United States Pharmacopeia:

Update for ON USP CHAPTERS FOR MATERIALS, COMPONENTS AND SYSTEMS USED 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 Used in Injectable Pharmaceutical Packaging/Delivery Systems.*

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

3. 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 is proposing the following revisions which will update and expand the scope of the current chapter.

- **<381> ELASTOMERIC COMPONENTS USED IN INJECTABLE PHARMACEUTICAL PACKAGING/DELIVERY SYSTEMS.**
- **<1381> ELASTOMERIC EVALUATION OF ELASTOMERIC COMPONENTS USED IN PHARMACEUTICAL PACKAGING/DELIVERY SYSTEMS.**
- **⟨382⟩ ELASTOMERIC CLOSURE FUNCTIONALITY IN INJECTABLE PHARMACEUTICAL PACKAGING/DELIVERY SYSTEMS.**
- **⟨1382⟩ ASSESSMENT OF ELASTOMERIC CLOSURE FUNCTIONALITY IN INJECTABLE PHARMACEUTICAL PACKAGING/DELIVERY SYSTEMS.**

Modifications to USP <381> (1)

1.Change the title to “Elastomeric Components Used 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 injection 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⟩ testing and replace with a modern method for extractable element determination. This modification has been put on hold pending further scientific review. However, a validated method is described in <1381>.

5.Move functionality tests and assessment to a new chapter <382>.

6.Develop a new informational chapter, Elastomeric Evaluation of Elastomeric Components Used in Pharmaceutical Packaging/Delivery Systems ⟨1381⟩, that will 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

5. **GLOSSARY**

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 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 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.

USP <661.1> Plastic Materials of Construction

Major Changes to <661.1> versus its Currently Published Version

1. The chapter has been reformatted so that all test methods and specifications are contained with each polymer section.
2. Text within the Introduction and Scope has been edited to simplify and clarify.
3. The requirement for extractable elements testing is being 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 is being removed. The testing of Plastic Additive 4 and 5 can be found under Test C.
5. No other testing requirement is being 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	All Other Dosage Forms
Physicochemical		
UV Absorbance	X	X
Acidity/alkalinity	X	X
TOC	X	X
Extractable Elements	–[b]	–[b]
Plastic Additives	–[a]	X
Biological Reactivity		
In Vitro per USP <87>	–	X

[a] 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

[b] As deemed necessary and appropriate by end-user.

Update on Timing for USP Plastics Chapters

- October 28, 2018
  - Notice of intent to Revise is posted on USP Website
- January 1, 2019
  - Pre-Posting of Chapters on USP Website
- March/April 2019
  - Proposed Revision appear in PF 45 (2)
- May 31, 2019
  - PF Comment period closes
- October 2019
  - Balloting of proposed revisions
- August 1, 2020
  - Proposed 45 (2) revisions become official
- December 1, 2025
  - Chapters fully enforcable

<665>; Manufacturing Items, Round 2 Comments

1. The use of grandfathering to deal with existing products is not regulatorily viable (aka <661.1> and <661.2>) and must be replaced by delayed implementation.
2. As a standard, <665> must be self-sufficient. Thus, portions of <665> and <1665> will have to be exchanged.
3. Should the Risk Evaluation Matrix be mandatory? Industry would like the flexibility to use Matrices they have developed and currently use.
4. Does the document apply to both drug substances and drug products?
5. Should the standard address both materials of construction and components?

<665>; Manufacturing Items, Round 2 Comments

6. What about the alignment of the USP Standard Extraction Protocol and the BPOG protocol? Single use component vendors have already performed BPOG testing and consider USP to be additional cost and unnecessary work that serves no purpose.
7. How should elemental impurities be addressed?
8. How should materials that are not specified in either <661.1> or <665> be handled? <661.1> is deficient in materials that are commonly used in manufacturing.
9. Does <665> cover selection, qualification or both?
10. How does <665> handle <87> and <88> in the context of a risk-based approach?

