<661.1> Plastic 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 <661.1> Plastic 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 <661.1> Plastic 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>

⟨661.1⟩ PLASTIC MATERIALS OF CONSTRUCTION

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 Packaging Systems for Pharmaceutical Use* ⟨661.2⟩ 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 this chapter or ⟨661.2⟩ is referenced in the *USP–NF*.)• (RB 1-May-2017)

INTRODUCTION

The use of well-characterized materials to construct packaging systems is a primary means of ensuring that the packaging system is suited for its intended use. Materials are characterized so that their properties and characteristics can be matched to the performance requirements of the packaging system, thus facilitating the intentional selection of appropriate materials. For the purposes of this chapter, a plastic material of construction is deemed to be well-characterized for its intended use if the following characteristics have been adequately established: its identity, biocompatibility (biological reactivity), general physicochemical properties, and composition (i.e., additives and extractable metals likely to be present).

Establishing the potential safety effect of a material of construction cannot rely on a single testing strategy, because a single testing strategy cannot cover all of the material's attributes that have a potential safety impact. The chemical testing prescribed in the chapter is orthogonal in that the *Physicochemical Tests* sections provide a general overview of extracted substances, the *Extractable Metals* sections address potential sources of elemental impurities; and the information provided by the *Plastic Additives* tests addresses potential organic extractables. Because chemical testing alone may not be adequate to establish a material's suitability for use, chemical testing is augmented by the orthogonal approach of establishing biological reactivity.

Change to read:

SCOPE

The purpose of this chapter is to provide test methods and specifications for plastic materials of construction used in packaging systems. This chapter solely applies to individual plastic materials and should not be applied to packaging systems or components consisting of multiple individual plastic materials. The testing and qualification of plastic packaging systems and components for pharmaceutical use are covered in *Plastic Packaging Systems for Pharmaceutical Use* ⟨661.2⟩.

This chapter contains tests, methods, and specifications for the following materials: cyclic olefins, polyethylene, polypropylene, polyethylene terephthalate, polyethylene terephthalate G, and plasticized polyvinyl chloride. Other plastic materials of construction can be used in packaging systems if their suitability for use has been established by testing that is consistent with the general procedures and specifications provided in this chapter for the above-mentioned materials. Alternatively, individual plastic materials of construction are deemed to be well characterized and appropriate for use if they are used in a packaging system that meets the requirements in ⟨661.2⟩. •• (RB 1-May-2017)

Given the wide variety of materials and packaging systems available, and the potential for new developments in materials and packaging systems, it is possible that plastic packaging systems could be constructed from materials that are not specifically addressed in this chapter. Materials of construction that are not specifically addressed in this chapter are termed "unaddressed materials". For an unaddressed material to be deemed compliant with this chapter, it must be characterized in ways that are comparable to those used for the materials specified in this chapter. Specifically, the unaddressed material of construction must be identified by appropriate methodology and tested for biocompatibility, physicochemical properties, additives, and relevant extracted metals.

Specifications must be established for unaddressed materials, and such specifications should be consistent with the specifications for materials addressed in this chapter. For example, unaddressed materials whose aqueous extracts are tested for their total organic carbon (TOC) levels shall have specifications for TOC that are consistent with the TOC specifications for materials addressed in this chapter. Alternatively, unaddressed materials may, in justified circumstances, comply with other specifications, subject to approval by an appropriate regulatory authority.

The test methods in this chapter are appropriate for their purpose, as evidenced by their longstanding use, and thus they reflect acceptable practices. However, other methods and procedures may be equally suitable. Therefore, alternative test methods and procedures can be used but must be suitable, validated, and equivalent to or better than the compendial methods.

Table 1 provides guidance on the appropriate application of the chemical tests and biological reactivity tests for oral and topical dosage forms, which include oral tablets, oral hard and soft gelatin capsules, oral powders, solutions and suspensions, topical powders, and aqueous-based topical solutions and suspensions. *Table 2* provides guidance on the appropriate application of the chemical tests and biological reactivity tests for all other dosage forms. [NOTE—For aqueous-based oral drug products that contain cosolvents (or if, for any reason, it may be expected to extract greater amounts of substances from plastic

packaging components than water), additional extractable information may be needed to address safety issues. If additional information is required, perform *Extractable Metals* and *Plastic Additives* tests as directed in *Table 2*.]

Table 1. Guidelines for Application of Tests for Oral and Topical Dosage Forms

Biological Reactivity Tests	Chemical Tests
• Perform *Biological Reactivity Tests, In Vitro* ⟨87⟩ • Materials that meet the requirements of this test are not required to undergo testing as described in *Biological Reactivity Tests, In Vivo* ⟨88⟩ • Materials that do not meet the requirements of the in vitro test are not suitable for these dosage forms	• Perform *Identification*, *Physicochemical*, and *Extractable Metals* tests • Provide appropriate reference to the Indirect Food Additive regulations in 21 CFR 174–186, specifically those addressing the purity criteria and limitations pertaining to use • Materials that do not meet these requirements are not suitable for packaging for these dosage forms unless the materials are established to be suitable by other means that have been approved by an appropriate regulatory authority

Table 2. Guidelines for Application of Tests for All Other Dosage Forms

Biological Reactivity Tests	Chemical Tests
• Perform *Biological Reactivity Tests, In Vitro* ⟨87⟩ • Perform *Biological Reactivity Tests, In Vivo* ⟨88⟩ to obtain the appropriate *Classification of Plastics* • Materials that do not meet the requirements of the in vivo or the in vitro tests are not suitable for containers for these dosage forms	• Perform *Identification*, *Physicochemical*, *Extractable Metals*, and *Plastic Additives* tests • Materials that do not meet these requirements are not suitable for containers for these dosage forms unless the materials are established to be suitable by other means that have been approved by an appropriate regulatory authority

Change to read:

SPECIFICATIONS

Polyethylene

IDENTIFICATION

Low-density polyethylene
Infrared spectrophotometry—Determine the infrared spectrum from 3800 cm^{-1} to 650 cm^{-1} (2.6–15 μm). The specimen exhibits an absorption spectrum that is substantially equivalent to that of the USP Low-Density Polyethylene RS. Substantial, as opposed to exact, equivalence allows for minor spectral differences arising from the natural compositional and/or physical variation among polymers of this class. Substantial equivalence is achieved when all differences between the sample and Reference Standard spectra can be explained in the context of such natural compositional and/or physical variations.
Differential scanning calorimetry—The thermogram of the specimen is similar to the thermogram of USP Low-Density Polyethylene RS, and the transition temperature (T_g) obtained from the thermogram of the specimen does not differ from that of the Reference Standard by more than 8.0°.
High-density polyethylene
Infrared spectrophotometry—Determine the infrared spectrum from 3800 cm^{-1} to 650 cm^{-1} (2.6–15 μm). The specimen exhibits an absorption spectrum that is substantially equivalent to that of USP High-Density Polyethylene RS. Substantial, as opposed to exact, equivalence allows for minor spectral differences arising from the natural compositional and/or physical variation among polymers of this class. Substantial equivalence is achieved when all differences between the sample and Reference Standard spectra can be explained in the context of such natural compositional and/or physical variations.
Differential scanning calorimetry—The thermogram of the specimen is similar to the thermogram of USP High-Density Polyethylene RS, and the transition temperature (T_g) obtained from the thermogram of the specimen does not differ from that of the Reference Standard by more than 6.0°.

