



## **Commentary**

### ***Second Supplement to USP 36–NF 31***

*Originally posted June 3, 2013; updated October 25, 2013*

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

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## General Chapters:

**General Chapter/Section(s):** <2> Oral Drug Products—Product Quality Tests  
**Expert Committee(s):** General Chapters—Dosage Forms  
**No. of Commenters:** 7

### **GENERAL**

**Comment Summary #1:** The commenter suggested moving the General Chapter to an informational general chapter or a submission guideline on preparing monograph submissions.

**Response:** Comment not incorporated. This General Chapter belongs to the general chapters <1> to <5> concept developed for product quality tests, according to routes of administration, and is intended to be suitable for application to articles recognized in *USP-NF*.

**Comment Summary #2:** The commenter suggested the adoption of the *Ph.Eur.* practice of seeking specific monographs for drug ingredients and relying on general chapters for dosage form requirements.

**Response:** Comment not incorporated. This approach does not fit with the current USP structure with specific monographs for drug products.

**Comment Summary #3:** The commenter suggested adding instructions to the *USP–NF General Notices* defining the purpose of general chapters <1> to <5>.

**Response:** Comment incorporated in the *Introduction* of the General Chapter.

**Comment Summary #4:** The commenter suggested focusing on product quality tests instead of product release, and aligning the content with ICH Q6 guideline.

**Response:** Comment incorporated with changes. Additional clarification was provided in the *Introduction* and the disintegration test was removed. References to *Ph.Eur.* also were incorporated.

**Comment Summary #5:** The commenter suggested reorganizing the General Chapter to improve the flow and simplify the text.

**Response:** Comment incorporated.

### **TITLE**

**Comment Summary #6:** The commenter suggested changing the *Title* to “Oral Drug Products” in order to align it with the content and allow for future expansion, such as, addition of a *Packaging* section, as in General Chapter <1>.

**Response:** Comment not incorporated. The proposed *Title* is aligned with the product quality general chapter's concept and revised content. There is no current intention to add sections later. General Chapter <1> was revised to include only product quality tests for injections.

### **INTRODUCTION**

**Comment Summary #7:** The commenter suggested ensuring consistency and alignment with dosage forms recognized by FDA.

**Response:** Comment not incorporated. This proposed General Chapter is aligned with revised General Chapter <1151> and is intended to be consistent with FDA policies.

**Comment Summary #8:** The commenter suggested adding text to clarify that general chapters numbered above <1000> were for informational purposes only.

**Response:** Comment incorporated. Individual footnotes were added to references for general chapters above <1000>, to emphasize that they noted for informational purposes only.

**Comment Summary #9:** The commenter requested clarifying whether drug products with multi-actives and biologics in solid dosage forms are included in the scope of the general chapter

**Response:** Comment incorporated. Drug products with multi-actives are included. Biologics in solid dosage forms are not included.

**Comment Summary #10:** The commenter requested clarifying the wording in the sentence: “For example, the chapter does not address oromucosal dosage forms intended for local action in the mouth,” because the previous paragraph includes the sentence “All oral drug products lead to systemic and/or local action in the oral cavity and/or gastrointestinal tract” and both sentences are inconsistent.

**Response:** Comment incorporated. A sentence in the Introduction was modified to clarify the scope of the chapter.

**Comment Summary #11:** The commenter suggested distinguishing between process control tests and tests performed at lot release by adding the following sentence: “Some of the tests indicated in this chapter may be performed on an in-process basis or omitted as routine tests based on process validation.”

**Response:** Comment incorporated.

### ***Drug Product Quality Tests and Performance Tests***

**Comment Summary #12:** The commenter requested removing the section *Drug Product Quality and Performance Tests*, because the distinction between product quality and performance tests is not useful.

**Response:** Comment not incorporated. This distinction is needed, was requested by other users, and is consistent with the product quality general chapters concept.

**Comment Summary #13:** The commenter suggested removing references to <701>, *Disintegration*, because this test could be interpreted as a performance test in a chapter focused on quality tests.

**Response:** Comment not incorporated. This proposed General Chapter makes references to <701> for detailed procedures only, and it is not incorporating new requirements.

**Comment Summary #14:** The commenter requested removing the word “control” in the following sentence: “Thus, they form the basis for the control tests of a monograph,” because the term is not appropriate in this context.

**Response:** Comment incorporated.

**Comment Summary #15:** The commenter requested deleting the sentence: “Only when disintegration has been correlated with dissolution of a dosage form can a disintegration test (see <701> *Disintegration*) be used as a product performance test,” because it should be the prerogative of regulatory authorities to decide whether

disintegration is the best indicator and predictor of drug release/dissolution and thereby in-vivo performance of the drug product of a case-by-case bases.

**Response:** Comment incorporated with changes. The sentence was relocated under “*Disintegration*” with additional clarification and references to ICH Q6A (original source).

### ***PRODUCT QUALITY TESTS FOR ORAL DRUG PRODUCTS***

**Comment Summary #16:** The commenter suggested changing the following sentence: “Tests for oral drug products fall into three categories:...” to “Drug product quality tests for oral drug products fall into three categories:...”

**Response:** Comment incorporated with changes to reflect that there are two categories of tests: Universal and Product Specific.

### ***UNIVERSAL TESTS***

#### ***Description***

**Comment Summary #17:** The commenter requested deleting the *Description* section, because it is not a test.

**Response:** Comment not incorporated. This section clarifies the nature of the information.

#### ***Identification***

**Comment Summary #18:** The commenter suggested clarifying that the terms “drug substance” and “active ingredient” are used synonymously.

**Response:** Comment incorporated in the *Introduction*.

**Comment Summary #19:** The commenter suggested aligning language with ICH Q6A, because Assay tests for drug products containing multi-active ingredients generally are not suitable for identification purposes.

**Response:** Comment incorporated with changes. The General Chapter is already aligned with ICH Guidance Q6A.

**Comment Summary #20:** The commenter requested replacing “content” with “drug substance” in the following sentence: “It is included in a monograph as an aid to confirm that the article contains the labeled content by providing a positive identification of the drug substance or substances in a drug product,” because “content” typically implies a quantitative measurement.

**Response:** Comment incorporated.

**Comment Summary #21:** The commenter suggested clarifying the sentence: “One method of confirming the identity is to compare the retention time of the sample with that obtained for the standard injections within the assay,” because it is applicable to chromatographic procedures only.

**Response:** Comment incorporated.

**Comment Summary #22:** The commenter suggested that the language regarding the analytical procedure and chromatographic system requirements be removed, because this information is covered under <621> *Chromatography*.

**Response:** Comment not incorporated. The references to chromatography are general in nature. Additional clarification was added.

**Comment Summary #23:** The commenter suggested clarifying the reference to other methods used to orthogonally confirm the identity of the active ingredient to ensure unambiguous understanding.

**Response:** Comment incorporated.

**Comment Summary #24:** The commenter indicated that methodologies such as IR, NMR, Near IR, and Raman Spectroscopy should not be limited as "orthogonal identification tests" as these may provide specific primary identification of active ingredient(s) in drug product.

**Response:** Comment incorporated with changes, because these methods are referenced only as examples.

**Comment Summary #25:** The commenter requested replacing the word "separate" to "distinguish," because separation typically is associated with chromatographic methods. Spectroscopic methods, in which a physical separation may not necessarily occur, also may be used as identification tests. Only discrimination is necessary.

**Response:** Comment incorporated.

**Comment Summary #26:** The commenter suggested deleting the reference to impurities in the sentence: "Care must also be taken to ensure that the chromatographic system separates the article from other closely related drug substances, impurities, and additives," because not all methods that contribute to a positive identification ensure a complete separation from all impurities.

**Response:** Comment not incorporated. The goal of the system is to discriminate or distinguish the drug substance from other related compounds, including impurities.

**Comment Summary #27:** The commenter suggested replacing the statement: "but the drug substance typically must be extracted from the product matrix" with a more general statement such as, "if the procedure has demonstrated to be selective for the drug substance via an appropriate validation or verification study."

**Response:** Comment incorporated.

**Comment Summary # 28:** The commenter requested removing the reference to USP Reference Standards in the sentence: "The results of the identification test must be compared to the results obtained from an authentic drug substance, for which USP Reference Standards should be used whenever possible," because it is too specific.

**Response:** Comment incorporated with changes. The sentence now states: "The results of the identification test must be compared to the results obtained from a similarly prepared, suitable reference standard."

## **Assay**

**Comment Summary #29:** The commenter requested removing the words "and controlled" in the sentence: "When a nonspecific assay (e.g. titration) is justified, other supporting analytical procedures should ensure that any interfering species can be detected and controlled," because analytical procedures or testing cannot control interfering species.

**Response:** Comment incorporated.

**Comment Summary #30:** The commenter requested replacing the sentence: "Assays often are reported as a percentage of the label claim with acceptance criteria that typically are in the range of 90.0%–110.0%," with "In general, the *a priori* acceptance of  $\pm 10\%$  variation in limits of a quality attribute (e.g. assay) from the target label claim

(100%) in most cases is intended to account for manufacturing variability and shelf-life stability and is primarily based on the notion that such variation in a quality attribute is less likely to have any noticeable adverse impact on the desired clinical outcome.”

**Response:** Comment incorporated.

**Comment Summary #31:** The commenter suggested removing the language regarding acceptance criteria ranges, because this typically is agreed upon between the manufacturer and health authority based on several factors, including patient safety, manufacturing capabilities, and method variability.

**Response:** Comment not incorporated. The criteria ranges are general limits and only for informational purposes.

### ***Impurities***

**Comment Summary #32:** The commenter requested replacing the word “controlled” with “limited” in the sentence: “These impurities are controlled by drug substance and excipient monographs.”

**Response:** Comment incorporated.

**Comment Summary #33:** The commenter suggested changing the sentence: “Over the shelf life of the product, degradation impurities can form,” to “During product manufacture and over the shelf life of the product, degradation impurities can form,” because degradation products can be formed both over the shelf-life of the product and during product manufacture.

**Response:** Comment incorporated.

**Comment Summary #34:** The commenter requested replacing the term “degradation impurities” with “degradation products” as it is a well established term used in ICH Q6C.

**Response:** Comment incorporated.

**Comment Summary #35:** The commenter requested rewording the sentence: “These can be a result of degradation of the drug substance, the excipient, or interactions between the drug substance and excipient(s),” to be more general, because there might be another origin that is not degradation in the strict sense.

**Response:** Comment incorporated.

**Comment Summary #36:** The commenter suggested removing narrative language, because reference to *USP General Notices: 5.60 Impurities and Foreign Substances* and <1086> *Impurities in Drug Substances and Drug Products* is sufficient.

**Response:** Comment not incorporated. Descriptive language is consistent with the structure of the General Chapter and intended to be informative only.

### ***SPECIFIC TESTS FOR SOLIDS***

**Comment Summary #37:** The commenter suggested changing the title to “Specific Tests for Oral Drug Products: Solid Dosage Forms” to improve clarity and consistency.

**Response:** Comment not incorporated. The title was changed to align it with the new structure of the General Chapter.

**Comment Summary #38:** The commenter suggested replacing the sentence: “The following specific tests for solids should be considered, depending on the nature of the drug substance and formulation,” with “The following specific tests for solids should be considered, depending upon the nature of the formulation,” because it is unclear why or how the nature of the drug substance has a bearing on the tests selected.

**Response:** Comment not incorporated. The nature of the drug substance could impact the selection of tests, for example volatile content.

## **SPECIFIC TESTS FOR SOLIDS**

### ***Volatile Content***

**Comment Summary #39:** The commenter suggested clarifying whether *Loss on Drying*, *Water Determination*, and *Residual Solvents* will be listed under this specific test attribute, because the title appears to be new terminology for a test attribute.

**Response:** Comment not incorporated. Under this title, the following general chapters are listed: <721> *Loss on Drying*, <921>, *Water Determination*, and <467> *Residual Solvents*.

**Comment Summary #40:** The commenter suggested changing the sentence: “When the presence of moisture or other volatile material may become critical, analysts must determine the amount of unbound volatile solvents or volatile matter of any kind that is driven off (see <731> *Loss on Drying*).” This is overly prescriptive, as water activity may also be a suitable test.

**Response:** Comment incorporated..

**Comment Summary #41:** The commenter suggested adding text to address drug substance hygroscopic properties. For drug substances that appear to contain water as the only volatile constituent, <731> *Loss on Drying* or <921> *Water Determination* may be suitable tests, depending on the volatile content of the product.

**Response:** Comment not incorporated. The intent is not to address all cases. The section starts with “...depending on the nature of the article.” There is no exclusion to any particular test.

**Comment Summary #42:** The commenter suggested removing or clarifying this section, because Expert Committees typically do not include specific tests for the presence of moisture in formulations when developing USP monographs. These specifications are typically dosage form dependent and not suitable for use in a public standard.

**Response:** Comment not incorporated. This section contains general statements, which are applicable to both drug substances and drug products.

**Comment Summary #43:** The commenter requested replacing the sentence: “Special consideration should be given to dosage forms for which water content has been shown to be a potential quality attribute,” with “Special consideration should be given to dosage forms for which water content has been shown to be a potential quality attribute and to products where solvent is used in the manufacture of the drug product.”

**Response:** Comment incorporated.

### ***Disintegration***

**Comment Summary #44:** The commenter indicated that disintegration should be regarded as a performance test and should be listed along with dissolution.

**Response:** Comment not incorporated. Additional clarification has been incorporated along with Q6A text.

**Comment Summary #45:** The commenter suggested adding the sentence: “Some of the tests indicated in this chapter may be performed on an in-process basis or omitted as routine tests based on process validation,” in the *Introduction* for clarification.

**Response:** Comment incorporated.

**Comment Summary #46:** The commenter suggested removing references to <701> *Disintegration* from this proposal, because disintegration is not generally conducted as a performance test on drug product.

**Response:** Comment not incorporated. The reference to General Chapter <701> is needed for consistency and reinforcement.

