United States Pharmacopeia:

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

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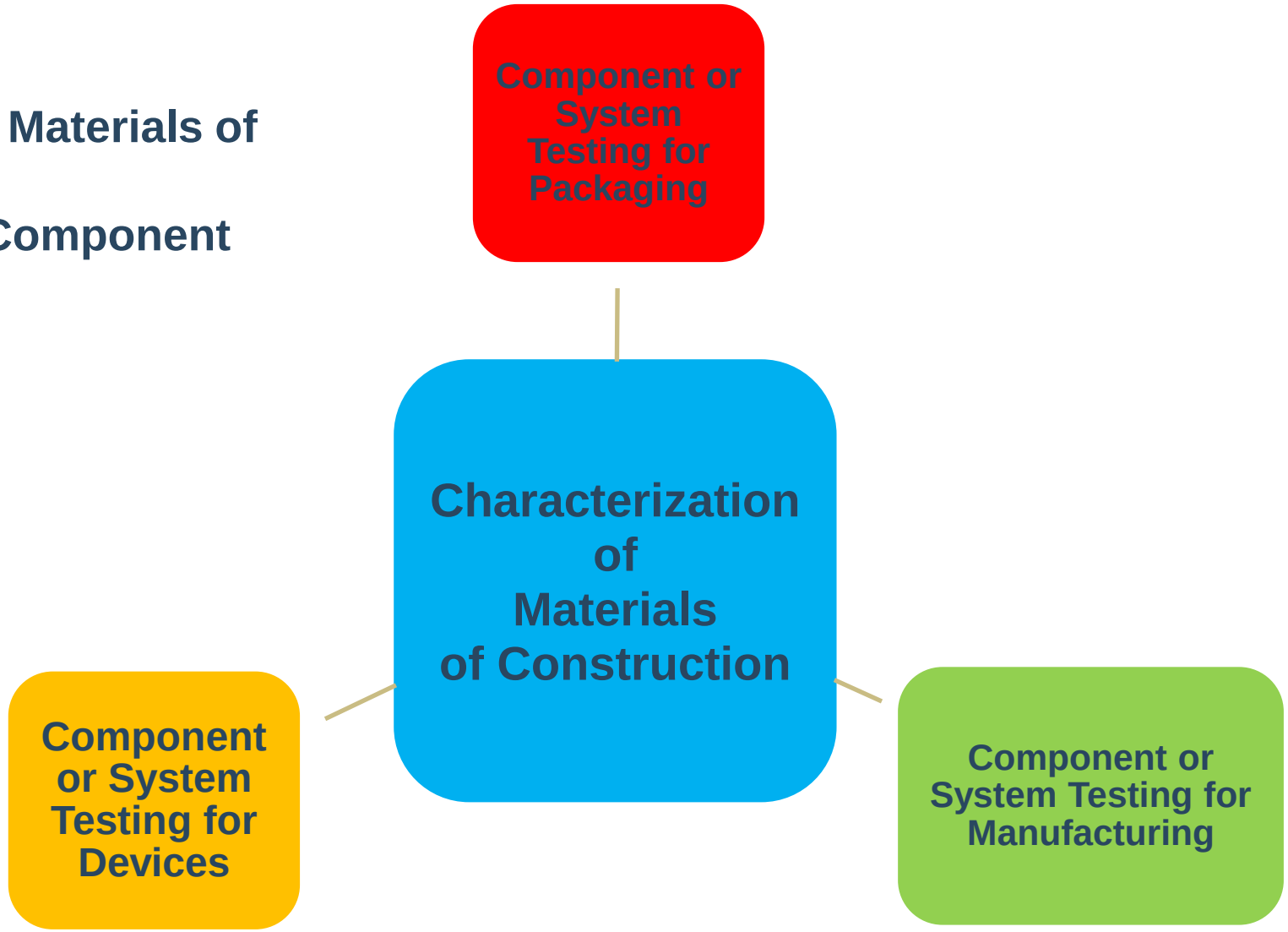
PDA – Europe Extractables and Leachables Workshop; Rome, March, 2018

The Essence of the USP Strategy for Plastics

- Standardize at the Materials of Construction level
- Customize at the Component or System level



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
- Pharmaceuticals, Small Molecules, Biopharmaceuticals products and Vaccines
- Single-Use Systems and Multi-Use Systems

Scope

So what is this about Drug Substances?

