United States Pharmacopeia:

Update for ON USP CHAPTERS FOR MATERIALS, COMPONENTS AND SYSTEMS USED IN PHARMACEUTICAL AND BIOPHARMACEUTICAL APPLICATIONS

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Empowering a healthy tomorrow

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Topics for Discussion

1. Chapters <381>, <1381>, <382> and <1382> for *Elastomeric Components in Injectable Pharmaceutical Product Packaging/Delivery Systems.*

2. Chapters <661.1> and <1661> for *Plastic Materials of Construction**.

3. Chapter <661.2> and <1661> for *Plastic Packaging Systems for Pharmaceutical Use*

4. Chapters <665> and <1665> for *Polymeric Materials, Components and Systems used in the Manufacturing of Pharmaceutical and Biopharmaceutical Drug Products*.

* for Packaging Systems

USP Chapters for Elastomeric Closures for Injections

USP <381>, A Whole New Ball-game?

The Packaging and Distribution Expert Committee has proposing the following revisions which will update and expand the scope of the current chapter.

- **<381> ELASTOMERIC COMPONENTS IN INJECTABLE PHARMACEUTICAL PRODUCT PACKAGING/DELIVERY SYSTEMS.**
- **<1381> ASSESSEMENT OF ELASTOMERIC COMPONENTS USED IN INJECTABLE PHARMACEUTICAL PRODUCT PACKAGING/DELIVERY SYSTEMS.**
- **⟨382⟩ ELASTOMERIC COMPONENT FUNCTIONAL SUITABILITY IN PARENTERAL PRODUCT PACKAGING/DELIVERY SYSTEMS.**
- **⟨1382⟩ ASSESSMENT OF ELASTOMERIC COMPONENT FUNCTIONAL SUITABILITY IN PARENTERAL PRODUCT PACKAGING/DELIVERY SYSTEMS.**

Modifications to USP <381> (1)

1. **Change the title** to “Elastomeric Components in Injectable Pharmaceutical Product Packaging/Delivery Systems”.

2. **Emphasize the baseline requirements for** the **selection** of thermoset and thermoplastic elastomeric components.

3. **Expand the scope to include all elastomeric components used in an injectable’s packaging system.** Elastomeric components include, but are not limited to, those used for vials, bottles, prefilled syringes (plungers, needle shields, and tip caps), cartridges (plungers and seal liners), injection ports for flexible bags and infusion sets, and plungers for single-use syringes.

4. **Delete the *Heavy Metals*** *<231>* and **Zinc testing.** A modern method for extractable element determination, suggested by not required, is described in <1381>.

5. **Delete Table 1 and delete sample washing and boiling prior to Physicochemical testing.**

6. **Move certain functionality tests** and assessment **to a new chapter** <382>.

7. **Develop a new informational chapter**, Assessment of Elastomeric Components used in Injectable Pharmaceutical Product Packaging/Delivery Systems, **to support** the revised **<381>**.

Contents of the Proposed <381> Chapter

1. **INTRODUCTION**
2. **SCOPE**
3. **TEST SAMPLE**
4. PROCEDURES

4.1 **Biological Reactivity***
4.2 Physicochemical Tests
4.2.1 Appearance (Turbidity/Opalescence)
4.2.2 Color
4.2.3 Acidity or Alkalinity
4.2.4 Absorbance
4.2.5 Reducing Substances
4.2.6 Volatile Sulfides
4.2.7 Ammonium
4.3 Functionality Tests
4.3.1 Penetrability
4.3.2 Fragmentation
4.3.3 Self-Sealing Capacity

Bolded titles indicate sections which were significantly changed or are new.

* Changes to the Biological Reactivity sections are largely cosmetic and not substantial.

Extractable elements (including zinc) may also be relevant in the selection of an elastomeric component since they can contribute to drug product impurities. Assessments for elemental impurities should be risked based. **It is the component user's responsibility to evaluate the need for extractable elements** testing and, if such testing is necessary, **to establish and justify the means by which testing is accomplished**, taking into account extraction conditions, target elements and reporting requirement.

Key Points in <381>

1. Every elastomeric component used in a pharmaceutical packaging/delivery system should be proven safe and compatible for its intended use.

2. The chapter provides baseline requirements for the selection of elastomeric components to be further qualified for use in a given system.

3. The chemical testing prescribed is orthogonal:
   - the physicochemical tests provide a general overview of extracted chemicals,
   - the extractable elements test, if performed, provides a quantitative assessment of potential elements of concern,
   - Because chemical testing alone may not be adequate, it is augmented by establishing biological reactivity.

4. If components comply with the <381>requirements, studies should then be designed to determine safety and compatibility as recommended in Assessment of Extractables Associated with Pharmaceutical Packaging - Delivery Systems ⟨1663⟩ and Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging - Delivery Systems ⟨1664⟩.

The Scope of <381>

1. Elastomeric components include, but are not limited to, those used for vials, bottles, prefilled syringes (plungers, needle shields, and tip caps), cartridges (plungers and seal liners), injection ports for flexible bags and infusion sets, and plungers for single-use syringes.

2. Elastomeric components can be either thermoset or thermoplastic.

3. Tests are always conducted on the components after surface modifications.
   - chlorinated surface treatments,
   - fluoropolymer coatings and films,
   - cross-linked polydimethylsiloxane,
   - polydimethylsiloxane that has been applied to the component surface as a lubricant

4. Baseline testing (biological reactivity, physicochemical) is to be performed on the finished components after completion of all manufacturing and processing (e.g., molding conditions, sterilization, etc.).

5. The tested components need to be representative of the final components as intended for use in a packaging or delivery system.

Status of <381> and Related Chapters

1. The four Chapters (<381>, <1381>, <382> and <1382>) appeared, in their revised form, in the *Pharmacopeial Forum* (*USP-PF*) in July (PF 45(4), July/August, 2019).
2. This opened up a 90-day review period for public comments.
3. Chapters are beingrevised in accordance with the comments received.
4. Assuming that the comments can readily be reconciled, the newly revised chapters <381> and <1381> would become official via the normal implementation time frame, which is 6 months from publication in the *USP-PF* (approximately December 1, 2020).
5. Even if the comments can be readily reconciled, the USP Packaging and Distribution Expert Committee is proposing a 5-year delayed implementation to allow industry adequate time to comply with the newly revised chapters <382> and <1382>.

USP <661> Monographs

The Present:

<661> PLASTIC PACKAGING SYSTEMS AND THEIR MATERIALS OF CONSTRUCTION

The "Future":

<661> PLASTIC PACKAGING SYSTEMS AND THEIR MATERIALS OF CONSTRUCTION

<661.1> Plastic Materials of Construction

<661.2> Plastic Packaging Systems for Pharmaceutical Use

<1661> Evaluation of Plastic Packaging Systems for Pharmaceutical Use and Their Materials of Construction

What is going on here?

