## BRIEFING

⟨661.3⟩ **Plastic Components and Systems Used in Pharmaceutical Manufacturing.** The General Chapters—Packaging and Distribution Expert Committee proposes this new chapter to address the qualification of plastic components used in the manufacture of both pharmaceutical and biopharmaceutical active pharmaceutical ingredients (APIs) and drug products (DPs). To support the use and understanding of this new general chapter, a section has been added to *Evaluation of Plastic Packaging and Manufacturing Systems and Their Materials of Construction with Respect to Their User Safety Impact* ⟨1661⟩, which appears in this issue of *PF*. This section, *Plastic Components and Systems Used to Manufacture Pharmaceutical Drug Products*, discusses material characterization and selection, and safety qualifications of plastic components and systems used to manufacture drug products.

This chapter is part of a suite of chapters, including *Plastic Packaging Systems and Their Materials of Construction* ⟨661⟩, *Plastic Materials of Construction* ⟨661.1⟩, *Plastic Packaging Systems for Pharmaceutical Use* ⟨661.2⟩, and ⟨1661⟩.

(GCPD: D. Hunt.)

Correspondence Number—C170363

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***Add the following:***

## ■⟨661.3⟩ PLASTIC COMPONENTS AND SYSTEMS USED IN PHARMACEUTICAL MANUFACTURING



## 1. INTRODUCTION

A pharmaceutical manufacturing process is the sum of those steps that are required to convert raw materials into an active pharmaceutical ingredient (API) and then into a drug product (DP). Manufacturing processes are performed by manufacturing suites that consist of the materials, components, and parts that may be either fully or partly constructed from plastic materials. These plastic materials consist of polymers with a range of molecular

weights and that contain additives such as antioxidants, stabilizers, lubricants, plasticizers, and colorants.

It is likely that raw materials, production intermediates, process streams, APIs, and DPs will contact one or more plastic components of the manufacturing suite during the manufacturing process, resulting in process-related impurities (PrIs). PrIs have the potential to alter a quality attribute of the contacting entity and also the DP, if the PrIs persist through the manufacturing process. These interactions must be such that neither the production process nor the suitability for use of the API and DP is adversely affected. The potential effect of these interactions on the quality and safety of APIs and DPs is addressed in this chapter.

## 2. SCOPE

This chapter addresses the qualification of plastic components used in the manufacture of both pharmaceutical and biopharmaceutical APIs and DPs. Although the manufacturing process may involve circumstances where plastic components are in contact with liquid, solid, or gaseous process streams and intermediates, this chapter is applicable solely to those that involve liquid process streams and process intermediates due to the expected increased degree of interaction with liquids.

Pharmaceutical manufacturing suites may contain both single-use systems (SUS) and multiple-use systems (MUS), with SUS being used extensively in biomanufacturing suites. Plastic materials and components are used in both MUS and SUS, in all or in part, and must be suitable for their intended use. That is, the manufacturing system 1) should be compatible with the pharmaceutical product and all process intermediates and process streams, 2) should be composed of materials that are safe for use with the pharmaceutical product and all process intermediates and/or process streams, and 3) should perform properly. Plastic manufacturing systems for pharmaceutical use include, but are not limited to, bags, cassettes, chromatographic columns, connectors, filling needles, filters, sensors, tanks, tubing, and valves. Elastomeric parts such as diaphragms, gaskets, and O-rings are outside of the scope of this chapter. A flow diagram that shows a typical bioprocess DP production suite is shown in *Evaluation of Plastic Packaging and Manufacturing Systems and Their Materials of Construction with Respect to Their User Safety Impact* ⟨1661⟩, *Figure 2*.

The manufacturer of APIs and DPs is responsible for establishing that these plastic components and systems are suited for their intended use by ensuring that they have been appropriately tested and that the test results have been appropriately evaluated. Plastic manufacturing components and systems are chemically suited for their intended use with respect to safety if:

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

The test methods in this chapter are appropriate for their purpose and 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 (see *General Notices 6.30*). *Table 1* provides guidance on the appropriate application of the biological reactivity and chemical tests for manufacturing components and systems.

