<661> Plastic Packaging Systems and Their Materials of Construction

Type of Posting	Revision Bulletin, Postponement
Posting Date	28–Apr–2017, revised 26-May-2017[1]
Official Date	01–May–2017
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> Plastic Packaging Systems and Their Materials of Construction.

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> Plastic Packaging Systems and Their Materials of Construction 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⟩ PLASTIC PACKAGING SYSTEMS AND THEIR MATERIALS OF CONSTRUCTION

Add the following:

•(If the option of early adoption of *Plastic Materials of Construction* ⟨661.1⟩ and *Plastic Packaging Systems for Pharmaceutical Use* ⟨661.2⟩ is not used prior to May 1, 2020, the requirements under this chapter will apply.)• (RB 1-May-2017)

Add the following:

•INTRODUCTION

It is the purpose of this chapter to provide standards for plastic materials and components used to package medical articles (pharmaceuticals, biologics, dietary supplements, and devices). Definitions that apply to this chapter are provided in *Packaging and Storage Requirements* ⟨659⟩. Standards and tests for the functional properties of containers and their components are provided in *Containers—Performance Testing* ⟨671⟩.

In addition to the standards provided herein, the ingredients added to the polymers, and those used in the fabrication of the containers, must conform to the requirements in the applicable sections of the *Code of Federal Regulations*, Title 21, *Indirect Food Additives*, or have been evaluated by the FDA and determined to be acceptable substances for the listed use.

Plastic articles are identified and characterized by IR spectroscopy and differential scanning calorimetry. Standards are provided in this chapter for the identification and characterization of the different types of plastic, and the test procedures are provided at the end of the chapter. The degree of testing is based on whether or not the container has direct contact with the drug product, and the risk is based on the route of administration.

Plastics are composed of a mixture of homologous polymers, having a range of molecular weights. Plastics may contain other substances such as residues from the polymerization process, plasticizers, stabilizers, antioxidants, pigments, and lubricants. These materials meet the requirements for food contact as provided in the *Code of Federal Regulations*, Title 21. Factors such as plastic composition, processing and cleaning procedures, surface treatment, contacting media, inks, adhesives, absorption and permeability of preservatives, and conditions of storage may also affect the suitability of a plastic for a specific use. Extraction tests are designed to characterize the extracted components and identify possible migrants. The degree or extent of testing for extractables of the component is dependent on the intended use and the degree of risk to adversely impact the efficacy of the compendial article (drug, biologic, dietary supplement, or device). Resin-specific extraction tests are provided in this chapter for polyethylene, polypropylene, polyethylene terephthalate, and polyethylene terephthalate G. Test all other plastics as directed for *Test Methods, Physicochemical Tests*. Conduct the *Buffering Capacity* test only when the containers are intended to hold a liquid product.

Plastic components used for products of high risk, such as those intended for inhalation, parenteral preparation, and ophthalmics, are tested using *Test Methods, Biological Tests*.

Plastic containers intended for packaging products prepared for parenteral use meet the requirements for *Test Methods, Biological Tests* and *Physicochemical Tests*. Standards are also provided for polyethylene containers used to package dry oral dosage forms that are not meant for constitution into solution.

POLYETHYLENE CONTAINERS

Scope

The standards and tests provided in this section characterize containers and components, produced from either low-density polyethylene or high-density polyethylene of either homopolymer or copolymer resins that are interchangeably suitable for packaging dry oral dosage forms not meant for constitution into solution. All polyethylene components are subject to testing by IR spectroscopy and differential scanning calorimetry. Where stability studies have been performed to establish the expiration date of a particular dosage form in the appropriate polyethylene container, then any other polyethylene container meeting these requirements may be similarly used to package such a dosage form, provided that the appropriate stability programs are expanded to include the alternative container, in order to ensure that the identity, strength, quality, and purity of the dosage form are maintained throughout the expiration period.

Background

High-density and low-density polyethylene are long-chain polymers synthesized under controlled conditions of heat and pressure, with the aid of catalysts from not less than 85.0% ethylene and not less than 95.0% total olefins. Other olefin ingredients that are most frequently used are butene, hexene, and propylene. High-density polyethylene and low-density polyethy-

lene both have an IR absorption spectrum that is distinctive for polyethylene, and each possesses characteristic thermal properties. High-density polyethylene has a density between 0.941 and 0.965 g per cm^3. Low-density polyethylene has a density between 0.850 and 0.940 g per cm^3. Other properties that may affect the suitability of polyethylene include modulus of elasticity, melt index, environmental stress crack resistance, and degree of crystallinity after molding.

