BRIEFING

⟨1661⟩ **Evaluation of Plastic Packaging Systems and Their Materials of Construction with Respect to Their User Safety Impact,** *USP 39* page 1827 and *PF* 40(6) [Nov.–Dec. 2014]. This chapter is being divided into two sections.

1. The first section, *Plastic Packaging Systems and Their Materials of Construction*, focuses on plastic materials of construction and packaging systems. The section describes all of the plastic materials that are included in *Plastic Materials of Construction* ⟨661.1⟩, the process of materials assessment, along with the applicability and application of ⟨661.1⟩. The chapter also goes on to discuss the importance of packaging system assessment and qualification and how *Plastic Packaging Systems for Pharmaceutical Use* ⟨661.2⟩ facilitates this assessment. With this revision, four new polymer descriptions are being added to the chapter [*Polyamide 6*; *Polycarbonates*; *Poly(ethylene-vinyl acetate)*; and *Polyvinyl chloride, non-plasticized*], which corresponds to the addition of these materials to ⟨661.1⟩ in PF 42 (4).

2. The second section, *Plastic Components and Systems Used to Manufacture Pharmaceutical Drug Products*, is meant to support the use and understanding of the new chapter *Plastic Components and Systems Used in Pharmaceutical Manufacturing ⟨661.3⟩*, appearing in the current *PF*.

Additionally, minor editorial changes have been made to update the chapter to *USP* style. (GCPD: D. Hunt.)

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Comment deadline: July 31, 2016

Change to read:

⟨1661⟩ EVALUATION OF PLASTIC PACKAGING ■AND MANUFACTURING■ 1S (*USP40*) **SYSTEMS AND THEIR MATERIALS OF CONSTRUCTION WITH RESPECT TO THEIR USER SAFETY IMPACT**

Add the following:

2.3 General Principles
2.4 Safety Qualification

■1S (*USP40*)

Change to read:

1. PLASTIC PACKAGING SYSTEMS AND THEIR MATERIALS OF CONSTRUCTION

■

1.1 Introduction■1S (*USP40*)

Drug products (DPs) can chemically interact with their associated packaging systems and/or the system's plastic materials and components of construction while the product is being manufactured, shipped, stored, and administered. The magnitude of these interactions must not be such that the interactions adversely affect the suitability for use of the DP or the packaging system. Although suitability for use includes several quality aspects of the packaged DP and its performance, the suitability for use aspect addressed in this chapter is patient safety.

The potential patient safety impact of interactions between a DP and its packaging is assessed and established via the appropriate testing of the packaging systems and their materials and components of construction. *Plastic Packaging Systems and Their Materials of Construction* ⟨661⟩ establishes the tests and specifications that are necessary and appropriate for ensuring that such systems are suitable and safe for use.

1.2 Scope

The purpose of this chapter is to communicate the key concepts behind ⟨661⟩ and its related subchapters,
■*Plastic Materials of Construction* ⟨661.1⟩■1S (*USP40*)
and
■*Plastic Packaging Systems for Pharmaceutical Use* ⟨661.2⟩,■1S (*USP40*)
and to provide additional information and guidance regarding the application and applicability of this set of 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 these chapters.

1.3 General Principles

THE OVERALL ASSESSMENT PROCESS

The objective of *USP* packaging systems standards is to establish tests and specifications that ensure packaging systems do not materially impact the safety or effectiveness of pharmaceutical products. Given the complex nature of packaging systems and their

manufacturing and development processes, multiple testing procedures are needed to establish their suitability for use with a specific pharmaceutical product. The logical development and manufacturing process progression for packaged DPs, starting with the packaging system's materials of construction, continuing with the packaging system itself, and ending with the packaged DP, forms the basis of a three-stage approach to packaging systems qualification, as illustrated in *Figure 1*.

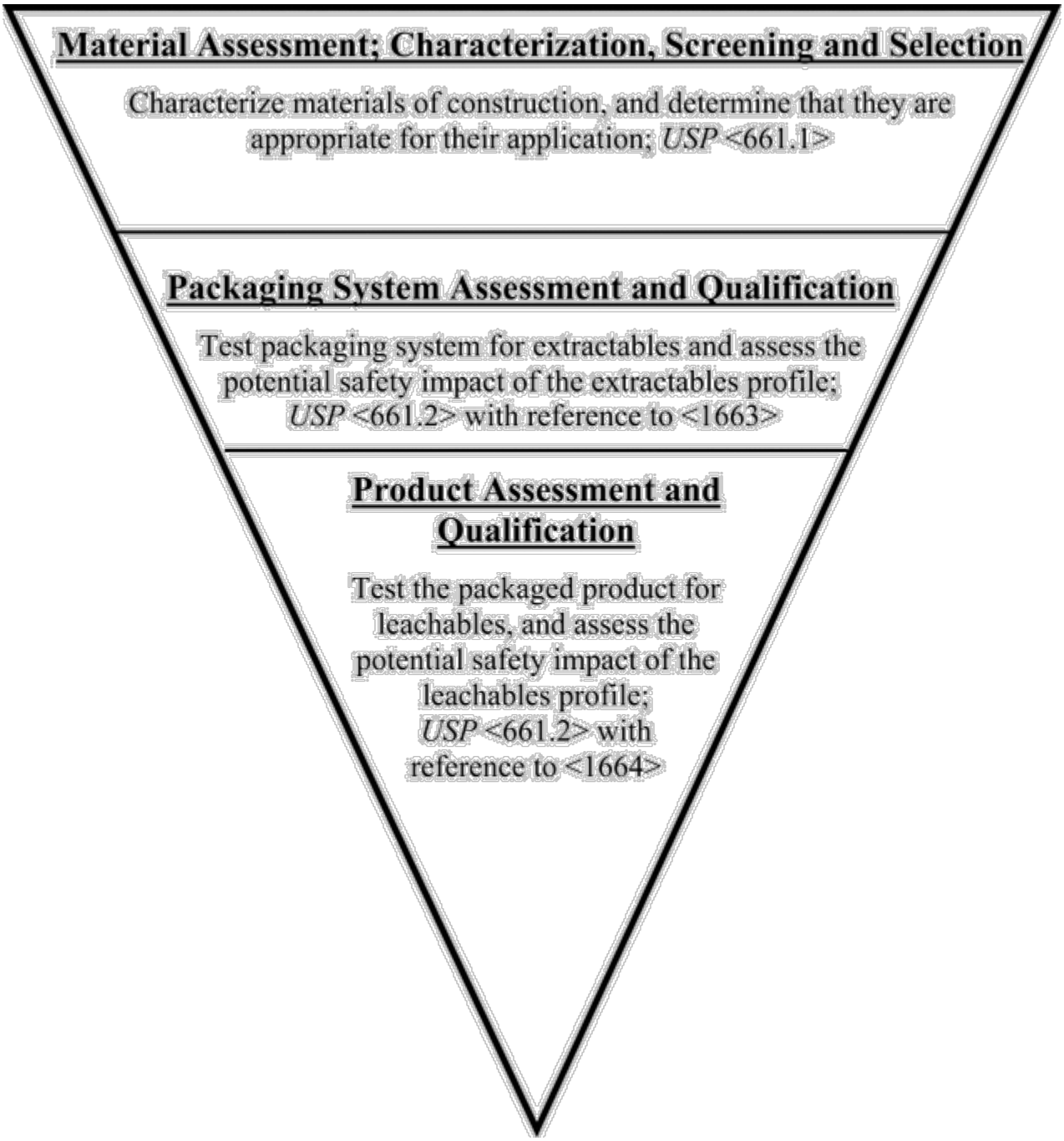

Figure 1. The three-stage process for the characterization and safety qualification of packaging systems and their materials of construction.

The process for establishing a packaging system's suitability for use includes: characterization of its materials of construction (ingredients); testing and assessment of the system itself (extractables); and testing and assessment of the packaged pharmaceutical product (leachables). The initial step of this process involves chemically characterizing candidate materials of construction to the extent that the choice of materials to use 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 the starting materials and testing the finished product, while providing a means for optimizing pharmaceutical product testing. The intermediate test is necessary because materials of construction undergo considerable stress, such as exposure to high temperatures, while being converted into either components of the packaging system or the packaging system itself. Furthermore, processing aids and additional additives may be introduced during the manufacturing process for a packaging system. Thus, the extractables profile of a system is likely to be different from, and potentially more complex than, the sum of the extractables profiles of its materials of construction. Therefore, the initial assessment of risk during material selection is appropriately revisited by testing and qualification of the overall packaging system itself.

