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Add the following:

▲⟨1665⟩ CHARACTERIZATION AND QUALIFICATION OF PLASTIC COMPONENTS AND SYSTEMS USED TO MANUFACTURE PHARMACEUTICAL DRUG PRODUCTS AND BIOPHARMACEUTICAL DRUG SUBSTANCES AND PRODUCTS

1. INTRODUCTION

A manufacturing process is the sum of the steps required to convert starting raw materials into a manufactured biopharmaceutical drug substance (DS) or a pharmaceutical or biopharmaceutical drug product (DP). Manufacturing processes are performed utilizing manufacturing systems which are the sum of the components that together comprise the equipment that converts starting raw materials into biopharmaceutical DSs or pharmaceutical or biopharmaceutical DPs.

Manufacturing systems can be partially or completely constructed from plastic materials. Plastics used in manufacturing systems possess a range of molecular weights and contain plastic additives such as antioxidants, stabilizers, lubricants, plasticizers, and colorants. Several factors dictate the types of plastics that are used in manufacturing components, the types and amounts of additives and polymeric resins that are used in plastic materials and the processes used to convert the plastic materials into components or systems.

The process stream, production intermediates, DS, or the DP itself could directly come in contact, and potentially interact, with one or more plastic components of the manufacturing system at some point during the manufacturing process. During contact, substances could leach from a manufacturing component and become incorporated into the process stream. If these substances persist in the process stream through subsequent process operations, they could accumulate in either a DS or DP as process equipment-related leachables (PERLs). If they are present in the DP, PERLs have the potential to alter critical quality attributes of the DP, such as safety, efficacy, and stability.

Plastic Components and Systems Used to Manufacture Pharmaceutical Drug Products and Biopharmaceutical Drug Substances and Products ⟨665⟩ addresses these interactions by providing a risk-based means for chemically characterizing and qualifying plastic components used to manufacture biopharmaceutical DSs and pharmaceutical and biopharmaceutical DPs. That chapter provides guidance on qualification procedures applicable to manufacturing components and systems that are within its scope. Chapter ⟨1665⟩ communicates the key concepts behind and provides additional information and guidance regarding the applicability and the application of ⟨665⟩.

2. SCOPE

In general, components of pharmaceutical and biopharmaceutical manufacturing systems can be grouped based on the function or operation that the component performs, including:

- Fluid transfer and transport (e.g., tubing and connectors)
- Mixing, reacting, and fermenting (e.g., tank liners, mixer bags, bioreactors, impellers, tubing, and container ports)
- Storage (e.g., containers [and associated ports and/or tubing] for raw materials, production reagents, and process intermediates)
- Processing (e.g., filters and chromatography columns)
- Filling devices (e.g., filling needles)
- Ancillary components (e.g., o-rings, gaskets, check valves, septa, diaphragms, polymer pump surfaces, and sensors)

This chapter is applicable to all manufactured DPs, including pharmaceuticals (“traditional” or “small molecule” products) and biopharmaceuticals (biologics), and is also applicable to manufactured biopharmaceutical DSs. This chapter is also applicable to substances that are manufactured (collected, isolated, purified, etc.) with plastic components and systems and used in gene and cell therapies or as antibody–drug conjugates (ADCs). Active pharmaceutical ingredients (APIs) that are the precursors to non-biologic and non-biopharmaceutical drug products and are typically manufactured via chemical, as opposed to biological, processes are referred to as “traditional” or “small molecule” drug substances and are out of scope with regard to ⟨665⟩ and this chapter as they are well-characterized substances that have sufficiently low levels of PERLs that they do not require characterization. Thus, manufacturing components used in the production of APIs are considered to be suitable for use without the chemical testing required in ⟨665⟩. However, APIs formulated in upstream processes, which include reactive process streams (i.e., containing organic solvents in large proportion, exceptionally high or low pH), high contact temperatures, long contact durations and/or multiple plastic components followed with limited purification processes, are considered to be at a higher risk. Applying ⟨665⟩ to the qualification of plastic components for such processes is determined on a case-by-case basis using good scientific judgment such as the concepts and processes described in ⟨665⟩.

This chapter is applicable to plastic manufacturing components that are used once and discarded (single-use systems) and components that are used once, rendered suitable for re-use (e.g., cleaning, sterilization) and then re-used in multiple-use systems.

Manufacturing components such as o-rings and gaskets may be constructed of rubber-based elastomers, which could be a source of PERLs and thus must be qualified. However, rubber-based components are not within the scope of ⟨665⟩ and thus qualification tests and specifications must be found elsewhere. Although rubber components used in manufacturing are outside the scope of *Elastomeric Components in Injectable Pharmaceutical Product Packaging/Delivery Systems* ⟨381⟩, that chapter contains tests and specifications that might be relevant to rubber-based elastomeric manufacturing components.

This chapter and ⟨665⟩ exclude items that are referred to as auxiliary items. While assorted plastic auxiliary items (e.g., scoops, funnels, pipettes, graduated cylinders, weighing dishes, and beakers) could be used in manufacturing operations for the dispensing and transferring of ingredients into a process stream or solution, their conditions of use are such that they are unlikely to contribute PERLs to the process stream. For example, such auxiliary items contact manufacturing ingredients for relatively short periods of time. Furthermore, many auxiliary items are used to transfer solid ingredients, which present a low risk of PERL transfer. The use of auxiliary items poses little risk in terms of the transfer of PERLs to the process stream. Thus, such auxiliary items are outside the scope of ⟨665⟩ and such items are considered to be qualified for use without ⟨665⟩ testing.

The applicant who secures and is responsible for the regulatory approval of a manufacturing system or the manufactured pharmaceutical or biopharmaceutical drug product derived from that system is accountable for establishing that the product's manufacturing system meets these expectations and is suited for its intended use.

This is accomplished by ensuring that the manufacturing system itself and/or the manufactured pharmaceutical DP or biopharmaceutical DS or DP has been appropriately tested and that the test results have been appropriately evaluated. The avenues through, and means by, which the applicant obtains test results and secures test result evaluations are left to the discretion of the applicant.

3. GENERAL PRINCIPLES

3.1 Discussion

The most effective means of ensuring that a manufacturing system is suitable for its intended use is to use well-characterized and intentionally selected components.

While the selection process for components increases the likelihood that a component and a system composed of components will be suitable for use, it does not necessarily establish that the component is actually suitable to use. Qualification testing of a component and/or system is required to establish the component's (or system's) ability to produce an acceptable DS or DP. When appropriate, system qualification may be augmented by DS or DP testing to directly establish what effect the manufacturing system had on the DS's or DP's key quality attributes.

This chapter and ⟨665⟩ both deal with the qualification of manufacturing components, where ⟨665⟩ specifically establishes the testing requirements for the qualification of plastic components.

Given the nature of manufacturing processes and systems, certain components may be isolated from the DS or DP. Although such components are essential aspects of the production system, they do not add PERLs to the DS or DP because they are isolated. If the isolation of a process component can be established (e.g., waste bag), then characterization of the component per ⟨665⟩ is not required.

3.2 Material Characterization

The most effective means of ensuring that a manufacturing component is suitable for its intended use is to use well-characterized and intentionally selected materials of construction. Thus, a component manufacturer is advised to collect chemical characterization data on candidate materials for the component, as such information may guide material selection. Guidance on how to chemically characterize materials of construction can be found in the following *USP* chapters:

- ⟨381⟩
- *Plastic Materials of Construction* ⟨661.1⟩

Although chemical characterization of materials may enable appropriate material selection, chemical characterization of materials is not a prerequisite for the qualification of manufacturing components or systems.

