BRIEFING

⟨1661⟩ Evaluation of Plastic Packaging Systems and Their Materials of Construction With Respect to Their User Safety Impact, *USP 42* page 8272. The General Chapters—Packaging and Distribution Expert Committee is proposing the following revisions, with the key changes being listed below:

1. The chapter is being revised to align with the revison of *Plastic Packaging Systems and Their Materials of Construction* ⟨661⟩, *Plastic Materials of Construction* ⟨661.1⟩, and *Plastic Packaging Systems for Pharmaceutical Use* ⟨661.2⟩, also appearing in this issue of*PF*.
2. Describe all of the plastic materials that are included in ⟨661.1⟩, and the process of materials assessment, along with the applicability and application of ⟨661.1⟩.
3. Add four new polymer descriptions to the chapter [polyamide 6; polycarbonates; poly(ethylene-vinyl acetate); and polyvinyl chloride], which correspond to the addition of these materials to ⟨661.1⟩, and expand the scope of the current chapter.
4. Discuss the importance of packaging system assessment and qualification and how ⟨661.2⟩ facilitates this assessment.

Additionally, minor editorial changes have been made to update the chapter to current *USP* style.

(GCPD: D. Hunt.)

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Change to read:

⟨1661⟩ EVALUATION OF PLASTIC PACKAGING SYSTEMS ▲FOR PHARMACEUTICAL USE▲ (USP 1-Aug-2020) AND THEIR MATERIALS OF CONSTRUCTION ~~WITH RESPECT TO THEIR USER SAFETY IMPACT~~▲ ▲ (USP 1-Aug-2020)

Add the following:

7. APPLICABILITY AND APPLICATION OF ⟨661.2⟩

7.1 Applicability

7.2 Application▲ (USP 1-Aug-2020)

Change to read:

▲1.▲ (USP 1-AUG-2020) INTRODUCTION

Drug products can chemically interact with their associated packaging systems and/or the system's plastic materials ~~and components~~▲▲ (USP 1-Aug-2020) of construction while the drug product is being manufactured, shipped, stored, and administered. The magnitude of these interactions should not ~~be such that the interactions~~▲▲ (USP 1-Aug-2020) adversely affect the suitability ~~for use~~▲▲ (USP 1-Aug-2020) of the ▲packaged▲ (USP 1-Aug-2020) drug product,~~or the packaging system. While 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~~▲which includes both quality aspects and performance aspects such as efficacy, stability, purity, and compendial compliance.▲ (USP 1-Aug-2020)

~~The potential patient safety~~▲Suitability for use, as determined by the▲ (USP 1-Aug-2020) impact of the interaction between a drug product and its packaging ▲system,▲ (USP 1-Aug-2020) is assessed and established via the appropriate testing of the ▲materials of construction, components, and▲ (USP 1-Aug-2020) packaging systems. ~~and their materials and components of construction~~▲▲ (USP 1-Aug-2020)*Plastic Packaging Systems and Their Materials of Construction* ⟨661⟩ establishes the tests ~~and specifications~~▲and acceptance criteria▲ (USP 1-Aug-2020)

that are necessary and appropriate for ensuring that such systems are suitable. ~~for use, specifically safe for use. Chapter ⟨661⟩ consists of two sub-chapters, *Plastic Materials of Construction* ⟨661.1⟩ and *Plastic Packaging Systems for Pharmaceutical Use* ⟨661.2⟩.~~ ▲ (USP 1-Aug-2020)

Change to read:

▲2. (USP 1-AUG-2020) SCOPE

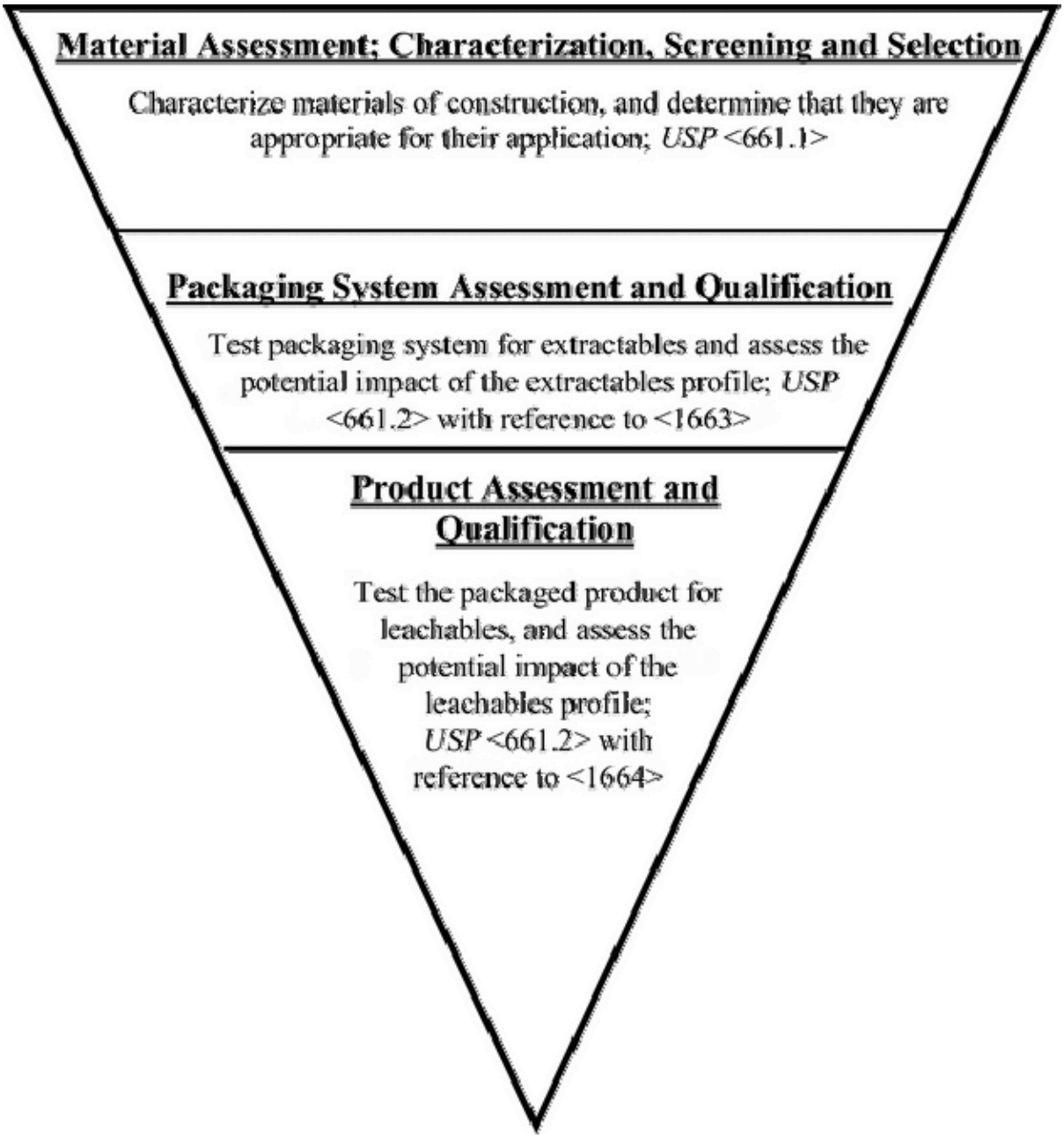
The purpose of this chapter is to communicate the key concepts behind ⟨661⟩ and its related sub-chapters, *Plastic Materials of Construction* ⟨661.1⟩ and *Plastic Packaging Systems for Pharmaceutical Use* ⟨661.2⟩, and to provide additional information and guidance regarding the application and applicability of these chapters. ~~Given the large and diverse nature of the pharmaceutical marketplace, the proper use and application of the ⟨661⟩ suite of chapters may not be intuitive to some stakeholders. Therefore, this chapter is intended to assist users in understanding and utilizing the ⟨661⟩ series of chapters.~~ ▲ (USP 1-Aug-2020)