High-Density Polyethylene

Infrared Spectroscopy—Proceed as directed for *Test Methods, Multiple Internal Reflectance*. The corrected spectrum of the specimen exhibits major absorption bands only at the same wavelengths as the spectrum of USP High-Density Polyethylene RS.

Differential Scanning Calorimetry—Proceed as directed for *Test Methods, Thermal Analysis*. The thermogram of the specimen is similar to the thermogram of USP High-Density Polyethylene RS, similarly determined, and the temperature of the endotherm (*melt*) in the thermogram of the specimen does not differ from that of the USP Reference Standard by more than 6.0°.

Heavy Metals and Nonvolatile Residue—Prepare extracts of specimens for these tests as directed for *Test Methods, Physicochemical Tests*, except that for each 20.0 mL of *Extracting Medium* the portion shall be 60 cm^2, regardless of thickness.

HEAVY METALS—Containers meet the requirements for *Test Methods, Physicochemical Tests, Heavy Metals*.

NONVOLATILE RESIDUE—Proceed as directed for *Test Methods, Physicochemical Tests, Nonvolatile Residue*, except that the *Blank* shall be the same solvent used in each of the following test conditions: the difference between the amounts obtained from the *Sample Preparation* and the *Blank* does not exceed 12.0 mg when water maintained at a temperature of 70° is used as the *Extracting Medium*; does not exceed 75.0 mg when alcohol maintained at a temperature of 70° is used as the *Extracting Medium*; and does not exceed 100.0 mg when hexanes maintained at a temperature of 50° is used as the *Extracting Medium*.

Components Used in Contact with Oral Liquids—Proceed as directed for *Test Methods, Physicochemical Tests, Buffering Capacity*.

Low-Density Polyethylene

Infrared Spectroscopy—Proceed as directed for *Test Methods, Multiple Internal Reflectance*. The corrected spectrum of the specimen exhibits major absorption bands only at the same wavelengths as the spectrum of USP Low-Density Polyethylene RS.

Differential Scanning Calorimetry—Proceed as directed for *Test Methods, Thermal Analysis*. The thermogram of the specimen is similar to the thermogram of USP Low-Density Polyethylene RS, similarly determined, and the temperature of the endotherm (*melt*) in the thermogram of the specimen does not differ from that of the USP Reference Standard by more than 8.0°.

Heavy Metals and Nonvolatile Residue—Prepare extracts of specimens for these tests as directed for *Test Methods, Physicochemical Tests, Testing Parameters, Sample Preparation*, except that for each 20.0 mL of *Extracting Medium* the portion shall be 60 cm^2, regardless of thickness.

HEAVY METALS—Containers meet the requirements for *Test Methods, Physicochemical Tests, Heavy Metals*.

NONVOLATILE RESIDUE—Proceed as directed for *Test Methods, Physicochemical Tests, Nonvolatile Residue*, except that the *Blank* shall be the same solvent used in each of the following test conditions: the difference between the amounts obtained from the *Sample Preparation* and the *Blank* does not exceed 12.0 mg when water maintained at a temperature of 70° is used as the *Extracting Medium*; does not exceed 75.0 mg when alcohol maintained at a temperature of 70° is used as the *Extracting Medium*; and does not exceed 350.0 mg when hexanes maintained at a temperature of 50° is used as the *Extracting Medium*.

Components Used in Contact with Oral Liquids—Proceed as directed for *Test Methods, Physicochemical Tests, Buffering Capacity*.

POLYPROPYLENE CONTAINERS

Scope

The standards and tests provided in this section characterize polypropylene containers, produced from either homopolymers or copolymers, that are interchangeably suitable for packaging dry solid and liquid oral dosage forms. Where suitable stability studies have been performed to establish the expiration date of a particular dosage form in the appropriate polypropylene container, then any other polypropylene container meeting these requirements may be similarly used to package such a dosage form, provided that the appropriate stability programs are expanded to include the alternative container, in order to ensure that the identity, strength, quality, and purity of the dosage form are maintained throughout the expiration period.