**Comment Summary #47:** The commenter suggested clarifying that this test should not be considered universal, because it does not apply to sachettes/powders and that the disintegration test is not required, if the dissolution test is performed.

**Response:** Comment incorporated.

#### ***Tablet Friability and Tablet Breaking Force***

**Comment Summary #48:** The commenter requested deleting these tests, because they are specific to tablets and therefore not a consideration for other solid oral drug products.

**Response:** Comment not incorporated. These tests are no longer universal tests.

**Comment Summary #49:** The commenter suggested adopting text that is more aligned with ICH Q6A. These tests are not typically performed during release testing/stability, because they do not have a critical impact on drug product quality.

**Response:** Comment incorporated with changes. A statement to use all the tests in this General Chapter either as in-process basis or end-release was added in the *Introduction*.

#### ***Uniformity of Dosage Units***

**Comment Summary #50:** The commenter suggested adding a statement that recognizes in-process monitoring of uniformity of dosage units and also testing of stratified samples of dosage units throughout the manufacturing process.

**Response:** Comment incorporated with changes. A statement to use all the tests in this General Chapter either as in-process basis or end-release was added in the *Introduction*.

#### ***ADDITIONAL TESTS FOR SPECIFIC TYPES OF SOLID DOSAGE FORMS***

**Comment Summary #51:** The commenter suggested changing the section title to “Additional Tests for Oral Drug Products: Specific Types of Solid Oral Dosage Forms” to improve clarity and consistency.

**Response:** Comment incorporated with changes. Title changed with a new structure.

**Comment Summary #52:** The commenter suggested changing the section introduction to read: “Below are additional tests for specific types of solid dosage forms that may be considered. It is recommended that product quality tests for a solid drug product also include the universal tests and the specific tests from the previous sections.”

**Response:** Comment incorporated with changes. The text has been removed and new wording added.

**Comment Summary #53:** The commenter suggested replacing the word “specific” with “may be applicable” to tests, because these tests are applied to multiple types, so they are not specific.

**Response:** Comment incorporated with changes. Now the tests are specific for a group of dosage forms.

**Comment Summary #54:** The commenter requested adding the symbol °C next to the temperature range.

**Response:** Comment incorporated.

**Comment Summary #55:** The commenter requested including 710 µm in parentheses after the two references to a No. 25 sieve.

**Response:** Comment incorporated.

### ***TABLETS***

**Comment Summary #56:** The commenter suggested changing the section introduction to read: “Product quality tests that are specific to the type of tablet may be appropriate for testing tablets include: tablet friability or tablet breaking force and volatile content (<731> and <921>),” because a risk assessment should be conducted to determine the need for volatile testing.

**Response:** Comment not incorporated. This paragraph has been removed.

### ***Uncoated Tablets***

**Comment Summary #57:** The commenter suggested including more explanation in the section *Introduction* regarding the scope of the chapter because the proposed revision only includes information on immediate release tablets. Some uncoated tablets can be monolithic controlled release matrix tablets, in which the excipients are selected to modify the release of the active substance in the digestive fluids.

**Response:** Comment not incorporated. An in-depth discussion on this topic is included in General Chapter <1151>. This General Chapter deals only with general statements.

### ***Effervescent Tablets***

**Comment Summary #58:** The commenter suggested replacing the text under *Disintegration* as follows: “The tablets comply with the test if – each of the 6 tablets used dissolves or disintegrates in the manner prescribed within 5 min, unless otherwise justified and authorized, and – the dispersion obtained from a disintegrated tablet passes through the specified sieve.” to specify the disintegration time (NMT 5 min) and the acceptance criterion for size of the agglomerate/particles.

**Response:** Comment not incorporated. This text has been removed.

### ***Chewable Tablets***

**Comment Summary #59:** The commenter suggested deleting this section, because it is not appropriate to apply a performance test against product misuse (i.e. a chewable tablet being swallowed without proper chewing by a patient).

**Response:** Comment incorporated with changes to clarify that dissolution test should be conducted on intact chewable tablets as a product performance test.

### ***Disintegrating Tablets***

**Comment Summary #60:** The commenter suggested deleting the test “Dispersion fineness,” because this is not a relevant quality test and has little impact on the performance of the product in the patient.

**Response:** Comment not incorporated. Dispersion fineness is a necessary product quality test.

### ***Soluble Tablets***

**Comment Summary #61:** The commenter suggested replacing the sentence: “These are uncoated or film-coated tablets intended to be dissolved in water before administration,” with “These are tablets intended to be dissolved in water before administration,” because it is unclear why a film coating would be applied to tablets intended to be dissolved in water before administration, as this would negate the purpose of the film coating.

**Response:** Comment not incorporated. The section has been removed.

### ***Tablets for Oral Solution and Tablets for Oral Suspension***

**Comment Summary #62:** The commenter suggested deleting the test “Dispersion fineness,” because this is not a relevant quality test and has little impact on the performance of the product in the patient.

**Response:** Comment not incorporated. Dispersion fineness is a necessary product quality test.

### ***Coated Tablets***

**Comment Summary #63:** The commenter requested deleting the following text:

“In addition, the disintegration test should be considered for the following dosage forms.

#### **EXTENDED-RELEASE TABLETS**

When disintegration is appropriate, suitable tests should be performed to demonstrate the appropriate release of the active substance. The test time points, generally three, are expressed in hours.

#### **DELAYED-RELEASE TABLETS**

When disintegration is appropriate, suitable tests should be performed to demonstrate the appropriate release of the active substance(s). The test includes an acid stage and a buffer stage. The test may be concluded in a shorter than prescribed time during the buffer stage if the requirement for minimum amount dissolved is met at an earlier time.”

This section appears to be imparting the properties of the Dissolution test to Disintegration. The Disintegration test is designed solely to monitor the physical properties of the tablet/capsule and not to assess the rate at which the active dissolves.

**Response:** Comment incorporated.

**Comment Summary #64:** The commenter requested replacing the sentence: “Tablets coated by sugar, film, or compression (modified release) include, but are not limited to: plain coated tablets, extended release tablets, and delayed-release tablets,” with “Tablets coated by sugar or film include, but are not limited to: immediate release coated tablets, extended release tablets, and delayed-release tablets,” because compression coating can be used for multiple purposes (i.e. improved stability).

**Response:** Comment incorporated with changes; however, “plain coated tablets” is the current terminology used in <701> and will remain in the section.

## **CAPSULES**

**Comment Summary #65:** The commenter indicated that liquid gels caps historically have been considered tablets by the FDA.

**Response:** Comment not incorporated because liquid gels caps are considered capsules by the FDA (example: Midol-Ibuprofen) and General Chapter <1151> provides a definition of Soft Gel Capsule.

**Comment Summary #66:** The commenter suggested replacing the sentence: “Two-piece capsules consist of two telescoping cap and body pieces in a range of standard sizes and are used to deliver solid material as powder, granules, or small tablets,” with “Two-piece capsules consist of two telescoping cap and body pieces in a range of standard sizes and are used to deliver solid material as powder, granules, semisolids, or small tablets,” because two-piece capsules can be used for liquid fill (liquid fill that often solidifies into a semisolid upon cooling).

**Response:** Comment not incorporated. Semisolids are covered in General Chapter <3> and the active is delivered as a solid.

**Comment Summary #67:** The commenter requested deleting the following text:

“In addition, the disintegration test should be considered for the following dosage forms.

### **MODIFIED-RELEASE CAPSULES**

Modified-release capsules include but are not limited to: delayed-release capsules and extended-release capsules.

### **DELAYED-RELEASE CAPSULES**

Disintegration: For capsules with an enteric coating, carry out the test for disintegration described in Uncoated Tablets with the following modifications: Use hydrochloric acid 0.1 M as the immersion fluid and operate the apparatus for 2 h or other time specified by the monograph, without the disks. Examine the state of the capsules. The time of resistance to the acid medium varies according to the formulation of the capsules. It is typically 2–3 h, but even with authorized deviations it must not be less than 1 h. No capsule shows signs of disintegration or rupture permitting the escape of the contents. Replace the acid with phosphate buffer solution pH 6.8. When justified and authorized, a buffer solution of pH 6.8 with added pancreatic powder can be used. Add a disk to each tube. Operate the apparatus for 60 min. Eighty-five percent of the drug should be dissolved in 60 min in pH 6.8 buffer solution. If the capsules fail to comply because of adherence to the disks, the results are invalid. Repeat the test on a further 6 capsules, omitting the disks.

### **EXTENDED-RELEASE CAPSULES**

When disintegration is appropriate, suitable tests should be performed to demonstrate the appropriate release of the active substance. The test time points, generally three, are expressed in hours. [NOTE—For information purposes only, refer to the proposed chapter

*Liquid-Filled Capsules—Dissolution Testing and Related Quality Attributes* <1094>, which may be a helpful, but not mandatory, resource.]”

This section appears to be imparting the properties of the dissolution test to disintegration. The disintegration test is designed solely to monitor the physical properties of the tablet/capsule and not to assess the rate at which the active dissolves. For such forms, the dissolution test is in most cases more appropriate.

**Response:** Comment incorporated.

## **GRANULES**

### ***Effervescent Granules***

**Comment Summary #68:** The commenter suggested deleting the disintegration test, because it is described as "dissolved or dispersed" and cannot be quantified.

**Response:** Comment incorporated.

### ***Coated granules, modified-release granules, and enteric coated Granules***

**Comment Summary #69:** The commenter requested deleting the text: "When disintegration is appropriate, suitable tests should be performed to demonstrate the appropriate release of the active substance," because it is in contradiction with <701> and implies that there needs to be a quantitative test.

**Response:** Comment incorporated.

## **MISCELLANEOUS**

### ***Lyophilized Oral Products***

**Comment Summary #70:** The commenter suggested clarifying the disintegration test, because such drugs may be either for direct application or a lyophilisate to be constituted with water to become an oral solution or suspension.

**Response:** Comment incorporated with changes. The disintegration test was removed from this dosage form.

**Comment Summary #71:** The commenter indicated that the disintegration test should specify that it does not apply to lyophilized vaccines. After reconstitution of lyophilized vaccine with the diluents (i.e., carbonate calcium suspension) a suspension is obtained. This disintegration test should apply to reconstituted solutions (for tablets, capsules, suppositories, etc.) and not to reconstituted suspensions. Moreover, this test is not required by the *European Pharmacopoeia* for lyophilized vaccines.

**Response:** Comment not incorporated. The test has been removed. The scope of the General Chapter was clarified as not being intended for biologics in solid dosage forms.

**Comment Summary #72:** The commenter suggested listing Water Content under the section for *Volatile Content* for consistency.

**Response:** Comment not incorporated. There is a specific reference to Method Ia of <921> *Water Determination* for this dosage form.

## **SPECIFIC TESTS FOR LIQUIDS**

**Comment Summary #73:** The commenter suggested changing the title to: "Specific Tests for Oral Drug Products: Liquid Dosage Forms" to improve clarity and consistency.

**Response:** Comment not incorporated. The title was changed to complement the new structure of the General Chapter.

**Comment Summary #74:** The commenter suggested replacing the sentence: "For example, weight variation may be used when the underlying distribution of the active

substance(s) in the blend is presumed to be uniform and well controlled, as in solutions,” to “For example, weight variation may be used when adequacy of mix for the active substance(s) and excipients in the blend is well controlled to ensure their uniform distribution, as in solutions.” for clarity.

**Response:** Comment incorporated.

**Comment Summary #75:** The commenter suggested adding a section on antioxidants that includes information consistent with ICH Guidance Q6C.

**Response:** Comment incorporated.

**Expert Committee-initiated Change #1:** The Expert Committee added a section titled *Extractables* that includes information consistent with ICH Guidance Q6C.

### ***Alcohol Determination***

**Comment Summary #76:** The commenter suggested replacing the sentence: “If the liquid formulation contains a quantity of alcohol, *Alcohol Determination* <611> should be included. The limits may be an absolute concentration...” with “Compliance check of the formula could be ensured by verification of the quantity engaged of alcohol within the batch formula.” This test could be replaced by the quantity engaged in the manufacturing or theoretical value as reported in the composition of the finished product.

**Response:** Comment not incorporated. There are several alternatives for reporting the alcohol content: absolute concentration, in percentage, or relative to a labelled content.

### ***pH***

**Comment Summary #77:** The commenter suggested clarifying the term "*Patient Compliance*," as this requirement is ambiguous.

**Response:** Comment not incorporated. The term “Patient Compliance” was deleted.

**Comment Summary #78:** The commenter suggested adding the following statement or note to the text: “The uptake of atmospheric CO<sub>2</sub> and pH change of oral liquid products is only relevant to aqueous based products,” because this requirement is not applicable to some oil based products.

**Response:** Comment incorporated.

### ***Microbial Content***

**Comment Summary #79:** The commenter suggested adding information on antimicrobial preservative content in line with ICH Guidance Q6C.

**Response:** Comment not incorporated. The microbial content is already considered and referred to in the monograph. Antimicrobial preservative testing is not a routine product quality test.

**Comment Summary #80:** The commenter suggested rewording the sentence: “Some liquid oral products can be subject to extreme microbiological control,” for clarity, regarding the reference to “extreme.”

**Response:** Comment not incorporated. The context is clear when considering the complete sentence: “Some liquid oral products can be subject to extreme microbiological control, and others require none.”

## **Syrups**

**Comment Summary #81:** The commenter suggested that the description of syrups be broadened to include "thick viscous liquid solutions" as formulations move away from using high concentrations of sucrose or other sugars.

**Response:** Comment not incorporated. The description of syrups was removed.

## **Powders and Granules for Syrups and Powders for Oral Drops**

**Comment Summary #82:** The commenter suggested replacing the sentence: "Tests that are specific to powders and granules for reconstitution include volatile content..." with "Volatile content may be an additional quality test for powders and granules," because volatile content should only be performed if necessary, based on the results of a risk assessment.

