesom force).

Response: Comment incorporated.

**Comment Summary #5:** The commenter recommended adding Pauli repulsive forces due to the exclusion principle as part of the van der Waals forces.

**Response:** Comment not incorporated. The Expert Committee felt it was not appropriate to mix the thermodynamic forces stated with quantum mechanics.

**Expert Committee-Initiated Change #1:** The title "Possible cause(s)" was changed to "Example cause(s)" in all tables for clarity. The table are not intended as a comprehensive list of causes.

# Table 1: Powders (excipients and drug substances)

**Comment Summary #6:** The commenter suggested revising the material category "Powders (excipients and drug substances)" to be more inclusive for other powders (e.g., granules, drug products).

**Response:** Comment incorporated. The material category was changed to "Powders (such as excipients and drug substances)." Combination of excipients and drug substances are drug products.

**Comment Summary #7:** The commenter suggested revising the failure mode "Caking or agglomeration" to "Caking or agglomeration/aggregation" because agglomeration is powder particles bound by weak forces, aggregation is powder particles strongly bound together, and caking is a severe and extensive form of aggregation. Including all three terms is more accurate.

**Response:** Comment incorporated.

**Comment Summary #8:** The commenter suggested revising the possible cause(s) "Temperature cycling during storage and distribution" to "Temperature cycling during storage and distribution, failure of seal on primary packaging, water sorption, presence of electrostatic charge" because caking can occur due to moisture, the presence of an electrostatic charge, or other causes.

**Response:** Comment partially incorporated. The example cause(s) was changed to "Temperature cycling during storage and distribution, water sorption and presence of electrostatic charge." This is not intended as a comprehensive list.

**Comment Summary #9:** The commenter suggested revising the possible cause(s) "Loss of crystallinity, polymorph change, change in hydration state" to "Physical transformations (e.g., loss of crystallinity), polymorph conversions, change in hydration/solvation state, and discoloration" to include additional causes.

**Response:** Comment partially incorporated. The example cause(s) was changed to "Change of crystallinity, polymorph change, change in hydration state." This is not intended as a comprehensive list.

#### Table 1: Tablets

**Comment Summary #10:** The commenter suggested revising the possible cause(s) "Spontaneous salt formation between a drug substance and an excipient" to "Spontaneous salt formation between a drug substance and an excipient, discoloration" because tablets can also become discolored, especially in the presence of a coloring agent.

**Response:** Comment not incorporated. The category is about possible causes of failure mode, and discoloration is not a cause.

**Comment Summary #11:** The commenter suggested revising the failure mode "Breakage or chipping" to "Breaking or chipping, fusion between tablets" because water sorption can also cause fusion between tablets.

**Response:** Comment not incorporated. Fusion is not commonly encountered.

## **Table 1: Solutions**

**Comment Summary #12:** The commenter suggested revising the failure mode "Subvisible or visible Particulate or haze formation/opalescence" and "Fibril or particulate formation" to consider them as part of the same "Failure Mode" or elaborating on which size ranges are ascribed to each.

**Response:** Comment partially incorporated. The failure mode was changed to "Haze formation/opalescence, which can lead to subvisible or visible particulate" for clarity.

**Comment Summary #13:** The commenter suggested revising the possible cause(s) "Formation of an insoluble degradation product" to "Formation of an insoluble degradation product, microbial growth" because microbial contamination can also cause haze formation.

**Response:** Comment incorporated.

**Comment Summary #14:** The commenter suggested changing the possible cause(s) "Formation of an insoluble degradation product" to a failure mode because the causes can be similar to those for fibrillation, aggregation, and particle formation.

**Response:** Comment partially incorporated. The possible cause(s) was changed to "Chemical degradation leading to the formation of an insoluble product, microbial growth, or product-package interaction" for clarity.

**Comment Summary #15:** The commenter suggested revising the possible cause(s) "Aggregation (biologics)" because it is very broad and dependent on product, but should mention different stressors (e.g., temperature, shear forces [including stirring], hydrophobic surface interactions, unfavorable pH).

**Response:** Comment partially incorporated. The possible cause(s) was changed to "Aggregation (biologics) due to stressors such as shear forces."

**Comment Summary #16:** The commenter suggested revising the possible cause(s) "Liquid crystal formation" to "Intermolecular crosslinking (e.g., hydrogen bonding, pi-pi stacking, liquid crystal formation)" because the appearance of a spatial network is due to intermolecular crosslinking resulting from physical interaction or chemical bonding (e.g., van der Waals interactions, hydrogen bonds between complementary functional groups, pi-pi stacking, anisotropy of the molecular structure).

**Response:** Comment partially incorporated. The possible cause(s) was changed to "Protein unfolding, hydrogen bonding, liquid crystal formation, intermolecular interactions."

# Table 1: Powder (prepared as a lyophilized cake)

**Comment Summary #17:** The commenter suggested revising the possible cause(s) "storage temperature greater than glass transition temperature" to "the primary drying temperature is higher than the glass transition temperature of the formulation" because in terms of lyophilization process, collapse of the lyophilized cake is generally due to the primary drying temperature being higher than the glass transition temperature of the formulation and/or the ramp rate being too high for the secondary drying.

**Response:** Comment not incorporated. The scope of this chapter is about stability and not manufacturing process.

**Comment Summary #18:** The commenter recommended adding the possible cause(s) "Formulation composition and lyophilization processing parameters; moisture retention and adsorption after lyophilization" because the formulation composition is essential for a drug product's performance. Additionally, moisture retention and adsorption after lyophilization can also lead to poor reconstitution.

**Response:** Comment not incorporated. Formulation composition is discussed in another section of this chapter in terms of controlled systems and packaging rather than as a cause (formulation design).

## Table 1: Gel

**Comment Summary #19:** The commenter suggested revising the possible cause(s) "Weakness of gel structure" to "Polymer length or solvent composition" because this is a physical characteristic of the gel due to the underlying cause. The possible cause could be chain length of polymer and the network structure of the gel due to how the polymers associate (e.g., aggregated helices with interconnected chains) as this has direct impact on elasticity effect and along with osmotic stress factors will influence the syneresis.

**Response:** Comment partially incorporated. The respective failure mode was changed to "Inhomogeneous polymer crosslinking of the gel or a change in composition of the liquid."

## Table 2: Drug Substance

**Comment Summary #20:** The commenter suggested adding the possible cause(s) "physical transformations (e.g., polymorphous transitions, pseudopolymorphic forms)" because physical transformations can affect dissolution profiles of the drug substance. This also includes polymorphous transitions or the appearance of pseudopolymorphic forms (e.g., solvation/desolvation).

**Response:** Comment partially incorporated. The following possible cause was added: "polymorphic transitions."

## Table 2: Suspension

**Comment Summary #21:** The commenter suggested revising the failure mode "Change in dissolution (of the suspended particles) rate" to "Change in reconstitution time (of the suspended particles) or suspendability" because the suspension dosage form is not favorable for dissolution; "dissolution rate" is not an adequate term for this dosage form. The commenter also recommended that this dosage form be removed from Table 2 and included in Table 1.

**Response:** Comment partially incorporated. Table 2 is not describing reconstitution or resuspension. A new table for "Examples of Physical Instability Leading to Changes in Rheological Properties of Suspensions or Solutions" has been incorporated, addressing the comment.

**Comment Summary #22:** The commenter suggested revising the possible cause(s) "Increase in particle size, agglomeration" to "Increase in particle size, agglomeration/aggregation; nonsuspendable sedimentation or cake formation" because change in re-suspendibility can cause cake formation, particle interactions, agglomeration.

**Response:** Comment partially incorporated. A new table for "Examples of Physical Instability Leading to Changes in Rheological Properties of Suspensions or Solutions" has been incorporated, addressing the comment.

## Table 3: Capsules (hard or soft shell)

**Comment Summary #23:** The commenter suggested adding the possible cause(s) "desorption, failure of seal on primary packaging, capsule shell brittleness due to the loss of moisture in capsule shells, increased mechanical strength due to pellicle formation" because they are common.

**Response:** Comment partially incorporated. The possible cause(s) was changed to "Inadequate primary packaging" for a more general category.

#### Table 4: Emulsion

**Comment Summary #24:** The commenter suggested revising the possible cause(s) "Increase in internal/disperse phase droplet-size upon temperature cycling" to "Increase in globule size upon temperature cycling" for clarity.

**Response:** Comment incorporated.

#### Table 5

**Comment Summary #25:** The commenter suggested adding aerosols and sprays, in order to characterize the effects of physical stresses on all forms of oral or nasally inhaled products because inhalation aerosols and sprays are available on the market and could also be negatively affected due to physical stresses.

**Response:** Comment incorporated. The table header was changed to "Examples of physical instability leading to changes in performance of inhaled and nasal drug products." Additional categories were added for "Metered dose inhaler (particles in liquid suspension, drug product)" and "Nasal spray (drug product)."

#### **Common Risks**

Comment Summary #26: The commenter recommended revising "High-shear processes (such as milling or homogenization) can induce physical changes in common pharmaceutical materials" to "High-shear processes (such as milling, homogenization or stirring) can induce physical changes in common pharmaceutical materials" because stirring is an example, as milling and homogenization do not really cover biologicals in solutions and several other processes with high shear forces can impact the physical stability.

**Response:** Comment incorporated.

**Comment Summary #27:** The commenter recommended revising "High-shear processes (such as milling or homogenization) can induce physical changes in common pharmaceutical materials" to "High-shear processes (such as milling or homogenization) and high heat treatment (such as terminal sterilization) can induce physical changes in common pharmaceutical materials" because terminal sterilization at 121° is a common sterilization process for sterile drug product production which may affect viscosity and particle size distribution of a suspension drug product.

**Response:** Comment incorporated. A new bullet point was added to describe synergistic effects of multiple factors (e.g., temperature) to physical stability. **Comment Summary #28:** The commenter requested revising "Changes in pH or ionic strength may induce aggregation of proteins and peptides" to "Changes in pH or ionic strength may induce aggregation of proteins and peptides, especially in connection with specific processing conditions (e.g., high temperatures, high shear forces including stirring or changes in hydrophobic surface interactions)" because causes for physical instability are often a synergistic effect.

**Response:** Comment incorporated. The text was changed to "Changes in pH or ionic strength may induce aggregation of proteins and peptides, sometimes synergistically with specific processing conditions (such as high shear forces, changes in hydrophobic surface interactions, etc.)." Effect due to high temperature was added in a new bullet. **Comment Summary #29:** The commenter recommended adding "High temperatures, changes in hydrophobic surface interactions may induce aggregation/fibrillation of proteins and peptides" because they may cause physical instability and may arise during the manufacturing process.

**Response:** Comment incorporated. A new bullet was added to describe synergistic effects of multiple factors (e.g., temperature) to physical stability.

# Analytical Testing Challenges

**Comment Summary #30:** The commenter recommended adding "size-exclusion chromatography" to the techniques used for biologics because it is a common size-based technique which determines the oligomeric state of large molecule drug products. **Response:** Comment incorporated.

**Comment Summary #31:** The commenter requested replacing "Spiking known amounts of a drug substance into a placebo formulation is one common approach, but accurate results only can be obtained with proper mixing, especially for low concentrations and/or low drug loads" with "Spiking known amounts of a drug substance into a placebo formulation is one common approach, but accurate results only can be obtained with proper sample preparation, especially for low concentrations and/or low drug loads in solids, semi-solids and high viscous liquids" because sample preparation is a critical part of analytical method procedures, and mixing is just one step in sample preparation.

**Response:** Comment incorporated.

**Comment Summary #32:** The commenter suggested replacing "Because of the lack of specificity or a non-linear concentration-response relationship, it may be necessary to build empirical models using reference standards to estimate the amount of physical change that has occurred" with "It may be necessary to build empirical models to describe the concentration-response relationship using reference standards to estimate the amount of physical change that has occurred" because the model does not need to be linear, but a valid analytical method is required to demonstrate adequate specificity and sensitivity to meet the goal of analysis.

Response: Comment incorporated.

**Comment Summary #33:** The commenter requested adding discussion about the possibility to overcome some of the analytical testing challenges with comparability studies. Some methods are inherently qualitative/non-specific and therefore not suitable for quantitative assessments, but nonetheless can be used to characterize the physical condition of the biological, especially in connection with comparability studies. Mention the possibility of characterization by orthogonal methods, alleviating some of the shortcomings in limits of detections for physical changes, as well as the need to quantify those changes.

**Response:** Comment incorporated. A new paragraph was added: "Some analytical challenges may require the use of orthogonal techniques to provide desired information; for example, where interferences or other matrix effects preclude the use of a desired technique. Even if qualitative, such methods could still be useful. Additionally, the use of multiple techniques may be required to profile the physical stability characteristics of the molecule or product to maximize the potential to detect issues or differences (useful in biological comparability exercises for example). These considerations may be important in the development of product understanding and ultimately an appropriate control strategy, as discussed in the next section."

## Building an Appropriate Control Strategy

**Comment Summary #34:** The commenter suggested replacing "QbD focuses on:" with "Attributes of QbD include:" for clarity.

**Response:** Comment incorporated.

**Expert Committee-Initiated Change #2:** The text "Identifying all possible influences that can affect the performance of a process" was changed to "Identifying all possible influences that may affect product performance" for clarity.

**Expert Committee-Initiated Change #3:** The text "Using risk assessment tools and scientific knowledge to identify potentially high-risk attributes or parameters" was changed to "Using risk assessment, guided by scientific knowledge and experience, to identify potentially high-risk attributes or parameters."

**Expert Committee-Initiated Change #4:** The text "Using risk levels to determine whether the influence should be considered critical" was changed to "Designing and executing experiments to determine whether the influence should be considered critical and at what levels (as such, edge of failure experiments at early development stages are encouraged)" for clarity.

**Comment Summary #35:** The commenter requested adding the following statement: "Submission strategy and impact classification are determined by the innovator based upon regulatory expectations and sound scientific strategy, which may include design space experimentation but may not meet the expectations of a QbD submission." **Response:** Comment incorporated.

**Comment Summary #36:** The commenter suggested replacing "For example, the dissolution behavior of an oral dosage form could be affected by multiple underlying physical changes, such as changes in tablet breaking force or interactions between the drug substance and excipients" with "For example, the dissolution behavior of an oral dosage form could be affected by multiple underlying physical changes, such as changes in tablet breaking force, or interactions between the drug substance and excipients, or drug substance polymorphic change" because changes in polymorphic form of the drug substance can affect dissolution behavior.