Background

Propylene polymers are long-chain polymers synthesized from propylene or propylene and other olefins under controlled conditions of heat and pressure, with the aid of catalysts. Examples of other olefins most commonly used include ethylene and

butene. The propylene polymers, the ingredients used to manufacture the propylene polymers, and the ingredients used in the fabrication of the containers conform to the applicable sections of the *Code of Federal Regulations,* Title 21.

Factors such as plastic composition, processing and cleaning procedures, contacting media, inks, adhesives, absorption, adsorption and permeability of preservatives, and conditions of storage may also affect the suitability of a plastic for a specific use. The suitability of a specific polypropylene must be established by appropriate testing.

Polypropylene has a distinctive IR spectrum and possesses characteristic thermal properties. It has a density between 0.880 and 0.913 g per cm^3. The permeation properties of molded polypropylene containers may be altered when reground polymer is incorporated, depending on the proportion of reground material in the final product. Other properties that may affect the suitability of polypropylene used in containers for packaging drugs are the following: oxygen and moisture permeability, modulus of elasticity, melt flow index, environmental stress crack resistance, and degree of crystallinity after molding. The requirements in this section are to be met when dry solid and liquid oral dosage forms are to be packaged in a container defined by this section.

Infrared Spectroscopy—Proceed as directed for *Test Methods, Multiple Internal Reflectance*. The corrected spectrum of the specimen exhibits major absorption bands only at the same wavelengths as the spectrum of the respective USP Homopolymer Polypropylene RS or copolymer polypropylene standard, similarly determined.

Differential Scanning Calorimetry—Proceed as directed for *Test Methods, Thermal Analysis*. The temperature of the endotherm (*melt*) in the thermogram does not differ from that of the USP Reference Standard for homopolymers by more than 6.0°. The temperature of the endotherm obtained from the thermogram of the copolymer polypropylene specimen does not differ from that of the copolymer polypropylene standard by more than 12.0°.

Heavy Metals and Nonvolatile Residue—Prepare extracts of specimens for these tests as directed for *Test Methods, Physicochemical Tests, Sample Preparation*, except that for each 20 mL of *Extracting Medium* the portion shall be 60 cm^2, regardless of thickness.

HEAVY METALS—Containers meet the requirements for *Test Methods, Physicochemical Tests, Heavy Metals*.

NONVOLATILE RESIDUE—Proceed as directed for *Test Methods, Physicochemical Tests, Nonvolatile Residue*, except that the *Blank* shall be the same solvent used in each of the following test conditions: the difference between the amounts obtained from the *Sample Preparation* and the *Blank* does not exceed 10.0 mg when water maintained at a temperature of 70° is used as the *Extracting Medium;* does not exceed 60.0 mg when alcohol maintained at a temperature of 70° is used as the *Extracting Medium;* and does not exceed 225.0 mg when hexanes maintained at a temperature of 50° is used as the *Extracting Medium*. Containers meet these requirements for *Nonvolatile Residue* for all of the above extracting media. [NOTE—Hexanes and alcohol are flammable. When evaporating these solvents, use a current of air with the water bath; when drying the residue, use an explosion-proof oven.]

Components Used in Contact with Oral Liquids—Proceed as directed for *Test Methods, Physicochemical Tests, Buffering Capacity*.

POLYETHYLENE TEREPHTHALATE BOTTLES AND POLYETHYLENE TEREPHTHALATE G CONTAINERS

Scope

The standards and tests provided in this section characterize polyethylene terephthalate (PET) and polyethylene terephthalate G (PETG) bottles that are interchangeably suitable for packaging liquid oral dosage forms. Where stability studies have been performed to establish the expiration date of a particular liquid oral dosage form in a bottle meeting the requirements set forth herein for either PET or PETG bottles, any other PET or PETG bottle meeting these requirements may be similarly used to package such a dosage form, provided that the appropriate stability programs are expanded to include the alternative bottle in order to ensure that the identity, strength, quality, and purity of the dosage form are maintained throughout the expiration period. The suitability of a specific PET or PETG bottle for use in the dispensing of a particular pharmaceutical liquid oral dosage form must be established by appropriate testing.

