



## ***Commentary***

### ***USP–NF 2021, Issue 2***

**February 1, 2021**

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 USP.NF.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**

[<1503> Quality Attributes of Synthetic Peptide Drug Substances](#)

[<2750> Manufacturing Practices for Dietary Supplements](#)

**Monographs**

[Asparagine](#)

[Bupropion Hydrochloride](#)

[Bupropion Hydrochloride Extended-Release Tablets](#)

[Bupropion Hydrochloride Tablets](#)

[Clocortolone Pivalate](#)

[Estradiol and Norethindrone Acetate Tablets](#)

[Estradiol Valerate](#)

[Gadobutrol](#)

[Japanese Sophora Flower](#)

[Japanese Sophora Flower Dry Extract](#)

[Japanese Sophora Flower Powder](#)

[Losartan Potassium](#)

[Magnesium Citrate](#)

[Potassium and Sodium Bicarbonates and Citric Acid Effervescent Tablets for Oral Solution](#)

[Prasugrel Tablets](#)

[Sodium Fluoride](#)

[Spironolactone Tablets](#)

**No comments were received for the following proposals:**

**Monographs**

Alcohol in Dextrose Injection

Arsanilic Acid

Asian Ginseng Root and Rhizome

Asian Ginseng Root and Rhizome Dry Extract

Butabarbital

Cephadrine Capsules

Cephadrine for Injection

Cephadrine for Oral Suspension

Cephadrine Tablets

Chloroprocaine Hydrochloride

Chloroquine Hydrochloride Injection

Ethyl Chloride

Guanfacine Extended-Release Tablets

Hepatitis B Immune Globulin

Idoxuridine Ophthalmic Ointment

Iothalamate Meglumine and Iothalamate Sodium Injection

Immune Globulin

Itraconazole Capsules  
Mephobarbital Tablets  
Microcrystalline Wax  
Pertussis Immune Globulin  
Potassium Bicarbonate Effervescent Tablets  
Procainamide Hydrochloride Extended-Release Tablets  
Procainamide Hydrochloride Tablets  
Propranolol Hydrochloride Tablets  
Pyrantel Pamoate  
Rabies Immune Globulin  
Rho (D) Immune Globulin  
S-Adenosyl-L-Methionine 1,4-Butanedisulfonate  
Sodium Chloride Inhalation Solution  
Sodium Chloride Ophthalmic Solution  
Tetanus Immune Globulin  
Vaccinia Immune Globulin  
Varicella-Zoster Immune Globulin  
Vinpocetine  
Vinpocetine Capsules  
Vinpocetine Tablets

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### **General Chapters**

**General Chapter/Sections:** <1503> *Quality Attributes of Synthetic Peptide Drug Substances*/Multiple Sections  
**Expert Committee:** Biologics Monographs 1–Peptides and Insulins  
**No. of Commenters:** 6

#### **General**

**Comment Summary #1:** The commenter recommended revising and expanding the chapter to include storage conditions and container closure recommendations.

**Response:** Comment not incorporated. The Expert Committee determined that the existing text was suitable and that providing storage conditions and container closure recommendations was outside the scope of the new General Chapter <1503>.

**Comment Summary #2:** The commenter recommended revising and expanding the chapter to address immunogenicity related to aggregation.

**Response:** Comment not incorporated. The Expert Committee determined that addressing issues related to immunogenicity due to aggregation is outside the scope for this chapter.

**Comment Summary #3:** The commenter recommended revising the chapter because the language is too prescriptive.

**Response:** Comment not incorporated. The Expert Committee determined that the existing text was suitable.

**Comment Summary #4:** The commenter recommended correcting all citations of the various guideline titles (e.g., the ICH Q7) as a “guide” instead of “guidance.”

**Response:** Comment partially incorporated. The reference to the ICH guidelines as “guidance” is correct, but the title of ICH Q7 was corrected to read, “Good Manufacturing Practice for Active Pharmaceutical Ingredients.”

**Comment Summary # 5:** The commenter recommended correcting the titles of the cited General Chapters when needed.

**Response:** Comment incorporated.

**Comment Summary # 6:** The commenter recommended removing the revision version from the referenced ICH guidelines.

**Response:** Comment incorporated.

### ***Introduction***

**Expert Committee (EC)-Initiated Change #1:** The section titled *Peptide Content and Assay* was revised to *Assay and Peptide Content*, and the section titled *Impurities and Related Compounds* was updated to *Impurities*.

### ***Peptide Definition***

**Comment Summary # 7:** The commenter recommended revising the sentence, “Peptides are natural or artificially manufactured short chains of two or more amino acids covalently linked by an amide bond,” by replacing “an amide bond” with “amide bonds.”

**Response:** Comment incorporated.

**Comment Summary #8:** The commenter recommended clarifying that the scope of the general chapter addresses synthetic peptide drug substances that are less than 100 amino acids in size.

**Response:** Comment incorporated. The EC clarified that the peptide definition aligns with the definition provided by FDA.

**Comment Summary #9:** The commenter recommended clarifying that the concept and approach in this general chapter apply to chemically synthesized polypeptides.

**Response:** Comment incorporated. The following sentence was added, “The concepts and approaches described in this general chapter generally are applicable to chemically synthesized peptides.”

**EC-Initiated Change #2:** The *Peptide Definition* section was updated to conform to the Final Rule on Definition of the Term, “Biological Product” (85 FR 10057, February 21, 2020).

**EC-Initiated Change #3:** The reference to 2015 Guidance for Industry Document Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009 is updated to Final Rule on Definition of the Term, “Biological Product” (85 FR 10057, February 21, 2020).

**EC-Initiated Change #4:** The paragraph that contained definitions of “proteins” and “peptide” was updated for consistency with FDA definitions.

**EC-Initiated Change #5:** The sentence regarding the statutory definition of peptides regulated under the Federal Food, Drug, and Cosmetic Act (FD&C Act) was revised to note that unless a peptide meets the statutory definition of a biological product (e.g., a peptide vaccine), it would be regulated as a drug product under the FD&C Act and that the concepts and approaches described in this general chapter generally are applicable to chemically synthesized peptides.

## ***Manufacturing Methods***

**Comment Summary #10:** The commenter recommended replacing the sentence, “A combination of LPPS and SPPS techniques is occasionally used for manufacturing large peptides and peptide conjugates” with “A hybrid SPPS/LPPS technique is also used for manufacturing large peptides and peptide conjugates.” The commenter noted that the previous iteration ignores the benefits of convergent synthesis, and a combination approach leverages advantages of SPPS in shorter fragments while allowing opportunity for purification prior to a solution coupling of fragments.

**Response:** Comment incorporated.

**Comment Summary #11:** The commenter recommended adding the following sentence to the end of the third paragraph of the *Manufacturing* method section: “Additionally, hybrid SPPS/LPPS can lead to higher purity and yielding processes.”

**Response:** Comment not incorporated. The EC does not believe the addition will add value to the chapter.

**Comment Summary #12:** The commenter recommended removing “of” from the phrase “to be washed off of the resin-bound peptide.”

**Response:** Comment incorporated.

**Comment Summary #13:** The commenter recommended revising the sentence, “a quality-by-design (QbD) strategy is often essential for a successful outcome” by replacing “essential” with “beneficial.”

**Response:** Comment incorporated.

**EC-Initiated Change #6:** The sentence regarding SPPS processes was revised to read, “In SPPS processes, the peptide chain is assembled on a solid support, enabling excess reagents and amino acid derivative to be washed off.” The phrase “and amino acid activated derivatives” was deleted.

## ***Raw Material***

**Comment Summary #14:** The commenter recommended replacing the term “chiral content” with “enantiomer content.”

**Response:** Comment partially incorporated. The term “chiral content” was replaced by “stereoisomeric impurities content.”

**Comment Summary #15:** The commenter recommended rewording the paragraph, “In some cases, amino acids, protected amino acid derivatives may not have a pre-existing, non-pharmaceutical use” to also include peptide fragments to align with ICH Q11 wording in “Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological Entities), Question & Answers, 23-Aug-2017,” Q&A 5.6.

**Response:** Comment partially incorporated. The EC revised the paragraph: “In some cases, amino acids, protected amino acid derivatives or any other compound such as dipeptide derivatives may not have a pre-existing, non-pharmaceutical use...”

**Comment Summary #16:** The commenter recommended revising the description of starting material to include “a peptide fragment comprised of multiple amino acids.”

**Response:** Comment not incorporated. The EC noted the addition is not required and does not add value to the text.

**Comment Summary #17:** The commenter recommended revising the wording from “origin of the SMs should be known in order to evaluate their potential risk of

contaminants including agents that cause transmissible spongiform encephalopathies (TSE)” to “The origin of the SMs should be known in order to evaluate their potential risk of contamination with adventitious agents.”

**Response:** Comment incorporated.

**Comment Summary #18:** The commenter recommended updating Table 1 to include the examples of synthetic impurities under the Impurity column and not in the Origin column.