Ultimately, the effect that packaging may have on the DP user is mediated by packaging-derived substances that are present in the DP. The third stage of the process is product assessment, specifically leachables testing of the packaged product and impact assessment, which considers the user's exposure to the leachables.

MATERIALS ASSESSMENT: CHARACTERIZATION, SCREENING, AND SELECTION, ⟨661.1⟩

To ensure that a packaging system is suited for its intended use, it is important to select materials of construction that are suitable. Testing and characterizing such materials of construction 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, the selection of safe materials increases the likelihood that packaging systems made from those materials will be safe. Therefore, the characterization of materials of construction is the first step in the process of developing and qualifying safe 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, whether potential material candidates could adversely affect the quality and safety of pharmaceutical products. The basic tenet of materials assessment, as reflected in ⟨661.1⟩, is that knowing the general composition and certain general characteristics of a material of construction allows one to:

- Rationally assess the potential safety impact of the 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 the 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) of a particular material in a particular packaging system

To this end, ⟨661.1⟩ defines a well-characterized material of construction as one whose:

- Identity has been definitively established
- Biocompatibility (biological reactivity) has been established
- General physicochemical properties have been established
- Additives and extractable metals have been quantified

Chapter ⟨661.1⟩ testing is not a guarantee that plastic systems constructed from materials meeting these specifications will be suitable for their intended use because it is not always the case that testing a system's materials of construction directly and completely correlates with subsequent testing of the plastic system. Characterization of a material using ⟨661.1⟩ merely establishes the composition or characteristics of the material and 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 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.

PACKAGING SYSTEM ASSESSMENT AND QUALIFICATION, ⟨661.2⟩

The impact of packaging systems on the chemical composition of packaged DP can be established in two ways~~. The~~
■: 1) the■ 1S (*USP40*)
packaging system itself can be characterized with respect to substances that can be extracted from it (extractables)~~. Secondly,~~
■; and 2)■ 1S (*USP40*)
the packaged DP can be tested for packaging-derived substances that have leached into it (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 of the relevant leachables can be discovered, identified, and quantified in the packaged product. In either case, ⟨661.2⟩ establishes the tests and specifications 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. Chapter ⟨661.2⟩ refers to this process of establishing the safety of packaging systems as chemical assessment and notes that a packaging system is chemically 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 by means of the appropriate chemical testing and toxicological assessment.
- The packaging system is chemically compatible with the packaged product, as established by appropriate compatibility assessments (e.g., stability studies).

Considering the last 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. In addition to being the basis for toxicological safety assessments, information about a packaging system's extractables can be used in several ways to optimize finished product testing for leachables. The potential quality, safety, 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 product within its packaging system. The targeting of specific leachables, as opposed to the screening of pharmaceutical 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. Further, 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 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. Additionally, if such extractables are assessed for their safety or quality impact, the results of that assessment can also be extrapolated to, and deemed to be relevant for, the pharmaceutical 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 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, justification should be provided if a leachable study is deemed unnecessary.

1.4 Applicability and Application of ⟨661.1⟩

APPLICABILITY

1. The holder of the DP application and 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 chapter are met. The means by which the holder of the DP application and manufacturer obtain information to meet the requirement are at the discretion of the holder.
2. The testing required and specifications for materials of construction contained within ⟨661.1⟩ are relevant to and applicable for all drug 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. However, 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 that the concepts and principles of risk management have a definite strategic role in terms of designing, implementing, and interpreting effective and efficient assessments of extractables and/or leachables. 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. Thus, ~~as noted in its~~

   ■ ■ 1S (*USP40*)

   Table 1 and

   ■ *Table 2* ■ 1S (*USP40*)

   of ⟨661.1⟩ establish biological reactivity and chemical tests that differ somewhat 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 DP and its packaging. This includes consideration of the DP 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. However, 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. Thus, 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 DP. This assessment is based on the biological reactivity testing, the physicochemical testing, and the extractable/leachables testing that are required by ⟨661.2⟩. Thus, 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 that a material of construction has met the requirements of ⟨661.1⟩. The first is to perform the testing and meet the specifications; the second is the use of a material with a currently approved finished DP.
5. Application of ⟨661.1⟩ and ⟨661.2⟩ to materials of construction or systems other than packaging systems for finished DPs is beyond the scope of these chapters, but the concepts and principles of these chapters may be applicable and relevant to other systems (and their materials for construction) such as medical devices for DP administration and packaging/storage systems for drug substances. It is the expectation that future compendial chapters will be developed to address these other pharmaceutically important systems.
6. The scope of ⟨661.1⟩ is materials of construction and of ⟨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.

   Because 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 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⟩.

7. Testing of materials of construction via ⟨661.1⟩ is predicated on the circumstance that the material will most likely interact with the packaged DP 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 DP 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 DP 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 DP 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 DP and these two items. However, if the flexible plastic primary container is permeable, the foil overpouch can be considered a potentially interacting component, because substances from the overpouch could migrate through the primary packaging, especially under the high-temperature conditions of terminal sterilization. On the other hand, 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 DP. 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⟩.

APPLICATION

1. There are two means of demonstrating that a material of construction has met the requirements of ⟨661.1⟩. The first is to perform the testing and meet the specifications in ⟨661.1⟩; the second is the use of a material with a currently approved finished DP. 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.

■ *Table 1* provides guidance for situations where ⟨661.1⟩ and ⟨661.2⟩ testing would be applicable.

Table 1. Guidance on Testing Requirements for Specific Circumstances

Situation		Required Testing	
General Situation	**Specific Circumstances**	⟨661.1⟩	⟨661.2⟩
Packaging system used with a currently marketed pharmaceutical product	—	No	No
Changes to a packaging system used with a currently marketed pharmaceutical product	A new material is introduced into the packaging system	Yes (for the new material)	Yes
	A material of construction in the packaging system is changed in either composition or process	Yes (for the changed material)	Yes
	The packaging system is changed, in either composition or process, in a manner that does not involve a change in its materials or to its materials (for example, changing the thicknesses of individual layers in a multi-layered film)	No	Yes
Packaging system used with a currently marketed pharmaceutical product is to be applied to a different pharmaceutical product	Dosage form and conditions of use are similar for the current and different pharmaceutical products	No	No
	Dosage form and/or conditions of use are different from the current pharmaceutical products (moving from High Risk to Low Risk)	No	No
	Dosage form and/or conditions of use are different from the current	Yes	Yes

Situation		Required Testing	
General Situation	**Specific Circumstances**	⟨661.1⟩	⟨661.2⟩
	pharmaceutical products (moving from Low Risk to High Risk)		
New packaging system that has not gained regulatory approval for use with a to-be-marketed pharmaceutical product	—	Yes	Yes

[NOTE—The provisions in ⟨661.2⟩ for packaging systems must be met for components whose testing has been deemed to be necessary.]

■ 1S (*USP40*)

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. However, 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 DP. 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 and 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. 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. The specifications 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 exacting quantitative specifications. Establishing substantial equivalence requires that the test results and test material versus Reference Standard be deemed 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 deemed to be a specification. For example, although the infrared (IR) identification specifications may include wavenumber targets, these targets are not specifications 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.

4. Establishing the potential safety impact of a material of construction cannot rely on a single testing strategy, because no single testing strategy is sufficient to identify all potential safety-impacting attributes of a material. Thus, the chemical testing ~~proscribed~~ ■prescribed■ 1S (*USP40*) in ⟨661.1⟩ is orthogonal: physicochemical tests provide a general overview of extracted substances; extractable metals tests address potential sources of elemental impurities, whereas plastic additives tests address potential organic extractables. It is also the case that chemical testing alone may not demonstrate all potential safety-impacting attributes. Thus, chemical testing is augmented by the orthogonal approach of establishing biological reactivity.

5. 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 DP dosage forms regardless of whether the source of the elemental impurities is intentionally or unintentionally added to the DP, its ingredients, or its packaging system.

6. 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⟩.