Change to read:

▲3. (USP 1-AUG-2020) GENERAL PRINCIPLES—THE OVERALL ASSESSMENT PROCESS

The objective of *USP* ▲plastic▲ (USP 1-Aug-2020) packaging ~~systems~~ ▲ (USP 1-Aug-2020) standards is to establish the tests and ~~specifications that~~▲acceptance criteria to▲ (USP 1-Aug-2020) ensure packaging systems do not materially impact the ~~safety or~~ ▲ (USP 1-Aug-2020) effectiveness of ~~pharmaceutical~~▲the drug▲ (USP 1-Aug-2020) product. Given the complex nature of packaging systems and their ~~manufacturing and~~ ▲ (USP 1-Aug-2020) development ▲and manufacturing▲ (USP 1-Aug-2020) processes, multiple testing procedures are needed to establish their

suitability ~~for use~~ (USP 1-Aug-2020) with a specific ~~pharmaceutical~~ drug (USP 1-Aug-2020) product. The logical development and manufacturing process ~~progression~~ (USP 1-Aug-2020) for packaged drug products, starts with the packaging system's materials of construction, continues with the packaging system itself, and ends with the packaged drug product. This progression (USP 1-Aug-2020) forms the basis of a three-stage approach to packaging systems qualification, as illustrated in Figure 1.



Click image to enlarge

Figure 1. The three-stage process for the characterization and ~~safety~~ ▲▲ (USP 1-Aug-2020) qualification of packaging systems and their materials of construction.

The process for establishing a packaging system's suitability ~~for use~~▲▲ (USP 1-Aug-2020) includes: characterization of its materials of construction (ingredients); testing and assessment of the system itself (extractables); and testing and assessment of the packaged ~~pharmaceutical~~▲drug▲ (USP 1-Aug-2020) product (leachables). The initial step of this process involves chemically characterizing candidate materials of construction ~~to the extent that the choice~~▲so the selection▲ (USP 1-Aug-2020) of materials ~~to use in the construction of a packaging system~~▲▲ (USP 1-Aug-2020) can be rationally made and scientifically justified. The intermediate step of system assessment is useful and necessary because it bridges the risk assessment gap between testing starting materials and testing the finished ▲drug▲ (USP 1-Aug-2020) product, while providing a means for optimizing ~~pharmaceutical~~▲drug▲ (USP 1-Aug-2020) product testing. This intermediate test is necessary because materials of construction undergo considerable stress, such as exposure to high temperatures, as they are being converted into either components of the packaging system or the packaging system itself. Processing aids and additional additives may be introduced during the manufacturing process for a packaging system, so the extractables profile ~~of a system~~▲▲ (USP 1-Aug-2020) is likely to be different from, and potentially more complex than, ~~the sum of~~▲▲ (USP 1-Aug-2020) the extractables profiles of its materials of construction. Therefore, the initial ~~assessment of risk made in~~ ▲hazard identification performed during▲ (USP 1-Aug-2020) material selection is appropriately revisited by testing and qualification of the overall packaging system. ~~itself.~~▲▲ (USP 1-Aug-2020)

Ultimately, the effect the packaging ▲system▲ (USP 1-Aug-2020) may have on the drug product ▲end-▲ (USP 1-Aug-2020)user is mediated by packaging ▲system▲ (USP 1-Aug-2020)-derived substances that are present in the drug product. The third stage of the process ~~is~~▲includes▲ (USP 1-Aug-2020) product assessment, specifically

leachables testing of the packaged product and impact assessment, which considers the user's exposure to the leachables.

Change to read:

▲4.▲ (USP 1-AUG-2020) MATERIALS ASSESSMENT: CHARACTERIZATION, SCREENING, AND SELECTION, *USP* ⟨661.1⟩

~~To ensure that a packaging system is suited for its intended use, it is important to select materials of construction which are suited for use in packaging systems.~~▲▲ (USP 1-Aug-2020) Testing and characterizing materials of construction for attributes relevant to their suitability provides a rational basis for material selection in designing a packaging system ~~The intentional selection of well-characterized materials minimizes the risk that a system made from those materials will be unsuitable. Considering safety specifically, selection of materials that have the tendency to be safe increases the likelihood that packaging systems made from those materials will be safe~~▲and minimizes the risk that a system made from those materials will be unsuitable.▲ (USP 1-Aug-2020) Therefore, the characterization of materials of construction is the first step in the process of developing and qualifying ~~safe~~▲suitable▲ (USP 1-Aug-2020) packaging materials. Additionally, chemical characterization data may also provide the basis for effective and appropriate change control.

The intent of ⟨661.1⟩ is to establish ~~with a degree of confidence,~~▲▲ (USP 1-Aug-2020) whether potential material candidates could adversely affect the quality ~~and safety~~▲▲ (USP 1-Aug-2020) of ~~pharmaceutical~~▲packaged drug▲ (USP 1-Aug-2020) products. The basic tenet of materials assessment~~, as reflected in ⟨661.1⟩,~~▲▲ (USP 1-Aug-2020) is that knowing the general composition and certain general characteristics of a material of construction allows one to:

- Rationally assess the potential ~~safety impact~~ ▲suitability▲ (USP 1-Aug-2020) of materials with a degree of certainty that is appropriate for early product development and/or manufacturing.
- Forecast with some degree of accuracy the identity of extractables from that material of construction and from systems that use that material of construction.
- Use the assessment and forecast to establish and justify the use (or ~~non-use~~▲rejection▲ (USP 1-Aug-2020)) of a particular material in a particular packaging system.

To this end, ⟨661.1⟩ defines a well-characterized ▲plastic▲ (USP 1-Aug-2020) material of construction as one whose:

- Identity has been definitively established.
- Biocompatibility (biological reactivity) has been established.
- General physicochemical properties have been established.
- ▲Extractable elements (when necessary).▲ (USP 1-Aug-2020)
- Additives ~~and extractable metals~~▲▲ (USP 1-Aug-2020) have been quantified.

Chapter ⟨661.1⟩ testing is not a guarantee that ~~plastic~~▲packaging▲ (USP 1-Aug-2020) systems constructed from ▲plastic▲ (USP 1-Aug-2020) materials meeting ⟨661.1⟩~~these specifications~~▲requirements▲ (USP 1-Aug-2020) will be suitable for their intended use. ~~because it is not always the case that testing of a system's materials of construction directly and completely correlates with subsequent testing of the plastic system~~▲▲ (USP 1-Aug-2020) Characterization of a material using ⟨661.1⟩ establishes the composition or characteristics of the material,~~and~~▲which can be used to determine▲ (USP 1-Aug-2020) if the material is an appropriate candidate for use in a packaging system. Nevertheless, ⟨661.1⟩ testing leverages the logical connection between material

additives, material extractables, and system extractables, and thus provides a useful indication of the probable suitability ~~for use~~ ▲ (USP 1-Aug-2020) issues for materials and systems. The actual qualification of the material occurs when the entire system is qualified for use in a particular application via ⟨661.2⟩ testing.