**Response:** Comment incorporated.

**Comment Summary #37:** The commenter suggested revising "Formulation design is an important factor and may be used to build physical stability into the product" because physical stability of drug components should also be regarded as an important factor used to build stability in the drug product formulation.

**Response:** Comment partially incorporated. The text was changed to "Formulation design and packaging selection may be used to build physical stability into the product." **Comment Summary #38:** The commenter recommended adding text to describe the selection of excipients because excipient selection is critical for the assurance of the drug product physical stability.

**Response:** Comment not incorporated. The current text describes details on this topic. **Comment Summary #39:** The commenter recommended replacing "In that case, high RH conditions should be avoided during distribution, storage, and use" with "In that case, high RH conditions should be avoided during manufacturing, distribution, storage, and use" because in case drug components are sensitive to water, the humidity of the manufacturing process should also be controlled.

**Response:** Comment not incorporated. The next paragraph in the chapter covers the recommendation.

**Comment Summary #40:** The commenter requested adding "For example, use of rayon/polyester coil or the use of a desiccant sachet instead of a desiccant canister

should be considered to avoid excessive agitation/stress" to include some text describing the use of desiccants when the drug product is soft/fragile.

**Response:** Comment incorporated.

Comment Summary #41: The commenter suggested revising "The development of a validated solid-state analytical method may be required in some instances, but in other cases, as noted earlier, certain research tools may not add value and less complex approaches may be preferred provided they are supported by earlier research during the development phase of the product" to reflect test system is qualified/validated for physical measurements. A physical test is not validated since by definition it is measuring a physical property of the sample. What is required is a properly qualified (validated) test system for performing the physical measurement.

**Response:** Comment incorporated. The text was change to "The development of a validated solid-state analytical method may be required in some instances. In other cases, less complex approaches may be preferred provided they are supported by earlier research during the development phase of the product. See <1225> for more information on validation of physical methods."

#### Conclusion

**Expert Committee-Initiated Change #5:** The text "The overarching understanding gained through a QbD approach will assist in identifying risks and vulnerabilities associated with drug product manufacturing, storage, and use, which will ultimately facilitate implementation of a control strategy" was changed to "The overarching understanding, such as that which may be gained through a QbD approach, will assist in identifying risks and vulnerabilities associated with drug product manufacturing, storage, and use, which will ultimately facilitate implementation of a control strategy" for alignment with the content.

## Appendix 2

**Comment Summary #42:** The commenter recommended including additional chapters to the examples of physical test methods and information in the *USP–NF* because they are helpful or commonly used (<729>, <785>, <786>, <858>, <1858>, <1761>).

Response: Comment incorporated. Chapter <179> was added.

**General Chapter/Section(s):** <1231> Water for Pharmaceutical Purposes

**Expert Committee(s):** General Chapters—Chemical Analysis

No. of Commenters: 4

#### General

**Comment Summary #1:** The commenter recommended including a table summarizing the various types of water and comparing the testing attributes and requirements for readability.

**Response:** Comment not incorporated. The proposal was not part of this revision proposal. The Expert Committee will review and consider development in a future revision to the chapter.

# Waters Used for Pharmaceutical Manufacturing and Testing Purposes

**Comment Summary #2:** The commenter recommended revising portions of the paragraph concerning antimicrobial agents for clarity.

**Response:** Comment not incorporated. The current wording aligns with current terminology in the *USP–NF*, e.g., "sterile water product" is packaged water. The existing language conforms to USP style.

### Carbon Dioxide-Free Water

**Comment Summary #3:** The commenter suggested adding sampling precautions, as follows: "Sample should be obtained by trained and qualified personnel and the sample maintained to ensure representative conditions of the sample."

**Response:** Comment not incorporated. This section describes types of water and not the appropriate location for sampling nor specific practices nor requirements. There is another section addressing this topic.

# **High-Purity Water**

**Comment Summary #4:** The commenter requested clarifying "conductivity parameters described below for high-purity water" because the next paragraph explains requirements for low conductivity assays, and therefore the new sentence could be misinterpreted.

**Response:** Comment incorporated. The text was changed to "conductivity parameters described in the following two paragraphs for high-purity water."

**Comment Summary #5:** The commenter recommended retaining the in-line conductivity parameter for high-purity water in the new text, for the reader's reference.

**Response:** Comment not incorporated. The text in this section is more descriptive and it is not prescriptive. Different analyses require different grades of water and the section provides flexibility.

## Monitoring

**Comment Summary #6:** The commenter recommended adding a reference for using a risk assessment defining monitoring frequency.

**Response:** Comment not incorporated. This section describes elements that will be part of an overall risk-based approach. Section 6.4.1. contains more elements for this assessment.

#### Microbial-Retentive Filtration

**Comment Summary #7:** The commenter suggested clarifying that the use of sterile filters to remove microorganisms residing in the pharmaceutical water systems should be an exception.

**Response:** Comment not incorporated. The existing text states the fact that this type of filtration is "widely employed."

Comment Summary #8: The commenter recommended eliminating text regarding 0.1  $\mu$ m filters because industry standard for sterile filtration is a 0.2- to 0.22- $\mu$ m sterilizing grade filter.

**Response:** Comment not incorporated. A 0.2- to 0.22-µm is not the best fit for some water applications. The section explains the differences in performance.

**Comment Summary #9:** The commenter suggested adding requirements to filter integrity test and filter retentivity validation, noting that vendor data is acceptable. **Response:** Comment not incorporated. More data to rationalize the change is needed, if deemed appropriate. The acceptability of using vendor data is considered a manufacturer activity and needs to be rationalized.

# **Ultraviolet Light**

**Comment Summary #10:** The commenter recommended replacing "sanitizing agents" with "agent for sanitization" for clarity.

**Response:** Comment not incorporated. The current wording aligns with current terminology in the *USP–NF* and within this chapter.

## Storage Tanks

**Comment Summary #11:** The commenter suggested adding that a surface finish of at least 0.8 Ra micron needs to be specified (if greater than 0.8 Ra then approval from Quality is required) because "smooth interiors" need further definition.

**Response:** Comment not incorporated. The risk-based determination of a surface finish depends on the water use. Other water applications could require more or less Ra micron with justification. The Expert Committee will consider a future revision to this text.

**Comment Summary #12:** The commenter suggested adding a reference for the requirement to utilize a bottom valve which is fully drainable and cleanable to the storage tank.

**Response:** Comment not incorporated. There is not only one ideal design. The chapter provides flexibility and intentionally does not provide requirements. The Expert Committee will consider a future revision to this text.

**Comment Summary #13:** The commenter recommended adding an external reference with information for consideration of using pressure relief valves instead of rupture discs, if applicable, to reduce opportunities for microbial growth.

**Response:** Comment not incorporated. Other internationally recognized references can be used. The Expert Committee will consider a future revision to this text.

# Distribution Systems

**Comment Summary #14:** The commenter recommended adding a definition for turbulence, by a Reynold's number of minimum 3000.

**Response:** Comment not incorporated. There could be other applicable definitions. Engineering references can be consulted. The Expert Committee will consider a future revision to this text.

**Comment Summary #15:** The commenter recommended inserting the term Double Tube Sheet Shell and Tube to describe the proper type of heat exchanger for compendial water systems.

**Response:** Comment not incorporated. This informational general chapter describes general principles of design and some considerations. The chapter is not intended to provide specific details that could vary depending on the application. The Expert Committee will consider a future revision to this text.

# Installation, Materials of Construction, and Component Selection

**Comment Summary #16:** The commenter suggested inserting orbital welds to provide more details.

**Response:** Comment not incorporated. Such level of detail is beyond the scope of this chapter. See ISPE baseline guidelines for more engineering details. The Expert Committee will consider a future revision to this text.

**Comment Summary #17:** The commenter suggested adding that a surface finish of at least 0.8 Ra micron needs to be specified (if greater than 0.8 Ra then approval from Quality is required) because "smooth interiors" need further definition.

**Response:** Comment not incorporated. The risk-based determination of a surface finish depends on the water use. Other water applications could require more or less Ra micron with justification. The Expert Committee will consider a future revision to this text.

**Comment Summary #18:** The commenter recommended adding a definition for turbulence, by a Reynold's number of minimum 3000.

**Response:** Comment not incorporated. There could be other applicable definitions. Engineering references can be consulted. The Expert Committee will consider a future revision to this text.

#### Preventive Maintenance

**Comment Summary #19:** The commenter recommended adding a reference for the requirement of system passivation prior to initial system start-up and major repairs because it is an industry standard.

**Response:** Comment not incorporated. Passivation and cleaning prior to use (prequalification activities) are described in other sections. The Expert Committee will consider a future revision to this text.

**Comment Summary #20:** The commenter recommended adding a reference for inspection of the system to be performed periodically to detect severe rouge. The inspection frequency should be established based on a risk assessment and be based on the analysis of historical data.

**Response:** Comment not incorporated. The chapter describes that periodicity is based on specific design and application. The Expert Committee will consider a future revision to this text.

**Comment Summary #21:** The commenter recommended mentioning that heat exchangers shall be visually checked on a defined basis (e.g., for corrosion and leakages).

**Response:** Comment not incorporated. Such level of detail is beyond the scope of this chapter. See ISPE baseline guidelines for more engineering details. The Expert Committee will consider a future revision to this text.

#### Change Control

**Comment Summary #22:** The commenter suggested adding a reference for a risk assessment to be utilized to evaluate the impact of proposed changes to the whole system.

**Response:** Comment not incorporated. The chapter describes elements that will be part of an overall risk-based approach. The Expert Committee will consider a future revision to this text.

**Comment Summary #23:** The commenter recommended adding a reference for the requirement of system passivation prior to initial system start-up and major repairs because it is an industry standard.

**Response:** Comment not incorporated. Passivation and cleaning prior to use (prequalification activities) are described in other sections. The Expert Committee will consider a future revision to this text.

## Sampling

**Comment Summary #24:** The commenter suggested adding clarification details of testing performed by trained and qualified personnel only.

**Response:** Comment not incorporated. This informational general chapter describes general principles of design and some considerations. The Expert Committee will consider a future revision to this text.

# **Purposes and Procedures**

**Comment Summary #25:** The commenter suggested adding a reference to sampling requirements. Water samples for microbiological tests shall be collected in sterile containers and by trained personnel using a technique designed to minimize microbial contamination of the samples.

**Response:** Comment not incorporated. This informational general chapter describes general principles. There are several sections explaining the guidelines for sampling. The Expert Committee will consider a future revision to this text.

#### Chemical Tests for Bulk Waters

**Comment Summary #26:** The commenter suggested revising "A multi-staged conductivity test that detects ionic (mostly inorganic) contaminants replaced, with the exception of the test for Heavy Metals, all of the inorganic chemical tests (i.e., Ammonia, Calcium, Carbon Dioxide, Chloride, Sulfate)" for clarity because it is not clear which tests have been replaced by a multi-staged conductivity test.

**Response:** Comment not incorporated. The section was not under revision. The Expert Committee will consider a future revision to this text.

#### Chemical Tests for Sterile Waters

**Comment Summary #27:** The commenter requested revising "Some packaging materials contain more leachables than others and may not be as suitable for some applications as other packaging systems or as suitable as the bulk water" for clarity because it is unclear what "as suitable as the bulk water" means.

**Response:** Comment incorporated. The sentence was modified as follows: "Some packaging materials contain more leachables than others and may not be as suitable for some applications as other packaging systems. Not all packaging materials are suitable for holding bulk water."

## Total Organic Carbon for Sterile Waters

**Comment Summary #28:** The commenter suggested expounding on the tests designed to address the concern of leachables from the package containers.

**Response:** Comment not incorporated. The Expert Committee felt that the level of detail incorporated is appropriate for an informational general chapter.

**Comment Summary #29:** The commenter suggested revising "The actual dose of leachables administered to a patient would be higher form the large volume containers" because the statement is only true when the dose volume is fixed.

**Response:** Comment not incorporated. The dose is generally proportional to the container size. The Expert Committee felt that the section contains an appropriate level of detail.

### **Test Methods**

**Comment Summary #30:** The commenter suggested introducing a cross-reference to <60> for potential presence of this microorganism in water.

**Response:** Comment not incorporated. General Chapter <60> is intended for testing products, not water. Its usage for water requires adapting the method in ways never intended, such as using a larger test volume or a filtration membrane instead of direct inoculation.

## **Defining Alert and Action Levels and Specifications**

**Comment Summary #31:** The commenter recommended adding a reference for risk assessment to define alert/action levels.

**Response:** Comment not incorporated. The chapter describes elements that will be part of an overall risk-based approach. The Expert Committee will consider a future revision to this text.

**General Chapter/Sections:** <1469> Nitrosamine Impurities.

**Expert Committee:** General Chapters—Chemical Analysis

No. of Commenters: 28

**Expert Committee-initiated Change #1:** The Expert Committee added subsection 5.2 Example Calculations of Nitrosamine Limits to separate the example from the derivation of the limits.

#### General

**Comment Summary #1:** The commenters noted that the chapter is not fully aligned with the FDA Guidance for Industry: Control of Nitrosamine Impurities in Human Drugs and recommended that USP make appropriate revisions to align with it.

**Response:** Comment not incorporated. The Expert Committee determined that the content of the chapter is aligned in principle with the stated FDA guidance.

**Comment Summary #2:** The commenters recommended that USP include nitrosamines identified after issuance of the FDA Guidance for Industry: Control of Nitrosamine Impurities in Human Drugs.

**Response:** Comment partially incorporated. The Expert Committee added the N-nitrosophenylmethylamine (NMPA) to the chapter and noted that the text says that the

list of nitrosamines is not all inclusive and that new nitrosamines are expected to be identified

**Comment Summary #3:** The commenters, noting that both "API" and "Drug Substance" are used interchangeably, recommended choosing and using only one throughout the document.

**Response:** Comment incorporated.

**Comment Summary #4:** The commenter suggested that it would be useful to provide information such as analytical methods suitable to detect low levels of nitrite in starting materials, intermediates, and excipients.

**Response:** Comment not incorporated. The Expert Committee determined that the suggestion was outside the scope of the chapter.