7. 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, such as vendor certification. ~~All relevent metals, regardless of their inclusion in ⟨661.1⟩, must be tested for.~~ ■■ 1S (*USP40*) Procedures and specifications for relevant metals that are not specified in ⟨661.1⟩ must be established and should be consistent with the procedures and specifications 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⟩.~~ ■■ 1S (*USP40*)

8. Extractable metals testing and specifications 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⟩. Extractable metals test procedures and specifications 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⟩. ~~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⟩.~~

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9. 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⟩.~~

■ ■ 1S (*USP40*)

10. The plastic additives testing and specifications 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 and specifications 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⟩. ~~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⟩.~~

■ ■ 1S (*USP40*)

11. For the materials that are not currently listed in ⟨661.1⟩, it is the responsibility of the user to: (a) develop those tests methods and specifications that are required per the points noted previously; (b) justify those test methods and specifications, specifically considering their consistency with test methods and specifications that exist for materials that are currently listed in ⟨661.1⟩; and (c) possess the test results obtained when the material is tested, in accordance with the tests outlined in the points noted previously.
12. 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 and specifications for additives 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⟩. ~~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⟩.~~

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13. 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.
14. 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⟩.
15. The previous point (*14*) notwithstanding, the substitution of alternate tests for those that are required by ⟨661.1⟩ is not appropriate. Thus, for example, substitution of an oxidizable substance test for *Plastic Materials of Construction* ⟨661.1⟩*, Total Organic Carbon* under *Physiochemical Tests* is not appropriate. Additionally, substitutions for specifications that exist in ⟨661.1⟩ are not allowed unless justified and are subject to approval by an appropriate regulatory authority.
16. For at least two topics in ⟨661.1⟩(*Plastic Materials of Construction* ⟨661.1⟩*, Extractable Metals* and *Plastic Materials of Construction* ⟨661.1⟩*, Plastic Additives*), 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. Thus, 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~~
■ Although■ 1S (*USP40*)
the material's vendor ~~would~~
■ may■ 1S (*USP40*)
decline to share detailed information about the use of a zinc-containing reagent in the preparation of a material, for the purpose of material characterization, it is adequate for the vendor to communicate that zinc should be a targeted analyte.

DESCRIPTION OF POLYMERS CONTAINED IN ⟨661.1⟩

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■ 1S (*USP40*)
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. Because 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■ 1S (*USP40*)
may contain residual processing aids, colorants, and antioxidants.

■ **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 (actyl 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).

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).■ 1S (*USP40*)

Polyethylenes: 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 polypropylene (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 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. Polyethylene materials that provide light protection can contain as much as 4% by weight titanium oxide.

Polyethylene terephthalate and polyethylene terephthalate G: Polyethylene terephthalate (PET) polymers are long-chain crystalline polymers prepared by the condensation of ethylene glycol with dimethyl terephthalate or terephthalic acid. PET copolymer resins
■ (e.g., polyethylene terephthalate glycol-modified, PETG)■ 1S (*USP40*)
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.

■ **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: (a) oleamide and/or erucamide at individual levels of 0.5 weight %; (b) calcium stearate, zinc stearate, or both at levels NMT 0.5 weight %; (c) sources of base at levels NMT 0.5 weight %; and (d) colloidal silica at 0.2 weight %.■1S (*USP40*)

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 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 ≤0.3% polypropylene that provides light protection can contain as much as 4% by weight of titanium dioxide.

■**Polyvinyl chloride, non-plasticized:** Non-plasticized polyvinyl chloride materials are 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 non-plasticized polyvinyl chloride materials are designed to produce levels of residual vinyl chloride monomer of <1 ppm on a weight basis. Non-plasticized polyvinyl chloride materials typically consist of poly(vinyl chloride), poly(vinyl chloride/vinyl acetate), or a mixture of poly(vinyl chloride) and poly(vinyl acetate). Non-plasticized polyvinyl chloride materials may contain NMT 15% by weight of (a) copolymers based on acrylic and/or methacrylic acids and/or their esters, (b) styrene, and/or (c) butadiene. To obtain the required mechanical and stability characteristics, materials based on non-plasticized polyvinyl chloride may contain: (a) epoxidized oils at levels up to 8 weight %; (b) calcium and/or zinc salts of long chain fatty acids at levels NMT 1.5 weight %; (c) liquid paraffin, waxes, and/or hydrogenated oils at individual levels NMT 2 weight %; (d) nonylphenyl phosphite-type compounds at levels NMT 1 weight %; (e) sorbitol and macrogel esters, NMT 1.5 weight % each; (f) stabilizers at levels of either 0.25 weight % (for tin-based stabilizers) or 1 weight % (for other stabilizers); and (g) colorants, pigments, or opacifiers. The additives used and their allowed levels are dictated by the application of the non-plasticized polyvinyl chloride.■1S (*USP40*)

~~**Plasticized poly(vinyl chloride)**~~

■**Polyvinyl chloride, plasticized:**■1S (*USP40*)

Poly(vinyl chloride) (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 0.1–45 weight %.
■The additives used and their allowed levels are dictated by the application of the plasticized polyvinyl chloride.■ 1S (*USP40*)

1.5 Applicability and Application of ⟨661.2⟩

APPLICABILITY

1. The holder of the DP application and DP manufacturer [in the case of many OTCs, where there is no application] bear primary responsibility and accountability for ensuring that the requirements of the chapter are met. The means by which the holder of the DP application and manufacturer obtain information to meet the requirement is at the discretion of the holder.
2. 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 DP application and as approved by regulatory authority. Materials of construction are not tested per ⟨661.2⟩.

APPLICATION

1. Chemical characterization of either extracts of packaging systems (extractables) or packaged DPs (leachables), followed by toxicological safety evaluation, is universally recognized as a necessary and appropriate means of establishing the safety impact between packaging systems and their contents.
   Thus, ⟨661.2⟩ requires that all packaging systems be demonstrated as safe by performing a chemical assessment. However,⟨661.2⟩ does not specify the details of the chemical assessment process, either in terms of the test methods or the specifications. Rather,⟨661.2⟩ references the relevant informational chapters (⟨1663⟩ for extractables and ⟨1664⟩ for leachables), thereby providing users of ⟨661.2⟩with a means for designing and implementing 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 DP applications and/or packaged DP 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. 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 DPs. In some manner, these specifications are relevant to packaging systems, as leachables of the appropriate composition represent a

certain proportion of a DP's elemental impurity burden. However, if the proportion is not known, then ⟨232⟩ specifications for DPs 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 it 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.

Add the following:

■

2. PLASTIC COMPONENTS AND SYSTEMS USED TO MANUFACTURE PHARMACEUTICAL DRUG PRODUCTS

2.1 Introduction

A manufacturing process is the sum of those steps that are required to convert raw materials into a manufactured pharmaceutical product, which in this case is an active pharmaceutical ingredient (API) or DP. Manufacturing processes are performed by manufacturing suites that consist of the equipment necessary to complete the conversion. A manufacturing suite refers to the sum of all materials, components and parts, and systems that together are used in the process of converting raw materials into APIs and DPs. Generalized manufacturing suites for the production of a biotechnology API and a DP are illustrated in *Figure 2*.

Manufacturing suites may either be constructed with plastic materials, components, and systems or may be constructed fully from plastics. The plastics used in these manufacturing suites consist of polymers with a range of molecular weights and that contain additives such as antioxidants, stabilizers, lubricants, plasticizers, and colorants. Several factors dictate the types and amounts of additives that are used in plastic materials of construction including the type of polymer, the polymer's use, and the processes used to convert the polymer into components, parts, or systems.

Either the process stream, production intermediates, API, or the DP itself will directly contact one or more components of the manufacturing suite at some point in the manufacturing process and may interact with some or all of manufacturing components, potentially resulting in an interaction. Specifically, substances from a manufacturing suite component could leach from that component and become incorporated into the contacting entity. Such leachables have the potential to alter a quality attribute of the contacting entity, and if they persist through the manufacturing process, the manufactured pharmaceutical product. These interactions must be such that neither the production process nor the DP's suitability for use, especially with respect to safety, is adversely affected by the interaction. *Plastic Components and Systems Used in Pharmaceutical Manufacturing* ⟨661.3⟩addresses these interactions by providing a risk-based means for

chemically qualifying plastic components used to manufacture pharmaceutical and biopharmaceutical APIs and DPs. This chapter communicates the key concepts behind ⟨661.3⟩ and provides additional information and guidance regarding the applicability and the application of ⟨661.3⟩.