PHYSICOCHEMICAL TESTS

Absorbance: Maximum absorbance is 0.2.
Acidity or alkalinity: NMT 1.5 mL of 0.01 N sodium hydroxide is required to change the color of the indicator to blue. NMT 1.0 mL of 0.01 N hydrochloric acid is required to reach the beginning of the color change of the indicator from yellow to orange.
Total organic carbon: The difference between the sample and blank TOC concentrations is NMT 5 mg/L.

EXTRACTABLE METALS

Aluminum: *Solution S3* (see *Table 3*) contains NMT 0.4 mg/L (ppm), corresponding to 1 μg/g.

Arsenic, cadmium, lead, mercury, cobalt, and nickel: Report the measured value in *Solution S3* at values above 0.01 mg/L (ppm), corresponding to 0.025 μg/g. If the measured values are below these values, report the result as less than 0.01 mg/L (ppm), corresponding to less than 0.025 μg/g.
Chromium: *Solution S3* contains NMT 0.02 mg/L (ppm), corresponding to 0.05 μg/g.
Titanium: *Solution S3* contains NMT 0.4 mg/L (ppm), corresponding to 1 μg/g.
Vanadium: *Solution S3* contains NMT 0.04 mg/L (ppm), corresponding to 0.1 μg/g.
Zinc: *Solution S3* contains NMT 0.4 mg/L (ppm), corresponding to 1 μg/g.
Zirconium: *Solution S3* contains NMT 0.04 mg/L (ppm), corresponding to •0.1 μg/g.• (ERR 1-Apr-2016)
Test results for additional relevant extractable metals are similarly reported.

PLASTIC ADDITIVES, PHENOLIC ANTIOXIDANTS, NONPHENOLIC ANTIOXIDANTS, COPOLYMER OF DIMETHYL SUCCINATE AND (4-HYDROXY-2,2,6,6-TETRAMETHYLPIPERIDIN-1-YL)ETHANOL, AMIDES, AND STEARATES

The test results from these analyses are reported.

Cyclic Olefins

IDENTIFICATION

Infrared spectrophotometry: Determine the infrared spectrum from 3800 cm^{-1} to 650 cm^{-1} (2.6–15 μm). The specimen exhibits an absorption spectrum that is substantially equivalent to that of USP Cyclic Olefin Polymer RS or USP Cyclic Olefin Copolymer RS. Substantial, as opposed to exact, equivalence allows for minor spectral differences arising from the natural compositional and/or physical variation among polymers of this class. Substantial equivalence is achieved when all differences between the sample and Reference Standard spectra can be explained in the context of such natural compositional and/or physical variations.
Differential scanning calorimetry: Given the amorphous nature of these polymers and their compositional variety, material-to-material variations in the transition temperature (T_g) can be anticipated. Thus, it is neither recommended nor required that differential scanning calorimetry be performed.

PHYSICOCHEMICAL TESTS

Absorbance: Maximum absorbance is 0.2.
Acidity or alkalinity: NMT 1.5 mL of 0.01 N sodium hydroxide is required to change the color of the indicator to blue. NMT 1.0 mL of 0.01 N hydrochloric acid is required to reach the beginning of the color change of the indicator from yellow to orange.
Total organic carbon: The difference between the sample and blank TOC concentrations is NMT 5 mg/L.

EXTRACTABLE METALS

Aluminum: *Solution S3* (see *Table 3*) contains NMT 0.4 mg/L (ppm), corresponding to 1 μg/g.
Arsenic, cadmium, lead, mercury, cobalt, nickel, and vanadium: Report the measured value in *Solution S3* at values above 0.01 mg/L (ppm), corresponding to 0.025 μg/g. If the measured values are below these values, report the result as less than 0.01 mg/L (ppm), corresponding to less than 0.025 μg/g.
Titanium: *Solution S3* contains NMT 0.4 mg/L (ppm), corresponding to 1 μg/g.
Zinc: *Solution S3* contains NMT 0.4 mg/L (ppm), corresponding to 1 μg/g.
Test results for additional relevant extractable metals are similarly reported.

PLASTIC ADDITIVES, PHENOLIC ANTIOXIDANTS, NONPHENOLIC ANTIOXIDANTS, COPOLYMER OF DIMETHYL SUCCINATE AND (4-HYDROXY-2,2,6,6-TETRAMETHYLPIPERIDIN-1-YL)ETHANOL, AMIDES, AND STEARATES

The test results from these analyses are reported.

Polypropylene

IDENTIFICATION

Infrared spectrophotometry: Determine the infrared spectrum from 3800 cm^{-1} to 650 cm^{-1} (2.6–15 μm). The specimen exhibits an absorption spectrum that is substantially equivalent to that of the USP Homopolymer Polypropylene RS. Substantial, as opposed to exact, equivalence allows for minor spectral differences arising from the natural compositional and/or physical

variation among polymers of this class. Substantial equivalence is achieved when all differences between the sample and Reference Standard spectra can be explained in the context of such natural compositional and/or physical variations.
Differential scanning calorimetry: The transition temperature (T_g) in the thermogram does not differ from that of the USP Homopolymer Polypropylene RS by more than 12.0°.

PHYSICOCHEMICAL TESTS

Absorbance: Maximum absorbance is 0.2.
Acidity or alkalinity: NMT 1.5 mL of 0.01 N sodium hydroxide is required to change the color of the indicator to blue. NMT 1.0 mL of 0.01 N hydrochloric acid is required to reach the beginning of the color change of the indicator from yellow to orange.
Total organic carbon: The difference between the sample and blank TOC concentrations is NMT 5 mg/L.

EXTRACTABLE METALS

Aluminum: *Solution S3* (see *Table 3*) contains NMT 0.4 mg/L (ppm), corresponding to 1 μg/g.
Arsenic, cadmium, lead, mercury, cobalt, nickel, and vanadium: Report the measured value in *Solution S3* at values above 0.01 mg/L (ppm), corresponding to 0.025 μg/g. If the measured values are below these values, report the result as less than 0.01 mg/L (ppm), corresponding to less than 0.025 μg/g.
Chromium: *Solution S3* contains NMT 0.02 mg/L (ppm), corresponding to 0.05 μg/g.
Titanium: *Solution S3* contains NMT 0.4 mg/L (ppm), corresponding to 1 μg/g.
Zinc: *Solution S3* contains NMT 0.4 mg/L (ppm), corresponding to 1 μg/g.
Test results for additional relevant extractable metals are similarly reported.