**Table 1. Guidelines for the Application of Tests for Manufacturing Components and Systems**

| Biological Reactivity Tests | Physicochemical Tests |
|---|---|
| • Perform *Biological Reactivity Tests, In Vitro* ⟨87⟩<br>• Materials that meet the test requirements do not need to undergo testing as described in *Biological Reactivity Tests, In Vivo* ⟨88⟩<br>• Materials that do not meet the test requirements are not suitable for manufacturing systems and components | • Provide appropriate reference to the Indirect Food Additive regulations in 21 CFR 174–186, specifically those addressing the purity criteria and limitations for use<br>• Polymeric materials of construction comply with ⟨661.1⟩<br>• Conduct an *Initial Assessment*<br>• Conduct a *Risk Assessment*<br>• Select the appropriate extraction protocol<br>• Perform *Physicochemical Tests and Extractable Metals* tests |

## 3. INITIAL ASSESSMENT

Plastic components and systems must be assessed based on the possibility that any extractables released into a process stream would persist through the manufacturing process and become PrIs in the process output, with the potential to adversely affect the safety of the process output. Matching the risk with the required level of characterization is achieved by using a two-stage approach to component characterization, consisting of an *Initial Assessment* (see *Figure 1*) followed by a *Risk Assessment* (see *Table 2*).

The *Initial Assessment* examines whether there are factors present that would support the conclusion that the plastic components and systems are fit for their intended use without further characterization. In order to qualify as a comparator component or system, equivalence should be established in the following areas:

- Equivalence in purpose and composition of component or system
- Equivalence in composition of DP(s)
- Equivalence in processing conditions
- Equivalence in product dosage form

Demonstration of equivalence with a comparator component or system would allow acceptance of the component without further characterization. Although it is highly preferred that the equivalence in all four circumstances be exact, essential equivalence may be established based on strong similarities between the component under consideration and the comparator. If equivalence cannot be established between the component under consideration and the comparator, then a *Risk Assessment* should be conducted.