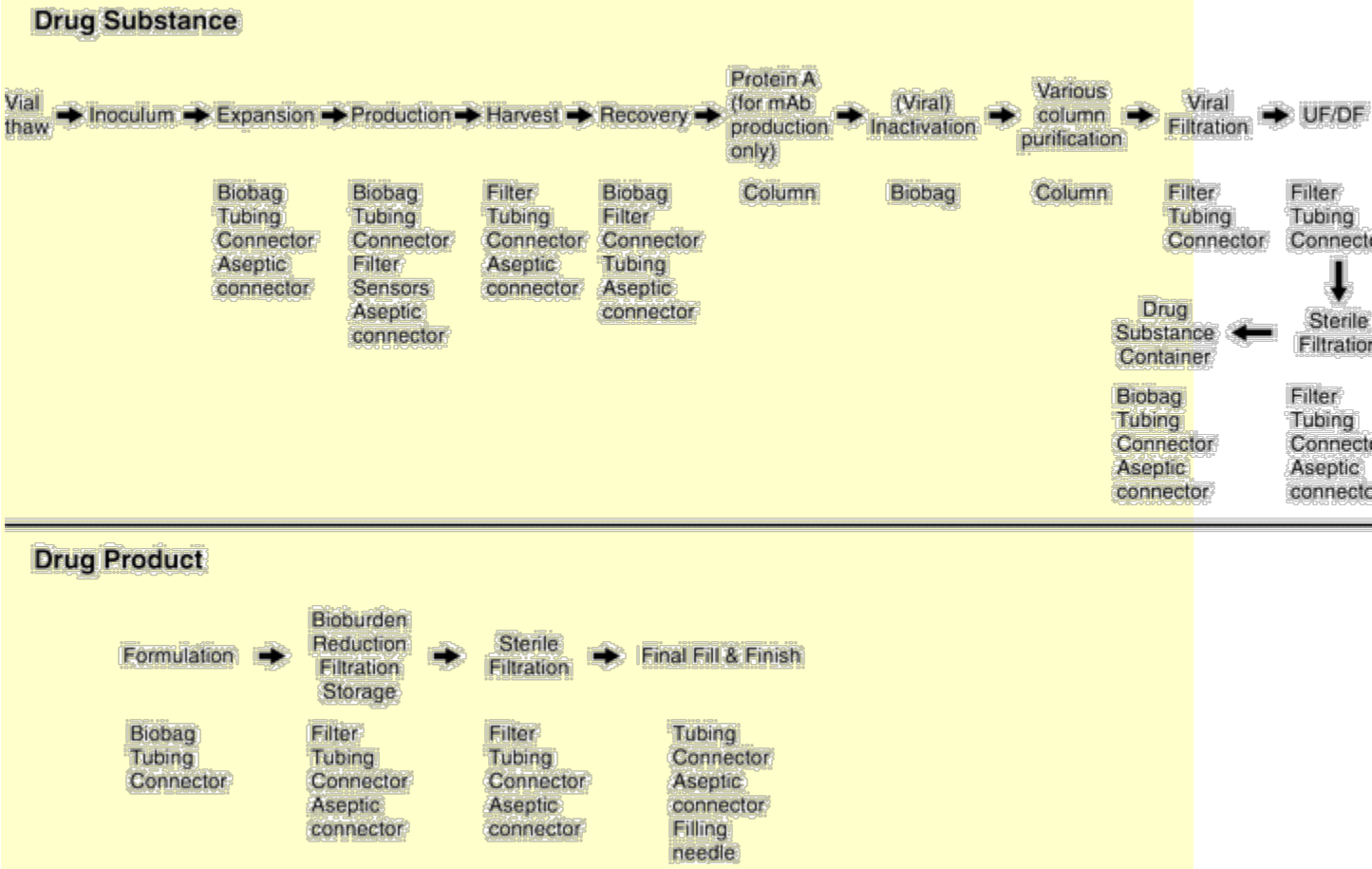

Figure 2. Flow diagram for a typical bioprocess to manufacture an API and DP.

2.2 Scope

In general, components used in pharmaceutical manufacturing suites can be divided into five groups based on the function or operation that the component performs, including:

- Solution transfer and transport (e.g., tubing and connectors),
- Mixing and reacting (e.g., tank liners, mixing bags and bioreactor bags, and stirrers),
- Storage (e.g., plastic containers for raw materials, production reagents, and process intermediates),
- Processing (e.g., filters and chromatography columns), and
- Miscellaneous (e.g., connectors, gaskets, sensors, and filling needles).

To accomplish these operations, plastic materials, components, and systems are commonly used in pharmaceutical manufacturing suites and must be suitable for their

intended use. The manufacturing system should be compatible with the API or DP and all process intermediates and process streams, be composed of materials that are safe for use with the API or DP, and should perform properly. The manufacturing suite should not release substances that accumulate in the pharmaceutical product as process-related impurities (PrIs) in quantities that could adversely affect user safety or product quality. It is this aspect of suitability for use that is the focus of this chapter.

This chapter is applicable to all manufactured APIs and DPs, including pharmaceuticals, biologics, and so-called “small molecule” products. Although manufacturing processes may involve circumstances where plastic components are contacted by either liquid, solid, or gaseous process streams and intermediates, it is generally the case that the propensity of the components and the process streams to interact is increased when the process stream is liquid. This chapter is applicable solely to those product processes that involve liquid process streams and liquid process intermediates.

Although this chapter does not address the absorption of ingredients, APIs or DPs onto plastic components or systems during manufacturing, this issue should be considered in the selection and qualification of manufacturing materials, components, and systems. This chapter specifically excludes elastomers used in manufacturing components and systems.

The applicant who secures and owns the regulatory approval of a manufacturing suite or the manufactured pharmaceutical product derived from that suite is responsible for establishing that the product’s manufacturing suite meets these expectations, and thus is suited for its intended use by ensuring that the manufacturing suite itself and/or the manufactured pharmaceutical product has been appropriately tested and that the test results have been appropriately evaluated.

2.3 General Principles

A manufacturing suite consists of manufacturing components and systems, many of which are either in part or totally composed of plastic materials. The most effective means of insuring that a manufacturing suite is suitable for its intended use is to use well-characterized and intentionally selected components that are constructed from well-characterized and intentionally selected materials. A manufacturing suite is assessed for its suitability for use via a three-step process:

1. Material characterization, supporting and justifying material selection,
2. Component characterization, supporting and justifying component selection, and
3. System qualification, establishing the system’s suitability for use.

The characterization of plastic materials produces information upon which material selections are based and justified. The characterization of plastic components produces information upon which component selections are based and justified. The purpose of the selection processes is to identify and eliminate unsuitable materials and components.

However, although selection processes increase the likelihood that a component or system will be suited for its intended use, it does not of itself necessarily establish suitability for use. Additional qualification testing of systems is performed to establish the system's potential to impact key product quality attributes and its ability to produce an acceptable API or DP. When appropriate, system qualification may be augmented by API or DPI testing to establish what effect the manufacturing system had on the API's or DP's key quality attributes.

Given the nature of manufacturing processes and suites, it is possible that certain components are isolated from the DP. Although such components are essential aspects of the production suite, they do not add PrIs to the API or DP. If the isolation of a process component can be established, then characterization of the component, and the component's materials of construction, is not required.

MATERIAL CHARACTERIZATION AND SELECTION

Typical materials of construction used in components of pharmaceutical manufacturing suites are listed in *Table 2*. If a material is well characterized (i.e., its compositional properties have been established), then the characterization information will guide and support the selection and use of the material regardless of the material's application or use. To this end, ⟨661.1⟩ defines a well-characterized plastic material of construction as one whose:

- Identity has been definitively established;
- Biocompatibility (biological reactivity) has been established;
- General physicochemical properties have been established; and
- Additives and extractable metals have been quantified.

Furthermore, ⟨661.1⟩ establishes those tests and specifications that are relevant to and appropriate for individual materials. Although initially applied to materials of construction for packaging systems, these tests and specifications are appropriate for, and relevant to, manufacturing systems and components. Given the wide variety of available manufacturing components and systems, it is possible that they are constructed from materials that are not specifically addressed in ⟨661.1⟩. In this case, these materials are termed "unaddressed materials", and they are compliant with ⟨661.1⟩ when they are identified by appropriate methodology and tested for biocompatibility, physicochemical properties, additives, and relevant extracted metals.

Although isolated materials may have little or no ability to contribute PrIs to the manufactured DP and their full characterization might not be required, it is appropriate that they be purposefully selected based on both their character and the degree of isolation afforded by the manufacturing process. When the degree of isolation is either incomplete or unsubstantiated, then material characterization becomes appropriate and necessary.