PLASTIC ADDITIVES, PHENOLIC ANTIOXIDANTS, NONPHENOLIC ANTIOXIDANTS, AMIDES, AND STEARATES

The test results from these analyses are reported.

Polyethylene Terephthalate and Polyethylene Terephthalate G

IDENTIFICATION

Infrared spectrophotometry: Determine the infrared spectrum from 3800 cm^{-1} to 650 cm^{-1} (2.6–15 μm). The specimen exhibits an absorption spectrum that is substantially equivalent to that of USP Polyethylene Terephthalate RS or USP Polyethylene Terephthalate G RS. Substantial, as opposed to exact, equivalence allows for minor spectral differences arising from the natural compositional and/or physical variation among polymers of this class. Substantial equivalence is achieved when all differences between the sample and Reference Standard spectra can be explained in the context of such natural compositional and/or physical variations.
Differential scanning calorimetry
Polyethylene terephthalate—The thermogram of the specimen is similar to the thermogram of USP Polyethylene Terephthalate RS. The glass transition temperature (T_g) obtained from the thermogram of the specimen does not differ from that of the Reference Standard by more than 4.0°.
Polyethylene terephthalate G—The thermogram of the specimen is similar to the thermogram of USP Polyethylene Terephthalate G RS. The glass transition temperature (T_g) obtained from the thermogram of the specimen does not differ from that of the Reference Standard by more than 6.0°.

PHYSICOCHEMICAL TESTS

Absorbance: Maximum absorbance is 0.2 for *Solution S1* and 0.05 for *Solution S5*. For colored polyethylene terephthalate, maximum absorbance between 400 and 800 nm is 0.05 for *Solution S1*.
Acidity or alkalinity: NMT 0.5 mL of 0.01 N sodium hydroxide is required to change the color of the indicator to blue. NMT 0.5 mL of 0.01 N hydrochloric acid is required to reach the beginning of the color change of the indicator from yellow to orange.
Total organic carbon: The difference between the sample and blank TOC concentrations is NMT 5 mg/L.

EXTRACTABLE METALS

Aluminum: *Solution S3* (see *Table 3*) contains NMT 0.4 mg/L (ppm), corresponding to 1 μg/g.
Antimony: *Solution S4* contains NMT 0.4 mg/L (ppm), corresponding to 1 μg/g.

Arsenic, cadmium, lead, mercury, cobalt, nickel, and vanadium: Report the measured value in *Solution S3* at values above 0.01 mg/L (ppm), corresponding to 0.025 μg/g. If the measured values are below these values, report the result as less than 0.01 mg/L (ppm), corresponding to less than 0.025 μg/g.
Barium: *Solution S3* contains NMT 0.4 mg/L (ppm), corresponding to 1 μg/g.
Germanium: *Solution S4* contains NMT 0.4 mg/L (ppm), corresponding to 1 μg/g.
Manganese: *Solution S3* contains NMT 0.4 mg/L (ppm), corresponding to 1 μg/g.
Titanium: *Solution S3* contains NMT 0.4 mg/L (ppm), corresponding to •1 μg/g.• (ERR 1-Apr-2016)
Zinc: *Solution S3* contains NMT 0.4 mg/L (ppm), corresponding to 1 μg/g.
Test results for additional relevant extractable metals are similarly reported.

Plasticized Polyvinyl Chloride

IDENTIFICATION

Infrared spectrophotometry: Determine the infrared spectrum from 3800 cm^{-1} to 600 cm^{-1} (2.6–16 μm). The specimen exhibits an absorption spectrum that is substantially equivalent to that of the USP Plasticized Polyvinyl Chloride RS. Substantial, as opposed to exact, equivalence allows for minor spectral differences arising from the natural compositional and/or physical variation among polymers of this class. Substantial equivalence is achieved when all differences between the sample and Reference Standard spectra can be explained in the context of such natural compositional and/or physical variations.
Differential scanning calorimetry: The thermogram of the specimen is similar to the thermogram of USP Plasticized Polyvinyl Chloride RS, and the transition temperature (T_g) obtained from the thermogram of the specimen does not differ from that of the Reference Standard by more than 8.0°. Note that the results of the differential scanning calorimetry (DSC) analysis are strongly dependent on the amount of plasticizer in the test article.

PHYSICOCHEMICAL TESTS

Absorbance: NMT 0.25 for *Solution S1*
Acidity or alkalinity: NMT 1.5 mL of 0.01 N sodium hydroxide is required to change the color of the indicator to blue. NMT 1.0 mL of 0.01 N hydrochloric acid is required to reach the beginning of the color change of the indicator from yellow to orange.
Total organic carbon: The difference between the sample and blank TOC concentrations is NMT 5 mg/L.

EXTRACTABLE METALS

Arsenic, cadmium, lead, mercury, cobalt, nickel, and vanadium: Report the measured value in *Solution S3* at values above 0.01 mg/L (ppm), corresponding to 0.025 μg/g. If the measured values are below these values, report the result as less than 0.01 mg/L (ppm), corresponding to less than 0.025 μg/g.
Barium: *Solution S3* (see *Table 3*) contains NMT 0.25 mg/L (ppm), corresponding to 5 μg/g.
Calcium: *Solution S3* contains NMT 35 mg/L (ppm), corresponding to 0.07 weight %.
Tin: *Solution S3* contains NMT 1 mg/L (ppm), corresponding to 20 μg/g.
Zinc: *Solution S3* contains NMT 100 mg/L (ppm), corresponding to 0.2 weight %.
Test results for additional relevant extractable metals are similarly reported.

PLASTIC ADDITIVES

Di(2-ethylhexyl)phthalate: Residue is NMT 40 mg.
***N′N″*-Diacylethylenediamines:** Residue is NMT 20 mg.
Epoxidized soya oil: The difference between the masses of both residues is NMT 10 mg.
Epoxidized linseed oil: The difference between the masses of both residues is NMT 10 mg.
Vinyl chloride: NMT 1 ppm. Note that vinyl chloride is not an additive but is monitored as a residual monomer.

Change to read:

TEST METHODS

Identification

The identification testing described in this chapter is required for all materials of construction used in packaging systems. The identification test should be accomplished by using the procedures specified in this chapter (infrared spectrophotometry and thermal analysis). If these procedures are not applicable for a particular material, then an alternative procedure can be

used. The alternate procedure must establish the identity on the basis of obtaining substantially equivalent results for the test article and its appropriate USP Reference Standard.

Specifications must be established for materials that are not specified in this chapter, and such specifications should be consistent with the specifications established for materials that are specified in this chapter. For example, a DSC specification for a material that is not currently listed in this chapter should be consistent, in language and in rigor, with a DSC specification for a material that is listed in this chapter [e.g., transition temperature (T_g) index agreement between sample and reference material].

