

<661.2> Plastic Packaging Systems for Pharmaceutical Use

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Posting Date	28–Apr–2017, revised 26-May-2017 ¹
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Expert Committee	General Chapters—Packaging and Distribution
Reason for Revision	Compliance

In accordance with the Rules and Procedures of the 2015-2020 Council of Experts, the General Chapters—Packaging and Distribution Expert Committee has revised General Chapter <661.2> Plastic Packaging Systems for Pharmaceutical Use.

The purpose of the revisions will be to provide a three-year period for implementation of the requirements specified in General Chapters <661.1> and <661.2>, which otherwise will become applicable on May 1, 2017 through General Chapter <659>; to reinstate requirements previously expressed in General Chapter <661> during this three-year period; to enable early adoption of the requirements in General Chapters <661.1> and <661.2> at any time during the three-year period in lieu of meeting the reinstated <661> requirements; and to remove the exemption to General Chapters <661.1> and <661.2> for previously approved plastic materials and packaging systems.

The specific revisions are as follows:

- Delay until May 1, 2020 the implementation of new requirements of General Chapters <661.1> and <661.2> as currently specified in General Chapter <659>.
- Incorporate into General Chapter <661> the requirements previously specified in the *USP 38–NF 33* version of General Chapter <661>. Reference General Chapter <661> in General Chapter <659> to make these previous requirements applicable until May 1, 2020.
- Clarify in General Chapter <659> that early adoption of the requirements of <661.1> and <661.2> is permitted by USP, and that packaging systems in compliance with these requirements in advance of May 1, 2020 will no longer need to comply with the reinstated <661> requirements to be considered by USP to be in conformance with the *USP–NF*.
- Remove the current exemption to General Chapters <661.1> and <661.2> for plastic materials and packaging systems previously approved by a regulatory authority.

The <661.2> Plastic Packaging Systems for Pharmaceutical Use Revision Bulletin will supersede the monograph becoming official in *USP 40–NF 35*. The Revision Bulletin will be incorporated in *USP 41–NF 36*.

Should you have any questions, please contact Desmond Hunt, Ph.D. (301-816-8341 or dgh@usp.org).

¹ The text of the notice was revised May 17, 2017 to clarify that the exemption is being removed from both chapters <661.1> and <661.2>

⟨661.2⟩ PLASTIC PACKAGING SYSTEMS FOR PHARMACEUTICAL USE

Add the following:

•(This chapter will become official on May 1, 2020. Early adoption of the requirements in this chapter and its companion chapter *Plastic Materials of Construction* ⟨661.1⟩ are permitted by USP. When early adoption is not used, *Plastic Packaging Systems and Their Materials of Construction* ⟨661⟩ will apply and must be met wherever ⟨661.1⟩ or this chapter is referenced in the *USP–NF.*) ● (RB 1-May-2017)

INTRODUCTION

A packaging system, as defined in *Packaging and Storage Requirements* ⟨659⟩, contains or is intended to contain a medical article such as a pharmaceutical drug product. As such, a packaging system provides the means for manufacturing, distributing, and storing these articles and products, and potentially for administering a drug product. A plastic packaging system is composed wholly or of a substantial portion of plastic materials. The term “plastic packaging system” refers to the sum of packaging components that together contain the pharmaceutical product, including closures. This sum of packaging components includes: 1) primary packaging components, which are those that directly contact the pharmaceutical product at some time during the product's manufacturing, distribution, storage, or use; and 2) secondary packaging components, which are those that may interact with the pharmaceutical product during the product's manufacturing, distribution, storage, and use, although the component does not directly contact the pharmaceutical product.

SCOPE

Plastic packaging systems for pharmaceutical use include, but are not limited to, bags, bottles, vials, ampoules, cartridges, dry powder and metered-dose inhalers, prefillable syringes, blisters, pouches, and their associated closures and secondary components like labels and printing overpouches. Plastic materials that are commonly used in packaging systems include polyethylene, polypropylene, cyclic olefins, polyethylene terephthalate, polyethylene terephthalate G, and plasticized polyvinyl chloride, among others.

Drug products can chemically interact with their associated packaging systems and/or the system's plastic materials and components of construction while the product is being manufactured, shipped, stored, and administered. The magnitude of these interactions must not be such that the interactions adversely affect the suitability for use of the drug product or the packaging system. Although suitability for use includes several quality aspects of the packaged drug product and its performance, the suitability for use aspect specifically addressed in this chapter is patient safety.