Background

PET resins are long-chain crystalline polymers prepared by the condensation of ethylene glycol with dimethyl terephthalate or terephthalic acid. PET copolymer resins are prepared in a similar way, except that they may also contain a small amount of either isophthalic acid (not more than 3 mole percent) or 1,4-cyclohexanedimethanol (not more than 5 mole percent). Polymerization is conducted under controlled conditions of heat and vacuum, with the aid of catalysts and stabilizers.

PET copolymer resins have physical and spectral properties similar to PET and for practical purposes are treated as PET. The tests and specifications provided in this section to characterize PET resins and bottles apply also to PET copolymer resins and to bottles fabricated from them.

PET and PET copolymer resins generally exhibit a large degree of order in their molecular structure. As a result, they exhibit characteristic composition-dependent thermal behavior, including a glass transition temperature of about 76° and a melting temperature of about 250°. These resins have a distinctive IR absorption spectrum that allows them to be distinguished from other plastic materials (e.g., polycarbonate, polystyrene, polyethylene, and PETG resins). PET and PET copolymer resins have a

density between 1.3 and 1.4 g per cm^3 and a minimum intrinsic viscosity of 0.7 dL per g, which corresponds to a number average molecular weight of about 23,000 Da.

PETG resins are high molecular weight polymers prepared by the condensation of ethylene glycol with dimethyl terephthalate or terephthalic acid and 15 to 34 mole percent of 1,4-cyclohexanedimethanol. PETG resins are clear, amorphous polymers, having a glass transition temperature of about 81° and no crystalline melting point, as determined by differential scanning calorimetry. PETG resins have a distinctive IR absorption spectrum that allows them to be distinguished from other plastic materials, including PET. PETG resins have a density of approximately 1.27 g per cm^3 and a minimum intrinsic viscosity of 0.65 dL per g, which corresponds to a number average molecular weight of about 16,000 Da.

PET and PETG resins, and other ingredients used in the fabrication of these bottles, conform to the requirements in the applicable sections of the *Code of Federal Regulations*, Title 21, regarding use in contact with food and alcoholic beverages. PET and PETG resins do not contain any plasticizers, processing aids, or antioxidants. Colorants, if used in the manufacture of PET and PETG bottles, do not migrate into the contained liquid.

Infrared Spectroscopy—Proceed as directed for *Test Methods, Multiple Internal Reflectance*. The corrected spectrum of the specimen exhibits major absorption bands only at the same wavelengths as the spectrum of USP Polyethylene Terephthalate RS, or USP Polyethylene Terephthalate G RS, similarly determined.

Differential Scanning Calorimetry—Proceed as directed for *Test Methods, Thermal Analysis*. For polyethylene terephthalate, the thermogram of the specimen is similar to the thermogram of USP Polyethylene Terephthalate RS, similarly determined: the melting point (T_m) of the specimen does not differ from that of the USP Reference Standard by more than 9.0°, and the glass transition temperature (T_g) of the specimen does not differ from that of the USP Reference Standard by more than 4.0°. For polyethylene terephthalate G, the thermogram of the specimen is similar to the thermogram of USP Polyethylene Terephthalate G RS, similarly determined: the glass transition temperature (T_g) of the specimen does not differ from that of the USP Reference Standard by more than 6.0°.

Colorant Extraction—Select three test bottles. Cut a relatively flat portion from the side wall of one bottle, and trim it as necessary to fit the sample holder of the spectrophotometer. Obtain the visible spectrum of the side wall by scanning the portion of the visible spectrum from 350 to 700 nm. Determine, to the nearest 2 nm, the wavelength of maximum absorbance. Fill the remaining two test bottles, using 50% alcohol for PET bottles and 25% alcohol for PETG bottles. Fit the bottles with impervious seals, such as aluminum foil, and apply closures. Fill a glass bottle having the same capacity as that of the test bottles with the corresponding solvent, fit the bottle with an impervious seal, such as aluminum foil, and apply a closure. Incubate the test bottles and the glass bottle at 49° for 10 days. Remove the bottles, and allow them to equilibrate to room temperature. Concomitantly determine the absorbances of the test solutions in 5-cm cells at the wavelength of maximum absorbance (see *Ultraviolet-Visible Spectroscopy* ⟨857⟩), using the corresponding solvent from the glass bottle as the blank. The absorbance values so obtained are less than 0.01 for both test solutions.

Heavy Metals, Total Terephthaloyl Moieties, and Ethylene Glycol—

EXTRACTING MEDIA—

Purified Water—See monograph.