The identities of materials of construction only need to be established by one test procedure.

Infrared Spectrophotometry

Apparatus: Use an infrared spectrophotometer capable of correcting for the blank spectrum and able to measure in transmission mode or equipped with an internal reflectance accessory and an appropriate internal reflectance plate.

Sample preparation

Transmission mode—Prepare a specimen of appropriate thickness (polyethylene about 250 μm; polypropylene about 100 μm) without visible defects (cracks or holes). The specimens can be compressed to form a thin, uniform film by exposure to elevated temperatures and pressures (2000 psi or more). The temperatures at which the thin films are generated represent a trade-off between producing a melt (which dictates the lowest temperature necessary) and degrading the sample (which dictates the highest temperature allowed). Ultimately, the temperatures that are used are appropriate if the film produced is conducive to the IR analysis.

Internal reflectance mode—Prepare a flat section, and trim it as necessary to obtain a segment that is convenient for mounting in the internal reflectance accessory. Taking care to avoid scratching the surfaces, wipe the specimen with dry paper or, if necessary, a soft cloth dampened with methanol, and permit the surfaces to dry. Before mounting the specimen on the plate, compress it to form a thin, uniform film by exposure to elevated temperatures under high pressure (2000 psi or more). Then securely mount the specimen on the internal reflection plate, ensuring adequate surface contact.

Procedure: Place the mounted specimen sections in the sample compartment of the infrared spectrophotometer or the internal reflectance accessory, and place the assembly in the specimen beam of the infrared spectrophotometer. For internal reflectance, adjust the specimen position and mirrors within the accessory to permit maximum light transmission of the unattenuated reference beam. (For a double-beam instrument, attenuate the reference beam after completing the adjustment in the accessory to permit full-scale deflection during the scanning of the specimen.)

Thermal Analysis

Refer to *Thermal Analysis* ⟨891⟩.

Sample preparation: Place about 12 mg of sample in the test specimen pan. [NOTE—Intimate contact between the pan and the thermocouple is essential for obtaining reproducible results.] Determine the thermogram under nitrogen, using heating/cooling conditions specified for the polymer type and using equipment capable of performing the determinations as described in ⟨891⟩. Thermograms are obtained for the test materials and their associated USP Reference Standards.

Procedure

Polyethylene—Determine the thermogram under nitrogen at temperatures between 40° and 200° at a heating range between 2° and 10°/min, followed by cooling, at a rate between 2° and 10°/min, to 40°.

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

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

Cyclic olefin—Determine the thermogram under nitrogen at temperatures ranging from ambient to 30° above the melting point. Maintain the temperature for 10 min, then cool to 50° below the peak crystallization temperature at a rate of 10° to 20°/min.

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

Plasticized polyvinyl chloride—Heat the specimen from –20° to 120° at a heating rate of about 10°/min. Quickly cool the specimen to room temperature.

Other materials—Specimens shall be heated and cooled in a manner that is appropriate for the test material and that facilitates the generation of a useable thermogram.

Extractions

Physicochemical testing of the plastic material requires that it be extracted or dissolved. Different tests are facilitated by various extraction methods. *Table 3* describes the extracts that are generated and the tests that are performed on those extracts. Subsequent discussions address methods for producing the extracts. Note that these extracts may be used for tests other than the physicochemical tests.

Table 3. Extractions Performed for Various Chemical Tests

		Tests Performed on Plastic Using the Specified Extracting Solution		
Extraction	**Extracting Solution**	**Polyethylene, Cyclic Olefin, and Polypropylene**	**Polyethylene Terephthalate and Polyethylene Terephthalate G**	**Plasticized Polyvinyl Chloride**
S1	Water	Absorbance Acidity/alkalinity Total organic carbon	Absorbance Acidity/alkalinity Total organic carbon	Absorbance[a] Acidity/alkalinity Total organic carbon
S2	Toluene	Phenolic antioxidants, non-phenolic antioxidants, amides, and stearates[a]	N/A	N/A
S3	Acid	Extractable metals: Al, As, Cd, Co, Cr,[b] Hg, Ni, Pb, Ti, V, Zn, and Zr[c]	Extractable metals: Al, ●● (ERR 1-Apr-2016) As, Ba, Cd, Co, ●● (ERR 1-Apr-2016) Hg, Mn, Ni, Pb, Ti, V, and Zn	Extractable metals: As, Ba, Ca, Cd, Co, Hg, Ni, Pb, Sn, V, and Zn
S4	Alkali	N/A	Extractable metals: Sb and Ge	N/A
S5	Alcohol	N/A	Absorbance	N/A

[a] Although this extract is suitable for use with these specific ingredient methods, such an extract could be useful for other tests designed to establish a material's composition.
[b] For ●● (ERR 1-Apr-2016) polyethylene only.
[c] Not applicable for cyclic olefins.

WATER EXTRACTION, *SOLUTION S1*

Polyethylene, cyclic olefins, and polypropylene: Place 25 g of the test material in a borosilicate glass flask with a ground-glass neck. Add 500 mL of *Purified Water*, and boil under reflux conditions for 5 h. Allow to cool, and filter the extracting solution through a sintered-glass filter. Collect the filtrate in a 500-mL volumetric flask and dilute with *Purified Water* to volume; the diluted solution is designated *Solution S1*. Use *Solution S1* within 4 h of preparation.
Polyethylene terephthalate and polyethylene terephthalate G: Place 10 g of the test material in a borosilicate glass flask with a ground-glass neck. Add 200 mL of *Purified Water*, and heat at 50° for 5 h. Allow to cool, decant the solution into a 200-mL volumetric flask, and dilute with *Purified Water* to volume; the diluted sample is designated *Solution S1*. Use *Solution S1* within 4 h of preparation.
Plasticized polyvinyl chloride—Place 25 g of the test material into a borosilicate glass flask. Add 500 mL of *Purified Water*, cover the flask's neck with aluminum foil or a borosilicate beaker, and heat in an autoclave at 121 ± 2° for 20 min. Allow the solution to cool and the solids to settle, decant the solution into a 500-mL volumetric flask, and dilute with *Purified Water* to volume; the diluted solution is designated *Solution S1*.

TOLUENE EXTRACTION, *SOLUTION S2*

Polyethylene, cyclic olefins, and polypropylene: Place 2.0 g of the test material in a 250-mL borosilicate glass flask with a ground-glass neck. Add 80 mL of toluene and boil under a reflux condenser for 1.5 h, stirring constantly. Allow to cool to 60° and add, with continued stirring, 120 mL of methanol. Pass the resulting solution through a sintered-glass filter. Rinse the flask and the filter with 25 mL of a mixture of 40 mL of toluene and 60 mL of methanol, add the rinsings to the filtrate, and dilute to 250 mL with the same mixture of solvents to produce *Solution S2*. Prepare a blank solution.