**Comment Summary #5:** The commenter, noting that they support the publication of methods in Section 8, recommended to include text to make it clear to the user that the scope of the four analytical methods described in Section 8 is limited to certain specified sartan drug substances.

**Response:** Comment incorporated. The Expert Committee revised the information in the text of each procedure to include the specific nitrosamines and the drug substance for which the procedures have been validated.

**Comment Summary #6:** The commenters, indicating that the chapter was broadly written and, in most cases, restates the FDA's guidance, recommended that USP focus on providing guidance for analytical methods for properly measuring material properties critical to performance, quality, and safety.

**Response:** Comment not incorporated. The Expert Committee determined that the current text is suitable. The Expert Committee and stakeholders who commented find the chapter's content valuable.

**Comment Summary #7:** The commenter recommended that USP revise specific monographs where there are identified risks for nitrosamine impurities.

**Response:** Comment not incorporated. The Expert Committee determined that the recommendation is outside the scope of the chapter. USP will address, on a case-by-case basis, if a monograph will need revision based on an article-specific nitrosamine.

**Comment Summary #8:** The commenter, noting that they have observed that the Thresholds of Toxicological Concern (TTC) are not aligned between the FDA and EMA, suggested as a general recommendation that the USP chapter include a value/guideline that provides alignment of TTC.

**Response:** Comment not incorporated. The Expert Committee determined that the recommendation is outside the scope of the chapter.

**Comment Summary #9:** The commenter, noting that the general chapter is primarily dedicated to the sartan family of compounds and the nitrosamines that may be present, stated that it may be more suitable to keep this general chapter as an informational chapter without the inclusion of the four analytical test procedures used for selected sartans. Further, the commenter suggested that the methods could be introduced as a separate general chapter and referenced in the monographs, or they could be included in the sartan monographs.

**Response:** Comment not incorporated. The Expert Committee decided that the content of the chapter and inclusion of the procedures are suitable. As indicated above, many stakeholders find the procedures valuable.

**Comment Summary #10:** The commenter, referring to the objective of the chapter as stated in the briefing, stated that it would be helpful if USP could provide clarification and specific guidelines if and how it applies to medical devices and combination products.

**Response:** Comment not incorporated. The Expert Committee determined that medical devices were outside the scope of the chapter.

**Comment Summary #11:** The commenter, noting that the maximum daily dose is on the higher side and hence the sample preparation techniques are quite challenging, request USP to add Analytical Methods for Metformin tablets too.

**Response:** Comment not incorporated. The Expert Committee determined that the request is outside the scope of the chapter.

**Comment Summary #12:** The commenter asked if they can consider <1469> as guidance for validating the method for quantifying other nitrosamine impurities not listed in the chapter.

**Response:** Comment not incorporated. The Expert Committee determined that the question is addressed in Section 7. Test Method Performance Characteristics of Nitrosamine Methods.

Comment Summary #13: The commenter noted that there is a concern with using the phrase "example analytical procedures" in sections 6 and 7. The commenter stated that they recognize that the chapter is numbered above 1000 and considered non-mandatory, but it does not preclude enforcement during a health authority inspection. The commenter suggested USP add language to state that the term "example" means that the respective test method may be used as such or replaced by a suitable, validated procedure.

**Response:** Comment not incorporated. The Expert Committee determined that the term example is clear in the context of the text and the content includes language similar to the suggestions.

**Comment Summary #14:** The commenter, noting that there are various nitrosamines which are non-carcinogenic and their acceptable intake (AI) are also very high (e.g., N-nitrosodibenzyl amine, NMBzA), asked if they are to be excluded from the 0.03 ppm limit of total nitrosamines.

**Response:** Comment not incorporated. The Expert Committee determined that the request is outside the scope of the chapter.

**Comment Summary #15:** The commenter asked if there was any concern about the use of detergent containing nitrosating agents (e.g., Bronopol) or amines for cleaning drug product residues.

**Response:** Comment not incorporated. The Expert Committee determined that the request is outside the scope of the chapter. Individual firms need to address on a case-by-case basis as part of their risk assessment.

#### 1. Introduction

**Comment Summary #16:** The commenter noted that in several places the term "synthetic" was used, but it is not clear whether the text deals with synthetic API and related drug product (DP) only. They recommended clarifying whether DPs of biologic origin are in scope. Further, the commenter requested that fermentation products should not be in the chapter's scope.

**Response:** Comment not incorporated. The Expert Committee determined that current text is suitable. This is an informational general chapter. The content of the chapter is relevant for all pharmaceutical products required to comply with the requirements for the content of nitrosamines.

**Comment Summary #17 (two commenters):** The first commenter recommended revising sentence four of the introduction. A second commenter, referring to the same sentence, noted that not all nitrosamines are carcinogenic and provided proposed language for clarification.

**Response:** Comment partially incorporated. The Expert Committee revised the sentence to "Given the potentially broad implications of the presence of carcinogenic members of this class of chemicals, this chapter has been developed to provide a science- and risk-based approach for the control of nitrosamine impurities to ensure that the potential presence of nitrosamines in drug substances and drug products is identified, assessed, and controlled."

**Comment Summary #18:** The commenter, stating that the introduction does not clearly bring in the risk-based focus of the chapter, recommend adding/rewording and provided a suggested statement.

**Response:** Comment partially incorporated. The Expert Committee revised the text to "Recommendations are provided regarding a) the establishment of controls of nitrosamine levels in order to ensure their elimination or reduction; and b) analytical procedure performance characteristics for procedures used to monitor nitrosamine levels."

**Comment Summary #19:** The commenter, stating that the subject requires more depth coverage than was provided in the chapter, recommended guidance be added and listed several resources.

**Response:** Comment not incorporated. The Expert Committee determined that the Section 9. Additional Sources of Information lists several resources, and other information is listed in the references.

### 2. Nitrosamine Impurities

Comment Summary #20 (two commenters): The commenter indicated that this section is missing information about drug substances that have amine functional groups that are at risk of forming nitrosamines if there are nitrosating agents in the excipients, and that these drug substances are at risk structurally independent of route of synthesis. Another commenter noted that the section does not include degradation products of the drug substance itself to form nitrosamines from either the DS or a secondary amine in an excipient.

**Response:** Comment not incorporated. The Expert Committee determined that the information is provided in Section 3 of the chapter.

Comment Summary #21 (two commenters): The commenter, referring to the second paragraph of the section, recommended deleting the sentence "N-nitroso compounds are listed as Class 1 mutagens in ICH M7: Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk" and recommended including the definition of "cohort of concern." Another commenter requested deleting the reference to ICH M7 class and referring to them as potentially high potency mutagenic carcinogens.

**Response:** Comment partially incorporated. The Expert Committee revised the entry to state "N-nitroso compounds are among the structural groups of high potency mutagenic carcinogens in several animal species, and some are classified as probable or possible human carcinogens referred to as the 'cohort of concern' in ICH M7" and provided the definition of the "cohort of concern."

**Comment Summary #22:** The commenter recommended removing the entry "it is unlikely that all of the listed nitrosamines will be anticipated or observed as impurities in any single material."

**Response:** Comment incorporated. The Expert Committee deleted the sentence as recommended

Comment Summary #23 (two commenters): The commenter, noting that the nitrosamine topic is still in the early stage of discovery process and more nitrosamines are being identified, recommended revising the sentence referring to the list of nitrosamines to indicate that and provided a suggested language. A second commenter noted that when publishing such table, it should be made clear that it reflects the current state of knowledge only and that the risk assessment should not be limited to the nitrosamines mentioned.

**Response:** Comment partially incorporated. The Expert Committee revised the entry to state "The list of nitrosamines is not intended to be exhaustive but represents those that have been observed and communicated by regulators and manufacturers as being potentially present or observed."

**Comment Summary #24 (two commenters):** The commenters, referring to Table 1, cautioned that the nitrosamine impurity listing was missing NMPA and suggested to also add 1-methyl-4-nitrosopiperazine (MNP) and 1-cyclopentyl-4-nitrosopiperazine (CPNP) to the table.

**Response:** Comment partially incorporated. The Expert Committee revised Table 1 to include NMPA. The other two nitrosamine impurities are drug substance specific and, if needed, could be addressed in the monograph in the future.

**Comment Summary #25:** The commenter noted that the Nitrosoethylisopropylamine is abbreviated as NEIPA in the chapter and recommended that this is aligned with US FDA guideline, Control of Nitrosamine Impurities in Human Drugs, September 2020, as NIPEA.

**Response:** Comment not incorporated. The Expert Committee determined that the nomenclature used in the chapter is suitable.

**Comment Summary #26:** The commenter noted that the chapter does not capture NMEA-(N-Nitrosomethyl-ethylamine) and NPDA-(N-nitroso-dipropylamine) which are potential nitrosamine impurity, and that NEIPA impurity is an extra impurity mentioned which is not the part of US FDA guideline.

**Response:** Comment not incorporated. The Expert Committee determined that the FDA guidance uses NIPEA instead of NEIPA, and the correct nomenclature is used in the chapter. The chapter states that the list is not exhaustive.

**Comment Summary #27:** The commenter, noting that there is limited consideration for the formation of nitrosamines within the DP matrix during or after manufacture of the DP, suggested including such information and provided a literature reference addressing this topic.

**Response:** Comment not incorporated. The Expert Committee determined that the suggestion is out of the scope of this chapter.

**Comment Summary #28:** The commenter, referring to the last sentence of the section, recommended removing the word "significant" from the "significant potential toxicity" phrase.

Response: Comment incorporated.

### 3. Sources of Nitrosamines

Comment Summary #29: The commenter noted that Sources of Nitrosamine Impurities are now described in the FDA Guidance "Control of Nitrosamine Impurities in Human Drugs"; therefore, the chapter does not need to go into detail regarding nitrosamine sources and risk assessment and should either remove these sections with reference to the FDA guidance or assure they are aligned with the FDA guidance."

Response: Comment not incorporated. The Expert Committee determined that the content of the section is suitable and is not intended to repeat the guidance.

Comment Summary #30: The commenter noted that the chapter is written in general

way and cannot be considered as standalone document. To make it more understandable, it is recommended to include reference to US FDA guideline, Control of Nitrosamine Impurities in Human Drugs, September 2020.

**Response:** Comment partially incorporated. The Expert Committee revised the chapter to add respective guidance documents as references.

**Comment Summary #31:** The commenter, referring to the first sentence of the first paragraph, recommended that it is better to specify the appropriate pH value of the acidic conditions, such as pH < 4.0, to provide clear guidance for the risk assessment of nitrosamine formation.

**Response:** Comment not incorporated. The Expert Committee determined that the technical detail, which may be relevant in certain cases, is outside the scope of the chapter.

**Comment Summary #32:** The commenter, referring to the first sentence of the first paragraph, recommended discussing the role of quaternary amines in forming nitrosamines, as quaternary amines are sometimes precursor amines to interact with nitrous acid.

**Response:** Comment not incorporated. The Expert Committee noted that quaternary amines do not react with nitrous acid. Their presence in the molecule of the drug substance is now included as a risk factor for the drug product in Table 2.

Comment Summary #33 (two commenters): The commenter, referring to the first sentence of the first paragraph, noted that while this is accurate for most secondary amines, for tertiary amines the reaction occurs to a lesser extent because it requires breaking carbon-nitrogen bonds. The presence of nitrous acid required for a tertiary amine to form a nitrosamine, and the rate of formation (~1000x slower), differs significantly from the conditions required for a secondary amine to form a nitrosamine. The second commenter, conveying the same idea, stated that secondary and tertiary amines may not be equally reactive under acidic conditions to readily form nitrosamine impurities.

**Response:** Comment partially incorporated. The Expert Committee revised the paragraph to state "Specifically, nitrosamines are formed by chemical reaction of

secondary or tertiary amines with nitrites (the latter via intermediate degradation) under acidic conditions (see 3.1. Nitrosamine Formation Reaction)" which addresses the comment about the rate of nitrosamine formation from these two amine classes.

**Comment Summary #34:** The commenter, referring to the first paragraph, noted that the examples of sources/pathways listed under paragraph 1 are missing the risk posed by drug substance molecules containing secondary and tertiary amine groups, which pose a risk of forming drug substance nitroso-related impurities.

**Response:** Comment not incorporated. The Expert Committee determined that their presence in the molecule of the drug substance is included as a risk factor in Table 2.

**Comment Summary #35 (two commenters):** The commenters noted that the redundancy and inconsistency between the text in Figure 1 and Table 2 should be minimized and corrected by removing Table 2. Furthermore, Table 2 does not adequately describe all potential risks per "source," nor does it distinguish between primary vs. secondary sources of risk.

**Response:** Comment partially incorporated. The Expert Committee revised the leading sentence for Table 2 to state "Some of the examples identified are summarized in Table 2" to clarify that the list there is not exhaustive.

**Comment Summary #36 (two commenters):** The commenters, referring to the "carry over of the reactive species" topic in first bullet of the list, noted that there is no published evidence to support this claim.

**Response:** Comment not incorporated. The Expert Committee determined that such evidence exist. It is also highlighted as a potential concern in regulatory guidance documents.

**Comment Summary #37:** The commenter, referring to Figure 1, suggested that it should be rearranged based on how drug products are manufactured.

**Response:** Comment not incorporated. The Expert Committee determined that the suggestion is a style preference and that the design of Figure 1 is based on the significance of the of component's contribution to the presence of nitrosamines in drug products.

**Comment Summary #38:** The commenter, referring to Figure 1, asked for clarification regarding the definition of packaging for injectable drugs/biologics.

**Response:** Comment not incorporated. The Expert Committee determined that the request is out of the scope, adding that packaging component risks vary by product type, and that the intent of the chapter is not to provide detailed discussion of each step of the risk assessment.

**Comment Summary #39:** The commenter, referring to the solvents row in Table 2, recommended deleting the phrase "that can degrade to form dialkyl amines."

**Response:** Comment partially incorporated. The Expert Committee revised the sentence to state "Presence of residual dialkyl amines or tri-substituted amines that can degrade to form intermediates that can further react with nitrosating agents."

**Comment Summary #40:** The commenter, referring to the water row in Table 2, recommended replacing the phrase "impurities that can degrade to form dialkyl amines" in the first bullet with "tri-substituted amines."

**Response:** Comment not incorporated. The Expert Committee determined that the current text is suitable, and the suggestion would narrow its applicability.