3.3 Component Characterization

Components shall be characterized to the extent that is consistent with the risk that the component could add PERLs into a process stream and that the PERLs could persist through the manufacturing process and adversely affect the suitability for use of the process output. Matching the risk with the required level of characterization is achieved by a two-stage component assessment approach consisting of an initial assessment followed by a risk assessment.

4. ASSESSMENT PROCESS

4.1 Initial Assessment

The initial assessment as illustrated in ⟨665⟩, *Figure 1* addresses three aspects of the component and its use:

1. Is the component with a process stream, a biopharmaceutical DS, or a pharmaceutical or biopharmaceutical DP during use?
2. Is the process stream, DS, or DP that contacts a manufacturing component either a liquid or semisolid?
3. Does a potential comparator component or system exist, and, if so, can equivalence be established between the comparator and the component or system under consideration?

Aspect 1 addresses whether the component contacts a process stream, biopharmaceutical DS, or pharmaceutical or biopharmaceutical DP directly. If the component contacts an auxiliary stream, then it is isolated from the process stream. It is unlikely that such a component's PERLs will become entrained into the biopharmaceutical DS, or pharmaceutical or biopharmaceutical DP. In this circumstance, the component is deemed to be qualified for use with no further assessment and is out of scope for ⟨665⟩.

Aspect 2 addresses the physical state of the process stream and is based on the generalization that interactions between a process stream and a component are likely to be more extensive if the process stream is a liquid or semisolid (as opposed to a gas or solid). Moreover, liquid and semisolid process streams are more common in pharmaceutical manufacturing than are solid or gaseous process streams. Thus, when components are contacted by either solid or gaseous process streams, the risk associated with PERLs is very low, no characterization is required, and the component is deemed to be qualified for use with no further assessment.

An example of such a component is one that is used during the transfer of drug product powders into their final packaging. As another example, it is noted that a DS may be stored frozen in a container at some point in the manufacturing process, raising the question as to whether the container is actually within the scope of ⟨665⟩ (a frozen DS is a solid). As such storage typically includes periods in which the DS is thawed in the container; this situation is within the scope of ⟨665⟩ and requires risk assessment and appropriate testing. As the PERL's risk during frozen storage is very low, such an assessment focuses solely on the conditions during which the DS exists in a liquid or semisolid form.

A component that does not contact a liquid or semisolid process stream is out of scope for ⟨665⟩. If the component or system is contacted by a liquid or semisolid process stream, process intermediate, biopharmaceutical DS, or biopharmaceutical or pharmaceutical DP, then Aspect 3 is addressed.

Aspect 3 addresses the concept of a comparator component. When a manufactured pharmaceutical or biopharmaceutical product has been approved for commercial marketing, then by direct association, the process and system used to manufacture that product has been established to be suitable for their intended purpose. Once a manufacturing system has been established to be suitable to manufacture a biopharmaceutical DS, or pharmaceutical or biopharmaceutical DP by the relevant regulatory authority, then every component used in that manufacturing system has been established to be acceptable. These manufacturing components or systems may then be used as comparators and may provide the means of establishing whether a component or system under consideration for use in another manufacturing process and/or to produce a different biopharmaceutical DS, or pharmaceutical or biopharmaceutical DP is suitable.

If equivalence can be established between a component under consideration and a comparator component, then this justification is adequate to establish that the component under consideration is suited for its intended use without testing the component per ⟨665⟩. In this case, a justification should be provided and the qualification process is complete.

Equivalence can be established if both the component under consideration and the comparator are:

1. Constructed from the same materials of construction
2. Manufactured via the same process and the same processing conditions
3. Equivalent in terms of the function they perform

4. Equivalent in terms of how they have been processed (e.g., sterilized) and/ or reprocessed, if appropriate, prior to their use, either by the component's vendor or the component's user. For multiuse components/systems, equivalence with respect to how they have been processed post use.
5. Equivalent in terms of their conditions of use in the manufacturing process
6. Prepared for use (e.g., flushed, sterilized) in the same manner
7. Used to produce the same type of output (biopharmaceutical DS or pharmaceutical or biopharmaceutical DP), and the outputs are administered in the same clinical manner (route of administration and dose)

Although it is highly desirable that the equivalence in all seven aspects be exact, it may be the case that essential equivalence can be established based on strong similarities between the component under consideration and the comparator. The concept of strong similarities implies that the differences in any of the above-listed seven items of comparison are minor. Here "minor" means the differences are sufficiently small that the PERLs derived from the component in question:

- Will be the same in identity and amount to the PERLs from the comparator, or
- Will have the same process or patient effect as the PERLs derived from the comparator

Any minor differences between the component under consideration and a largely representative comparator component may be addressed by risk assessing the minor differences in a manner consistent with ⟨665⟩ and this chapter. Alternatively, minor differences between the component of interest and a largely representative comparator component may be addressed by an alternate risk assessment process. The purpose of this risk assessment is to ensure that a minor difference will have a minor impact on the suitability of a component for its intended use. If it is established that the minor difference will likely have a minor and insignificant impact on a component's suitability, then the comparator approach is an appropriate means of qualifying the component. However, if it is possible that the minor difference could have a significant effect on the component's suitability, then the comparator approach is not an appropriate means of qualifying the component and the component must be qualified by testing as established by risk assessment.

Ultimately, it is the responsibility of the component's user to establish and justify equivalence, or essential equivalence, to a comparator.

4.2 Risk Assessment of Components

Components that have direct contact with a liquid or semisolid process stream, starting material, reagent, process intermediate, biopharmaceutical DS, or pharmaceutical or biopharmaceutical DP, and that do not have comparators, must be characterized to the extent dictated by their risk profiles whereby a greater risk is associated with a more extensive characterization. The risk profile of a component or system, used in a particular circumstance, is established by the application of a risk evaluation matrix constructed so that it:

- Establishes the appropriate contributors to, or dimensions of, risk
- Provides a means of quantifying the risk, in each of its dimensions (e.g., see *Table A-1*)
- Provides a means of quantifying the total risk as a combination of the individual risks established for each dimension
- Links the quantified total risk to appropriate characterization strategies (e.g., see *Table A-3*)

4.2.1 Development and Application of the 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 likely contain potentially impactful PERLs and that the PERLs will likely persist in the process stream to be incorporated in the production output. The matrix then links that risk to a prescribed level of chemical characterization.

If the contact conditions between a process stream and a manufacturing component are mild, then it is unlikely that the leaching of PERLs will occur. On the other hand, if the contact conditions are harsh, then it is very likely that PERL leaching will occur.

Secondly, a PERL generally is likely to have an adverse effect on a key drug product quality attribute only if it persists through the manufacturing process and is incorporated into the finished DP. If the PERL is cleared from the process stream by subsequent manufacturing steps, then it will not persist to the end of the manufacturing process. As a result, the PERL will not be incorporated into the DP, and it will not have an effect on any of the DP's key quality attributes. Conversely, if the PERL is not removed from the process stream, then it will likely be entrained into the DP. [Note—For biologics, key quality attributes and process performance parameters can also be potentially impacted by a PERL during drug substance manufacturing prior to the finished DP.]

These two actions, leaching and persistence, can be used as dimensions in a risk evaluation diagram (see *Figure 1*), where the risk that is being evaluated is whether the finished DP will contain PERLs at high enough levels that they could have an adverse effect on a key quality attribute of the DP. The level of risk is associated with the nature and amount of testing that is required for components per ⟨665⟩.