ACID EXTRACTION, *SOLUTION S3*

Polyethylene, cyclic olefins, and polypropylene: Place 100 g of the test material in a borosilicate glass flask with a ground-glass neck. Add 250 mL of 0.1 N hydrochloric acid and boil under a reflux condenser for 1 h with constant stirring. Allow to cool, decant the solution into a 250-mL volumetric flask, and dilute with 0.1 N hydrochloric acid to volume; the diluted solution is designated *Solution S3*.
Polyethylene terephthalate and polyethylene terephthalate G: Place 20 g of the test material in a borosilicate glass flask with a ground-glass neck. Add 50 mL of 0.1 N hydrochloric acid, and heat at 50° for 5 h. Allow to cool, decant the solution

into a 50-mL volumetric flask, and dilute with 0.1 N hydrochloric acid to volume; the diluted solution is designated *Solution S3*. Use *Solution S3* within 4 h of preparation.

Plasticized polyvinyl chloride: Place 5 g in a borosilicate glass flask with a ground-glass neck. Add 100 mL of 0.1 N hydrochloric acid, and boil under a reflux condenser for 1 h with constant stirring. Allow to cool and the solids to settle, decant the solution into a 100-mL volumetric flask, and dilute with 0.1 N hydrochloric acid to volume; the diluted solution is designated *Solution S3*.

ALKALI EXTRACTION, *SOLUTION S4*

Polyethylene terephthalate and polyethylene terephthalate G: Place 20 g of test material in a borosilicate glass flask with a ground-glass neck. Add 50 mL of 0.01 N sodium hydroxide, and heat at 50° for 5 h. Allow to cool and the solids to settle, decant the solution into a 50-mL volumetric flask, and dilute with 0.01 N sodium hydroxide to volume; the diluted solution is designated *Solution S4*. Use *Solution S4* within 4 h of preparation.

ALCOHOL EXTRACTION, *SOLUTION S5*

Polyethylene terephthalate and polyethylene terephthalate G: Place 10 g of the test material in a borosilicate glass flask with a ground-glass neck. Add 100 mL of alcohol, absolute, and heat at 50° for 5 h. Allow to cool and the solids to settle, then decant the solution, producing *Solution S5*. Use *Solution S5* within 4 h of preparation.

Physicochemical Tests

ABSORBANCE

Refer to *Ultraviolet-Visible Spectroscopy* ⟨857⟩.

Polyethylene, cyclic olefins, and polypropylene: Determine the spectrum between 220 and 340 nm in *Solution S1*.

Polyethylene terephthalate and polyethylene terephthalate G: Determine the spectrum between 220 and 340 nm in *Solution S1*. For colored polyethylene terephthalate, determine the spectrum between 400 and 800 nm in *Solution S1*. For colored and noncolored polyethylene terephthalate, determine the spectrum between 400 and 800 nm in *Solution S5*.

Plasticized polyvinyl chloride: Evaporate 100 mL of *Solution S1* to dryness. Dissolve the resulting residue in 5 mL of hexane to produce the hexane sample. Pass the hexane sample, if necessary, through a filter previously rinsed with hexane. Determine the spectrum between 250 and 310 nm in the hexane sample. •● (ERR 1-Apr-2016)

ACIDITY OR ALKALINITY

BRP indicator solution: •1.0 mg/mL of bromothymol blue,● (ERR 1-Dec-2016) 0.2 mg/mL of methyl red, and 0.2 mg/mL of phenolphthalein in alcohol. Filter the resulting solution.

Methyl orange solution: Dissolve 100 mg of methyl orange in 80 mL of *Purified Water*, and dilute with alcohol R to 100 mL. Test for sensitivity: Add 0.1 mL of *Methyl orange solution* to 100 mL of carbon dioxide–free *Purified Water*. NMT 0.1 mL of 1 N hydrochloric acid is required to change the color from yellow to red.

Polyethylene, cyclic olefins, and polypropylene: To 100 mL of *Solution S1* add 0.15 mL of *BRP indicator solution*. Determine the titration volume of 0.01 N sodium hydroxide required to change the color of the indicator to blue. To a separate, 100-mL portion of *Solution S1* add 0.2 mL of *Methyl orange solution*. Determine the titration volume of 0.01 N hydrochloric acid required to reach the beginning of the color change of the indicator from yellow to orange.

Polyethylene terephthalate and polyethylene terephthalate G: To 50 mL of *Solution S1* add 0.15 mL of *BRP indicator solution*. Determine the titration volume of 0.01 N sodium hydroxide required to change the color of the indicator to blue. To a separate 50 mL of *Solution S1* add 0.2 mL of *Methyl orange solution*. Determine the titration volume of 0.01 N hydrochloric acid required to reach the beginning of the color change of the indicator from yellow to orange.

Plasticized polyvinyl chloride: To 100 mL of *Solution S1* add 0.15 mL of *BRP indicator solution*. Determine the titration volume of 0.01 N sodium hydroxide required to change the color of the indicator to blue. To 100 mL of *Solution S1* add 0.2 mL of *Methyl orange solution*. Determine the titration volume of 0.01 N hydrochloric acid required to reach the beginning of the color change of the indicator from yellow to orange.

TOTAL ORGANIC CARBON

The TOC content of *Solution S1* is measured according to the general methodologies outlined in *Total Organic Carbon* ⟨643⟩. However, although ⟨643⟩ is designed for the testing of high-purity water with low TOC values, material extracts may have TOC values that are higher than those of purified water because of extracted organic substances. Thus, the method used to perform the TOC analyses should have a limit of detection of 0.2 mg/L (ppm) and should have a demonstrated linear dynamic range

from 0.2 to 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, they must be diluted appropriately for analysis.

Extractable Metals

The *Extractable Metals* testing described in this chapter is required for all plastic materials of construction used in packaging systems, regardless of whether the material is specified in this chapter. Specifically, all materials must be tested for those extractable metals listed in *Table 3* and any other metals that are relevant in the sense that their presence in the test material is known or can be reasonably anticipated.

PROCEDURE FOR EXTRACTION

Plastic materials used in packaging systems for medical articles do not dissolve under the conditions of use. Rather, substances derived from packaging systems accumulate in the packaged articles by the process of leaching (extraction). Thus, the appropriate and relevant sample-preparation process for assessing metals in a packaging system's materials of construction is extraction, as opposed to complete digestion, of the plastic material. *Solution S3* (acidic extraction) and *Solution S4* (alkaline extraction) prepared for *Physicochemical Tests* (*Table 2*) are the material extracts that are tested for extractable metals.

PROCEDURE FOR EXTRACT ANALYSIS

Instrumentation and methods are those specified in *Elemental Impurities—Procedures* ⟨233⟩ and include an inductively coupled plasma–atomic emission spectrometer and an inductively coupled plasma–mass spectrometer (see *Atomic Absorption Spectroscopy* ⟨852⟩), as directed.

Plastic Additives

POLYETHYLENE, CYCLIC OLEFINS, AND POLYPROPYLENE

These tests should be carried out in whole or in part as required due to the stated composition of the material.