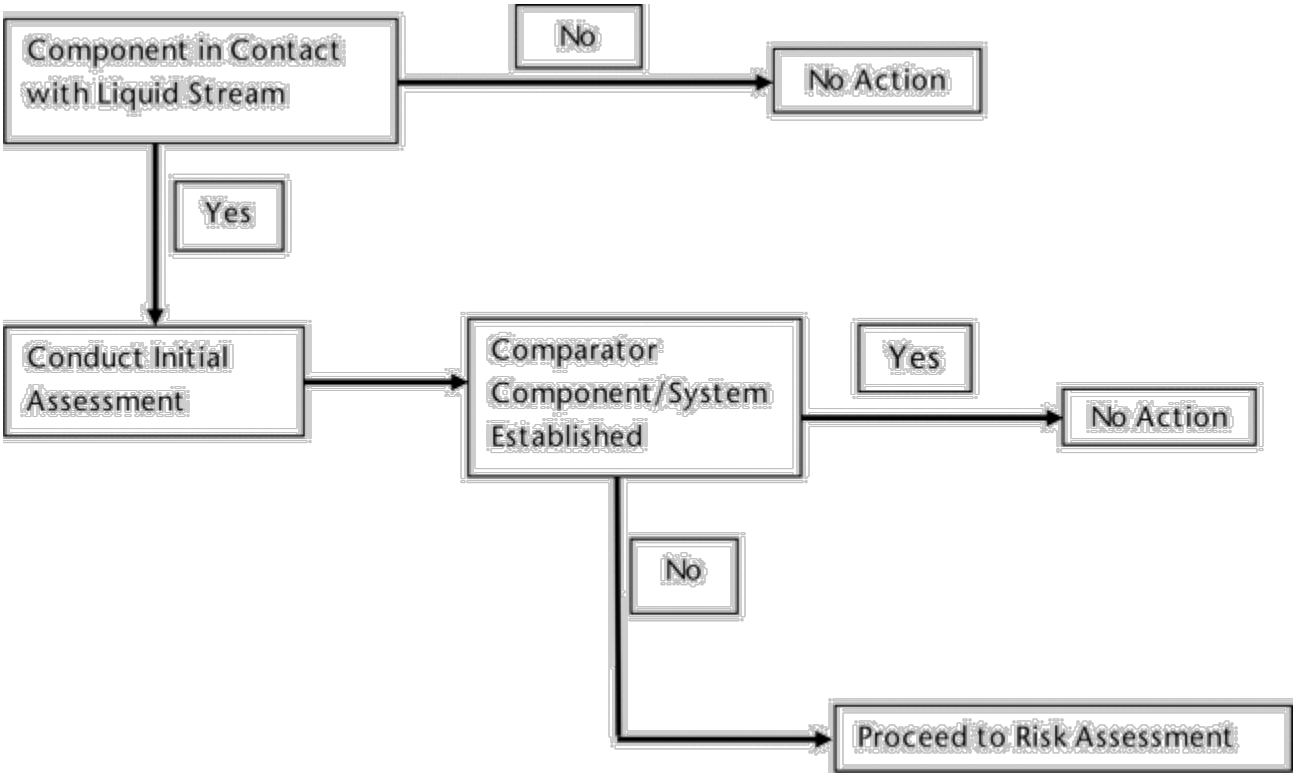


Figure 1. Initial assessment.

## 4. RISK ASSESSMENT

The two-step process for using the risk assessment matrix is provided in detail in ⟨1661⟩. The risk assessment matrix is constructed in order to:

- Establish the appropriate contributors to, or dimensions of, risk
- Provide a means of quantifying the risk in each of its dimensions
- Link the quantified risk to appropriate characterization strategies

The outcome of this assessment establishes three levels of risk: low (Level A), moderate (Level B), and high (Level C). These levels are linked to the following test requirements as shown in *Table 2*.

**Table 2. Testing Requirements for Three Risk Levels**

| Risk Level | Dosage Forms | Characterization of Plastic Components or Systems | Testing Requirements |
|---|---|---|---|
| A | Low-risk dosage forms, e.g., solid oral and liquid oral, where the liquid process stream is part of the manufacturing process for either APIs or DPs | Baseline assessment | • ⟨87⟩<br>• Materials of construction comply with ⟨661.1⟩ for identity (individual polymers only)<br>• Extracts comply with physicochemical characteristics (*Solution C1*) and extractable metals (*Solution C2*)<br>• Additives (by proper reference to 21 CFR Indirect Food Additive regulations) |
| B | Dosage forms other than solid oral and liquid oral | Expanded baseline assessment | • ⟨87⟩ and Class VI in ⟨88⟩<br>• Materials of construction comply with ⟨661.1⟩ for identity (individual polymers only)<br>• Extracts comply with physicochemical characteristics (*Solution C1*) and extractable metals (*Solution C2*)<br>• Additives are determined by testing |
| C | Dosage forms other than solid oral and liquid oral | Full assessment | • ⟨87⟩ and Class VI in ⟨88⟩<br>• Materials of construction comply with ⟨661.1⟩ for |

| Risk Level | Dosage Forms | Characterization of Plastic Components or Systems | Testing Requirements |
|---|---|---|---|
| | | | identity (individual polymers only)<br>• Perform extraction studies (see Tables 3 and 4)<br>• Extracts: *Solution C2* complies with extractable metals; *Solution C3*, *Solution C4*, and *Solution C5*comply with physicochemical characteristics and extractable organic compounds |

Selection of such isolated components may be based on a reduced level of testing, as justified by both the components' character and the degree of isolation afforded by the manufacturing process.

All three risk levels require that the component or system be tested for identity as specified in ⟨661.1⟩. However, components and systems may be constructed of multiple materials of construction; therefore, identity is only required for those components or systems that consist of single materials of construction. Both Baseline assessment (Risk Level A) and Expanded baseline assessment (Risk Level B) require that the component or system be tested as specified in ⟨661.1⟩ for physicochemical characteristics and extractable metals characteristics using *Solution C1* and *Solution C2*, respectively (see *Table 3*). It may be more practical to characterize the component or system than to characterize its individual materials of construction when determining USP class VI designation and plastic additives.