Table 2. Materials of Construction Used with Certain Manufacturing Suite Components

Component	Commonly Used Materials of Construction[a]
Biobags	Ethylene vinyl acetate,[b] low density polyethylene[b]
Filters	Polyamide,[b] polyetherimide, polyethersulfone, polyethylene terephthalate,[b] polypropylene,[b] polysulfone, polyvinylidenefluoride
Connectors/Disconnectors	Polycarbonate,[b] polypropylene,[b] polysulfone, polyvinylidenefluoride, silicone
Chromatography columns	Polymethylmethacrylate
Tubing	Silicone, thermoplastic elastomers
Sensors	Silicone, polycarbonate, polysulfone
Filling needles	Polyetheretherketone

[a] This list is not comprehensive, and additional plastics may be used in the indicated components.
[b] Materials currently present in ⟨661.1⟩.

COMPONENT CHARACTERIZATION AND SELECTION

Conversion of a single or several material(s) of construction to a component may expose the materials to high stress conditions, the addition of processing aids, bonding solvents and other chemical agents, and “finishing” processes such as sterilization via radiation. Thus, component selection may require that the components themselves be characterized to an extent that may be beyond the baseline established by material characterization. However, not all situations will require supplementary characterization studies to be performed and there may be circumstances where a component’s selection could be based on the comprehensive characterization of its individual materials of construction. For example, the component may be compositionally simple, the component may be produced by a relatively mild process, or the conditions of contact between the component and the API or DP (or process stream) in the manufacturing process may be mild. In such circumstances, rigorous and extensive characterization of the component may not be required, subject to agreement by an appropriate regulatory authority.

Components shall be characterized to an extent that is consistent with the risk that the component could leach extractables into a process stream, and that these extractables would persist through the manufacturing process and become PrIs in the process output, adversely affecting the safety of the process output. Matching the risk with the required level of characterization is achieved by a two-staged approach comprising of an initial assessment followed by a risk assessment.

INITIAL ASSESSMENT

The initial assessment procedure addresses two issues:

1. Is the component contacted by a liquid process stream or intermediate under the component's conditions of use?
2. Can a comparator for a component or system be established?

If a component is contacted by an auxiliary stream, it is isolated from the product generated by the manufacturing process, and thus can be established to be a viable candidate with no further characterization. If the component does not contact a liquid process stream or intermediate, then an interaction between the component and the process stream is unlikely. In this case, no characterization is required, and the component is considered to be a viable candidate with no further assessment. If the component or system is contacted by a liquid process stream or intermediate, then the following two further issues are addressed:

1. Does a potential comparator component or system exist?
2. If so, can equivalence between the comparator and the component or system under consideration be established?

The concept of a comparator component is as follows. Once a manufactured pharmaceutical product has secured regulatory approval, then by direct association, the process used to manufacture that product has been approved. Once a manufacturing suite has been established to be acceptable to manufacture an API or DP by the relevant regulatory authority, then every component or system used in that manufacturing suite has been established to be acceptable, consistent with the conditions upon which acceptability is based. These manufacturing components or systems may then be considered to be comparators and may provide the means of establishing whether a component or system under consideration is suitable for use.

If equivalence can be established between a component under consideration and a comparator component, then this is all the justification that is required to establish that the component under consideration is suited for its intended use. In this case, the component under consideration is deemed to be suited for its use, and the selection and justification process is complete. If the comparison does not establish equivalence between the component under consideration and the comparator component, then the component under consideration must undergo some degree of characterization to establish its suitability for use, starting with a *Risk assessment*.

ESTABLISHING COMPARATOR STATUS

Three aspects are relevant in establishing equivalence between a component under consideration and a comparator:

1. The component under the consideration and the comparator are equivalent in terms of their materials of construction and design,

2. The component under the consideration and the comparator are equivalent in terms of how they have been processed up to and during their use, and
3. The component under the consideration and the comparator are equivalent in terms of their conditions of use in the manufacturing process.

Although it is highly desirable that the equivalence in all three circumstances be exact, it may be the case that essential equivalence may be established based on strong similarities between the component under consideration and the comparator. If equivalence cannot be established and no comparator is identified, proceed to the *Risk assessment*.

Risk assessment: Components that have direct contact with a process steam, process intermediate, API, or DP, and which do not have comparators, must be characterized to the extent dictated by their risk profiles; where greater risk is associated with more extensive characterization. The risk profile of a component or system, used in a particular circumstance, is established by application of a *Risk evaluation matrix*. Such a matrix is constructed so that it:

1. Establishes the appropriate contributors to, or dimensions of risk,
2. Provides a means of quantifying the risk, in each of its dimensions, and
3. Links the quantified risk to appropriate characterization strategies.

Risk evaluation matrix: The *Risk evaluation matrix* establishes the relative risk that a plastic component or system will be leached with sufficient tenacity that a process stream contacting the plastic component will contain potentially impactful extractables and links that risk to a prescribed level of characterization. The level of characterization established by the application of the matrix is adjusted by considering two factors that could mitigate the product impact of extracted substances. One adjusting factor considers the relative risk that the extractables would endure in the process stream to the point that they would be incorporated into the finished DP as PrIs. The second adjusting factor considers the clinical use of the DP as clinical use establishes the product user's exposure to the impurities. These factors are addressed via the matrix and application of the matrix establishes the degree of component testing that must be performed.

Application of the *Risk evaluation matrix*: The *Risk evaluation matrix* considers four dimensions that address the risk that a plastic component will be leached by a process stream to such an extent that process streams could contain potentially impactful extractables. These dimensions include:

1. The duration of contact,
2. The temperature of contact,
3. The chemical composition of the process stream, and
4. The nature of the component's materials of construction.

The matrix then considers each dimension separately and assigns a level of risk associated with certain measures relevant to each dimension. Considering duration of contact, it is observed that as the duration increases, the risk of leaching increases. Durations of contact relevant to components or systems used in manufacturing suites were established and the duration of contact dimension was divided into three levels; short term (<24 h, Level 1), intermediate term (1–7 days, Level 2), and long term (>7 days, Level 3). A similar assessment was made for the remaining three dimensions, resulting in the matrix shown in *Table 3*:

Table 3. Dimensions Relevant to Risk Level

Risk Dimension	Duration	Temperature[a]	Solvent	Material Reactivity
Level 1	<24 h	Frozen (< −10°)	Aqueous pH >3 or <9	Inert
Level 2	1–7 days	Refrigerated (2°–8°) Ambient (15°–25°)	Somewhat organic	Intermediate
Level 3	>7 days	Elevated (>30°)	Highly organic or extreme pH (<3 or >9)	Reactive

[a] The gaps in the temperature ranges reflect temperature ranges that are rarely experienced in manufacturing processes.

The terms “aqueous”, “somewhat organic”, and “highly organic” are defined as follows:

- If the level of organic solvents in the process stream is <5% by volume, then the process stream is “aqueous”.
- If the level of organic solvents in the process stream is 5% –40% by volume, then the process stream is “somewhat organic”.
- If the level of organic solvents in the process stream is 40% by volume or more, then the process stream is “highly organic”.

Presence of surfactants in the process stream:

- If the level of surfactants (for example, polysorbate 80) in the process stream is <0.1% by weight, then the process stream is “aqueous”.
- If the level of surfactants in the process stream is between 0.1% and 0.5% by weight, then the process stream is “somewhat organic”.
- If the level of surfactants in the process stream is >0.5% by weight or more, then the process stream is “highly organic”.

Process streams consisting of blood or containing blood-derived substances:

- If the process stream contains blood-derived substances (for example, albumin) at levels <1% by weight, then the process stream is “aqueous”.
- If the process stream contains blood-derived substances (for example, albumin) at levels between 1% and 25% by weight, then the process stream is “somewhat organic”.
- If the process stream is blood or if it consists of blood-derived substances (for example, albumin) at levels of 25% by weight or more, then the process stream is “highly organic”.

Presence of lipids and proteins in the process stream:

- If the level of lipids or proteins in the process stream is <1% by weight, then the process stream is “aqueous”.
- If the level of lipids or proteins in the process stream is between 1% and 5% by weight, then the process stream is “somewhat organic”.
- If the level of lipids or proteins in the process stream is >5% by weight or more, then the process stream is “highly organic”.

Material reactivity: The terms “reactive”, “intermediate”, and “inert” are defined as follows:

- If the total level of additives in the component is <0.1% by weight, then the component is considered to be “inert”.
- If the total level of additives in the component is between 0.1% and 1% by weight, then the component is considered to be “intermediate”.
- If the total level of additives in the component is >1% by weight, then the component is considered to be “reactive”.
- If the component is irradiated or chemically treated prior to its use in the manufacturing suite, then the component is considered to be“reactive”.
- If the assembly of the component requires the use of bonding solvents, adhesives, or other chemical means of connecting a component’s materials or subassemblies, then the component must be considered either “intermediate” or “reactive”, depending on the amount of bonding agents used and documented evidence of their loss from the component prior to its use.