**Comment Summary #41 (two commenters):** The commenters, referring to the water row of Table 2, noted that acid is not a risk but can be a contributing factor in the reaction to form nitrosamines from a vulnerable amine and a nitrosating agent and suggested that it should not be listed as a risk.

**Response:** Comment partially incorporated. The Expert Committee revised the entry to state "Presence of acid and nitrosating agents."

**Comment Summary #42:** The commenters, referring to the water row of Table 2, noted that "chloramines are included as a risk for Drug Substance, but wondered whether this should be a consideration for Water (i.e., should any water used in drug product manufacture be assessed for chloramines?)."

**Response:** Comment partially incorporated. The Expert Committee noted that the suggestion is addressed by adding the leading sentence to Table 2 which states that the list contains examples and is not intended to include every potential scenario for every item.

**Comment Summary #43 (two commenters):** The commenters, referring to the excipients row of Table 2, noted that excipients can also contain vulnerable amines.

**Response:** Comment not incorporated. The Expert Committee determined that the content is suitable, and the intention of the table was not to include all the possible contributing factors but to include the key contributors from each source. The revised leading sentence of Table 2 states, "Some of the examples identified."

**Comment Summary #44 (two commenters):** The commenter, referring to the drug substance row of Table 2 and noting that use of sodium azide itself is not a risk and that the risk arises from the use of sodium nitrite to quench residual sodium azide, suggested it would be better to state "the use of potential nitrosating agents such as nitrite as either a reagent or quenching agent."

**Response:** Comment partially incorporated. The Expert Committee revised the entry to state "Use of sodium azide in the synthesis followed by use of nitrates in acidic medium (nitrous acid) for quenching excess azides."

**Comment Summary #45:** The commenter, referring to the drug substance row of Table 2, requested clarification on why the "need of additional purification steps (e.g., crystallization)" is a highlighted risk.

**Response:** Comment partially incorporated. The Expert Committee revised the entry to replace with the questioned entry with "Insufficient purification."

**Comment Summary #46 (two commenters):** The commenter, referring to the drug substance row of Table 2, stated that it is unclear how "Need of additional purification steps" increases risk of nitrosamines and that additional purification steps are a mitigation approach, not a risk-adding action. The second commenter provided recommended replacement text.

**Response:** Comment partially incorporated. The Expert Committee revised the entry to replace the entry with "Insufficient purification."

**Comment Summary #47:** The commenter, referring to the manufacturing process row of Table 2, noted that the "poor quality solvents" is effectively listed twice.

**Response:** Comment incorporated. The Expert Committee deleted the redundant "poor quality solvents" entry.

**Comment Summary #48:** The commenter, referring to the manufacturing process row of Table 2, questioned what was meant by poor quality and if there are lower limits that would be considered too low.

**Response:** Comment partially incorporated. The Expert Committee deleted the redundant "poor quality solvents" entry. The Expert Committee noted that the "Solvents" entry defines the risk as "Limited controls/specification limits for recycled solvents."

**Comment Summary #49:** The commenter, referring to the manufacturing process row of Table 2, recommended adding "Carry over of reactive species into subsequent steps" as an observed risk.

**Response:** Comment partially incorporated. The Expert Committee revised the row adding an entry stating, "Carry over of relevant reactive species into subsequent steps." **Comment Summary #50 (three commenters):** The commenter, referring to the drug product row of Table 2, requested clarification about the risk from the presence of nitrate counter ions, reasoning that, as written, it is misleading, as the risk is simply from the "presence of nitrite in excipients" whether there as a counter ion or a contaminant, for example in potato-starch-derived excipients.

**Response:** Comment partially incorporated. The Expert Committee, noting that solvents could also be contaminated with nitrates (nitrites), revised the entry to state "Presence of nitrate counter ions (potentially containing nitrite as an impurity)."

**Comment Summary #51 (two commenters):** The commenters, referring to the drug product row of Table 2, questioned if the nitrate in the middle bullet was a typo/error, and suggested it should be "nitrite" instead, and recommended using the entry "presence of nitrite counter ions (potentially as an impurity)."

**Response:** Comment partially incorporated (see response in the comment 50) **Comment Summary #52:** The commenter, referring to the Container-Closures row of Table 2, requested including the fact that the existence of amines is needed for these reactions to occur, reasoning that the container-closure incidence was due to reaction of nitrocellulose in the lidding foil with amines in the printing ink during heat-sealing blister process via vaporization and condensation on the finished products.

**Response:** Comment partially incorporated. The Expert Committee revised the entry to state, "Packaging materials containing vulnerable amines that might react with nitrosating agents present in the packaging material itself (e.g., amines in inks reacting with nitrocellulose print base)."

**Comment Summary #53 (two commenters):** The commenters, referring to the container-closures row of Table 2, noted that the chapter states "Bio-degradation of Nitrocellulose" and to their knowledge no evidence to support this has ever been published, and they requested providing a reference to supporting evidence or justification of how this relates to current understanding.

**Response:** Comment partially incorporated. The Expert Committee revised the entry as shown in the response of comment 52.

Comment Summary #54 (two commenters): The commenters, referring to the container-closures row of Table 2 regarding decomposition of nitrocellulose to produce nitrites followed by migration to the drug product, noted that this "risk" is related to aluminum foil blister lidding with an external layer of nitrocellulose print backing that reacted with amines in the ink to form nitrosamines. The commenter stated that it appears to be a single instance that may have been reported to a health agency, and

the event could not be recreated by the foil component manufacturer. Other companies have not reported similar occurrences; therefore, the risk is undocumented and speculative, and the commenter recommended removal of the two bullets related to the same. The commenter recommended a replacement entry.

**Response:** Comment partially incorporated. The Expert Committee revised the entry as shown in the response to comment 52.

### 3.1. Nitrosamine Formation Reaction

Comment Summary #55: The commenter, referring to the last paragraph of Section 3, noted that per the FDA guidance, three steps are recommended to industry: 1) If there is a risk for nitrosamine presence, confirmatory testing of batches should be conducted using sensitive and appropriately validated methods; 2) The manufacturer should develop an appropriate control strategy when a nitrosamine impurity is detected above the LOQ; and 3) Any batches found to contain levels of nitrosamine impurities at or above the AI limits should not be release by the manufacturer for distribution. The commenter recommended revising this section entirely to be harmonized with the recommendations from the FDA guidance.

**Response:** Comment not incorporated. The Expert Committee determined that while the content is structurally different, the content of the section is substantially aligned with the FDA guidance in all of the key areas. The content of the chapter addresses the step 1 and step 2 of the guidance and achieving the conclusion for step 3. Step 3 is outside the scope of the chapter.

**Comment Summary #56:** The commenter recommended that "water should be added to the reaction scheme."

**Response:** Comment partially incorporated. The Expert Committee revised the reaction scheme to include the loss of a water molecule above the reaction arrow.

**Comment Summary #57:** The commenter, referring to the last paragraph of the section, recommended to add "When the presence of nitrosamines is confirmed above the LOQ, an appropriate control strategy should be developed."

**Response:** Comment partially incorporated. The Expert Committee revised the paragraph to state "If the potential for the presence of nitrosamines is identified, where appropriate, a control strategy should be developed."

**Comment Summary #58:** The commenter, referring to the second sentence of the last paragraph of the section, recommended revising it to state, "Under certain conditions it is requested to establish a control strategy. Detailed guidance should not conflict with existing regulations."

**Response:** Comment partially incorporated. The Expert Committee added the entry "The control strategy should be aligned with the current regulatory requirements in place" in Section 4.

4. Nitrosamine Risk Assessments-Development of a Control Strategy

**Comment Summary #59:** The commenter, referring to the first paragraph of the section, noted that the proposed risk assessment approach does not align with the FDA guidance and ICH Q9 Guidelines, recommended revising this paragraph and Figure 3 entirely to be aligned with the three-step recommendations from the FDA guidance.

**Response:** Comment partially incorporated. The Expert Committee revised Figure 3. The Expert Committee determined that the content of the section is aligned with the FDA guidance key aspects. The content of the chapter addresses the step 1 and step 2 of the guidance and achieving the conclusion for step 3. Step 3 is outside the scope of the chapter.

**Comment Summary #60:** The commenter, referring to the first paragraph of the section, stated that they consider Section 4 Nitrosamine Risk Assessments – Development of a Control Strategy to be of limited value and inappropriate for inclusion in a pharmacopeial standard and that, since the scientific understanding of the risk factors for the presence of N-nitrosamine impurities in finished drug products is still evolving, they believe that attempting to revise public standards in the way proposed by the USP in <1469> ahead of this increased understanding will likely be counterproductive.

**Response:** Comment not incorporated. The Expert Committee determined that the chapter has public health impact and is valuable for many stakeholders, and this was supported by many comments USP has received, noting appreciation for the development of the chapter.

**Comment Summary #61:** The commenter, referring to the control strategy, stated that it is unclear from the chapter in which cases a routine control of nitrosamine needs to be established. Furthermore, the recommendations are not aligned between US FDA and EMA guideline for Nitrosamines, which creates additional workload for the Industry.

**Response:** Comment not incorporated. The Expert Committee determined that the request regarding harmonization is beyond the intent of the chapter.

**Comment Summary #62:** The commenter, noting that the term "Provisional acceptable intake" is used, requested clarification on what "provisional" means.

**Response:** Comment partially incorporated. The Expert Committee revised the text to replace the "provisional acceptable intake" with "acceptable intake (AI)."

**Comment Summary #63:** The commenter, referring to the first paragraph of the section, noted that there needs to be testing to evaluate and confirm whether there is risk prior to implementing a control strategy. Therefore, Section 4 and Figure 3 should follow discussion on testing for the nitrosamines presence to confirm potential risk and support development of an appropriate control strategy.

**Response:** Comment not incorporated. The Expert Committee determined that the content of the chapter is suitable. It outlines the assessment, confirmation, and control approach.

**Comment Summary #64:** The commenter, referring to Figure 3, noted that in this figure it is foreseen that a control strategy is established even if no risk of nitrosamine contamination has been identified. This is not in line with the requirements outlined by the EMA and not in line with the new FDA Guidance Control of Nitrosamine Impurities in Human Drugs. The commenter, stating that the figure should be revised to clarify the approach to be taken if a risk for nitrosamine contamination can indeed be excluded, recommended that step P3 in the table should not be the establishment of a control strategy, as such a strategy is not needed if there is no risk.

**Response:** Comment partially incorporated. The Expert Committee, noting that many inputs of the risk assessment could change during the product life cycle changed the content of P3 to "Establish the control strategy over the life cycle."

**Comment Summary #65:** The commenter, referring to Figure 3, noted that it is oversimplified and could lead to oversight of risks associated with raw materials, process equipment, and process risk and requested to represent in the figure the risks associated with raw materials, equipment, and process.

**Response:** Comment not incorporated. The Expert Committee determined that the level of details included is suitable and the title says it is a "high level."

**Comment Summary #66:** The commenter, noting that changes are recommended to Figure 3 to capture an appropriate process for developing a control strategy more accurately, recommended including under P1 "A risk assessment should include known risks, not be limited to only the manufacturing process as presented in the figure" and under D1 "Based on testing, nitrosamine presence confirmed."

**Response:** Comment partially incorporated. The Expert Committee determined that the P1 is not limited only to manufacturing process. It includes a second entry "Address potential modes of contamination as applicable." The Expert Committee revised the P3 of Figure 3 to state, "Establish control strategy over life cycle."

**Comment Summary #67:** The commenter, referring to process 1 (P1) in Figure 3, stated that it is unclear whether the risk assessment is for the API manufacturing process or finished product manufacturing process, or both.

**Response:** Comment not incorporated. The Expert Committee determined that the content is suitable. The preceding paragraph states that all these sources should be included in the risk assessment and control strategy.

**Comment Summary #68:** The commenter, referring to the last sentence of the section recommended replacing the phrase "if nitrosamines are predicted in the risk assessment or confirmed to be present through testing in the drug product" with "if nitrosamines are confirmed to be present through testing in a material or drug product." **Response:** Comment partially incorporated. The Expert Committee revised the sentence to state, "if nitrosamines are predicted by the risk assessment or confirmed to be present through testing of the drug substance, drug product, or other materials."

## 5. Limits of Nitrosamines

**Comment Summary #69:** The commenter stated that Section 5 Limits of Nitrosamines is not consistent with the FDA guidance, and EFPIA considers the content inappropriate for inclusion in a pharmacopeial standard.

**Response:** Comment not incorporated. The Expert Committee determined that the text is suitable and aligned with the FDA guidance.

**Comment Summary #70:** The commenter stated that the chapter refers to the US FDA guideline regarding Als. However, the recommendations are not aligned between US FDA and EMA guideline for nitrosamines, which creates additional workload for the Industry.

**Response:** Comment not incorporated. The Expert Committee determined that the comment is out of the scope of the chapter.

**Comment Summary #71:** The commenter stated that there are differences between EMA and FDA in certain limits for nitrosamines (NMPA – FDA limit 26.5 ng/day versus EMA limit 34.3 ng/day). EMA proposes limits for additional two nitrosamines (MeNP and NDBA). The approach for calculating limit for multiple nitrosamines is not completely aligned between FDA and EMA.

**Response:** Comment not incorporated. The Expert Committee determined that the comment is out of the scope of the chapter.

**Comment Summary #72 (two commenters):** The commenter, noting that the document discusses meeting "established interim Als," recommended to future proof the document by saying "current Al's" or just "Al" instead. Another commenter recommended revising "interim limits" to "limits" for nitrosamines listed in the FDA guidance.

**Response:** Comment incorporated. The Expert Committee replaced all references to "interim Al" with "Al."

**Comment Summary #73:** The commenter, stating that Section 5 as written is very restrictive regarding acceptable intake limits, and that there are occasions where acceptable intake limits may not be appropriate such as where the API itself is genotoxic where S9 may apply which is not covered, requested to consider revision of this section.

**Response:** Comment not incorporated. The Expert Committee determined that the content of the section is suitable, and that the commenter's request is out of the scope of the chapter.

**Comment Summary #74:** A commenter, referring to the second sentence of the section, noted that it is incorrect and recommended replacing it with "Nitrosamines are cohort of concern, therefore Threshold of Toxicological Concern (TTC) does not apply. A case-by-case assessment should be conducted to establish compound-specific AI." Another commenter recommended deleting the reference to ICH M7 classes (i.e., Class 1, Class 2) and referring to them as potentially high potency mutagenic carcinogens instead.