The applicant who secures and owns the regulatory approval of a packaging system or packaged drug product is responsible for establishing that the product's packaging system meets these expectations, and thus is suited for its intended use, by ensuring that the packaging system itself and/or the packaged pharmaceutical product has been appropriately tested and that the test results have been appropriately evaluated. A packaging system is chemically suited for its intended use with respect to safety if:

- The packaging system is constructed from well-characterized materials that have been intentionally chosen for use as established by testing according to *Plastic Materials of Construction* ⟨661.1⟩.
- The packaging system's general physicochemical properties have been established.
- The packaging system's biocompatibility (biological reactivity) has been appropriately established.
- The packaging system has been established to be safe by means of the appropriate chemical testing, such as extractables or leachables profiling, and toxicological assessment of the test data. This combination of chemical testing and toxicological assessment is termed “chemical safety assessment”.

This chapter applies specifically to plastic packaging systems and should not be applied to materials from which plastic packaging systems are constructed. The testing and qualification of materials of construction used in packaging systems are addressed in ⟨661.1⟩. As deemed appropriate by the applicant who secures and owns the regulatory approval of a packaging system or packaged drug product, components of packaging systems may be tested by the methods and held accountable to the specifications provided in this chapter.

The test methods and specifications contained within this chapter have been developed for general application to plastic packaging systems. In view of the wide variety of materials of construction and packaging systems available, and recognizing possible new developments in materials and packaging systems, the publication of a test method and specification does not exclude the use, in justified circumstances, of packaging systems that have been tested with different methods or that comply with other specifications, subject to approval by the appropriate regulatory authority.

Change to read:**TEST METHODS****Biological Reactivity**

In vitro biological tests are performed on the packaging systems according to the test procedures described in *Biological Reactivity Tests, In Vitro* (87). Packaging systems that meet the requirements of the in vitro tests are not required to undergo any further in vivo testing. In addition, the in vivo testing described in *Biological Reactivity Tests, In Vivo* (88) is not required for packaging systems used with certain dosage forms (oral and topical products). Packaging systems that do not meet the requirements of the biological reactivity tests ((87) and (88), if appropriate) are not suitable as packaging systems for pharmaceutical use. If a plastic class designation (classes I–VI) is needed, analysts should perform the appropriate in vivo tests specified by (88). Information about the appropriate plastic class that should be selected is provided in *The Biocompatibility of Materials Used in Drug Containers, Medical Devices, and Implants* (1031).

Physicochemical Tests**WATER EXTRACTION**

Solution C1: Fill the packaging system to its nominal capacity with *Purified Water* and close it, if possible, using the normal means of closure. Otherwise, close with an inert closure. Heat in an autoclave until $121 \pm 2^\circ$ is reached (typically in 20–30 min), and maintain at this temperature for 30 min. If heating at 121° leads to the deterioration of the container, heat at $100 \pm 2^\circ$ for 2 h or at $70 \pm 2^\circ$ for 24 ± 2 h. Cool the filled packaging system and empty its contents. The emptied contents are *Solution C1*. Use *Solution C1* within 4 h of preparation. Prepare a blank by heating *Purified Water* in a borosilicate glass flask closed with an inert closure; heat the flask at the same temperature and for the same length of time as used for the preparation of *Solution C1*.

Absorbance: Determine the spectrum of *Solution C1* between 230 and 360 nm, using the *Solution C1* blank as the compensation liquid.

Acidity or alkalinity: Conduct the test for *Acidity or alkalinity* only when packaging systems are intended to hold a liquid product or a product that is dissolved in its container before use.

To 20 mL of *Solution C1* obtained either as a portion of the fill solution or by combining the fill solution from several containers, add 0.1 mL of phenolphthalein TS; note the solution's color. Add 0.4 mL of 0.01 N sodium hydroxide; note the solution's color. Add 0.8 mL of 0.01 N hydrochloric acid and 0.1 mL of methyl red TS 2; note the solution's color.

Methyl red TS 2: Test for sensitivity: Add 0.1 mL of methyl red solution to 100 mL of carbon dioxide-free *Purified Water* and 0.05 mL of 0.02 N hydrochloric acid. •NMT 0.1 mL of 0.02 N sodium hydroxide. (ERR 1-Dec-2016) is required to change the color from red to yellow.

TOTAL ORGANIC CARBON

Refer to *Total Organic Carbon* (643).