Change to read:

▲5.▲ (USP 1-AUG-2020) PACKAGING SYSTEM ASSESSMENT AND QUALIFICATION, *USP* ⟨661.2⟩

The impact of packaging systems on the chemical composition of packaged drug product can be established in two ways: 1) the packaging system itself can be characterized with respect to substances that can extract from it (extractables); ▲or▲ (USP 1-Aug-2020) 2) the packaged drug product can be tested for packaging-derived substances that have leached into the drug product (leachables). In the case of extractables assessment, the impact is predicted based on a relationship that is established (or inferred) between extractables and leachables. In the case of leachables assessment, the impact is specifically measurable, assuming that all the relevant leachables can be discovered, identified, and quantified in the packaged ▲drug▲ (USP 1-Aug-2020) product. In either case, ⟨661.2⟩ establishes the tests and ~~specifications~~ ▲acceptance criteria▲ (USP 1-Aug-2020) for the packaging system, while referring users to relevant informational chapters (e.g., *Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems* ⟨1663⟩ for extractables and *Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery Systems* ⟨1664⟩ for leachables) for insights on how to design and execute relevant studies.

Considering the packaging system as the test article, the intent of ⟨661.2⟩ is to define and delineate the testing needed to produce the data required for

establishing the packaging system's ~~safety~~ suitability. (USP 1-Aug-2020) Chapter ⟨661.2⟩ refers to this process of establishing the ~~safety~~ suitability (USP 1-Aug-2020) of packaging systems as chemical suitability for use (USP 1-Aug-2020) assessment and notes that a packaging system is ~~chemically~~ (USP 1-Aug-2020) suited for its intended use if:

- The packaging system is constructed from well-characterized materials, as established by testing according to ⟨661.1⟩.
- The packaging system's general physicochemical properties have been established.
- The packaging system's biocompatibility (biological reactivity) has been established.
- The packaging system has been established to be ~~safe~~ suitable (USP 1-Aug-2020) by means of the appropriate chemical ~~testing and toxicological assessment.~~ suitability for use assessment. (USP 1-Aug-2020)
- The packaging system is chemically compatible with the packaged product, as established by appropriate compatibility assessments (e.g., stability studies).

~~Considering the fourth bullet point, ⟨661.2⟩ notes that appropriate chemical testing includes performing extractables testing, leachables testing, and the relevant toxicological assessment of the extractables and/or leachables results.~~

5.1 Extractables and Leachables (USP 1-Aug-2020)

~~In~~ For high risk dosage forms, in (USP 1-Aug-2020) addition to being the basis for toxicological ~~safety~~ (USP 1-Aug-2020) assessments, information about a packaging system's extractables can be used in several ways to optimize finished product testing for leachables. The potential quality ~~and/or~~

~~safety~~ ▲ (USP 1-Aug-2020) or impact of extractables may facilitate identification of leachables that might adversely affect product quality. Such leachables of potential concern would necessarily be among the targeted analytes in testing of a final ~~pharmaceutical~~ drug ▲ (USP 1-Aug-2020) product within its packaging system. The targeting of specific leachables, as opposed to the screening of ~~pharmaceutical~~ drug ▲ (USP 1-Aug-2020) products for unspecified leachables, has significant analytical benefits, including the ability to develop, validate, and utilize test procedures that are appropriately sensitive, specific, and accurate. Extractables (and their accumulation levels in extracts) can be used to forecast the levels of leachables in the finished product, depending on how well the extraction conditions mimic the ~~pharmaceutical~~ drug ▲ (USP 1-Aug-2020) product's composition and actual conditions of clinical use. If the extraction conditions are such that they accelerate and modestly exaggerate the product's clinical use conditions, then the extractables and their levels in the extracts can be extrapolated to estimate the maximum levels of leachables in the finished product. If such extractables are assessed for their ~~safety or~~ ▲ (USP 1-Aug-2020) quality impact, the results of that assessment can also be extrapolated to, and ~~deemed~~ considered ▲ (USP 1-Aug-2020) to be relevant for, the ~~pharmaceutical~~ drug ▲ (USP 1-Aug-2020) product. Finally, if no adverse impact is found based on the extractables data, then no adverse impact can be inferred for the leachables in the packaged ~~pharmaceutical~~ drug ▲ (USP 1-Aug-2020) product. ~~Consistent with certain regulatory guidelines, leachables studies may not be required when extractables studies establish the maximum amount of individual leachables that may be present in the active substance/medicinal product and when such maximum levels have been demonstrated to be toxicologically safe. However, should a leachable study~~

~~be considered to be to be unnecessary, a justification should be provided.~~ ▲ (USP 1-Aug-2020)

Change to read:

▲6. (USP 1-AUG-2020) APPLICABILITY AND APPLICATION OF ⟨661.1⟩

▲6.1 (USP 1-Aug-2020) Applicability

1. The holder of the drug product application and drug product manufacturer [in the case of many over-the-counter products (OTCs), where there is no application] bear primary responsibility and accountability for ensuring that the requirements of the chapters are met. The means by which the holder of the drug product application and drug product manufacturer obtain information to meet the requirement is at the discretion of the holder.
2. The testing required and ~~specifications~~▲acceptance criteria▲ (USP 1-Aug-2020) for materials of construction contained within ⟨661.1⟩ are relevant to and applicable for all ~~drug~~▲ ▲ (USP 1-Aug-2020) dosage forms, because it is the universal expectation that packaging materials be constructed from well-characterized materials, regardless of the potential interaction between a dosage form. ~~The use of risk-management principles and concepts to address the potential product safety risk associated with leachables (and extractables as potential leachables) is a cornerstone of global regulatory and industry thinking on this topic. Industrial scientists and regulators agree~~▲It has been established▲ (USP 1-Aug-2020) that the concepts and principles of risk management ~~have a definite~~▲has a▲ (USP 1-Aug-2020) strategic role in designing, implementing, and interpreting effective and efficient ▲material suitability testing and▲ (USP 1-Aug-2020) assessments. ~~of extractables and/or leachables~~▲ ▲ (USP 1-Aug-2020) It is well-established that risk-management tools and principles can be used to define the nature and magnitude of assessment (including testing), where low-risk situations require reduced or alternate assessment (testing) versus high-risk situations noted in *Plastic Materials of Construction* ⟨661.1⟩*, Table 1*, ~~and Table 2~~▲ ▲ (USP 1-Aug-2020) which establishes biological reactivity and chemical tests that differ ~~somewhat~~▲ ▲ (USP 1-Aug-2020) for low-risk dosage forms (such as oral and

topical) versus high-risk dosage forms (such as inhalation and injections).~~Moreover, an essential principle reflected in ⟨661.2⟩ is that packaging systems be tested for extractables and that the approach be consistent with the nature of the interaction between the drug product and its packaging. This includes consideration of the drug product contact condition (e.g., liquid versus dry) and the potential interaction between the dosage form and its packaging system. By referencing ⟨1663⟩ for extractables testing, ⟨661.2⟩ provides the means by which extractables studies relevant for specific dosage forms can be designed, implemented, and interpreted. By allowing for study designs that reflect the nature and clinical use of various dosage forms, ⟨661.2⟩ supports and uses risk-based strategies and assessments.~~

3. ~~The outcome of ⟨661.1⟩ testing is that the tested construction material has been well-characterized. Characterization data generated during ⟨661.1⟩ testing can be used to support decisions on the proper use of the tested material. The characterization data does not specifically or universally qualify the material for use in packaging systems, because the material's use can vary depending on the packaging applications. It is the responsibility of the developer or user of the tested material to decide if the material is appropriate for their intended application. It is the developer's or user's expert review of the ⟨661.1⟩ test results, coupled with additional information as necessary and appropriate, that establishes whether a well-characterized material is suitable for use in a specific application. Alternatively, the outcome of testing plastic packaging systems via ⟨661.2⟩ is an assessment of the probable safety impact of that system on the packaged drug product. This assessment is based on the biological reactivity testing, the physiocochemical testing, and the extractable/leachables testing that are required by ⟨661.2⟩. A packaging system that has been tested per ⟨661.2⟩ and meets the specifications contained within ⟨661.2⟩, including a toxicological safety assessment of the extractables and/or leachables data, is qualified for use consistent with the conditions under which it was tested, subject to review by the appropriate regulatory authority.~~