**Response:** Comment partially incorporated. The Expert Committee revised the text to state, "Because nitrosamines are among the structural groups of high potency mutagenic carcinogens of the 'cohort of concern' in ICH M7 (1), the threshold of toxicological concern (TTC) does not apply. Instead, the available safety data should be used to establish a material-specific AI on a case-by-case basis."

**Comment Summary #75:** The commenter, noting that the limits for nitrosamines are discussed in section 5, recommended that the chapter include the following statement "The interim acceptable intake limits (ng/day) published by FDA in the Guidance for Industry: Control of Nitrosamine Impurities in Human Drugs, September 2020 for NDMA, NDEA, NMBA, NMPA, NIPEA, and NDIPA in drug products, as shown below" for alignment.

**Response:** Comment not incorporated. The Expert Committee determined that the content of the section is suitable. The chapter references the FDA guidance for numerical values.

**Comment Summary #76:** The commenter, referring to the last sentence of the first paragraph of this section, commented that "health risk" is too broad and should be accurately reflected as a potential cancer risk and recommended to revise it to state that "AI is defined as an intake level that poses a negligible health risk cancer risk that is based on available toxicological data."

**Response:** Comment not incorporated. The Expert Committee determined that the content of the section is suitable, and the recommendation would contradict the ICH M7.

### 5.1. Derivation of AI Limits

**Comment Summary #77:** The commenter, summarizing the actions of the FDA (and other regulatory bodies) to establish interim limits on nitrosamine impurities, which balanced risks of patient safety and access to medication while industry investigations, reporting, and corrective actions were conducted as necessary, noted that it is unclear what value would be provided in discussing interim limits where the USP chapter would be effective after the transition timeline and proposed adding additional information to the chapter based on ICH M7.

**Response:** Comment not incorporated. The Expert Committee determined that the content of the section is suitable, and the chapter references ICH M7 as appropriate. **Comment Summary #78:** The commenter, referring to the subsection's previous title "Derivation of Interim Limits," suggested that USP not address limits but refer to regulatory guidance for the currently established limits for nitrosamines. The reference in this section for AI limits should be updated to reference FDA's nitrosamine guidance from 2020.

**Response:** Comment partially incorporated. The Expert Committee, noting that USP did not put forth any limit, revised the text to clearly reference the FDA guidance for Al values

**Comment Summary #79:** The commenter, noting that the principles described in sections 5 come from ICH M7 and that this guideline should be referenced to avoid conflicts and confusion, recommended stating in the chapter that "Detailed methodology for establishing AI is described in the ICH M7 guideline."

**Response:** Comment partially incorporated. The Expert Committee revised the first paragraph of the section which references ICH M7.

Comment Summary #80: The commenter, noting that while some nitrosamines are Class 1 (i.e., known mutagenic carcinogens), the mutagenicity and carcinogenicity data is not available for all compounds in this class, and it is more appropriate to refer to nitrosamines as "cohort of concern" as described in ICH M7. They recommended adding text to this subsection to address cases where compound-specific carcinogenicity data is not available (options include application of a class-based limit or utilizing data for closely related structural analogs to establish an AI (i.e., read-across)) and that limits can be increased for drugs that are administered for less than a lifetime.

**Response:** Comment not incorporated. The Expert Committee determined that the recommendations are beyond the scope of the chapter.

**Comment Summary #81:** The commenter, referring to the second sentence of the subsection regarding the TD50, noted that it is not entirely accurate and recommended clarifying it.

**Response:** Comment partially incorporated. The Expert Committee revised the entry to remove the calculations and add references to ICH M7 and FDA guidance.

**Comment Summary #82:** The commenter, referring to the AI, recommended adding 70 years of exposure into the basis of AI calculation.

**Response:** Comment not incorporated. The Expert Committee determined that the text was suitable, noting that detailed information explaining the calculation of AI is out of the scope of the chapter.

**Comment Summary #83:** The commenter, noting that the section uses both "MDD of the drug substance" and "MDD of the drug" which are confusing to the readers, suggested revising them to be consistent with the FDA Nitrosamine guidance.

**Response:** Comment incorporated.

**Comment Summary #84:** The commenter, noting that: "The TD50 data were derived from rodent carcinogenicity data, but these were not animal models; and that the extrapolation was to a probability of 1 in 100,000 increased cancer risk, but this was achieved by dividing the TD50 by 50,000," suggested that the section be rewritten for clarity.

**Response:** Comment partially incorporated. The Expert Committee revised the paragraph and added references to ICH M7 and FDA guidance.

**Comment Summary #85:** The commenter, referring to the acceptable intake (AI) in ng/day, noted that in biology the absolute weight does not mean a lot. What is important is the number of molecules. This is best conveyed if doses are expressed in µmol/day. Hence, the commenter recommended to change the units of acceptable intake of nitrosamines to µmol/day or µmol/kg body weight/day.

**Response:** Comment not incorporated. The Expert Committee determined that the current text is suitable, noting that all references from the regulatory agencies are in ng/g, ug/g or more specifically ng/day.

**Comment Summary #86:** The commenter, referring to the references in the section, recommended referring to the official FDA guidance instead of the FDA Updates and Press Announcement on Angiotensin II Receptor Blocker (ARB) Recalls (Valsartan, Losartan, and Irbesartan).

**Response:** Comment incorporated.

**Comment Summary #87:** The commenter, referring to the equation of calculating concentration limits, stated that it is not needed and that it is confusing. They recommended deleting it.

**Response:** Comment not incorporated. The Expert Committee determined that the information is valuable to USP stakeholders as indicated by their comments.

**Comment Summary #88:** The commenter, stating that Table 3 has no added benefits, recommended removing it. The commenter further suggested adding a table of Al limits for several nitrosamines listed in the FDA guidance and stating that if a nitrosamine which is not listed in the table is found, the manufacturer should contact their regulatory authority for determining appropriate Al limits.

**Response:** Comment not incorporated. The Expert Committee determined that the table provides value to the USP stakeholders as indicated by their comments. Regarding the second part of the request, the Expert Committee noted that the nitrosamines listed in FDA guidance are entered in Table 1 in Section 2. Section 5.1 also includes a statement regarding the unlisted nitrosamines that the commenter suggested.

**Comment Summary #89:** The commenter, referring to the equation for calculating concentration limits and acceptable nitrosamine content, asked that the difference between these equations be clarified and if a similar approach could be used to determine limits in other raw materials, not just the drug substance.

**Response:** Comment not incorporated. The Expert Committee determined that the limits are based on what the patient sees, and this is the drug product. The only

standard that can be a reference for the drug product is the maximum daily dose of the drug substance in it.

## 6. Testing for The Presence of Nitrosamines

**Comment Summary #90:** The commenter, stating that this section is not general enough to capture the nuances of method development for various APIs and final drug products, recommended that it should be clarified that these are suggested methods (possibly for specific materials) and that other methods can be used and must be validated.

**Response:** Comment not incorporated. The Expert Committee determined that the current text is suitable. The chapter states that they are example methods.

**Comment Summary #91:** The commenter suggested that this section should be moved up, before the control strategy section (currently Section 4).

**Response:** Comment not incorporated. The Expert Committee determined that the current text is suitable.

**Comment Summary #92:** The commenter, noting that the monograph should also provide guidance regarding what to do when the dose-dependent calculated acceptable concentration is lower than the analytical procedures can reliably quantify (LOQ not low enough), recommended adding "If the dose-dependent necessary limit corresponding to AI is lower than the LOQ of the corresponding analytical procedure the relevant health authority should be consulted to determine a path forward."

**Response:** Comment not incorporated. The Expert Committee, noting that the method needs to suitable for its purpose and that the methods in <1469> are examples only, determined that the current text is suitable.

**Comment Summary #93:** The commenter, referring to the AI limits for multiple nitrosamines, asked for updated information aligned with the FDA guidance. Currently FDA recommends the total nitrosamine level not to exceed 26.5 ng/day.

**Response:** Comment incorporated. The Expert Committee revised the text to add a footnote in Table 3, addressing the recommendation.

**Comment Summary #94:** The commenter, stating that the chapter specifies the limit of 1 nitrosamine present in drug substance, requested clarification for when multiple nitrosamines are present in the drug substance based on the combined nitrosamines limit in the chapter.

**Response:** Comment incorporated. See response to comment 93 above.

## 7. Test Method Performance Characteristics of Nitrosamine Methods

Comment Summary #95: The commenter, in reference to the first paragraph, noted that USP is used as a reference in markets outside of the US and that industry has experience where regulatory agencies may (mistakenly) mandate the use of published methods for other drug substances and/or drug products, even where the USP chapter is above 1000 and should be considered non-mandatory. They recommended that the limitation of the methods to sartan drug substances and the listed nitrosamines should be reflected clearly in the title and/or section of the chapter. Introductory text that explains these limitations would assist the user of the USP.

**Response:** Comment not incorporated. The Expert Committee determined that the current text is suitable, and it includes the commenter's recommendations.

**Comment Summary #96:** The commenter recommended adding "for Implementing a Control Strategy" to the end of the header to differentiate performance characteristics for risk assessment/screening purposes vs. performance characteristics to support implementing a control strategy.

**Response:** Comment not incorporated. The Expert Committee determined that the current title is suitable. The criteria are for the test methods, not for their area of application.

# 7.1. Considerations for Sample Preparation

**Comment Summary #97 (two commenters):** The commenters, noting that it is good to see potential false positives discussed, recommended a more comprehensive list (e.g., potential coelution of DMF with NDMA, contamination from certain brands of nitrile gloves).

**Response:** Comment not incorporated. The Expert Committee determined that the recommendation is out of the scope of the chapter.

**Comment Summary #98 (two commenters):** The commenters, referring to the first bullet of this subsection, recommend adding a note stating that the temperature set for the GC analyses is critical and the user needs to ensure that the analysis temperature is not causing formation of artifacts.

**Response:** Comment not incorporated. The Expert Committee determined that the recommendation is out of the scope of the chapter.

**Comment Summary #99:** The commenter, referring to the "Examples of quantitative analytical procedures included in section 8. *Analytical Procedures*" entry, recommended adding a non-sartan example method since required analyses have moved beyond the class of sartan drugs and they provided references for such examples.

**Response:** Comment not incorporated. The Expert Committee noted that the methods are examples and users can validate them for other classes.

Comment Summary #100 (three commenters): USP received contradicting recommendations regarding entries in Table 4 and Table 5. One commenter recommended tightening the recommended range for Repeatability and Intermediate Precision and that %RSD of standard solutions at LOQ concentration should be checked for the system suitability test, as the LOQs are associated with acceptance criteria of these nitrosamines. The commenter also recommended adding a statement stating that the methods should have LOQ in the parts-per-billion (ppb) range to meet the low Als recommended for nitrosamines for consistency with the FDA guidance. A second commenter requested that USP consider a broader range as acceptance criterion for accuracy (70% to 150%).

**Response:** Comment partially incorporated. The Expert Committee revised the section to remove Tables 4 and 5 and to provide general recommendations regarding performance characteristics that need to be evaluated by the users depending on their specific situation.

**Comment Summary #101:** The commenter, referring to Table 5, noting that the acceptance criteria for the results in the recommended limit test performance criteria assumes the use of an internal standard, stated that it may not be a valid assumption and the variables should just be indicated to represent the response rather than the

ratio to the internal standard and that they believe that the response would be inclusive of the ratio if an internal standard were used.

**Response:** Comment not incorporated. The Expert Committee moved the result part of the table into Section 8. The Expert Committee noted that this is a recommended approach and the use of internal standard is highly recommended for MS and MS-MS methods.

**Comment Summary #102 (two commenters):** The commenters, referring to Table 5, noted that the purpose of the results parameter is unclear as written. If this is intended to be a measurement of the adequate concentration to achieve a recovery of an internal standard, more detail would be required.

**Response:** Comment incorporated. Expert Committee moved the result part of the table into Section 8.

**Comment Summary #103 (two commenters):** The commenters, referring to Table 5, noted that a signal-to-noise (S/N) ratio of 10:1 for LOD is not consistent with the ICH standard S/N of 3:1. One of them recommended that this should be the LOQ requirement and not the LOD requirement.

**Response:** Comment not incorporated. The Expert Committee noted that this is not a classic limit test but rather a quantitative test used in a limit test approach.

# 8. Analytical Procedures

**Comment Summary # 104:** Commenter suggested that the publication in the USP of the analytical methods described in section 8 of <1469> should be the limit of the content included in <1469> at this stage in the development of scientific understanding of the formation of nitrosamine impurities.

**Response:** Comment not incorporated. The Expert Committee determined that current text is suitable. Other commenters (see comment 106) recommended keeping the other content and removing the methods. The Expert Committee and many stakeholders who submitted comments find the content of other chapter sections valuable.

**Comment Summary #105:** The commenter suggested that the text in procedures should clearly limit the use of these methods for the sartan active substances and that there should be no reference to their use for other materials or products.

**Response:** Comment not incorporated. The Expert Committee determined that the text is suitable, stating that these methods are general methods. The validation provided in the chapter is for sartan drug substance. The chapter indicates that users should validate these methods while considering the effect of sample solubility and extraction efficiency on the test results for other materials for which they are intended to be applied.

Comment Summary #106 (two commenters): The commenters noted that the methods provided are specific to sartans and should not be used as general methods. Therefore, it is recommended that these specific methods be removed from the chapter. Response: Comment not incorporated. Expert Committee determined that the text is suitable, stating that these methods are general methods (see response to 104). Comment Summary #107: The commenter recommended that the text clearly state that these analytical procedures should be considered as "examples" but not generally applicable to other drug substances/drug products other than "selected sartans." The

commenter also recommended clarifying that method validation is required instead of "verification" when these methods are adopted for other drug substance/drug product.

**Response:** Comment partially incorporated. The Expert Committee indicated that the text in Section 6 has the following statement: "Example analytical procedures can be found in 8. Analytical Procedures." The Expert Committee also revised the text to include the specified sartan drug substances in each procedure and to state, "The procedures have been established as suitable for their intended (specified) purpose. Users should validate these methods while considering the effect of sample solubility and extraction efficiency on the test results for other materials for which they are intended to be applied."