• **PHENOLIC ANTIOXIDANTS**

Solvent mixture: Acetonitrile and tetrahydrofuran (50:50, v/v)

Sample solution S7: Evaporate 50 mL of *Solution S2* to dryness under a vacuum at 45°. Dissolve the resulting residue with 5.0 mL of the *Solvent mixture* to produce *Sample solution S7*. Prepare a blank solution from the blank solution corresponding to *Solution S2*.

Sample solution S8: Evaporate 50 mL of *Solution S2* to dryness under a vacuum at 45°. Dissolve the residue with 5.0 mL of methylene chloride to produce *Sample solution S8*. Prepare a blank solution from the blank solution corresponding to *Solution S2*.

Sample solution S9 (cyclic olefins only): Evaporate 50 mL of *Solution S2* to dryness under a vacuum at 45°. Dissolve the residue in 5.0 mL of a mixture of equal volumes of acetonitrile and a 10 g/L solution of *tert*-butyl hydroperoxide in tetrahydrofuran. Close the flask and allow to stand for 1 h. The resulting solution is *Sample solution S9*. Prepare a blank solution using the blank of *Solution S2*.

Reference solutions

Of the following reference solutions, prepare only those that are necessary for the analysis of the phenolic antioxidants stated in the composition of the substance to be examined.

Reference solution A: 0.1 mg/mL of USP Butylated Hydroxytoluene RS and 0.24 mg/mL of USP Plastic Additive 01 RS prepared in the *Solvent mixture*

Reference solution B: 0.24 mg/mL of USP Plastic Additive 02 RS and 0.24 mg/mL of USP Plastic Additive 03 RS prepared in the *Solvent mixture*

Reference solution C: 0.24 mg/mL of USP Plastic Additive 04 RS and 0.24 mg/mL of USP Plastic Additive 05 RS prepared in methylene chloride

Reference solution D: 0.1 mg/mL of USP Butylated Hydroxytoluene RS prepared in the *Solvent mixture*

Reference solution E: 0.24 mg/mL of USP Plastic Additive 01 RS prepared in the *Solvent mixture*

Reference solution F: 0.24 mg/mL of USP Plastic Additive 06 RS prepared in the *Solvent mixture*

Reference solution G: 0.24 mg/mL of USP Plastic Additive 02 RS prepared in the *Solvent mixture*

Reference solution H: 0.24 mg/mL of USP Plastic Additive 03 RS prepared in the *Solvent mixture*

Reference solution I: 0.24 mg/mL of USP Plastic Additive 04 RS prepared in methylene chloride

Reference solution J: 0.24 mg/mL of USP Plastic Additive 05 RS prepared in methylene chloride

Test A: If the substance to be examined contains additive butylated hydroxytoluene and/or additive ethylene bis[3,3-bis[3-(1,1-dimethylethyl)-4-hydroxyphenyl]butanoate]

Chromatographic system

(See *Chromatography* ⟨621⟩*, Liquid Chromatography*.)

Column: 4.6-mm × 25-cm; 5-μm packing L1

Mobile phase: Acetonitrile and *Purified Water* (70:30, v/v)

Flow rate: 2 mL/min

Injection volume: 20 μL of *Sample solution S7*, corresponding blank solution, *Reference solution A*, and *Reference solution D*, *Reference solution E*, or both

Detector: UV 280 nm

Run time: 30 min

System suitability

Resolution: Minimum 8.0 between the additive butylated hydroxytoluene and additive ethylene bis[3,3-bis[3-(1,1-dimethylethyl)-4-hydroxyphenyl]butanoate] peaks, *Reference solution A*

Sample solution S7 shows only peaks caused by antioxidants stated in the composition and minor peaks that also correspond to the blank solution.

Analysis: The peak areas of *Sample solution S7* are less than the corresponding peak areas of *Reference solution D* or *Reference solution E*.

Test B: If the substance to be examined contains one or more of the following antioxidants: pentaerythrityl tetrakis[3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propionate; 2,2′,2″,6,6′,6″-hexa-*tert*-butyl-4,4′,4″-[(2,4,6-trimethyl-1,3,5-benzene-triyl)trismethylene]triphenol; octadecyl 3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propionate; •tris(2,4-di-*tert*-butylphenyl) phosphite;• (ERR 1-Dec-2016) 1,3,5-tris(3,5-di-*tert*-butyl-4-hydroxybenzyl)-*s*-triazine-2,4,6(1*H*,3*H*,5*H*)-trione

Chromatographic system: Carry out the test as described in *Test A* with the following modifications.

Mobile phase: Acetonitrile, tetrohydrofuran, and *Purified Water* (60:30:10, v/v/v)

Flow rate: 1.5 mL/min

Injection volume: 20 μL of *Sample solution S7*, corresponding blank solution, *Reference solution B*, and any *Reference solutions* of the antioxidants listed above that are stated in the composition

Detector: UV 280 nm

System suitability

Resolution: Minimum 2.0 between the additive pentaerythrityl tetrakis[3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propionate and additive 2,2′,2″,6,6′,6″-hexa-*tert*-butyl-4,4′,4″-[(2,4,6-trimethyl-1,3,5-benzene-triyl)trismethylene]triphenol peaks, *Reference solution B*

Sample solution S7 shows only peaks caused by antioxidants stated in the composition and minor peaks that also correspond to the blank solution.

Analysis: The peak areas of *Sample solution S7* are less than the corresponding areas of the *Reference solutions* of the antioxidants that are listed above and that are stated in the composition.

Test C: If the substance to be examined contains additive octadecyl-3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propionate and/or additive tris(2,4-di-*tert*-butylphenyl) phosphite

Chromatographic system: Carry out the test as described in *Test A* with the following modifications.

Mobile phase: Methanol, 2-propanol, and *Purified Water* •(50:45:5, v/v/v)• (ERR 1-Dec-2016)

Flow rate: 1.5 mL/min

Injection volume: 20 μL of *Sample solution S8*, corresponding blank solution, *Reference solution C*, and either *Reference solution I* or *Reference solution J*

Detector: UV 280 nm

System suitability

Resolution: Minimum 2.0 between the additive octadecyl-3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propionate and additive tris(2,4-di-*tert*-butylphenyl) phosphite peaks, *Reference solution C*

Sample solution S8 shows only peaks due to antioxidants stated in the composition and minor peaks that also correspond to the blank solution.

Analysis: The peak areas of *Sample solution S8* are less than the corresponding peak areas of *Reference solution I* or *Reference solution J*.

• **Nonphenolic Antioxidants**

Methylene chloride, acidified: To 100 mL of methylene chloride add 10 mL of hydrochloric acid, shake, allow to stand, and separate the two layers. Use the lower layer.

Sample solution S10: Evaporate 100 mL of *Solution S2* to dryness under a vacuum at 45°. Dissolve the resulting residue with 2 mL of *Methylene chloride, acidified*.