In its previous versions, <665> was applicable to drug products, drug substances (biopharmaceuticals), and active pharmaceutical ingredients (APIs. “traditional” pharmaceuticals). In its currently revised version, <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>.

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 also 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
- Biological Reactivity
- Physicochemical Properties
- Extractable Metals
- Polymer Additives

Required Biological Reactivity tests include:

- Cytotoxicity
- Sensitization
- Systemic toxicity (acute)
- Systemic toxicity (sub-acute)
- Genotoxicity
- Chronic toxicity
- Carcinogenicity

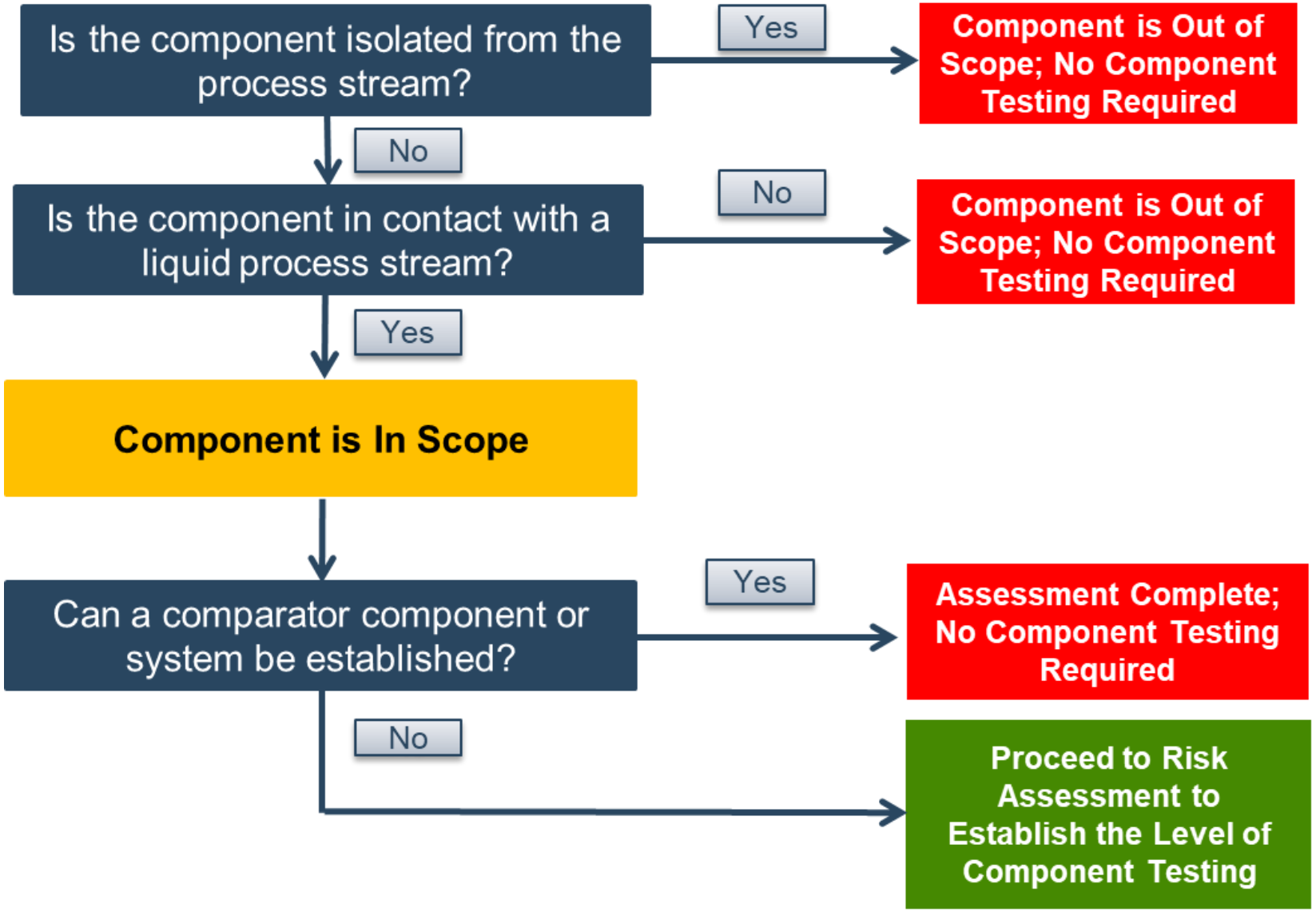
Navigating through <665>; Materials

Polymeric materials of construction that are not specifically addressed in ⟨661.1⟩ are termed "**unaddressed materials**". For an unaddressed material to be deemed compliant with this chapter, it must be characterized in ways that are comparable to those used for the materials specified in ⟨661.1⟩. Specifically, the unaddressed material of construction must be identified by appropriate methodology and tested for biocompatibility, physicochemical properties, additives, and relevant extracted metals.

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”?

In its previous versions, 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” (suggesting that the drug product, with it’s impurities from any source, was deemed to be safe).

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

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

The Concept of Risk and its Application to <665>

The concept that “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” is universally accepted as sound and appropriate product stewardship.

Specifically considering manufacturing equipment, the magnitude of testing required to establish that manufacturing equipment is safe for use depends on (a) the likelihood that the manufacturing equipment is leached by a process solution under typical manufacturing conditions and (b) the likelihood that an extracted substance would persist in the process stream and become iincorporated in the drug product. The greater the likelihood of either (a) or (b), the greater the amount of testing required for manufacturing materials and components.