4. ~~There are two means of demonstrating a material of construction has met the requirements of ⟨661.1⟩. The first is to perform the testing and meet the specifications contained in ⟨661.1⟩ the second means is the~~

~~use of a material with a currently approved finished drug product.~~ ▲ (USP 1-Aug-2020)

5. Application of ⟨661.1⟩~~and ⟨661.2⟩~~ ▲ (USP 1-Aug-2020) to materials of construction ~~or systems~~ ▲used for systems▲ (USP 1-Aug-2020) other than packaging systems for finished drug product is beyond the scope of this chapter ▲at the present time,▲ (USP 1-Aug-2020) but the concepts and principles of the chapter may be applicable and relevant to other systems and their materials for construction ~~such as medical devices for drug product administration, manufacturing systems for pharmaceutical products, and packaging/storage systems for drug substances. Future compendial chapters will be developed to address these other pharmaceutically important systems.~~ ▲(e.g., manufacturing systems for pharmaceutical products, and packaging/storage systems for drug substances).▲ (USP 1-Aug-2020)
6. The scope of ⟨661.1⟩ is materials of construction ▲for packaging systems for finished drug products▲ (USP 1-Aug-2020) and ⟨661.2⟩ is packaging systems ~~A third type of test article, components, is not directly considered in the *Scope* of either chapter. In this context, a component is defined as an individual part of a packaging system and is constructed from one or more materials of construction. Thus, a plastic bag consisting of a laminated film is considered to be a component of the packaging system that includes the bag. Since a component is constructed from materials and is part of a system, if component testing is deemed to be necessary, the relevant testing and specifications for the component are contained within ⟨661.2⟩. The provisions in ⟨661.2⟩ for packaging systems must be met for components whose testing has been deemed to be necessary. The component must be constructed from materials that meet the requirements of ⟨661.1⟩ and the component must be tested by the methods, and meet the specifications, contained in ⟨661.2⟩.~~ ▲for finished drug products. A third type of test article is components and if component testing is considered to be necessary, the relevant testing and acceptance criteria for the component are contained within ⟨661.2⟩.▲ (USP 1-Aug-2020)
7. ~~Testing of materials of construction via ⟨661.1⟩ is predicated on the circumstance that the material will most likely interact with the~~

packaged drug product when the material is used in a packaging system. It is not necessary for a material used in a packaging system to be well-characterized if there is little or no chance of the material and the packaged drug product interacting. Under these conditions the materials of construction would be considered non-interacting and would be exempt from ⟨661.1⟩ testing. The designation of a material of construction as "non-interacting" must be accepted by the appropriate regulatory authority.

Although it is beyond the scope of ⟨661.1⟩ to establish the means by which a material of construction is established as "non-interacting". It is relevant to differentiate between the potentially similar terms "no direct contact" and "non-interacting", where the term "no direct contact" means that the material and the packaged drug product do not come into direct physical contact under the clinical conditions of use.Although it may well be the case that in a specific application a "no direct contact" material of construction is also a "non-interacting" material of construction, it may also be the case that "no direct contact" does not insure "non-interacting", especially when the conditions of contact include long durations and/or substantially elevated temperatures.

To explain the concepts of "no direct contact" and "non-interacting", consider the following example. An aqueous drug product is packaged in a flexible plastic container. The flexible container is further placed in a foil overpouch. The overpouched product is terminally sterilized. An adhesive label is applied to the outside of the foil overpouch. after the product unit has been cooled after terminal sterilization.

In this case, both the foil overpouch and the label are "no direct contact",because there is at least one physical barrier (the primary container) between the packaged drug product and these two items. However, if the flexible plastic primary container is permeable, the foil

~~overpouch can be considered a "potentially interacting" component, as substances from the overpouch could migrate through the primary packaging, especially under the high-temperature conditions of terminal sterilization. The label is a "non-interacting" component because 1) the foil overpouch is impermeable and 2) the label is applied after the thermal stress associated with terminal sterilization.~~

~~Thus, the difference between a "potentially interacting" and "non-interacting" "no direct contact" component is the permeability of the barrier that separates the "no direct contact" components from the drug product. If the barrier is incomplete, then the component (and its materials of construction) is "potentially interacting" and the materials must be tested per ⟨661.1⟩. If the barrier is complete, then the component (and its materials of construction) is "non-interacting" and the materials need not be tested per ⟨661.1⟩.~~ ▲ (USP 1-Aug-2020)

▲6.2▲ (USP 1-Aug-2020) Application

1. There are two means of demonstrating that a ▲plastic▲ (USP 1-Aug-2020) material of construction has met the requirements of ⟨661.1⟩. The first is to perform the testing contained within ⟨661.1⟩ and meet the ~~specifications in ⟨661.1⟩~~ ▲acceptance criteria.▲ (USP 1-Aug-2020) The second ~~means is the use of a material in the packaging system of a currently approved finished drug product. Specifically, ⟨661.1⟩ states "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⟩ or if the packaging system has been deemed appropriate for pharmaceutical use by the appropriate regulatory authority". However, it is noted that such a conclusion is only valid for the specific packaging system meeting the requirements of ⟨661.2⟩ and cannot be extended to other packaging systems using the same material (or materials) of construction. If the same material of construction is used in another packaging system, then its suitability~~

~~for use in that packaging system must be established.~~ ▲is the use of the material in a packaging system that meets the requirements of ⟨661.2⟩.▲ (USP 1-Aug-2020)

2. The outcome of ⟨661.1⟩ testing is that the tested material of construction has been well-characterized. Characterization data generated during ⟨661.1⟩ testing can be used to support decisions on the proper use of the tested material. The characterization data do not specifically or universally qualify the material for use in packaging systems because the material's use can vary depending on the packaging applications. ~~Alternately, the outcome of testing plastic packaging systems via ⟨661.2⟩ is an assessment of the probable safety impact of that system on the packaged drug product. This assessment is based on the biological reactivity testing, the physicochemical testing, and the extractables/leachables testing that are required by ⟨661.2⟩. Thus, a packaging system that has been tested per ⟨661.2⟩ and which meets the specifications for ⟨661.2⟩, including a toxicological safety assessment of the extractables and/or leachables data, is qualified for use consistent with the conditions under which it was tested, subject to approval by the appropriate regulatory authority.~~

3. ~~It is reasonable to anticipate that there may be some information that the vendor is not in a position to share with a material's user. Nevertheless, it is in the interest of both the vendor and the user that a material be well-characterized and that the characterization include all relevant analytes. Thus, it is strongly recommended that the vendor and the user find a means of establishing all relevant analytes. For example, consider the case of extractable metals. While it may be the case that the material's vendor would decline to share detailed information about the use of a zinc-containing reagent in the preparation of a material, it is adequate for the purpose of material characterization for the vendor to communicate that zinc should be a targeted analyte.~~ ▲It is the responsibility of the user of the tested material to decide if the material is appropriate for their intended application. It is the user's expert review of ⟨661.1⟩ test results, coupled with additional information as necessary and appropriate, that establishes whether a well-characterized material is suitable for a specific application.