## 8.1. Quantitative Procedures

**Comment Summary #108:** The commenter suggested that all procedures use amber glassware as is stated in procedure 3.

**Response:** Comment not incorporated. The Expert Committee determined that the current test is suitable. The different types of lighting in labs may suffice based on how the methods were developed and validated.

**Comment Summary #109 (two commenters):** The commenters request that the chapter explicitly state the respective LOQs of the methods for the individual nitrosamines.

**Response:** Comment not incorporated. The Expert Committee determined that the current text includes the requested information. The concentration of the sensitivity solution indicates that in procedure 1 the LOQ is 50 ppb for NDMA, NDEA, NDIPA, NEIPA, NMBA, NMPA, and NDBA, and in procedure 2 the LOQ is 20 ppb for NDMA, NDEA, NDIPA, and NEIPA. The LOQ for procedure 3 is 10 ppb for NDEA and 19.95 ppb for the five other nitrosamines (NDMA, NMBA, NDBA, NEIPA, and NDIPA). The LOQ for procedure 4 is 5 ppb for NDMA, NDEA, NDIPA, NEIPA, NMPA, and NDBA. **Comment Summary #110 (two commenters):** The commenter requested listing which "sartans" have been validated by each method in each procedure and recommended adding LOQs and LODs to each of the four procedures as references.

**Response:** Comment partially incorporated. The Expert Committee revised the text to include the specified sartan drug substances that each procedure has been validated for and recommended that the user should determine the LOQs for their system when the procedure is evaluated.

**Comment Summary #111:** The commenter recommended including analytical procedures for additional nitrosamines, including NMPA.

**Response:** Comment partially incorporated. The Expert Committee revised the text to include NMPA in Procedures 1 and 4.

**Comment Summary #112:** The commenter, stating that all of the methods that have been developed focused on sartans, requested that the chapter highlight that there is no evidence that these methods can be used for other matrices. They recommended including a statement indicating that suitability for any other matrices and/or N-Nitrosamines needs to be established when using these methods.

**Response:** Comment not incorporated. See response to Comment 106.

**Comment Summary #113:** The commenter, referring to the sartan samples' solubility, noted that for determination of trace level impurities, it is mandatory to solubilize API during sample preparation, which does not happen in the USP methods and that sample preparation cannot be considered appropriate if the API itself is insoluble, which doubts the integrity on the accuracy of the method.

**Response:** Comment not incorporated. The Expert Committee determined the accuracy data in the validation report supports the nitrosamine impurities analysis in each of the procedures.

**Comment Summary #114:** The commenter noted that internal standard, NMDA d6/NDEA d10/NMBA d3/NMDA d18, used in the procedures is highly expensive and not readily commercially available and would increase the product cost if used frequently.

**Response:** Comment not incorporated. The Expert Committee determined that the comment is beyond the scope of the chapter. User may choose to develop, without using internal standards, and validate alternative procedures for the analysis.

**Comment Summary #115:** The commenter requested to use a less complicated and robust method. They noted that with the final published methods, USP shall mention that manufacturers can use alternate in-house validated and simpler/superior methods.

**Response:** Comment not incorporated. The Expert Committee determined that the text is suitable. It currently states that the methods listed are examples.

# **Procedure 1**

**Comment Summary #116:** The commenter recommended specifying the HRMS instrument used in the method validation or verification in the procedure.

**Response:** Comment not incorporated. The Expert Committee stated that, as per USP policy, standards generally do not include specific brands of instruments. The Expert Committee determined that such information on validation is mentioned in the briefing. **Comment Summary #117:** The commenter noted that better sensitivity for NEIPA is obtained using PRM rather than SIM, and they recommended testing both if not already completed. The NEIPA peak is observed to be two peaks that are not baseline resolved which should be integrated together for calculation.

**Response:** Comment not incorporated. The Expert Committee determined that PRM and SIM were both tested for NEIPA. Better sensitivity was obtained using SIM. NEIPA was observed as two peaks, and they were integrated together.

**Comment Summary #118:** The commenter, noting that peak areas in the extracted ion chromatograms (EIC) with an m/z tolerance of 15 ppm are used for quantitation, recommended revising peak areas in the EIC with an m/z extraction window of  $\pm$  15 ppm for quantitation.

**Response:** Comment incorporated. The Expert Committee revised the text as recommended.

**Comment Summary #119:** The commenter expressed concerns about the suitability requirements for relative standard deviation and recommended tightening the variation to ensure the system suitability criteria are meaningful for quantifying these impurities.

**Response:** Comment not incorporated. The Expert Committee determined the relative standard deviation requirement in the suitability is adequate for procedure.

**Comment Summary #120:** The commenter commented on the suitability requirements for signal-to-noise ratio and recommended using precision (RSD%) at the LOQ level.

**Response:** Comment not incorporated. The Expert Committee determined that a typical signal-to-noise ratio of 10:1 in the suitability requirement is appropriate as defined in <1225> and ICH Q2(R1).

Comment Summary #121: The commenter commented on the units for the sensitivity solution, standard solution, and sample solution and suggested converting these units to  $\mu g/mL$  to be consistent with the unit used in the calculation.

**Response:** Comment not incorporated. The Expert Committee determined that the units for the solutions are appropriate, and the user should covert these units as needed in the calculation.

**Comment Summary #122** (three commenters): The commenters, noting that no labeled internal standard is used in this procedure, recommended revising the method to use an appropriate internal standard.

**Response:** Comment not incorporated. The Expert Committee determined that the method was validated without the use of internal standard, and the precision, accuracy, and sample preparation are adequate.

**Comment Summary #123:** The commenter noted that the resolution suggested for SIM scan type is 60,000 and for PRM scan type resolution suggested is 30,000 except for NDMA (for which SIM scan type and resolution of 30,000 suggested) and asked to confirm these values.

**Response:** Comment not incorporated. The Expert Committee determined that the current text is suitable. The scan type and resolution are appropriate for the required sensitivity.

**Comment Summary #124:** The commenter commented on the blank interference at the NDBA peak and requested specific precautions for removing the interference peak at the NDBA retention time.

**Response:** Comment not incorporated. The Expert Committee noted that NDBA interferences in the blank may be due to carry over after injecting a higher concentration sample. Injecting multiple blanks until a blank does not have this background peak will resolve the issue.

**Comment Summary #125:** The commenter commented on the methods and requested that it should be made very clear that they potentially need adaptation for testing other API and DP or other nitrosamines.

**Response:** Comment incorporated. Expert Committee revised the text to state: "The procedures have been established as suitable for their intended (specified) purpose. Users should validate these methods while considering the effect of sample solubility and extraction efficiency on the test results for other materials for which they are intended to be applied."

**Comment Summary #126:** The commenter requested that the chapter indicate that HRMS ion source parameters can be adjusted to achieve desired sensitivity.

**Response:** Comment not incorporated. The Expert Committee determined that although Thermo Orbitrap Fusion Lumos was specified as the platform, "the performance criteria for these parameters should be properly set and confirmed through validation to ensure that the method is suitable for its intended use based on the specific analytes, matrices, and required precision and accuracy of the analytical procedures."

**Comment Summary #127:** The commenter requested that the chapter specify a set of scan type, resolution, and other parameters in the procedure to achieve desired sensitivity.

**Response:** Comment not incorporated. The Expert Committee determined that the HRMS parameters in the procedure are adequate.

**Comment Summary #128:** The commenter requested that the chapter include the following statement under system suitability: "The area of an interference peak for NDBA in the blank injection, if present, should be no more than 10% of the peak area of NDBA in the standard solution."

**Response:** Comment not incorporated. The Expert Committee determined that the current text is suitable (see response to comment 124).

## 8.1 Quantitative Procedures

## Procedure 2

**Comment Summary #129:** The commenter, noting that both Procedure 2 and Procedure 4 are based on MS/MS while Procedure 2 is headspace GC and Procedure 4 is direct injection GC, suggested changing the title of the procedure to "Headspace GC-MS/MS."

**Response:** Comment partially incorporated. The Expert Committee changed the procedure title to "Headspace GC-MS."

**Comment Summary #130:** The commenter noted that there are two MRM transitions in the procedure and requested clarification on which is used for quantitation.

**Response:** Comment incorporated. The Expert Committee added a note in the procedure.

**Comment Summary #131:** The commenter, referring to the suitability requirements, expressed concerns for the relative standard deviation of more than 20% from six replicate injections and recommended tightening the variation to ensure the system suitability criteria are meaningful for quantifying these impurities.

**Response:** Comment not incorporated. The Expert Committee determined that the relative standard deviation requirement in the suitability is adequate for the procedure. **Comment Summary #132:** The commenter, referring to the suitability requirements for signal-to-noise ratio, expressed reservation regarding a signal-to-noise ratio of NLT 10 to define instrument suitability for analytical methods for nitrosamines and recommended using precision (RSD%) at the LOQ level.

**Response:** Comment not incorporated. The Expert Committee determined that the current text is suitable. The requirement is for the sensitivity solution which has a concentration four times lower than the standard solution.

**Comment Summary #133 (two commenters):** The commenters, noting that the solvent used in the procedure is methanol and that all OMCL N-Nitrosamine head space GC methods use higher boiling solvents as diluent (for example NMP or DMSO), requested to clarify the diluent, blank, and sample preparations, including the use of imidazole in the blank and sample preparations.

**Response:** Comment not incorporated. The Expert Committee determined that the current text is suitable. The procedures were validated as written.

**Comment Summary #134:** The commenter noted that methanol and acetonitrile solvents are used as the diluent and used after adding imidazole (256°C) in the headspace method and that these solvents are low boiler solvents and not preferred for Head Space methods.

**Response:** Comment not incorporated. The Expert Committee determined that the current text is suitable. See response to comment 133.

**Comment Summary #135:** The commenter noted a typographical error, an extra sentence, "Apply the stopper, cap, and crimp tightly," in the *Sensitivity stock solution*.

**Response:** Comment incorporated. The Expert Committee deleted the extra sentence. **Comment Summary #136 (two commenters):** The commenter noted a typographical error in the *Oven temperature program* under *Column temperature*.

**Response:** Comment incorporated.

**Comment Summary #137:** The commenter stated that the %RSD system suitability requirement of 20% is too high despite the use of the internal standard.

**Response:** Comment not incorporated. The Expert Committee determined that the %RSD requirement in the suitability of the procedure is appropriate based on the supporting data from the validation.

**Comment Summary #138:** The commenter stated that GC cycle time was not mentioned.

**Response:** Comment not incorporated. The Expert Committee determined that the current head space/GC parameters are adequate for the test.

**Comment Summary #139:** The commenter stated that the high pressurization and loop fill time given in the method are not preferred and claimed they may lead to loss of vapors, which can lead to repeatability issues in routine analysis.

**Response:** Comment not incorporated. The Expert Committee determined that the current headspace parameters are adequate based on the supporting validation data. **Comment Summary #140:** The commenter, noting that the temperature rate of 10°C/min is described and that the loop size is not specified in the procedure, requested elaborating on the significance of the temperature rate and incorporating the loop size.

**Response:** Comment not incorporated. The Expert Committee determined that the current text is suitable and that the headspace parameters are adequate based on the supporting validation data.

## 8.1 Quantitative Procedures

#### Procedure 3

**Comment Summary #141:** The commenter, noting that three internal standards are listed in the Table 14, requested clarification on which internal standard should be used for each nitrosamine impurity.

**Response:** Comment not incorporated. The Expert Committee determined that the current text is suitable. The footnote in Table 4 has the requested information.

**Comment Summary #142:** The commenter recommended replacing "amu" with "m/z" in *Scan setting* table under *MS conditions*.

**Response:** Comment incorporated.

**Comment Summary #143:** The commenter requested clarification on the unit of "a" (slope of the calibration curve) as  $(\mu g/mL)$ -1 in the equation and asked that the text indicate which MRM transition(s) is used for the calculation of the results for each nitrosamine impurity.

**Response:** Comment incorporated.

**Comment Summary #144 (two commenters):** The commenters, noting that this procedure states that all solutions should be stored at -18 to -20°C and that this is not stated in any of the other procedures and has not been mandated in any OMCL methods, requested to confirm that this requirement is necessary.

**Response:** Comment not incorporated. The Expert Committee determined that the temperature requirements were set using the procedure's supporting validation data. **Comment Summary #145:** The commenter commented on the sample preparation in the procedure, noting that all the sartans are not soluble in the specified diluent (1% formic acid) at a concentration of 80 mg/1.2 mL.

**Response:** Comment not incorporated. The Expert Committee determined that the sample preparation in the procedure is adequate based on the validation data.

**Comment Summary #146:** The commenter noted that retention time of the sartan API is not mentioned in the method, diverter programs are not mentioned for the different sartans, and mass spectrometric conditions like, interface temperature, desolvation line temperature, nebulizing gas flow rate, heat block temperature and drying gas flow are not specified.

**Response:** Comment not incorporated. The Expert Committee determined that the current text is suitable. Sartan retention time is not relevant. The other parameters are user optimized and will depend on the specific instrument brand used.

Comment Summary #147: The commenter noted that several parameters of Procedure 3 have deficiencies as follows: 1) It does not explicitly state which API [DS] of Sartan analysis is feasible; 2) Specified column chemistry in this procedure is found to be inadequate in terms of specificity or nonspecific of all nitrosamine analytes; 3) Aqueous Diluent [0.1% formic acid in water] for sample/standard preparation is found to be non-suitable in terms of solubility and leads to inconsistency of reproducibility with variance of result; 4) Sample final volume of 1.2 mL followed by filtration is found to be

formidable on day-to-day analysis at QC front; 5) Some of chosen MRM of specific analytes (e.g., NDBA 159.2>41.1) has been found to be most challenging, considering 40Da has many other trace level, unlimited background noise would suppress sensitivity of selected analytes.

**Response:** Comment not incorporated. The Expert Committee determined that the procedure is suitable for its intended use and validated for the sartans and nitrosamines listed.

**Comment Summary #148:** The commenter, noting that two MRM transitions are described for NDMA, for which the m/z 75-> m/z 43 transition is the quantifier and m/z  $75 \rightarrow m/z$  44 is the qualifier but that many methods describe the m/z  $75 \rightarrow m/z$  58 transition as the qualifier, which is scientifically more rigorous, recommended consistency with this approach.

**Response:** Comment not incorporated. The Expert Committee determined that the current text is suitable, and the method have been validated as written. MRM transitions for NDMA in the procedure are supported by the validation data.