Using the *Risk evaluation matrix:* The *Risk evaluation matrix* uses a two-step process. *Step A: Establish values for each risk dimension*—A component being assessed for risk is “rated” with respect to these four dimensions shown in *Table 4*, and the resulting rating results in a level assignment of either *1*, *2*, or *3* in each of the four dimensions. A numerical risk sequence can be generated based on these assignments. For example, a component or system that is rated as highest risk in all four dimensions has a generated numerical risk sequence of *3333*. The numerical order of the risk sequence values is largely inconsequential, and the proper use of the numerical risk sequence requires that the sequence be given in order of decreasing digit values. Although the numerical risk

sequences *3212* and *3221* reflect different risk profiles, both sequences are linked to the same level of characterization. Thus, both risk sequences can be expressed as *3221* for ease of use in establishing the proper level of characterization.

Step B: Linking the numerical risk sequence with a level of characterization—On the basis of a consideration of all possible outcomes of the application of the *Risk evaluation matrix,* the following links between the numerical risk sequence and the characterization level have been established.

Table 4. Linking the Numerical Risk Sequence with a Level of Characterization

If ...	And ...	Characterization Level
Four dimension scores are Level 3	No additional qualifier (3333)	Level C
Three dimension scores are Level 3	Other dimension score is Level 2 (3332)	Level C
	Other dimension score is Level 1 (3331)	Level C
Two dimension scores are Level 3	Other two dimension scores are both Level 2 (3322)	Level C
	One dimension score of Level 2 (3321)	Level B or C[a]
	Other two dimension scores are Level 1 (3311)	Level A or B[b]
One dimension score is Level 3	All of the three other dimension scores are Level 2 (3222)	Level B
	One of the other dimension scores is Level 1 (3221)	Level B
	Two of the other dimension scores are Level 1 (3211)	Level A or B[c]
	All of the three other dimension scores are Level 1 (3111)	Level A
No dimension score is Level 3	All of the dimension scores are Level 2 (2222)	Level B
	Not all of the four dimension scores are Level 2	Level A

[a] If the Level 2 score is in temperature, solvent, or duration dimensions, then Level C; otherwise, Level B.
[b] If one of the Level 1 scores is in the material reactivity dimension, then Level B; otherwise, Level A.
[c] If one of the Level 1 scores is in the material reactivity dimension, then Level B; otherwise, Level A. In these cases the temperature, solvent, or duration dimensions have a greater influence on risk than does material reactivity.

Use of mitigating factors to adjust the characterization level: Mitigating factors take into account the fact that the leaching of a component alone does not necessarily mean that the leached substance will have an adverse effect on the production process output. For example, extractables from a component that are removed (or cleared) from a process stream by a process step that comes after the leaching cannot affect the production process output because the extractables will not be present in the output. Furthermore, the clinical use of the production process output may be such that any adverse effect that the PrI would be moderated. Considering safety, for example, the potential safety impact of a leachable in a low-risk dosage form (e.g., solid or liquid oral) used in an acute therapy is much less than the potential safety risk of the same leachable in a high-risk dosage form (liquid injectable) used in a chronic therapy. Therefore, both clearance and clinical mitigating factors must be taken into account when establishing the characterization level.

Clearance: Is there a post-contact processing step that is capable of clearing extracted substances?

- Yes, use the mitigating factor (clearance mitigating factor value = 1).
- No, do not use the mitigating factor.

Clinical use: What is the safety risk of leachables given the clinical use of the process output? Factors to consider include dosage form, duration of clinical use, daily dose volume (if applicable).

a. If the dosage form is solid or liquid oral, then use the mitigation factor (mitigating factor value = 1).
b. If the duration of clinical use is <7 days, then use the factor (mitigating factor = 1).
c. If the daily dose volume is <10 mL, then use the factor (mitigating factor = 1).
d. Otherwise, do not use the factor.
e. Note that a mitigating factor is used only in the first instance that requirements *a* through *c* are met. Mitigating factors obtained considering *a*through *c* are not additive; thus, the highest value that the mitigating factor can have due to clinical use is 1.

The mitigating factors are used as follows. Add the clearance mitigating factor and the mitigating factor due to clinical use. Possible values of this sum are 0, 1, and 2.

- If the sum = 0, then there is no adjustment of the characterization level.
- If the sum is = 1, then the characterization level established in step c of *Clinical use* is reduced by one level of testing (e.g., *Level B* testing is reduced to *Level A* testing).
- If the sum is = 2, then: Characterization *Level A* is applicable in all circumstances.

Linking risk to characterization methodologies: The various adjusted characterization levels established previously are linked to the following characterization methodologies:

- *Level A* = Baseline Assessment
- *Level B* = Expanded Baseline Assessment
- *Level C* = Full Testing

ESTABLISHING THE LEVEL OF CHARACTERIZATION

Baseline assessment: The baseline assessment for components includes a materials of construction element and a component element. Considering the materials of construction element, the baseline requirement is that all materials of construction must comply with ⟨661.1⟩, specifically relevant for low-risk dosage forms. Thus, all materials of construction must be tested to establish their:

- Identity,
- Physicochemical characteristics,
- Biological reactivity, see *Biological Reactivity Tests, In Vitro* ⟨87⟩,
- Additives (by proper reference to 21 CFR Indirect Food Additives Used in Food Contact Substances), and
- Levels of extractable metals.

The testing must be performed as specified in ⟨661.1⟩, and the results derived from the testing must conform to the specifications contained in⟨661.1⟩.

Considering the component element, the component must be tested for biological reactivity as described in ⟨87⟩.

Although isolated components may have little or no ability to contribute leachables to the manufactured DP, they should be characterized to the extent that they can be purposefully selected. A robust manufacturing process relies on appropriate materials and components of construction so that the manufactured DP is safe and effective; it does not rely on isolating steps to mitigate the potential impact of using potentially inappropriate materials or components. Selection of such isolated components may be justifiable based on a reduced level of testing, as deemed appropriate by considering both their character and the degree of isolation afforded by the manufacturing process.

Expanded baseline assessment: Consistent with the greater risk, components that were risk assessed as *Level B* require either additional or more rigorous characterization to augment or supplement the *Baseline assessment*. This requirement is analogous to the requirement that the ⟨661.1⟩approach addresses low- and high-risk dosage forms in a manner consistent with their relative risk. The *Expanded baseline assessment* for components includes a material of construction element and a component element. Considering the materials of construction element, although the *Expanded baseline assessment* addresses the same component aspects as does the *Baseline assessment*, the *Expanded baseline assessment* does so in a more rigorous manner for two of the aspects, biological reactivity and additives. In the case of biological reactivity, the rigor of the testing is increased by changing the baseline requirement of ⟨87⟩ testing to the more

rigorous requirement that the materials of construction must be classifiable as Plastic Class VI as defined in *Biological Reactivity Tests, In Vivo* ⟨88⟩. For additives, the baseline requirement of "compliance with indirect food additive regulations" is replaced with a more rigorous requirement that the materials of construct specifically be tested to establish the additives they contain and the levels of those additives.

Thus, all materials of construction for components that fall into risk *Level B* must be tested to establish their:

- Identity,
- Physicochemical characteristics,
- Biological reactivity, by meeting the requirements for Plastic Class VI designation,
- Additives (by proper testing), and
- Levels of extractable metals.

The testing must be performed as specified in ⟨661.1⟩, and the results derived from the testing must conform to the specifications contained in⟨661.1⟩.

Considering the component element, while components in *Level A* were tested for biological reactivity ⟨87⟩, components in *Level B* are additionally tested for Plastic Class VI requirements ⟨88⟩ and for extractable metals.

When a component is made up of multiple materials of construction, it is reasonable to observe that it may be more practically efficient to characterize the component than it is to characterize its individual materials of construction. Although the concept of component versus material testing is not relevant to *Baseline assessment*, it may be relevant to those tests that are augmented in the *Expanded baseline assessment*, specifically Plastic Class VI designation and plastic additives. For example, rather than testing each individual material of construction to Plastic Class VI standards, it may be more efficient to test the entire component to establish that it meets the requirements for this class designation. Thus, the augmenting testing required to achieve *Expanded baseline* characterization can be performed on either the component or all its individual materials of construction.