**Response:** Comment incorporated. Table 1 was revised accordingly.

**EC-Initiated Change #7:** The reference to the “Harmonization (ICH) guidelines” was revised to “Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines.”

**EC-Initiated Change #8:** In the fifth paragraph, “because they are usually simple enough in structure, they may be accepted as SMs with the appropriate justification” was revised to read, “but provided they are simple enough in structure, they may be acceptable as SMs with the appropriate justification.”

**EC-Initiated Change #9:** The word “adequate” was added to the following statement: The determination of adequate acceptance criteria for the SM quality attributes is based on development data, validation of the manufacturing process, and the corresponding risk assessment.

**EC-Initiated Change #10:** The EC revised the fifth paragraph by adding the phrase, “but is not limited” after the word “includes.” The word “used” was changed to “proposed.” Additionally, the section referenced as 3.1 was updated to 5.1. The revised paragraph reads: “A rationale should be provided explaining why the SM is considered appropriate and why the proposed strategy is suitable for controlling impurities in the drug substance. This usually includes but is not limited to justification of the proposed SM specifications, including the acceptance criteria for amino acid impurities and their enantiomers [and diastereomers for isoleucine (Ile) and threonine (Thr)], as well as data to support that the proposed control strategy is adequate for manufacturing a peptide drug substance of acceptable purity. Likewise, fragments proposed as SMs in the synthesis of peptides are considered custom synthesized chemicals. Therefore, manufacturers should consider all of ICH Q11 Section 5.1, General Principles and ICH Q11—Questions and Answers, clarifications for the selection and justification of such fragments as SMs.

### ***Peptide General Characteristics and Specifications***

**Comment Summary #19:** The commenter recommended clarifying in Table 2 that the method used for Identification of the active pharmaceutical ingredient (API) may be the same method used for the Assay, or for detection of related substances.

**Response:** Comment incorporated.

**Comment Summary #20:** The commenter recommended updating the text from, “For reference, the USP general chapters that describe the test methods most frequently used for the characterization and quality control of the peptide drug substance are listed in Table 2” to read “For reference, the USP general chapters that describe the test methods most frequently used for characterization and quality control of ~~the~~ peptide drug substances are listed in Table 2.”

**Response:** Comment incorporated.

**Comment Summary #21:** The commenter recommended removing footnote “a” from Table 2 and its designations throughout Table 2, and recommended changing the title of the table to “Summary of Tests Considered for Characterization and Quality Control of the Drug Substance.”

**Response:** Comment partially incorporated. The EC noted that footnote “a” identifies the tests that are recommended and not the tests that are mandatory. Similarly, the EC noted that Table 2 provides the list of tests that can be used for the assessment of quality. The table title was revised to read: “Summary of Tests for Characterization and Quality Control of the Drug Substance,” and the word “used” was removed.

**Comment Summary #22:** The commenter recommended adding a footnote to Table 2 to indicate the test recommended to be performed as part of the stability program, and a separate footnote to indicate the test recommended for the post-registration stability program.

**Response:** Comment incorporated. The EC notes that recommendations on stability programs pre- and post-registration are not in the scope of this general chapter.

**Comment Summary #23:** The commenter recommended replacing, referring to the high-performance liquid chromatography (HPLC) test in Table 2, “co-elution with reference standard” with “Retention time matches with well characterized reference standard”

**Response:** Comment incorporated. The EC noted that the comment is not in line with the USP current practices.

**Comment Summary #24:** The commenter recommended adding to the Assay test in Table 2, the reasons, and under what circumstances co-injection is recommended.

**Response:** Comment not incorporated. Co-elution is regarded as a standard best practice for HPLC identification

**Comment Summary #25:** The commenter recommended adding to the NMR test in Table 2 examples of possible NMR methods such as <sup>1</sup>H, <sup>13</sup>C and <sup>15</sup>N.

**Response:** Comment incorporated.

**Comment Summary #26:** The commenter recommended adding to the Peptide Mapping test in Table 2 “by chemical or enzymatic cleavage” to differentiate peptide mapping by MS-MS.

**Response:** Comment incorporated.

**Comment Summary #27:** The commenter recommended revising “complementary to MS-MS” with “equivalent to MS-MS” referring to the Peptide mapping test in Table 2.

**Response:** Comment incorporated.

**Comment Summary #28:** The commenter recommended replacing the reference to General Chapter <621> and General Chapter <736> with “Chiral chromatography using chiral stationary phases in the enantiomeric purity test” in Table 2.

**Response:** Comment Incorporated. “Chiral AAA” was replaced with “AAA in combination with chiral chromatography and MS detection.”

**Comment Summary #29:** The commenter recommended adding reference to the “higher order structure” test in Table 2, Raman Spectroscopy, Intrinsic Fluorescence, and Differential Scanning Calorimetry as examples.

**Response:** Comment not incorporated. The EC noted that the methods mentioned are not widely used.

**Comment Summary #30:** In the *Bio-Identity* test in Table 2, the commenter recommended replacing, “not a routine test for most peptides” with “no longer a routine test for most peptides.”

**Response:** Comment incorporated.

**Comment Summary #31:** The commenter recommended adding in Table 2 that the Assay method can be used also for identification.

**Response:** Comment incorporated.

**Comment Summary #32:** The commenter recommended adding the average mass in addition to monoisotopic mass for the Mass Spectrometry test in Table 2.

**Response:** Comment not incorporated. The EC noted that using the monoisotopic mass is consistent with the current USP practice and that the current resolution of mass spectrometry instruments require the use of the monoisotopic mass.

**Comment Summary #33:** The commenter recommended that enantiomeric purity, infrared spectroscopy, and higher order be moved from the *Identification* section of Table 2 to the *Special Tests* section, with comments entered similarly to those for Optical Rotation, i.e., “For characterization only.”

**Response:** Comment incorporated. The EC noted the table title clarifies that the tests are not prescriptive and can be used for characterization and release.

**Comment Summary #34:** The commenter recommended replacing, “tryptophan (Trp), tyrosine (Tyr), or phenylalanine (Phe)” with “suitable chromophores” in the UV Spectroscopy test in Table 2.

**Response:** Comment partially incorporated. The sentence revised to “Only useful for drug substances containing amino acids with suitable chromophores.”

**Comment Summary #35:** The commenter recommended revising the UV Spectroscopy test in Table 2 because Phenylalanine contributes very little to UV absorbance.

**Response:** Comment incorporated.

**Comment Summary #36:** The commenter recommended revising, the reference from “<621>” to “<621>, LC-MS” referring to the “Peptide-related substances” test in Table 2,

**Response:** Comment incorporated.

**Comment Summary #37:** The commenter recommended referring to the Residual Fluoride Test in Table 2 and revising the text to indicate that tert-butyloxycarbonyl protecting group or tert-butoxycarbonyl protecting group [Boc]-chemistry are only examples because the use of HF is not restricted to Boc-chemistry or the presence of Boc-protecting groups.

**Response:** Comment incorporated.

**Comment Summary #38:** The commenter recommended revising the sentence, “elemental residues are only tested if justified” to “elemental impurities test may be required based on the risk assessment” in the Elemental Impurities Test in Table 2.

**Response:** Comment Incorporated.

**Comment Summary #39:** The commenter recommended revising the text to replace “only required” to “required” in the residual fluoride test in Table 2.

**Response:** Comment Incorporated.

**Comment Summary #40:** The commenter recommended revising the text from “only required” to “required” in the residual trifluoroacetic acid in Table 2.

**Response:** Comment Incorporated.



**Comment Summary #41:** The commenter recommended adding an appropriate reference to support the statement that non-peptide impurity limits are required to follow ICH Q3A (R2) Impurities in New Drug Substances in “Other small-molecule impurities” in Table 2.

**Response:** Comment partially incorporated. The text was revised to state that non-peptide impurity limits are recommended to follow ICH Q3A(R2); they are not required.

**Comment Summary #42:** The commenter recommended referring to other small-molecule impurities in Table 2 and revising “potential genotoxic” to “potentially mutagenic” impurities as per ICH M7.

**Response:** Comment incorporated.

**Comment Summary #43:** The commenter recommended adding a reference to General Chapter <621> and a *Counter-Ion Content* test for chloride using silver nitrate to the *Counter-Ion Content* test in Table 2.

**Response:** Comment incorporated.

**Comment Summary #44:** The commenter recommended adding a reference to General Chapter <731> to the *Water Content* test in Table 2.

**Response:** Comment not incorporated. The EC stated that loss on drying is not a suitable method for water determination for certain peptides.

**Comment Summary #45:** The commenter recommended removing “preferred” from the reference “Method 1, Method 1c” as methods for water determination in the *Water Content* test in Table 2.

**Response:** Comment not incorporated; Karl Fisher is a commonly used and recommended method for water determination.

**Comment Summary #46:** The commenter recommended clarifying that Method I is a coulometric titration in the *Water Content* test in Table 2.

**Response:** Comment incorporated.

**Comment Summary #47:** The commenter recommended adding a reference to General Chapter <1112> to the *Water Content* test in Table 2.