**Response:** Comment incorporated.

**General Chapter/Section(s):** <41> Balances/Multiple Sections

**Expert Committee(s):** General Chapters—Physical analysis

**No. of Commenters:** 10

## **Introduction**

**Comment Summary #1:** The commenter proposed that the requirements for balance repeatability and accuracy be combined to form a comprehensive requirement for the uncertainty (0.14%) of the weighing results.

**Response:** Comment not incorporated. Two alternative acceptance criteria would be allowed instead of one (each of the two properties smaller than 0.10%; alternatively combinations smaller than 0.14%), which could trigger questions and ambiguities. Furthermore, combined uncertainties are first and foremost absolute numbers calculated from the individual (absolute) uncertainties, and only at the end of the calculation, a relative uncertainty can be derived. From a practical point of view, it is easy to achieve an accuracy of much less than 0.10%, thus in practice most companies would be able to have a less tight repeatability requirement (close to 0.14%), which was not the intention of the Weight and Balances Expert Panel.

**Comment Summary #2:** The commenter indicated that "Trueness" is an ISO VIM term, which is correct in its context, but the terminology is not defined within the General Chapter. It is recommended to omit the term to avoid confusion.

**Response:** Comment incorporated.

**Comment Summary #3:** The commenter indicated that the statement: "For balances used for other applications, the balance repeatability and accuracy should be commensurate with the requirements for its use" is sufficiently addressed in the GxPs and does not need to be included in <41>.

**Response:** Comment not incorporated. It was the intention of the Weight and Balances Expert Panel that advised the Expert Committee to highlight the need for repeatability/accuracy requirements for all weighing instruments.

**Comment Summary #4:** The commenter suggested using the word "shall" instead of "should" in the sentence: "Unless otherwise specified, when substances must be "accurately weighed", the weighing should be performed using a calibrated balance that

meets the requirements defined for repeatability and accuracy [...]", to confirm that this is a mandatory requirement.

**Response:** Comment incorporated.

### ***Repeatability***

**Comment Summary #5:** Several commenters indicated that it is unclear how to use the "0.41*d*" in calculations.

**Response:** Comment incorporated.

**Comment Summary #6:** The commenter suggested that the weight for testing repeatability should be equal to or smaller than 5% of balance capacity to ensure that the acceptance criteria, which is expressed as a percentage of that weight (0.10%), has significance. Otherwise a pass against this requirement could be generated by simply lifting the test weight used.

**Response:** Comment not incorporated. The General Chapter states that the test weight must be within the balance's operating range.

### ***Accuracy***

**Comment Summary # 7:** The commenter indicated that the approach in *NIST Handbook 44*, states that the percent difference criteria between the weighing value and the test weight value is based on the balance's readability and the weight of the test load being used.

**Response:** Comment not incorporated. USP defines accuracy requirements that are appropriate for weighings within the scope of <41> (0.10%). *NIST Handbook 44* stipulates other criteria that are applicable for weighings within the scope of *Handbook 44* ("legal metrology") and which are not necessarily applicable for <41>.

**Comment Summary #8:** The commenter suggested that more than one weight is required to verify the accuracy of the full balance range. Additional information is needed in order to practically address the accuracy of a balance through its full range.

**Response:** Comment incorporated.

**Comment Summary #9:** The commenter indicated that testing between 5% and 100% of a balance capacity effectively eliminates use of the balance in the range below 5% of capacity for USP applications.

**Response:** Comment not incorporated. A "calibrated balance" is required to be used for USP <41> weighings, and a formal calibration of an appropriate weighing range ensures that the balance can also be used below 5% of the capacity. It is not within the scope of <41> to provide further detail on a generic calibration procedure.

**Comment Summary #10:** The commenter indicated that the *Accuracy* section is unclear on the weight range to be used. It states a range of 5-100% of balance capacity, but then also seems to imply that other weights can be used by stating, "alternatively, if the certified value of the test weight is considered, a test weight is suitable if its calibration uncertainty is NMT one-third of the applied test limit of the accuracy test."

**Response:** Comment incorporated.

**Comment Summary #11:** The commenter indicated that the range for the sample weight should take into consideration the intended use of the balance, as the typical analytical weights and weighing vessels are not expected at 100% of the balance capacity.

**Response:** Comment not incorporated. A "calibrated balance" is required to be used for USP <41> weighings, and a formal calibration of an appropriate weighing range ensures that the balance can also be used below 5% of the capacity. It is not within the scope of <41> to further detail on a generic calibration procedure.

**Expert Panel-initiated Change #1:** In the *Repeatability* section the term "operating range" is used instead of "balance's capacity." The use of the term "operating range" makes evident to the user that calibration ensures that the balance can be used at the working point, if it additionally fulfills the requirements on repeatability and accuracy, even though repeatability and accuracy might be tested with test weights different from the working point of the instrument.

**General Chapter/Section(s):** <401> Fats and Fixed Oils/Omega-3 Fatty Acids Determination and Profile  
**Expert Committee(s):** General Chapters—Chemical Analysis  
**No. of Commenters:** 2

**Comment Summary #1:** The commenter suggested that the adjustment to split ratio and/or sample dilution to obtain a tailing factor of 0.8–1.5 should also be applied to the System Suitability Solution 1.

**Response:** Comment incorporated.

**Comment Summary #2:** The commenter suggested replacing the theoretical area percent in Table 8 with the theoretical relative correcting factors, because this would have no effect on the final results, but would make the calculation more understandable for the users.

**Response:** Comment not incorporated. If the theoretical area percents are replaced with the relative correcting factors in Table 8, users would be required to perform extra steps in the calculation to get the final results.

**Comment Summary #3:** The commenter suggested replacing methyl tricosanoate with tritricosanoate (TG C23:0) as the internal standard for triglyceride oil based samples.

**Response:** Comment not incorporated. There are no advantages of using tritricosanoate over methyl tricosanoate as the internal standard. In addition, methyl tricosanoate also is currently used as the internal standard for triglyceride oil based samples by *Ph.Eur.*

**Comment Summary #4:** The commenter proposed replacing methyl tricosanoate with 1,2-ditricosanoyl-sn-glycero-3-phosphatidylcholine (23:0 PC) as the internal standard for phospholipid oil based samples.

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

**General Chapter/Section(s):** <698> Deliverable Volume/Multiple Sections  
**Expert Committee(s):** General Chapters—Dosage Forms  
**No. of Commenters:** 5

### **Scope**

**Comment Summary #1:** The commenter recommended incorporation of a standard for the number of individual doses delivered from multiple-unit containers. The commenter indicated that multiple-unit containers are intended to deliver a number of individual doses. The entire contents of such containers typically are not delivered at one time.

**Response:** Comment not incorporated. The Expert Committee determined that the recommended change would alter the scope of the General Chapter. A standard for uniformity of delivered dose from oral liquid products is part of the Work Plan of the Expert Committee and is under investigation.

**Comment Summary #2:** The commenters recommended incorporation of a specific procedure for products with flow restrictors. Liquid oral products with Press In Bottle Adapters (PIBA) or flow restrictors are specifically designed to prevent the unintended delivery of the container contents in a short time. Products in such containers are dispensed with the use of an oral syringe or by squeezing the container. The procedures used to evaluate delivered volume are directed at products without flow restrictors.

**Response:** Comment incorporated with changes. The Expert Committee modified the text under Scope to clarify that the test is only intended to apply to products that are dispensed by pouring from the container.

### ***Density Determination***

**Comment Summary #1:** The commenter recommended incorporation of the possibility of air entrainment due to shaking the oral liquid.

**Response:** Comment incorporated.

**Comment Summary #2:** The commenter recommended that the use of a pycnometer be specifically incorporated as an alternative procedure for density determination. Additionally, the commenter offered an alternative calculation of the density of an oral liquid product.

**Response:** Comment not incorporated. The Expert Committee noted that the use of alternative procedures is not forbidden and that the included procedure is only given as an example of possible approaches.

### ***Test Preparations***

**Comment Summary #1:** The commenters recommended incorporation of specific language for the shaking used to prepare the product for testing. The language should be appropriate for various types of preparations (such as viscous preparations) and should include the attributes of a suitably shaken test preparation (such as container contents are free of any sediment).

**Response:** Comment not incorporated. The Expert Committee found that additional specific instructions risk the appearance of an inflexible and overly comprehensive approach. The test preparation should reflect the instructions on the product labeling.

### **Procedure**

**Comment Summary #1:** The commenter recommended incorporation of a statement to indicate that the instruction to support the container at a 30° angle to the horizontal is an alternative and that the procedure should mimic the behavior of the consumer who might invert the depleted container to obtain as much of the contents as possible.

**Response:** Comment incorporated.

**Comment Summary #2:** The commenter requested the replacement of the word “pour” with the word “discharge” in the by-volume procedure in this section. The change would bring the wording of the by-volume procedure into alignment with the wording in the by-weight procedure in this section.

**Response:** Comment incorporated.

**General Chapter/Section(s):** <1030> Biological Assay Chapters—Overview and Glossary/Multiple Sections

**Expert Committee:** Statistics

**No. of Commenters:** 2

### **General Terms Related to Bioassays**

**Comment Summary #1:** The commenter stated that the two sentences in Note 4 of the definition of *Similar preparations (Similarity)* are redundant and suggested deleting or rephrasing the second sentence to include further detail.

**Response:** Comment incorporated by clarifying this entire section. One section is still called *Similar preparations* and has been revised to incorporate the suggestion and a new section *Similarity (algebraic)* has been created. The second sentence of the original Note 4 beginning with “To demonstrate...” is now modified and is Note 2 of *Similarity (algebraic)*.

### **Terms Related to Validation**

**Comment Summary #2:** The commenter stated that the definition of *Dilutional linearity* does not need to be restricted to only “Log” relative potency and suggested deleting “log” in two places in the definition sentence beginning, “The ability (within a given range)...”

**Response:** Comment incorporated.

**Comment Summary #3:** The commenter stated that Note 1 of *Dilutional linearity* does not need to be restricted to only “Log” relative potency and suggested deleting “log” in two places in the definition sentence beginning “To determine....”.

**Response:** Comment not incorporated. Working with log relative potencies is considered best statistical practice. Nearly all analyses of potency (combining, variation, trends, bias, etc.) should be done on log potency.

**Comment Summary #4:** The commenter indicated that the statements in *Validation, Assay* are very general and asked if this concept will be covered more

fully elsewhere. More explanation around validation parameters could be important to include for biological assays –especially for in vivo versus in vitro assays, which may have different requirements.

**Response:** Comment incorporated. The definition was edited and a reference to chapter <1033>, which contains further information on this topic, was added.

### ***Terms Related to Statistical Design and Analysis***

**Comment Summary #5:** The commenter requested addition of a sentence to the *Crossed (and partially crossed)* Note 4 to emphasize that the blocking factor typically is a source of variability that is of no interest. The interaction effect of the blocking factor and treatment factor is considered a random error.

**Response:** Comment incorporated by editing Note 1 of *Blocking* and adding the phrase “not of primary interest.” The Expert Committee agreed that an edit was needed, but thought it belonged in the over-arching *Blocking* section instead.

**Comment Summary #6:** The commenter requested that the statement, "Most relative potency bioassay measurements are log normally distributed" be deleted, because it really only applies to "log transformed" data. A *Lognormal distribution* is only considered "lognormal" if "logging" the values results in a "normal distribution." This is not two distinct definitions.

**Response:** Comment incorporated. The definition of lognormal distribution was revised in a manner consistent with this comment, using what had been Note 2, and a new Note 2 was also provided.

**Comment Summary #7:** The commenter suggested reducing the amount of comments regarding *Pseudoreplication* by deleting Notes 2-4.

**Response:** Comment partially incorporated by deleting Note 3, but Notes 2 and 4 (now Note 3) were kept because the Expert Committee believes they are useful.

**Comment Summary #8:** The commenter suggested deleting Note 3 and deleting three sentences in Note 2 of the *Randomization* notes, because randomization should not be “required” to control plate effects or systemic bias.

**Response:** Comment incorporated. The Notes were rewritten to emphasize that randomization can help and is good practice, but it is not required.

**General Chapter/Section:** General Chapter <1059> Excipients  
Performance/Multiple Sections

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

**No. of Commenters:** 4

**Expert Committee-initiated Change #1:** To reflect the current titles of General Chapters <911> and <912>, the Expert Committee updated the titles from Newtonian Viscosity <911> and Non-Newtonian Rheology <912> to Viscosity–Capillary Viscometer Methods <911> and Rotational Rheometer Methods <912>, respectively, in different sections of this General Chapter.

***Tablets and Capsules, Functional Category: Diluent***

**Comment Summary #1:** The commenter recommended including “crystal form” to the list of physical properties that have a direct effect on diluent and formulation performance.

**Response:** Comment incorporated.

**Comment Summary #2:** The commenter stated it was not clear why microcrystalline cellulose or starch was termed multi-component, in the *Chemical Properties* subsection, and recommended including an example of an excipient that was a mixture of two or more components.

**Response:** Comment incorporated.

**Comment Summary #3:** The commenter indicated that a better term to describe “complex” would be “large molecular weight.”

**Response:** Comment not incorporated. The Expert Committee retained the term “complex.”

***Tablets and Capsules, Functional Category: Coloring Agent***

**Comment Summary #4:** The commenter suggested including the property of a coloring agent to protect photo-labile API in the *Definition* subsection.

**Response:** Comment incorporated. The Expert Committee substituted “photo-labile components of the dosage form” for “photo-labile API.”

**Comment Summary #5:** The commenter proposed including a general statement regarding the fact that there are specified allowable limits for dyes, which can vary by regulatory agency, and a statement that the daily and cumulative intake for a commercial product should be considered when developing products containing colorants.

**Response:** Comment incorporated.

***Tablets and Capsules, Functional Category: Capsule Shell***

**Comment Summary #6:** The commenter recommended revising a paragraph in the *Physical Properties* subsection that describes cross-linking of gelatin due to chemical exposure and environmental conditions. In addition, the commenter proposed including a statement that cross-linking slows in-vitro dissolution.

