Change to read:

▲⟨661.2⟩ PLASTIC PACKAGING SYSTEMS FOR PHARMACEUTICAL USE

(This chapter will become official on December 1, 2025. Early adoption of the requirements in this chapter and its companion chapter *Plastic Materials of Construction* ⟨661.1⟩ **are permitted by USP. If** ⟨661.1⟩ **or** ⟨661.2⟩ **are referenced elsewhere in *USP-NF* prior to December 1, 2025, the standards in** *Plastic Packaging Systems and Their Materials of Construction* ⟨661⟩ **will apply if early adoption of** ⟨661.1⟩ **or** ⟨661.2⟩ **has not occurred.**

INTRODUCTION

A packaging system, as defined in *Packaging and Storage Requirements* ⟨659⟩, contains or is intended to contain a drug product, including pharmaceuticals and biologics. The packaging system provides the means for storing and distributing drug products, and in some cases the means for administering the drug product. A plastic packaging system is composed wholly or of a substantial portion of plastic materials and/or components and refers to the sum of packaging components that together contain the drug product, including closures (e.g., rubber seals, foil closures, laminated closures).

SCOPE

This chapter applies specifically to plastic packaging components and systems used for packaging final drug products. Associated components, as defined in ⟨659⟩, are not within the scope of this chapter. The testing of materials of construction used in packaging systems is addressed in *Plastic Materials of Construction* ⟨661.1⟩. The requirements of ⟨661.1⟩ are met by performing the tests in ⟨661.1⟩ or if the material is used in a packaging component or system that meets the requirements of ⟨661.2⟩. A product's packaging component or system is deemed chemically suited for its intended use, if it meets the requirements in ⟨661.2⟩.

The packaging component or system should be constructed from well-characterized materials as defined in ⟨661.1⟩ and is chemically suited for its intended use if:

- The packaging component's or system's general physicochemical properties have been established.
- The packaging component's or system's biological reactivity has been appropriately established.
- The packaging component or system has been established to be suitable by means of the appropriate chemical suitability for use assessment.

Table 1 indicates the appropriate application of the physicochemical and biological reactivity tests.

Table 1. Application of Tests

Test Parameter	Oral and Topical Dosage Forms[a]	All Other Dosage Forms
Physicochemical Tests		
UV absorbance	X	X
Acidity/alkalinity	X[b]	X[b]
TOC	X	X
Appearance of solution	X	X
Total terephthaloyl moieties	PET and PETG only[c]	PET and PET G only[c]
Ethylene glycol	PET and PETG only[c]	PET and PET G only[c]
Biological Reactivity Tests		
Biological Reactivity Tests, In Vitro ⟨87⟩[d]	—	X
▲Chemical Suitability for Use		
Assessment	Risk-based testing	Risk-based testing
Functionality▲ (ERR 1-Dec-2020)		
Spectral Transmission	If light protection is necessary	If light protection is necessary▲▲ (ERR 1-Dec-2020)

[a] For aqueous-based oral drug products that contain cosolvents (or if, for any reason, the drug product is expected to extract greater amounts of substances from plastic packaging components than water), additional extractables information may be needed to determine suitability.

[b] 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.

[c] Polyethylene terephthalate (PET) and polyethylene terephthalate G (PETG).

[d] Biological reactivity testing in support of plastic packaging components and systems used for final pharmaceutical product packaging/delivery systems (drugs and drug/device combination products) provides baseline information and will often not be sufficient to assess the final suitability for use expectations of regulatory authorities. Thus, it is important to work with the appropriate regulatory authority for guidance regarding a product specific application.

BIOLOGICAL REACTIVITY AND PHYSICOCHEMICAL TEST METHODS

Biological Reactivity

In vitro biological reactivity testing described in *Biological Reactivity Tests, In Vitro* ⟨87⟩ is not required for packaging components and systems used for oral and topical dosage forms.

ACCEPTANCE CRITERIA

Test results are consistent with ⟨87⟩.

Physicochemical Tests

SOLUTION C1: Fill the packaging system to its nominal capacity [1] 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 ± 2° 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 ± 2° for 2 h or at 70 ± 2° for 24 ± 2 h in an autoclave or oven. Cool the filled packaging system and empty its contents. The emptied contents are *Solution C1*.