**Response:** Comment not incorporated. General Chapter <1112> applies to drug products, not to drug substances.

**Comment Summary #48:** The commenter recommended replacing parental with parenteral in the *Bioburden and Bacterial Endotoxin* comment sections in Table 2.

**Response:** Comment incorporated.

**Comment Summary #49:** The commenter recommended adding pyro glutamic acid (Pyr) to the amino acids that the Amino Acid Analysis (AAA) test cannot differentiate.

**Response:** Comment incorporated.

**Comment Summary #50:** The commenter recommended adding additional references to the elemental nitrogen analysis section in Table 2 rather than only reference General Chapter <461>. Peptide content can also be determined by other methods such as Kjeldahl analysis, or chromatographic methods with nitrogen chemiluminescence detection (NCD) (see <1057>).

**Response:** Comment not incorporated. The EC noted that the general chapter provided sufficient number of references.

**EC-Initiated Change #11:** In the *Bio-Identity* test in Table 2, the sentence “may be required for longer peptides or complex sequences” was revised to read “may be required for large peptides or those with complex sequences.”

### ***Color and Appearance***

**Comment Summary #51:** The commenter recommended adding a reference to General Chapter <631> in the *Color and Appearance* test in Table 2.

**Response:** Comment not incorporated. The reference to General Chapter <631> does not apply to peptides.

### ***Identification***

**Comment Summary #52:** The commenter recommended adding in the *Identification* section pyro glutamic acid as one of the amino acids that *Amino Acid Analysis* is not able to differentiate.

**Response:** Comment incorporated.

**Comment Summary #53:** The commenter recommended that the *Identification* section include additional information describing why and under what circumstances co-injection is recommended and adding: “Co-injection of an equal mixture of a reference standard and the sample is the recommended best practice.”

**Response:** Comment not incorporated. Co-elution is regarded as a standard best practice for HPLC identification.

**EC-Initiated Change #12:** The sentence starting with “Identity is normally verified by multiple orthogonal techniques” was revised to “identity is normally verified by multiple orthogonal techniques generally including at least one specific test.”

**EC-Initiated Change #13:** The sentence, “ICH Q6A and VICH GL-39 recommend two orthogonal chromatographic procedures if identification is based on retention time only” was deleted.

**EC-Initiated Change #14:** The section, “Other identification tests such as MS, amino acid analysis (AAA), peptide mapping, or nuclear magnetic resonance (NMR) spectroscopy may be used in combination with HPLC retention time” was revised to read, “Other identification tests such as amino acid analysis (AAA), peptide mapping, or nuclear magnetic resonance (NMR) spectroscopy may be used.”

**EC-Initiated Change #15:** In the *Identification* section, the statement, “for molecules larger than 4 kDa, determination of the average mass may be appropriate” was deleted because the average mass is not the most appropriate.

### ***Bioassay***

**Comment Summary #54:** The commenter recommended revising in the *Bioassay* section statement, “Bioassays are laboratory tests that mimic the mechanism of action of a therapeutic target” with “Bioassays are laboratory tests that mimic the drug substance's mechanism of action towards a therapeutic target.”

**Response:** Comment incorporated.

**Comment Summary #55:** The commenter recommended adding the following statement after the first sentence of the second paragraph: “Bioassays may be needed because a very small chemical change may cause a loss of functional activity.”

**Response:** Comment incorporated.

**EC-Initiated Change #16:** The sentence, “Because peptides do not commonly require bioassays for release, manufacturers of long or complex peptides are encouraged to contact regulators early in development to understand if a bioassay or bioidentity test

will need to be part of the control strategy” was replaced by “Manufacturers are encouraged to contact regulators early in development for control strategy related to bioassays, e.g., the need for a bioassay, its purpose, etc.”

### ***Assay and Peptide Content***

**Comment Summary #56:** The commenter recommended rewording the paragraph starting “Peptide content is needed” to “may be helpful” as this is too prescriptive, because there are other means of qualifying reference standards that use more specific analytical techniques (e.g., qNMR).

**Response:** Comment incorporated.

**Comment Summary #57:** The commenter recommended adding the definitions of peptide content, HPLC assay, and provided recommendations.

**Response:** Comment not incorporated. The EC noted that the text is clear as written.

**Comment Summary #58:** The commenter recommended deleting the entire fourth paragraph of the *Assay and Peptide Content* section: “The easiest approach to determine the net peptide content is a simple mass balance calculation that consists of deducting the percentage of water, of counter ion, and, if relevant, of total impurities from tests other than HPLC from 100%.”

**Response:** Comment partially incorporated. The paragraph was rewritten as, “The easiest approach to determine the net peptide content is a simple mass balance calculation that consists of deducting the percentage of water, of counter ion, and, if relevant, of total other non-peptide impurities from 100%.”

**Comment Summary #59:** The commenter recommended removing the reference to HPLC from the section describing the calculation of net peptide content.

**Response:** Comment incorporated. The section was reworded as, “The easiest approach to determine the net peptide content is a simple mass balance calculation that consists of deducting the percentage of water, of counter ion, and, if relevant, of total other non-peptide related impurities from 100%.”

**Comment Summary #60:** The commenter recommended deleting the last sentence from the *Assay and Peptide Content* section, “UV absorption may be applied as a fast and simple method for frequent or on-line, in-process determination of peptide concentrations.” The commenter noted that, in actuality, the molar absorption coefficient is related to the exact number of amino acids and will change as the polypeptide chain length increases, making this a very complex technique.

**Response:** Comment not incorporated. The EC noted that UV absorption is a valuable tool to determine peptide content.

**Comment Summary #61:** The commenter recommended deleting Phenylalanine from the list of amino acids contributing to absorption at 280 nm.

**Response:** Comment incorporated.

**EC-Initiated Change #17:** The title of the “*Peptide Content and Assay*” section was updated to “*Assay and Peptide Content*” for clarity.

**EC-Initiated Change #18:** The following paragraph was added at the beginning of the section: “Peptide drug substance assay is normally defined on an anhydrous, counter ion-free basis. Routine assay testing is normally performed by a specific chromatographic method. Assay by HPLC, based on the use of an established, quantitative standard, e.g., a pharmacopeial reference standard or an in-house

developed peptide standard, is a relative method that is often the method of choice for peptides. If the HPLC method separates all peptide-related impurities, no correction for impurities is generally required. However, a correction for levels of additional impurities determined from a separate method may be applied. The specific method(s) used and the basis for the calculation should be defined and justified for each peptide drug substance. It is important to note that significant variability of assay results must be considered when establishing acceptable ranges. The main causes for assay variability are difficulty of sample preparation due to the hygroscopicity of peptides and batch-to-batch variability of reference standards.”

**EC-Initiated Change #19:** The following section was deleted: “Routine assay testing is normally performed by a specific chromatographic method. Assay by HPLC, based on the use of an established, quantitative standard, e.g., a pharmacopeial reference standard or an in-house developed peptide standard, is a relative method that is often the method of choice for peptides.

The assay is normally defined on an anhydrous, counter ion-free basis. If the HPLC method separates all peptide-related impurities, no correction for impurities is generally required. However, a correction for levels of additional impurities determined from a separate method may be applied. The specific method(s) used and the basis for the calculation should be defined and justified for each peptide drug substance.

It is important to note that significant variability of assay results must be considered when specifying acceptable ranges. The main causes for assay variability are difficulty of sample preparation due to the hygroscopicity of peptides and batch-to-batch variability of reference standards.”

**EC-Initiated Change #20:** The following paragraph, “It is important to consider that most absolute methods are non-specific and will only determine the total peptide content, not discriminating between the drug substance and peptide-related impurities, low levels of which generally can be neglected. Otherwise, the peptide content may be corrected for the total related impurities, usually determined by HPLC. Occasionally, other impurities, such as oligomers measured by size-exclusion chromatography (SEC) or peptide impurities measured by ion-exchange chromatography, may also be included in the correction,” was updated to “It is important to consider that most absolute methods are non-specific and will only determine the peptide content, not discriminating between the drug substance and peptide-related impurities. If a specific result for peptide drug substance assay is needed to substitute for an HPLC assay result, the peptide content may be corrected for the total related impurities, which are usually determined by HPLC. Where relevant, other impurities, such as oligomers measured by size-exclusion chromatography (SEC), or peptide impurities measured by ion-exchange chromatography should also be included in the correction.”

### ***Impurities***

**Comment Summary #62:** The commenter recommended removing the paragraph, “A peptide impurity profile may differ significantly depending on the technology used for manufacturing. Hence, no generalizations regarding the impurities and their control strategies can be made. In addition, because the manufacturing technologies for the production of peptides are diverse and complex compared to small molecules, the

impurity guidelines applicable to small molecules usually cannot be applied to peptides” because it is inaccurate.

**Response:** Comment not incorporated. The EC noted the text is accurate as written.

**Comment Summary #63:** The commenter recommended clarifying the difference between related impurities as well as substances and related substances.