**Response:** Comment incorporated.

***Tablets and Capsules, Functional Category: Coating Agent***

**Comment Summary #7:** The commenter recommended including “taste masking” in the list of desirable pharmaceutical properties in the *Functional Mechanism—Film Coating* subsection.

**Response:** Comment incorporated.

***Tablets and Capsules, Functional Category: Plasticizers***

**Comment Summary #8:** The commenter pointed out that the same information about modern plasticizers being synthetic esters such as citrates and phthalates appeared in the *Description* and *Chemical Properties* subsections. The commenter suggested deleting this information from the *Description* subsection.

**Response:** Comment incorporated.

**Comment Summary #9:** The commenter questioned whether the statement in the *Functional Mechanism* subsection: “Plasticizers function by increasing the intermolecular and intramolecular mobility of the macromolecules that comprise polymeric materials” has been confirmed in polymer literature.

**Response:** Comment not incorporated. The Expert Committee responded that it is a well known and accepted fact.

***Tablets and Capsules, Functional Category: Film-forming Agent***

**Expert Committee-initiated Change #2:** The Expert Committee corrected the typo in the reference to a General Chapter from Microscopy <766> to Optical Microscopy <776>.

***Oral Liquids, Functional Category: Antioxidants***

**Comment Summary #10:** The commenter suggested deleting the phrase from the *Chemicals Properties* subsection, which stated that the safety limits of the antioxidants, throughout the dosage form's expected shelf life, depended on the antioxidant's function.

**Response:** Comment incorporated.

***Dry Powder Inhalers, Functional Category: Carrier***

**Comment Summary #11:** The commenter recommended adding “surface energy” to the list of physical properties of carriers.

**Response:** Comment incorporated.

***Parenterals, Functional Category: Pharmaceutical Waters***

**Comment Summary #12:** In the *Description* subsection, the commenter recommended using Water for Injection as the water of choice rather than Purified Water.

**Response:** Comment incorporated.

**Comment Summary #13:** The commenter suggested deleting a reference to oral solution, solid oral dosage forms, ointments, and gels in the *Description* subsection, because they are not considered parenterals.

**Response:** Comment incorporated.

***Parenterals, Functional Category: Bulking Agent***

**Comment Summary #14:** The commenter recommended a consistent use of the term “bulking agent” throughout the section, and that the term “bulking agent” should be substituted for “diluent” and “lyophilization diluent.”

**Response:** Comment incorporated.

***Parenterals, Functional Category: Tonicity Agent***

**Comment Summary #15:** The commenter recommended moving the calculations for tonicity from the *Chemical Properties* subsection to the *Physical Properties* subsection, because these calculations are based on physical properties of solutions. In addition, the commenter requested including a few sentences describing how sodium chloride equivalents are used to calculate

overall tonicity and the derivation and practical application of the equation for those who are not familiar with its use.

**Response:** Comment not incorporated. The Expert Committee deleted the example of the tonicity calculation based on the sodium chloride equivalent method because <1160> *Pharmaceutical Calculation in Prescription Compounding* and <785> *Osmolality and Osmolarity* have some guidance on this. The Expert Committee added <785> *Osmolality and Osmolarity* to the list of the General Chapters suitable for the tonicity section.

**Expert Committee-initiated Change #3:** The Expert Committee deleted the reference to <1151> *Pharmaceutical Dosage Forms* from the list of the General Chapters suitable for tonicity because the current revision of this General Chapter does not contain the *Ophthalmic Preparation* section.

**General Chapter/Section(s):** <1087> Apparent Intrinsic Dissolution—  
Dissolution Testing Procedures for Rotating Disk  
And Stationary Disk/Introduction

**Expert Committee(s):** General Chapters—Dosage Forms

**No. of Commenters:** 1

**Comment Summary #1:** The commenter recommended incorporation of wording that acknowledges that solid dispersions are not a common approach to modification of the physicochemical properties of chemical entities so that solubility and dissolution properties are enhanced. The commenter observed that the open literature does not support such a claim.

**Response:** Comment incorporated. The Expert Committee determined that the use of amorphous solid dispersions is among the investigational approaches that can be used to modify the chemical entity to enhance solubility and dissolution properties.

**General Chapter/Sections:** General Chapter <1104> Immunological Test  
Methods—Immunoblot Analysis/Multiple  
Sections

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

**No. of Commenters:** 3

### **Assay Selection**

**Comment Summary #1:** Two commenters requested that the choice of a radioactive method be removed from the *Electrophoresis Assay* subsection and *Table 1*.

**Response:** Comments not incorporated. This method is an option and the General Chapter describes the positive and negative aspects of this detection method to assist the reader with their choice.

**Comment Summary #2:** The commenter requested that the following sentence be added after the sentence starting “A number of blocking agents...” within the *Blocking Reagents* subsection: “Proteins should be unrelated to the antigens used in the study.”

**Response:** Comment incorporated.

**Comment Summary #3:** The commenter requested addition of a statement to the *Primary Antibody* sub-subsection within the *Methods of Detection* subsection, stating that monoclonal antibodies are preferred, because polyclonal antibodies may be difficult to reproduce leading to difficulties qualifying new lots.

**Response:** Comment incorporated.

### ***Method Development***

The commenter suggested that the text be modified to reflect that mass spectrometry methods are preferred for identity testing over ELISAs and other immunological methods, particularly for adjuvanted methods.

**Response:** Comment not incorporated. Mass spectrometry is not preferred by all laboratories, and because this General Chapter is focused on immunological test methods the comment is outside the scope of the general chapter.

### ***Procedures***

**Comment Summary #5:** The commenter stated that the temperature and timing for denaturing samples is evaluated during development and the 95-100° for 5 minutes proposed in the chapter text (see the *Electrophoresis* subsection) is not always appropriate.

**Response:** Comment incorporated by modifying the sentence to make these conditions an example since it is common but not required. Sentence now reads: "...analysts denature samples (e.g., heat at 95-100° for 5 min)."

### ***Method Validation***

**Comment Summary #6:** A commenter stated that in ICH Q2R1 limit tests require LOD and specificity, but not LOQ, and therefore requested deletion of LOQ in the sentence.

**Response:** Comment incorporated.

**Comment Summary #7:** A commenter suggested development of an informational general chapter for robustness testing, because it is required for quantitative tests.

**Response:** Comment not incorporated. Robustness testing is applicable to this General Chapter; however, the comment was shared with other Expert Committees focusing on these topics.

**General Chapter/Sections:** General Chapter <1229.3> Monitoring of Bioburden

**Expert Committee:** General Chapters—Microbiology

**No. of Commenters:** 6

**Comment Summary #1:** The commenter suggested adding a statement indicating that AAMI/ISO 11737 provides guidance for establishing methods to estimate bioburden levels on medical devices prior to irradiation to the Radiation section

**Response:** Comment incorporated.

**Comment Summary #2:** The commenter suggested enlarging Figure 1 to make it more legible.

**Response:** Comment incorporated.

**Comment Summary #3:** The commenter suggested revising the part of the *Monitoring and Sampling* section that includes a list of physical parameters of a product that can diminish the viability of microorganisms.

**Response:** Comment incorporated.

**Comment Summary #4:** The commenter suggested the addition of objectionable microorganisms to the figure.

**Response:** Comment not incorporated. These microorganisms have limited resistance and thus are largely irrelevant in a general chapter focused on the sterilization processes.

**Comment Summary #5:** The commenter suggested establishing limits in Figure 1 on a container basis.

**Response:** Comment incorporated.

**Comment Summary #6:** The commenter suggested inserting the sentence, “Bioburden within products subjected to radiation processes are evaluated as part of dose setting activities and is explained in the Radiation section that follows.”

**Response:** Comment incorporated.

**Comment Summary #7:** The commenter suggested including text to indicate that monitoring of in-process Bioburden of pharmaceutical components and products is essential.

**Response:** Comment incorporated.

**Comment Summary #8:** The commenter suggested including “holding times” in the bullet point, “Time limits for process execution” in the Bioburden Control section.

**Response:** Comment not incorporated. Hold times are included in this context.

**Comment Summary #9:** Commenter suggested including text on bioburden consideration and monitoring control when establishing New Sterilization Processes.

**Response:** Comment incorporated.

**Comment Summary #10:** The commenter suggested replacing the term “total heterotrophic count with a more general term such as “total microbial count.”

**Response:** Comment incorporated.

**Comment Summary #11:** The commenter suggested deleting the term “seasonality of the bioburden.”

**Response:** Comment incorporated.

**Comment Summary #12:** The commenter suggested adding the rationale that is used in dual filtration setup for sterilizing filtration and risk associated with filter penetration.

**Response:** Comment incorporated.

**Comment Summary #13:** The commenter suggested clarifying that the General Chapter is guidance on bioburden in sterilization processes, and not guidance for non-sterile production.

**Response:** Comment not incorporated. This chapter is a part of <1229> series, and therefore only deals with sterilization processes.

**Comment Summary #14:** The commenter suggested changing the title of *Bioburden Screening* sub-section, because it does not cover non-  $VD_{max}$  radiation.

**Response:** Comment not incorporated.  $VD_{max}$  radiation is used for bioburden screening in all radiation sterilization validation methods.

**Comment Summary #15:** The commenter indicated that the text provides no distinction for product specific and overkill design processes.

**Response:** Comment not incorporated. The Expert Committee determined that no such distinction was warranted.

**Comment Summary #16:** The commenter indicated that the completion of risk assessment is a new pharmacopeial requirement and is prescriptive.

**Response:** Comment not incorporated. The Expert Committee finds risk assessment to be best practice and the General Chapter is intended to be informational unless specifically called out for application.

**Monograph or General Chapter/Section(s):** <1251> Weighing on an Analytical Balance/Multiple Sections

**Expert Committee(s):** General Chapters—Physical analysis

**No. of Commenters:** 8

### ***Introduction***

**Comment Summary #1:** A commenter indicated chapter <1251> should present only weighing techniques, checks, and aspects of operation that are relevant to analytical balance use.

**Response:** Comment not incorporated. Prerequisite for weighing is also a proper qualification, and the content of General Chapter <1251> is necessary to allow for proper weighing.

**Comment Summary #2:** The commenter indicated that balance manufacturers are not equivalent to independent authoritative bodies such as NIST and ASTM, nor can they be considered unbiased entities.

**Response:** Comment not incorporated. The user's manual of a balance provides necessary information about IQ/OQ (e.g., warm-up time) that needs to be considered.

### ***Qualification***

**Comment Summary #3:** Several commenters indicated that a calibration program fulfills all IQ/OQ/PQ requirements for the typical stand-alone laboratory balance.

Qualification of these balances is not required based on their application as non-networked, non-automated devices that indicate, but do not store or process data.

**Response:** Comment not incorporated. Qualification is required for any instrument, but the depth of qualification depends on the instrument, the application, and the risk, among other factors. General Chapter<1251> describes standard procedures that need to be routinely done, such as control of mechanical movability of parts. The official process of calibrating a non-automatic weighing instrument comprises the determination of the measurement uncertainty (also in relation to ISO/IEC 17025). Because this

General Chapter is not intended to describe how measurement uncertainty is assessed, the word calibration should not be used in the title.

**Comment Summary #4:** A commenter indicated that further clarifications may be needed under *Performance Qualification* regarding how the tolerance budget is distributed among all the balance properties.

**Response:** Comment incorporated.

**Comment Summary #5:** The commenter proposed to allow the use of two weights for the *Performance qualification* test. This would allow checking the performance of a balance as close as possible to the weights measured in routine.

**Response:** Comment incorporated.

**Comment Summary #6:** A commenter indicated that under *Performance Qualification*, the nominal weight value of the test weights should only be used for class 1 high precision balances.

**Response:** Comment not incorporated. Users should decide whether they utilize the nominal or the conventional mass, as long as the 1/3 criterion is fulfilled (weight m.p.e. or uncertainty must be smaller than 1/3 of the acceptance criterion). This is already written in General Chapter <41>.

**Comment Summary #7:** A commenter suggested adding, under *Performance qualification*, the phrase: "If more than one weight is used to perform the test, the calibration uncertainties of the weights must be summed and the sum should not exceed one-third of the acceptance criterion."

**Response:** Comment incorporated.

**Comment Summary #8:** A commenter proposed that the title of the table be changed to "*Suggested performance tests and acceptance criteria*."

**Response:** Comment incorporated.

**Comment Summary #9:** A commenter suggested that it would be more efficient if Table 1 presented the different tests in the same order as in a Performance Qualification session (i.e.: repeatability, sensitivity, eccentricity, then linearity).

**Response:** Comment not incorporated. Based on the user's decision of which properties are selected to be assessed for performance qualification, all of them need to be assessed, with the order not playing a substantial role.

**Comment Summary #10:** A commenter indicated that in Table 1 Sensitivity is defined as a slope, ideal value 1; however, in the second sentence, sensitivity can be "expressed as" a number in mass units, ideal value 0.

**Response:** Comment incorporated.

**Comment Summary #11:** A commenter suggested modification of the last sentence of the text in Table 1, under *eccentricity* to align it with OIML R76 and HB44.

**Response:** Comment incorporated.

**Comment Summary #12:** The commenter proposed to revise the weight value used for the test to align with Section 5.3 of Guidelines on the Calibration of Non-Automatic Weighing Instruments, Euramet cg-18 Version 3.0 03/2011, under Table 1-Eccentricity.

**Response:** Comment incorporated.

**Comment Summary #13:** The commenter suggested allowing the use of six replicates for industrial scale balances for Table 1, Repeatability,

**Response:** Comment not incorporated. Industrial scales are outside the scope of the General Chapter.

**Comment Summary #14:** A commenter suggested changing the section title "Balance checks" to "Balance routine tests."

**Response:** Comment not incorporated. The word "routine tests" could be misinterpreted as tests described within the PQ section.. In the existing text of General Chapter <1251> a balance check clearly refers to a test with a single test weight (either internal or external) and thus it cannot be confounded with tests described in the PQ section.