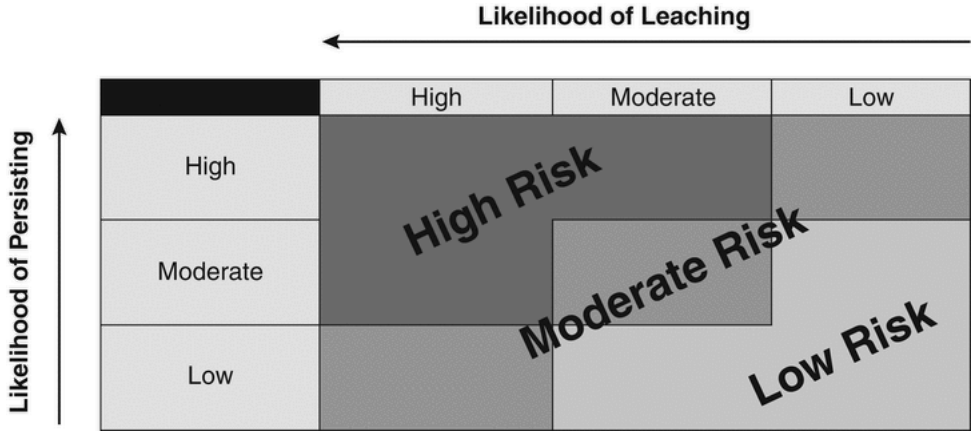

Figure 1. Risk evaluation diagram.

An individual manufacturing circumstance (e.g., component type or process conditions under which the component is contacted by the process stream) is positioned in this risk evaluation diagram to establish the component's required level of testing per ⟨665⟩. Although each individual drug product sponsor must establish the manufacturing circumstance's position in the risk evaluation diagram, the means by which this is accomplished is not specified in ⟨665⟩, and it is the responsibility of the sponsor to establish and justify these means. In establishing and justifying the means, the sponsor must consider the multitude of factors that impact the likelihood of leaching and the likelihood of PERLs to persist. Although general comments on how to fit a specific circumstance into the risk evaluation diagram can be found in this chapter, the finished drug product's sponsor has the ultimate responsibility for performing and justifying the risk evaluation.

While the individual details of individual sponsors' risk evaluation processes may differ, it is proper and reasonable to expect that the processes would be similar in terms of the general concepts applied. To properly address the issue of PERLs, the risk evaluation process should address the following points:

1. The chemical and physical nature of the contacted component, establishing the component's "propensity to be leached"
2. The chemical nature of the contacting process stream, establishing the process stream's "leaching power"
3. The conditions of contact, addressing the "driving force" for leaching (e.g., temperature, duration)
4. The ability of purification process operations to eliminate the PERL from the process stream or to dilute the PERL to such an extent that an adverse effect is unlikely
5. The inherent risk associated with the manufactured drug product, considering such factors as the nature of the manufactured dosage form, e.g., inhalation solution (higher risk) versus parenteral solutions (moderate risk) versus aqueous-based oral and topical (lower risk); the clinical dosing of the DP (e.g., daily dose volume); and the duration of the clinical therapy (acute versus chronic)

Regardless of the justified means by which the risk assessment is carried out, the outcome of the risk assessment must be that the risk is defined as low, moderate, or high, consistent with the risk levels illustrated in *Figure 1*. However, it is recognized that the final risk output from some drug product sponsors may differ from the three levels of risk evaluation matrix as shown in *Figure 1*. Other risk models outputs may yield two or more risk evaluation levels. In these cases, it is the responsibility of the drug product sponsor to align their risk outputs with the three risk levels required in ⟨665⟩. In addition, at least one of the sponsor's risk evaluation levels must be aligned with the ⟨665⟩ high risk level.

An example of a risk evaluation matrix can be found in the *Appendix*. As the purpose of this example is education and illustration, it is not required that the matrix in the *Appendix* be adopted in order for a sponsor to claim that their assessment complies with ⟨665⟩.

4.2.2 LINKING RISK TO CHARACTERIZATION METHODOLOGIES

The various adjusted characterization levels established previously are linked to the following characterization processes:

- Low Risk = general chemistry testing, "worst-case" extraction solution
- Moderate Risk = organic extractables profiling, "worst-case" extraction solution
- High Risk = organic extractables profiling, multiple extraction solutions reflecting the effects of pH and polarity on extractions, and extracted elements as deemed appropriate by the component's user

4.3 Establishing the Level of Component Chemical Characterization

4.3.1 LOW RISK ASSESSMENT

Low risk chemical characterization data are generated by subjecting the component of interest to an extraction involving the ethanol–water solvent *Solution C1* from the standard extraction protocol described in ⟨665⟩, *4.2 Test Methods*. The ethanol–water extraction solution is chosen as it is generally recognized as producing the most substantial organic extractables profile of all three extraction solutions specified in the standard extraction protocol, where substantial means the largest number of extractables at their highest levels. This extraction solution is profiled, in general, for organic extractables by measuring its level of nonvolatile residue (NVR) and UV absorbance, where NVR provides a level of total extracted nonvolatile substances and UV absorbance provides an indication of the amount and type of UV-absorbing organic extractables. NVR and UV absorbance are chosen because they are tests that are compatible with the extraction solution. Although pH and total organic carbon (TOC) are useful general chemistry tests, they are not compatible with the extraction solution.

Although these general chemical properties of the extracts may not serve as the only basis for a risk assessment, they are important and relevant indicators that the component in question may have levels or types of extractables that could present a higher risk than was indicated by the risk assessment. For example, a large value for NVR would suggest that large amounts of non-volatile extractables were present in the extract. In such a circumstance, even though the component has been judged to be low risk, the judgment may have underestimated the risk. The conclusion that the risk has been underestimated would mean that the risk level should be elevated to moderate risk, triggering the generation of full extractables profiling in *Solution C1*. It is reasonable to expect that the extractables profile would establish those extractables responsible for the general test result that triggered the extractables profiling effort.

4.3.2 MODERATE RISK ASSESSMENT

Consistent with the greater risk, moderate risk components require a more rigorous chemical characterization whereby extractables are addressed by full organic extractables profiling of extraction *Solution C1*. As noted under *Low Risk Assessment*, *Solution C1* is chosen as the extraction solution as it is generally the case that, of the three extraction solutions specified in ⟨665⟩, the most complex organic extractables profile is obtained with this extraction solution, where "most complex" means the greatest number of individual extractables at their individually highest concentration in the extract.

4.3.3 HIGH RISK ASSESSMENT

High risk components must be characterized to the extent that a full organic extractables profile has been established, addressing potentially extreme process conditions such as process solutions with a high “leaching power” or conditions of contact with a high “driving force” for leaching (e.g., higher temperatures or longer duration periods of contact). Such a rigorous and complete characterization is obtained by implementing the standard extraction protocol, which adds two more extraction solutions (low pH and high pH aqueous *Solution C2* and *Solution C3*) to the ethanol–water solution, whereas *Solution C1* is required in the low and moderate risk cases. This extraction protocol is discussed in detail in *5.1 Standard Extraction Protocol*.

5. TESTING OF PLASTIC COMPONENTS AND SYSTEMS

5.1 Standard Extraction Protocol

Components and systems are used in many different ways and perform many different functions in manufacturing systems. 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 of the component (and the chemical nature of the process solutions at the relevant stage of manufacturing), component extraction procedures vary across the various component functions.

Given the diversity of components used in manufacturing systems and the widely varying conditions of contact 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 because it would inevitably lead to testing and test results that are irrelevant. The 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 majority of circumstances and is more completely relevant in the more commonly encountered circumstances.

The standard extraction protocol was designed to produce extracts whose analytical characterization would generate extractables profiles that can be used to drive component qualification in commonly encountered situations. As such, it represents a compromise between completeness and practicality.

5.1.1 EXTRACTION SOLUTIONS

From a practical perspective, it is desirable to limit the number of extraction solutions to a minimal number of solutions with a sufficiently varied chemical composition that effectively addresses the diversity in the composition of process streams. Furthermore, the solvents themselves should be analytically expedient, facilitating the chemical analysis of the extracts.