**Response:** Comment partially incorporated. The EC clarified that related impurities may also be referred to as “related substances.”

**Comment Summary #64:** The commenter recommended that terminology be added describing “Peptide related substances” as impurities that are related to the structure of the target molecule and are biologically active. The commenter also recommended that the terms “peptide-related impurities” and “related substances” be used consistently throughout the general chapter.

**Response:** Comment partially incorporated. The EC clarified that related impurities may also be referred to as “related substances.”

**Comment Summary #65:** The commenter recommended removing “and therefore may have biological activity” from the description of the peptide-related impurities.

**Response:** Comment incorporated.

**Comment Summary #66:** The commenter recommended adding that anionic and cationic resin chromatography may be useful for detection of impurities in peptides.

**Response:** Comment incorporated.

**Comment Summary #67:** The commenter recommended adding the specifications for the specified and unspecified impurities.

**Response:** Comment not incorporated. Specifications are not reported in general chapters.

**Comment Summary #68:** The commenter recommended rewording the statement: “The higher threshold (0.5% for identification) proposed by the *European Pharmacopoeia (Ph. Eur.)* is only recognized by authorities of *Ph. Eur.* member states. Other authorities, e.g., the FDA, may consider the limits for unidentified impurities for new peptides on a ‘case-by-case basis’ as not accurate.”

**Response:** Comment partially incorporated. The EC revised the text to read: “The higher threshold (0.5% for identification) adopted by the *European Pharmacopoeia (Ph. Eur.)* is recognized by authorities of *Ph. Eur.* member states. Other authorities, e.g., the FDA may consider the limits for unspecified impurities for new peptides on a case-by-case basis.”

**Comment Summary #69:** The commenter recommended rewording the section regarding qualified identified and unidentified impurities in the final release specification as follows: “If present in the drug substance, qualified identified and unidentified impurities are usually included in the final release specification as specified impurities >0.5%. Non-qualified impurities should be limited by a general acceptance criterion for ‘any unspecified impurity’ with a limit of ≤0.5% when scientifically justified, and otherwise clinically qualified as safe and effective.”

**Response:** Comment not incorporated. The addition of threshold limits is outside the scope of this general chapter.

**Comment Summary #70:** The commenter recommended rewording the last sentence of the *Impurities in Peptides* section starting with “In order to define appropriate targets

...” by adding “with the understanding that these may change as development progresses.”

**Response:** Comment not incorporated. The EC believe that the text was clear as written.

**Comment Summary #71:** The commenter recommended rewording the last paragraph in the *Impurity* section, just prior to Table 3, beginning: “HPLC with UV detection is often chosen ...” to remove “however.”

**Response:** Comment incorporated.

**Comment Summary #72:** The commenter recommended adding this statement for clarification: “UV detection is not specific for peptide-related impurities and cannot unequivocally identify these impurities by retention time and UV absorbance, or quantify impurities that co-elute. Understanding the impurity profile is important to ensure drug quality and safety such as any adverse events associated with immunogenicity. Hence, more sensitive and specific LC-HRMS method is recommended for characterizing and quantifying peptide-related impurities.”

**Response:** Comment partially incorporated. The EC determined that the statement was applicable for characterization. UV detection is not specific for peptide-related impurities and cannot unequivocally identify these impurities by retention time and UV absorbance, or quantify impurities that co-elute. Understanding the impurity profile is important to ensure drug quality and safety such as any adverse events associated with immunogenicity. Hence, more sensitive and specific LC-HRMS method is recommended for characterizing and ~~quantifying~~ peptide-related impurities was added to the end of the *Impurities* sections.

**Comment Summary #73:** The commenter recommended adding examples of Deletion.

**Responses:** Comment incorporated. The following examples were added: clipped forms, fragments, and truncations.

**Comment Summary #74:** The commenter recommended expanding the description of the origin of substitution in Table 3 beyond Starting Materials contaminants to include insufficient washes and process errors.

**Responses:** Comment partially incorporated. Insufficient washes were added as possible causes of substitutions.

**Comment Summary #75:** The commenter recommended adding storage as a possible cause of rearrangement of Structural Isomer in Table 3.

**Responses:** Comment incorporated. The section was written as, “Rearrangement of Aspartate or Asparagine residues during synthesis or storage.”

**Comment Summary #76:** The commenter recommended adding to the Structural Isomer in Table 3: “Asp/Asn side chains can cyclize to form aspartimide/succinimide impurities during synthesis, and hydrolysis of these impurities can cause mixed isomerization and/or racemization impurities. These impurities can be predicted based on the peptide sequence and synthesis methods. These impurities are typically identified and quantified by LC-MS or LC-MS-MS but may be difficult to identify by RP-HPLC alone.”

**Responses:** Comment not incorporated. Identification of the impurities is not in the scope of the Table.

**Comment Summary #77:** The commenter recommended adding to the detection methods of Oligomers in Table 3 “Composition-Gradient MALS and Gel Electrophoresis.”

**Responses:** Comment not incorporated. The EC noted that most commonly used methods for detection of oligomer were mentioned.

**Comment Summary #78:** The commenter recommended clarifying for the “Other Impurities” listed in Table 3, that “Asparagine” and “C-terminus” are separate structural features, by revising “Deamidation of glutamine/asparagine C-terminus” to “Deamidation of glutamine/asparagine/C-terminus.”

**Responses:** Comment incorporated.

**Comment Summary #79:** The commenter recommended using a more general statement to reference the oxidations in Other Impurities in Table 3.

**Response:** Comment incorporated. The description was changed from “Oxidation of aromatic and sulfur-containing side-chains” to “Oxidation of certain residues.”

**Comment Summary #80:** The commenter recommended reviewing Table 3, including insertions to replace the wording “Raw materials” with “Starting Materials” and expanding the description to account for the presence of unprotected amino acids. The commenter provided recommendations as raw materials (SMs containing the respective protected dipeptide) or synthesis (loss of the N-protecting group during coupling, presence of unprotected amino acids in the starting material).

**Response:** Comment incorporated.

**Comment Summary #81:** The commenter recommended adding, “oxidation of sulfur-containing residues” as a separate type of peptide-related impurity because oxidation almost always occurs with Met (and sometimes with Cys). The EC believes the text is sufficiently specific.

**Response:** Comment not incorporated.

**Comment Summary #82:** The commenter recommended adding a statement after the sentence “For many process-related impurities, it is possible to rely on the manufacturing process to remove them.” For example, “Where such impurities have been shown to be removed through manufacturing or purification processes, routine testing is not necessary.”

**Response:** Comment not incorporated. The EC noted that the text was clear as written.

**Comment Summary #83:** The commenter recommended expanding the description in the origin column of the elemental impurities to include starting materials as contributors of elemental impurities.

**Response:** Comment incorporated.

**EC-Initiated Change #21:** The title of the *Impurities and Related Compounds* section was updated to *Impurities* for improved clarity.

**EC-Initiated Change #22:** Reaction “product” was revised to “by-product.”

**EC-Initiated Change #23:** The classification of impurities was revised. “Identified or unidentified” was replaced by “specified or unspecified.”

**EC-Initiated Change #24:** “Both identified and unidentified impurities can be either qualified or non-qualified” was replaced with “Specified impurities can be identified or non-identified.”

**EC-Initiated Change #25:** In the *Bio-Identity* test in Table 2, the sentence, “may be required for longer peptides or complex sequences” was rewritten as “may be required for “large peptides or those with complex sequences.”

**EC-Initiated Change #26:** The word “impurities” was replaced with “substances” in the following sentence: “Control strategy should then comprise the control of related substances for appropriate key intermediates, e.g., the peptide prior to conjugation.”

**EC-Initiated Change #27:** Title of Table 3 was revised from “Peptide-Related Impurities: Origin and Identification Methods” to “Peptide-Related Impurities: Origin and Commonly Used Analytical Techniques” for consistency with the title of Table 4 and to clarify that the listed analytical techniques are not meant to be all inclusive.

### ***Specific Test, Water***

**Comment Summary #84:** The commenter recommended using “typically hygroscopic” instead of “generally highly hygroscopic.”

**Response:** Comment incorporated.

**Comment Summary #85:** The commenter recommended rewording, “This specification parameter is stability-indicating, and it is usually included in the stability study of the peptide drug substance as water content is not stability indicating.”

**Response:** Comment incorporated. The section was reworded to, “This specification parameter may contribute to the peptide stability. It is usually included in the stability study of the peptide drug substance since it is required for the calculation of Assay by HPLC.”

**General Chapter/Sections:** <2750> Manufacturing Practices for Dietary Supplements/  
Multiple Sections

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

**No. of Commenters:** 4

**Comment Summary #1:** The commenter suggested replacing the “quality control unit” with the “quality unit” or “quality assurance” in the paragraph for *Quality Management System* under *General Provisions* section.