6.2.1 IDENTIFICATION TESTS ▲(USP 1-Aug-2020)

The identification tests required in ⟨661.1⟩ serve the purpose of categorizing a material so that it is properly tested and evaluated against the appropriate ~~specifications~~▲acceptance criteria.▲ (USP 1-Aug-2020) The ~~specifications~~▲acceptance criteria▲ (USP 1-Aug-2020) for identification are based on a comparison of the test result obtained for the test material versus the relevant Reference Standard. This comparison is based on the concept of substantial equivalence as opposed to an exact quantitative ~~specifications~~▲acceptance criteria.▲ (USP 1-Aug-2020)

Establishing substantial equivalence requires that the test results and test material versus Reference Standard be considered to be equivalent. ~~Although the individual specifications for the individual materials contained in ⟨661.1⟩ may include information that is relevant to establishing substantial equivalence, this information in and of itself is not considered to be a specification.~~▲▲ (USP 1-Aug-2020) For example, although the infrared (IR) identification ~~specifications~~▲acceptance criteria▲ (USP 1-Aug-2020) may include wavenumber targets, these targets are not ~~specifications~~▲acceptance criteria▲ (USP 1-Aug-2020) but rather serve the purpose of establishing the expected general characteristics of the IR spectra. An identification test is considered successfully completed if the analytical results obtained for the test article and the appropriate Reference Standard are substantially equivalent, and where all differences between the test results for the article and the Standard are explained by the nature, processing, and/or composition of the test article.

~~Establishing the potential safety impact of a material of construction cannot rely on a single testing strategy, as no single testing strategy is sufficient to identify all potential safety-impacting attributes of a material.~~

▲6.2.2 CHEMICAL TESTING▲ (USP 1-Aug-2020)

The chemical testing prescribed in ⟨661.1⟩ is orthogonal: physicochemical tests provide a general overview of extracted substances~~; extractable metals tests address potential sources of elemental impurities; while~~▲whereas,▲ (USP 1-Aug-2020) plastic additives tests address potential organic extractables. It is also the case that chemical testing alone may not demonstrate all potential ~~safety~~ ▲▲ (USP 1-Aug-2020) impacting attributes. Thus, chemical testing is augmented by the orthogonal approach of establishing biological reactivity.

~~A well-characterized plastic material is tested for its extractable levels of all metals that are known components of the plastic material. They could originate from the starting materials used to manufacture the plastic material, reagents used in the manufacturing process (e.g., catalysts), and from additives present in the plastic materials. Such metals are termed "relevant metals". Additionally, materials are tested for metals that are specified in other compendial documents as being relevant for plastic materials. Lastly, materials are tested for metals that have been deemed to be elemental impurities that are applicable to all drug product dosage forms regardless of whether the source of the elemental impurities is intentionally or unintentionally added to the drug product, its ingredients, or its packaging system.~~

~~Extractable metals reporting thresholds contained within ⟨661.1⟩ are not to be construed as limits. Rather, the reporting thresholds establish the convention for reporting extractable metals results. In this regard, the *USP* specification for extractable levels is not that they be below a certain limit, but rather that they be reported as specified in ⟨661.1⟩.~~

~~It may be that not all of the relevant metals for a particular material of construction are specified in ⟨661.1⟩, and that some relevant metals~~

become known by another means (for example, vendor certification). All relevant metals, regardless of their inclusion in ⟨661.1⟩, must be tested for. Procedures for relevant metals that are not specified in ⟨661.1⟩ must be established and should be consistent with the procedures used for metals that are specified in ⟨661.1⟩. Specifications must be established for relevant metals that are not specified in ⟨661.1⟩; such specifications should be consistent with the specifications established for metals that are specified in ⟨661.1⟩.

Extractable metals testing described in ⟨661.1⟩ is required for all materials of construction used in packaging systems, regardless of whether the material is specified in ⟨661.1⟩. Extractable metals test procedures for materials that are not specified in ⟨661.1⟩ must be established and should be consistent with the procedures used for materials that are specified in ⟨661.1⟩. Extractable metals specifications must be established for materials that are not specified in ⟨661.1⟩; such specifications should be consistent with the specifications established for materials that are specified in ⟨661.1⟩.

The listing of specific extractable metals in ⟨661.1⟩ is not meant to limit material sponsors or users who may seek to establish the level of extractable metals other than those specified in ⟨661.1⟩. This may be the case, as additional extractable metals may be applicable to certain dosage forms and as the analytical methods that may be applied to extractable metals analyses could routinely supply data for extracted metals other than those specified in ⟨661.1⟩. In cases where individual sponsors obtain test results for extractable metals other than those specified in ⟨661.1⟩, it is expected that such additional extractable metals would be reported in the manner specified in ⟨661.1⟩ for those extractable metals that are specified in ⟨661.1⟩.

6.2.3 EXTRACTABLE ELEMENTS

Knowledge of the potential extractable elements present in the materials of construction for plastic packaging components is important in establishing that the material is well-characterized. Knowledge of the elements that are likely to be present and the concentrations at which they may be observed provides information to determine potential drug product quality risk. Materials of construction can vary widely in terms of their intentionally and unintentionally added elements and their potential use. Because of this, it is challenging to provide universally effective and efficient tests methodologies, lists of target elements, and reporting requirements. It is the material user's responsibility to evaluate the need for extractable elements testing and, if such testing is necessary, to establish and justify the means by which testing is accomplished, taking into account target elements, extraction conditions, extract analysis, and reporting requirements. Example of an extractable elements testing strategy (extraction conditions, target elements and reporting threshold) is provided below.

Target elements:

Relevant elements that should be tested for extractable elements reflects those elements that have been intentionally added (e.g., catalyst and processing aids) and elements of toxicological concern. Relevant elements for the various plastics are listed in Table 1.

Table 1. Extractable Elements for Plastics

Extraction	Extracting Solution	Cyclic Olefin, Polyethylene, and Polypropylene	Polyamide 6	Polycarbonate	Polyethylene Terephthalate and Polyethylene Terephthalate G	Poly(ethylene-vinyl acetate)	Polyvinyl Chloride	Polyvinyl Chloride, Plasticized

Extraction	Extracting Solution	Cyclic Olefin, Polyethylene, and Polypropylene	Polyamide 6	Polycarbonate	Polyethylene Terephthalate and Polyethylene Terephthalate G	Poly(ethylene-vinyl acetate)	Polyvinyl Chloride	Polyvinyl Chloride, Plasticized
Solution EE1	Acid	Al, As, Cd, Co, Cr,[a] Hg, Ni, Pb, Ti, V, Zn, and Zr[b]	Al, As, Ba, Cd, Co, Hg, Mn, Ni, Pb, Ti, V, and Zn	As, Ba, Ca, Cd, Co, Hg, Ni, Pb, Sn, V, and Zn	Al, As, Ba, Cd, Co, Hg, Mn, Ni, Pb, Ti, V, and Zn	Al, As, Cd, Co, Hg, Ni, Pb, V, and Zn	Al, As, Ba,[c] Cd, Co, Hg, Ni, Pb, Ti, V, and Zn	As, Ba, Ca, Cd, Co, Hg, Ni, Pb, Sn, V, and Zn
Solution EE2	Alkali	N/A	N/A	N/A	Sb and Ge	N/A	N/A	N/A

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[a] For polyethylene only.

[b] Not applicable for cyclic olefins and polypropylene.

[c] For material used for containers for non-injectable aqueous solutions.

Relevant extractable elements can be established by analysis of the materials of construction using the method described in*Procedure for extraction*.

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 elements in a packaging system's materials of

construction is extraction, as opposed to complete digestion, of the plastic material. *Solution EE1* (acidic extraction) and *Solution EE2* (alkaline extraction) are examples of extraction solutions for plastics listed in Table 1.

Acid extraction, Solution EE1

POLYETHYLENE, CYCLIC OLEFINS, POLYPROPYLENE, POLY(ETHYLENE-VINYL ACETATE), POLYCARBONATE, AND POLYAMIDE 6:

Place 100 g of the test material into a suitable plastic container. 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 EE1*.

POLYETHYLENE TEREPHTHALATE AND POLYETHYLENE TEREPHTHALATE G:

Place 20 g of the test material into a suitable plastic container. 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 EE1*. Use *Solution EE1* within 4 h of preparation.