Three extraction solutions are specified in ⟨665⟩: a 50% by volume ethanol–water solution to address process streams that contain organic solvents, organic solubilizing or stabilizing agents, lipids (up to 15% of the process stream’s composition by weight), proteins, and blood or blood-derived components (*Solution C1*); a pH 3 salt solution to address low pH (*Solution C2*); and a pH 10 buffer to address high pH (*Solution C3*). The pH values or ethanol content of the extraction solutions encompass many of the process streams encountered in typical manufacturing operations. The differing nature of the solvents could produce three separate extractables profiles, the combination of which would be relevant to the most commonly encountered manufacturing situations.

Other solvents may be used in addition to the three solvents specified in the standard extraction protocol at the discretion of the assessor. For example, there may be process situations where the pH of the process solutions falls outside the range encompassed by *Solution C2* and *Solution C3*, and in those situations it may be appropriate to consider alternative or additional extraction solutions.

Considering aqueous solvents, the pH range specified in the standard extraction protocol was chosen to 1) reflect a reasonable range of pH values for process solutions commonly encountered in pharmaceutical manufacturing processes and 2) encompass the pH range over which pH materially impacts the “extracting power” of the solvent.

For extraction at a low pH specifically, studies that included the pH 3 extraction solution (*Solution C2*) specified in ⟨665⟩ and a more acidic 0.1 M phosphoric acid extraction solution have demonstrated that the extractables profiles produced are sufficiently similar that these solvents can be considered interchangeable. Thus, an extraction performed with 0.1 M phosphoric acid as the extraction solution meets the extraction requirements in ⟨665⟩ for *Solution C2*. Furthermore, extraction solutions that achieve pH 3 by various means (e.g., the use of different acids to achieve the pH) are considered to be appropriate surrogates for the pH 3 solution specified in the standard extraction protocol, so long as the surrogate solvent is analytically viable.

For extraction at a high pH, studies that included the pH 10 extraction buffer *Solution C3* specified in ⟨665⟩ and more caustic extraction solutions (e.g., 0.5 N sodium hydroxide) have demonstrated that the extractables profiles produced may be sufficiently dissimilar that these solvents cannot be considered interchangeable. This circumstance is noteworthy as high pH caustic solutions such as 0.5 N sodium hydroxide are used in certain commonly encountered process situations. For example, it is fairly commonplace in biopharmaceutical manufacturing for manufacturing components to be cleaned and/or sanitized prior to use by contact with caustic solutions. Although extractables may be released from the components and become entrained in the caustic solution, such situations are not of concern with respect to ⟨665⟩, as the caustic solutions are directed to waste and contact between the component and the caustic solution is usually followed by rinsing, with the rinsate also being directed to waste. Thus, the released extractables do not enter the process stream and cannot become PERLs.

On the other hand, caustic solutions are frequently used in biopharmaceutical manufacturing to adjust the pH of process solutions (e.g., media fills in bioreactors). Such caustic solutions may be stored in plastic containers, clarified by plastic filters, or delivered to the process stream by plastic tubing and connectors. In these situations, extractables from the plastic components that become entrained in the caustic solution enter the process stream and become PERLs, making this situation relevant to ⟨665⟩. However, the manufacturing process is such that the caustic solutions are greatly diluted by the process streams. The levels of these PERLs in the actual process stream are small and likely to be inconsequential.

These circumstances notwithstanding, if all of the following criteria are met, then the pH 10 extraction solution specified in ⟨665⟩ can be replaced with the contact solution or the proposed simulating solvent. Alternatively, if an extraction study has already been performed with the contact solution or the proposed simulating solvent, the extractables profile obtained from that study can be used in place of the organic extractables data obtained with the pH 10 extraction solution.

1. The pH of the contacting solution is >10
2. There is a reasonable expectation that extractables resulting from the action of the high pH contacting solution will remain in the process stream (or else the component is isolated from the process stream and extraction is not required per ⟨665⟩, *3.1 Initial Assessment*)
3. Assessment of the risk associated with this contact situation produces a high risk characterization (as other risk characterizations do not require a high pH extraction)
4. The contact solution itself, or a proposed simulating solvent, are analytically expedient (meaning that the analytical process of extractables discovery, identification, and quantitation can be accomplished at the necessary concentration levels via the expert application of generally practiced, state-of-the-art analytical practices and technology)

A component that is tested with the replacement extraction solution and meets the requirements of ⟨665⟩ is considered to be compliant with ⟨665⟩.

Substitution of a high pH contact solution or simulating solvent for the pH 10 extraction solution (*Solution C3*) in circumstances where all four of these criteria are not met is an inappropriate application of ⟨665⟩.

An alternative solvent should not be used in place of *Solution C1*, *Solution C2*, or *Solution C3* if the “extraction (or leaching) power” of the process stream used in the manufacturing process is less than that of the corresponding solution (*Solution C1*, *Solution C2* or *Solution C3*).

The options available for extractions solvents are summarized in *Figure 2*.

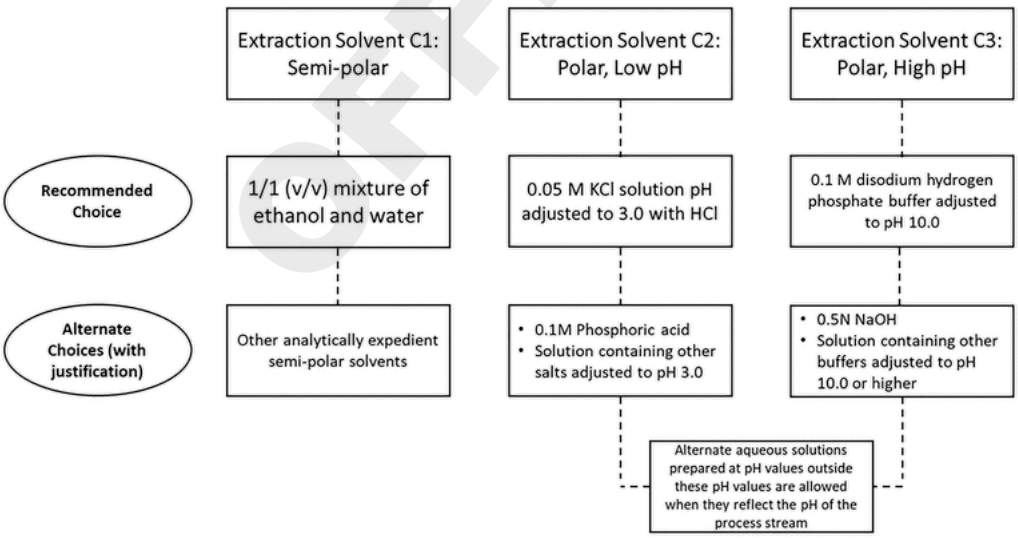

Figure 2. Extraction solution selection for manufacturing components.

The required extraction solutions do not include water, as the extractables profile obtained in water will be intermediate between the combined extractables profiles obtained from the pH extreme aqueous solvents. The extraction solutions do not include a high inorganic salt solution (e.g., 5 M sodium chloride), as the high salt will reduce leaching. The extraction solutions do not include solvents containing surfactants as the “leaching power” because the ethanol–water solvent generally has the same or greater “leaching power” as a surfactant-containing process stream. Additionally, extraction solutions containing surfactants are more difficult to analyze than an ethanol–water solutions.

5.1.2 EXTRACTION TEMPERATURE

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

5.1.3 EXTRACTION DURATION

Durations of extraction 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 time during manufacturing operations. Profiles generated by testing extracts obtained at such intermediate durations will generally apply to manufacturing conditions at both contact duration extremes and will be sufficient to facilitate and justify component qualification.