**Response:** Comment not incorporated. In the Dietary Supplement CGMPs rule (21 CFR Part 111), the FDA has defined “Quality Control” and “Quality Control Personnel,” which makes them terms of art for the Industry. Therefore, wherever practical, an attempt should be made to try to preserve these terms of art.

**Comment Summary #2:** The commenter suggested clarifying that “water systems” refers to both “equipment system” and “material system” in the paragraph for *Physical Plant and Equipment System* under the *General Provisions* section.

**Response:** Comment incorporated.

**Comment Summary #3:** The commenter suggested replacing “or” with “and” in the following statement “...There must be a quality unit(s) that is independent of production (or any other conflicts of interest) and that fulfills both quality assurance (QA) and quality control (QC) responsibilities” under Section 1. *Quality Management, 1.1 General Principles*, since both provisions are needed.

**Response:** Comment incorporated.

**Comment Summary #4:** The commenter suggested adding one more bullet regarding the review and approval of cGMP training documentation and ensuring that these



records are maintained under Section 1. *Quality Management, 1.2.2. Responsibilities of the Quality Unit(s).*

**Response:** Comment incorporated.

**Comment Summary #5:** The commenter proposed to modify the statement, “Ensuring that manufacturing validation protocols and reports are reviewed and approved” under Section 1. *Quality Management, 1.2.3 Responsibilities for Production Operations*, because the current regulations set forth in 21 CFR part 111 do not contain any requirements for or provisions concerning system or process validation.

**Response:** Comment incorporated. The statement rephrased as, “Ensuring that manufacturing verification /validation protocols and reports are reviewed and approved if available.”

**Comment Summary #6:** The commenter proposed to add information regarding GMP training and maintenance of training records in Section 1. *Quality Management, 1.2.4 Personnel Qualifications and 1.2.5 Personnel Training.*

**Response:** Comment incorporated. The statement, “Training should be periodically assessed by reviewing and approving GMP training documentation and ensuring that these records are maintained” is added under *1.2.5 Personnel Training.*

**Comment Summary #7:** The commenter proposed, considering the advent of COVID-19, to update the language of the section *1.2.6 Personnel Responsibilities, 1.2.6.1 Preventing Microbial Contamination* to include fever, coughing, and sneezing as part of the illness.

**Response:** Comment incorporated.

**Comment Summary #8:** The commenter suggested adding request of wearing face mask and maintaining footwear protocol when working within the production and packaging areas under section *1.2.6.2 Hygienic Practices.*

**Response:** Comment incorporated.

**Comment Summary #9:** The commenter proposed adding a statement to store clothing or other personal belongings in areas other than where clean work uniforms and gowning are stored and clarify that eating and drinking should be banned from all production, packaging, and laboratory areas under section *1.2.6.2 Hygienic Practices.*

**Response:** Comment incorporated.

**Comment Summary #10:** The commenter proposed adding the following statement: “If the firm chooses to maintain its documentation electronically, the resulting documents and related records must be 21 CFR Part 11 compliant” under section *1.3 Documentation and Records, 1.3.1 General.*

**Response:** Comment incorporated.

**Comment Summary #11:** The commenter commented on section *1.3.2 Control of Documentation* that there should be a specific requirement for each form to be associated with one or more SOPs and numbered accordingly and recommended adding several bullets, such as “Standard operating procedures (SOPs) and work instructions,” “Forms: content, revision, review; each form must be associated with one or more SOPs and correspondingly numbered/ versioned/ dated,” “Master manufacturing records (MMRs),” and “Laboratory testing methods,” under the phrase, “There should be proper control over:”

**Response:** Comment incorporated.

**Comment Summary #12:** The commenter proposed deleting the statements about spreadsheets, uncontrol documents, for reference only documents, and employee notes and memos from the following statement: “There should be proper control over: Forms: content, revision, review; Spreadsheets: spreadsheet for specific project—accuracy checked by reviewer, spreadsheet for routine use—validated, access/revision controlled); External documents: proprietary documents, guidance documents issued by outside agency; Uncontrolled document; For reference only documents; Employee notes and memos” under section *1.3.2 Control of Documentation*.

**Response:** Comment not incorporated. The EC determined that the text is appropriate as written.

**Comment Summary #13:** The commenter questioned the statement, “Serious adverse event reports must be kept, at minimum, for six (6) years from the date the report is received by the responsible party” under section *1.3.3 Records Retention*.

**Response:** Comment not incorporated. EC clarified that the six-year retention period is specified in the CFR on serious adverse event reporting.

**Comment Summary #14:** The commenter commented that the statement, “This classification system should be used to determine the level of testing, validation, and documentation needed to justify changes to a validated process,” under section *1.4 Change Control*, is too specific.

**Response:** Comment incorporated. The wording “validated process” was replaced with “system or process.”

**Comment Summary #15:** The commenter suggested modifying the statement, “A written risk-based supplier qualification program must be established and implemented for components for which the manufacturer has identified a hazard that requires a supply-chain-applied control” under section *1.7 Supplier Qualification*, by adding the wording “where appropriate” because for smaller companies with few suppliers, risk-based may not be required.

**Response:** Comment incorporated.

**Comment Summary #16:** The commenter suggested modifying the statement, “All contract manufacturers and contract laboratories should comply with the requirements of this general chapter,” under section *1.8 Contract Manufacturers and Contract Laboratories*, by adding a compliance with “equivalent regulatory oversight system requirements.”

**Response:** Comment incorporated.

**Comment Summary #17:** The commenter proposed to clarify the statement, “The contract should include provisions for the contract giver to audit the contract acceptor’s facilities for compliance with GMPs,” under section *1.8 Contract Manufacturers and Contract Laboratories*, that the audit can be performed on site and/or virtually.

**Response:** Comment incorporated.

**Comment Summary #18:** The commenter suggested modifying the statement, “All serious adverse event reports associated with the use of a dietary supplement must be submitted to the relevant regulatory agency, with a copy of the dietary supplement label, within 15 business days after the report is received,” under section *1.9.2 Adverse Event Reporting*, by adding “or within time required by regulatory authority after the report is received.”

**Response:** Comment incorporated.

**Comment Summary #19:** The commenter proposed including a definition of “responsible party,” mentioned in the section *1.9.3 Retention of Adverse Event Reporting Records*, in the *Glossary* section.

**Response:** Comment incorporated.

**Comment Summary #20:** The commenter suggested removing the statement regarding written procedures that must be established and followed for “Creating and maintaining job position descriptions, listing job responsibilities and required qualifications for education, training and experience,” under section *1.12 Quality Management Documentation, 1.12.1 Written Procedures*, because HR procedures should not be part of the GMP general chapter.

**Response:** Comment not incorporated. The EC found that the statement is consistent with 21 CFR 111.

**Comment Summary #21:** The commenter proposed removing the statement, “Conducting materials reviews” from procedures to be established and followed, under section *1.12.1 Written Procedures*, because APQR (Annual Product Quality Review) is not a requirement for dietary supplements.

**Response:** Comment not incorporated. The provided statement is applicable for the dietary supplement industry.

**Comment Summary #22:** The commenter proposed adding the statement regarding “Approving and rejecting materials as well as reprocessing and reworking” for written procedures that must be established and followed under section following the statement: “If the firm chooses to maintain its documentation electronically, the resulting documents and related records must be 21 CFR Part 11 compliant” under section *1.12.1 Written Procedures*.

**Response:** Comment not incorporated. The EC determined that the proposed statement is not always required.

**Comment Summary #23:** The commenter suggested adding clarifications to the section *2.3.1 Cleaning Compounds, Sanitizing Agents, Pesticides, and Other Toxic Materials* that, when the lubricant used is placed in direct contact with an in-process material (e.g., in the production of soft gelatin capsule film), it must be food grade.

**Response:** Comment incorporated.

**Comment Summary #24:** The commenter suggested removing recommendations regarding the quality of water that contacts components, in-process materials, dietary supplements, or any contact surface, under section *2.3.3 Water Supply*, because product shelf life is not related to the type of water, and correlation would be hard to make.

**Response:** Comment not incorporated. The use of more pure water will help with the sensory attributes of products.

**Comment Summary #25:** The commenter suggested removing reference to 21 CFR 117.20(b)(2), under section *2.3.7 Allergen Cross-contamination Reduction Control*, because this is not relevant to 21 CFR 111.

**Response:** Comment not incorporated. The EC found the reference to 21 CFR 117.20(b)(2) appropriate.

**Comment Summary #26:** The commenter suggested adding a statement that all non-room temperature storage facilities should be mapped prior to use to ensure that the

desired storage temperature is maintained anywhere inside regardless of location in the section *2.4 Equipment, Instruments, and Utensils, 2.4.2 Installation and Maintenance*.

**Response:** Comment not incorporated. The EC determined that mapping is not needed, monitoring is needed.

**Comment Summary #27:** The commenter commented that the statement, “Instruments and controls used in manufacturing or testing a component, in-process material or dietary supplement must be calibrated against a reference standard before first use; at a frequency specified in writing by the manufacturer of the instrument or control, and at routine intervals or as otherwise necessary to ensure the accuracy and precision of the instrument and control” under section *2.4.3 Operation and Calibration*, is a weak and suggested adding statement that “Calibration must be verified for every such scale and balance on each day of use using several reference weights.”