In certain situations, packaging systems may have such small fill volumes that an alternative testing method is necessary to produce sufficient extract volume for testing. One possible means to obtain a sufficient volume to accomplish the required analytical testing would be to combine the contents of many individual systems. Alternatively, it might also be possible to construct a model packaging system of sufficient fill volume. When the modeling packaging system approach is being used care must be taken to preserve the required contact conditions (e.g., solution contact surfaces, extracted surface area per unit volume of extraction solution, etc.).

If the test is being performed on a component, then the component is placed in an inert extraction vessel and put into contact with an amount of *Purified Water* that is equal to the packaging system's nominal capacity. The extraction vessel is closed and then heated as described above for a packaging system. Cool the extraction vessel and empty its contents. The emptied contents are *Solution C1*.

BLANK: 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*. Use *Solution C1* and the blank within 4 h of preparation.

APPEARANCE OF SOLUTION, COLOR

Standard solution CS1: Mix 3 mL of cobaltous chloride CS, 3 mL of ferric chloride CS, 2.4 mL of cupric sulfate CS, and 1.6 mL of 10 g/L of hydrochloric acid to produce the standard solution.
Reference solution RS1: Add 1.0 mL of *Standard solution CS1* to a 100-mL volumetric flask and dilute with 10 g/L of hydrochloric acid to volume.
Procedure: Transfer equal portions of *Reference solution RS1*, *Purified Water*, and *Solution C1* to individual identical, colorless, transparent, neutral, flat-based glass vessels (internal diameter of 15–25 mm). Compare the colors in diffuse daylight, viewing vertically against a white background.

Solution C1 is colorless if it has the appearance of *Purified Water* and is not more intensely colored than *Reference solution RS1*.
Acceptance criteria: *Solution C1* is colorless.

APPEARANCE OF SOLUTION, CLARITY (VISUAL METHOD)

Hydrazine sulfate solution: Dissolve 1.0 g of hydrazine in *Purified Water* and dilute with *Purified Water* to 100 mL. Allow to stand for 4–6 h.
Hexamethylenetetramine solution: Using a 100-mL stoppered flask, dissolve 2.5 g of hexamethylenetetramine in 25.0 mL of *Purified Water*.
Primary opalescent suspension: Add 25 mL of the *Hydrazine sulfate solution* to the volumetric flask containing the *Hexamethylenetetramine solution*. Mix and allow to stand for 24 h. This suspension is stable for 2 months, provided that it does not adhere to the glass and it is well mixed prior to use.
Standard of opalescence: Dilute 15 mL of the *Primary opalescent suspension* with *Purified Water* to 1000 mL. This solution can be stored for 24 h.
Reference suspension: Add 5 mL of the *Standard of opalescence* and 95 mL of *Purified Water* and mix well.
Procedure: Transfer equal portions of *Reference suspension*, *Purified Water*, and *Solution C1* to individual identical, colorless, transparent, neutral, flat-based glass vessels (internal diameter of 15–25 mm). Compare the solutions in diffuse daylight 5 min after preparation, viewing vertically against a black background.

Solution C1 is clear if its clarity is the same as *Purified Water* and its opalescence is not more pronounced than that of the *Reference suspension*.
Acceptance criteria: *Solution C1* is clear.

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

[1] "Nominal volume" is the labeled volume of a commercial drug product contained in its packaging system. If the drug product is a solid dosage form, the nominal volume can be established as the total volume of solid contained in the packaging system.

Acceptance criteria: NMT 0.20. If the acceptance criteria for absorbance is exceeded, then the packaging system can still be considered acceptable if the chemicals responsible for the test results can be established (identity and concentration) and the chemicals are assessed to establish that the probable risk posed by all the chemicals, considered individually, is within acceptable parameters.

ACIDITY OR ALKALINITY: Conduct the test for *Acidity or alkalinity* when packaging systems are intended to hold a liquid product.

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 TS 2 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 is required to change the color from red to yellow.

Acceptance criteria: 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 TS 2 solution.