**Comment Summary #15:** A commenter suggested applying requirements of General Chapter <41> Weights and Balances to the balance check.

**Response:** Comment not incorporated. General Chapter <1251> allocates 50% of the accuracy budget to a single property. A balance check essentially is a sensitivity test, and is not a full accuracy test.

**Comment Summary #16:** The commenter indicated that balance users have requested an example of the "partial" replacement of external checks with adjustment via internal weights, as it is mentioned under *Balance checks*.

**Response:** Comment not incorporated. The Weight and Balances Expert Panel deliberately refrained from providing an example as this might be seen by users as preferred choice and thus might prevent users from thinking about other options. This statement is intended to be in alignment with current FDA thinking.

**Comment Summary #17:** A commenter recommended that the value for minimum weight obtained using the calculations be physically tested.

**Response:** Comment not incorporated. Although this can be done, it may not be necessary. As a general rule, the weight of the net sample weight must be larger than the minimum weight.

**Comment Summary #18:** A commenter indicated that minimum weight is a measure of standard deviation and yet is being applied in this instance to confirm accurate weighing or trueness. There is an inherent high variability associated with the minimum weight value (due to equipment, operator, and environment). As this test is simplified by using a balance weight and not a sample, this minimum weight value also does not take into account any special characteristics of a sample that will be encountered during routine laboratory use. Given the total error associated with weighing, and additional errors associated with sample extraction, detection, and quantitation, where applicable, the tolerance of 0.10% seems overly stringent as a baseline for accurate weighing when one considers acceptance criteria for finished goods.

**Response:** Comment not incorporated. It is the intention of the Expert Committee to have a stringent repeatability requirement in order to allow not taking into account the weighing error when determining the error of a whole analysis chain. The minimum weight will not be influenced by the new requirement as the more stringent 0.10% is compensated for by the changed coverage factor  $k=2$ .

**Comment Summary #19:** A commenter suggested that the Minimum Weight Test indicate the frequency of the determination of minimum weight

**Response:** Comment not incorporated. It is not the intention of the Expert Committee to provide the frequency for this test. This should be handled under each organization's SOPs or other internal procedures.

**Comment Summary #20:** A commenter indicated that the Minimum Weight Test does not need to be performed for balances that are always used above 2% of their range. The test should be optional based on a company's use of the balance

**Response:** Comment not incorporated. It is stated under Performance Qualification: "Depending on the risk of the application and the required weighing process tolerance, some of these tests may be omitted."

### ***Operation of the Analytical Balance***

**Comment Summary #21:** The commenter suggested emphasizing the importance of good analytical technique, receiver size and weight, and weighing method to ensure accurate weighing.

**Response:** Comment not incorporated. The section "Operation of the Analytical Balance" sufficiently addresses this issue.

**Comment Summary #22:** The commenter suggested removing the word "topical," because the term "topical ointments" rarely is used.

**Response:** Comment incorporated.

**Comment Summary #23:** A commenter suggested removing the references to radioactive materials, because the use of radioactive elements is forbidden or restricted in most countries.

**Response:** Comment not incorporated. The chapter provides other options if the use of radioactive material for this purpose is forbidden in a particular country,

**Expert Panel-initiated Change #1:** The use of properly qualified third-party vendors as calibration technicians was allowed.

**General Chapter/Sections:** <1660> Evaluation of the Inner Surface Durability of Glass Containers/Multiple Sections

**Expert Committee(s):** General Chapters—Packaging, Storage & Distribution

**No. of Commenters:** 18

### ***Purpose***

**Comment Summary #1:** The commenter suggested adding text that would help the converter or user predict the potential of the container to delaminate.

**Response:** Comment Incorporated.

### ***Scope***

**Comment Summary #2:** The commenter requested clarifying that the chapter addresses bottles and vials manufactured only by molding.

**Response:** Comment not incorporated. The Expert Committee believes that the General Chapter can be broadly applied.

**Comment Summary #3:** The commenter suggested including Type II and III glass to the focus of the General Chapter.

**Response:** Comment incorporated.

**Comment Summary #4:** The commenter suggested expanding the focus beyond just the biopharmaceutical industry to include the pharmaceutical industry.

**Response:** Comment incorporated.

**Comment Summary #5:** The commenter suggested expanding the General Chapter to include the use of contract manufacturing and filling organizations.

**Response:** Comment incorporated.

**Comment Summary #6:** The commenter suggested adding text stating that accelerated treatment of sample still can be used to predict the delamination propensity of a vial lot.

**Response:** Comment incorporated.

**Comment Summary #7:** The commenter suggested revising the text to note that glass delamination is not specific to parenteral products.

**Response:** Comment incorporated.

**Comment Summary #8:** The commenter requested that the term “glass corrosion” or “glass degradation” be used instead of “glass delamination.”

**Response:** Comment not incorporated. Delamination is a term accepted by FDA and industry. It is not the same as glass particles.

**Comment Summary #9:** The commenter requested that the term “fall in pH” be changed to “change in pH”.

**Response:** Comment incorporated.

**Comment Summary #10:** The commenter recommended adding clarifying text specifying who should conduct predictive tests.

**Response:** Comment incorporated.

### ***Glass Type***

**Comment Summary #11:** The commenter suggested adding text to the section to note Type II and III glass can be impacted by glass delamination.

**Response:** Comment incorporated.

**Comment Summary #12:** The commenter suggested that a correction be made to the coefficient of expansion value for soda-lime glass, which should be “8 – 10.”

**Response:** Comment incorporated.

**Comment Summary #13:** The commenter requested a change to the Type I silica range from 70-80% to 65-80%, because the aforementioned is not correct.

**Response:** Comment incorporated.

### ***Formation of Molded and Tubing Glass Containers***

**Comment Summary #14:** The commenter suggested changing the word “tube” to “tubular” in the heading of the section because it is the most accurate.

**Response:** Comment incorporated.

**Comment Summary #15:** The commenter recommended adding text stating sterilization of filled vials significantly influences vial shelf life and the probability of glass particle formation.

**Response:** Comment incorporated.

**Comment Summary #16:** The commenter recommended removing the statement that Type I glass with pure silica improves the container's durability, because it is not supported by data.

**Response:** Comment not incorporated. There is data to support this statement.

**Comment Summary #17:** The commenter recommended revising the statement that containers are exposed to a temperature of approx. 570°C after forming, because this is not true for all containers.

**Response:** Comment incorporated.

**Comment Summary #18:** The commenter recommended adding the temperature ranges to Table 1.

**Response:** Comment incorporated.

**Comment Summary #19:** The commenter suggested removing the general information on delamination, to make it more streamlined.

**Response:** Comment not incorporated. Expert Committee believes the details are required for understanding delamination.

**Comment Summary #20:** The commenter suggested that the wording "aggressive liquid for a parenteral solution" is misleading and should be removed or revised.

**Response:** Comment not incorporated. The Expert Committee needs clarification of this comment before being able to respond.

**Comment Summary #21:** The commenter suggested clarifying whether temperature treatment includes depyrogenation.

**Response:** Comment incorporated.

**Comment Summary #22:** The commenter recommended adding a statement that sulfur treatment was neutral to delamination under the conditions studied.

**Response:** Comment incorporated.

**Comment Summary #23:** The commenter recommended adding language about the impact of environmental storage conditions at the glass manufacturer.

**Response:** Comment incorporated.

### ***Good Glass Supply-Chain Practices***

**Comment Summary #24:** The commenter recommended revising the section heading to better reflect the content.

**Response:** Comment incorporated. The heading was changed to "Glass Container Sourcing."

**Comment Summary #25:** The commenter suggested discussing the importance of early collaborations of glass and product manufacturing, which leads to process and product understanding and lifecycle quality management.

**Response:** Comment incorporated.

**Comment Summary #26:** The commenter suggested discussing the importance of user knowledge of the glass manufacturing process and glass composition to qualify.

**Response:** Comment incorporated.

### ***Glass Surface Chemistry***

**Comment Summary #27:** The commenter recommended deleting equation 3 or 4, because they are the same.

**Response:** Comment incorporated.

### ***Factors that Influence Inner Surface Durability***

**Comment Summary #28:** The commenter recommends revising the list in the table to note that these items do not cause delamination.

**Response:** Comment incorporated.

**Comment Summary #29:** The commenter recommends adding washing and depyrogenation to the list in the table.

**Response:** Comment incorporated.

**Comment Summary #30:** The commenter suggested adding more background information to explain how factors in Table 2 chemically or physically degrade the glass surface.

**Response:** Comment incorporated.

### ***Screening Methods to Evaluate Inner Surface Durability***

**Comment Summary #31:** The commenter recommended revising the section heading to better reflect the content.

**Response:** Comment incorporated. The heading was changed to “Evaluation of the Inner Surface Durability.”

**Comment Summary #32:** The commenter suggested replacing the words “glass particles” with “glass lamellae,” to prevent any industry confusion

**Response:** Comment incorporated.

### ***Predictive Screening Methods***

**Comment Summary #33:** The commenter requested the tests be more precise and specification added.

**Response:** Comment not incorporated. General Chapter <1660> is an informational general chapter and is not meant to contain detailed methods and specifications.

**Comment Summary #34:** The commenter requested adding information about the correlation between predictive tests and the actual appearance of flakes.

**Response:** Comment incorporated.

**Comment Summary #35:** The commenter requested clarification within Table 3 to differentiate the analytical method from its corresponding test parameter.

**Response:** Comment incorporated.

**Comment Summary #36:** The commenter recommended adding information on the applicability of the analytical method at the different processing stages.

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

**Comment Summary #37:** The commenter recommended mentioning the use of visual inspection for the detection of visible glass lamellae.

**Response:** Comment incorporated.

### ***Aggressive Screening Conditions***

**Comment Summary #38:** The commenter recommended adding more specific experimental conditions to the section.

**Response:** Comment not incorporated. Experimental conditions are determined by the manufacturer.

**Comment Summary #39:** The commenter suggested including mechanical stress test as a testing option.

**Response:** Comment not incorporated. The Expert Committee needs clarification of this comment before being able to respond.

**Comment Summary #40:** The commenter suggested excluding the example at 30°C and to replace the text with “the most appropriate accelerated stress conditions should be stated (or refer to ICH).”

**Response:** Comment incorporated.

### ***Screening Strategy for Drug Products***

**Comment Summary #41:** The commenter recommended adding specific experimental conditions to Table 5.

**Response:** Comment not incorporated. Experimental conditions are determined by the manufacturer.

### **Monographs:**

**Monograph/Sections:** Aminobenzoic Acid/Limit of Aniline and *p*-Toluidine

**Expert Committee:** Monographs—Small Molecules 3

**Expert Committee-initiated Change #1:** The equation is revised to determine the result in ppm rather than in percentage to be consistent with the *Acceptance criteria*.

**Monograph/Sections:** Ampicillin Capsules/Multiple Sections

**Expert Committee:** Monographs—Small Molecules 1

**No. of Commenters:** 1

**Comment Summary #1:** The commenter requested revising the *Dissolution* test to replace the procedure for a pooled sample with a method that involves testing of individual units.

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

**Expert Committee Initiated Change #1:** The definition for the variable “*I*” in the Assay calculation was revised to indicate that this term represents the volume of titrant consumed by the *Inactivation and Titration of the Sample solution*.

**Monograph/Sections:** Ampicillin Tablets/Multiple Sections

**Expert Committee:** Monographs—Small Molecules 1

**No. of Commenters:** 1

**Comment Summary #1:** The commenter requested revising the *Dissolution* test to replace the procedure for a pooled sample with a method that involves testing of individual units.

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

**Expert Committee Initiated Change #1:** The definition for the variable “*P*” in the Assay calculation was revised to indicate that this term represents the volume of titrant consumed by the *Inactivation and Titration* of the *Sample solution*.

**Monograph/Sections:** Atomoxetine Capsules/Multiple Sections

**Expert Committee:** Monographs—Small Molecules 4

**No. of Commenters:** 4

**Comment Summary #1:** The commenter requested allowing the evaporation of the *Sample* in *Identification* test *A* to be done using a stream of air.

**Response:** Comment incorporated.

**Comment Summary #2:** The commenter requested revising the text in *Identification* test *A* from “(±1)” to “(±5)” in the phrase “IR spectrum exhibits main bands at or near (±1) wavenumbers (cm<sup>-1</sup>)”.

**Response:** Comment not incorporated. The specified band at 1603 wavenumbers (cm<sup>-1</sup>) has been replaced with a range of wavenumbers: 1599-1604. Additionally, the phrase has been revised to “IR spectrum exhibits main bands at (±2) wavenumbers (cm<sup>-1</sup>)”.

**Comment Summary #3:** The commenter requested replacing the IR procedure in *Identification* test *A* with a UV procedure.

**Response:** Comment not incorporated. The Expert Committee will consider future revisions to the *Identification* section when appropriate.

**Comment Summary #4:** The commenter requested replacing the *Organic Impurities* procedure with a validated gradient HPLC procedure that is specific for all currently known impurities.

**Response:** Comment not incorporated. The Expert Committee will consider future revisions to the monograph when appropriate.

**Comment Summary #5:** The commenters requested including Dissolution Tests to support their products.

**Response:** Comment not incorporated. The Expert Committee will consider future revisions to the monograph when appropriate.

**Expert Committee-initiated Change #1:** The text of the *Standard* in *Identification* test *A* is revised to indicate that the solution is to be dried to a dry powder under an air or nitrogen purge for a minimum of 3 h for consistency with the preparation of the *Sample*.

**Monograph/Section:** Bethanechol Chloride/Organic Impurities

**Expert Committee:** Monographs—Small Molecules 4

**No. of Commenters:** 1

**Comment Summary #1:** The commenter requested tightening of the specification for “any individual unspecified impurity” to comply with what has been approved by the FDA.