Reference solution M: 6.0 mg/mL of USP Plastic Additive 08 RS prepared in methylene chloride. Dilute 2 mL of the solution with *Methylene chloride, acidified* to 10 mL.

Reference solution N: 6.0 mg/mL of USP Plastic Additive 09 RS prepared in methylene chloride. Dilute 2 mL of the solution with *Methylene chloride, acidified* to 10 mL.

Reference solution O: 6.0 mg/mL of USP Plastic Additive 10 RS prepared in methylene chloride. Dilute 2 mL of the solution with *Methylene chloride, acidified* to 10 mL.

Reference solution P: 6.0 mg/mL of USP Plastic Additive 10 RS, and 6.0 mg/mL of USP Plastic Additive 09 RS prepared in methylene chloride. Dilute 2 mL of the solution with *Methylene chloride, acidified* to 10 mL.

Chromatographic system
(See *Chromatography* ⟨621⟩*, Liquid Chromatography*.)
Plate: TLC silica gel GF_{254}
Mobile phase A: Hexane
Mobile phase B: Methylene chloride
Application: •20 µL of *Sample solution S10* and the reference solutions corresponding to• (ERR 1-Dec-2016) all of the phenolic and nonphenolic antioxidants expected to be present in the test material
Development A: Over a path of 18 cm with *Mobile phase A*; dry in air
Development B: Over a path of 17 cm with *Mobile phase B*; dry in air
Detector: UV 254 nm; spray with alcoholic iodine solution and examine after 10–15 min
System suitability
Resolution: The chromatogram shows two clearly separated spots, *Reference solution P*.
Analysis: Any spots in the chromatogram of *Sample solution S10* are not more intense than the spots in the same positions in the chromatograms of the *Reference solutions*.

• **Copolymer of Dimethyl Succinate and (4-Hydroxy-2,2,6,6-tetramethylpiperidin-1-yl)ethanol (Cyclic Olefins Only)**
Solvent mixture: Hexane and anhydrous ethanol (89:11, v/v)
Sample solution S11: Evaporate 25 mL of *Solution S2* to dryness under a vacuum at 45°. Dissolve the residue with 10 mL of toluene and 10 mL of a 10-g/L solution of tetrabutylammonium hydroxide in a mixture of 35 volumes of toluene and 65 volumes of anhydrous ethanol. Boil under a reflux condenser for 3 h. Allow to cool, and filter if necessary, to produce *Sample solution S11*.
Reference solution Q: 6.0 mg/mL of USP Plastic Additive 11 RS prepared in toluene. Add 1 mL of this solution to 25 mL of the blank solution corresponding to *Solution S2*, and evaporate to dryness under a vacuum at 45°. Prepare a blank solution from the blank solution corresponding to *Solution S2*. Dissolve the residue with 10 mL of toluene and 10 mL of a 10-g/L solution of tetrabutylammonium hydroxide in a mixture of 35 volumes of toluene and 65 volumes of anhydrous ethanol. Boil under a reflux condenser for 3 h. Allow to cool, and filter if necessary.
Chromatographic system
(See *Chromatography* ⟨621⟩*, Liquid Chromatography*.)
Column: 4.6-mm × 25-cm; 5-µm packing L8
Mobile phase: Hexane and anhydrous ethanol (89:11, v/v)
Flow rate: 2 mL/min
Injection volume: 20 µL of *Sample solution S11*, the corresponding blank solution, and *Reference solution Q*
Detector: UV 227 nm
System suitability
Resolution: Minimum 7 between the peaks of the diol component and the diluents of *Reference solution Q*.
Analysis: The peak area of the diol component in *Sample solution S11* is less than the corresponding peak areas of *Reference solution Q*.

• **Amides and Stearates**
Sample solution: Use *Solution S10* described in *Nonphenolic Antioxidants*.
Reference solution R: 2.0 mg/mL of USP Stearic Acid RS prepared in methylene chloride
Reference solution S: 2.0 mg/mL of USP Plastic Additive 12 RS prepared in methylene chloride
Reference solution T: 2.0 mg/mL of USP Plastic Additive 13 RS prepared in methylene chloride
Test A
Chromatographic system
(See *Chromatography* ⟨621⟩*, Thin-Layer Chromatography*.)
Plate: TLC silica gel GF_{254}
Mobile phase: Dehydrated trimethylpentane and alcohol (75:25, v/v)
Application: 10 µL of *Sample solution S10* and *Reference solution R*
Development: Over a path of 10 cm with *Mobile phase*; dry in air
Detector: Spray with a 2-g/L solution of 2,6-dichlorophenol-indophenol sodium in dehydrated alcohol and heat in an oven at 120° for a few minutes to intensify the spots.
Analysis: Any spot corresponding to additive stearic acid in *Sample solution S10* is identical in position (R_F about 0.5) but is not more intense than the spot in the same position in *Reference solution R*.
Test B
Mobile phase A: Hexane
Mobile phase B: Methylene chloride and methanol (95:5, v/v)
Application: 10 µL of *Sample solution S10* and *Reference solution S* and *Reference solution T*
Development A: Over a path of 13 cm with *Mobile phase A*; dry in air
Development B: Over a path of 10 cm with *Mobile phase B*; dry in air
Detector: Spray with a 40-g/L solution of phosphomolybdic acid in alcohol, dehydrated, and heat in an oven at 120° until spots appear.

Analysis: Any spots corresponding to additives oleamide or erucamide in *Sample solution S10* are identical in position (R_F about 0.2) but are not more intense than the corresponding spots in *Reference solution S* and *Reference solution T*.

PLASTICIZED POLYVINYL CHLORIDE

• Plasticized Polyvinyl Chloride

Additives are di(2-ethylhexyl) phthalate, *N′N″*-diacylethylenediamines, epoxidized soya oil, and epoxidized linseed oil. Vinyl chloride monomer (VCM) is also monitored although it is a residual monomer and not an additive.

Solution A1: Add 2.0 g of the test material to 200 mL of peroxide-free ether and heat under a reflux condenser for 8 h. Separate the resulting residue B and extraction solution A by filtration. Evaporate extraction solution A to dryness under reduced pressure in a water bath at 30°, producing residue C. Dissolve residue C in 10 mL of toluene to produce *Solution A1*.

Precipitate B2: Dissolve residue B in 60 mL of ethylene chloride heating on a water bath under a reflux condenser, producing solution D. Filter the resulting solution D. Add the filtered solution D dropwise and with vigorous shaking to 600 mL of heptanes heated almost to boiling. Separate by hot filtration the coagulum B1 and the organic solution E. Allow solution E to cool; separate the precipitate B2 that forms upon cooling, and pass through a tared sintered-glass filter (pore size of 16–40 μm).