- October 28, 2018
  - Notice of Intent to Revise: Revisions to Plastics Packaging Chapters <659>, <661>, <661.1>, <661.2>, and <1661>; posted 28-Dec-2018 on the USP Website.

  The General Chapters–Packaging and Distribution Expert Committee intends to revise:

  <659> Packaging and Storage Requirement
  <661> Plastic Packaging Systems and Their Materials of Construction
  <661.1> Plastic Materials of Construction
  <661.2> Plastic Packaging Systems for Pharmaceutical Use
  <1661> Evaluation of Plastic Packaging Systems And Their Materials of Construction With Respect to Their User Safety Impact
- January 1, 2019
  - Pre-Posting of Chapters on USP Website
- March/April, 2019
  - Proposed revisions appeared in PF 45(2), March/April, opening up a 90-day comment period.
- August, 2019
  - Comments were received and reviewed. Modifications to chapters were made.

So where does that leave us?

- **Delayed implementation**, **until December 1, 2025,** of new requirements of **General Chapters <661.1> and <661.2> (and <1661>)**as referenced in General Chapter <659>.
- To make **General Chapter <661>**, as referenced in General Chapter <659>, **applicable until December 1, 2025**.
- Clarify in General Chapter <659> that early adoption of the requirements of <661.1>, <661.2> and <1661> is allowed by USP, and that packaging systems conforming to these requirements in advance of December 1, 2025 are considered by USP to be in conformance with the USP–NF.

The Version of <661> that will be enforceable until December 1, 2025 includes:

Tests and Specifications for:

- **Polyethylene Containers**
- **Polypropylene Containers**
- **Polyethylene Terephthalate Bottles and Polyethylene Terephthalate G Containers**

Tests include:

- **Identity**
- **Physicochemical Properties of a Water Extract**
  - **Non-volatile Residue**
  - **Residue on Ignition**
  - **Heavy Metals**
  - **Buffering Capacity**

USP <661> Monographs

Major Changes to <661.1> as Reflected in its Recently Published Revision

1. The chapter was reformatted so that all test methods and specifications are contained with each polymer section.
2. Text within the Introduction and Scope was edited to simplify and clarify.
3. The requirement for extractable elements testing was removed from this chapter. It is being left up to the material user to evaluate the need for extractable elements testing and, if such testing is necessary, to establish and justify the means by which testing is accomplished. Example of an extractable elements testing strategy is provided in *Evaluation of Plastic Packaging Systems for Pharmaceutical Use and their Materials of Construction with Respect to Their User Safety <1661>.*
4. For the testing of Phenolic Antioxidants under the Plastic Additive section for Cyclic Olefins, Polyethylene, and Polypropylene, the testing requirement for Plastic Additive 4 and 5 for Test B was removed. The testing of Plastic Additive 4 and 5 can be found under Test C.
5. No other testing requirement was added or removed.

<661.1> and Extractable Elements

Extractable elements may also **be relevant to** the **selection** of a **packaging** system's **materials of construction** and therefore a relevant aspect of material characterization. Materials of construction can vary widely in terms of their intentionally and unintentionally added elements and their potential use. Because of this, it is challenging to provide universally effective and efficient tests methodologies, lists of target elements and reporting requirements. **It is the material user's responsibility to evaluate the need for extractable elements testing and, if such testing is necessary, to establish and justify the means by which testing is accomplished, taking into account extraction conditions, target elements and reporting requirement. An example** of an extractable elements testing strategy **is provided in** Evaluation of Plastic Packaging Systems for Pharmaceutical Use and their Materials of Construction with Respect to Their User Safety **<1661>**.

Tests Required in <661.1>

Test Parameter	Oral and Topical Dosage Forms[a]	All Other Dosage Forms
Physicochemical		
UV Absorbance	X	X
Acidity/alkalinity	X	X
TOC	X	X
Extractable Elements	–[b]	–[b]
Plastic Additives	–[c]	X
Biological Reactivity[d]		
In Vitro per USP <87>	–	X

[a] For aqueous-based oral drug products that contain cosolvents (or if, for any reason, it may be expected to extract greater amounts of substances from plastic packaging components than water), additional extractables information may be needed to determine suitability. If additional information is required, perform Additives tests as directed in this table.

[b] As deemed necessary and appropriate by end-user. See ⟨1661⟩ for additional information.

[c] Provide appropriate reference to the Indirect Food Additive regulations in 21 CFR 174–186, specifically those addressing the purity criteria and limitations pertaining to use.

[d] Biological reactivity testing in support of plastic packaging materials used for final pharmaceutical product packaging/delivery systems (drugs and drug/device combination products) provide baseline information and will often not be sufficient to assess the final suitability for use expectations of regulatory authorities. Thus, it is important to work with the appropriate regulatory authority for guidance regarding a product specific application.

Tests Required in <661.2>

Testing Requirements for Packaging Systems per USP <661.2>			
Test Category	**Test**	**Testing Required?**	
		Oral & Topical Dosage[a]	**All Other Dosage Forms**
Physicochemical	UV Absorbance	X	X
	Acidity/Alkalinity	X[b]	X[b]
	TOC	X	X
	Appearance	X	X
Biological Reactivity[c]	USP <87>	---	X
Chemical Assessment	Extractables and/or leachables	X[d]	X[d]

[a] For aqueous-based oral drug products that contain cosolvents (or if, for any reason, the drug product is expected to extract greater amounts of substances from plastic packaging components than water), additional extractables information may be needed to determine suitability.

[b] Conduct the test for *Acidity* or *alkalinity* only when packaging systems are intended to hold a liquid product or a product that is dissolved in its container before use.

[c] Biological reactivity testing in support of plastic packaging components and systems used for final pharmaceutical product packaging/delivery systems (drugs and drug/device combination products) provide baseline information and will often not be sufficient to assess the final suitability for use expectations of regulatory authorities. Thus, it is important to work with the appropriate regulatory authority for guidance regarding a product specific application.

[d] Risk based testing approach.

Update on Timing for USP <661> Plastics Chapters

- November, 2019
  - Balloting (within USP) of the proposed comment-based revisions was successfully completed.
- March 1, 2020
  - Revised text becomes official in USP 43 – NF 38 Supplement 1
- December 1, 2025
  - Chapters fully enforceable

USP <665> and <1665> Update

<665> PLASTIC MATERIALS, COMPONENTS AND SYSTEMS USED IN THE MANUFACTURING OF PHARMACEUTICAL DRUG PRODUCTS AND BIOPHARMACEUTICAL DRUG SUBSTANCES AND PRODUCTS

<1665> CHARACTERIZATION OF PLASTIC MATERIALS, COMPONENTS AND SYSTEMS USED IN THE MANUFACTURING OF PHARMACEUTICAL DRUG PRODUCTS AND BIOPHARMACEUTICAL DRUG SUBSTANCES AND PRODUCTS

- March/April 2019
  - Proposed Revisions of both <665> and <1665> appeared in PF 45 (2)
- May 31, 2019
  - PF Comment period closed. Over 250 comments received on <665> and over 140 comments received on <1665> including detailed comments from the FDA.