What the Risk Evaluation Accomplishes

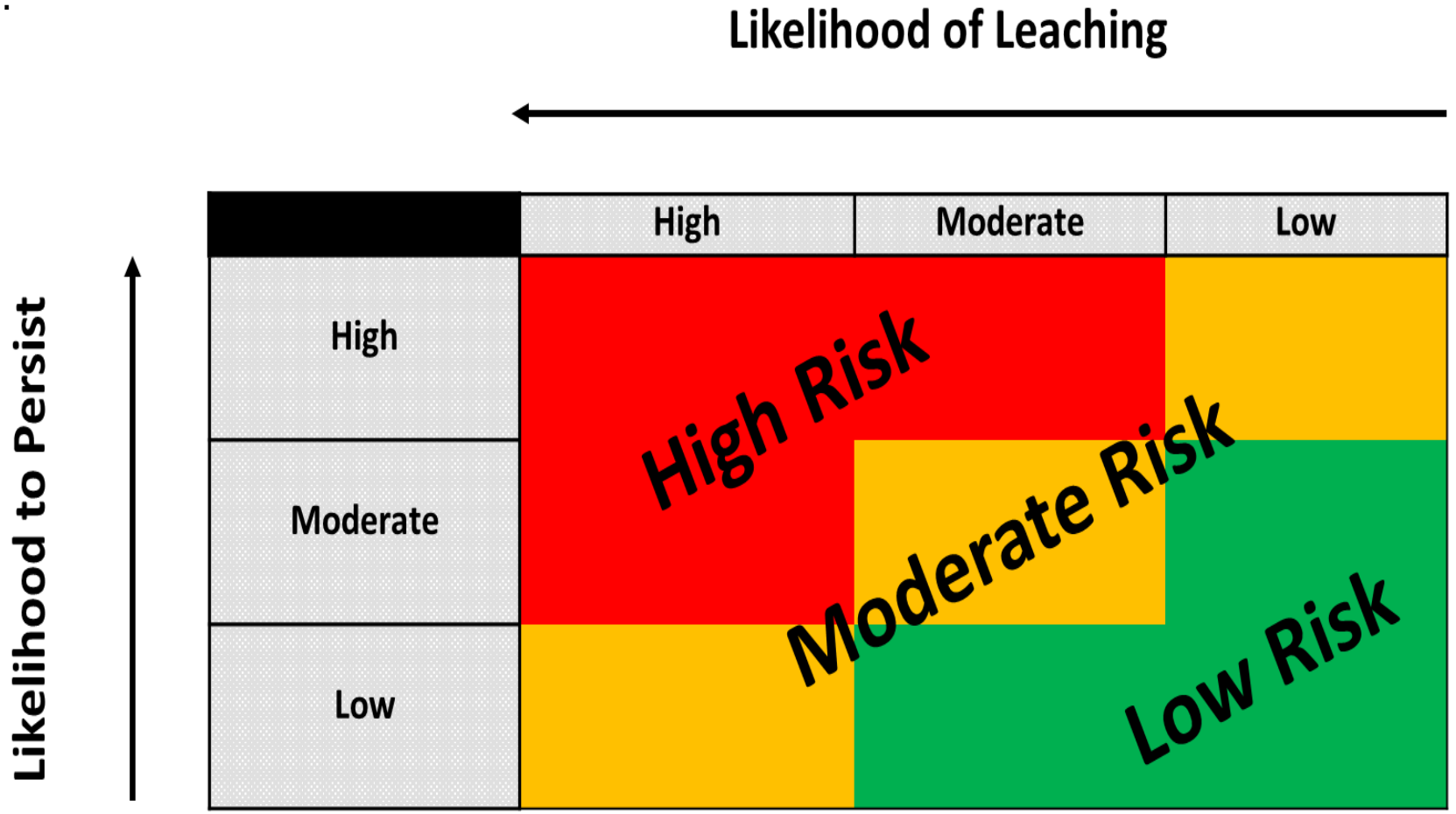
1. Establishes the appropriate contributors to, or dimensions of, risk,
2. Provides a means of quantifying the risk, in each of its dimensions, and
3. Links the quantified risk to appropriate characterization strategies.

How is the Risk Evaluation accomplished?

Via application of a Risk Evaluation Matrix.

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>.



The Risk Assessment Required in <665>

An individual manufacturing circumstance (component type, process conditions under which the component is contacted by the process stream, mitigating factors) is positioned in this Risk Evaluation Diagram to establish the component's required level of testing per <665>.

Although each individual finished 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.

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.

The Risk Assessment Required in <665>

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

In its previous versions, <1665> contained a specific Risk Evaluation Matrix with which to perform the Risk Assessment. This Matrix was going to be placed into the revised <665> document 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> provided review comments that pointed out (a) that many organizations had already developed their own Risk Evaluation Matrices and (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> does not appear in <665>. Rather, it is the responsibility of the sponsor to establish and justify their own Matrices.