#### 8.1 Quantitative Procedures

### Procedure 4

**Comment Summary #149:** The commenter recommended replacing "amu" with "m/z" in *Scan setting* table under *MS conditions*.

**Response:** Comment incorporated.

**Comment Summary #150:** The commenter recommended the correlation coefficient to be revised from "NLT 0.98" to "NLT 0.99" in the *Suitability requirements*.

**Response:** Comment not incorporated. The Expert Committee determined that the correlation coefficient is adequate for the procedure.

**Comment Summary #151:** The commenter noted that auto sampler methods are not preferred when high-concentration APIs are injected directly into the column since it can choke the mass detector, ion source, and column. Thus, those methods are not preferred where APIs are injected directly, and continuous long sequences are to be run in QC.

**Response:** Comment not incorporated. The Expert Committee determined that the method with direct injection is suitable and was supported by validation.

**Comment Summary #152:** The commenter, noting that as per methodology, 500 mg sample is dissolved in 5 mL internal standard prepared in dichloromethane and except for Candesartan cilexetil, no other sartan is soluble in dichloromethane. They stated that sample preparation is not appropriate.

**Response:** Comment not incorporated. The Expert Committee determined that the sample preparation in procedure is adequate based on the validation data.

## 8.2. Limit Test Procedures

**Comment Summary #153:** The commenter commented on the limit test and suggested including guidance when the limit test may be applied.

**Response:** Comment not incorporated. The Expert Committee determined that the recommendations for the limit test performance characteristics are provided in the chapter.

# **Monographs**

Monograph/Section(s): Alcohol/Specific Gravity

**Expert Committee(s):** Simple Excipients

No. of Commenters:

**Comment Summary #1:** The commenter acknowledged that the note included under the test for Specific Gravity is to make stakeholders aware of the Alcoholometric Table, so they can utilize suitable conversion factor in the table to calculate the content of alcohol. However, the amount of water allowed in the alcohol is not specified in the monograph as there is no test and acceptance criteria in the monograph for the content of water.

**Response:** Comment not incorporated. Although there is not a water content determination test in the monograph, the result of Specific Gravity indicates the water content in the alcohol, just as what the commenter pointed out, "Depending on the amount of water present, the specific gravity will change." The Expert Committee will consider a future revision to the monograph to update the Definition by clarifying that the remainder of the solution consists of water, and/or introducing additional tests. **Comment Summary #2:** The commenter pointed out that some alcohol products may be out of the range, defined in the monograph "NLT 92.3% and NMT 93.8%, by weight, corresponding to NLT 94.9% and NMT 96.0%, by volume," and thus would not meet the monograph. Therefore, the monograph should provide a conversion factor based on the content of water (e.g., see the table in Perry's Chemical Engineers' Handbook). **Response:** Comment not incorporated. The Alcoholometric Table states that it is only valid for ethanol-water mixtures and it does not apply if other components are added. Additionally, the Alcoholometric Table contains the conversion factors for converting Specific Gravity results measured at 25° to 15.56° (60° F) which is required by regulations from the Bureau of Alcohol, Tobacco, Firearms and Explosives (ATF) and the USP monograph, while the table in Perry's Chemical Engineers' Handbook lacks the conversion factors to 15.56° (60° F).

Regarding the alcohol-water mixtures outside the monograph defined range, the Expert Committee will gather more information from stakeholders and regulatory agencies and have further discussion on whether the monograph should be expanded to cover other concentrations of alcohol-water mixtures used in legally marketed products in the United States. The Expert Committee may consider a future revision to the monograph to address this issue.

**Monograph/Section:** Azelastine Hydrochloride/Organic Impurities

**Expert Committee:** Small Molecules 5

No. of Commenters:

**Comment Summary #1:** The commenter recommended removing the reporting threshold as it will vary based on product-specific factors.

**Response:** Comment not incorporated. Based on comments received on a proposed policy for reporting thresholds, USP determined that removal of reporting thresholds from monographs needs further stakeholder engagement. USP intends to do further stakeholder engagement.

**Comment Summary #2**: The commenter requested retaining the column with the 10µm particle size in the procedure.

**Response:** Comment not incorporated. Columns with the specified packing chemistry are no longer commercially available in a 10-μm format. Therefore, columns with the same column packing chemistry and 5-μm particle size were determined to be suitable to replace the columns with 10-μm particle size.

**Monograph/Section(s)**: Calcipotriene Cream/Organic Impurities

**Expert Committee**: Small Molecules 3

No. of Commenters: 1

**Comment Summary #1:** The commenter requested removing the "reporting threshold." **Response**: Comment not incorporated. Based on comments received on a proposed policy for reporting thresholds, USP determined that removal of reporting thresholds from monographs needs further stakeholder engagement. USP intends to do further stakeholder engagement.

**Comment Summary #2:** The commenter recommended revising the limits for the specified impurities and the total impurities for consistency with what has been approved.

**Response:** Comment incorporated. The calcipotriene related compound B was deleted; the limit for cyclophosphamide related compound C was revised from NMT 1.5% to NMT 2.0%; the limit of cyclophosphamide related compound D was revised from NMT 2.0% to NMT 3.6%; Total Impurities of NMT 4.5% was revised to Total Degradation Products of NMT 4.6%.

**EC-Initiated Change #1:** Revised "Any individual unspecified impurity" to "Any individual unspecified degradation product."

Monograph/Sections: Choline C 11 Injection/Radiochemical purity

**Expert Committee:** Small Molecules 4

No. of Commenters:

**EC-initiated change #1:** The typographical error in the *Relative standard deviation* requirement was corrected from "NLT" to "NMT."

Monograph/Section(s): Clonidine Transdermal System / Organic Impurities

**Expert Committee:** Small Molecules Monograph 2

No. of Commenters:

Comment Summary #1: The commenter recommended expressing impurity limits for transdermal systems on the basis of % drug content based on the Reference Listed Drug. Response: Comment not incorporated. This comment is outside of the scope of the revision. The Expert Committee will consider future revisions to this monograph upon receipt of the necessary supporting data.

Monograph/Section:
Expert Committee: Diphenoxylate Hydrochloride/Organic Impurities

**Small Molecules 3** 

No. of Commenters:

Comment Summary #1: The commenter requested removing the "reporting threshold" as it will vary based on product-specific factors.

Response: Comment not incorporated. The comment is outside of the scope of the revision. Based on comments received on a proposed policy for reporting thresholds, USP determined that removal of reporting thresholds from monographs needs further stakeholder engagement. USP intends to do further stakeholder engagement.

Monograph/Section: Ethacrynic Acid /Organic Impurities

**Expert Committee:** Small Molecules 2

No. of Commenters:

**Comment Summary #1:** The commenter requested widening the acceptance criterion for total impurities for consistency with what has been approved.

Response: Comment incorporated. The limit has been revised from NMT 0.8% to NMT 1.0% based on additional information obtained.

**Comment Summary #2**: The commenter requested removing the "reporting threshold."

Response: Comment not incorporated. Based on comments received on a proposed policy for reporting thresholds, USP determined that removal of reporting thresholds from monographs needs further stakeholder engagement. USP intends to do further stakeholder engagement."

Etoposide Phosphate/Multiple Sections Monograph/Section(s):

**Small Molecules 3** Expert Committee:

No. of Commenters:

**Comment Summary #1:** The commenter reported different relative retention times obtained for etoposide in the test of Organic Impurities.

**Response**: Comment not incorporated. The relative retention time provided is for informational purposes.

**EC-Initiated Change #1:** Deleted the relative response factor of 0.96 for etoposide in Table 1 in the test of *Organic Impurities*, as the reference standard is etoposide. **EC-Initiated Change #2:** Added the UNII code in the *Chemical Information* section.

**Monograph/Section(s)**: Etoposide Phosphate for Injection/Organic Impurities

**Expert Committee**: Small Molecules 3

No. of Commenters:

**EC-Initiated Change #1:** Deleted the "(x 1/F)" and the notation for "F" from the calculation formula for etoposide and removed the relative response factor of "0.96" for etoposide in Table 1, as the reference standard is etoposide.

Monograph/Section: Fluorometholone Acetate/Organic Impurities

**Expert Committee:** Small Molecules 5

No. of Commenters:

**Comment Summary #1:** The commenter recommended removing the reporting threshold as it will vary based on product-specific factors.

**Response:** Comment not incorporated. Based on comments received on a proposed policy for reporting thresholds, USP determined that removal of reporting thresholds from monographs needs further stakeholder engagement. USP intends to do further stakeholder engagement.

**Monograph/Section(s):** Gabapentin Compounded Oral Suspension

**Expert Committee(s):** Compounding

No. of Commenters:

**Comment Summary #1:** A commenter indicated that the monograph is a copy of an FDA-approved commercial product.

**Response:** Comment not incorporated. The commercial product contains xylitol, licorice, and strawberry flavoring and cannot be given to veterinary patients. Also the compounded preparation is used in Canada, where the commercial product is not available. Additionally, the commercial product is a different strength. The monograph may be used so that compounders have a formulation to follow when they need to compound the preparation during times of shortage.

**Comment Summary #2:** A commenter suggested removing "from powder" because the formula allows starting with either capsules or powder.

**Response:** Comment incorporated.

**Monograph/Section(s):** Ketamine Compounded Oral Solution

**Expert Committee(s):** Compounding

No. of Commenters:

**Comment Summary #1:** Commenter suggested providing the ingredients in the proprietary excipient Mucolox.

**Response:** Comment not incorporated. The Expert Committee determined that the comment was outside the scope of the monograph. The Expert Committee will consider developing an FAQ to encourage compounders to request additional information from suppliers of proprietary bases.

Monograph/Section(s): Latanoprost Compounded Topical Solution

**Expert Committee(s):** Compounding

No. of Commenters:

**Comment Summary #1:** Commenter suggested providing the ingredients in the proprietary excipient Pracamac Oil.

**Response:** Comment not incorporated. The Expert Committee determined that the comment was outside the scope of the monograph. The xpert Committee will consider developing an FAQ to encourage compounders to request additional information from suppliers of proprietary bases.

**Comment Summary #2:** Commenter indicated that the formulation specifies final weight (g) and the instructions refer to final volume, and recommended revising to ensure consistency.

**Response:** Comment incorporated.

Monograph/Section: Lorazepam/Multiple sections

**Expert Committee**: Small Molecules 4

No. of Commenters: 2

**Comment Summary #1:** The commenter requested shortening the *Run time* and increasing the *Column temperature* to 10 °C in the *Assay*.

**Response**: Comment not incorporated. The *Run time* and *Column temperature* are based on validated data. The Expert Committee will consider future revisions to the monograph upon receipt of supporting data.

**Comment Summary #2:** The commenter suggested including Lorazepam *N*-oxide and Lorazepam dione in the *Acceptance Table* of the *Organic Impurities* test.

**Response**: Comment not incorporated. The comment is outside of the scope of the revision. The Expert Committee will consider future revisions to the monograph upon receipt of supporting data.

**Monograph/Section(s):** Methyl Salicylate/Optical Rotation

**Expert Committee(s):** Simple Excipients

No. of Commenters:

**Comment Summary #1:** The commenter recommended adding a statement that the Optical Rotation <781A>, *Procedures, Angular Rotation* test is not required for synthetic Methyl Salicylate.

**Response:** Comment incorporated.

**Expert Committee-initiated Change#1:** Betula lenta L. (Fam. Betulaceae), another source of Methyl Salicylate, was included in the statement requested by the commenter

in Comment Summary #1. Methyl Salicylate from both sources does not exhibit optical activity.

Monograph/Section: Mupirocin Calcium/Organic Impurities

**Expert of Committee**: Small Molecules 1

No. of Commenters:

**Comment Summary #1**: The commenter requested removing the "reporting threshold." **Response**: Comment not incorporated. Based on comments received on a proposed policy for reporting thresholds, USP determined that removal of reporting thresholds from monographs needs further stakeholder engagement. USP intends to do further stakeholder engagement.

**Comment Summary #2:** The commenter requested widening the acceptance criteria to NMT 1% for Pseudomonic acid N, Mupirocin furonyl analog, Mupirocin pyranyl analog, Pseudomonic acid B, and Pseudomonic acid C, and to NMT 0.5% for Pseudomonic acid E and Any unspecified impurity, to be consistent with the FDA-approved specifications.

Response: Comment incorporated.

Monograph/Section: Mupirocin Ointment/Multiple Sections

**Expert of Committee**: Small Molecules 1

No. of Commenters: 2

Comment Summary #1: The commenter indicated that the acceptance criteria for Mupirocin pyranyl analog, Pseudomonic acid N, Pseudomonic acid D, Pseudomonic acid B, Pseudomonic acid C, Any other impurity, and Total impurities are different from the acceptance criteria in the Organic Impurities test in FDA-approved applications. Response: Comments partially incorporated. The acceptance criterion for Mupirocin pyranyl analog is consistent with what has been approved for the sponsor's product. The acceptance criteria were widened to NMT 1.0% for Pseudomonic acid N, Pseudomonic acid B, Pseudomonic acid C, and Any other impurity, and to NMT 3.0% for Pseudomonic acid D. The control of Total impurities was removed from the monograph to accommodate the FDA-approved application.

**Comment Summary #2**: The commenter recommended including their single method for Assay and Organic Impurities.

**Response**: Comment not incorporated. The Expert Committee determined that the methods included in the proposal are suitable for their intended use.

Monograph/Section(s): Naltrexone Hydrochloride Compounded Cream

**Expert Committee(s):** Compounding

No. of Commenters:

**Comment Summary #1:** The commenter suggested removing "a sufficient quantity to make" from XemaTop Base, since exactly 93.5 g must be used to obtain the final concentration of 10 mg/g.

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**Response:** Comment incorporated.

Monograph/Section: Norethindrone Acetate and Ethinyl Estradiol Tablets

/Organic Impurities

**Expert Committee:** Small Molecules 5

No. of Commenters:

**Comment Summary #1:** The commenter recommended working with approved manufacturers to include a suitable organic impurity test in the monograph. **Response:** Comment not incorporated. The comment is outside the scope of this revision. The Expert Committee will consider a future revision to the monograph upon receipt of supporting data.

Monograph/Section: Oxacillin Injection/Multiple Sections

**Expert of Committee**: Small Molecules 1

No. of Commenters: 1

**Comment Summary #1**: The commenter recommended including a suitable test for Organic Impurities.

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

**Comment Summary #2:** The commenter recommended replacing <151> with <85>. **Response**: Comment not incorporated. The Expert Committee will consider a future revision to the monograph upon receipt of supporting data.