General Themes in 2nd Round <665> Comments

11. What specific chemical tests should be performed in the context of the risk classes (lower risk, moderate risk and higher risk).

12. There is general “moaning and groaning” about the extractions specified in the Standard Extraction Protocol (don’t like the durations, don’t like the surface area to solution volume, don’t like dynamic extractions, etc.).

13. Why do we need a standard (and why can’t we do things any way we want to so long as we can secure regulatory approvals)?

14. **What will the FDA say?**

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 ingredients.

- **These auxiliary items contact these ingredients for relatively short periods of time.**
- **The transferred ingredients may be solids.**

Thus, auxiliary items poses little risk in terms of the transfer of extractables to the process stream and are not within the Scope of this Chapter and testing of such items per 665 is not required.


A Brief Introduction to <665> (1)

1. <665> speaks to the **characterization of materials of construction, enabling the selection of proper materials** used in manufacturing components, and to the **characterization of components, enabling the proper selection of components** used in manufacturing operations.
2. <665> **does not speak to the qualification** of materials, components or systems, **although testing performed for the purpose of selection may be relevant to qualification**.
3. **Materials of construction must** be tested consistent with, and **meet the requirements of, <661.1>**.

A Brief Introduction to <665> (2)

4. **Components are further characterized depending on the level of risk** associated with their application in a particular manufacturing operation. USP <1665>, which is essentially a "user's manual for <665>, describes a **Risk Evaluation Process** whose purpose is to classify components and their associated conditions of use into three risk categories.
5. **High risk components must be profiled** for extractables **using a Standard Extraction Protocol (SEP)** as provided in <665>.

Navigating through <665>; Materials

All polymeric materials used to construct components and systems **must, regardless of risk, be tested as defined** in *Plastic Materials of Construction* **⟨661.1⟩**, *Table 2*:

- Identity
- Physicochemical Properties
- Extractable Metals (as necessary and appropriate)
- Polymer Additives

Required Biological Reactivity tests include:

- In vitro test for Cytotoxicity (USP <87>)
- In vivo tests for Systemic Injection and Intracutaneous (USP <88>)

Note: Materials that do not meet the requirements of <87> are not qualified for use in manufacturing components or systems and may not proceed to testing by <88>.

Navigating through <665>; 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,
  - Physicochemical properties,
  - Additives,
  - Relevant extracted metals (as necessary and appropriate).