USP <665> and <1665> Update

BASED ON THE NUMBER AND NATURE OF COMMENTS *MAJOR* CHANGES HAVE BEEN MADE TO BOTH <665> and <1665> including:

- The Scope was narrowed to include Components only. Material testing was removed from <665> and thus is not mandatory. However, material characterization was placed into <1665> as a recommended good practice to aid material selection. This essentially decouples <665> from <661.1>.
- The Purpose of <665> was changed from selection to qualification.
- Biological reactivity testing (e.g., USP <87> and <88>) requirements were re-visited.
- A proper home was found for the test methods and specifications for Cured Silicone Materials (and alignment of the text, tests and specifications with Chapter 3.1.9 in the European Pharmacopeia.
- Other, more focused and more tactical, changes were made.

Scope

<665> POLYMERIC COMPONENTS AND SYSTEMS USED IN THE MANUFACTURING OF PHARMACEUTICAL AND BIOPHARMACEUTICAL DRUG PRODUCTS

Scope: Items covered

- Drug Substances (with exclusions) and Drug Products
- (“Traditional”) Pharmaceuticals, “Small Molecule” Drug Products, Biopharmaceuticals and Vaccines
- Single-Use Systems and Multi-Use Systems

Scope

So what is this about Drug Substances?

Previously, <665> was applicable to drug products, drug substances (biopharmaceuticals), and active pharmaceutical ingredients (APIs. "traditional" pharmaceuticals). Currently, <665> recognizes that **APIs are generally highly purified and well-characterized substances which are highly unlikely to contain manufacturing equipment–related impurities** in them at levels sufficiently high to adversely affect the safety of the drug product. Thus **components used to manufacture APIs are no longer "in scope" for <665>**.

Scope

Auxiliary Items!?

Assorted polymeric auxiliary items, such as scoops, funnels, pipettes, graduated cylinders, weighing dishes, beakers, etc, may be used in manufacturing operations for the dispensing and transferring of ingredients.

- These auxiliary items contact these ingredients for relatively short periods of time.
- The transferred ingredients are typically solids.

Thus, auxiliary items pose little risk in terms transferring extractables to the process stream and are not within the Scope of this Chapter. Thus, testing of such items per 665 is neither necessary or required.


A Brief Introduction to a Revised <665> (1)

1. <665> speaks to the **characterization of components, enabling the proper qualification (and selection) of components** used in manufacturing operations.
2. **Materials of construction are no longer part of <665> (and therefore <665> is decoupled from <661.1>)**. Rather, the characterization of materials of construction, enabling the proper selection of materials used in manufacturing, will become a recommended practice, and not an enforceable requirement by placing the text around material characterization into <1665>.
3. **Components are characterized depending on the level of risk** associated with their application in a particular manufacturing operation.
4. **High risk components must be profiled for extractables** using a multi-solvent Standard Extraction Protocol (SEP) as provided in <665>.

Navigating through <1665>; Materials

All polymeric materials used to construct components and systems **should be tested, regardless of risk, as defined** in *Plastic Materials of Construction* **⟨661.1⟩**, *Table 2* as the results from these tests could facilitate the selection of safe and effective materials.

Suggested Chemical tests include:

- Identity
- Physicochemical Properties
- Extractable Metals (as necessary and appropriate at the discretion of the user)
- Polymer Additives

Suggested Biological Reactivity tests include:

- In vitro test for Cytotoxicity (USP <87>), at the discretion of the user

Navigating through <1665>; Materials

Polymeric materials of construction that are not specifically addressed in ⟨661.1⟩ are termed "**unaddressed materials**". An unaddressed material must be characterized in ways that are comparable to those used for the materials specified in ⟨661.1⟩:

- The unaddressed material of construction must be identified.
- The unaddressed material must be tested for:
  - Biocompatibility (as necessary and appropriate),
  - Physicochemical properties,
  - Additives,
  - Relevant extracted metals (as necessary and appropriate).

We need to get more materials into <661.1>!

Rubber elastomers are out of scope, to be addressed at a future date by <381>. A chapter on silicone elastomers is currently being developed (<668>).