50 Percent Alcohol—Dilute 125 mL of alcohol with water to 238 mL, and mix.

25 Percent Alcohol—Dilute 125 mL of *50 Percent Alcohol* with water to 250 mL, and mix.

n-Heptane

GENERAL PROCEDURE—[NOTE—Use an *Extracting Medium* of *50 Percent Alcohol* for PET bottles and *25 Percent Alcohol* for PETG bottles.] For each *Extracting Medium,* fill a sufficient number of test bottles to 90% of their nominal capacity to obtain not less than 30 mL. Fill a corresponding number of glass bottles with *Purified Water*, a corresponding number of glass bottles with *50 Percent Alcohol* or *25 Percent Alcohol*, and a corresponding number of glass bottles with *n-Heptane* for use as *Extracting Media* blanks. Fit the bottles with impervious seals, such as aluminum foil, and apply closures. Incubate the test bottles and the glass bottles at 49° for 10 days. Remove the test bottles with the *Extracting Media* samples and the glass bottles with the *Extracting Media* blanks, and store them at room temperature. Do not transfer the *Extracting Media* samples to alternative storage vessels.

HEAVY METALS—Pipet 20 mL of the *Purified Water* extract of the test bottles, filtered if necessary, into one of two matched 50-mL color-comparison tubes, and retain the remaining *Purified Water* extract in the test bottles for use in the test for *Ethylene Glycol*. Adjust the extract with 1 N acetic acid or 6 N ammonium hydroxide to a pH between 3.0 and 4.0, using short-range pH paper as an external indicator. Dilute with water to about 35 mL, and mix.

Into the second color-comparison tube, pipet 2 mL of freshly prepared (on day of use) *Standard Lead Solution* (see *Test Methods, Physicochemical Tests, Heavy Metals*), and add 20 mL of *Purified Water*. Adjust with 1 N acetic acid or 6 N ammonium hydroxide to a pH between 3.0 and 4.0, using short-range pH paper as an external indicator. Dilute with water to about 35 mL, and mix.

To each tube add 1.2 mL of thioacetamide–glycerin base TS and 2 mL of *pH 3.5 Acetate Buffer* (see *Test Methods, Physicochemical Tests, Heavy Metals*), dilute with water to 50 mL, and mix: any color produced within 10 minutes in the tube containing the *Purified Water* extract of the test bottles does not exceed that in the tube containing the *Standard Lead Solution*, both tubes being viewed downward over a white surface (1 ppm in extract).

TOTAL TEREPHTHALOYL MOIETIES—Determine the absorbance of the *50 Percent Alcohol* or *25 Percent Alcohol* extract in a 1-cm cell at the wavelength of maximum absorbance at about 244 nm (see ⟨857⟩), using as the blank the corresponding *Extracting Medium* blank: the absorbance of the extract does not exceed 0.150, corresponding to not more than 1 ppm of total terephthaloyl moieties.

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⟩), using as the blank the *n-Heptane Extracting Medium*: the absorbance of the extract does not exceed 0.150, corresponding to not more than 1 ppm of total terephthaloyl moieties.

ETHYLENE GLYCOL—

Periodic Acid Solution—Dissolve 125 mg of periodic acid in 10 mL of water.

Dilute Sulfuric Acid—To 50 mL of water add slowly 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 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 water, and dilute quantitatively, and stepwise if necessary, to obtain a solution having a known concentration of about 1 μg per mL.

Test Solution—Use the *Purified Water* extract.

Procedure—Transfer 1.0 mL of the *Standard Solution* to a 10-mL volumetric flask. Transfer 1.0 mL of the *Test 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 each of the three flasks, add 100 μL of *Periodic Acid Solution,* swirl to mix, and allow to stand for 60 minutes. 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 hour 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 *Test Solution* in 1-cm cells at the wavelength of maximum absorbance at about 575 nm (see ⟨857⟩), using as the blank the solution from the *Purified Water Extracting Medium*: the absorbance of the solution from the *Test Solution* does not exceed that of the solution from the *Standard Solution,* corresponding to not more than 1 ppm of ethylene glycol.