Requirements for a Risk Evaluation Matrix per <665>

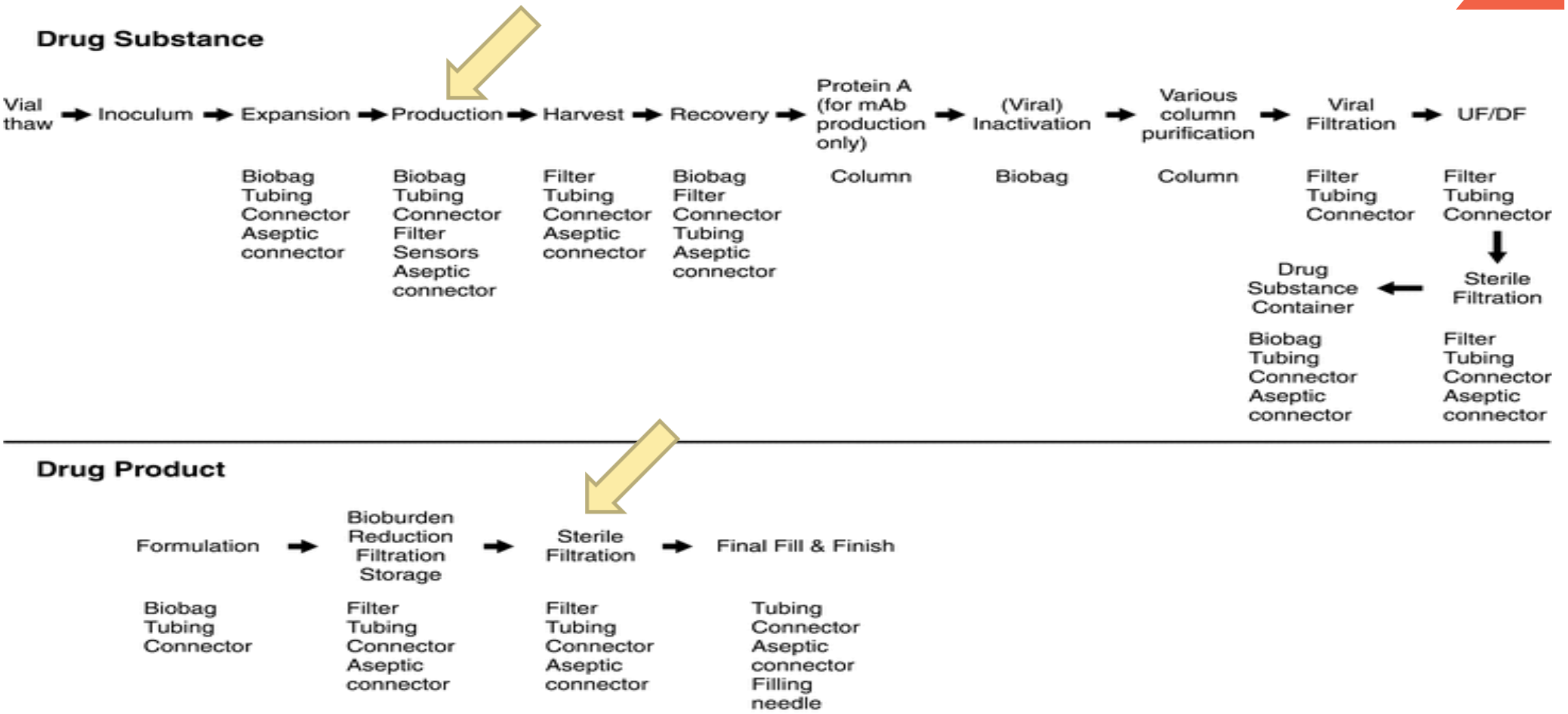
The risk evaluation matrix must address the following considerations:

1. The chemical and physical nature of the contacted material or component, establishing the material's or 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,
4. The ability of upstream process operations to either eliminate the PERL from the process stream or to dilute the PERL to such an extent to an adverse effect is unlikely,
5. The inherent safety risk associated with the manufactured drug product, considering such factors as the nature of the manufactured dosage form [for example, inhalation solution (higher risk) versus solid oral (lower risk)], the clinical dosing of the drug product (for example, daily dose volume), and the duration of the clinical therapy.

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

The required **Biological Reactivity** tests for components, regardless of risk, includes:

- Cytotoxicity
- Sensitization
- Systemic toxicity (acute)
- Systemic toxicity (sub-acute)
- Genotoxicity
- Chronic toxicity
- Carcinogenicity

PROPOSED

Testing of Components Consistent with the Level of Risk

Depending on the level of risk established via the risk evaluation process, polymeric components are **chemically** tested as specified in *Table 1*.