Components in the highest-risk category (Risk Level C) must be more rigorously characterized than those represented in the Baseline assessment (Risk Level A) or the Expanded baseline assessment (Risk Level B) in that an extractables profile must be established using *Solution C3*, *Solution C4*, and *Solution C5* (see *Table 3*).

## 5. TEST METHODS

### 5.1 Biological Reactivity

In vitro biological tests are performed on the components or systems according to the test procedures described in ⟨87⟩. Manufacturing components or systems that meet the requirements of these in vitro tests are not required to undergo any further in vivo testing. The in vivo test procedures described in ⟨88⟩ are not required for manufacturing components or systems used with oral dosage forms. Manufacturing components or systems that do not meet the requirements of the biological reactivity tests (see ⟨87⟩ and ⟨88⟩, if appropriate) are not suitable as manufacturing components or systems for pharmaceutical use. Where a plastic class designation (classes I–VI) is needed, analysts should perform the appropriate in vivo tests specified in ⟨88⟩. Information about selecting the appropriate plastic class is provided in *The Biocompatibility of Materials Used in Drug Containers, Medical Devices, and Implants* ⟨1031⟩.

### 5.2 Extractions

Given the diversity of materials and components used in the manufacturing suite and the widely varying conditions of contact experienced in manufacturing operations, it is not possible to establish a single extraction procedure that is a perfect match for every manufacturing circumstance. On the other hand, it is impractical to impose a large set of extraction conditions on the entire industry because it is clear that, in most circumstances, doing so will yield irrelevant test results. The compromise here is to establish a standard extraction protocol based on a minimum set of extraction conditions. This does not limit the use of additional extraction conditions if warranted by the API or a DP formulation. *Table 3* indicates which extraction condition is appropriate for a particular test.

**Table 3. Extractions Performed for Various Chemical Tests**

| Extraction | Solution Composition | Tests Performed on Plastic Components or Systems |
|---|---|---|
| *Solution C1* | Water | *Absorbance, Acidity or alkalinity, Total organic carbon* |
| *Solution C2* | 0.1 N hydrochloric acid | *Extractable metals* |
| *Solution C3* | Acid/salt buffer, pH 3 | Organic extractables |
| *Solution C4* | Phosphate buffer, pH 10 | Organic extractables |
| *Solution C5* | Ethanol and water (50:50) | Organic extractables |

The five model extraction solutions included in *Table 3* simulate the broad range of aqueous fluids that may be encountered in the production of both pharmaceutical and biopharmaceutical manufacture. The solvents represent water, low and high pH, salt concentration, an organic solvent, and 0.1 N hydrochloric acid for extractable metals. The pH range may be adjusted if the pH range of the extraction solution is outside of the plastic component or system range of compatibility. Additional extraction solutions may be utilized

where appropriate, e.g., to optimize the levels of specific extractables or to simulate formulations with special characteristics.

PREPARATION OF EXTRACTION SOLUTIONS

**Solution C1:** Use purified water.

**Solution C2:** Dilute HCl with purified water to 0.1 N.

**Solution C3:** Dissolve 14.9 g of potassium chloride in 1 L of purified water to give a 0.2 M solution. Add 53 mL of 0.2 N hydrochloric acid to 250 mL of 0.2 M potassium chloride solution, adjust with 0.2 N hydrochloric acid (if necessary) to a pH of 3 ± 0.1, and adjust with purified water to 1 L.

**Solution C4:** Dissolve 14.2 g of disodium hydrogen phosphate in purified water, adjust with 0.1 N hydrochloric acid (if necessary) to a pH of 10 ± 0.1, and adjust with purified water to 1 L.