**Response:** Comment not incorporated. Calibration is usually done on a daily basis.

**Comment Summary #28:** The commenter suggested adding the statement, “This should include the determination and posting of the minimum accurate weight on all scales and balances used throughout the production and laboratory testing units” after the wording “Balances used to accurately weigh material should comply with <41> and <1251>” under section *2.4.3 Operation and Calibration*.

**Response:** Comment incorporated.

**Comment Summary #29:** The commenter proposed to modify the statement, “The quality unit must approve these calibrations, inspections, or checks” under section *2.4.3 Operation and Calibration*, to show that the quality unit should be involved only if there is an out of tolerance that needs to be evaluated for product impact.

**Response:** Comment incorporated. The statement rephrased to include the word, “periodically.”

**Comment Summary #30:** The commenter commented that statements such as, “The appropriate controls must be established and used to ensure that the equipment functions in accordance with its intended use. These controls must be approved by the quality control unit” under section *2.4.3 Operation and Calibration*, are already specified in the 21 CFR 111 and therefore should not be repeated in the general chapter.

**Response:** Comment not incorporated. The EC considered the inclusion of the statements appropriate.

**Comment Summary #31:** The commenter commented that statement under section *2.4.3 Operation and Calibration* that all the records should be periodically reviewed by the quality unit is an interpretation of the regulation. Periodic review can be a spot check of documents based on risk.

**Response:** Comment not incorporated. The EC found that the statement is consistent with 21 CFR 111.

**Comment Summary #32:** The commenter suggested eliminating the statement, “At minimum, heat treated pallets must be used in areas where components, in-process materials, dietary supplements, and contact surfaces are exposed” under section *2.4.4 Cleaning and Maintenance*.

**Response:** Comment not incorporated. The EC found that the statement is consistent with 21 CFR 111.

**Comment Summary #33:** The commenter commented that recommendations of using design qualification (DQ), installation qualification (IQ), operational qualification (OQ),

and performance qualification (PQ) as equipment or instrument qualification activities necessary to establish “fitness for purpose” presented under section *2.4.5 Equipment and Instrument Qualification*, are validation concepts specific to pharmaceutical requirements and thus are too restrictive for dietary supplement industry to demonstrate “fit for purpose.”.

**Response:** Comment not incorporated. This is a global standard for all manufacturers.

**Comment Summary #34:** The commenter suggested revising the statement, “When an equipment or instrument undergoes major repairs or modifications, this should be evaluated using change control” under section *2.4.5 Equipment and Instrument Qualification*, because assessment for validation impact or fit for purpose can be done via different methods and not only through a change control.

**Response:** Comment not incorporated. The EC found the current wording of the statement appropriate.

**Comment Summary #35:** The commenter suggested that section *2.4.6 Computerized Systems* be referred to the 21 CFR 111 rather than detailing and pointing out computer systems procedures and controls and electronic signatures.

**Response:** Comment not incorporated. The EC considered the inclusion of the statements suitable.

**Comment Summary #36:** The commenter commented that the statement, “The purity of water used as a component of a dietary supplement should be appropriately defined to maintain the stability of the dietary supplement throughout its shelf life” under section *3.1 Establishing Material and In-Process Production Specifications, 3.1.1 Component Specifications*, is not applicable for probiotics, therefore it would be more appropriate to mention ICH guidelines for stability and mention that methods should be stability indicating for a given product.

**Response:** Comment not incorporated. The EC found the wording of the statement appropriate.

**Comment Summary #37:** The commenter suggested that section *3.1.1 Component Specifications* be referred to 21 CFR 111, because many of the statements provided in the section represent interpretation to the regulation rather than summarizing the regulation requirements.

**Response:** Comment not incorporated. The EC found the wording of the section appropriate.

**Comment Summary #38:** The commenter suggested adding information on PCR containers under section *3.1.3 Labeling and Packaging Material Specifications*.

**Response:** Comment not incorporated. The EC determined that this information is outside of the scope of this General Chapter.

**Comment Summary #39:** The commenter commented on section *3.1.4 In-process (bulk) Dietary Supplement Specification* that in-process bulk processing may be done at the same facility as per previous manufacturing steps, and therefore having to again test for identify, purity, strength or composition, contaminants, and other specific characteristics may be redundant. Instead, these specifications should be looked at across the entire process span and may include risk assessments and reduced testing.

**Response:** Comment not incorporated. The EC determined that the statements provided in the section are consistent with 21 CFR 111.

**Comment Summary #40:** The commenter suggested modifying the information regarding “defect action levels” under section 3.1.4 *In-process (bulk) Dietary Supplement Specification* because the provided information states a theory while it could simply refer to Acceptable Quality Level (AQL) or AQL/RQL (rejectable quality level).

**Response:** Comment not incorporated. The EC found the wording of the section appropriate.

**Comment Summary #41:** The commenter commented that the statement, “The specification must provide sufficient assurance that the in-process (bulk) dietary supplement received is adequately identified and consistent with the purchase order, or supplier quality agreement” under section 3.1.5 *Received In-process (bulk) Dietary Supplement specifications*, is too specific to call out purchase order or supplier quality agreement as this level of detail may not appear in these types of documents.

**Response:** Comment not incorporated. The EC determined that the statement is consistent with 21 CFR 111.

**Comment Summary #42:** The commenter suggested revising the statement, “The specification must provide sufficient assurance that the in-process (bulk) dietary supplement received is adequately identified and consistent with the purchase order, or supplier quality agreement” under section 3.1.5 *Received in-process (bulk) dietary supplement specifications*, by adding “and meets compendial requirements where applicable.”

**Response:** Comment incorporated. The phrase was modified as “...consistent with the purchase order, and the CoA meets agreed-upon specifications or supplier quality agreement.”

**Comment Summary #43:** The commenter proposed including a definition of “responsible party” mentioned in the section 1.9.3 *Retention of Adverse Event Reporting Records*, in the *Glossary* section.

**Response:** Comment incorporated.

**Comment Summary #44:** The commenter suggested adding the wording, “Final approval by the quality unit should be withheld until which time the reprocessing or in-process adjustment has been completed and the materials tested pass all specifications” under section 3.2.8 *Disposition decision for materials*, to make clear that the quality unit’s approval of a reprocessing step alone and its completion by production staff does not constitute final approval without passing specification tests.

**Response:** Comment not incorporated. The EC found the current wording of the section appropriate.

**Comment Summary #45:** The commenter proposed simplifying the information under section 3.2.9 *Treatments, In-process Adjustments, and Reprocessing* and adding a statement that rejected material should be appropriately identified and segregated.

**Response:** Comment not incorporated. The EC found the current wording of the section appropriate.

**Comment Summary #46:** The commenter proposed adding several statements under section 3.3 *Receiving and Release of Materials*, 3.3.1 *Components, Packaging materials, and Labels*.

**Response:** Comment incorporated. The statements were added with some modifications.

**Comment Summary #47:** The commenter suggested adding a recommendation regarding a construction of the sampling room under section *3.4 Representative Samples and Reserve Samples, 3.4.1 Representative Samples*.

**Response:** Comment incorporated.

**Comment Summary #48:** The commenter suggested adding statement regarding monitoring and mapping of temperature and humidity of each warehouse under section *3.5 Holding, Distribution, and Transportation, 3.5.1 Holding*.

**Response:** Comment incorporated.

**Comment Summary #49:** The commenter suggested adding a statement that the storage of different materials within a single, designated storage location should be avoided to prevent picking errors in the absence of an electronic inventory control system under section *3.5.1 Holding*.

**Response:** Comment not incorporated. The EC found the existing wording of the section sufficient.

**Comment Summary #50:** The commenter suggested adding the statement, “The rejected materials storage location should be physically secure with access only to those with authority for disposition” under section *3.5.2 Rejected Materials*.

**Response:** Comment not incorporated. The EC found the existing wording of the section sufficient.

**Comment Summary #51:** The commenter suggested removing the statement, “The first manufactured batch of a dietary supplement should be distributed first” from the paragraph “Dietary supplements must be distributed under conditions that will protect the dietary supplement against contamination and deterioration. The first manufactured batch of a dietary supplement should be distributed first” under section *3.5.4 Distribution*.

**Response:** Comment incorporated.

**Comment Summary #52:** The commenter suggested removing the statement that vehicles and transportation equipment used in transportation operations must be “Adequately designed, maintained in a sanitary condition for their intended use to prevent components and dietary supplements from becoming adulterated during transportation operations,” under section *3.5.5 Transportation operations*, because transportation carriers do not consult the companies, and most will not take into consideration any recommendations made.

**Response:** Comment incorporated.

**Comment Summary #53:** The commenter suggested rephrasing the statement that records must be made and kept for “Documentation for why the results of appropriate reduced tests or examinations for dietary supplements ensure that the dietary supplement meets all product specifications” under section *3.7 Materials Management Operations and Controls Documentation, 3.7.2 Records*.