Table 1. Chemical Testing for Components as Established by Risk

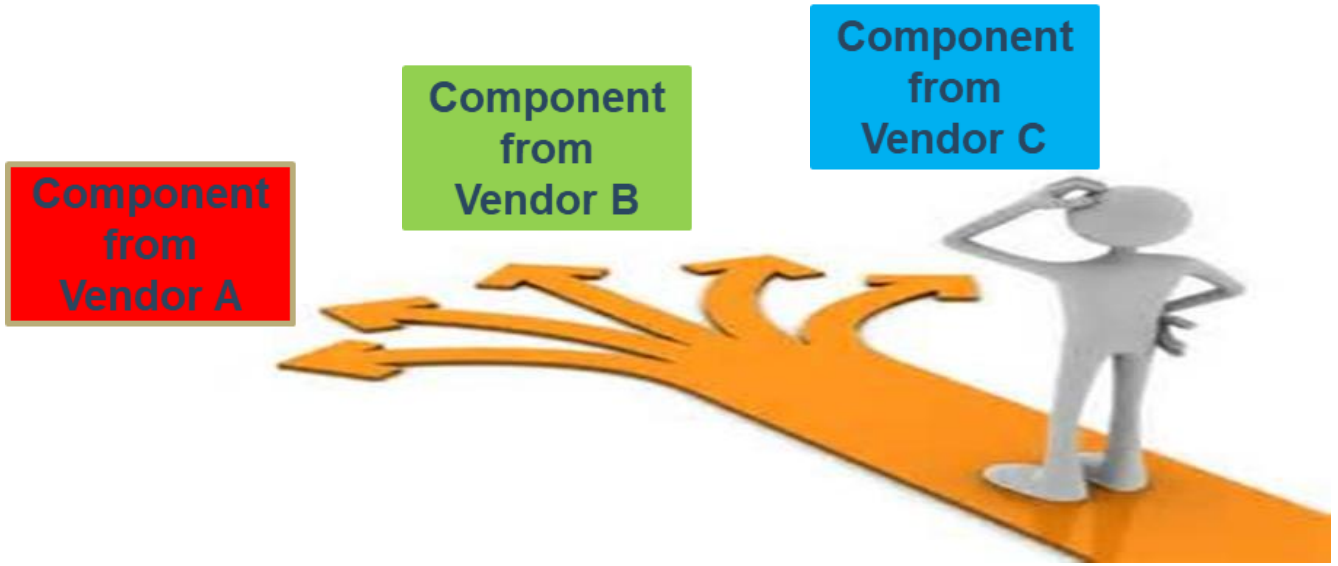
Risk Level	Chemical Testing
Low	Partial Chemical Assessment (Extraction with solvent C1 only, test for TOC and Extracted Metals) ***PROPOSED***
Moderate	Limited Chemical Assessment (all Low Risk testing + ethanol/water extraction coupled with organic extractables profiling) ***PROPOSED***
High	Full Chemical Assessment (all extraction solvents, all specific tests)