TEST METHODS

Multiple Internal Reflectance

Apparatus—Use an IR spectrophotometer capable of correcting for the blank spectrum and equipped with a multiple internal reflectance accessory and a KRS-5 internal reflection plate.[1] A KRS-5 crystal 2-mm thick having an angle of incidence of 45° provides a sufficient number of reflections.

Specimen Preparation—Cut two flat sections representative of the average wall thickness of the container, and trim them as necessary to obtain segments that are convenient for mounting in the multiple internal reflectance accessory. Taking care to avoid scratching the surfaces, wipe the specimens with dry paper or, if necessary, clean them with a soft cloth dampened with methanol, and permit them to dry. Securely mount the specimens on both sides of the KRS-5 internal reflection plate, ensuring adequate surface contact. Prior to mounting the specimens on the plate, they may be compressed to thin uniform films by exposing them to temperatures of about 177° under high pressures (15,000 psi or more).

General Procedure—Place the mounted specimen sections within the multiple internal reflectance accessory, and place the assembly in the specimen beam of the IR spectrophotometer. Adjust the specimen position and mirrors within the accessory to permit maximum light transmission of the unattenuated reference beam. (For a double-beam instrument, upon completing the adjustments in the accessory, attenuate the reference beam to permit full-scale deflection during the scanning of the specimen.) Determine the IR spectrum from 3500 to 600 cm^{-1} for polyethylene and polypropylene and from 4000 to 400 cm^{-1} for PET and PETG.

Thermal Analysis

General Procedure—Cut a section weighing about 12 mg, and place it in the test specimen pan. [NOTE—Intimate contact between the pan and the thermocouple is essential for reproducible results.] Determine the thermogram under nitrogen, using the heating and cooling conditions as specified for the resin type and using equipment capable of performing the determinations as specified under *Thermal Analysis* ⟨891⟩.

For Polyethylene—Determine the thermogram under nitrogen at temperatures between 40° and 200° at a heating rate between 2° and 10° per minute followed by cooling at a rate between 2° and 10° per minute to 40°.

For Polypropylene—Determine the thermogram under nitrogen at temperatures ranging from ambient to 30° above the melting point. Maintain the temperature for 10 minutes, then cool to 50° below the peak crystallization temperature at a rate of 10° to 20° per minute.

[1] The multiple internal reflectance accessory and KRS-5 plate are available from several sources, including Beckman Instruments, Inc., 2500 Harbor Blvd., Fullerton, CA 92634, and from Perkin Elmer Corp., Main Ave., Norwalk, CT 06856.

For Polyethylene Terephthalate—Heat the specimen from room temperature to 280° at a heating rate of about 20° per minute. Hold the specimen at 280° for 1 minute. Quickly cool the specimen to room temperature, and reheat it to 280° at a heating rate of about 5° per minute.

For Polyethylene Terephthalate G—Heat the specimen from room temperature to 120° at a heating rate of about 20° per minute. Hold the specimen at 120° for 1 minute. Quickly cool the specimen to room temperature, and reheat it to 120° at a heating rate of about 10° per minute.

Biological Tests

The in vitro biological tests are performed according to the procedures set forth under *Biological Reactivity Test, In Vitro* ⟨87⟩. Components that meet the requirements of the in vitro tests are not required to undergo further testing. No plastic class designation is assigned to these materials. Materials that do not meet the requirements of the in vitro tests are not suitable for containers for drug products.

If a plastic class designation is needed for plastics and other polymers that meet the requirements under ⟨87⟩, perform the appropriate in vivo test specified for *Biological Reactivity Test, In Vivo* ⟨88⟩*, Classification of Plastics*.

Physicochemical Tests

The following tests, designed to determine physical and chemical properties of plastics and their extracts, are based on the extraction of the plastic material, and it is essential that the designated amount of the plastic be used. Also, the specified surface area must be available for extraction at the designated temperature.

Testing Parameters—

Extracting Medium—Unless otherwise directed in a specific test below, use *Purified Water* (see monograph) as the *Extracting Medium,* maintained at a temperature of 70° during the extraction of the *Sample Preparation*.

Blank—Use *Purified Water* where a blank is specified in the tests that follow.

Apparatus—Use a water bath and the *Extraction Containers* as described in *Biological Reactivity Tests, In Vivo* ⟨88⟩*, Classification of Plastics, Apparatus*. Proceed as directed in the first paragraph of *Classification of Plastics, Preparation of Apparatus*. [NOTE—The containers and equipment need not be sterile.]