Extraction durations longer than contact time during typical use are 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 shorter than contact time during typical use are 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 approximately 2.5 months of contact at ambient temperature and 8 months storage under refrigerated conditions, estimated as follows.

The accelerated aging techniques noted in ASTM F1980-16 (*1*) are based on the hypothesis that the chemical reactions being considered follow the Arrhenius reaction rate function and can be applied generally to temperatures between 2° (non-frozen) and 70° (depending on the glass transition temperature of the plastic being considered).

The technique is based on an accelerated aging factor (AAF), which is expressed mathematically in *Equation 1*.

$$\text{AAF} = Q_{10}^{[(T_{AA} - T_{RT})/10]} \quad \text{Equation 1}$$

Q_{10} = aging factor, which has a conventionally accepted value of 2.0 for a first-order chemical reaction

T_{AA} = elevated temperature to be used for extraction

T_{RT} = temperature at which the manufacturing operation is performed

For example:

If T_{AA} = 40° and T_{RT} = 22° (ambient temperature), then the AAF = 3.48.

If T_{AA} = 40° and T_{RT} = 5° (refrigerated temperature), then the AAF = 11.3.

The AAF value is used to calculate the accelerated aging time (AAT) as expressed in *Equation 2*.

$$t_{RT} = \text{AAT} \times \text{AAF} \quad \text{Equation 2}$$

t_{RT} = contact time at T_{RT}

Using the example of the values of AAF obtained above and a 21 days extraction period, the calculated AATs for process steps that occur at ambient or refrigerated temperatures become 73 and 237 days, respectively. Even if these values are not exactly correct due to the assumptions inherent in the calculation, they establish the extent to which the duration specified in the standard extraction protocol reflect actual manufacturing conditions.

For extrapolation of 21 days of extraction at 40° to the equivalent storage duration at ambient room temperature (22°), *Equation 2* becomes:

t_{RT} = AAT × AAF

t_{RT} = 21 days × 3.48

t_{RT} = 73.1 days

For extrapolation of 21 days of extraction at 40° to the equivalent storage duration at nominal refrigerated temperature (5°), *Equation 2* becomes:

t_{RT} = AAT × AAF

t_{RT} = 21 days × 11.3

t_{RT} = 237.3 days

5.1.4 DYNAMIC EXTRACTION

Many manufacturing operations involve flowing or agitated process streams. Additionally, extractions may be facilitated by movement of extraction solutions by either agitation or recirculation. Thus, dynamic extractions are performed on components via either agitation or recirculation. Specific dynamic requirements are detailed for individual components in ⟨665⟩.

5.1.5 EXTRACTED SURFACE AREA TO EXTRACT SOLUTION VOLUME RATIO (SA/V)

It is generally the case that extractions described in relevant regulatory guidelines and relevant standards are defined in terms of the ratio of a test article's contact surface area and the volume of the extraction solution. To be consistent with these precedents, extractions in ⟨665⟩ are defined in terms of SA/V. Additionally, since components used in manufacturing are available in multiple sizes and configurations, specifying extractions based on SA/V allows for a consistent basis of comparison. The target SA/V of 6 cm^2/1 mL was adopted from relevant regulatory guidelines and standards. In all cases, the SA/V used in an extraction must be specified. In cases where components are extracted via immersion, reporting the mass/extraction volume or the number of components/extraction volume ratios may also facilitate the assessment of the extractables data.

5.1.6 NON-STANDARD EXTRACTIONS

Extractions that replace those specified in the standard extraction protocol may be necessary and appropriate in certain circumstances. It is a fundamental aspect of extractables assessment that the item being extracted is compatible with the conditions of extraction; that is, the item should not be altered chemically or physically by the extraction process. Although the extreme circumstance of complete dissolution of the test item is an obvious indication of an incompatibility (as it is surely the case that a manufacturing component is not dissolved by a process stream during use), less extreme indicators of incompatibility exist (e.g., deformation or discoloration of the test item or generation of a precipitate-laden extract).

If an extraction solution specified in the standard extraction protocol is incompatible with the component being tested (i.e., the component is rendered nonfunctional by the extraction), then an alternate extraction solution should be established, and the alternate solution should replace the specified solution. The alternate extraction solution must be suitable for determining either the NVR and UV absorbance or the organic extractables profile and, as appropriate, extractable elements, meaning that the solvents must be analytically compatible with the analytical techniques used for organic and inorganic extractables and profiling.

Considering the required surface area to solution volume ratio of 6 cm^2/1 mL specifically, when such an extraction ratio cannot be readily achieved, then an alternate extraction should be designed so that it is based on the highest possible surface area to solution volume ratio and a justification for the alternate extraction ratio must be provided.

Additionally, the standard extraction protocol was established to be applicable to a majority of the most commonly encountered manufacturing circumstances. However, one can encounter extreme manufacturing circumstances where the contact conditions between the process stream and a manufacturing component are more aggressive, in terms of extraction potential, than the extraction conditions in the standard extraction protocol. An example of such a circumstance is the situation where the pH of the process stream exceeds the pH of the basic extraction *Solution C3*. In this specific circumstance, the use of an extraction solution with a pH greater than *Solution C3* (pH 10) as a substitute for *Solution C3* may be appropriate (see *5.1.1 Extraction Solutions*).

As another example, higher temperature or longer extraction duration may be appropriate based upon the worst-case conditions of use in the manufacturing process (e.g., maximum component use time including holding/pause and restart). In this case, the higher temperature and/or longer duration is used in place of the temperature or duration established in the standard extraction protocol.

In other circumstances of extreme manufacturing conditions, an alternate extraction process that is as aggressive as the manufacturing conditions must be designed and justified. This alternate extraction process is then used in place of the process established in the standard extraction protocol.

On the other hand, it is possible that the extraction conditions of the standard extraction protocol are more aggressive than the manufacturing conditions of contact. The substitution of a less aggressive extraction for the extraction specified in the standard extraction protocol is not appropriate, as it is the intent of the standard extraction protocol to produce an extractables profile in the laboratory that is at least as complex as the PERL profile under actual process conditions, where complex refers to the number of compounds and their concentrations.

The generation and testing of extracts produced by alternate extractions will generate extractables profiles that could replace those profiles generated by the implementation of the standard extraction protocol at the discretion of the component's 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 unless:

1. The substitution is driven by incompatibilities, or
2. The substitution can be justified by a rigorous technical discussion of the “extracting power” of the proposed substitution solvent and the solvent (*Solution C1*, *Solution C2*, or *Solution C3*) it is replacing, or
3. The alternative testing condition represents the worst-case scenario of the extraction power of the process stream during manufacturing.

An example of such a justification would be the discussion about the interchangeability of the pH 3 extraction *Solution C2* and an extraction solution consisting of 0.1 M phosphoric acid.

It is noted that any alternate extraction process can only replace the extraction conditions that it directly addresses. For example, the use of a high pH process stream in manufacturing means that while *Solution C3* can be replaced with an alternate extraction solution, it does not mean that testing with *Solution C1* and *Solution C2* can be eliminated; testing of these solutions must still be performed.

The circumstances just discussed address the substitution of an alternate extraction process for an extraction process specified in the standard extraction protocol. Extractions performed in addition to those specified in the standard extraction protocol may be performed at the discretion of the component's assessor.

5.1.7 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 to affect their extractables profiles. For example, tubing may be cleaned, rinsed, or sterilized by autoclaving or irradiation 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 must be tested by extracting them with solutions and under conditions that mimic such process steps. Since 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, the components do not have to be extracted with the cleaning, rinsing, or conditioning solutions. Nevertheless, it still may be necessary to establish that the components are compatible with these manufacturing processes and solutions.