POLYVINYL CHLORIDE, AND POLYVINYL CHLORIDE, PLASTICIZED:

Place 5 g into a suitable plastic container. 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 EE1*.

Alkali extraction, Solution EE2

POLYETHYLENE TEREPHTHALATE AND POLYETHYLENE TEREPHTHALATE G:

Place 20 g of test material into a suitable plastic container 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 EE2*. Use *Solution EE2* within 4 h of preparation.

Procedure for extract analysis and reporting threshold:

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 *Plasma Spectrochemistry* ⟨730⟩ as directed.) The reporting threshold is for values above 0.01 mg/L (ppm), corresponding to 0.025 µg/g.

6.2.4 PLASTIC ADDITIVES ▲(USP 1-Aug-2020)

~~The plastic additives testing described in ⟨661.1⟩ are required for all materials of construction used in packaging systems, regardless of whether the material is specified in ⟨661.1⟩. Procedures for materials that are not specified in ⟨661.1⟩must be established and should be consistent with the procedures and specifications used for materials that are specified in ⟨661.1⟩.~~ ▲▲ (USP 1-Aug-2020)

The sole purpose of the tests for plastic additives is to establish which additives are present and to ensure that the levels of these additives are known. This information is relevant because additives are typically a source of extractables and leachables.

~~Additionally, it is possible that materials specified in the chapter may contain additives that are not addressed in ⟨661.1⟩. These materials must be tested for such additives. Procedures for additives that are not specified in~~

~~⟨661.1⟩ must be established and should be consistent with the procedures used for materials that are specified in ⟨661.1⟩. Specifications must be established for additives that are not specified in ⟨661.1⟩; such specifications should be consistent with the specifications established for materials that are specified in ⟨661.1⟩.~~ ▲▲ (USP 1-Aug-2020)

In ⟨661.1⟩, the chapter requires that materials be tested for all relevant analytes. Clearly, an analyte will be present in a material if it is intentionally or knowingly added to the material during its production or if testing of the material has revealed the presence of the analyte. Although test methods included in ⟨661.1⟩ may be of sufficiently broad scope to detect all relevant additives, this is not always the case and one cannot rely on these methods to reveal all relevant analytes. It may be the case that the material's vendor has knowledge that may be unavailable to the material's user, which is germane to establishing relevant analytes. It is reasonable to expect that material vendors and users work together to produce a complete and robust list of relevant analytes. ~~It is particularly important that a material's vendor inform the material's user when it is clear to the vendor that the user has missed a relevant analyte in the user's testing.~~ ▲▲ (USP 1-Aug-2020)

It is reasonable to anticipate that there may be some information that the vendor is not in a position to share with a material’s user. Nevertheless, it is in the interest of both the vendor and the user that a material be well characterized and that the characterization include all relevant analytes. Thus, it is strongly recommended that the vendor and the user find a means of establishing all relevant analytes.

6.2.5 UNADDRESSED MATERIALS (USP 1-Aug-2020)

For the materials that are not currently listed in ⟨661.1⟩ (unaddressed plastics), (USP 1-Aug-2020) it is the responsibility of the user to: 1) develop ~~those~~ (USP 1-Aug-2020) tests methods (physiochemical, biological reactivity, and plastic additives) and ~~specifications that are required per the points noted previously;~~ acceptance criteria; (USP 1-Aug-2020) 2) justify those test methods and ~~specifications~~ acceptance criteria, (USP 1-Aug-2020) specifically considering their consistency with test methods and ~~specifications~~ acceptance criteria, (USP 1-Aug-2020) that exist for materials that are ~~currently~~ (USP 1-Aug-2020) listed in ⟨661.1⟩; and 3) possess the test results obtained when the material is tested.~~in accordance with the tests outlined in the points noted previously.~~

~~The recommendation for specific tests, test methods, and test parameters in ⟨661.1⟩ does not preclude the use of other suitable methods, procedures, or parameters, but rather the conditions presented in ⟨661.1⟩ take precedence. Alternative test methods and conditions must be demonstrated to be suitable by means of appropriate and sufficient validation data. Important aspects of alternative methods include the completeness of the extraction process and the specificity, sensitivity, and applicability of the analytical test methods. Extraction methods employed must have a demonstrated ability to quantitatively transfer additives from the material to the extracting medium and must do so without modifying the chemical nature of the additive unless such modification is an integral part of the test methodology. Test methods employed must have equivalent ability compared with the test methods contained in ⟨661.1⟩ to produce a clear and unambiguous identification of all relevant additives at levels at least as low as the levels specified in ⟨661.1⟩.~~

~~Point 14 notwithstanding, the substitution of alternate tests for those that are required by ⟨661.1⟩ is not appropriate. For example, substitution of an oxidizable substance test for *Physicochemical Tests*, *Total Organic Carbon* under in ⟨661.1⟩ is not appropriate and substitutions for specifications that exist in ⟨661.1⟩ are not allowed unless justified and are subject to approval by an appropriate regulatory authority.~~

▲6.2.6 CONCEPT OF NON-INTERACTION OF MATERIALS▲ (USP 1-Aug-2020)

Testing of materials of construction via ⟨661.1⟩ is predicated on the circumstance that the material will most likely interact with the packaged drug product when the material is used in a packaging system. It is not necessary for a material used in a packaging system to be well-characterized if there is little or no chance of the material and the packaged drug product interacting. Under these conditions the materials of construction would be considered non-interacting and would be exempt from ⟨661.1⟩ testing.~~The designation of a material of construction as "non-interacting" must be accepted by the appropriate regulatory authority.~~▲▲ (USP 1-Aug-2020)

It is relevant to differentiate between "no direct contact" and "non-interacting", where the term "no direct contact" means that the material and the packaged drug product do not come into direct physical contact under the clinical conditions of use.

In certain applications a "no direct contact" material of construction is also a "non-interacting" material of construction, ~~it may also be the case that "no direct contact"~~▲this▲ (USP 1-Aug-2020) does not ~~insure "non-interacting"~~▲ensure no interaction,▲ (USP 1-Aug-2020) especially when the conditions of contact include

long durations and/or substantially elevated temperatures. To explain the concepts of "no direct contact" and "non-interacting", consider the following example. An aqueous drug product is packaged in a flexible plastic container~~. The flexible container~~ which (USP 1-Aug-2020) is ~~further~~ (USP 1-Aug-2020) placed in a foil overpouch ~~The overpouched product~~ and the combination (USP 1-Aug-2020) is terminally sterilized. An adhesive label is then (USP 1-Aug-2020) applied to the outside of the foil overpouch. ~~after the product unit has been cooled after terminal sterilization~~ (USP 1-Aug-2020)

Here, both the foil overpouch and the label are examples of (USP 1-Aug-2020) "no direct contact", because there is at least one physical barrier (the primary container) between the packaged drug product and these two items. However, if the flexible plastic primary container is permeable, the foil overpouch can be considered a "potentially interacting" component, as substances from the overpouch could migrate through the primary packaging, especially under the high-temperature conditions of terminal sterilization. The label is a "non-interacting" component because 1) the foil overpouch is impermeable and 2) the label is applied after the thermal stress associated with terminal sterilization.

The difference between a "potentially interacting" and "non-interacting" "no direct contact" component is the permeability of the barrier that separates the "no direct contact" components from the drug product. If the barrier is incomplete, then the component (and its materials of construction) is "potentially interacting" and the materials should be tested per ⟨661.1⟩. If the barrier is complete, then the component (and its materials of construction) is "non-interacting" and the materials need not be tested per ⟨661.1⟩.