Sample Preparation—From a homogeneous plastic specimen, use a portion, for each 20.0 mL of *Extracting Medium,* equivalent to 120 cm^2 total surface area (both sides combined), and subdivide into strips approximately 3 mm in width and as near to 5 cm in length as is practical. Transfer the subdivided sample to a glass-stoppered, 250-mL graduated cylinder of Type I glass, and add about 150 mL of *Purified Water*. Agitate for about 30 seconds, drain off and discard the liquid, and repeat with a second washing.

Sample Preparation Extract—Transfer the prepared *Sample Preparation* to a suitable extraction flask, and add the required amount of *Extracting Medium.* Extract by heating in a water bath at the temperature specified for the *Extracting Medium* for 24 hours. Cool, but not below 20°. Pipet 20 mL of the prepared extract into a suitable container. [NOTE—Use this portion in the test for *Buffering Capacity*.] Immediately decant the remaining extract into a suitably cleansed container, and seal.

Nonvolatile Residue—Transfer, in suitable portions, 50.0 mL of the *Sample Preparation Extract* to a suitable, tared crucible (preferably a fused-silica crucible that has been acid-cleaned), and evaporate the volatile matter on a steam bath. Similarly evaporate 50.0 mL of the *Blank* in a second crucible. [NOTE—If an oily residue is expected, inspect the crucible repeatedly during the evaporation and drying period, and reduce the amount of heat if the oil tends to creep along the walls of the crucible.] Dry at 105° for 1 hour: the difference between the amounts obtained from the *Sample Preparation Extract* and the *Blank* does not exceed 15 mg.

Residue on Ignition ⟨281⟩—[NOTE—It is not necessary to perform this test when the *Nonvolatile Residue* test result does not exceed 5 mg.] Proceed with the residues obtained from the *Sample Preparation Extract* and from the *Blank* in the test for *Nonvolatile Residue* above, using, if necessary, additional sulfuric acid but adding the same amount of sulfuric acid to each crucible: the difference between the amounts of residue on ignition obtained from the *Sample Preparation Extract* and the *Blank* does not exceed 5 mg.

Heavy Metals—Pipet 20 mL of the *Sample Preparation Extract*, filtered if necessary, into one of two matched 50-mL color-comparison tubes. Adjust with 1 N acetic acid or 6 N ammonium hydroxide to a pH between 3.0 and 4.0, using short-range pH paper as an external indicator, dilute with water to about 35 mL, and mix.

Into the second color-comparison tube pipet 2 mL of *Standard Lead Solution*, and add 20 mL of the *Blank*. Adjust with 1 N acetic acid or 6 N ammonium hydroxide to a pH between 3.0 and 4.0, using short-range pH paper as an external indicator, dilute with water to about 35 mL, and mix. To each tube add 1.2 mL of thioacetamide–glycerin base TS and 2 mL of *pH 3.5 Acetate Buffer*, dilute with water to 50 mL, and mix: any brown color produced within 10 minutes in the tube containing the *Sample Preparation Extract* does not exceed that in the tube containing the *Standard Lead Solution*, both tubes being viewed downward over a white surface (1 ppm in extract).

Lead Nitrate Stock Solution—Dissolve 159.8 mg of lead nitrate in 100 mL of water to which has been added 1 mL of nitric acid, then dilute with water to 1000 mL. Prepare and store this solution in glass containers free from soluble lead salts.

Standard Lead Solution—On the day of use, dilute 10.0 mL of *Lead Nitrate Stock Solution* with water to 100.0 mL. Each mL of *Standard Lead Solution* contains the equivalent of 10 μg of lead. A comparison solution prepared on the basis of 100 μL of

Standard Lead Solution per gram of substance being tested contains the equivalent of 1 part of lead per million parts of substance being tested.

pH 3.5 Acetate Buffer—Dissolve 25.0 g of ammonium acetate in 25 mL of water, and add 38.0 mL of 6 N hydrochloric acid. Adjust, if necessary, with 6 N ammonium hydroxide or 6 N hydrochloric acid to a pH of 3.5, dilute with water to 100 mL, and mix.