**Solution C5:** Dilute 500 mL of ethanol, absolute with 500 mL of purified water.

## 5.3 Physicochemical Tests

WATER EXTRACTION

**Solution C1:** If testing the bag, fill it with purified water to its nominal capacity and close it using the normal means of closure, if possible; otherwise, close with an inert closure. If testing the tubing, fill a length of tubing sufficient to generate 100 mL of purified water and close the ends of the tubing with inert closures. For all other test articles, place a weighed amount of test article equal to a contact surface area of 600 $cm^2$ into a borosilicate glass flask containing 100 mL of purified water. Ensure that the test article is well contacted by the extraction solution, and close the flask with aluminum foil. The aforementioned processes will produce the extraction unit. Heat the extraction units in an oven at 55 ± 2° for a period of 96 ± 2 h. Cool the extraction units, and transfer the liquid into clean borosilicate glass flasks (*Solution C1*). Use *Solution C1* within 4 h of preparation. Prepare a blank by heating purified water in a borosilicate glass flask closed with aluminum foil at the same temperature for the same amount of time as *Solution C1*.

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

**Acidity or alkalinity:** To 50 mL of *Solution C1*, add 0.1 mL of phenolphthalein TS; note the solution's color. Add 0.4 mL of 0.01 N sodium hydroxide; note the solution's color. Add 0.8 mL of 0.01 N hydrochloric acid and 0.1 mL of methyl red TS 2 solution; note the solution's color.

**Methyl red TS 2 test for sensitivity:** Add 0.1 mL of methyl red solution to a mixture of 100 mL of carbon dioxide-free purified water and 0.05 mL of 0.02 N hydrochloric acid. NMT 0.1 mL of 0.02 N hydrochloric acid is required to change the color from red to yellow.

**Total organic carbon:** See *Total Organic Carbon* ⟨643⟩. The total organic carbon (TOC) content of *Solution C1* is measured according to ⟨643⟩. However,⟨643⟩ is designed for

testing high-purity water that has low TOC values. Because of the extracted organic substances, material extracts may have TOC values that are much higher than those of purified water. Thus, the TOC analyses performed have a limit of detection of 0.2 mg/L (ppm) and have a demonstrated linear dynamic range 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, then they should be appropriately diluted for analysis.

EXTRACTABLE METALS

**Solution C2:** Perform the extraction procedure as described for *Solution C1* using 0.1 N hydrochloric acid. Cool the extraction units and transfer the liquid into clean borosilicate glass flasks (*Solution C2*). Prepare an extraction blank by adding 0.1 N hydrochloric acid to a borosilicate glass flask closed with aluminum foil and exposing this unit to the same temperature for the same amount of time as *Solution C2*.

**Extract testing:** Instrumentation and methods for proper extract testing are specified in *Elemental Impurities—Procedures* ⟨233⟩. The instrumentation includes an inductively coupled plasma–optical emission spectrometer and an inductively coupled plasma–mass spectrometer (see *Plasma Spectrochemistry* ⟨730⟩).

**Relevant metals:** A well-characterized plastic is tested for its extractable levels of all metals that are known components of the plastic material. These metals could originate from the starting materials used to manufacture the plastic, the reagents used in the manufacturing process (e.g., catalysts), or the additives present in the plastic; such metals are termed “relevant metals”. Additionally, relevant metals include those that are specified in compendial and regulatory documents as being relevant for plastics (see *Elemental Impurities—Limits* ⟨232⟩ and ICH Guideline for Elemental Impurities Q3D). Test for all relevant metals.

EXTRACTION PROTOCOL FOR COMPONENTS OR SYSTEMS DESIGNATED AS RISK LEVEL C

**Solution C3:** Perform the extraction procedure as described for *Solution C1* using acid/salt buffer, pH 3. Cool the extraction units, and transfer the liquid into clean borosilicate glass flasks (*Solution C3*). Prepare an extraction blank by adding acid/salt buffer, pH 3 to a borosilicate glass flask closed with aluminum foil and exposing this unit to the same temperature for the same amount of time as *Solution C3*.

**Solution C4:** Perform the extraction procedure as described for *Solution C1* using phosphate buffer, pH 10. The resulting liquid is designated *Solution C4*. Prepare an extraction blank by adding phosphate buffer, pH 10 to a borosilicate glass flask closed with aluminum foil and exposing this unit to the same temperature for the same amount of time as *Solution C4*.