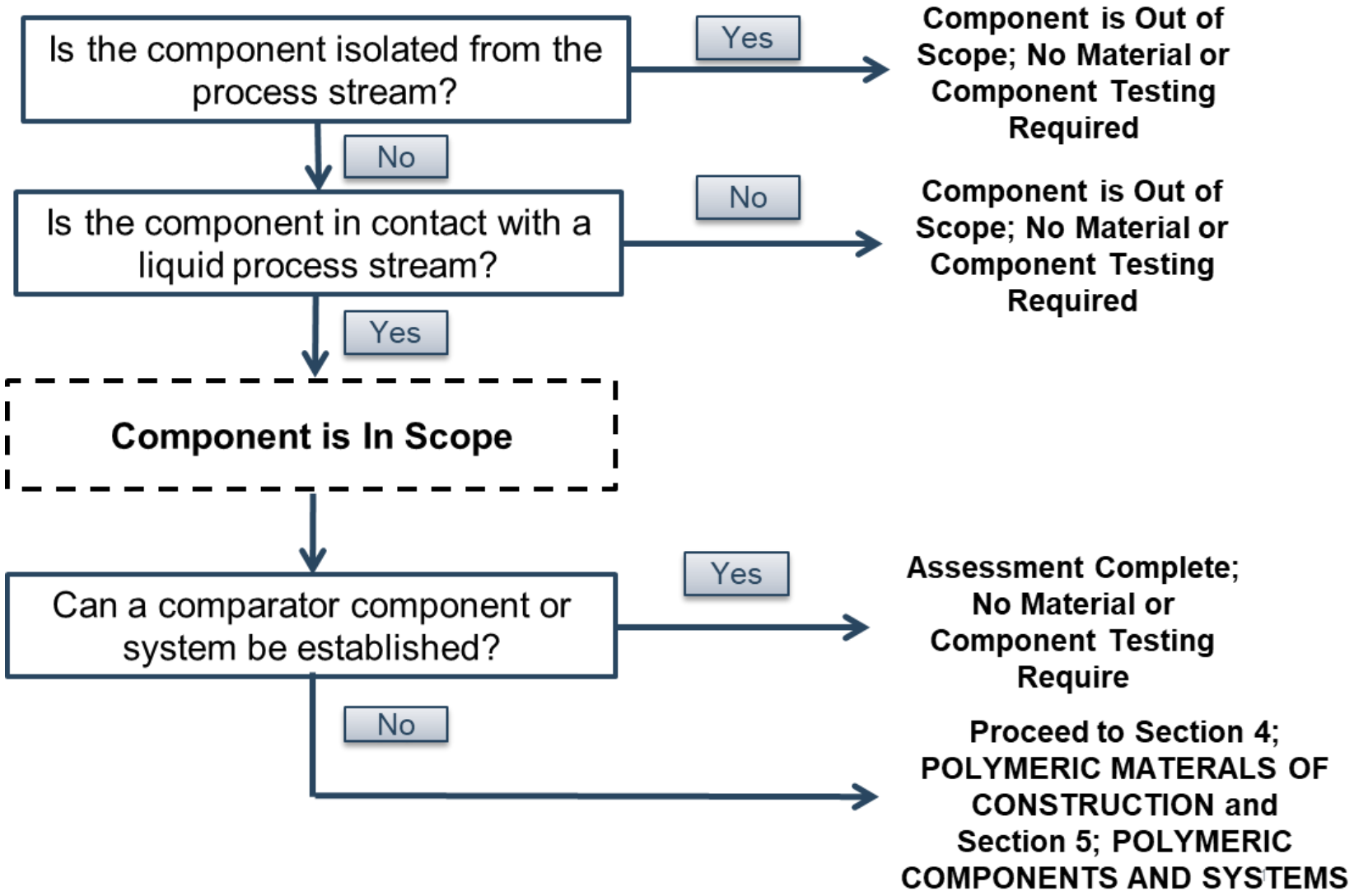
Navigating through <1665>; Materials

~~**If a component has been tested per this chapter and meets the specifications contained in this chapter, then the component's materials of construction are deemed to be compliant with this chapter without having been tested per ⟨661.1⟩.**~~

This text, which was regarded as a grandfathering clause to ensure that unnecessary material testing was not being performed, is no longer necessary as material testing in no longer required for qualification in <665> but is only suggested for selection in <1665>.

An escape clause is no longer necessary because there is nothing left to escape from.

Navigating through <665>; Components



Navigating through <665>; Frozen Storage

Considering the second bullet point, it is noted that a DS may be stored frozen in a container at some point in a manufacturing process, raising the question as to whether the container is within the scope of <665> (as a frozen DS is a solid). As such storage typically involves long storage times and 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.

Navigating through <665>

So what happened to the “grandfather clause”?

Previously, the <665> Flow Chart contained a step that considered whether the product being manufactured had secured regulatory approval. Manufacturing systems that produced such a registered product were deemed to be compliant with <665> without the testing specified in <665>, presumably because the drug product had been deemed “approvable” (and safe).

This exemption has been replaced by a “delayed implementation” strategy in which the document, although published, would not become official until some later date (e.g., beyond 2020).

“Early adoption” of <665> prior to it becoming official will be encouraged.

The Concept of Equivalence

Equivalence between a component and a comparator component is established if:

1. Their materials of construction are compositionally equivalent
2. Their materials of construction have been manufactured and processed (for example, sterilized) in equivalent manners
3. Their designs are equivalent
4. The functions they perform are equivalent
5. Their preparation for use (e.g., flushing) is performed in the same manner
6. Their processing during use is equivalent
7. Their conditions of use in the manufacturing processes are equivalent
8. They are used to manufacture an equivalent item (DS or DP) and the item is used in the same clinical manner, i.e., route of administration and dose

Although it is highly desirable that the equivalence in all 8 circumstances be exact, it may be the case that exact equivalence cannot be established but that essential equivalence could be established based on strong similarities between the component under consideration and 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.

The Concept of Risk and its Application to <665>

"The magnitude of testing required to establish that an item is safe should be directly proportional to the risk that the item could be unsafe"

The magnitude of testing required to establish that manufacturing equipment is safe for use depends on:

1. the likelihood that the manufacturing equipment is extracted by a process solution under typical manufacturing conditions,
2. the likelihood that an extracted substance would persist in the process stream and become incorporated in the drug product.

The greater the likelihood of either (1) or (2), **the greater the amount of testing required** for manufacturing components.

What the Risk Evaluation Accomplishes

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.

How is Risk Evaluation accomplished?

Via application of a Risk Evaluation Matrix.

The Risk Assessment Required in <665>

So what's happening to the Risk Evaluation Matrix that appeared in previous version of <1665>?

The Risk Evaluation Matrix that was in <1665> was going to be put into <665> so that <665> contained all the information required for its implementation. This action would have made use of the Risk Evaluation Matrix mandatory.

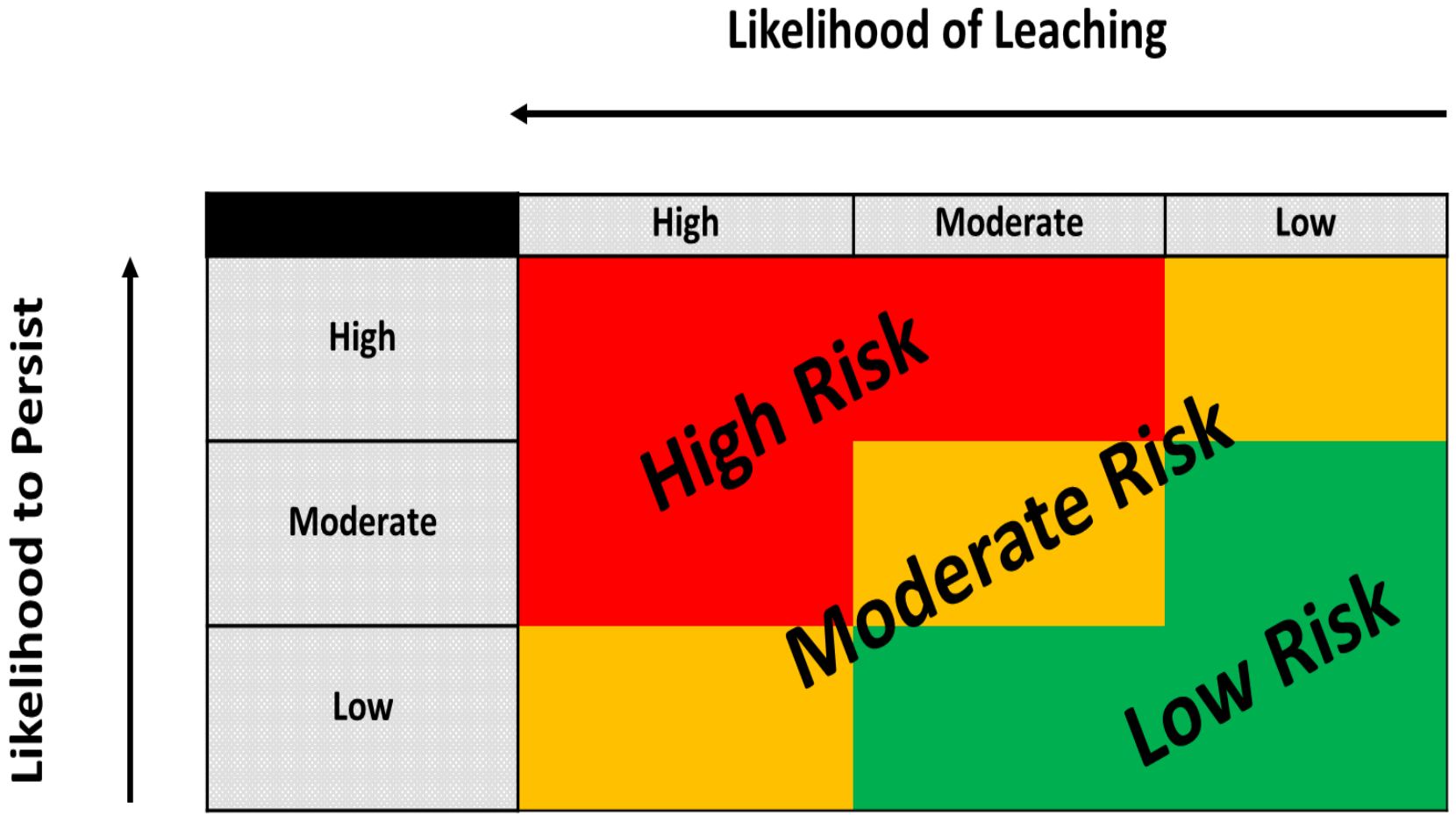
Industrial users of <665> pointed out:

- that many organizations had already developed their own Risk Evaluation Matrices,
- That it was unreasonable to expect these organizations to adopt a new Matrix that could produce a different outcome than their own Matrix.

Thus, the Risk Evaluation Matrix from <1665> will not be required by <665>. Rather, **it is the responsibility of the sponsors to establish and justify their own Matrices.**

The Risk Evaluation Diagram

Risk Evaluation Diagram Establishing the Risk that Process Equipment-related Leachables (PerLs) could be Present in the Final Drug Product at Levels Sufficiently High that they could Adversely Affect Patient Safety. The level of risk is associated with the nature and amount of testing that is required per <665>.



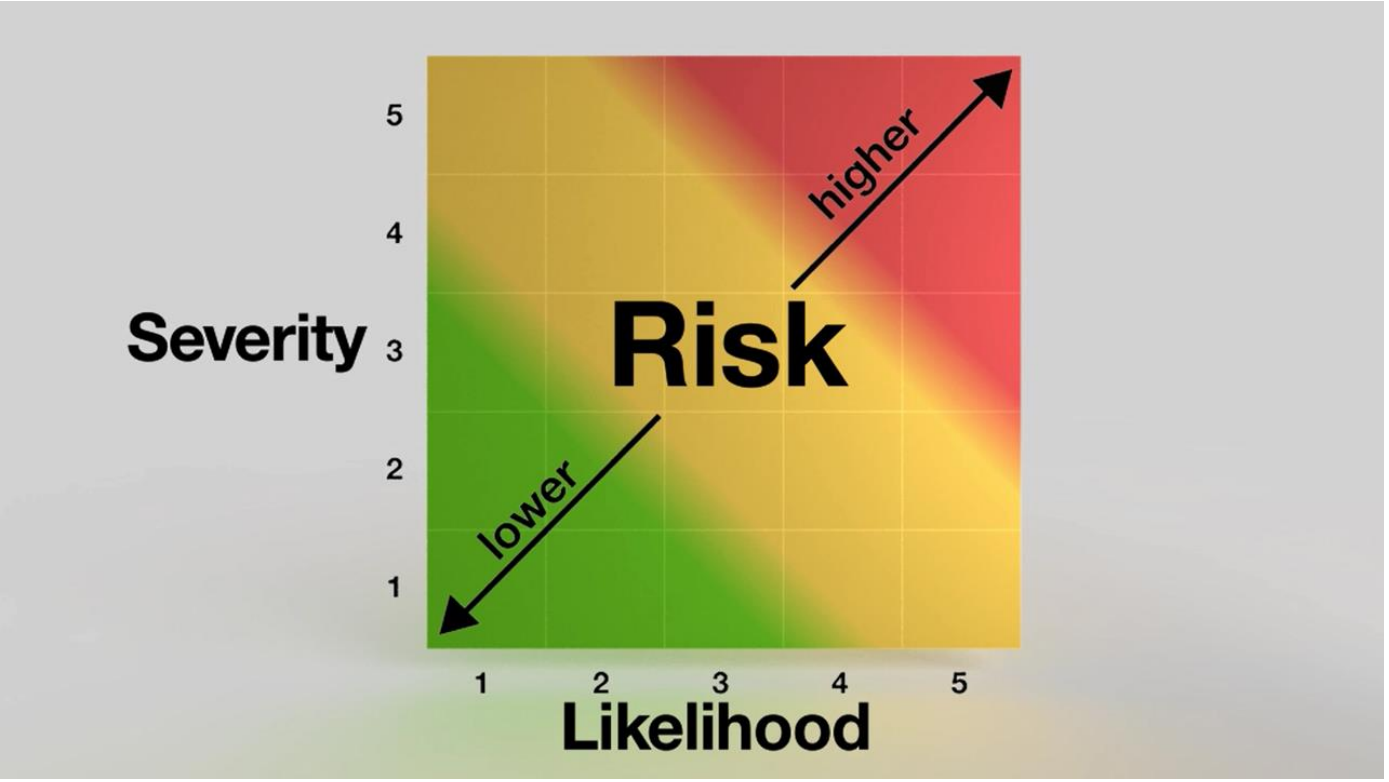
Requirements for a Risk Evaluation Matrix per <665>

The risk evaluation matrix must address the following considerations:

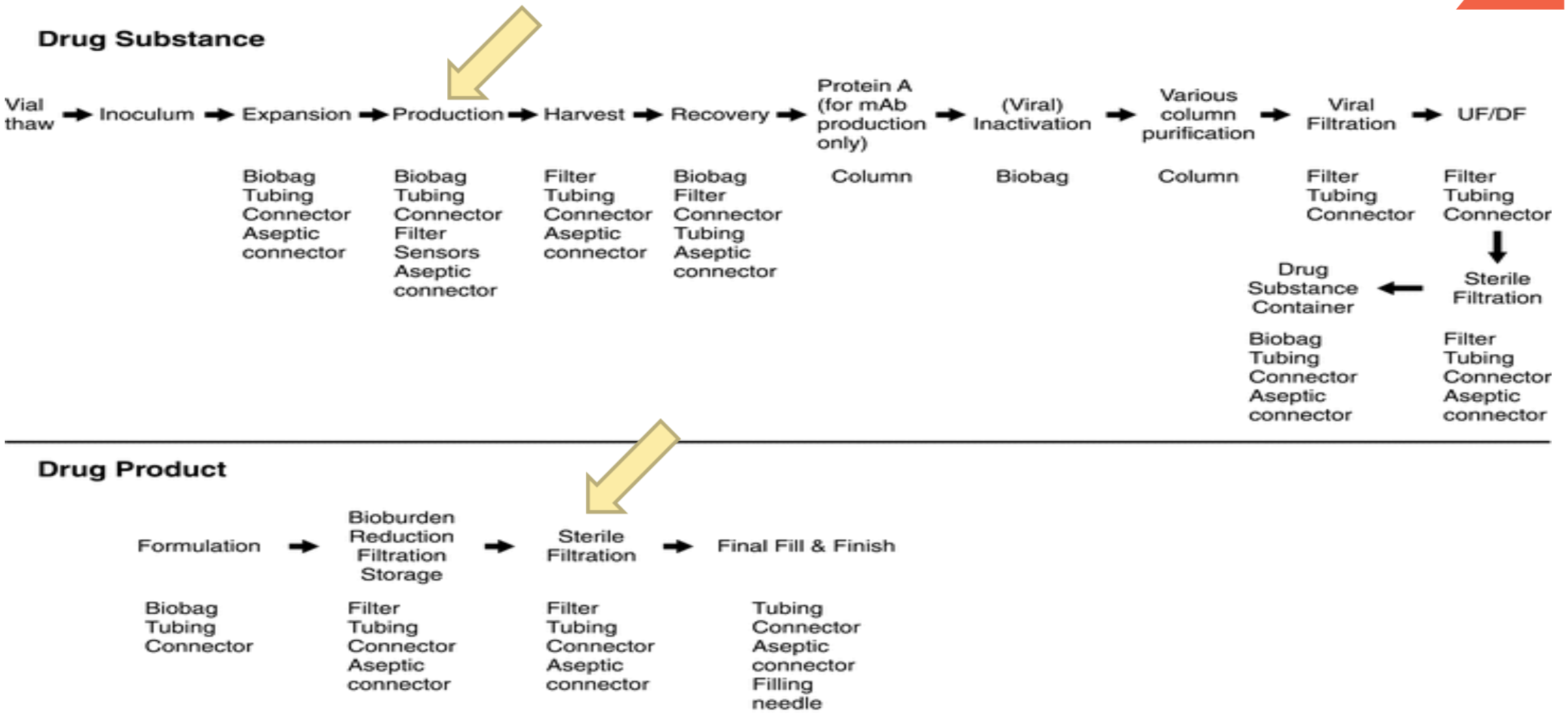
1. The material's or component's "propensity to be leached",
2. The process stream's "leaching power",
3. The "driving force" for leaching (contact conditions),
4. Elimination or dilution of PERLs from the process stream by upstream process steps,
5. The inherent safety risk associated with the manufactured drug product.

Requirements for a Risk Evaluation Matrix per <665>

The outcome of any risk assessment process (including the use of a Risk Evaluation Matrix) must be such that the circumstance being assessed is assigned to one of three risk categories, low risk, moderate risk and high risk.



Expected Outcomes of a Risk Assessment



Expected Outcomes of a Risk Assessment

Example 1: Biobag used in Production

1. Short term, ambient temperature contact
2. Aqueous, near-neutral pH contact solutions
3. Generally safe materials of construction
4. Early use in process means there are process steps where extractable can be cleared from the process stream

Expected Outcome of the Risk Assessment: Low Risk

Example 2: Sterilizing Filter Used Before Final Fill

1. Short term, ambient temperature contact
2. DP contains solubilizing agent
3. Sterilization by gamma irradiation
4. Late use in process means there are no later process steps clear extractables from the process stream

Expected Outcome of the Risk Assessment: High Risk

Testing of Components Consistent with the Level of Risk

Table 1. Guidelines for Application of Component Tests as Established by Risk

Risk Level	Current Biological Reactivity Tests[1]	Chemical Assessment	Extraction Solutions for Chemical Testing	Chemical Testing of Extracts
Low	No Testing	Partial Chemical Assessment	*C3*	• Non Volatile Residue • UV absorbance • Delta pH
Moderate	*Biological Reactivity Tests, In Vitro* <87>[a] • *Cytotoxicity*	Limited Chemical Assessment	*C3*	• Organic extractables profiling of solution C3
High	*Biological Reactivity Tests, In Vitro* <87>[a] • *Cytotoxicity*	Full Chemical Assessment	*C1, C2, C3*	• Organic extractables profiling of all three solutions • Extracted elements (as necessary and appropriate)[b]

[a] Biological reactivity testing in support of plastic manufacturing system components provides baseline information and will often not be sufficient to assess the final suitability for use expectations of regulatory authorities. Thus, it is important to work with the appropriate regulatory authority for guidance regarding a product specific application.

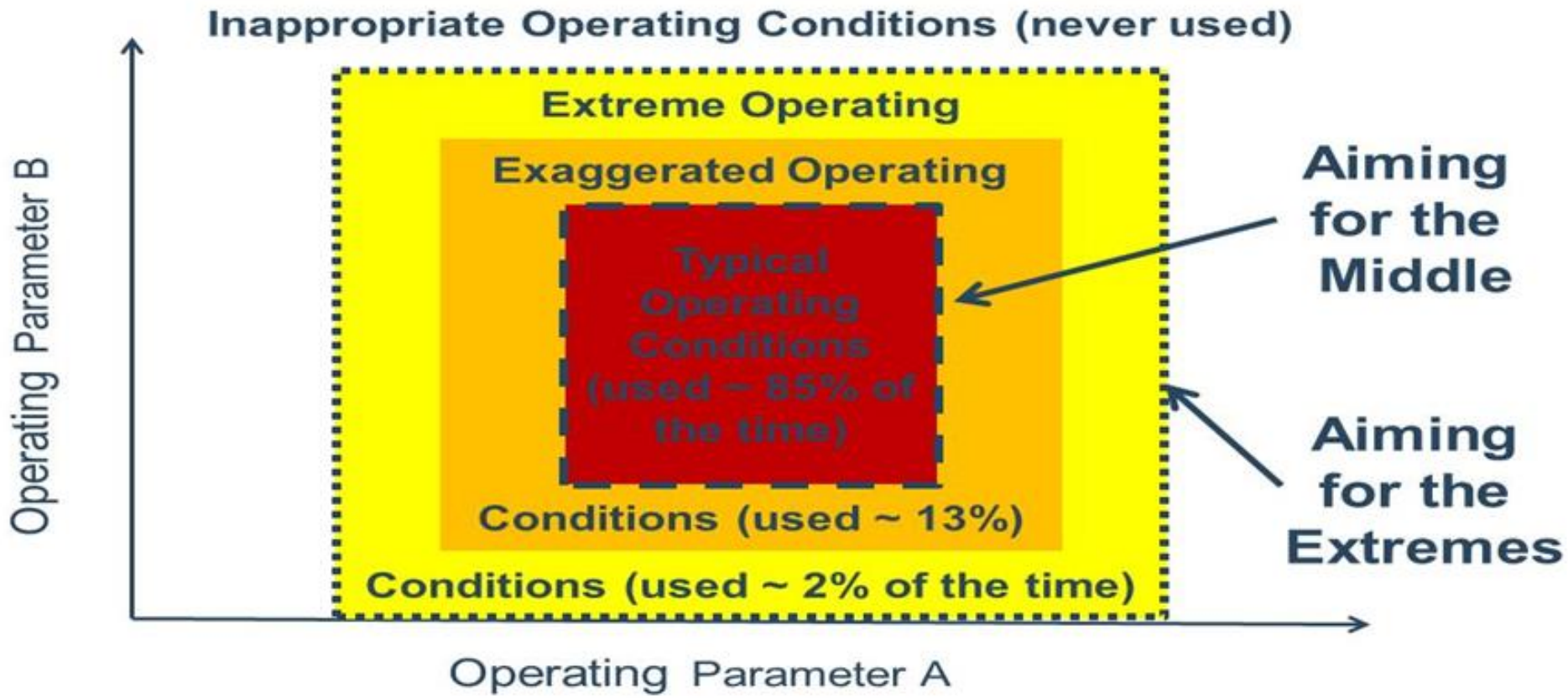
[b] The relevance of extractable elements testing should be considered by the component's potential user. Should such testing be deemed to be necessary, it is the user's responsibility to establish and justify the means by which testing is accomplished, taking into account extraction conditions, target elements, and reporting requirements.