Reference solutions: 0.1 mg/mL solutions of USP Plastic Additive 14 RS, USP Plastic Additive 15 RS, and USP Plastic Additive 16 RS, respectively, in toluene

Chromatographic system

(See *Chromatography* ⟨621⟩*, Thin-Layer Chromatography*.)

Plate: TLC silica gel GF_{254} (1-mm thick)

Method: Apply 0.5 mL of *Solution A1* to the plate as a 30-mm × 3-mm band. Apply 5 μL of each *Reference solution* to the plate. Develop the plate over a path of 15 cm using toluene. Dry the plate carefully.

Additive di(2-ethylhexyl) phthalate: UV 254 nm; locate the zone corresponding to additive di(2-ethylhexyl) phthalate (R_f about 0.4). Remove the area of silica gel corresponding to this zone, mix with 40 mL of ethyl ether, and shake for 1 min. Filter, rinse filter with two quantities each of 10 mL of ethyl ether, add the rinsings to the filtrate, and evaporate to dryness. The residue weighs NMT 40 mg.

Additives epoxidized soya oil and epoxidized linseed oil: Expose the plate to iodine vapor for 5 min. Examine the chromatogram, and locate the band corresponding to additives epoxidized soya oil and epoxidized linseed oil ($R_f = 0$). Remove the area of silica gel corresponding to this band. Similarly, remove a corresponding area of silica gel as a blank reference. Separately mix both samples with separate 40-mL portions of methanol, shaking for 15 min. Filter, rinse the filter with two quantities of 10 mL of methanol, add the rinsings to the filtrate, and evaporate to dryness. The difference between the masses of both residues is NMT 10 mg.

Additive *N,N′*-diacylethylenediamines: Wash precipitate B2 with alcohol, absolute. Dry to constant mass over diphosphorus pentoxide, and weigh the filter. The precipitate weighs NMT 20 mg.

• Vinyl Chloride

Internal standard solution: Using a microsyringe, inject 10 μL of ethyl ether into 20.0 mL of *N,N*-dimethylacetamide, immersing the tip of the needle in the solvent. Immediately before use, dilute the solution to 1000 times its volume with *N,N*-dimethylacetamide.

Sample solution: Place 1.0 g of the test material in a 50-mL vial, and add 10.0 mL of the *Internal standard solution*. Close the vial, and secure with a stopper. Shake, avoiding contact between the stopper and the liquid. Place the vial in a water bath at 60 ± 1° for 2 h.

Vinyl chloride primary solution: [NOTE—Prepare under a ventilated hood.] Place 50.0 mL of *N,N*-dimethylacetamide in a 50-mL vial, stopper the vial, secure the stopper, and weigh to the nearest 0.1 mg. Fill a 50-mL polyethylene or polypropylene syringe with gaseous vinyl chloride, allow the gas to remain in contact with the syringe for about 3 min, empty the syringe, and fill again with 50 mL of gaseous vinyl chloride. Fit a hypodermic needle to the syringe, and reduce the volume of gas in the syringe from 50 to 25 mL. Inject the remaining 25 mL of vinyl chloride slowly into the vial, shaking gently and avoiding contact between the liquid and the needle. Weigh the vial again; the increase in mass is about 60 mg (1 μL of the solution obtained contains about 1.2 μg of vinyl chloride). Allow to stand for 2 h. Store the primary solution in a refrigerator.

Vinyl chloride standard solution: To 1 volume of the *Vinyl chloride primary solution* add 3 volumes of *N,N*-dimethylacetamide.

Reference solutions: Place 10.0 mL of the *Internal standard solution* in each of six 50-mL vials. Close the vials, and secure the stoppers. Inject 1, 2, 3, 5, and 10 μL, respectively, of the *Vinyl chloride standard solution* into five of the vials. The six solutions thus obtained contain, respectively, 0, 0.3, 0.6, 0.9, 1.5, and 3 μg of vinyl chloride. Shake, avoiding contact between the stopper and the liquid. Place the vials in a water bath at 60 ± 1° for 2 h.

Chromatographic system

(See *Chromatography* ⟨621⟩*, Gas Chromatography*.)

Column: Stainless steel 3-m × 3-mm packed with silanized diatomaceous earth for gas chromatography impregnated with 5% m/m of dimethylstearylamide and 5% m/m of polyethylene glycol 400

Gas carrier: Nitrogen for chromatography

Flow rate: 30 mL/min

Temperatures
Column: 45°
Injection port: 100°
Detector: 150°

Analysis

Sample: Inject 1 mL of the head space of each vial containing the *Sample solution* and the *Reference solutions*. Calculate the amount of vinyl chloride in the *Sample solution* by comparing the test result of the *Sample solution* with the test results of the *Reference solutions*. Calculate the amount of vinyl chloride in the test material by dividing the amount of vinyl chloride in the *Sample solution* by 1.0 g, producing a result in μg/g or ppm.

• **USP Reference Standards** ⟨11⟩

USP Butylated Hydroxytoluene RS
USP Cyclic Olefin Polymer RS
USP Cyclic Olefin Copolymer RS
USP High-Density Polyethylene RS
USP Homopolymer Polypropylene RS
USP Low-Density Polyethylene RS
USP Plastic Additive 01 RS
Ethylene bis[3,3-bis[3-(1,1-dimethylethyl)-4-hydroxyphenyl]butanoate].
USP Plastic Additive 02 RS
Pentaerythrityl tetrakis[3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propionate].
USP Plastic Additive 03 RS
2,2′,2″,6,6′,6″-Hexa-*tert*-butyl-4,4′,4″-[(2,4,6-trimethyl-1,3,5-benzenetriyl)trismethylene]triphenol.
USP Plastic Additive 04 RS
Octadecyl 3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propionate.
USP Plastic Additive 05 RS
●Tris(2,4-di-*tert*-butylphenyl) phosphite.● (ERR 1-Dec-2016)
USP Plastic Additive 06 RS
1,3,5-Tris(3,5-di-*tert*-butyl-4-hydroxybenzyl)-*s*-triazine-2,4,6(1*H*,3*H*,5*H*)-trione.
USP Plastic Additive 08 RS
Dioctadecyl disulfide.
USP Plastic Additive 09 RS
Didodecyl 3,3′-thiodipropionate.
USP Plastic Additive 10 RS
Dioctadecyl 3,3′-thiodipropionate.
USP Plastic Additive 11 RS
Copolymer of dimethyl succinate and (4-hydroxy-2,2,6,6-tetramethylpiperidin-1-yl)ethanol.
USP Plastic Additive 12 RS
Oleamide.
USP Plastic Additive 13 RS
Erucamide.
USP Plastic Additive 14 RS
Di(2-ethylhexyl) phthalate.
USP Plastic Additive 15 RS
Epoxidized soya oil.
USP Plastic Additive 16 RS
Epoxidized linseed oil.
USP Polyethylene Terephthalate RS
USP Polyethylene Terephthalate G RS
USP Plasticized Polyvinyl Chloride RS
USP Stearic Acid RS