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 lifetime (e.g., if the component is reused after processing), it is necessary to establish a component's extractables profile at various points during its useful lifetime, unless the assessor can provide evidence that the extractables profile does not change with each successive processing and reuse.

5.2 Testing the Extracts and Generating the Extractables Profile

5.2.1 ORGANIC EXTRACTABLES

For moderate and high risk components, the extracts shall be analytically tested to establish the identities of the organic extractables and to estimate their concentration in the extracts using appropriate and orthogonal analytical methods, consistent with *Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems* ⟨1663⟩. Thus, chromatographic methods with appropriate sampling and detection processes are used to screen extracts for organic extractables.

The reporting of organic extractables must be consistent with the application of relevant and appropriate reporting thresholds. An example of such a reporting threshold is the analytical evaluation threshold (AET), as defined in ⟨1663⟩. The reporting threshold should be clearly communicated and justified in conjunction with the extractables profile.

Chromatographic methods used to address organic extractables should be qualified as being suited for this intended use.

5.2.2 EXTRACTED ELEMENTS (POTENTIAL ELEMENTAL PERLS)

Techniques such as atomic spectroscopy (e.g., inductively coupled plasma–optical emission spectroscopy [ICP–OES]—see *Elemental Impurities—Procedures* ⟨233⟩) can be used to screen extracts for extracted elements.

Considering the reporting of extracted elements, the relevance of extractable elements testing should be considered by the component's potential user. Should such testing be deemed necessary, it is the user's responsibility to establish and justify the means by which testing is accomplished, taking into account extraction conditions, target elements, and reporting requirements. Furthermore, the component's user may wish to consult ⟨233⟩ when establishing its manufacturing components' extracted elements strategy, recognizing that ⟨233⟩ is specifically applicable to finished drug products and elements listed in the chapter do not reflect all potentially impactful elements but rather those elements for which permissible daily exposures (PDEs) could be derived.

5.3 Evaluation of the Extractables Profile Established by Implementing the Standard Extraction Protocol

Although the generation of a component's extractables profile is a necessary step in component qualification, 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 key quality attributes of either the process itself or the process output if the extractables were to become PERLs.

It is beyond the scope of this document to specify the exact means by which the probable impact of a component's extractables (as potential PERLs), as revealed by application of the standard extraction protocol, is established. However, *Section 6* discusses certain aspects of such a qualification process.

6. QUALIFICATION OF MANUFACTURING COMPONENTS AND SYSTEMS

6.1 General

A manufacturing system is chemically suited and qualified for its intended use if:

1. The manufacturing system is constructed from well-characterized components that have been intentionally chosen for use as established by testing.
2. The manufacturing system has been established to be safe by means of the appropriate chemical testing of components, such as extractables profiling, or DPs, leachables testing as necessary and appropriate, and toxicological assessment of the test data. In this context, a manufacturing system is considered to be safe if the DS or DP it produces contains PERLs at levels sufficiently low that they pose a negligible risk to patient safety. This combination of chemical testing and toxicological assessment is termed "chemical suitability for use assessment".

In certain circumstances and at the drug product sponsor's discretion, the suitability for use assessment could consider the possibility that the efficiency and/or effectiveness of the manufacturing process would be adversely impacted by PERLs that are derived from manufacturing components and present in the process stream(s).

This section of this chapter deals solely with manufacturing components and systems and should not be applied to materials from which manufacturing systems are constructed. It is also noted that it is relatively rare that the entire manufacturing system is qualified by performing extraction studies on the entire system, given the practical difficulties in so doing, and that, most commonly, a manufacturing

system is qualified by performing extraction studies on the components that make up the system and then using the individual components' extractables profiles to establish the components' cumulative potential effect as a system. The means used to establish either the cumulative extractables profile and/or its cumulative potential effect must be justified.

In certain circumstances, individual manufacturing components may be connected to produce a manufacturing assembly and it may be desired that the assembly be tested per ⟨665⟩. Such a desire potentially complicates the testing of an assembly versus the component particularly when the assembly is comprised of components that individually would be tested in different manners, for example, duration of extraction.

It is beyond the scope of ⟨665⟩ to envision all possible assemblies that could be used in manufacturing and to provide extraction conditions for such assemblies. Ultimately, it the assembly user who is responsible for establishing and justifying the extraction conditions used to ascertain the assembly's compliance with ⟨665⟩. If appropriate, the justification must specifically address the situation where the extraction conditions used for the assembly are less rigorous (e.g., of shorter duration) than the most rigorous extraction conditions specified in ⟨665⟩ for the assembly's individual components.

6.2 Chemical Qualification

A manufacturing system is qualified as being suitable for use based on relevant and appropriate chemical testing of the manufacturing system, its components of construction, or the system's output. Generally, an appropriate and rigorous chemical assessment would include extractables testing of the manufacturing system (and/or its components) and/or PERL testing of the manufactured biopharmaceutical DS or pharmaceutical or biopharmaceutical DP. It is expected that the design of the extractables study would be based on sound and justifiable scientific principles and that the studies themselves would be consistent with the:

- Composition of the components
- Conditions of use of the components
- Chemical properties of the process stream
- Clinical use of the process output
- Perceived risk associated with the manufacturing system and the process output

No manufacturing system or process output is excluded from extractables or leachables testing; however, the nature and degree of testing depends on factors listed above and the risk that PERLs from the manufacturing component could affect the effectiveness of the manufacturing process or the quality of the manufactured DS or DP. Thus ⟨665⟩ has established a process for qualifying components that establishes three levels of risk and utilizes three levels of testing.

Considering a component that has been classified as low risk, such a component is deemed to be qualified for use, consistent with ⟨665⟩ if:

1. The tests specified for low risk components have been performed.
2. The test results have been reviewed in the context of the validity of the risk classification.

As an example of the second point, consider one of the required tests for a low-risk component, NVR. If the component assessor establishes that the potential process- or patient-impact of the measured NVR is likely to be low, then the risk classification is verified, and the component is qualified for use. On the other hand, if the component assessor establishes that the impact of the measured NVR could be significant, then the risk classification of "low" is refuted, and the component can only be qualified by performing the required moderate- or high-risk testing, as established by the assessor.

The concept of an NVR result being "high" is subjective and can only be established on a case by case basis by the assessor based on the exact manufacturing process being considered, the exact DS or DP being assessed, and the component's conditions of use.

Considering a component that has been classified as either moderate or high risk, such a component is deemed to be qualified for use, consistent with ⟨665⟩, if:

1. The test(s) specified for moderate or high risk components have been performed.
2. The resulting extractables profiles have been assessed for possible process impact and to establish the suitability of the manufactured DS or DP for use.
3. The outcome of the assessment is that the impact of the extractables (as PERLs) is such that process efficiency and/or product suitability for use is not adversely affected by the PERLs.

The means by which a component assessor establishes that the extractables (as PERLs) would have no adverse impact on the efficiency or effectiveness of the manufacturing process must be established by the assessor. Similarly, the means by which the component assessor establishes that the extractables (as PERLs) would not adversely affect the output's (DS or DP) suitability for use must be established by the assessor. Most typically, interpretation of the chemical data includes the toxicological assessment of extractables and/or PERL data, supported, as appropriate, by other relevant testing to establish the potential patient safety impact of PERLs in the DS or DP. In this circumstance, the toxicological assessment should be performed for each individual relevant extractable (or each relevant PERL as appropriate) to demonstrate that patient safety is not adversely affected by each individual PERL (or extractable as worst-case PERLs). The term "relevant extractable" or "relevant PERL" refers to those extractables that are present in a manufacturing system and those PERLs that are present in a DS or DP at levels sufficiently high that they could affect a key quality attribute of the drug product such as patient safety (e.g., extractables or PERLs whose levels are greater than the AET).