Buffering Capacity—Titrate the previously collected 20-mL portion of the *Sample Preparation Extract* potentiometrically to a pH of 7.0, using either 0.010 N hydrochloric acid or 0.010 N sodium hydroxide, as required. Treat a 20.0-mL portion of the *Blank* similarly: if the same titrant was required for both the *Sample Preparation Extract* and the *Blank*, the difference between the two volumes is not greater than 10.0 mL; and if acid was required for either the *Sample Preparation Extract* or the *Blank* and alkali for the other, the total of the two volumes required is not greater than 10.0 mL.

(The text above is official until April 30, 2020. The text beginning below becomes official on May 1, 2020.) • (RB 1-May-2017)

Change to read:

•INTRODUCTION

Systems are used to package therapeutic products (pharmaceuticals, biologics, dietary supplements and devices). Such systems and their associated materials and components of construction are considered and defined in *Packaging and Storage Requirements* ⟨659⟩. Such systems may be constructed from plastic materials and components. The plastics used in packaging systems are composed of homologous polymers with a range of molecular weights and contain additives such as antioxidants, stabilizers, lubricants, plasticizers, colorants, and others. The nature and amount of additives in the plastics used for packaging systems are dictated by the type of polymer, the polymer's use, and the process used to convert the polymer into components, containers, or packaging systems.

Therapeutic products come into direct contact with packaging systems and their plastic materials of construction as the product is manufactured, stored, and administered. Such contact may result in an interaction between the therapeutic products and the packaging systems and its materials or components of construction. These interactions must be such that the suitability for use (including its safety and efficacy) of the therapeutic product and the packaging systems is not adversely affected by the interaction. Although suitability for use includes several quality aspects of the packaged drug product and its performance, the suitability for use aspect addressed in this chapter is patient safety. Obtaining such a necessary and desirable outcome is facilitated by the use of well-characterized plastic materials of construction in components, containers, and packaging systems and by the appropriate testing of packaging systems.

SCOPE

Establishing the suitability of plastic packaging systems for therapeutic products involves multiple tests and testing procedures, as briefly outlined below:

- Material screening: Characterization of a packaging system's materials of construction to evaluate ingredients as probable extractables and potential leachables. Such a characterization facilitates the identification of materials that are suitable for use in packaging systems.
- Controlled extraction (simulation) study: Worst-case controlled extraction (simulation) study to determine the extent to which extractables may become probable leachables (for additional information, see *Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems* ⟨1663⟩).
- Product assessment: Actual-case measurement of confirmed leachables in the therapeutic product in the pharmaceutical packaging/delivery system intended for the commercial market (for additional information, see *Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery Systems* ⟨1664⟩).

Additionally, information provided by the vendor(s) of plastic packaging systems and their associated materials or components of construction can facilitate suitability assessments, as such information may be appropriate additions to or surrogates for the results obtained by performing the tests noted previously.

The process of manufacturing a packaged therapeutic product is complex. Considering the packaging system specifically, packaging systems typically consist of components that are individually manufactured from plastic materials of construction. These individual plastic materials of construction are initially generated from reagents that are reacted to produce a base polymer, which is then compounded with various additives to produce a base resin. Individual base resins either are materials of construction themselves or may be combined with additional additives and processing aids to form a plastic material of construction. Testing of these plastic materials of construction to establish that they are well characterized and suitable for use, specifically considering safety, in packaging systems is within the scope of this series of chapters and is addressed in *Plastic Materials of Construction* ⟨661.1⟩.

Individual plastic materials of construction are combined to form components of the packaging system. The packaging system is completed by assembling its various components into its final form. Testing of packaging systems to establish that they are suited for their intended uses, specifically considering safety, is within the scope of this series of chapters and is addressed in *Plastic Packaging Systems for Pharmaceutical Use* ⟨661.2⟩.

Assembled packaging systems are filled to contain the therapeutic product by various means and at various points in the packaging system manufacturing process, thereby generating the packaged therapeutic product. Testing of packaged therapeutic products to establish that they are suited for their intended uses is addressed in compendial monographs relevant to the specific therapeutic product and falls outside of the scope of this series of chapters.

For more information on the scope of, applicability of, and other topics related to the ⟨661⟩ suite of general chapters, see *Evaluation of Plastic Packaging Systems and Their Materials of Construction with Respect to Their User Safety Impact* ⟨1661⟩.

● (Official 1-May-2020)

●(Postponed until May 1, 2020.)● (RB 1-May-2017)