Application of the Standard Extraction Protocol, SEP

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

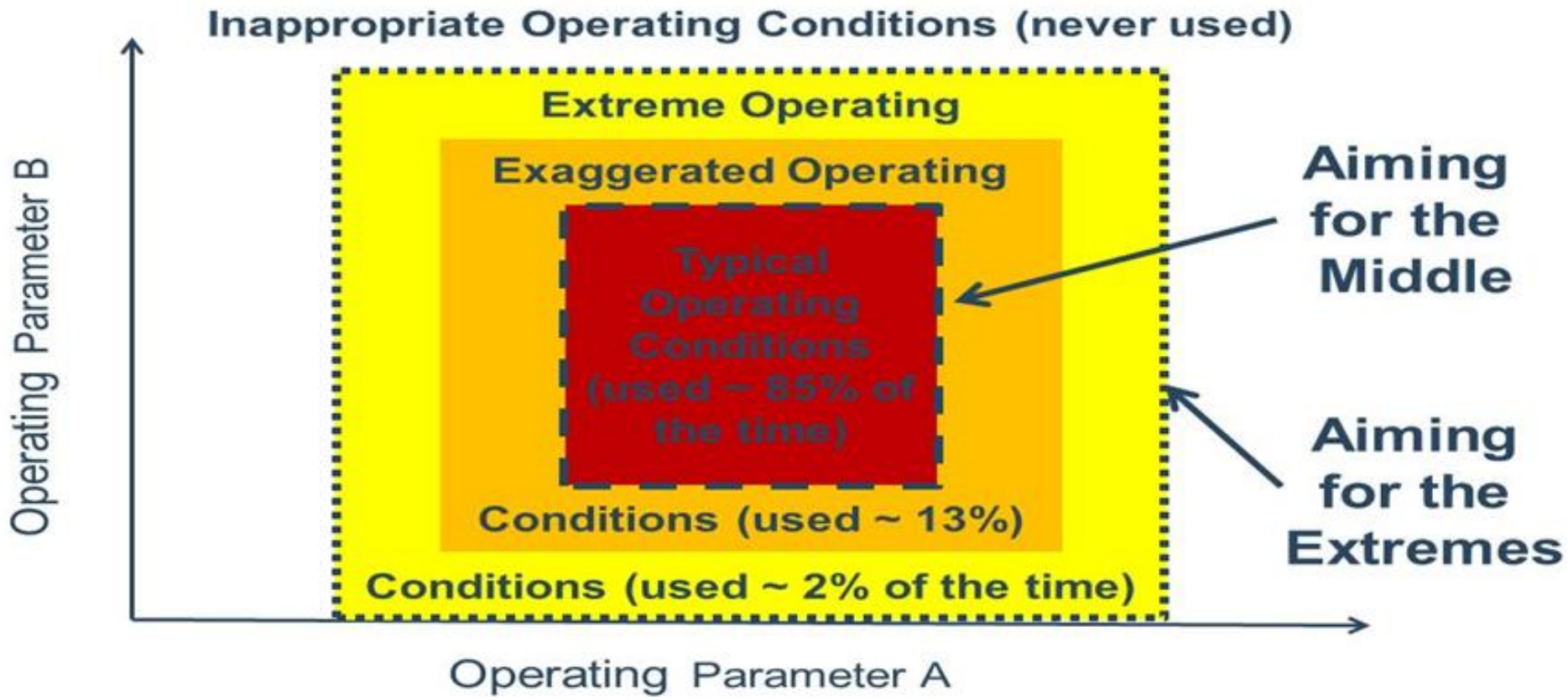
Purpose of the SEP

The Standard Extraction Protocol (SEP) is used to generate extractables data to aid **in the selection of components** to be used in a particular manufacturing operation.