Considering the impact of PERLs on the suitability for use of a DP or DS, the previously mentioned approach of interpreting extractables data (as potential PERLS) is one means of establishing that a component is qualified. A second means would be the actual characterization of the manufactured DS and DP for PERLs. If it is established that the actual levels of PERLs in the DS and DP are acceptable (meaning that

assessment of the PERLs has concluded that the PERLs do not compromise the DS's or DP's suitability for use), then the manufacturing system, and each of the individual manufacturing components, have been qualified.

6.3 Alternate Approaches for Qualification

Chapter ⟨665⟩ establishes qualification procedures and qualification acceptance criteria applicable to manufacturing components that are within its scope. Alternative chemical qualification procedures and acceptance criteria may be appropriate in justified circumstances, subject to agreement by an appropriate regulatory authority. When considering such alternate approaches, the sponsor is advised to consult with the regulatory authority during the development of such alternate procedures so that regulatory concurrence with the outcome of the alternate qualification is more likely.

Chapters ⟨1663⟩ and *Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery Systems* ⟨1664⟩, are applicable to pharmaceutical packaging/delivery systems but may be helpful resources for designing and justifying rigorous and appropriate studies by establishing general essential principles and demonstrated best-practice recommendations for extractables and leachable studies and assessments.

GLOSSARY

Additional terms are defined in *Packaging and Storage Requirements* ⟨659⟩.

Auxiliary stream:

A solution or semisolid that is used during manufacturing but is decoupled from the process stream and thus the manufactured DP. For example, filling lines may be rinsed with cleaning solutions in preparation for product manufacturing. Additionally, filters and chromatography columns may be rinsed and conditioned prior to use. As these rinsing and conditioning solutions are directed to waste, they do not become part of the process stream and they are designated as auxiliary streams. As substances extracted from components, or systems by auxiliary streams cannot be entrained into the manufactured DP as leachables, auxiliary streams are not tested for process equipment-related leachables and components or systems contacted solely by auxiliary streams do not require rigorous chemical assessment supported by testing.

Characterization:

The process of establishing the characteristics or properties of a test article. In the context of this chapter, characterization is defined as the process of establishing physicochemical and chemical characteristics of components used in manufacturing operations. Characterization is accomplished by extraction testing of components as specified in ⟨665⟩.

Comparator component:

A component that can be established as equivalent (or nearly equivalent) to another component in terms of its composition, design, processing, performance, and conditions of use in the manufacturing process. Generally, the comparator component is (or has been) used in a regulatory-approved manufacturing process or is used to produce a regulatory-approved and marketed biopharmaceutical DS, or pharmaceutical or biopharmaceutical DP. Linking a component under consideration to a comparator component is the sole necessary justification that is required to approve and qualify the component under consideration for use.

Component:

An item consisting of one or more materials that performs a single function in a manufacturing system or process. Silicone tubing is an example of a component that consists of a single material. A filter is an example of a component that likely consists of multiple materials such as its membrane (a single material), its housing (a single material), and its various gaskets (each of which may be a single material).

Extractable:

An organic or inorganic chemical entity that is released from a manufacturing component or system into an extraction solution 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 including the substance's identity and concentration (or amount) in the extract. The extractables profile typically includes only those substances whose level in the extract is above a chosen and justified reporting threshold.

Extraction study:

A study, performed under laboratory conditions, whose purpose is to establish what substances are extracted from a test article and at what levels the substances are extracted under the conditions of the study. Extraction studies are also referred to as "controlled extraction studies".

Isolated component or system:

A component or system that is chemically isolated, in terms of process equipment related leachables, from the manufactured DP due to the nature of its use in the manufacturing process. For example, while a drain or waste bag contacts an auxiliary solution, its purpose is to collect waste solutions after their use. The waste solutions collected in the drain bag are meant to be discarded and thus are not part of the process stream.

Leachable:

A foreign organic or inorganic chemical entity that is present in a manufactured biopharmaceutical DS, or pharmaceutical or biopharmaceutical DP because it has leached from a component used in the manufacturing system and has persisted through the entire manufacturing process.

Manufacturing system:

The sum total of all components that together are used to convert inputs (starting raw materials) into an output (manufactured DS or DP).

Process:

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

Process equipment-related leachable (PERL):

A foreign organic or inorganic chemical entity that is present in a process stream because it has leached from a component used in the manufacturing system. A PERL may be present in a manufactured biopharmaceutical DS or pharmaceutical or biopharmaceutical DP as a leachable if it persists through the entire manufacturing process.

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.

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 use.

System:

An entity, consisting of multiple components, that accomplishes the intended purpose of a manufacturing process, producing either a DS or a DP.

APPENDIX

An Example of a Risk Evaluation Matrix

As noted in *4.2 Risk Assessment of Components* and in ⟨665⟩, components are risk assessed with respect to their ability to contribute PERLs to DPs and the outcome of the risk assessment establishes the level of chemical characterization that must be performed. Although the DP sponsor is responsible for developing and justifying the risk evaluation matrix used to accomplish the risk assessment, ⟨665⟩ provides requirements for the risk dimensions that must be addressed in the matrix. This appendix provides one example of a risk evaluation matrix that meets these requirements.

The risk evaluation matrix evaluates those dimensions that address the risk that a plastic component will be leached by a process stream to such an extent that its extractables may be impactful. These dimensions include the:

1. Duration of contact
2. Temperature of contact
3. Chemical composition of the process stream
4. Nature of the component's materials of construction

The matrix then evaluates each dimension separately and assigns a level of risk based on certain measures relevant to each dimension (see *Table A-1*).

In most cases, the individual risk dimensions are considered to be equal in terms of their impact and in terms of their use in the risk evaluation matrix. However, in certain cases, especially those at the boundaries between the characterization levels, the logical application of the risk evaluation matrix is facilitated if a distinction is made between the dimensions in terms of their effect on the accumulation of PERLs. When it is necessary and appropriate to do so, the dimensions of temperature, solvent, and duration are weighted more heavily than the material dimension as it is logical that these dimensions could have a greater effect on leaching than does the material dimension.

Table A-1. Dimensions Relevant to Risk Level

Risk Dimension	Duration of Contact	Temperature of Contact[a]	Chemical Composition of the Process Stream	Chemical Composition of the Component
Level 1	<24 h	Refrigerated (2°–8°)	Aqueous (≤5% organic v/v; pH ≥3 and pH ≤9)	Low risk
Level 2	1–7 days	Ambient (15°–25°)	Somewhat organic (>5% and ≤40% v/v)	Intermediate risk
Level 3	>7 days	Elevated (>30°)	Highly organic (>40% v/v) or aqueous, extreme pH (pH <3 or pH >9)	High risk

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

DURATION OF CONTACT

It is observed that as the duration increases, the magnitude of leaching increases. Durations of contact between components or systems and manufacturing process streams 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). When determining the duration of contact, any holding and pausing times should be included so that the worst-case scenario for the manufacturing process is represented.

TEMPERATURE OF CONTACT

It is observed that as the temperature increases, the magnitude of leaching increases. Temperatures relevant to components or systems used in manufacturing systems were established and the temperature dimension was divided into three levels: low (refrigerated, Level 1), intermediate (ambient, Level 2), and high (elevated, Level 3).