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

**Monograph/Section:** Butyl Alcohol/Multiple Sections

**Expert Committee(s):** Monographs—Excipients

**No. of Commenters:** 1

**Comment Summary #1:** The commenter recommended specifying *Reference solution* in the *Assay* for clarity, deleting the term of wide bore for the GC column used, and providing detailed information for a needle wash.

**Response:** Comments incorporated.

**Expert Committee-initiated Change #1:** Subsequently, to accommodate the commenter's comments, the Expert Committee changed "**Sample:** *Sample solution*" to "**Samples:** *Reference solution* and *Sample solution*" in the *Analysis* section of the *Assay*.

**Expert Committee-initiated Change #2:** In the *Assay*, the Expert Committee changed "due to artifact and peaks below the *Disregard limit* (see *Table 4*)" to "each with an area less than 0.1 times the area of the major peak from the *Reference solution*" in the definition for  $r_T$  because the term for "Disregard limit" is not defined.

**Expert Committee-initiated Change #3:** In the *Limit of Butyraldehyde, 2-Butanol, Isobutyl Alcohol (2-Methyl-1-Propanol), and Butyl Ether*, the Expert Committee changed "**Disregard limit:** 0.1 times the area of the major peak in the chromatogram from the *Reference solution*, corresponding to 0.01%" to "Disregard any peak with an area less than 0.1 times the area of the major peak from the *Reference solution*, corresponding to 0.01%" because the term for "Disregard limit" is not defined.

**Monograph/Section(s):** Calcium 5-L-Methyltetrahydrofolate/Multiple Sections

**Expert Committee:** Monographs—Dietary Supplements

**No. of Commenters:** 1

**Comment Summary #1:** The commenter indicated that the Calcium 5-L-Methyltetrahydrofolate was incorrectly defined in the *Definition* section and suggested the following definition: "Calcium L-5-Methyltetrahydrofolate contains NLT 95.0% and NMT 102.0% of calcium 5-methyltetrahydrofolate (C<sub>20</sub>H<sub>23</sub>CaN<sub>7</sub>O<sub>7</sub>), sum of L-and D-diastereoisomer, calculated on anhydrous and solvent free basis, of which NMT 1.0% corresponds to calciumD-5-methyltetrahydrofolate."

**Response:** Comment incorporated.

**Comment Summary #2:** The commenter suggested adding to the test for *Identification C* the requirement of meeting the acceptance criteria in the test for *Enantiomeric Purity*.

**Response:** Comment incorporated.

**Comment Summary #3:** The commenter suggested changing wordings in the *Analysis* section of the *Assay* to reflect the suggested changes in the *Definition* section. The suggested text changes were as follows: "Calculate the percentage of calcium 5-methyltetrahydrofolate (C<sub>20</sub>H<sub>23</sub>CaN<sub>7</sub>O<sub>7</sub>), sum of L-and D-isomer, in the portion of Calcium L-5-Methyltetrahydrofolate..."

**Response:** Comment incorporated.

**Comment Summary #4:** The commenter indicated that their previously submitted chemical name for the USP Calcium 5-D,L-Methyltetrahydrofolate RS, *N*[4-[[[(6*R*,*S*)-2-Amino-1,4,5,6,7,8-hexahydro-5-methyl-4-oxo-6*R*,*S*-pteridinyl)methyl]amino]benzoyl]-*L*-glutamic acid, calcium salt was incorrect and submitted the correct name as follows: *N*[4-[[2-Amino-1,4,5,6,7,8-hexahydro-5-methyl-4-oxo-6-pteridinyl)methyl]amino]benzoyl]-*L*-glutamic acid, calcium salt (1:1).

**Response:** Comment incorporated.

**Monograph/Sections:** Capsicum/Contaminants, Elemental Impurities—Procedures <233>

**Expert Committee:** Monographs—Dietary Supplements and Herbal Medicines

**No. of Commenters:** 1

**Comment Summary #1:** The commenter requested that the specific requirements for elemental contaminants be removed from this monograph and be included only in the product monograph.

**Response:** Comment not incorporated. Given the literature suggesting that the elemental contamination may increase when this article is not processed in accordance with Good Agricultural Practices, the Expert Committee found it necessary to include limits for elemental contaminants in this ingredient monograph. The inclusion of limits for elemental contaminants is important to define the quality of this ingredient. In addition, there are no dosage forms for Capsicum in the *USP*.

**Comment Summary #2:** The commenter indicated that there is no justification for lower limits for mercury or cadmium compared to the limits in General Chapter <232>.

**Response:** Comment not incorporated. The Expert Committee determined that the available literature on the typical content of mercury and cadmium in Capsicum indicate that the lower limits are achievable for the elements in this ingredient, and higher levels of elemental contamination may indicate that the article is not processed in accordance with Good Agricultural Practices. The proposed levels are also consistent with requirements in *European Pharmacopoeia* standards for herbal drugs. In addition, there are no dosage forms for Capsicum in USP for application of General Chapter <232>.

**Comment Summary #3:** The commenter indicated that the monograph content for elemental impurities should follow the delayed implementation of General Chapters <232> *Elemental Impurities—Limits* and <233> *Elemental Impurities—Methods*.

**Response:** Comment not incorporated. The implementation of General Chapters <232> *Elemental Impurities—Limits* and <233> *Elemental Impurities—Procedures* through General Notices provision 5.60.30 is intended to apply common limits to all drug product monographs. The General Notice provision does not preclude monograph specific limits.

**Monograph/Sections:** Capsicum Oleoresin/Contaminants, Elemental Impurities—Procedures <233>

**Expert Committee:** Monographs—Dietary Supplements and Herbal Medicines

**No. of Commenters:** 1

**Comment Summary #1:** The commenter requested that the specific requirements for elemental contaminants be removed from this monograph and be included only in the product monograph.

**Response:** Comment not incorporated. Given the literature suggesting that the elemental contamination may increase when this article is not processed in accordance with Good Agricultural Practices, the Expert Committee found it necessary to include limits for elemental contaminants in this ingredient monograph. The inclusion of limits for elemental contaminants is important to define the quality of this ingredient. In addition, there are no dosage forms for Capsicum Oleoresin in the *USP*.

**Comment Summary #2:** The commenter indicated that there is no justification for lower limits for mercury or cadmium compared to the limits in General Chapter <232>.

**Response:** Comment not incorporated. The Expert Committee determined that the available literature on the typical content of mercury and cadmium in Capsicum Oleoresin indicate that the lower limits are achievable for the elements in this ingredient, and higher levels of elemental contamination may indicate that the article is not processed in accordance with Good Agricultural Practices. The proposed levels are also consistent with requirements in *European Pharmacopoeia* standards for herbal drugs. In addition, there are no dosage forms for Capsicum Oleoresin in the *USP* for application of General Chapter <232>.

**Comment Summary #3:** The commenter indicated that the monograph content for elemental impurities should follow the delayed implementation of General Chapters <232> *Elemental Impurities—Limits* and <233> *Elemental Impurities—Methods*.

**Response:** Comment not incorporated. The implementation of General Chapters <232> *Elemental Impurities—Limits* and <233> *Elemental Impurities—Procedures* through General Notices provision 5.60.30 is intended to apply common limits to all drug product monographs. The General Notice provision does not preclude monograph specific limits.

**Monograph/Section:** Carbidopa and Levodopa Orally Disintegrating Tablets/  
Dissolution

**Expert Committee:** Monographs—Small Molecules 4

**No. of Commenters:** 1

**Comment Summary #1:** The commenter requested correcting the error in the column description from 150-cm to 15.0-cm.

**Response:** Comment incorporated.

**Monograph/Sections:** Cyclobenzaprine/Multiple sections

**Expert Committee:** Monographs—Small Molecules 4

**No. of Commenters:** 3

**Comment Summary #1:** The commenter requested revising the *Mobile phase* preparation in the test for *Organic Impurities* to allow the pH to be adjusted using diluted acetic acid as well as using diluted ammonia.

**Response:** Comment incorporated.

**Comment Summary #2:** The commenter requested tightening of the specification for “Total impurities” to comply with what has been approved by the FDA in the procedure for *Organic Impurities*.

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

**Comment Summary #3:** The commenter indicated that the amitriptyline peak may not be completely separated from the cyclobenzaprine peak and requested adding a resolution requirement between these compounds in the test for *Organic Impurities*.

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

**Expert Committee-initiated Change:** The chemical names for USP Cyclobenzaprine Related Compound A RS and the chemical information for USP Cyclobenzaprine Related Compound B RS are revised in the <11> Reference Standard section.

**Monograph/ Section(s):** Diphenhydramine Citrate/Organic Impurities

**Expert Committee:** Monographs—Small Molecules 4

**No. of Commenters:** 1

**Comment Summary #1:** The commenter requested adding benzophenone, which is the last eluting specified impurity, to the system suitability mixture as a retention time marker.

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

**Monograph/Sections:** Filgrastim/Multiple Sections

**Expert Committee:** Monographs – Biologics and Biotechnology 1

**No. of Commenters:** 3

### **Definition**

**Comment Summary #1:** The commenter requested changing the concentration of Filgrastim to NLT 0.9 mg/mL in the *Definition*, instead of NLT 1.0 mg/mL, to take into account stability studies demonstrating that the drug substance is stable in the concentration range 0.90 to 1.20 mg/mL under refrigerated (2–8°) storage conditions.

**Response:** Comment incorporated.

**Expert Committee-initiated Change #1:** Changed molecular mass from 18,800 daltons to 18,799 daltons for accuracy.

**Expert Committee-initiated Change #2:** Clarified the “biological potency of NLT 80% and NMT 125% relative to standard” by adding “on a mass to mass basis” in the *Definition*.

### **Peptide Mapping**

**Comment Summary #2:** The commenter requested that the monograph indicate a particular grade of methylamine in the *Peptide Mapping* method or consider conducting the proteolytic digestion in the absence of methylamine.

**Response:** Comment incorporated. A suitable grade of methylamine will be added to the *Reagents* section of *USP–NF*. The USP monograph procedure and specifications

must be aligned with the FDA approved product. Users have the option of using alternative procedures as long as the methods are validated and shown to produce equivalent or better results (*USP36–NF31, General Notices*).

### **Assay**

**Comment Summary #3:** The commenter indicated that the Assay procedure is too prescriptive. For example, parameters such as the cell line, media, growth read-out, and statistical evaluation should allow for other options when shown to be appropriate.

**Response:** Comment not incorporated. The USP monograph procedure and specifications must be aligned with the FDA approved product. Users have the option of using alternative procedures as long as the methods are validated and shown to produce equivalent or better results (*USP36–NF31, General Notices*).

**Comment Summary #4:** The commenter requested that the signal to noise ratio in the Assay, *System suitability criteria* be increased to  $\geq 10$ .

**Response:** Comment not incorporated. The validated Assay method shows that a signal to noise ratio of  $\geq 3$  is suitable.

**Expert Committee-initiated Change #3:** Medium designations A, B, C, and D were changed to simplify the Assay procedure. Medium A (three components) and Medium B (five components plus Medium A) were combined to make an eight component Medium A. The components of Medium C and Medium D were changed to reflect the creation of the new eight component Medium A. Overall, no compositions were changed except for Medium E. In *PF 36(5)* Medium E lacked glucose, buffer, sodium pyruvate, and 2-mercaptoethanol. Medium E designation was changed to Medium B and the composition corrected.

**Expert Committee-initiated Change #4:** Footnote #1 was inaccurately written in the proposed *PF 36(5)* monograph and was corrected.

**Expert Committee-initiated Change #5:** Information on number of passages per week and cell re-seeding density at time of passage was added to the Assay, *Cell culture preparation*. Instructions were added for cell banking.

**Expert Committee-initiated Change #6:** Information on preparing the cells for analysis was removed from the Assay, *Analysis* section and placed in a new section. Mixing instructions were added to the *Analysis* section.

**Expert Committee-initiated Change #7:** The Assay, *Calculations* section was clarified by replacing “in IU/mL” with “in percent” followed by “using statistical methods for parallel-line assays”, and adding the phrase, “then calculate potency in IU/mL” at the end of the sentence.

### **Impurities**

**Comment Summary #5:** The commenter indicated that the *Ph.Eur.* impurities method is more sensitive than the USP *Related Compounds* method with respect to quantifying major impurities and degradants. The levels of the three most abundant impurities (oxidized Filgrastim 1, oxidized Filgrastim 2, and reduced Filgrastim) are greater when analyzed by the *Ph.Eur.* method relative to the USP method. The *Ph.Eur.* method detects an impurity (RRT 1.46, 0.14%) in addition to oxidized Filgrastim 1, oxidized Filgrastim 2, and reduced Filgrastim. The USP *Related Compounds* method detects three other impurities, all less than 0.10%, in addition to oxidized Filgrastim 1, oxidized

Filgrastim 2, and reduced Filgrastim. The *Ph.Eur.* method provides a more rigorous approach for assessment of Filgrastim purity.

**Response:** Comment not incorporated. The USP monograph procedure and specifications must be aligned with the FDA approved product. Users have the option of using alternative procedures as long as the methods are validated and shown to produce equivalent or better results (*USP36–NF31, General Notices*).

**Comment Summary #6:** Two commenters indicated the USP *Related Compounds* method does not provide adequate resolution of the oxidized Filgrastim 2 peak for quantization, while the *Ph.Eur.* method provides resolution; however, the *Ph.Eur.* method may not adequately resolve the reduced Filgrastim peak. The acceptance criterion in the *Related compounds* method for total impurity of NMT 2.0% is considerably tighter than the 3.5% specified in the *Ph.Eur.* monograph. It is recommended that the *Ph.Eur.* specification be adopted as the difference in acceptable impurity could possibly be due to the difference in resolution of the impurities between the two methods.

**Response:** Comment not incorporated. The USP monograph procedure and specifications must be aligned with the FDA approved product. Users have the option of using alternative procedures as long as the methods are validated and shown to produce equivalent or better results (*USP36–NF31, General Notices*).