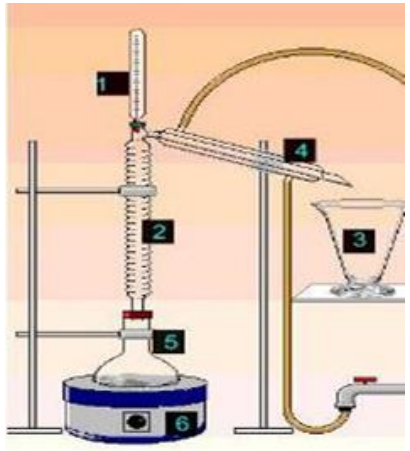
Focus of the SEP

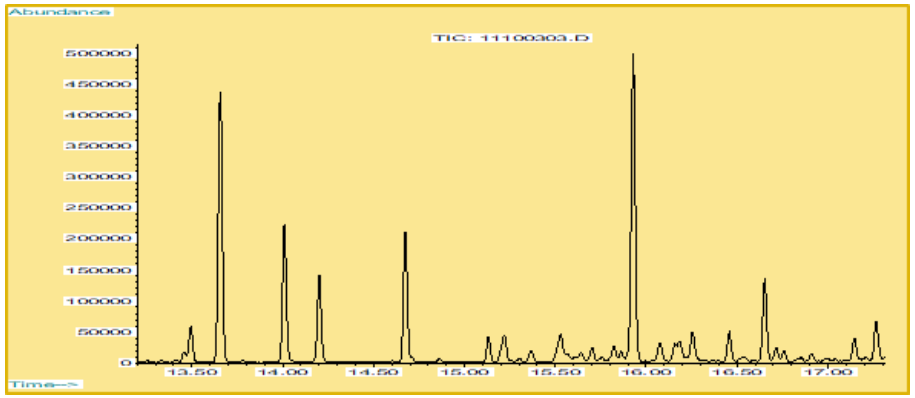
The Standard Extraction Protocol (SEP) “aims for the middle”, seeking to represent those conditions most commonly encountered in pharmaceutical manufacturing.