Full testing, extractables profiling: The full testing assessment for components includes a materials of construction element and a component element. Considering the materials of construction element, all materials of construction must be tested by the same procedures and against the same specifications that were appropriate for risk *Level B*, because these procedures and specifications are consistent with the highest risk dosage form categories as specified in ⟨661.1⟩.

Considering the component element, components that are used in the highest risk situations (risk Level C) must be more rigorously characterized than the more or less general testing represented in the *Baseline* and *Expanded baseline assessments*.

Specifically, components at risk *Level C* must be characterized to the extent that its extractables profile has been established.

The nature of the generated extractables profile must be such that the profile fulfills its intended purpose, which is to facilitate and justify component selection. Presumably, an extractables profile that is suited for this purpose would be one that is produced by testing an extract that is generated by a standard method (thus facilitating consistent and comparative assessment) and one which provides insight into extractables that are relevant to situations generally experienced in the manufacturing suite. This intended purpose is different than the safety qualification of the component, which is the process of performing the testing and data interpretation required to establish that the component is suitable for use in a specific certain circumstance.

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 unreasonable and impractical to impose a large set of extraction conditions on the entire industry because it is clear that in most circumstances so doing will just lead to testing and test results that are largely irrelevant. The proper compromise between universal applicability and practicality is to establish a *Standard Extraction Protocol*, based on a minimum set of extraction conditions, which provides information that is useful in a vast majority circumstances and which is more completely relevant in the more commonly encountered circumstances.

STANDARD EXTRACTION PROTOCOL

Components and systems are used in many different ways and perform many different functions in manufacturing systems and suites. Because it is reasonable to anticipate that the conditions of contact between the process stream and a manufacturing component may be strongly influenced by the function that the component performs (and the chemical nature of the process solutions at the relevant stage of manufacturing), component extraction procedures vary across the various component functions.

The *Standard Extraction Protocol* was designed to produce extracts whose analytical characterization would produce extractables profiles that can be used to drive and justify component selection in most manufacturing situations and which might be applicable for the more rigorous purpose of component qualification in the more commonly encountered situations. As such, it represents a compromise between completeness and practicality.

Extraction solvents: From a practical perspective it is desirable to minimize the number of extraction solvents while maintaining a sufficiently varied chemical composition that effectively addresses the diversity in the composition of process streams. The solvents themselves should be analytically expedient, facilitating their chemical analysis of the extracts.

Three extraction solvents were specified: a pH 3 salt solution to address low pH, a pH 10 buffer to address high pH, and a 50% (by volume) ethanol solution to address process streams that contain organic solvents, organic solubilizing or stabilizing agents, lipids, proteins, and blood or blood-derived components. The pH values or ethanol content of extraction solvents encompass many of the process streams encountered in typical manufacturing operations. The differing nature of the extracting solvents has the potential of producing three separate extractables profiles, any combination of which would be relevant to a majority of the commonly encountered manufacturing circumstances.

Extraction temperature: The choice of the extraction temperature (40°) was dictated by the desire to accelerate, but not alter, the extraction process. Use of 40° provides an appropriate acceleration factor but is not so much higher than the temperature of typical manufacturing operations that the nature of the components at the extraction temperature would be greatly different than the nature of the component at the manufacturing temperature.

Extraction duration: Durations of contact were established specifically for individual components, consistent with the duration of contact between the component and a process stream during typical manufacturing operations. In some cases, such as bioreactor bags, the duration of contact specified in the *Standard Extraction Protocol* is a value intermediate between the shortest and longest possible contact during manufacturing operations. Profiles generated by testing extracts obtained at such intermediate durations will be generally, but not wholly, applicable to manufacturing conditions at both contact duration extremes and will be sufficiently useful to facilitate and justify component selection.

Extraction durations longer than contact time during typical use were used for manufacturing situations where the contact between the component and the process stream is short, such as manufacturing operations involving a flowing process stream. The shortest extraction time was established as 1 day. Extraction durations that could be shorter than contact time during typical use were used for manufacturing situations where the contact between the component and the process stream is long, such as long-term storage of process intermediates. Nevertheless, the longest extraction time established, 21 days, still reflects nearly 3 months of contact at ambient temperature and 1 year or more storage under refrigerated or frozen conditions.

Accomplishing extraction: In addition to specifying the extraction conditions, the *Standard Extraction Protocol* establishes the means of accomplishing the extraction. These means were established consistent with the way the component/process stream contact occurs in the manufacturing operation while recognizing the constraints imposed by performing operations at the laboratory, versus the manufacturing, scale.

Use of static extraction: When the contact between the component or system and the process solution is static (e.g., storage of buffers in bags), then it is proper that the extraction of the component be static. However, in many manufacturing operations, a component or system is contacted by a flowing or moving process stream. Given the

practical difficulty in simulating manufacturing flow contact situations in the laboratory, appropriately designed static extractions are used with components or systems whose manufacturing use involves a flowing process stream.

Agitation of extracts: Under certain extraction conditions, such as short extraction times, it may be the case that the agitation of extraction units produces a more effective and/or more reproducible extraction process by insuring that the extraction solution is well mixed; however, the effect of agitation is difficult to quantify. The more "aggressive" longer duration extraction conditions specified in the *Standard Extraction Protocol* (7 and 21 days) are sufficiently rigorous that agitation is unnecessary. Nevertheless, gentle agitation, such as that achieved by rotation using an orbital shaker, may be used at the discretion of the component evaluator. In the case of the short-term extractions (1 day), agitation using slow rotation is recommended.

NON-STANDARD EXTRACTIONS

Extractions in addition to those specified in the *Standard Extraction Protocol* may be appropriate in certain circumstances, depending on the specific circumstances being addressed by the component assessor. The generation and testing of such additional extracts can be performed to augment the extractables profiles generated by implementation of the *Standard Extraction Protocol* at the discretion of the component assessor. However, the generation and testing of such additional extracts cannot be used to replace or substitute for the extractables profiles generated by implementation of the *Standard Extraction Protocol*.

ACCOUNTING FOR CONDITIONING AND RELATED STEPS EMPLOYED IN MANUFACTURING

Certain components used in manufacturing suites may be subjected to processes during manufacturing that have the potential of affecting their extractables profiles. For example, tubing may be cleaned, rinsed, or sterilized prior to or between manufacturing events. In addition to cleaning, rinsing, and sterilization, filters and chromatography columns may be conditioned prior to or after use.

Two aspects of such process steps are potentially important. The first aspect is whether manufacturing components need to be tested by extracting with solutions and conditions that mimic such process steps. Although it is likely that the solutions used in these processing steps are isolated from the process stream, and thus that the finished DP is not exposed to extractables leached during such steps, it may be necessary to establish that the components are compatible with these manufacturing processes.

The second aspect is that such process steps could alter the extractables profile of the affected components. Especially when such process steps are repeated numerous times over the component's useful life time (e.g., if the process component is re-used after processing), it may be appropriate to establish a component's extractables profile at various points during its useful lifetime.

TESTING THE EXTRACTS; GENERATION OF THE EXTRACTABLES PROFILE

The extracts shall be analytically tested to establish the identities of the extractables and to estimate their concentration in the extracts using appropriate and orthogonal analytical methods, consistent with ⟨1663⟩. The reporting of extractables must be consistent with the application of relevant and appropriate reporting thresholds, such as the analytical evaluation threshold (AET), as defined in ⟨1663⟩.

EVALUATION OF THE EXTRACTABLES PROFILES ESTABLISHED BY IMPLEMENTING THE STANDARD EXTRACTION PROTOCOL

Although generation of a component's extractables profiles is a necessary step in component selection and justification, the mere existence of an extractables profile does not establish whether a component is appropriate for use. Rather, the extractables profile must be interpreted in terms of the probable impact that the extractables would have on key performance and/or quality attributes of either the process itself or the process output.

It is beyond the scope of this document to specify the exact means by which the probable impact of a component's extractables, as revealed by application of the *Standard Extraction Protocol*, is established. However, it is noted that since the extractables profiles being evaluated were generated by application of a *Standard Extraction Protocol* (which may or may not be an effective simulation of the component's conditions of use) and since the assessment is for the purpose of selection and not qualification, a rigorous and fully quantitative assessment may not be necessary or appropriate.

2.4 Safety Qualifications

GENERAL

A manufacturing suite is chemically suited for its intended use with respect to safety if:

- The manufacturing suite is constructed from well-characterized materials and components that have been intentionally chosen for use as established by testing according to this chapter.
- The manufacturing suite's general physicochemical properties have been established.
- The manufacturing suite's biocompatibility (biological reactivity) has been appropriately established.
- The manufacturing suite has been established to be safe by means of the appropriate chemical testing, such as extractables and/or leachables profiling, and toxicological assessment of the test data. This combination of chemical testing and toxicological assessment is termed chemical safety assessment.