TOTAL ORGANIC CARBON

Refer to *Total Organic Carbon* ⟨643⟩.

The total organic carbon (TOC) content of *Solution C1* is measured according to ⟨643⟩,*Procedures, Bulk Water*. 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.

Acceptance criteria: The difference in TOC concentrations between *Solution C1* and a suitable blank is NMT 8 mg/L. If the acceptance criteria for TOC is exceeded, then the packaging system can still be considered acceptable if the chemicals responsible for the test results can be established (identity and concentration) and the chemicals are assessed to establish that the probable risk posed by all the chemicals, considered individually, is within acceptable parameters.

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

Polyethylene terephthalate extracting media: 50% alcohol (dilute 125 mL of alcohol 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 in *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.

Acceptance criteria: 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.

ETHYLENE GLYCOL IN POLYETHYLENE TEREPHTHALATE AND POLYETHYLENE TEREPHTHALATE G PACKAGING SYSTEMS

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, 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 *Purified Water*. Use this solution within 7 days.

Disodium chromotropate solution: Dissolve 100 mg of disodium chromotropate 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.
Acceptance criteria: 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.

Chemical Suitability Assessment

The suitability 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⟩. With regard to the testing of the packaging system (and/or its components as appropriate) and the packaged drug product, an appropriate and rigorous chemical suitability for use assessment may include extractables testing of the packaging component or 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 a chemical suitability for use assessment, it is anticipated that the nature and degree of testing would be dosage form-dependent and consistent with a risk-based approach. For example, the testing of packaging components or systems for low-risk dosage forms, such as solid and aqueous-based oral and topicals, should be consistent with the low risk associated with these dosage forms. 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 suitability for use assessment may be appropriate in justified circumstances, subject to agreement by an appropriate regulatory authority.

FUNCTIONALITY TEST METHOD

Spectral Transmission Requirements for Light-Resistant Components and Systems

APPARATUS

If the suitability of the packaging system is demonstrated through stability testing, spectral transmission testing is not required, otherwise use a UV-visible spectrophotometer of suitable sensitivity and accuracy (see ⟨857⟩), adapted for measuring the amount of light transmitted by plastic materials used for pharmaceutical containers.

PROCEDURE

Select a section to represent the average wall thickness. Cut a circular section from the packaging component or system, and trim as necessary to get a segment convenient for mounting in the spectrophotometer. After cutting, wash and dry the specimen, taking care to avoid scratching the surfaces. If the specimen is too small to cover the opening in the specimen holder, mask the uncovered portion of the opening with opaque paper or masking tape, provided that the length of the specimen is greater than that of the slit in the spectrophotometer. Immediately before mounting in the specimen holder, wipe the specimen with lens tissue. Mount the specimen with the aid of a tacky wax, or by other convenient means, taking care to avoid leaving fingerprints or other marks on the surfaces through which light must pass. Place the section in the spectrophotometer with its cylindrical axis parallel to the plane of the slit and approximately centered with respect to the slit. When properly placed, the light beam is normal to the surface of the section, and reflection losses are at a minimum.

Continuously measure the transmittance of the section with reference to air in the spectral region of interest with a recording instrument or at intervals of about 20 nm with a manual instrument, in the region of 290–450 nm.

ACCEPTANCE CRITERIA

The observed spectral transmission is NMT the limits given in *Table 2* for plastic packaging components and systems intended for parenteral use. The observed spectral transmission for plastic containers for products intended for oral or topical administration does not exceed 10% at any wavelength in the range of 290–450 nm.

Table 2. Spectral Transmission Limits for Plastic Packaging Components or Systems

Nominal Size (mL)	Maximum Percentage of Spectral Transmission at Any Wavelength between 290 and 450 nm (%)
1	25
2	20
5	15

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Table 2. Spectral Transmission Limits for Plastic Packaging Components or Systems *(continued)*

Nominal Size (mL)	Maximum Percentage of Spectral Transmission at Any Wavelength between 290 and 450 nm (%)
10	13
20	12
50	10
>50	10

[NOTE—For components or systems of an intermediate size, the acceptance criterion is the spectral transmission of the next larger size.▲ (Official 1-Dec-2025)]