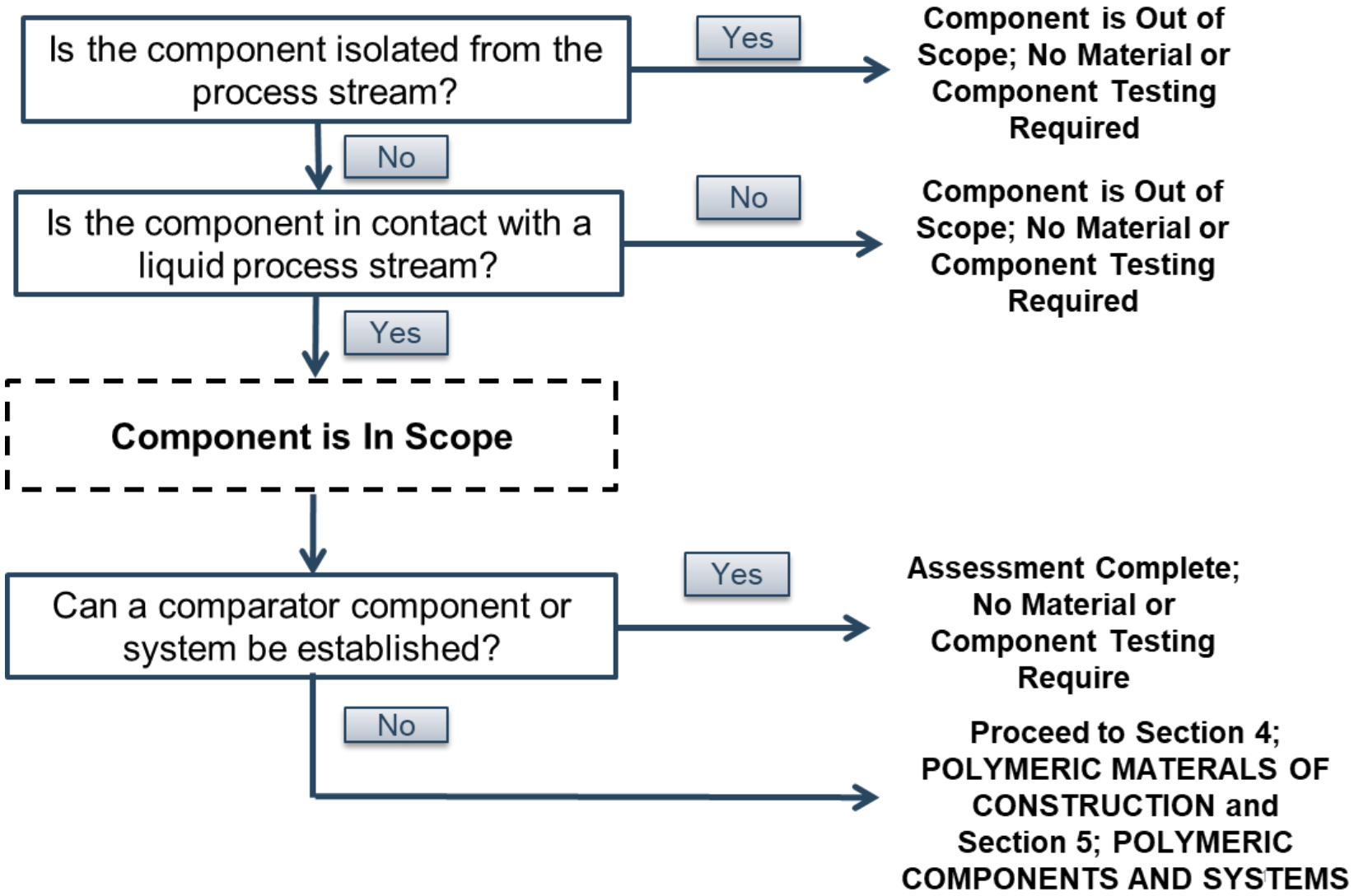
We need to get more materials into <661.1>!

Elastomers are out of scope, to be addressed at a future date by <381>.

Navigating through <665>; 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⟩.

Navigating through <665>; Components



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 is encouraged.

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 materials and 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:

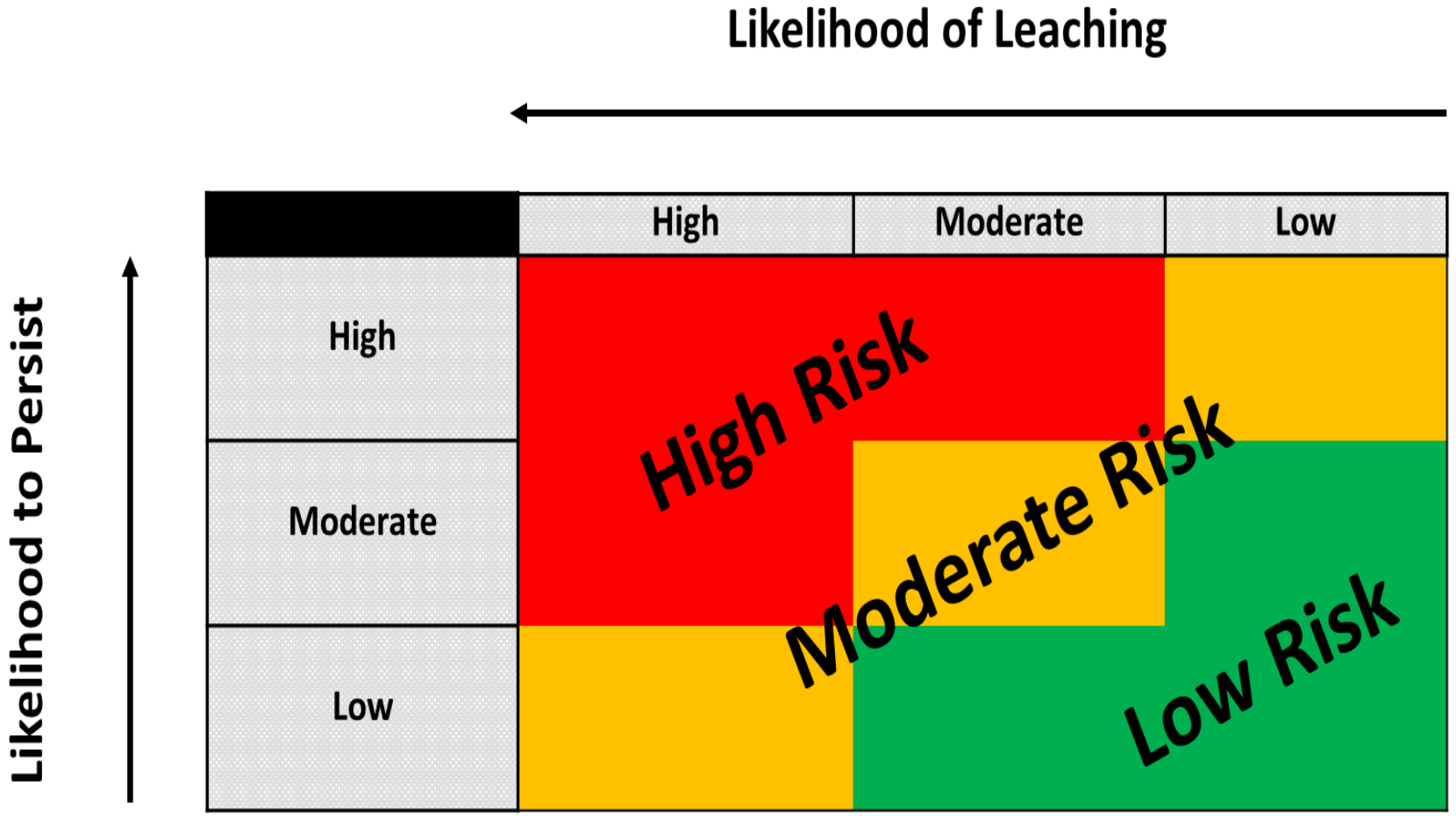
(a) that many organizations had already developed their own Risk Evaluation Matrices,

(b) 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 appear in <665>. Rather, **it is the responsibility of the sponsor 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>.