**Response:** Comment incorporated. The text was updated as, “Documentation that justify why a reduced testing program is appropriate.”

**Comment Summary #54:** The commenter proposed modifying the wording, “The master manufacturing record may include all manufacturing, packaging and labeling directions and controls, or be separated into two records: one for manufacturing and another for packaging and labeling” under section *4.1 Master Manufacturing Records*, to include practices used in soft gelatin product manufacturing.

**Response:** Comment incorporated.

**Comment Summary #55:** The commenter suggested adding the wording, “or for the adulteration of raw materials, in-process materials, and finished product” to the statement, “Performing manufacturing operations under conditions and controls that protect against the potential for growth of microorganisms and the potential for allergen cross-contact and contamination” under section *4.3 Manufacturing Operations Production and Process Controls*.

**Response:** Comment incorporated

**Comment Summary #56:** The commenter proposed removing the statement, “Label reconciliation is not required for cut or rolled labels if a 100-percent examination for correct labels is performed by appropriate electronic or electromechanical equipment during or after completion of finishing operations” under section *5.4 Labeling Issuance and Control*.

**Response:** Comment not incorporated. The wording was modified to clarify that a 100% examination needs to be done first.

**Comment Summary #57:** The commenter commented that the statement, “Packaging and labeling facilities must be inspected immediately before use to ensure that all materials not needed for the next packaging operation have been removed, and that packaging and labeling facilities have been properly cleaned” under section *5.5 Packaging and Labeling Operations* is an interpretation of the regulation. Line clearances do not always happen immediately before use of the room/equipment.

**Response:** Comment not incorporated. The EC determined that the statement is consistent with 21 CFR 111.

**Comment Summary #58:** The commenter commented that information under section *6.6 Reduced Testing, 6.6.2 Reduced Testing Requirements* provides examples of how to manage reduced testing, but the essential element to mention is risk management that should be highlighted, and that can be done differently than what is written.

**Response:** Comment not incorporated. The EC found the current wording of the section appropriate.

**Comment Summary #59:** The commenter suggested referring accelerated stability testing, under section *6.8 Stability Testing*, to ICH guidance and include information for microbiological degradation for probiotic products.

**Response:** Comment not incorporated. The EC found the wording of the section appropriate and additional information for microbiological degradation for probiotic products is outside the scope of this General Chapter.

**Comment Summary #60:** The commenter suggested adding a definition for “responsible party” under *Glossary* section.

**Response:** Comment incorporated.

**Comment Summary #61:** The commenter suggested adding the definitions for “risk,” “risk assessment,” “risk control,” and “risk management (quality)” under *Glossary* section.

**Response:** Comment incorporated.

**Comment Summary #62:** The commenter expressed disagreement with the proposed revisions because presented information is a blend of various requirements from 21 CFR Part 111 with additional interpretation and inclusion of pharmaceutical



requirements. Some additions involve validation of manufacturing steps, which is not a requirement set out by the regulation for foods and dietary supplements.

**Response:** Comment not incorporated. The EC noted that the proposed revision could help dietary supplement manufacturers to ensure that dietary supplements are consistently manufactured and controlled to quality standards appropriate for their intended use and in accordance with USP product specification requirements.

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## Monographs

**Monograph/Sections:** Asparagine/Multiple Sections

**Expert Committee:** Simple Excipients

**No. of Commenters:** 1

**Comment Summary #1:** The commenter recommended changing the amount of potassium phosphate from 13.61 g to 13.6 g in mobile phase preparation in the *Assay* test.

**Response:** Comment not incorporated. The EC determines it is not necessary to make this change because based on General Chapter <621>, within  $\pm 10\%$  of concentration of salts in buffer is allowed.

**Comment Summary #2:** The commenter recommended harmonizing the *Organic Impurities* test with the impurity method in the Asparagine EP monograph in term of sample concentration.

**Response:** Comment not incorporated. The EP method was used as a starting point in developing the new impurity method. In batch analysis of NF grade Asparagine samples procured from the U.S. market, the EP method can't achieve satisfactory separations among peaks of interest in many batches.

**EC-Initiated Change #1:** The term, "unspecified impurity" was changed to "unidentified impurity" under the *Organic Impurities* test.

**EC-Initiated Change #2:** The number of decimal places of relative retention time was changed from 2 to 1 in Table 1 under the *Organic Impurities* test.

**Monograph/Section:** Bupropion Hydrochloride/Multiple Sections

**Expert Committee:** Small Molecules 4

**No. of Commenters:** 5

**Comment Summary #1:** The commenter requested reducing the concentration of the *Standard solution* and *Sample solution* within the *Assay*. Commenter has observed high peak responses and insufficient repeatability to meet the proposed *Relative standard deviation* requirement of NMT 0.73%.

**Response:** Comment partially incorporated. The currently official *Relative standard deviation requirement* of NMT 2.0% was retained. The EC will consider future revisions to the monograph upon receipt of the necessary supporting data.

**Comment Summary #2:** The commenter requested the identification of an alternate column with a different inner diameter for use with the *Assay*, *Identification*, and *Organic Impurity* procedures.

**Response:** Comment not incorporated. General Chapter <621> contains information about adjustments to procedures. The EC will consider future revisions to the monograph upon receipt of the necessary supporting data.

**Comment Summary #3:** The commenter requested renaming “any other individual impurity” as “any unspecified impurity” to address any unspecified impurities within the test for *Organic Impurities*.

**Response:** Comment incorporated.

**Comment Summary #4:** The commenters requested revisions to or replacement of the proposed test for the *Limit of Bupropion Related Compound G* because the proposed procedure is not suitable and bupropion related compound G should be identified as a potential mutagenetic impurity.

**Response:** Comment partially incorporated. The test for the *Limit of Bupropion Related Compound G* was not approved for inclusion within the monograph. The EC will consider future revisions to the monograph upon receipt of the necessary supporting data.

**EC-Initiated Change #1:** Bupropion Related Compound G is removed from Table 3 and from the *USP Reference Standards* section.

**Monograph/Section:** Bupropion Hydrochloride Extended-Release  
Tablets/Organic Impurities

**Expert Committee:** Small Molecules 4

**No. of Commenters:** 2

**Comment Summary #1:** The commenter requested replacing the test with a different analytical procedure that has better sensitivity and is more robust.

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

**Comment Summary #2:** The commenter requested removing the “reporting threshold” as it will vary 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:** Bupropion Hydrochloride Tablets/Organic Impurities

**Expert Committee:** Small Molecules 4

**No. of Commenters:** 2

**Comment Summary #1:** The commenters requested revising the procedure, impurity profile, and acceptance criteria for the proposed test.

**Response:** Comments partially incorporated. The proposed test for *Organic Impurities* was not approved for inclusion within the monograph. The EC will consider future revisions to the monograph upon receipt of the necessary supporting data.

**Monograph/Section:** Gadobutrol/Multiple Sections

**Expert Committee:** Small Molecules 4

**No. of Commenters:** 2

**Comment Summary #1:** The commenter requested clarifying the preparation of *Solution A* to indicate whether the pH adjustment is to be done before or after mixing acetonitrile and water in the *Assay*.

**Response:** Comment incorporated. The preparation of *Solution A* is revised as, “Adjust 995 mL of water with *Diluted formic acid* to a pH of 3.6. Add 5 mL of acetonitrile.”

**Comment Summary #2:** The commenter requested clarifying that relative response factors of 1 should be used for the three specified impurities in the test for *Organic Impurities*.

**Response:** Comment not incorporated. The text as written is consistent with current USP style. When a relative response factors other than 1 is needed to quantitate at least one compound, then relative response factors are specified for all of the compounds.

**Comment Summary #3:** The commenter requested removing the “reporting threshold” as it will vary 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:** Clocortolone Pivalate/Organic Impurities

**Expert Committee:** Small Molecules 5

**No. of Commenters:** 1

**Comment Summary #1:** The commenter requested removing the “reporting threshold” because it will vary 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/Sections:** Estradiol and Norethindrone Acetate Tablets/Multiple Sections

**Expert Committee:** Small Molecules 5

**No. of Commenters:** 1

**Comment Summary #1:** The commenter requested retaining the current official procedure in *Identification A*, which includes the use of TLC and a toxic solvent or adding the procedure, which includes the use of a diode array detector if accompanied by a statement indicating that it is an optional procedure.

**Response:** Comment not incorporated. The procedure, which utilizes diode array detection, is appropriate for inclusion in the public standard and avoids the use of a toxic solvent.

**Comment Summary #2:** The commenter requested allowing the use of a UV detector instead of requiring the use of a diode array detector in the *Assay*.

**Response:** Comment not incorporated. The use of a diode array detector is required to conduct the *Identification A* and is not required to conduct the *Assay*.

**Comment Summary #3:** The commenter requested removing the specific particle size and the *Run time* requirement from the *Assay*.