**Monograph/Sections:** Oxycodone Hydrochloride Extended-Release Tablets

/ Organic Impurities

**Expert Committee:** Small Molecules 2

No. of Commenters: 1

**Comment Summary #1**: The commenter requested removing the "reporting threshold." **Response:** Comment not incorporated. Based on comments received on a proposed policy for reporting thresholds, USP determined that removal of reporting thresholds from monographs needs further stakeholder engagement. USP intends to do further stakeholder engagement.

**Monograph/Sections:** Phenobarbital Sodium for Injection

**Expert Committee:** Small Molecules 4

No. of Commenters:

**Comment Summary #1:** The commenter recommended retaining this monograph as phenobarbital is still used in medicine.

**Response:** Comment not incorporated. The monographs for Phenobarbital Sodium and Phenobarbital Sodium Injection are retained. No Phenobarbital Sodium for Injection drug products are on the US market.

**Monograph/Section(s):** Pyrroloquinoline Quinone Disodium (PQQ)/Multiple

Sections

**Expert Committee:** Non-Botanical Dietary Supplements

No. of Commenters: 1

**Comment Summary #1:** The commenter noted that the *Assay* and *Organic Impurities* procedures do not specify the total run time of the HPLC method. Insufficient run times can cause hinderance in the detection of impurities. Therefore, the total run time of the HPLC assay must be specified to ensure that all impurities in the sample are detected and analyzed. The commenter recommended adding "Run time: NLT 3 times the retention time of PQQ" to the procedure.

**Response:** Comment incorporated. A parameter for run time was added to the procedure.

Comment Summary #2: The commenter objected to the removal of the statement "is produced by fermentation process" from the definition due to regulatory and safety concerns raised by FDA in two NDI notifications for synthetic PQQ. The commenter also provided supporting information showing that 1) some commercially available synthetic PQQ ingredient samples contain high levels of impurities and 2) dietary supplements made with synthetic PQQ may have dissolution properties distinct from those that are produced with fermentative PQQ. The commenter encouraged USP to not include synthetic PQQ in the monograph development.

Response: Comment not incorporated. Both committees involved in the monograph development process have concluded that questions about the safety of synthetic PQQ have been adequately and appropriately addressed. Further, USP's role in monograph development process is distinct from the FDA regulatory process. Because synthetic PQQ is currently being marketed as a dietary ingredient, and FDA issued a "no questions" in response to a GRAS Notification for synthetic PQQ subsequent to its responses to the two NDINs for synthetic PQQ, the Expert Committee determined that the inclusion of synthetic PQQ in the monograph is appropriate. With regard to high impurity content and differing dissolution properties, any ingredient that does not comply with the monograph requirements of NMT 0.1% for any impurity would not be in compliance with USP standards. The USP PQQ monograph pertains to the PQQ ingredient only, and dissolution properties of dosage forms of this ingredient are outside the scope of this monograph.

Monograph/Section: Ringer's Injection/Assay

**Expert Committee(s):** Small Molecules 5

No. of Commenters:

**Comment summary #1:** The commenter recommended not adding <71> to the monograph because it would conflict with the Parametric Release program.

**Response:** Comment not incorporated. The Expert Committee has determined that it is appropriate to include this test in the monograph.

Monograph/Section: Riociguat/Organic Impurities

**Expert Committee**: Small Molecules 5

No. of Commenters: 2

**Comment Summary #1:** The commenter requested removing the "reporting threshold" as it will vary based on product-specific factors.

**Response**: Comment not incorporated. Based on comments received on a proposed policy for reporting thresholds, USP determined that removal of reporting thresholds from monographs needs further stakeholder engagement. USP intends to do further stakeholder engagement.

**Comment Summary #2:** The commenter requested replacing the Organic Impurities method.

**Response:** Comment not incorporated. The Expert Committee determined that the proposed Organic Impurities method is suitable for its intended use in the monograph. The Expert Committee may consider revisions in the future upon receipt of supporting data.

**Monograph/Section**: Scopolamine Hydrobromide/Organic Impurities

**Expert Committee**: Small Molecules 3

No. of Commenters:

**Comment Summary #1:** The commenter requested removing the "reporting threshold" from the test for *Organic Impurities*.

**Response**: Comment not incorporated. Based on comments received on a proposed policy for reporting thresholds, USP determined that removal of reporting thresholds from monographs needs further stakeholder engagement. USP intends to do further stakeholder engagement.

**Monograph/Section(s):** Sodium Lauroyl Sarcosinate/Acidity and Alkalinity

**Expert Committee(s):** Complex Excipients

**Expert Committee-initiated Change#1:** The title of *Acidity and Alkalinity* test was changed to *pH* <791> to be consistent with USP practice in assigning names to tests.

**Monograph/Section(s):** Sour Jujube Seed/Multiple Sections

**Expert Committee:** Botanical Dietary Supplements and Herbal Medicines

No. of Commenters: 5

Identification A

**Comment Summary #1**: The commenter suggested changing *Standard solution A* from 1 mg/mL to 0.5 mg/mL and changing *Standard solution B* to a simpler approach by directly putting samples in 2 mL of methanol instead of drying and then adding methanol.

**Response:** Comment incorporated.

**Comment Summary #2**: The commenter suggested removing ferulic acid from system suitability and acceptance criteria because it was not clearly observed. The commenter requested information on why the original monograph mentioned ferulic acid.

Response: Comment incorporated. The original monograph was proposed based on sponsor's report that a de-fatting process was employed for sample solution preparation. Considering de-fatting procedures were time consuming and complicated, USP did an investigation to prepare the sample solution without de-fatting. The results showed that the HPTLC chromatograms for the sample solutions with and without defatting were similar, but the ferulic acid band was not very clear in non-defatted samples. To avoid confusion due to the unclear ferulic acid band in the non-defatted sample solution, the suggested removal of ferulic acid from the system suitability and acceptance criteria was incorporated. This will not impact the identity of sour jujube seed because ferulic acid is not a unique compound.

## Identification A and Identification B

**Comment Summary #3**: The commenter suggested combining *Identification A* and *Identification B* for detection of flavonoids using derivatization with NP reagent and subsequently using derivatization with an anisaldehyde reagent for detecting Jujubosides A and B in one analysis as it is done in EP.

**Response:** Comment not incorporated. Currently there is no data to support the combination of ID A and ID B. The two current HPTLC methods work well. USP will consider revising the monograph later upon receiving data that uses the suggested derivatizations to test both components with one HPTLC method.

# Identification C

**Comment Summary #4:** The commenter suggested changing "magnoflorine peak" to "magnoflorine and its isomer" based on LC-MS data.

Response: Comment incorporated.

## Composition

**Comment Summary #5:** The sour jujube seeds are very rich in fat, which disturbs HPLC. Appropriate de-fatting would be advised for reproducible results.

**Response:** Comment not incorporated. In the original report from the sponsor, the sample solution preparation needed 3h de-fatting using a Soxhlet extractor, which was time consuming and complicated. USP investigated and showed that the HPLC chromatograms were the same with and without de-fatting. The HPLC assay results were not impacted when de-fatting was omitted.

Monograph/Section(s): Sour Jujube Seed Dry Extract/Multiple

Sections

**Expert Committee:** Botanical Dietary Supplements and Herbal

Medicines

No. of Commenters: 4

## Identification A

**Comment Summary #1**: The commenter suggested changing *Standard solution A* from 1 mg/mL to 0.5 mg/mL and changing *Standard solution B* to a simpler approach by directly putting samples in 2 mL of methanol instead of drying and then adding methanol.

**Response:** Comment incorporated.

**Comment Summary #2**: The commenter suggested removing ferulic acid from system suitability and acceptance criteria because it was not clearly observed. The commenter requested information on why the original monograph mentioned ferulic acid.

Response: Comment incorporated. The original monograph was proposed based on sponsor's report that a de-fatting process was employed for sample solution preparation. Considering de-fatting procedures were time consuming and complicated, USP did an investigation to prepare the sample solution without de-fatting. The results showed that the HPTLC chromatograms for the sample solutions with and without defatting were similar, but the ferulic acid band was not very clear in non-defatted samples. To avoid confusion due to the unclear ferulic acid band in the non-defatted sample solution, the suggested removal of ferulic acid from the system suitability and acceptance criteria was incorporated. This will not impact the identity of sour jujube seed because ferulic acid is not a unique compound.

## Identification A and Identification B

**Comment Summary #3**: The commenter suggested combining *Identification A* and *Identification B* for detection of flavonoids using derivatization with NP reagent and subsequently using derivatization with an anisaldehyde reagent for detecting Jujubosides A and B in one analysis as it is done in EP.

**Response:** Comment not incorporated. Currently there is no data to support the combination of ID A and ID B. The two current HPTLC methods work well. USP will consider revising the monograph later upon receiving data that uses the suggested derivatizations to test both components with one HPTLC method.

### Identification C

**Comment Summary #4:** The commenter suggested changing "magnoflorine peak" to "magnoflorine and its isomer" based on LC-MS data.

**Response:** Comment incorporated.

Monograph/Section(s): Sour Jujube Seed Powder/Multiple Sections
Expert Committee: Botanical Dietary Supplements and Herbal

Medicines

No. of Commenters: 5

## Identification A

**Comment Summary #1**: The commenter suggested changing *Standard solution A* from 1 mg/mL to 0.5 mg/mL and changing *Standard solution B* to a simpler approach by directly putting samples in 2 mL of methanol instead of drying and then adding methanol.

Response: Comment incorporated.

**Comment Summary #2**: The commenter suggested removing ferulic acid from system suitability and acceptance criteria because it was not clearly observed. The commenter requested information on why the original monograph mentioned ferulic acid.

Response: Comment incorporated. The original monograph was proposed based on sponsor's report that a de-fatting process was employed for sample solution preparation. Considering de-fatting procedures were time consuming and complicated, USP did an investigation to prepare the sample solution without de-fatting. The results showed that the HPTLC chromatograms for the sample solutions with and without defatting were similar, but the ferulic acid band was not very clear in non-defatted samples. To avoid confusion due to the unclear ferulic acid band in the non-defatted sample solution, the suggested removal of ferulic acid from the system suitability and acceptance criteria was incorporated. This will not impact the identity of sour jujube seed because ferulic acid is not a unique compound.

## Identification A and Identification B

**Comment Summary #3**: The commenter suggested combining *Identification A* and *Identification B* for detection of flavonoids using derivatization with NP reagent and subsequently using derivatization with anisaldehyde reagent for detecting Jujubosides A and B in one analysis as it is done in EP.

**Response:** Comment not incorporated. Currently there is no data to support the combination of ID A and ID B. The two current HPTLC methods work well. USP will consider revising the monograph later upon receiving data that uses the suggested derivatizations to test both components with one HPTLC method.

### Identification C

**Comment Summary #4:** The commenter suggested changing "magnoflorine peak" to "magnoflorine and its isomer" based on LC-MS data.

**Response:** Comment incorporated.

# Composition

**Comment Summary #5:** The sour jujube seeds are very rich in fat, which disturbs HPLC. Appropriate de-fatting would be advised for reproducible results.

**Response:** Comment not incorporated. In the original report from the sponsor, the sample solution preparation needed 3h de-fatting using a Soxhlet extractor, which was time consuming and complicated. USP investigated and showed that the HPLC chromatograms were the same with and without de-fatting. The HPLC assay results were not impacted when de-fatting was omitted.

**Monograph/Section**: Thioguanine/Chemical information

**Expert Committee**: Small Molecules 3

No. of Commenters: 1

**Comment Summary #1:** The commenter requested denoting the anhydrous form as  $C_5H_5N_5S$  without the 'x H2O' as the value of x = 0 for the anhydrous form.

Response: Comment incorporated.

Monograph/Section(s): Ursodiol Compounded Oral Suspension

**Expert Committee(s):** Compounding

No. of Commenters:

**Comment Summary #1:** The commenter suggested clarifying whether or not the Ora-Sweet/Ora-Plus formulation can be refrigerated.

**Reseponse:** Comment incorporated. A statement was added to clarify that the formulation can be refrigerated.

Monograph/Section: Zoledronic Acid/Multiple sections

**Expert Committee:** Small Molecules 3

No. of Commenters: 5

**Comment Summary #1:** The commenter indicated that the baseline is not stable and USP Related Compound B RS was not well resolved.

**Response:** Comment not incorporated. The USP lab could meet this requirement and received no adverse comments on the resolution requirement from other manufacturers. **Comment Summary #2:** The commenter noted that the text "from Phosphorus acid stock solution" was omitted from the Standard solution in the test for Limit of Phosphate and Phosphite.

**Response:** Comment incorporated. The Standard solution was changed from "0.013 mg/mL of phosphoric acid from Phosphoric acid stock solution and 10  $\mu$ g/mL of Phosphorus acid stock solution" to "0.013 mg/mL of phosphoric acid from Phosphoric acid stock solution and 10  $\mu$ g/mL of phosphorous acid from Phosphorus acid stock solution."

**Comment Summary #3:** The commenter noted that the elution order for the organic impurities were different.

**Response:** Comment not incorporated. The elution order is the same for both. USP Zoledronic Acid Related Compound A and EP impurity D are the same compound. **Comment Summary #4:** The commenter requested to propose a Limit of Phosphate and Phosphite procedure using an IC detector.

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

**Comment Summary #5:** The commenters requested widening the acceptance criterion for water content for consistency with what has been approved.

**Response:** Comment incorporated. The criterion for water content for the monohydrate form was changed from 5.5% - 7.5% to 5.0% - 7.5%; for the anhydrous form, NMT 0.5%.

**Comment Summary #6:** The commenters requested widening the acceptance criterion for the total combined molds and yeasts count for consistency with what has been approved.

**Response:** Comment incorporated. The criterion for the total combined molds and yeasts count was changed from NMT 50 cfu/g to NMT 100 cfu/g.

**Comment Summary #7:** The commenter requested removing the "reporting threshold" because it will vary based on product-specific factors.

**Response:** Comment not incorporated. Based on comments received on a proposed policy for reporting thresholds, USP determined that removal of reporting thresholds from monographs needs further stakeholder engagement. USP intends to do further stakeholder engagement.