The total organic carbon (TOC) content of *Solution C1* is measured according to (643). However, (643) is designed for testing high-purity water that has low TOC values. Because of extracted organic substances, material extracts may have TOC values that are much higher than those of *Purified Water*. Thus, the TOC analyses performed have a limit of detection of 0.2 mg/L (ppm) and have a demonstrated linear dynamic range of 0.2–20 mg/L (which encompasses the TOC limit). A linear range with a higher upper concentration can be used if linearity is established. If sample extracts exceed this upper linear range, then they should be diluted appropriately for analysis.

TOTAL TEREPHTHALOYL MOIETIES IN POLYETHYLENE TEREPHTHALATE AND POLYETHYLENE TEREPHTHALATE G PACKAGING SYSTEMS**Preparations**

Polyethylene terephthalate extracting media: 50% alcohol (dilute 125 mL of alcohol, dehydrated R with *Purified Water* to 238 mL, and mix), *n*-heptane, and *Purified Water*. For each extracting medium, fill a sufficient number of test packaging systems to 90% of their nominal capacity to obtain NLT 30 mL. Fill a corresponding number of glass bottles with each extracting medium for use as blanks. Fit the bottles with impervious seals such as aluminum foil and apply closures. Incubate the test packaging systems and the glass bottles at 49° for 10 days. Remove the test systems and glass bottles, and store at room temperature. Do not transfer the extracting medium samples to alternative storage vessels.

Polyethylene terephthalate G extracting media: 25% alcohol (dilute 125 mL of 50% alcohol with *Purified Water* to 250 mL, and mix), *n*-heptane, and *Purified Water*. Proceed as directed for *Polyethylene terephthalate extracting media*.

Procedure: Determine the absorbance of the 50% alcohol or 25% alcohol extracts in a 1-cm cell at the wavelength of maximum absorbance at about 244 nm (see *Ultraviolet-Visible Spectroscopy* (857)). For the blank, use the corresponding extracting medium blank.

Determine the absorbance of the *n*-heptane extract in a 1-cm cell at the wavelength of maximum absorbance at about 240 nm (see (857)). For the blank, use the *n*-heptane extracting medium.

ETHYLENE GLYCOL IN POLYETHYLENE TEREPHTHALATE AND POLYETHYLENE TEREPHTHALATE G PACKAGING SYSTEMS

Preparations

Periodic acid solution: Dissolve 125 mg of periodic acid in 10 mL of *Purified Water*.

Dilute sulfuric acid: To 50 mL of *Purified Water* slowly add and with constant stirring 50 mL of sulfuric acid, and allow to cool to room temperature.

Sodium bisulfite solution: Dissolve 0.1 g of sodium bisulfite in 10 mL of water. Use this solution within 7 days.

Disodium chromotropate solution: Dissolve 100 mg of chromotropic acid, disodium salt R in 100 mL of sulfuric acid. Protect this solution from light, and use within 7 days.

Standard solution: Dissolve an accurately weighed quantity of ethylene glycol in *Purified Water*, and dilute quantitatively and stepwise if necessary to obtain a solution having a known concentration of about 1 µg/mL.

Sample solution: Use the *Purified Water* extract from *Total Terephthaloyl Moieties in Polyethylene Terephthalate and Polyethylene Terephthalate G Packaging Systems*.

Procedure: Transfer 1.0 mL of the *Standard solution* to a 10-mL volumetric flask. Transfer 1.0 mL of the *Sample solution* to a second 10-mL volumetric flask. Transfer 1.0 mL of the *Purified Water* extracting medium to a third 10-mL volumetric flask to serve as the method blank. To each of the three flasks, add 100 µL of *Periodic acid solution*, swirl to mix, and allow to stand for 60 min. Add 1.0 mL of *Sodium bisulfite solution* to each flask, and mix. Add 100 µL of *Disodium chromotropate solution* to each flask, and mix. [NOTE—All solutions should be analyzed within 1 h after addition of the *Disodium chromotropate solution*.] Cautiously add 6 mL of sulfuric acid to each flask, mix, and allow the solutions to cool to room temperature.

[CAUTION—Dilution of sulfuric acid produces substantial heat and can cause the solution to boil. Perform this addition carefully. Sulfur dioxide gas will be evolved. Use of a fume hood is recommended.]