The Objective of the SEP

The Standard Extraction Protocol (SEP) seeks to generate extractables information which informs effective and science-based component selection via hazard identification.





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 11, 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 adequate justification is provided.

SEP Extraction Temperature and Durations

Component	Extraction Solutions C1 through C3	Extraction Temperature 40°	Extraction Duration		
			1 day	7 days	21 days
Storage Container	X	X			X
Mixing Bag	X	X	X		
Bioreactor Bag	X	X			X
Tubing Connector/disconnector	X	X			X
Aseptic/Sterile Connector/disconnector	X	X		X	
Sensor/Valve	X	X	X		
Molded Parts of Mixers	X	X	X		
Polymer pump surfaces	X	X	X		
Tubing	X	X			X
Gasket, O-ring	X	X		X	
Sterilizing Filter	X	X	X		
Process Filter	X	X	X		
Tangential flow Filtration	X	X	X		
Chromatography Column	X	X	X		
Filling Needle	X	X	X		

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.
- If addition of the extracting solvent to a test unit creates an open extraction system, the open access points must be closed by an appropriate means with inert materials.
- Extraction at higher temperature/longer durations may lead to loss of extraction solvent due to transpiration through the test article/unit. To mitigate this, the filled test article can be encased in inert secondary containment materials (for example, properly chosen aluminum foil).
- 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 SEP Score Card

- 50% Ethanol; **Alignment**
- Water, 5 M NaCl, 1% Polysorbate 80; **Alignment** (USP allows for the use of additional solvents at the discretion of the sponsor)
- Low pH; **Alignment** (interchangeable solvents)
- High pH; Alignment (pH 10 is the standard, other alternate or additional solutions may be used, at the sponsor's discretion, with justification).
- The USP has adopted an extraction process which is a subset of the BPOG protocol. Thus the USP is fully aligned with the BPOG protocol because USP allows for the use of additional conditions at the discretion of the sponsor.

Profiling the SEP Extracts

- The extracts and extraction blanks shall be analytically tested to establish the identities of the extractables and to estimate their concentration in the extracts using appropriate and orthogonal analytical methods, consistent with *Good Manufacturing and Stability Practices—Determination of Extractables Associated with Pharmaceutical Packaging Systems,* <*1663*> .
- The reporting of extractables shall be consistent with the application of relevant and appropriate reporting thresholds, such as the analytical evaluation threshold (AET) as defined in *<1663>.*
- Considering the extraction of elemental impurities, the extracts shall be tested for such elemental impurities via methodologies consistent with *Elemental Impurities – Procedures* <233>.

Current Status, <665> and <1665>

- **In-Process Revision: <665> POLYMERIC COMPONENTS AND SYSTEMS USED IN THE MANUFACTURING OF PHARMACEUTICAL AND BIOPHARMACEUTICAL DRUG PRODUCTS. Pharmacopeial Forum; 43(3), 2017.**
- **In-Process Revision: <1665> PLASTIC COMPONENTS AND SYSTEMS USED TO MANUFACTURE PHARMACEUTICAL DRUG PRODUCTS Pharmacopeial Forum; 43(3), 2017.**

Both these documents have recently completed (September 30, 2017) their public review (second cycle). Comments received from “interested parties” are in the process of addressed by the Expert Panel.

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*, 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 opinions expressed by stakeholders, every effort will be 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.

“My guess is no better then anyone else’s at this point”

Questions

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Thank You

Contact the presenter at: dennisjenke@triadscientificsolutions.com; (www.triadscientificsolutions.com)

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