CHEMICAL COMPOSITION OF THE PROCESS STREAM

The terms “aqueous”, “somewhat organic”, and “highly organic” are defined as shown in *Table A-2*:

Table A-2. Chemical Composition of the Process Stream

Process Streams Containing...	Definition of Process Stream		
	Aqueous	**Somewhat Organic**	**Highly Organic**
Organic solvents	<5% by volume	>5% and ≤40% by volume	>40% by volume
Surfactants, (e.g., polysorbate 80)	≤0.1% by weight	>0.1% and ≤0.5% by weight	>0.5% by weight
Blood or blood-derived substances, (e.g., albumin)	<1% by weight	≥1% and <25% by weight	≥25% by weight
Lipids and proteins	<1% by weight	≥1% and <5% by weight	≥5% by weight

Some process streams could possess multiple solubilizers (e.g., protein solutions that also contain surfactants). In such circumstances, the process stream is risk assessed as the compounded risk associated with the individual agents. For example, a process stream containing 2% protein would be classified as “somewhat organic” and a process stream containing 0.2% surfactants would also be classified as “somewhat organic”. A process stream that contains both 2% protein and 0.2% surfactants would be classified as “highly organic”, reflecting the compounding of the classifications of the individual agents.

Solubilizers could also include agents such as cyclodextrins, chelators, and niacinamide. As the effect of such agents on leaching has not been extensively studied and quantified, distinctions such as those applied to surfactants cannot be proposed for these additional agents, and it is therefore the risk assessor’s responsibility to properly account for these agents in the risk assessment.

CHEMICAL COMPOSITION OF THE COMPONENT

Certain materials are more likely to contribute extractables to solutions they contact, based on their composition and physical properties. For example, the greater the number and level of additives in a plastic material, the greater the total pool of potential extractables and the greater the risk that extractables will migrate into a contacting solution. Additionally, high energy processing of materials such as sterilization may cause degradation of the plastic and its plastic additives, further increasing the number and pool of potential extractables. Lastly, in-use processing of materials and components, such as rinsing, could reduce extractables levels.

The term “chemical composition of the component” is used to assess the component's likely overall risk of extractables. It is based on the logic that the greater the number of additives (or the greater the level of the additives), the greater risk of extractables, as additives are logical sources of extractables. The terms “low risk”, “intermediate risk”, and “high risk” are applied to the material's contribution and are defined as follows:

- If the total level of plastic additives in the component is ≤0.1% by weight, then the component is considered to be “low risk”
- If the total level of plastic additives in the component is > 0.1% and ≤ 1% by weight, then the component is considered to be “intermediate risk”
- If the total level of plastic additives in the component is >1% by weight, then the component is considered to be “high risk”.

If the component is irradiated or heated at high temperature (e.g., autoclaved) prior to its use during manufacturing, then the component is considered to be “high risk”.

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 risk” or “high risk”, depending on the amount of bonding agents used and documented evidence of their loss from the component prior to its use.

If the component is flushed or rinsed during use and the flush/rinse solution is directed towards waste and thus is not part of the process stream, then the flushing and rinsing has the potential to reduce the number or amount of extractables. If the ability of flushing/rinsing to eliminate or reduce extractables has been established, then such flushing/rinsing can be used to reduce the material reactivity term's risk level by one level; for example, a rinsed “high risk” component becomes an “intermediate risk” component.

This assessment of component composition focuses on the concept that the greater the number and quantity of plastic additives, the greater the likelihood that the plastic additives and their related substances will become extractables. Furthermore, when components are stressed as part of their processing, plastic additives degrade, producing additional extractables that may be more soluble. The assessment notes that certain processes used to prepare a component for use can either reduce the levels of extractables available to the process stream (such as rinsing) or increase the number of potential extractables (such as solvent bonding).

Other factors, such as the diffusion of compounds through a component, may affect the compound's ability to be extracted from the component. As diffusivity through a component is impacted by the nature of the component, this is a reasonable factor to consider in assessing a component's propensity to be leached.

Additional factors may also be relevant. For example, the propensity of a component to be leached could be assessed by considering information other than merely the levels of additives and the component's treatment prior to use. The use of additives levels discussed previously is one approach to assess risk and its inclusion in this chapter is not meant to imply that all risk assessors be limited to using this approach.

Component evaluators should consider taking these additional factors and information into account in assessing the component's propensity to be leached. Such assessments must be science-based in that they are supported by information or data that justify the ranking of the component in terms of its propensity to be leached.

USING THE RISK EVALUATION MATRIX

The risk evaluation matrix uses a 3-step process:

Step 1—Establish values for each risk dimension: A component being assessed for risk is "rated" with respect to these four dimensions shown in *Table A-1*, and the resulting rating results in a level assignment of 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. Both risk sequences can be expressed as 3221 for ease of use in establishing the proper level of characterization.

Step 2—Link 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, links between the numerical risk sequence and the characterization level have been established (see *Table A-3*).

Step 3—Use 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 safety of a manufactured DP because the extractables will not be present in the DP as leachables. Furthermore, the clinical use of the manufactured DS or DP may be such that any adverse effect of the PERL would be moderate. The potential adverse patient safety impact of a leachable in a low-risk dosage form (e.g., liquid oral or topical) used in acute therapy is much less than the potential adverse patient safety impact 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 component's risk and characterization level.

Clearance: Is there a post-contact (downstream) processing step that clears extracted substances?

- If yes, then use the factor (mitigating factor = 1)
- If no, then do not use the factor

To a certain extent, dilution can be considered similar to clearance in terms of its ability to mitigate the effect of extractables. While some process steps may not eliminate extractables from the process stream, they can reduce the concentration of extractables by diluting them via the process stream, for example, the addition of a concentrated acid or base used for pH adjustment. In such circumstances, extractables associated with the small volume reagent are diluted by the process stream, mitigating their potential hazard. In such cases, dilution can be the basis of assigning a value of 1 to the clearance mitigating factor if the effect of dilution can be quantified and the use of the factor can be justified.

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

- **a.** If the dosage form is a solid oral, liquid oral (not containing surfactants, co-solvents [such as alcohols] or other solubilizing agents) or topical (semisolid or solid), then use the factor (mitigating factor = 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

[Note—A mitigating factor is used only in the first instance that requirements *a*–*c* are met. Mitigating factors obtained by considering requirements *a*–*c* are not additive; so 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 = 1, then the characterization level established by the other dimensions is reduced by one level of testing (e.g., Level B testing is reduced to Level A testing or Level C testing is reduced to Level B testing)
- If the sum = 2, then characterization Level A is applicable in all circumstances.

Table A-3. Linking the Numerical Risk Sequence with a Level of Characterization

If...	And...	Then the Characterization Level is...
Four of the dimension scores are Level 3	There is no additional qualifier (3333)	Level C (High Risk)
Three of the dimension scores are Level 3	The other dimension score is Level 2 (3332)	Level C
	The other dimension score is Level 1 (3331)	Level C
Two of the dimension scores are Level 3	The other two dimension scores are both Level 2 (3322)	Level C
	One dimension score is Level 2 (3321)	Level B (Moderate Risk) or C[a,b]
	The other two dimension scores are Level 1 (3311)	Level A (Low Risk) or B[b,c]
One of the dimension scores is Level 3	All of the 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[b,c]
	All of the other dimension scores are Level 1 (3111)	Level A
None of the dimension scores is Level 3	All of the dimension scores are Level 2 (2222)	Level B
	Not all of the 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] In these cases the temperature, solvent, or duration dimensions have a greater influence on risk than do component composition.

[c] If one of the Level 1 scores is in the component composition dimension, then Level A; otherwise, Level B.

REFERENCES

1. ASTM F1980. *Standard Guide for Accelerated Aging of Sterile Barrier Systems for Medical Devices*, ASTM International, 100 Barr Harbor Drive, P.O. Box C700, West Conshohocken, PA 19428-2959.

▲ (USP 1-May-2022)

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Topic/Question	Contact	Expert Committee
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