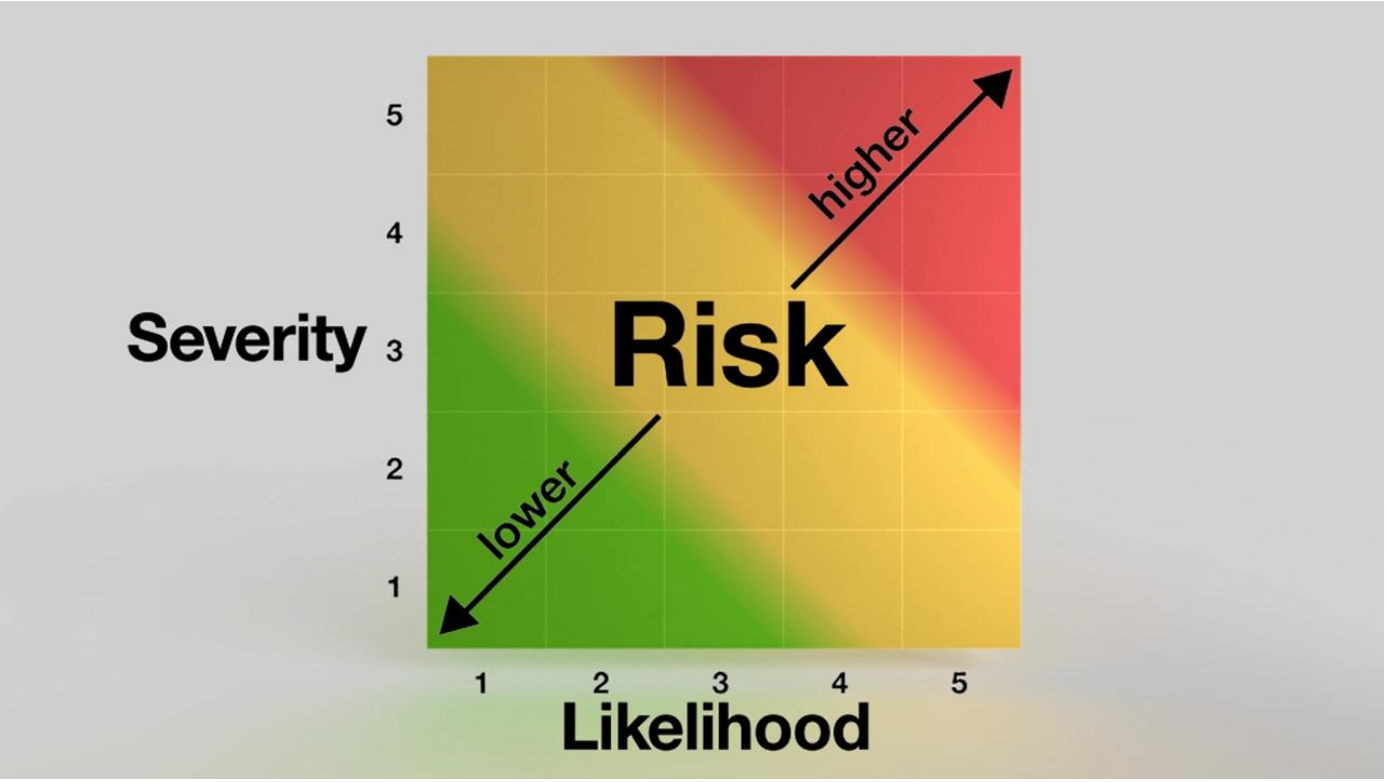
Requirements for a Risk Evaluation Matrix per <665>

The risk evaluation matrix must address the following considerations:

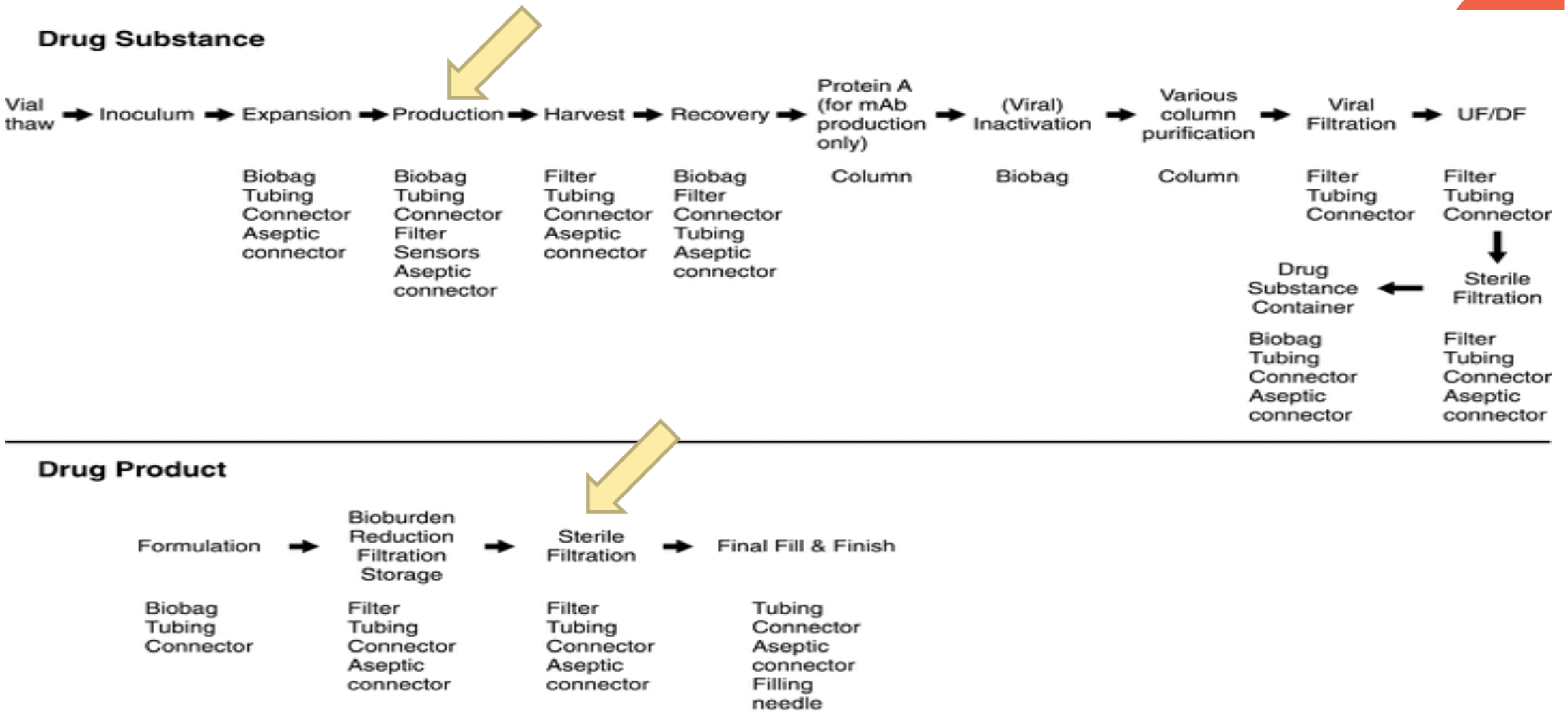
1. The material's or component's "propensity to be leached",
2. The process stream's "leaching power",
3. The "driving force" for leaching (contact conditions),
4. Elimination or dilution of PERLs from the process stream by upstream process steps,
5. The inherent safety risk associated with the manufactured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



Example 1: Biobag used in Production

Manufacturing Conditions of Contact:

1. Contact Duration = 72 hours
2. Contact Temperature = Ambient
3. Process Fluid= pH 6 buffer
4. Materials of Construction = multiple materials, total additives between 0.1% and 1%

Expected Outcome of the Risk Assessment:

Given the relatively “gentle” conditions of contact and the circumstance that the bag is used very early in the manufacturing process (increasing the likelihood of clearance and/or dilution), the expected outcome of the Risk Assessment is:

Low Risk

Example 2: Sterilizing Filter Used Before Final Fill

Manufacturing Conditions of Contact:

1. Contact Duration = 40 hours
2. Contact Temperature = Ambient
3. Process Fluid = drug product formulation contains 1% of a “solubilizing agent”
4. Materials of Construction = multiple materials, total additives > 1%

Expected Outcome of the Risk Assessment:

Given the relatively more “harsh” conditions of contact and the circumstance that the filter is used very late in the manufacturing process (increasing the likelihood that extractables will not be cleared), the expected outcome of the Risk Assessment is:

High Risk

Testing of Components Consistent with the Level of Risk

Table 2. Testing for Components as Established by Risk

Risk Level	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> • *Cytotoxicity*	Limited Chemical Assessment	*C3*	• Low Risk tests • Organic extractables profiling
High	*Biological Reactivity Tests, In Vitro* <87> • *Cytotoxicity* *Biological Reactivity Tests, In Vivo* <88> • *Systemic Injection* • *Intracutaneous*	Full Chemical Assessment	*C1, C2, C3*	• Low Risk tests (performed on *C3*) • Organic extractables profiling • Extracted elements (as necessary and appropriate)