**Response:** Comment not incorporated. The inclusion of column particle size information is useful for users who would like to make changes to parameters within

isocratic procedures as described in <621>. The inclusion of a *Run time* requirement in isocratic procedures is consistent with the expectations of the EC.

**Comment Summary #4:** The commenter requested retaining the existing USP trivial names along with the updated names in the test for *Organic Impurities*.

**Response:** Comment not incorporated. The trivial names reflect current USP nomenclature convention.

**Comment Summary #5:** The commenter requested retaining the current acceptance criterion description of “Any other single norethindrone acetate related impurity.”

**Response:** Comment not incorporated. The monograph should reflect current USP style.

**Monograph/Sections:** Estradiol Valerate/Organic Impurities

**Expert Committee:** Small Molecules 5

**No. of Commenters:** 1

**Comment Summary #1:** The commenter requested removing the “reporting threshold” because it will vary 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/Sections:** Japanese Sophora Flower/Multiple Sections

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

**No. of Commenters:** 6

#### **Definition**

**Comment Summary #1:** The commenter suggested removing Japanese sophora flower bud from Japanese sophora flower monograph because the flavonol glycosides content in these two plant parts is significantly different. Japanese sophora flower bud monograph should be developed separately.

**Response:** Comment incorporated. Information related to Japanese sophora flower bud was removed.

#### **Identification A**

**Comment Summary #2:** The commenter suggested using PEG 400 instead of PEG 4000 in *Derivatization reagent B* without any parameters changes because PEG 400 is less cumbersome to use and more easily dissolved in ethanol.

**Response:** Comment incorporated.

**Comment Summary #3:** The commenter suggested adding detection at UV 254 nm.

**Response:** Comment incorporated.

#### **Composition**

**Comment Summary #4:** The commenter suggested changing HPLC column temperature from 25° to 35° to increase resolution between kaempferol–3–O–rutinoside and isorhamnetin–3–O–rutinoside peaks to ensure the system suitability to meet the requirement of NLT 1.5.

**Response:** Comment incorporated. Column temperature was changed from 25° to 35°.

**Comment Summary #5:** The commenter suggested adding 5 minutes more to wash the column after HPLC gradient to make sure baseline is reached even before next injection.

**Response:** Comment incorporated.

**Comment Summary #6:** The commenter suggested adding ultrasonic bath power and frequency for sample solution preparation to avoid using different power and frequency that could impact flavonol glycosides concentration in sample solution.

**Response:** Comment incorporated by adding, “140 W and 100 KHz” after “sonicate for 30 min.”

**Monograph/Sections:** Japanese Sophora Flower Dry Extract/Multiple Sections

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

**No. of Commenters:** 5

#### **Identification A**

**Comment Summary #1:** The commenter suggested using PEG 400 instead of PEG 4000 in *Derivatization reagent B* without any parameters changes because PEG 400 is less cumbersome to use and more easily dissolved in ethanol.

**Response:** Comment incorporated.

**Comment Summary #2:** The commenter suggested adding detection at UV 254 nm.

**Response:** Comment incorporated.

#### **Composition**

**Comment Summary #3:** The commenter suggested changing HPLC column temperature from 25° to 35° to increase resolution between kaempferol–3–O–rutinoside and isorhamnetin–3–O–rutinoside peaks to ensure the system suitability to meet the requirement of NLT 1.5.

**Response:** Comment incorporated. Column temperature was changed from 25° to 35°.

**Comment Summary #4:** The commenter suggested adding 5 minutes more to wash the column after HPLC gradient to make sure baseline is reached even before next injection.

**Response:** Comment incorporated.

**Comment Summary #5:** The commenter suggested adding ultrasonic bath power and frequency for sample solution preparation to avoid using different power and frequency that could impact flavonol glycosides concentration in sample solution.

**Response:** Comment incorporated by adding, “140 W and 100 KHz” after “sonicate for 30 min.”

**Monograph/Sections:** Japanese Sophora Flower Powder/Multiple Sections

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

**No. of Commenters:** 6

#### **Definition**

**Comment Summary #1:** The commenter suggested to remove Japanese sophora flower bud from Japanese sophora flower monograph because the flavonol glycosides

content in these two plant parts is significantly different. Japanese sophora flower bud monograph should be developed separately.

**Response:** Comment incorporated. Information related to Japanese sophora flower bud was removed.

### **Identification A**

**Comment Summary #2:** The commenter suggested using PEG 400 instead of PEG 4000 in *Derivatization reagent B* without any parameters changes because PEG 400 is less cumbersome to use and more easily dissolved in ethanol.

**Response:** Comment incorporated.

**Comment Summary #3:** The commenter suggested adding detection at UV 254 nm.

**Response:** Comment incorporated.

### **Composition**

**Comment Summary #4:** The commenter suggested changing HPLC column temperature from 25° to 35° to increase resolution between kaempferol-3-O-rutinoside and isorhamnetin-3-O-rutinoside peaks to ensure the system suitability to meet the requirement of NLT 1.5.

**Response:** Comment incorporated. Column temperature was changed from 25° to 35°.

**Comment Summary #5:** The commenter suggested adding 5 minutes more to wash the column after HPLC gradient to make sure baseline is reached even before next injection.

**Response:** Comment incorporated.

**Comment Summary #6:** The commenter suggested adding ultrasonic bath power and frequency for sample solution preparation to avoid using different power and frequency that could impact flavonol glycosides concentration in sample solution.

**Response:** Comment incorporated by adding, “140 W and 100 KHz” after “sonicate for 30 min.”

**Monograph/Sections:** Losartan Potassium/Organic Impurities

**Expert Committee:** Small Molecules 2

**No. of Commenters:** 1

**Comment Summary #1:** The commenter recommended 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 on the topic.

**Comment Summary #2:** The commenter recommended correcting the typographic error for the requirement of Relative standard deviation from NMT 5.0 to NMT 5.0%.

**Response:** Comment incorporated.

**Comment Summary #3:** The commenter recommended replacing, “Individual impurities” with “Any specified impurity” or “Any unspecified impurity” with appropriate limits.

**Response:** Comment not incorporated. The acceptance criteria were not proposed for changes in the published *PF* proposal. The EC will consider future revisions upon receipt of supporting data.

**Monograph/Section:** Magnesium Citrate/Multiple Sections

**Expert Committee:** Small Molecules 3

**No. of Commenters:** 1

**Comment Summary #1:** The commenter recommended using ICP-OES in Assay and the test for *Limit of Calcium*.

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

**Monograph/Sections:** Potassium and Sodium Bicarbonates and Citric Acid Effervescent Tablets for Oral Solution/Assay

**Expert Committee:** Small Molecules 5

**No. of Commenters:** 1

**Comment Summary #1:** The commenter recommended that USP works with the manufacturers of marketed products to ensure that they will be able to meet the requirements in the proposed monograph in order to avoid a drug shortage.

**Response:** Comment incorporated. The EC changed the official date for the proposed revision from August 1, 2021, to February 1, 2022, providing additional time to prepare for compliance.

**Monograph/Sections:** Prasugrel Tablets/Multiple sections

**Expert Committee:** Small Molecules 2

**No. of Commenters:** 3

**Comment Summary #1:** The commenter recommended 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 on the topic.

**Comment Summary #2:** The commenter indicated that their approved tolerances for *Dissolution* test are different from the ones in the proposal and requested to add a new *Dissolution* test based on their FDA-approved application.

**Response:** Comment not incorporated. The Expert Committee decided to add the *Dissolution Test 2* via Revision Bulletin to reflect the approved dissolution tolerances.

**Comment Summary #3:** The commenter requested including their method for *Organic impurities* test.

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

**Comment Summary #4:** The commenter requested the clarification of why different wavelengths are used for the *Assay* and *Organic Impurities* tests.

**Response:** Comment not incorporated. The wavelengths are consistent with the validation data and are suitable for the intended use.

**Monograph/Section:** Sodium Fluoride/Multiple Sections

**Expert Committee:** Small Molecules 3

**No. of Commenters:** 2

**Comment Summary #1:** The commenter recommended including an assay procedure or a purity method and limit for sodium.

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

**Comment Summary #2:** The commenter recommended renaming “Assay” to “Fluoride Assay” because this specific method only determines the level of fluoride ion.

**Response:** Comment not incorporated. The EC determined that the title as, “Assay” is consistent with current USP style.

**Monograph/Section:** Spironolactone Tablets/Organic Impurities

**Expert Committee:** Small Molecules Monograph 2

**No. of Commenters:** 2

**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 on the topic.

**Comment Summary #2:** The commenter requested revising the monograph to state that spironolactone related compound D and Spironolactone epimer, which are controlled in the USP drug substance monograph (Spironolactone), should be disregarded or added with acceptance criteria aligned with the drug substance monograph.

**Response:** Comment not incorporated. The acceptance criteria are consistent with an FDA-approved application. The EC will consider future revisions to the monograph upon the receipt of supporting data.