6.2.6 RELEVANT ANALYTES

In at least two places (*Extractable Metals* and *Plastic Additives*), in ⟨661.1⟩, the chapter requires that materials be tested for all relevant analytes. Clearly, an analyte will be present in a material if it is intentionally or knowingly added to the material during its production or if testing of the material has revealed the presence of the analyte. Although test methods included in ⟨661.1⟩ may be of sufficiently broad scope to detect all relevant metals or additives, this is not always the case and one cannot rely on these methods to reveal all relevant analytes. It may be the case that the material's vendor has knowledge that may be unavailable to the material's user, which is germane to establishing relevant analytes. It is reasonable to expect that material vendors and users work together to produce a complete and robust list of relevant analytes. It is particularly important that a material's vendor inform the material's user when the user has missed a relevant analyte in the user's testing.

It is reasonable to anticipate that there may be some information that the vendor is not in a position to share with a material’s user. Nevertheless, it is in the interest of both the vendor and the user that a material be well characterized and that the characterization include all relevant analytes. Thus, it is strongly recommended that the vendor and the user find a means of establishing all relevant analytes. For example, consider the case of extractable metals. While it may be the case that the material's vendor would decline to share detailed information about the use of a zinc-containing reagent in the preparation of a material, it is adequate for the purpose of material characterization for the vendor to communicate that zinc should be a targeted analyte. ▲▲ (USP 1-Aug-2020)

▲6.3▲ (USP 1-Aug-2020) Description of ~~Polymers~~▲Plastics▲ (USP 1-Aug-2020) Contained in ⟨661.1⟩

▲6.3.1▲ (USP 1-Aug-2020) CYCLIC OLEFINS

Cyclic olefin copolymers are manufactured by the copolymerization of cyclic ~~olefin (e.g., cyclopentene, norbornene) with an olefin such as ethylene or propylene. The reaction of polymerizing a cycloolefin resulting in a polymer is known as ring opening polymerization (ROMP) and is facilitated via Ziegler-Natta catalysts. Cyclic olefin polymer resins~~▲monomers, such as tetracyclododecene or norbornene, with an olefin such as ethylene or propylene; or by ring-opening metathesis polymerization (ROMP) of cyclic monomers, followed by hydrogenation facilitated by Ziegler-Natta catalysts to produce cyclic olefin polymers. Cyclic olefins▲ (USP 1-Aug-2020) are commonly supplied in pellet form and are suited for standard polymer processing techniques such as extrusion, injection molding, injection blow molding, compression molding, thermoforming, and others. As they are amorphous, and given their high purity, moisture barrier, clarity, and sterilization compatibility, cyclic olefins are an excellent alternative to glass in a wide range of medical products, including packaging. Cyclic olefins exhibit good chemical resistance and are generally considered to be of high purity with low levels of extractables. Nevertheless, cyclic ~~olefin copolymers~~▲olefins,▲ (USP 1-Aug-2020) may contain residual processing aids, colorants, and antioxidants.

▲6.3.2 POLYAMIDE 6

Polyamide 6 is synthesized by ring-opening polymerization of caprolactam. Hydrolytic or catalytic ring-opening polymerization of caprolactam produces epsilon-aminocaproic acid, which readily condenses to polyamide

6 at high temperatures and under a vacuum. The high strength, flexibility, and chemical resistance of crystalline polyamide 6 make it well suited for pharmaceutical applications ranging from soft and flexible tubing to catheters and containers to stiff components for surgical and dental instruments. Entities present in commercial polyamide 6 include residual monomers, residual reaction intermediates, residual catalysts (copper and chromium oxides) and activators (acetyl lactams, oxazolines, ethylenebisamides, and isocyanates) and certain additives including stabilizers (mixtures of metal and alkali metal halides), processing aids (nucleating agents and lubricants), and modifiers (chain extenders, plasticizers, and impact modifiers).

6.3.3 POLYCARBONATES

Polycarbonates are a group of thermoplastic polymers containing carbonate groups in their chemical structures. In interfacial polymerization, the polycarbonate material is produced by the reaction of bisphenol A (BPA) and phosgene. This process is being replaced by an alternative, termed "melt polymerization", which entails transesterification from BPA and diphenyl carbonate, thus avoiding the use of phosgene. Entities present in commercial polycarbonates include residual monomers, solvents or catalysts (triethylamine or lithium halides, and hydroxides or aluminum hydrides), processing aids (e.g., mold release agents), UV stabilizers, impact modifiers, flame retardants, colorants, and sterilization stabilizers (free radical scavengers including propylene glycol, aromatic bromate, or disulfide compounds).

High- and low-density polyethylenes are long-chain ethylene-based polymers synthesized under controlled conditions of heat and pressure with the aid of catalysts from NLT 85.0% ethylene and NLT 95.0% total olefins. Other olefin ingredients that are most frequently used are butene, hexene, and propylene. Low-density polyethylene (LDPE) contains many long-chain branches along the polymer backbone, preventing the alignment and packing of the chains, thus forming a low-density material. Linear low-density polyethylene (LLDPE) contains several short chains along the polymer backbone that prevent the alignment and packing of the polymer chains, thus creating a poor crystalline material. High-density polyethylene (HDPE) contains relatively few side chains, allowing the polymer backbone to align and pack together, thus forming a crystalline, high-density plastic. High-, low-, and linear low-density polyethylene all 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/cm^3. Low-density polyethylene has a density between 0.850 and 0.940 g/cm^3. Additives are added to the polymer in order to optimize its chemical, physical, and mechanical properties, thereby rendering it suitable for its intended use. These additives may include nucleating agents, clarifying agents, antioxidants, colorants, lubricants, antiblocking agents, and others. These additives typically are present individually in the polyethylene at levels of 0.01–0.3 weight %, and the total levels of the antioxidants typically are < 0.3%. Other additives, specifically amides and stearates, typically are present in polyethylenes individually at levels of NMT 0.5 weight %. ~~or less~~▲▲ (USP 1-Aug-

▲(USP 1-Aug-2020) Polyethylene materials that provide light protection can contain as much as 4% by weight titanium oxide.

▲6.3.5▲ (USP 1-Aug-2020) POLYETHYLENE TEREPHTHALATE AND POLYETHYLENE TEREPHTHALATE G

Polyethylene terephthalate (PET) polymers are long-chain crystalline ▲[e.g., polyethylene terephthalate glycol-modified (PETG)]▲ (USP 1-Aug-2020) 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 (NMT 3 mole %) or 1,4-cyclohexanedimethanol (NMT 5 mole %). Polymerization is conducted with the aid of catalysts and stabilizers. PET polymers may contain silica or silicates (NMT 0.5% by weight) and may contain colorants.

▲6.3.6 POLY(ETHYLENE-VINYL ACETATE)

Poly(ethylene-vinyl acetate) polymers are typically obtained by copolymerization of mixtures of ethylene and vinyl acetate. Poly(ethylene-vinyl acetate) used in containers has a defined quantity of vinyl acetate of NMT 25%. Poly(ethylene-vinyl acetate) used in tubing has a defined quantity of vinyl acetate of NMT 30%. A certain number of additives are present in the polymer to optimize its chemical, physical, and mechanical properties, thereby rendering it suitable for its intended use. These additives may include antioxidants, amides, stearic acid salts, a source of base (calcium carbonate or potassium hydroxide), and inorganic fillers. Poly(ethylene-vinyl acetate) can contain NMT 3 antioxidants with individual levels of NMT 0.2 weight %. This material may also contain: 1) oleamide and/or erucamide at individual levels of 0.5 weight %; 2) calcium stearate,

zinc stearate, or both at levels NMT 0.5 weight %; 3) sources of base at levels NMT 0.5 weight %; and 4) colloidal silica at 0.2 weight %.