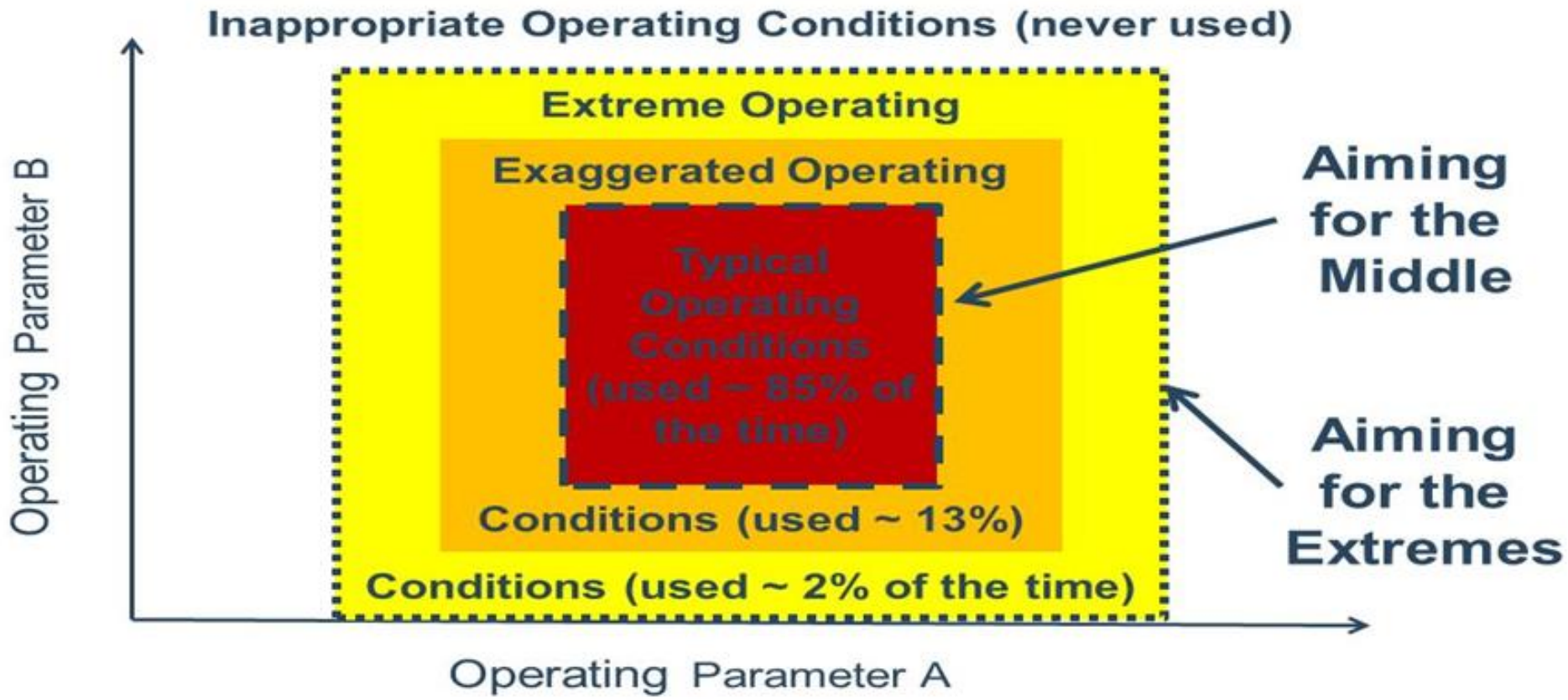
Note: [1]Components that do not meet the requirements of <87> are not qualified for use in manufacturing systems and may not proceed to testing by <88>.

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.



Is/Is Not Diagram for SEP

Aspect	Is	Is Not
Application	Components (systems)	Materials of Construction
	High Risk	Low or Moderate Risk
Purpose	Component Selection[1]	Component Qualification[1]
Scope	Hazard Identification	Risk Assessment
Focus	"Aim for the Middle" (most commonly encountered)	"Aim for the Extreme" (most extreme conditions possible)
Objective	Generate Useful Information	Generate Worst Case Information

Note: (1) Under certain circumstances, information for selection may be appropriate as information for qualification.

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.