Regarding the last point, it is relatively rare that an entire manufacturing suite is safety qualified by performing extraction studies on the entire suite. More commonly,

manufacturing suites are safety qualified by performing relevant simulated-use extraction studies on the components and systems that make up the suite.

This section of this chapter deals solely with manufacturing components, systems, and suites and should not be applied to materials from which manufacturing suites are constructed. The testing and selection of materials of construction used in manufacturing suites were addressed previously.

The test methods and specifications contained within this document have been developed for general application to manufacturing systems consisting of plastic components. In view of the wide variety of materials of construction, components, and manufacturing systems available and recognizing possible new developments in materials, components, and systems, the publication of a test method and/or specification does not exclude the use, in justified circumstances, of manufacturing components and systems that have been tested with different methods and/or which comply with other specifications, subject to agreement by the appropriate regulatory authority.

CHEMICAL SAFETY QUALIFICATION

The safety of the manufacturing system must be established based on relevant and appropriate chemical testing of the manufacturing system, its components of construction, or the system's output, which is either an API or DP. Considering testing of the manufacturing systems (and/or its components) and the process output, an appropriate and rigorous chemical safety assessment would include extractables testing of the manufacturing system (and/or its components) and/or PrIs testing of the packaged DP. It is expected that the design of the extractables and impurities study would be based on sound and justifiable scientific principles and that the studies themselves would be consistent with:

- The nature of both the manufacturing systems and process output,
- The clinical use of process output, and
- The perceived safety risk associated with the manufacturing system and the process output.

Although no manufacturing systems or process output is excluded from this testing requirement, it is anticipated that the nature and degree of testing would depend on the process output and its clinical use. In view of the considerable diversity of manufacturing systems and process outputs, it is not possible to establish specific test conditions for performing extractables and/or leachables studies. Nevertheless, general essential principles and demonstrated best-practices recommendations for extractable and leachable studies can be found in ⟨1663⟩ and ⟨1664⟩, respectively. These chapters may be helpful resources for designing and justifying rigorous and appropriate studies.

Alternate chemical safety assessment testing strategies may be appropriate in justified circumstances, subject to agreement by an appropriate regulatory authority.

The data and information obtained in the *Chemical Safety Qualification* must be interpreted in the context of establishing the patient safety risk associated with the clinical use of the manufactured pharmaceutical product. Most typically, such an interpretation of the chemical data involves the toxicological safety assessment of extractables and/or impurities data, supported, as appropriate, by other relevant testing. In this circumstance, the toxicological safety assessment should be performed for each individual relevant member of the manufacturing system's extractables profile (or each member of the process output's impurities profile as appropriate) to demonstrate that the user safety risk associated with each individual PrI (or extractable is worst-case impurity) is acceptable and that the probable safety risk posed by all impurities (or extractables as worst-case impurities), considered individually, is within acceptable parameters. The term relevant extractable or impurity refers to those extractables that are present in a manufacturing system and those impurities that are present in a process output at levels sufficiently high that they have been deemed to have a potential safety impact based, for example, on comparison of the extractables or impurities levels with a recognized and well-established safety alert threshold.

Considering PrIs that are also elemental impurities, it is noted that limits for elemental impurities in marketed pharmaceutical DPs (but not specifically for systems used to manufacture the marketed DPs) can be found in ⟨232⟩.

ADDITIONAL SAFETY QUALIFICATION

Although *Chemical Safety Qualification* is an important and necessary means of establishing that a manufacturing system (or component thereof) is safe for use (i.e., that it produces an output that does not adversely affect the health of users of the output), it is not necessarily the only means by which safety is established and in many cases it may not be the only means required to establish safety. Where relevant or appropriate, *Chemical Safety Qualification* should be augmented by orthogonal test methods, subject to the approval of a relevant regulatory authority.

■ 1S (*USP40*)

Add the following:

■

GLOSSARY

Additional terms are discussed and defined in *Packaging and Storage Requirements* ⟨659⟩*, General Definitions*.

Auxiliary streams: Include those solutions encountered in manufacturing that are decoupled from the manufactured DP due to the nature of the manufacturing process. For example, filling lines may be rinsed with auxiliary solutions in preparation for product manufacturing. Filters and chromatography columns may be rinsed and conditioned prior to

use. When such auxiliary solutions are directed to waste, they do not become part of the process stream, and substances extracted from materials, components, or systems by auxiliary streams cannot be entrained into the manufactured DP as leachables. Therefore, auxiliary streams would not typically be tested for leachables; and materials, components, or systems contacted solely by auxiliary streams may not require rigorous chemical assessment supported by testing.

Characterization: The process of establishing the characteristics or properties of a test article. In the content of this document, characterization has been defined in terms of establishing certain physicochemical, chemical, and biocompatibility characteristics of materials and components used in manufacturing operations.

Closed vessel extraction: An extraction that is performed by placing the portion of the sample to be tested and the proper amount of an extracting solvent in a secondary, inert extraction vessel. After loading the vessel with sample and solvent, the vessel is closed and placed in the proper environment to accomplish the extraction. After the extraction has been completed, the extraction solvent is typically removed from the vessel for testing.

Comparator component: A component that can be established as equivalent (or nearly equivalent) to another component in terms of its composition, design, materials of construction, processing, performance and conditions of use in the manufacturing process. Typically, the comparator component is (or has been) used in a regulatory approved manufacturing process or is used to produce a regulatory approved and marketed pharmaceutical API or DP. Linking a component under consideration for use to a comparator component is all the evidence that is required to approve and justify the use of the component.

Component: An entity, consisting of one or more materials that perform a single function in a system or process. Some examples include: silicone tubing (as a component) consists of a single material; a filter (as a component) may consist of its membrane (a single material), its housing (a single material) and various gaskets (each of which is a single material and all of which may be the same material).

Extractables: Organic and inorganic chemical entities that are released from a manufacturing component or system into an extraction solvent under laboratory conditions. Depending on the specific purpose of the extraction study, these laboratory conditions (e.g., solvent, temperature, stoichiometry, and others) may accelerate or exaggerate the normal conditions of use for a manufacturing component or system.

Extractables profile: A list of all substances that are extracted from a test article and the concentration (or amount) of the substances that is extracted. The extractables profile might list only those substances whose level in the extract is above a chosen and justified threshold.

Extraction studies: Determine if the overall laboratory processes are required to create extractables profile(s) for particular manufacturing components or systems. Extraction studies are also referred to as Controlled Extraction Studies.

Isolated materials, components, and systems: A material, component, or system that is chemically isolated, in terms of leachables, from the manufactured DP due to the nature of one or more steps in the manufacturing process. For example, there are certain steps in a manufacturing process that have a demonstrated ability to segregate material or component-derived extractables from the process stream (e.g., ultrafiltration). Although the process stream may leach extractables from materials and components used in process steps prior to such segregating steps, the process stream leaving such steps will be depleted in such extractables.

Manufacturing suite: The sum total of all materials, components and systems that together are used to convert inputs (ingredients) into an output (manufactured DP).

Material: A single polymer or copolymer that is used to construct components or systems. Some examples include: cyclic olefins, polypropylene, polyamide 6, polyethylenes, and polyethylene terephthalate.

Process: A series of steps involving the use of materials, systems, or components that start with a DP's ingredients, converts those ingredients into process streams, and then converts the process stream(s) into the manufactured DP.

Process stream: Those solutions encountered in manufacturing that can be directly linked throughout the manufacturing process to the manufactured DP. Process streams either carry process intermediates through the manufacturing process or are process intermediates themselves. In essence, the manufacturing process converts the various process streams into the manufactured DP.

Process-related impurity (PrI): A foreign organic or inorganic chemical entity that is present in a manufactured DP because it has leached from a material, component, or system used in the manufacturing suite and has persisted through the entire manufacturing process.

Qualification: The process of establishing that a test article is suited for its intended use in terms of a key performance attribute. This process typically includes obtaining and documenting evidence that addresses suitability. For example, *Safety Qualification* is the process of establishing that a manufacturing suite (or a component thereof) is safe from the perspective that the system does not leach chemical entities that are entrained in the process output in such quantities that the entities pose a risk to the health of users of the process output.

System: An entity, consisting of multiple components, that performs one or more functions in a process, e.g., a single-use bioreactor.■ 1S (*USP40*)