6.3.7 ▲(USP 1-AUG-2020) POLYPROPYLENE

Propylene polymers are long-chain polymers synthesized from propylene or other olefins, for example, ethylene or butene, under controlled conditions of heat and pressure with the aid of catalysts. A certain number of additives are added to the polymer in order to optimize its chemical, physical, and mechanical properties, thereby rendering it suitable for its intended use. These additives may include nucleating agents, clarifying agents, antioxidants, colorants, lubricants, antiblocking agents, and others. These additives typically are present individually in the polypropylene at levels of 0.01–0.3 weight %, and the total levels of the antioxidants typically are less than 0.3%. Polypropylene that provides light protection can contain as much as 4% by weight titanium dioxide.

▲6.3.8 POLYVINYL CHLORIDE

Polyvinyl chloride (PVC) is produced by polymerization of the vinyl chloride monomer in a process that uses initiators that break down to start the radical chain reaction. The polymerization reactions used to produce PVC are designed to produce levels of residual vinyl chloride monomer of <1 ppm on a weight basis. Polvvinyl chloride may contain NMT 15% by weight of: 1) copolymers based on acrylic and/or methacrylic acids and/or their esters, 2) styrene, and/or 3) butadiene. To obtain the required mechanical and stability characteristics, materials based on PVC may contain: 1) epoxidized oils at levels up to 8 weight %; 2) calcium and/or zinc salts of long chain fatty acids at levels NMT 1.5 weight %; 3) liquid paraffin,

waxes, and/or hydrogenated oils at individual levels NMT 2 weight %; 4) nonylphenyl phosphite-type compounds at levels NMT 1 weight %; 5) sorbitol and macrogel esters, NMT 1.5 weight % each; 6) stabilizers at levels of either 0.25 weight % (for tin-based stabilizers) or 1 weight % (for other stabilizers); and 7) colorants, pigments, or opacifiers. The additives used and their allowed levels are dictated by the application of the polyvinyl chloride.

6.3.9 ▲(USP 1-Aug-2020) POLYVINYL CHLORIDE, PLASTICIZED

PVC polymers are long-chain vinyl chloride polymers synthesized from vinyl chloride monomers via free radical polymerization. Various additives are compounded into PVC to provide the materials with properties that render it suitable for its intended use. These additives may include heat stabilizers, primary and secondary plasticizers, stabilizers, impact modifiers, lubricants, pigments, and others. These additives typically are present individually in the PVC at levels ranging from 0.1 to 45 weight %. ▲The additives used and their allowed levels are dictated by the application of the plasticized PVC.▲ (USP 1-Aug-2020)

Change to read:

▲7.▲ (USP 1-AUG-2020) APPLICABILITY AND APPLICATION OF ⟨661.2⟩

▲7.1▲ (USP 1-Aug-2020) Applicability

1. The holder of the drug product application and drug product manufacturer [in the case of many OTCs, where there is no application] bear primary responsibility and accountability for ensuring the requirements of the chapter are met. The means by

which the holder of the drug product application and drug product manufacturer obtain information to meet the requirement are at the discretion of the holder.

2. ▲The scope of ⟨661.2⟩ is packaging systems for finished drug products. If component testing is considered to be necessary, the relevant testing and acceptance criteria for components are contained within ⟨661.2⟩.▲ (USP 1-Aug-2020)

3. ~~Chapter ⟨661.2⟩ deals solely with packaging systems. Components of packaging systems can be tested per ⟨661.2⟩ at the discretion of the holder of the drug product application and as approved by regulatory authority. Materials of construction are not tested per ⟨661.2⟩~~▲Application of ⟨661.2⟩ to systems other than packaging systems for finished drug products is beyond the scope of these chapters at the present time, but the concepts and principles of these chapters may be applicable and relevant to other systems.

7.2▲ (USP 1-Aug-2020) Application

1. ~~Chemical characterization of either extracts of packaging systems (extractables) or packaged drug product (leachables), followed by toxicological safety evaluation, is universally recognized as a necessary and appropriate means of establishing the safety impactinteraction between packaging systems and their contents.~~▲▲ (USP 1-Aug-2020) Chapter ⟨661.2⟩ requires that all packaging systems be demonstrated to be ~~safe~~▲suitable▲ (USP 1-Aug-2020) by performing a chemical ▲suitability for use▲ (USP 1-Aug-2020) assessment but does not specify the details of the chemical ▲suitability for use▲ (USP 1-Aug-2020) assessment process ~~, either in terms of the test methods or the specifications~~▲acceptance criteria.▲ (USP 1-Aug-2020) Rather, ▲for the chemical suitability for use assessment, ⟨661.2⟩ discusses the use of a risk-based approach in determining the level of testing that is deemed necessary for a packaging system. It is currently a regulatory expectation that extractables and leachables

testing be performed for high risk dosage forms. Thus, ⟨661.2⟩▲ (USP 1-Aug-2020) references chapters ⟨1663⟩ for extractables and ⟨1664⟩ for leachables, thereby providing users ~~of ⟨661.2⟩~~▲▲ (USP 1-Aug-2020) with a means for designing and implementing an effective, efficient, risk-based, and more or less customized extractables or leachables assessments that comply with regulatory requirements.

2. Chapter ⟨661.2⟩ provides holders of packaging system or drug product applications and/or packaged drug products manufacturers with the flexibility to operate within the context of their own specific situation and their own specific risk-management philosophy. The trade-off for having such flexibility is that it is the responsibility of the holders and manufacturers to justify their test methods and ~~specifications~~▲acceptance criteria.▲ (USP 1-Aug-2020) It is proper and appropriate that the justification exists and that it be judged (and approved) on the basis of its individual scientific and risk-management merits.

3. ~~Leachables whose chemical formula includes transition metals, metalloids, other metals, and lanthanides and actinides are elemental impurities. To the extent that extractables mirror leachables, extractables can be construed to be potential elemental impurities. *Elemental Impurities—Limits* ⟨232⟩ contains specifications for elemental impurities in drug products. In some manner, these specifications are relevant to packaging systems, as leachables of the appropriate composition represent a certain proportion of a drug product's elemental impurity burden. However, if the proportion is not known, then ⟨232⟩ specifications for drug products cannot be directly translated to specifications for leachables which themselves are elemental impurities. Thus, ⟨661.2⟩ requires that leachables that are elemental impurities be appropriately assessed toxicologically for their potential safety impact and correctly notes the existence of ⟨232⟩. However, ⟨661.2⟩ does not specifically attempt to use the product specifications in ⟨232⟩ to set leachables specifications as the means to establish safety impact.~~

4. ~~Alternatively, the outcome of testing plastic packaging systems via ⟨661.2⟩ is an assessment of the probable suitability for use of that system on the packaged drug product. This assessment is based on~~

the biological reactivity testing, the physiochemical testing, and the extractable/leachables testing that are required by ⟨661.2⟩. A packaging system that has been tested per ⟨661.2⟩ and meets the acceptance criteriaspecifications contained within ⟨661.2⟩, including a toxicological assessment of the extractables and/or leachables data, is qualified for use consistent with the conditions under which it was tested, subject to review by the appropriate regulatory authority.

5. An essential principle reflected in ⟨661.2⟩ is that packaging systems be tested for extractables and that the approach be consistent with the nature of the interaction between the drug product and its packaging. This includes consideration of the drug product contact condition (e.g., liquid versus dry) and the potential interaction between the dosage form and its packaging system. By referencing ⟨1663⟩ for extractables testing, ⟨661.2⟩ provides the means by which extractables studies relevant for specific dosage forms can be designed, implemented, and interpreted. By allowing for study designs that reflect the nature and clinical use of various dosage forms, ⟨661.2⟩ supports and uses risk-based strategies and assessments.▲▲ (USP 1-Aug-2020)