Application of the Standard Extraction Protocol, SEP

The Standard Extraction Protocol (SEP) is used to characterize **high risk** manufacturing components or systems for extractables.

Focus of the SEP

The Standard Extraction Protocol (SEP) “aims for the middle”, seeking to represent those conditions most commonly encountered in pharmaceutical manufacturing.



The <665> SEP Extraction Solvents (1)

Standard Extraction Protocol for Components or Systems Designated as High Risk

- **Extraction Solvents**
  - **Solution C1, Acidic Extraction, pH 3**
  - **Solution C2, Basic Extraction, pH 10**
  - **Solution C3, Organic Extraction, 1/1 (v/v) Ethanol/water**

Concept: Extractables profiles obtained with these three solvents will capture those extractables that are present in the most commonly encountered process streams and will provide an estimate of the extractable's typical accumulation levels in those process streams.

The <665> SEP Extraction Solvents (2):

Considering Additional Extraction Solvents

1. Any additional extraction solvent should provide information in addition to information provided by the adopted solvents (different extractables and/or higher levels of extractables).

2. Any additional extraction solvent should be analytically expedient (meaning that it should be able to be screened for organic extractables down to AET levels and slightly lower).

The <665> SEP Extraction Solvents (3)

What about Water?

- Water provides no additional information that is not already provided by the pH extreme solvents.

What about 5 M NaCl?

- 5 M NaCl is the weakest extraction solvent (for organics) and provides no additional information that is not already provided by the pH extreme solvents.
- 5 M NaCl is an analytically challenging solution.

What about 1% Polysorbate 80?

- 50% Ethanol may be an appropriate simulant for 1% PS80.
- 1% PS80 is an **extremely** challenging solution to analyze.

Thus, the USP sees no compelling reason to include these solvents in its SEP.

The <665> SEP Extraction Solvents (4)

What about low pH?

- Data suggests that pH 3 salt solution and 0.1% phosphoric acid produce similar extractables profiles.
- Phosphate matrix produces minor analytical challenges.
- **USP has adopted a statement that makes 0.1% phosphoric acid and pH 3 salt solutions (including its own Solution C1) "interchangeable".**

If an extraction has been performed with 0.1% phosphoric acid, then the extractables profile generated in that solvent fulfills the USP requirement for generating an extractables profile in Solution C1.

The <665> SEP Extraction Solvents (5)

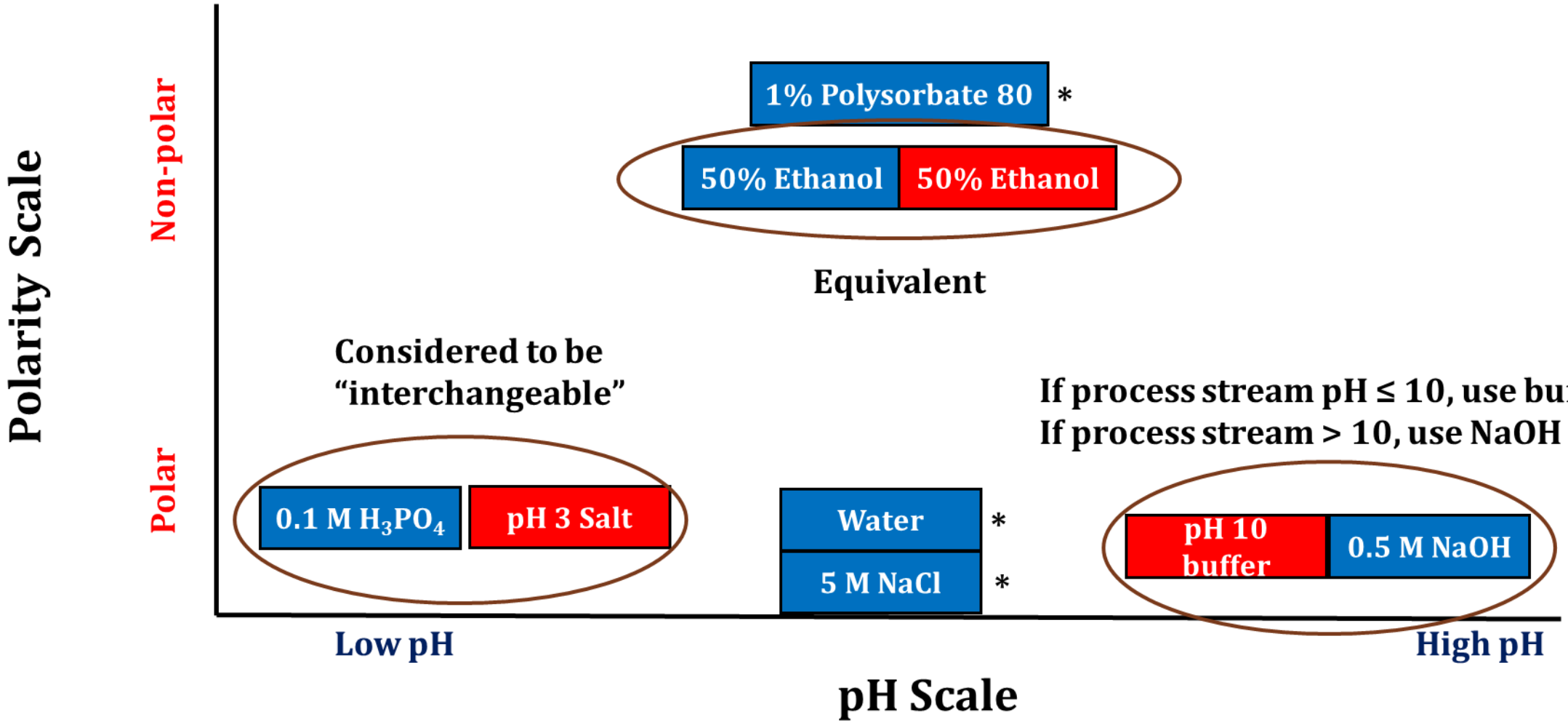
What about high pH?