Dilute each solution with *Dilute sulfuric acid* to volume, and mix. Concomitantly determine the absorbances of the solutions from the *Standard solution* and the *Sample solution* in 1-cm cells at the wavelength of maximum absorbance at about 575 nm (see (857)), using the solution from the *Purified Water* extracting medium as the method blank.

Chemical Safety Assessment

The safety of the packaging system must be established on the basis of relevant and appropriate chemical testing of 1) the packaging system, 2) its materials of construction, 3) its components of construction as appropriate, or 4) the packaged drug product. Appropriate chemical testing of materials of construction is specified in (661.1) and may include the demonstration of conformance with the appropriate sections of 21 CFR Indirect Food Additives regulations. With regard to the testing of the packaging system (and/or its components of construction as appropriate) and the packaged drug product, an appropriate and rigorous chemical safety assessment would include extractables testing of the packaging system and leachables testing of the packaged drug product. It is expected that the design of the extractables and leachables study would be based on sound and justifiable scientific principles, and that the studies themselves would be consistent with 1) the nature of both the packaging system and packaged drug product, 2) the clinical use of the packaged drug product, and 3) the perceived safety risk associated with the packaging system and dosage form. Although no dosage form is excluded from this testing requirement, it is anticipated that the nature and degree of testing would be dosage form-dependent and consistent with a risk-based approach. In view of the considerable diversity of packaging systems, dosage forms, and packaged drug products, it is not possible to provide specific test conditions for performing extractables and leachables studies. Nevertheless, general essential principles and demonstrated best-practices recommendations for extractable and leachable studies can be found in *Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems* (1663) and *Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery Systems* (1664), respectively. These chapters may serve as helpful resources for designing and justifying rigorous and appropriate studies.

Alternative testing strategies for chemical safety assessment may be appropriate in justified circumstances, subject to agreement by an appropriate regulatory authority.

SPECIFICATIONS

Biological Reactivity

Test results are consistent with the relevant chapters ((87) or (88)).

Physicochemical Tests

Appearance of solution: *Solution C1* is clear and colorless.

Absorbance: NMT 0.20

Acidity or alkalinity: The solution is colorless after the addition of phenolphthalein solution, pink after the addition of 0.01 N sodium hydroxide, and orange-red or red after the addition of 0.01 N hydrochloric acid and 0.1 mL of methyl red solution.

Total organic content: The difference in TOC concentrations between *Solution C1* and a suitable blank is NMT 8 mg/L.

Ethylene glycol in polyethylene terephthalate and polyethylene terephthalate G packaging systems: The absorbance of the solution from the *Sample solution* does not exceed that of the solution from the *Standard solution*, corresponding to NMT 1 ppm of ethylene glycol.

Total terephthaloyl moieties in polyethylene terephthalate and polyethylene terephthalate G packaging systems: The absorbance of the 50% alcohol, 25% alcohol, and *n*-heptane extracts does not exceed 0.150, corresponding to NMT 1 ppm of total terephthaloyl moieties.

Chemical Safety Assessment

The data and information obtained in the *Chemical Safety Assessment* must be interpreted in the context of establishing the patient safety risk associated with the use of the packaging system and the administration of the packaged drug product. Most typically, such an interpretation of the chemical data involves the toxicological safety assessment of extractables and leachables data, supported, as appropriate, by other relevant testing. In this circumstance, the toxicological safety assessment should be performed for each individual relevant member of the packaging system's extractables profile (or each relevant member of the contained product's leachables profile, as appropriate). The assessment should demonstrate that the user safety risk associated with each individual relevant leachable (or extractable as a worst-case leachable) is acceptable and that the probable safety risk posed by all leachables (or extractables as worst-case leachables), considered individually, is within acceptable parameters. The term "relevant extractable or leachable" refers to those extractables that are present in a packaging system and those leachables that are present in a packaged drug product at levels sufficiently high that they have been deemed to have a potential safety impact, based, for example, on a comparison of the levels of extractables or leachables with a recognized and well-established safety alert threshold. Establishing and justifying the acceptable parameters used to assess the safety impact is the responsibility of the applicant who secures and owns the regulatory approval of a packaging system or packaged drug product; such acceptable parameters must be based on and derived from the sound application of established principles of toxicological safety assessment.

For leachables that are also elemental impurities, note that limits for elemental impurities in marketed pharmaceutical drug products (but not specifically packaging systems) can be found in *Elemental Impurities—Limits* (232).

Alternative chemical safety assessment specifications may be appropriate in justified circumstances, subject to agreement by an appropriate regulatory authority.