2. Any additional extraction solvent should be analytically expedient.

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)

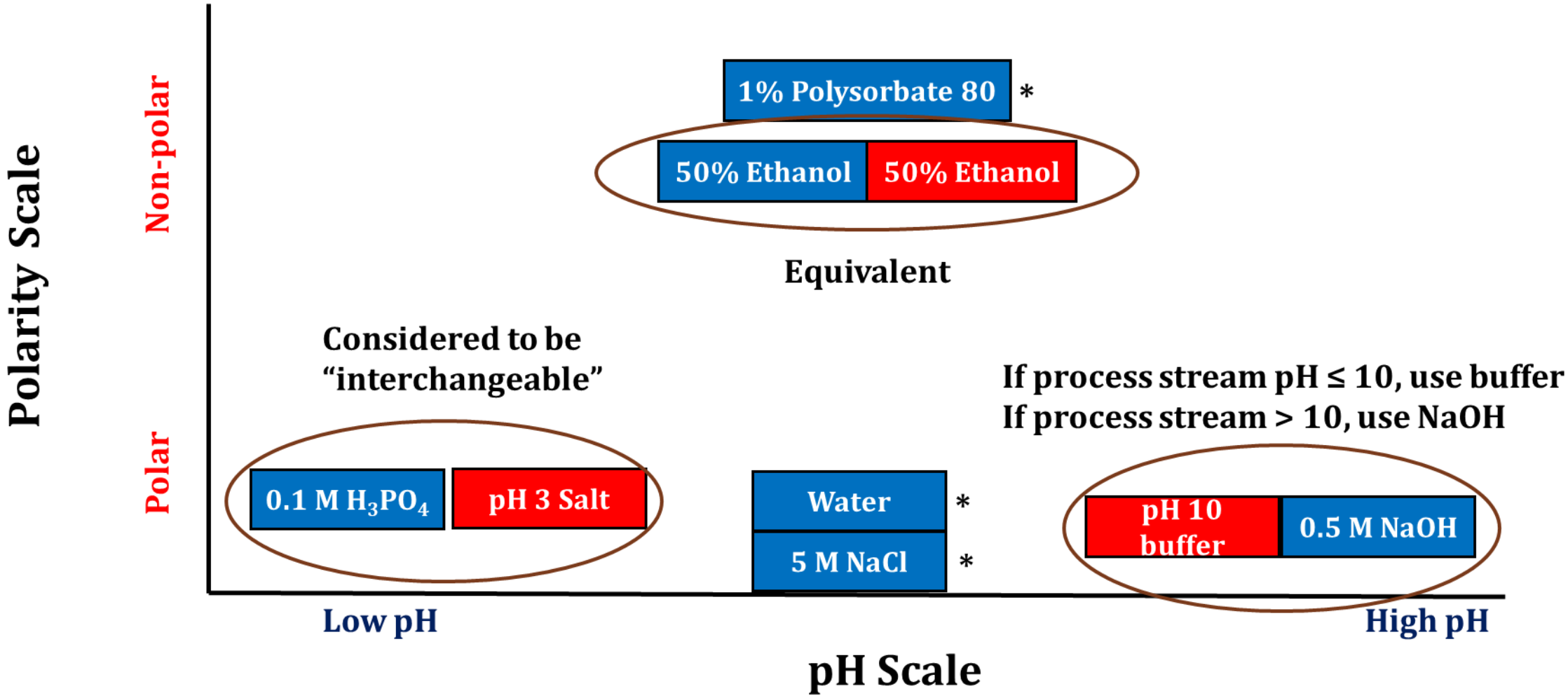
What about high pH?

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.

The Future of <665> and <1665>

Possible Outcomes of the Revision Process

1. Both <665> and <1665> will be sufficiently changed that they will be re-published in a future edition of the *Pharmacopeial Forum (March, 2019)*, thus initiating a third round of public review and comment.

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 then anyone else’s at this point (but enforceable in 2025 is looking to be the best bet).”

Questions

Empowering a healthy tomorrow