USP considers the pH 10 extraction solvent to be consistent with the intent of the SEP and thus it is the required high pH solvent. However, if the pH of a contact solution exceeds 10 then the pH 10 solvent may be replaced with the contact solution or an appropriate higher pH simulant (with justification).

If an extraction has been performed with 0.5 M NaOH, then the extractables profile generated in that solvent could fulfill the USP requirement for generating an extractables profile in Solution C2, provided the pH of the contact solution is greater than 10 and an adequate justification is provided.

The <665> SEP Extraction Solvents (6)

Where did we end up when the dust cleared?



Red = USP Conditions

Blue = BPOG Conditions

* Additional solvents to be used as desired

SEP Extraction Temperature and Durations

Component	Extraction Solvent	Extraction Conditions				
		At 25°C	At 40°C			
		≤ 30 minutes	1 Day	7 Days	21 Days	70 Days
Storage Bags	All	X	X		X	X
Mixing Bags	All	X	X		X	X
Bioreactor Bags	All	X	X		X	X
Tubing	All	X	X		X	X
Tubing Connector/Disconnector	All	X	X		X	
Aseptic Connector/Disconnector	All	X	X	X		
Sensor/Valve	All	X	X		X	
Molded Parts of Mixer	All	X	X		X	
Gasket, O-ring (elastomers)	All	X	X			
Sterilizing Filters	All	X	X			
Process Filters	All	X	X			
Polymer Pump surfaces	All	X	X			
Tangential Flow Filtration Cassettes	All	X	X		X	
Chromatography Columns	All	X	X	X		
Filling Needle	All	X	X	X		
Stir bars	All					

Red = USP Conditions

X = BPOG Conditions

Additional Extraction Details

- Extractions performed in the SEP are dynamic, accomplished by either agitation of the test system or circulation of the extraction solvent.
- Extractions are based on a defined contact surface area to extraction solution volume ratio.
- Extraction blanks, which are portion of the extracting solutions that are not contacted by the test article, must be generated and tested in order to differentiate extracted substances from analytical artifacts.
- Extraction instructions are provided for the major component types.

Alternate Extractions

Alternate extractions versus the Standard Extraction Protocol are allowed (and encouraged) when:

1. The item being extracted is incompatible with the conditions of the Standard Extraction Protocol:

    - Conditions specified in the SEP cannot be satisfied (e.g., the surface area to solution volume ratio cannot be achieved).
    - Conditions specified in the SEP lead to a situation where requirements for extraction cannot be met (e.g. the extraction conditions produce greater then 20% extraction solvent loss)
    - Conditions specified in the SEP lead to a clearly compromised extract (e.g., excessive cloudiness or coloration, particulate matter, etc.).
    - Conditions specified in the SEP lead to a clearly compromised test article (e.g., test article dissolved, distorted and otherwise rendered non-functional).

2. The item's conditions of use in the manufacturing are more "extreme" than the extraction conditions of the SEP:

    - The pH of the process stream falls outside the range of 3 to 10.
    - The combination of temperature and duration of contact between the item and the process stream is more "harsh" then the same combination specified in the SEP.

Alternate Extractions

What are the requirements for performing an Alternate Extraction?

- In circumstances of an incompatible extraction process, an alternate extraction process must be established and justified with respect to its appropriateness for accelerating and simulating the component's conditions of use. This alternate extraction process is then used in place of the process established in the Standard Extraction Protocol.
- In 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. The alternate extraction conditions must be justified.
- In any event, the extract resulting from an Alternate Extraction must be analytically expedient, , meaning that the extract must be analytically compatible with the analytical techniques used for organic and inorganic extractables and profiling.

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. 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 worst case data.

Acceptance Criteria, Low Risk

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

- The tests specified for low risk components (UV absorbance, NVR, delta pH) have been performed
- The test results have been reviewed in the context of the validity of the risk classification.

If the component is assessed as being low risk but the results of one or more of the general chemistry tests are “high”, then it is possible that the low risk classification was in error and that a higher risk classification is justified.

The concept of a 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.

Acceptance Criteria, Moderate and High Risk

1. The organic extractables profile is interpreted by establishing the risk posed by the use of the plastic components and systems via the toxicological assessment of the extractables data. The toxicological assessment should:

   - be performed for each individual relevant component's or system's organic extractable
   - be performed considering the clinical use of the DS or DP being manufactured.
   - demonstrate that the user risk associated with each individual extractable is acceptable and that the probable risk posed by all extractables is within acceptable parameters.

2. Establishing and justifying the acceptable parameters used to assess the impact is the responsibility of the applicant who secures and owns the regulatory approval of a manufacturing system or the manufactured DP.

   - Such acceptable parameters must be based on and derived from the sound application of established principles of toxicological assessment.
   - Alternative acceptance criteria may be appropriate in justified circumstances, subject to agreement by an appropriate regulatory authority.

Alternate Qualification Procedures

Alternative chemical qualification procedures and acceptance criteria may be appropriate in justified circumstances, subject to agreement by an appropriate regulatory authority. **Chapters <1663> and <1664>, applicable to pharmaceutical packaging/delivery systems, 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.**

The Future of <665> and <1665>

1. Both <665> and <1665> will be sufficiently changed that they will need to be re-published in a future edition of the *Pharmacopeial Forum,* thus initiating a record fourth round of public review and comment. As this is necessary, it will delay these monograph's inclusion in the USP.

2. While it will likely be impossible to address all comments to the satisfaction of all stakeholders, due in part to the differing and conflicting opinions expressed by stakeholders, every effort will be (and has been) made to find that compromise which:

    - Protects patients,
    - Ensures the quality of marketed drug products,
    - Leverages sound principles of good science, practically applied,
    - Is most widely applicable to the more commonly encountered pharmaceutical manufacturing conditions.

WHEN WILL <665> AND <1665> BECOME OFFICIAL?

"My guess is no better than anyone else's at this point (but official no sooner than 2021 is looking like a good bet). Once it is official, there will likely be a delayed implementation. "

Questions

Empowering a healthy tomorrow