**Comment Summary #7:** The commenter requested that the *Sample solution* in the *Related Compounds* test be prepared with placebo instead of water to preserve sample solution stability.

**Response:** Comment not incorporated. The USP monograph procedure and specifications must be aligned with the FDA approved product. Users have the option of using alternative procedures as long as the methods are validated and shown to produce equivalent or better results (*USP36–NF31, General Notices*).

**Comment Summary #8:** The commenter indicated that laboratory investigations of the *Impurities with Charges Different from Filgrastim* method were not undertaken. However, based on a technical review it is recommended that there be a harmonization with the *Ph.Eur.* monograph which specifies the use of a pH range of 4.5–8.0.

**Response:** Comment not incorporated. The USP monograph procedure and specifications must be aligned with the FDA approved product. Users have the option of using alternative procedures as long as the methods are validated and shown to produce equivalent or better results (*USP36–NF31, General Notices*).

**Comment Summary #9:** The commenter requested deleting *Coomassie destaining solution* and using the *Gel Wash* solution instead for gel destaining in the *Impurities with Charges Different from Filgrastim* method in order to reduce background noise and obtain better visualization of the bands.

**Response:** Comment not incorporated. The method indicates the gel can be stained over a period of 15 to 60 minutes. If staining concludes at the lower end of this range, e.g., 15 minutes, the background noise will be reduced using *Coomassie destaining solution*. The USP monograph procedure and specifications must be aligned with the FDA approved product. Users have the option of using alternative procedures as long

as the methods are validated and shown to produce equivalent or better results (*USP36–NF31, General Notices*).

**Comment Summary #10:** The commenter requested changing the concentration of *Reference solution A* to 0.5 mg/mL (instead of 1 mg/mL) and *Reference solution B* to 50 µg/mL (instead of 20 µg/mL) and loading 20 µL (instead of 10 µL) in the *Impurities with Charges Different from Filgrastim* method.

**Response:** Comment not incorporated. The proposal would increase the acceptance criterion for the intensity of minor bands from 2% to 10%.

**Comment Summary #11:** The commenter indicated that the gel preparation method in the *Impurities with Charges Different from Filgrastim* requires clarification as the percentage of bisacrylamide is not sufficient for polymerization.

**Response:** Comment incorporated. The monograph method is intended for a horizontal gel apparatus and this clarification has been incorporated, along with the temperature at which the gel should be run.

**Comment Summary #12:** The commenter requested that the *Impurities with Molecular Weight Different from That of Filgrastim* method be harmonized with the *Ph.Eur.* method as the procedures are comparable. It is recommended that the harmonized monograph includes use of a 16% Tris-Glycine gel. The recommended harmonization would include the acceptance criteria (*USP*: No single impurity is >1%; *Ph.Eur.*: No single impurity is >2%).

**Response:** Comment not incorporated. The USP monograph procedure and specifications must be aligned with the FDA approved product. Users have the option of using alternative procedures as long as the methods are validated and shown to produce equivalent or better results (*USP36–NF31, General Notices*).

**Comment Summary #13:** The commenter requested reducing the staining time in the *Impurities with Molecular Weight Different from That of Filgrastim* method by replacing the *Gel Wash I* and *Gel Wash II* solutions with a fixing solution containing 95% ethanol, glacial acetic acid, and water (500:100:400).

**Response:** Comment not incorporated. The USP monograph procedure and specifications must be aligned with the FDA approved product. Users have the option of using alternative procedures as long as the methods are validated and shown to produce equivalent or better results (*USP36–NF31, General Notices*).

**Comment Summary #14:** The commenter requested replacing the *Reducer solution* in the *Impurities with Molecular Weight Different from That of Filgrastim* method with a solution containing sodium thiosulfate instead of dithiothreitol, and to also change the composition of the *Developer* to shorten the procedure time.

**Response:** Comment not incorporated. The USP monograph procedure and specifications must be aligned with the FDA approved product. Users have the option of using alternative procedures as long as the methods are validated and shown to produce equivalent or better results (*USP36–NF31, General Notices*).

**Comment Summary #15:** The commenter requested changing the gel description in the *Impurities with Molecular Weight Different from That of Filgrastim* method as the current text is not clear.

**Response:** Comment incorporated. The *Gel* section has been sub-divided into *Resolving gel* and *Stacking gel* with clear descriptions.

**Comment Summary #16:** The commenter indicated that in the *Limit of High Molecular Weight Proteins* test, the *USP–NF* method calls for a SEC-HPLC running buffer of pH 2.5 which has the potential to break up any non-covalent aggregates formed and thus return an inaccurate measure of aggregation. The *Ph.Eur.* method for SEC-HPLC calls for a running buffer of pH 7 which is much nearer the pI of Filgrastim and also near physiological pH. The running buffer of pH 7 would not produce the potential artifacts of the pH 2.5 running buffer.

**Response:** Comment not incorporated. The USP monograph procedure and specifications must be aligned with the FDA approved product. Users have the option of using alternative procedures as long as the methods are validated and shown to produce equivalent or better results (*USP36–NF31, General Notices*).

**Comment Summary #17:** Two commenters indicated that the chromatogram of the *Resolution solution* prepared according to the proposed *PF 36(5)* monograph *Limit of High Molecular Weight Proteins* method displays only the peak resulting from large aggregates. The Filgrastim monomer, dimer, and oligomer peaks are not present.

**Response:** Comment incorporated. The procedure for preparing the *Resolution solution* has been revised and appears in the official USP monograph.

**Comment Summary #18:** Two commenters indicated that in contrast to the USP *Limit of High Molecular Weight Proteins* method, the *Ph.Eur.* method provides improved resolution of oligomer peaks, lacks potential interference from a placebo, and specifies a simple and rapid preparation of the *Resolution solution*. The *USP–NF* method does not demonstrate the resolution of high molecular weight (oligomer) species.

**Response:** Comment not incorporated. The USP monograph procedure and specifications must be aligned with the FDA approved product. Users have the option of using alternative procedures as long as the methods are validated and shown to produce equivalent or better results (*USP36–NF31, General Notices*).

**Comment Summary #19:** The commenter requested that the description of the *Relative standard deviation* procedure in the *Limit of High Molecular Weight Proteins* test be modified to identify the material under analysis.

**Response:** Comment incorporated.

**Expert Committee-initiated Change #8:** The *Acceptance criteria* in the *Impurities with Molecular Weight Different from That of Filgrastim* method were modified to direct the user to compare the *Sample solution* results to *Reference solution A*.

### **Specific Tests**

**Comment Summary #20:** The commenter requested removing the word “buffer” in the *Protein Concentration* method since the *5% Sorbitol solution, pH 3.25 buffer* is not a buffer in composition.

**Response:** Comment incorporated.

**Comment Summary #21:** The commenter requested that a 0.1% hydrochloric acid solution is used to adjust the pH of the *5% Sorbitol solution, pH 3.25 buffer* in the *Protein Concentration* method instead of concentrated hydrochloric acid.

**Response:** Comment incorporated.

**Comment Summary #22:** The commenter requested the extinction coefficient in the *Protein Concentration* method be changed from 0.86 to 0.872 based on the literature.

**Response:** Comment not incorporated. The USP monograph procedure and specifications must be aligned with the FDA approved product. Users have the option of using alternative procedures as long as the methods are validated and shown to produce equivalent or better results (*USP36–NF31, General Notices*).

**Comment Summary #23:** The commenter requested that protein concentration be determined using reverse phase HPLC analysis as required by the *Ph.Eur.* monograph. The *Ph.Eur.* stipulates the protein concentration be determined from the main peak and thus does not include impurities, because some methionine-oxidized Filgrastims have reduced biological activity. The use of UV absorbance to determine protein concentration would include such reduced activity species.

**Response:** Comment not incorporated. The USP monograph procedure and specifications must be aligned with the FDA approved product. Users have the option of using alternative procedures as long as the methods are validated and shown to produce equivalent or better results (*USP36–NF31, General Notices*).

**Comment Summary #24:** Two commenters requested increasing the acceptance limit of 0 cfu/10 mL for total aerobic count in *Microbial Enumeration Tests <61>*, with one commenter suggesting <1 cfu/5 mL.

**Response:** Comment not incorporated. The USP monograph procedure and specifications must be aligned with the FDA approved product. Users have the option of using alternative procedures as long as the methods are validated and shown to produce equivalent or better results (*USP36–NF31, General Notices*).

**Comment Summary #25:** The commenter requested changing the *Labeling* section to read, “Label to indicate the content of the drug substance in mg/mL” instead of g/container.

**Response:** Comment not incorporated. The present text is consistent with the FDA approved product labeling.

### ***Additional Requirements***

**Comment Summary #26:** The commenter requested that the USP provide more clarity on the apparent difference in storage conditions of the drug substance and USP Filgrastim RS in the proposed *PF 36(5)* monograph, particularly whether the Filgrastim drug substance can be stored long term under frozen conditions (e.g., at -20° or -70°). The Packaging and Storage section specifies to “Store between 2° and 8°”, the Assay (Potency) section indicates that after thawing the USP Filgrastim RS *Standard solution* is stable for up to 1 week at 2°–8°.

**Response:** Comment incorporated. The Packing and Storage section refers to the drug substance and does not infer storage conditions for the USP Filgrastim RS. The USP Filgrastim RS is presented as lyophilized material and the storage conditions are described on the ampoule label. The text, “After thawing, the *Standard solution* is stable for up to 1 week at 2°–8°” has been removed from the USP Filgrastim monograph.

**Monograph/Section:** Fluticasone Propionate Inhalation Aerosol/Multiple sections

**Expert Committee:** Monographs—Small Molecules 4

**No. of Commenters:** 2

**Comment Summary #1:** The commenter requested revising the text in the Acceptance criteria section to state “44 µg/actuation” instead of “44 µg” within the test for *Delivered Dose Uniformity*.

**Response:** Comment incorporated.

**Comment Summary #2:** The commenter requested adding a test for valve delivery with appropriate acceptance criteria.

**Response:** Comment not incorporated. The Expert Committee determined that a separate test for valve delivery is not needed in the public standard, because the monograph includes suitable acceptance criteria for *Delivered Dose Uniformity*, which is a better indicator of the valve performance.

**Expert Committee-initiated Change #1:** In the test for *Organic Impurities*, the variable “ $r_s$ ” is replaced with the variable “ $r_T$ ” for clarity and consistency with USP style.

**Monograph/Section:** Fluticasone Propionate Inhalation Powder/Particle Size Distribution by Cascade Impaction

**Expert Committee:** Monographs—Small Molecules 4

**No. of Commenters:** 1

**Comment Summary #1:** The commenter requested revising the *Standard solution* and *Sample solutions* by correcting the concentration ranges, the figure referenced, and the required number of *Sample solutions*.

**Response:** Comment incorporated.

**Monograph/Section:** Gadopentetate Dimeglumine Injection/Content of Pentetic Acid

**Expert Committee:** Monographs—Small Molecules 4

**No. of Commenters:** 1

**Comment Summary #1:** The commenter requested correcting the calculation by removing the variable “ $L$ ” (label claim of Injection, mg/mL) from the equation.

**Response:** Comment incorporated.

**Monograph/Section:** Gemcitabine Hydrochloride/Assay

**Expert Committee:** Monographs—Small Molecules 3

**No. of Commenters:** 1

**Comment Summary #1:** The commenter requested deleting the note which contains typical relative retention times for gemcitabine  $\alpha$ -anomer and gemcitabine in the *Assay*, because these relative retention times are already provided in Table 2 within the test for *Organic impurities*.

**Response:** Comment not incorporated. The chromatographic procedures in the *Assay* and the test for *Organic impurities* are different and result in different relative retention times for the components.

**Monograph/Section:** Gemcitabine for Injection/Assay

**Expert Committee:** Monographs—Small Molecules 3

**No. of Commenters:** 1

**Comment Summary #1:** The commenter requested deleting the note which contains typical relative retention times for gemcitabine  $\alpha$ -anomer and gemcitabine in the Assay, because these relative retention times are already provided in Table 2 within the test for *Organic impurities*.

**Response:** Comment not incorporated. The chromatographic procedures in the Assay and test for *Organic impurities* are different and result in different relative retention times for the components.

**Monograph/Section:** Isobutyl Alcohol/Multiple Sections

**Expert Committee(s):** Monographs—Excipients

**No. of Commenters:** 1

**Expert Committee-initiated Change #1:** Based on comments received for Butyl Alcohol, the Expert Committee specified *Reference solution* in the Assay for clarity, deleted the term of wide bore for the GC column used, and provided detailed information for a needle wash.

**Expert Committee-initiated Change #2:** Subsequently, to accommodate the commenter's comments, the Expert Committee changed "**Sample:** *Sample solution*" to "**Samples:** *Reference solution* and *Sample solution*" in the Analysis section of the Assay.

**Expert Committee-initiated Change #3:** In the Assay, the Expert Committee changed "due to artifact and peaks below the *Disregard limit* (see Table 4)" to "each with an area less than 0.1 times the area of the major peak from the *Reference solution*" in the definition for  $r_T$  because the term for "Disregard limit" is not defined.

**Expert Committee-initiated Change #4:** in the *Limit of Isobutyraldehyde, Butyraldehyde, 2-Butanol, 1-Butanol, and Other Volatile Impurities*, the Expert Committee changed "**Disregard limit:** 0.1 times the area of the major peak in the chromatogram from the *Reference solution*, corresponding to 0.01%" to "Disregard any peak with an area less than 0.1 times the area of the major peak from the *Reference solution*, corresponding to 0.01%" because the term for "Disregard limit" is not defined.

**Monograph/Section:** Isopropyl Alcohol/Multiple Sections

**Expert Committee(s):** Monographs—Excipients

**No. of Commenters:** 1

### ***Identificaton***

**Comment Summary #1:** The commenter recommended deleting the proposed *Identification* test B based on retention time agreement with the USP Reference Standard by GC assay.