**Solution C5:** Perform the extraction procedure as described for *Solution C1* using ethanol and water (50:50). The resulting liquid is designated *Solution C5*. Prepare an extraction blank by adding ethanol and water (50:50) to a borosilicate glass flask closed with aluminum foil and exposing this unit to the same temperature for the same amount of time as *Solution C5*.

**Table 4. Standard Extraction Protocol for Components or Systems Designated as Risk Level C**

| Component | Extraction Solutions C3, C4, and C5 | Extraction Temperature 40° | Extraction Duration | | |
|---|---|---|---|---|---|
| | | | 1 day | 7 days | 21 days |
| Storage container | X | X | | | X |
| Mixing bag | X | X | X | | |
| Bioreactor bag | X | X | | X | |
| Connector | X | X | | X | |
| Disconnector | X | X | | X | |
| Sensor/valve | X | X | | X | |
| Molded parts of mixers | X | X | | | X |
| Polymer pump surfaces | X | X | | | X |
| Tubing | X | X | | | X |
| Gasket, O-ring | X | X | | X | |
| Sterilizing filter | X | X | X | | |
| Process filter | X | X | | X | |
| Tangential flow filtration | X | X | | X | |
| Chromatography column | X | X | X | | |
| Filling needle | X | X | X | | |

ABSORBANCE

Refer to *Ultraviolet-Visible Spectroscopy* ⟨857⟩. Determine the spectrum of *Solution C3*, *Solution C4*, and *Solution C5* between 230 and 360 nm using the respective *Solution C3*, *Solution C4*, and *Solution C5* blanks as the compensation liquid.

ACIDITY OR ALKALINITY

**BRP indicator solution:** Combine 1.0 mg/mL of bromophenol blue, 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 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. To 100 mL of *Solution C3*, 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 C3*, 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. Repeat the process for *Solution C4* and *Solution C5*.

### TOTAL ORGANIC CARBON

The TOC content of *Solution C3*, *Solution C4*, and *Solution C5* is measured according to the general methodologies outlined in ⟨643⟩. However, although the specifications in ⟨643⟩ are 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 a demonstrated linear dynamic range of 0.2–20 mg/L, which encompasses the TOC limit. A linear range with a higher upper concentration can be used if linearity is established. If sample extracts exceed this upper linear range, they must be diluted appropriately for analysis.

### EXTRACTABLE METALS

Test *Solution C2* for the following metals: arsenic, cadmium, lead, mercury, cobalt, and nickel. In addition, test *Solution C2* for any other metals that are relevant in the sense that their presence in the test material is known or can be reasonably anticipated. Instrumentation and methods for proper extract testing are specified in ⟨233⟩. The instrumentation includes an inductively coupled plasma–atomic emission spectrometer and an inductively coupled plasma–mass spectrometer (see ⟨730⟩).

### EXTRACTABLE ORGANIC COMPOUNDS

A range of analytical methodologies should be used to analyze *Solution C3*, *Solution C4*, and *Solution C5*, including gas chromatography, high-performance liquid chromatography, and mass spectrometry.

## 6. SPECIFICATIONS

### 6.1 Physicochemical Tests

### ABSORBANCE

The 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

Test *Solution C3*, *Solution C4*, and *Solution C5* for the following metals: arsenic, cadmium, lead, mercury, cobalt, and nickel. Report the measured values >0.01 mg/L (ppm), corresponding to 0.025 mg/g. If the measured values are below these values, report the result as <0.01 mg/L (ppm), corresponding to <0.025 mg/g.

## EXTRACTABLE ORGANIC COMPOUNDS

Because of the considerable diversity of manufacturing materials, components, and systems, specific test conditions for analyzing extracts for organic extractables cannot be established. Nevertheless, general principles and recommended best practices can be found in *Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems* ⟨1663⟩. As indicated in ⟨1663⟩, a rigorous analytical approach for assessing organic extractables includes orthogonal methodologies such as gas and liquid chromatography, coupled with appropriate sampling and detection techniques. The confirmed identity and quantity of extracted organic compounds should be reported.■ 1S (*USP40*)

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