**Response:** Comment not incorporated. The Expert Committee agrees that IR as a stand-alone identification test cannot uniquely identify isopropyl alcohol, as it does not specifically differentiate between an authentic and a substandard sample. When IR and chromatographic peak identifications are used together, they provide a greater assurance of uniquely identifying isopropyl alcohol.

### ***Limit of Volatile Impurities***

**Comment Summary #2:** The commenter recommended that the limit of diethyl ether, acetone, *n*-propyl alcohol, and 2-butanol be changed from 0.1% to 0.5% to align it with the limits provided in General Chapter <467> *Residual Solvents*.

**Response:** Comments not incorporated. The proposed limits represent specifications of isopropyl alcohol in commerce. The Expert Committee has contacted isopropyl alcohol manufacturers, and they do not have any issue with the proposed limit of each volatile impurity at 0.1%.

**Monograph/Section:** Levetiracetam Extended Release Tablets/Multiple sections

**Expert Committee:** Monographs—Small Molecules 4

**No. of Commenters:** 3

**Comment Summary #1:** The commenter requested including their assay and organic impurities procedures in the monograph.

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

**Comment Summary #2:** The commenters requested adding dissolution tests for drug products approved by the FDA.

**Response:** Comment incorporated.

**Comment Summary #3:** The commenter requested widening the limit for Total impurities from 0.60% to 1.0% to be consistent with the FDA-approved limit in the test for *Organic Impurities*.

**Response:** Comment incorporated.

**Expert Committee-initiated change #1:** A Labeling section is added to support the addition of *Dissolution Test 2, Dissolution Test 3, and Dissolution Test 4*.

**Monograph/Section:** Lomustine/Specific Tests

**Expert Committee:** Monographs—Small Molecules 3

**No. of Commenters:** 1

**Comment Summary #1:** The commenter requested adding a test for *Melting Range or Temperature* to the monograph.

**Response:** Comment not incorporated. The Expert Committee has determined that a test for *Melting Range or Temperature* does not need to be included in the public standard because the monograph already includes a specific HPLC procedure for *Organic impurities*.

**Monograph/Section:** Lomustine Capsules/Multiple Sections

**Expert Committee:** Monographs—Small Molecules 3

**No. of Commenters:** 2

**Comment Summary #1:** The commenter requested tightening of the limit for total impurities in the test for *Organic impurities* to be consistent with the FDA-approved limit.

**Response:** Comment not incorporated. The limit for total impurities is adapted from the *British Pharmacopoeia* monograph. The Expert Committee will consider

future revisions to the monograph upon the receipt of the necessary supporting data.

**Comment Summary #2:** The commenter requested adding a procedure for *Water Determination* to the monograph to be consistent with the FDA-approved specifications.

**Response:** Comment not incorporated. The moisture content of the drug product is formulation-specific and it is not included in the public standard.

**Comment Summary #3:** The commenter requested including a UV procedure for *Uniformity of Dosage Units* to be consistent with the FDA approved specification.

**Response:** Comment incorporated.

**Expert Committee-initiated Change #1:** In *Identification* test A, the solvent is corrected from chloroform to methylene chloride.

**Expert Committee-initiated Change #2:** In Table 2, the footnotes are revised to indicate that lomustine related compound D is a process impurity that is included in the table for identification only and that it is not to be reported or included in the *Total impurities*.

**Expert Committee-initiated Change #3:** In the test for *Organic Impurities*, the relative standard deviation requirement, the calculation, and the limit for lomustine related compound D are deleted.

**Monograph/Section(s):** Methylphenidate Hydrochloride/Multiple sections

**Expert Committee:** Monographs—Small Molecules 4

**No. of Commenters:** 1

**Comment Summary #1:** The commenter requested revising the chemical names and CAS numbers to reflect the correct stereochemistry.

**Response:** Comment incorporated.

**Monograph/Section(s):** Metolazone/Multiple sections

**Expert Committee:** Monographs—Small Molecules 2

**No. of Commenters:** 1

**Comment Summary #1:** The commenter requested replacing the use of tetrahydrofuran with methanol in the preparation of *Standard stock solutions*, *Sample stock solution*, and *Sample solution* in the *Assay* and the test for *Organic Impurities*.

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

**Comment Summary #2:** The commenter requested clarifying that the chromatographic column used in the test for *Organic Impurities* has a 5- $\mu$ m particle size.

**Response:** Comment incorporated.

**Expert Committee-initiated change #1:** *Identification* test C based on the retention time agreement of the major peaks in *Standard solution* and *Sample solution* using the *Assay* procedure is added.

**Monograph/Section(s):** Moxidectin/Multiple Sections

**Expert Committee:** Monographs—Small Molecules 3

**No. of Commenters:** 1

**Comment Summary #1:** The commenter requested revising the resolution between moxidectin deoxydiene/methylthiomethoxymoxidectin and 20b-methylthiomoxidectin from NLT 2 to NLT 1.0 in the test for *Late-Eluting Impurities*.

**Response:** Comment incorporated.

**Expert Committee-initiated Change #1:** The phrase “small amounts of” is removed from the *Definition*.

**Monograph/ Section(s):** Nifedipine/Multiple Sections

**Expert Committee:** Monographs—Small Molecules 2

**No. of Commenters:** 1

**Comment Summary #1:** The commenter recommended replacing the *Perchloric Acid Titration* test with a HPLC based procedure.

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

**Comment Summary #2:** The commenter recommended adding specifications for any individual impurity and for Total impurities.

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

**Monograph/Sections:** Omeprazole/Multiple Sections

**Expert Committee:** Monographs—Small Molecules 3

**No. of Commenters:** 2

**Comment Summary #1:** The commenters indicated that the chloromethylmethoxylutidine impurity is considered to be genotoxic, and recommended establishing a separate procedure to control this impurity with an appropriately tight limit.

**Response:** Comment partially incorporated. The chloromethylmethoxylutidine impurity, its limit, and its chemical information are deleted from Table 2 in the test for *Organic Impurities*. The Expert Committee will consider adding a separate procedure to control this impurity in a future revision to this monograph upon the receipt of the necessary supporting data.

**Expert Committee-initiated Change #1:** In the *Assay*, the system suitability requirements for capacity factor and column efficiency are deleted because the remaining criteria are sufficient to establish suitability of the chromatographic system.

**Monograph/Sections:** Pioglitazone and Glimepiride Tablets/Multiple Sections

**Expert Committee:** Monographs—Small Molecules 3

**No. of Commenters:** 1

**Comment Summary #1:** The commenter requested including the final volume of the *Sample stock solution* under the *Assay*.

**Response:** Comment incorporated.

**Comment Summary #2:** The commenter requested widening of the *Assay* acceptance criteria for both pioglitazone and glimepiride from “NLT 95.0% and NMT 105.0%” to “NLT 90.0% and NMT 110.0%,” to reflect the FDA-approved limits.

**Response:** Comment incorporated.

**Comment Summary #3:** The commenter requested widening the limit of glimepiride sulfonamide in the test for *Organic Impurities: Glimepiride* from NMT 1.3% to NMT 1.5% and the limit of total glimepiride-related impurities from NMT 1.5% to NMT 2.5%, to reflect the FDA-approved limits.

**Response:** Comment incorporated.

**Comment Summary #4:** The commenter requested including an additional *Dissolution* test to accommodate their FDA-approved specifications.

**Response:** Comment not incorporated. The Expert Committee will consider addressing this request upon receipt of the necessary supporting data

**Expert Committee-initiated Change #1:** Throughout the monograph, the column temperature range is widened from “ $25 \pm 2.5^\circ$ ” to “ $25 \pm 5^\circ$ ” to be consistent with the validation data.

**Expert Committee-initiated Change #2:** The Notes in the Chromatographic system sections in the *Assay*, test for *Organic impurities*, and test for *Dissolution* are revised to indicate that the flow rate may be adjusted to achieve a given retention time.

**Monograph/Sections:** Pioglitazone and Metformin Hydrochloride Tablets/  
Multiple Sections

**Expert Committee:** Monographs—Small Molecules 3

**No. of Commenters:** 3

**Comment Summary #1:** The commenters requested revising the test for *Organic Impurities: Metformin* to remove the specific references to the metformin impurities listed in Table 4 because these impurities are process impurities and not degradation products. As part of this revision request, Table 4 should be replaced with the acceptance criteria: “NMT 0.1% of any individual impurity is found, and NMT 0.5% of total impurities is found” to be consistent with the requirements in the existing monographs for metformin-containing drug products. The calculation should be updated to remove the relative response factor, and the USP Reference Standards for metformin related compounds B and C should be removed from the *System suitability solution* and from the <11> Reference Standard section.

**Response:** Comment incorporated.

**Comment Summary #2:** The commenter requested specifying a *Run time* of 15 min in the test for *Organic Impurities: Metformin*, because the remaining part of the gradient serves to elute pioglitazone and re-equilibrate the column, and any peaks eluting after 15 minutes should not be integrated.

**Response:** Comment incorporated.

**Comment Summary #3:** The commenter requested revising the Note in the test for *Organic Impurities: Metformin, Acceptance criteria*, to specify the relative retention time in addition to the elution time.

**Response:** Comment incorporated.

**Comment Summary #4:** Commenter indicated that the *pH 2.5 McIlvaine buffer* used as a *Medium* in the test for *Dissolution* could be prepared in a different way, and requested providing flexibility in preparation of the buffer.

**Response:** Comment incorporated.

**Expert Committee-initiated Change #1:** Throughout the monograph, the column temperature range is widened from “25±2.5°” to “25±5°” to be consistent with the validation data.

**Expert Committee-initiated Change #2:** The Notes in the Chromatographic system sections in the *Assay*, test for *Organic impurities* and test for *Dissolution* are revised to indicate that the flow rate may be adjusted to achieve a given retention time.

**Monograph/Sections:** Polymyxin B Sulfate/Multiple Sections

**Expert Committee:** Monographs—Small Molecules 1

**No. of Commenters:** 1

**Comment Summary #1:** The commenter requested tightening of the limit in the test for *Residue on Ignition* from 5.0% to 0.75%.

**Response:** Comment not incorporated. The acceptance criteria in the monograph reflect the FDA-approved limits.

**Comment Summary #2:** The commenter requested tightening of the limit in the test for *Loss on Drying* from 7.0% to 6.0%.

**Response:** Comment not incorporated. The acceptance criteria in the monograph reflect the FDA-approved limits.

**Monograph/ Section(s):** Ritonavir Capsules/Organic Impurities

**Expert Committee:** Monographs—Small Molecules 1

**No. of Commenters:** 1

**Comment Summary #1:** The commenter requested deleting the acceptance criteria for ureidovaline, because this peak cannot be quantified due to solvent front and placebo interferences as indicated in the footnotes.

**Response:** Comment incorporated.

**Monograph/ Section(s):** Ritonavir Oral Solutions/Multiple sections

**Expert Committee:** Monographs—Small Molecules 1

**No. of Commenters:** 2

**Comment Summary #1:** The commenter requested deleting the acceptance criteria for ureidovaline in the test for *Organic Impurities*, because this peak cannot be quantified due to solvent front and placebo interferences as indicated in the footnotes.

**Response:** Comment incorporated.

**Comment Summary #2:** The commenter requested deleting the reference to General Chapter <62> *Tests for Specified Microorganisms*, because there is no test or limit for specified organism in the approved product application.

**Response:** Comment not incorporated. General Chapters <62> *Tests for Specified Microorganisms* and <61> *Microbial Enumeration Tests* need to be referenced together per the current USP style.

**Expert Committee-initiated change #1:** The units in total aerobic microbial count were corrected from cfu/g to cfu/mL.

**Monograph/ Section(s):** Ritonavir Tablets/Packaging and Storage

**Expert Committee:** Monographs—Small Molecules 1

**No. of Commenters:** 1

**Comment Summary #1:** The commenter requested revising the storage condition from “Store at controlled room temperature” to “Store at or below 30°” to be consistent with the product label.

**Response:** Comment incorporated.

**Monograph/ Section(s):** Torsemide Tablets/Multiple Sections

**Expert Committee:** Monographs—Small Molecules 2

**No. of Commenters:** 1

**Comment Summary #1:** The commenter requested widening of the limit for torsemide related compound E from 0.20% to 0.2%.

**Response:** Comment not incorporated. The limit for torsemide related compound E is consistent with the FDA-approved limit.

**Comment Summary #2:** The commenter requested adding a dissolution test for a drug product approved by the FDA.

**Response:** Comment incorporated.

**Expert Committee-initiated change #1:** A footnote is added within Table 2 to clarify that torsemide related compounds B, C, and D are process related impurities and are controlled in the drug substance.

**Expert Committee-initiated change #2:** A Labeling section is added to support the addition of *Dissolution test 2*.

**Monograph/Section:** Zolpidem Tartrate Tablets/Organic Impurities

**Expert Committee:** Monographs—Small Molecules 4

**No. of Commenters:** 2

**Comment Summary #1:** The commenters requested removing the limits for the process impurities in Table 2 and adding a footnote stating that these impurities are included in the table for peak identification only.

**Response:** Comment incorporated.

**Comment summary #2:** The commenter requested widening of the limit for zolpidem related compound A from NMT 0.15% to NMT 0.20% to be consistent with their FDA-approved limit.

**Response:** Comment incorporated.

## **Additional Sections:**

**Section:** USP and NF Excipients Listed By Functional Categories/Multiple Sections

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

**No. of Commenters:** 1

**Expert Committee-initiated Change #1:** Under Bulking Agent, the Expert Committee listed the following excipients: Alpha-Lactalbumin, Polydextrose, Polydextrose, and Hydrogenated Pullulan independent of the dosage form; and deleted these excipients from Parenterals, because their use in parenterals was not confirmed.

**Expert Committee-initiated Change #2:** Under Wetting and/or Solubilizing Agent, the Expert Committee removed Betadex Sulfobutyl Ether Sodium from the dosage form Oral Liquids because it has not been reported to be used in Oral Liquids; and listed this excipient independent of the dosage form under the same functional category.